David Alberts
Lisa M. Hess *Editors*

Fundamentals of Cancer Prevention

Third Edition

Springer

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In my 45 years as a medical oncologist (38 of which were dedicated to building the University of Arizona Cancer Center), I have evolved from a hematologic malignancy specialist to a medical gynecologic oncologist, and finally to a clinical and translational cancer preventionist. If we are to "stem the terrible tide of cancer in the 21st century, cancer prevention research, training and dissemination must become the dominant theme in our everyday medical lives! I hope that this will be my legacy while I turn to my magnificent wife, Heather (the most accomplished cancer preventionist in the Alberts Family), and my remarkable children, Sabrina, Danny, Tim, and Angelle, and amazing grandchildren, Sammy, Sophie, Sydney, Emma and Tate for love and comfort in the twilight of my exciting and fulfilling medical career. Finally, a very heartfelt thank you to my brilliant Co-Editor, Dr. Lisa Hess, who has been most responsible for the success of Fundamentals of Cancer Prevention!

Thank You,
Dave

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Introduction to Cancer Prevention

1

David S. Alberts and Lisa M. Hess

1.1 Introduction

The concept of cancer prevention is changing gradually as we gain a greater understanding of the genetic and molecular basis of carcinogenesis. Certainly, it is understood that the cancer patient is not well one day and the next day diagnosed with cancer. It is estimated that there is an average lag of at least 20 years between the development of the first cancer cell and the onset of end-stage metastatic disease for a broad range of solid tumors. In that there were an estimated 1,660,290 new cancer cases and 580,350 cancer deaths in the USA in 2013 (Siegel et al. 2013) and given the 20+-year lag time, more than 11 million "healthy" Americans currently harbor ultimately deadly cancers, many of which may be fully preventable.

Given the average 20-year lag time from the point of the first altered cell to carcinoma, secondary and tertiary prevention strategies represent effective and cost-effective opportunities to dramatically reduce cancer mortality in the next decades. Cancer costs exceeded US$201.5 billion in 2008 alone (ACS 2013). These represent both direct and indirect economic costs (not considering the psychosocial costs to patients and families) that could be avoided. Chapter 2 discusses the human and economic benefits of cancer prevention in more detail.

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1.2 Summary of Changes to Third Edition

In 2009, the Union of International Cancer Control Annual Report stated that our current knowledge shows that "40 % of cancers can be prevented" and 25–33 % can be avoided by eating a healthy diet, maintaining a healthy body weight, and remaining physically active; however, the tragedy is that we are not using this knowledge to reduce the global burden of cancer (UICC 2010). Many researchers worldwide have focused their life's work to identify ways to prevent cancer. One reason why current knowledge and information about cancer and its prevention is not fully applied to the general public is due to an overload of complicated, contradictory, and even inaccurate information through various Internet and printed sources (Cline and Hayes 2001). The dissemination of complicated information is problematic, but comprehensive information is essential to reduce the burden of cancer. The third edition of this book is designed to provide this information in the form of a comprehensive overview on the science and practice of cancer prevention for primary caregivers and the research community.

Because of the rapid advancement in cancer prevention research, several important changes have been made to the third edition of this book. The first section of this book (Chaps. 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11) provides information on economic issues in cancer prevention, dietary and environmental risk, immune response, drug development, the role of telemedicine technology, and cultural considerations in cancer prevention. New chapters included in this section address topical drug delivery systems, the global issues in cancer prevention, reaching underserved populations, and regulatory considerations in cancer prevention. The second section of the book (Chaps. 12, 13, 14, 15, 16, 17, 18, and 19) focuses on the prevention of specific cancers by site of origin and provides the reader with a discussion of the epidemiology, screening, and prevention of each disease, including practice guidelines as well as theories and future research directions. The book concludes with Chap. 20, discussing issues related to cancer survivorship.

The field of cancer prevention is constantly changing as research progresses and our knowledge about cancer expands. Each chapter has been revised in the third edition. Important new chapters in this revised edition include Chap. 6, which addresses the important issue of inequity in health care and proposes solutions to reduce inequalities. Additionally, a second new chapter has been added (Chap. 10), which focuses on cancer as a global issue that our world is facing.

1.3 Overview of Cancer Prevention

Cancer is a global term for a variety of diseases that share some similar characteristics, such as uncontrolled cellular growth, enhanced angiogenesis, and/or reduced programmed cell death. The site of origin of the disease is used to define general categories of disease (e.g., breast cancer, skin cancer). It is increasingly apparent that despite the variation across cancer types, the majority of cancers proceed from the first initiated tumor cell (e.g., mutated DNA) to mild, moderate, and severe

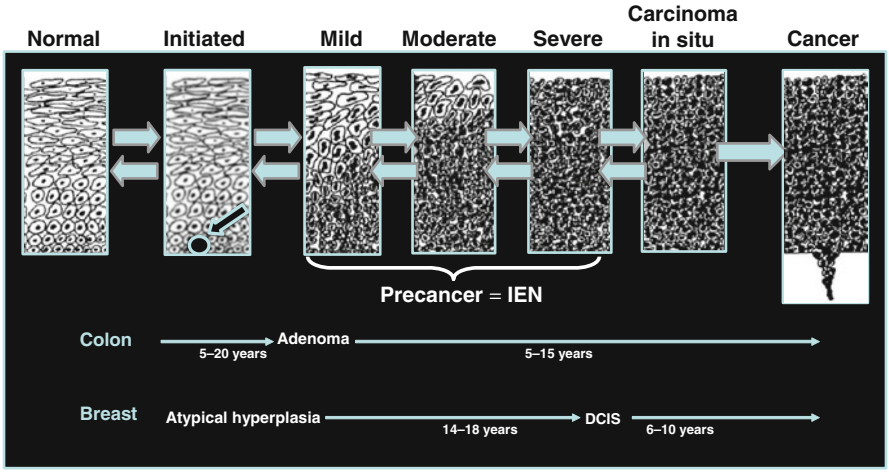

Fig. 1.1 Progression of precancer to cancer in humans is a multiyear process (Adapted from O'Shaughnessy et al. (2002))

dysplasia, invasive carcinoma (invasion of cells through the basement membrane), and metastatic disease (Fig. 1.1). A single mutated cell can begin to divide incorrectly and produce additional abnormal cells. Cancer prevention research is working to identify these changes as early as possible to intervene to prevent their progression to cancer. If abnormal cells continue to divide and expand, they can develop into precancerous lesions. These lesions (IENs) can be identified both histologically and by molecular signatures, using a variety of analytical methods (e.g., cDNA microarray) (O'Shaughnessy et al. 2002). They are represented by small, intermediate, and advanced adenomatous polyps in the colon; atypical hyperplasia and ductal carcinoma in situ in the breast; and simple hyperplasia, atypical hyperplasia, and carcinoma in situ in the endometrium. As atypia increases, these dysplasias are believed to develop into cancer and if left unchecked have the great potential to metastasize to adjacent and distant organs.

It is estimated that there are over 12.7 million cases of cancer diagnosed and 7.6 million deaths each year worldwide (Jemal et al. 2011). The five most common worldwide cancers, excluding nonmelanoma skin cancer, include lung, stomach, breast, colorectal, and liver cancer (Table 1.1). There are gender and regional differences in worldwide cancer diagnoses. Although less than 20 % of the world's population lives in developed nations, close to half (44 %) of all cancer cases and 36 % of cancer deaths occur in these countries (Jemal et al. 2011). Eighty-two percent (82 %) of all cervical cancer cases and 70 % of all stomach cancers occur in developing nations, whereas 71 % of all prostate cancers, 50 % of breast cancers, and 58.9 % of all colorectal cancers are diagnosed in developed nations (Jemal et al. 2011). The highest rates of esophageal cancer are found in Eastern Asia and East Africa, and half of all liver cancers are diagnosed in China.

Similar to the rest of the developed world, cancer is a major health burden in the USA, responsible for approximately 580,350 deaths in 2013. Cancer is the leading

Table 1.1 Worldwide annual cancer incidence and mortality of selected common cancers (Jemal et al. 2011)

	Number of new cases each year	Number of deaths each year
Males		
Lung	1,095,200	951,000
Prostate	903,500	258,400
Colon/rectum	663,600	320,600
Stomach	640,600	464,400
Liver	522,400	478,300
Esophagus	326,600	276,100
Bladder	297,300	112,300
Females		
Breast	1,383,500	458,400
Colon/rectum	570,100	288,100
Cervix	529,800	275,100
Lung	513,600	427,400
Stomach	349,000	273,600
Liver	225,900	217,680
Ovary	225,500	140,200

cause of death among those under the age of 80 years in the USA (Siegel et al. 2013). The leading modifiable causes of increased cancer risk include tobacco use, infection, alcohol abuse, physical inactivity, and obesity. Obesity and body weight alone account for 20 % of all cancers in the USA (Wolin et al. 2010). In the USA, 68.8 % of the population is overweight or obese and 35.7 % are obese, and the numbers are increasing rapidly (Flegal et al. 2012). Globally, obesity rates doubled from 1980 to 2008 and are increasing (Stevens et al. 2012). As this trend continues, global cancer incidence rates will also continue to rise.

Unfortunately, another pervasive problem in the USA and many other nations is poor access to health care because of a lack of health insurance (USA) and/or lack of services (rural or remote regions and many developing nations). Access to screening programs and improved health-care programs are essential to prevent cancer. For example, among nations with organized cervical cancer screening programs, the risk of cervical cancer morbidity and mortality has been continuously declining (e.g., Sweden, Finland, and France have all seen cervical cancer decrease by greater than 4 % per year since the initiation of cervical cancer screening programs), whereas among nations that lack these programs, cervical cancer remains a major health risk for all women (e.g., Slovakia and Slovenia have seen annual increases in cervical cancer without these programs) (Mackay et al. 2006). Similarly, nations that have organized tobacco control policies have shown decreases in youth tobacco use. However, even among nations that have established public health policies, individuals must have access to these programs for them to be effective. The USA has the greatest health-care expenditures in the world and substantial per capita medical expenses at approximately US$8,000 per person per year, which is substantially higher than many other nations (e.g., in Norway, spending is $5,352; Canada $4,363; France $3,978; the UK $3,487; Australia $3,445; and Japan $2,878 per person per year) (Martin et al. 2012; Squires 2012). Despite this investment, 50 million

Americans (15.7 % of the total US population) lack even the most basic health insurance coverage and therefore do not have access to general or preventive health care (ACS 2013). Lack of access to health care has been demonstrated to result in late cancer diagnosis (e.g., at an advanced stage) when costs are greater and outcomes are poor, more cancer treatment delays, and ultimately higher mortality (ACS 2008). Even when patients without insurance are diagnosed at the same stage as patients with insurance, they still have a significantly increased risk of death (e.g., patients without insurance have a 30–50 % higher rate of death from colorectal or breast cancer than patients with insurance) (IOM 2002).

The goal of cancer prevention is to reduce the morbidity and mortality from cancer by reducing the incidence of cancer due to these modifiable factors as well as to reduce the impact of unmodifiable factors contributing to cancer. The development of effective cancer prevention strategies has the potential to impact a significant portion of the cancer-related deaths each year worldwide (Jemal et al. 2011). Therefore, cancer prevention is the best approach possible to reduce the burden of cancer worldwide. Cancer prevention research takes a three-pronged approach to target different aspects reducing cancer morbidity and mortality: primary, secondary, and tertiary prevention.

1.4 Primary Prevention

Primary prevention involves a reduction of the impact of carcinogens, such as through administration of a chemopreventive agent or the removal of environmental carcinogens. The goal of primary prevention is to prevent a cancer from beginning to develop by reducing individual risk. Current primary prevention methods include lifestyle modification or interventions that modify risk. Primary prevention methods are best suited for those cancers in which the causes are known. There are many factors known to reduce overall cancer incidence, such as minimizing exposure to carcinogens (e.g., avoiding tobacco), dietary modification, reducing body weight, increasing physical activity, avoiding infection, or through medical intervention (surgery and/or chemoprevention). Among developed nations, the leading risk factors for cancer include an unhealthy diet, obesity, and tobacco use (together accounting for 40 % of cases), whereas among developing nations, poor diet/nutrition is the leading risk factor in 20 % of all cancer cases, and infection accounts for another 26 % of all cancer cases.

Tobacco use, which represents the greatest preventable cause of cancer death by far, is the direct cause of more than 20 % of all cancer deaths worldwide each year (primarily lung cancer, but smoking also increases the risk of cancers of the larynx, oral cavity, lip, nasal cavity, esophagus, bladder, kidney, cervix, stomach, liver, and many other sites) (Thun et al. 2010). Tobacco use is the leading cause of smoking-related cancer death among both men and women (80 % of all lung cancers among males and 50 % among females are directly attributed to tobacco) (Jemal et al. 2011). However, all damage done during smoking is not completely irreversible. Smoking cessation can begin to reverse the risk of cancer. Benefits from quitting

smoking begin within the first year of cessation and continue to increase over time. The risk of lung, oral, and laryngeal cancers can be significantly reduced following smoking cessation, with an estimated overall 9-year gain in life expectancy associated with smoking cessation (Jha et al. 2013). The results of tobacco cessation are particularly pronounced if a person quits smoking before the age of 40 (associated with a 90 % reduction in premature death that is associated with smoking in midlife) (Jha et al. 2013). Primary tobacco prevention efforts include cessation support programs (behavioral and pharmacologic), public awareness and education, smoke-free public policies, increased tobacco pricing through taxation, and very importantly efforts to reduce the initiation of the use of any form of burnt and smokeless tobacco, all of which are carcinogenic and deadly (Thun et al. 2010; Jemal et al. 2011).

Many cancers are directly attributable to viral or bacterial infections (e.g., human papillomavirus, HPV, infection is a necessary factor in the development of cervical cancer; *Helicobacter pylori* is an initiator and promoter for gastric cancer). Advances in vaccination research led to the development of HPV vaccines that are available to adolescent males and females (See Chap. 17). If these vaccines would be used and available worldwide, nearly all cervical cancers could be prevented. Unfortunately, even in the USA where the vaccine is widely available, less than one third of all eligible young women are vaccinated and remain at risk for cervical cancer (Jemal et al. 2013). These rates are lowest in the regions and among populations with the highest rates of cervical cancer (Jemal et al. 2013). Primary prevention research and efforts continue to remain underfunded. In the USA and Europe, less than 10 % of all cancer research funding is dedicated to cancer prevention efforts (Mackay et al. 2006). This lack of prioritization results in delays in improving and delivering early detection and prevention strategies that have the potential to save millions of lives.

1.5 Secondary Prevention

Secondary prevention involves the concept of a precancerous lesion, or abnormal changes that precede the development of malignancy. Secondary prevention involves screening and early detection methods (e.g., mammogram, colonoscopy) that can identify abnormal changes before they become cancerous, thereby identifying and removing the precancer before it fully develops or before it becomes malignant. In some cases, secondary prevention can involve the treatment of precancerous lesions in an attempt to reverse carcinogenesis (e.g., causes the lesion to regress). Secondary prevention is described in more detail specific to each disease site (Chaps. 12, 13, 14, 15, 16, 17, 18, and 19) in this book.

1.6 Tertiary Prevention

Tertiary prevention involves the care of established disease and the prevention of disease recurrence as well as the prevention of disease-related complications and often encompasses the treatment of patients at high risk of developing a second

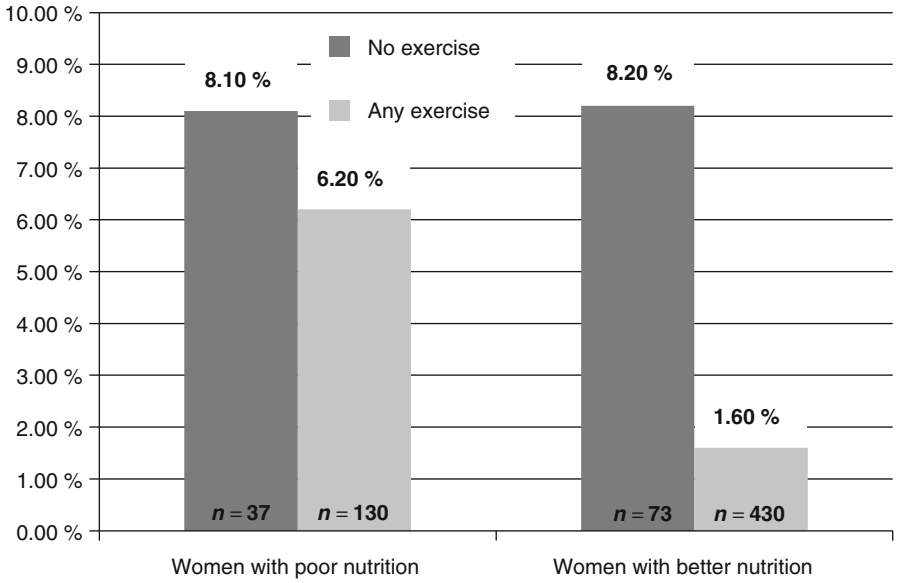

Fig. 1.2 Percentage of deaths due to breast cancer in patients with early-stage disease according to amount of exercise and nutrition after diagnosis (George et al. 2011)

primary cancer. In this setting, emerging evidence suggests that physical activity may have an even greater impact on reducing cancer risk than nutritional interventions to reduce the risk of disease recurrence and to prolong survival in early-stage breast cancer. In a prospective study of women with early-stage breast cancer (George et al. 2011), women with any physical activity and better quality diets had a lower risk of death from breast cancer than those who had poor nutrition and exercise; nutrition alone did not demonstrate any differences between groups (Fig. 1.2). These findings are hypothesis generating rather than confirmatory due to the self-reported diet and activities and non-randomized study design. Additional research is ongoing to explore this hypothesis in breast cancer and a variety of other tumor types. Tertiary prevention is most often referred to as cancer control and involves a variety of aspects of patient care, such as quality of life, maintenance or adjuvant therapies, surgical intervention, palliative care, and control of obesity. These efforts are described in more detail in Chap. 20.

1.7 Multistep Carcinogenesis Pathway

Prevention of cancer requires an understanding of the process of cancer initiation and the steps to progression of disease. This process is referred to as carcinogenesis, a process of genetic alterations that cause a normal cell to become malignant. Cancer prevention involves the identification and classification, as well as

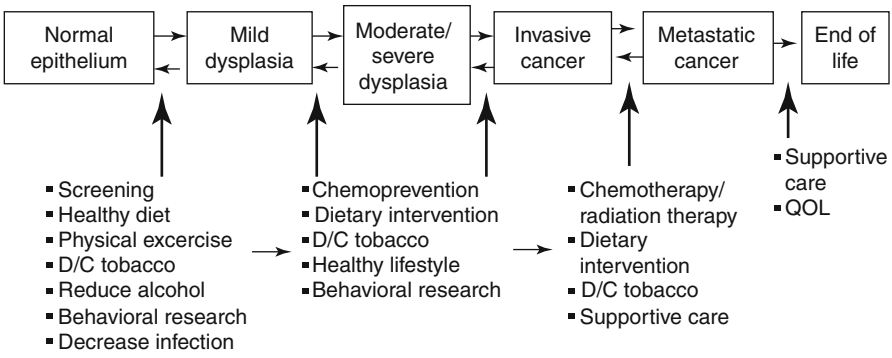

Fig. 1.3 Multistep carcinogenesis pathway (Adapted from Alberts (1999))

interventions for the regression or removal of precursor lesions, often referred to as intraepithelial neoplasia (IEN), before they can become cancerous. As shown earlier in Fig. 1.1, the process of carcinogenesis may take many years. In the case of colorectal cancer, it may take up to 35 years from the first initiated colonic mucosal cell to an adenomatous polyp to develop invasive cancer (see Chap. 13). The same is true for prostate cancer, which progresses over as many as 40–50 years from mild to moderate, then severe intraepithelial neoplasia, to latent or invasive cancer (see Chap. 16). Other cancers, however, such as ovarian cancer (see Chap. 18) is not known to follow the same lengthy carcinogenic process and as a result has many challenges for interventions for early detection and prevention.

The vast majority of current treatment modalities are used to treat far advanced and/or metastatic cancers, however, now that it is possible to identify IENs for many solid tumor types. Lifestyle changes, simple surgical procedures, and chemopreventive agents can be used to impede the development of these potentially dangerous precancerous lesions (Fig. 1.3). For example, multiple lifestyle changes, taken together, could profoundly reduce the risk of the first initiated cell progressing to mild dysplasia or stop the progression of IENs to invasive cancer. This would include reducing dietary fat intake, increasing the number of servings of fruits and vegetables, minimizing alcohol intake, tobacco exposure cessation, and increasing physical activity (Brown et al. 2003; Chlebowski et al. 2002; Ornish et al. 2005; Schmitz et al. 2005; Davies et al. 2006; Meyerhard et al. 2006; Holmes et al. 2005; Rock and Deark-Wahnefried 2002; Nagle et al. 2003). Furthermore, the addition of an effective chemoprevention agent, such as tamoxifen for moderately or severely dysplastic intraepithelial neoplasia such as ductal carcinoma in situ, can reduce cancer risk by as much as 50 % (Fisher et al. 1998). Thus, the concept of cancer prevention is now evolving into the mainstream of cancer therapeutics.

The process of carcinogenesis involves multiple molecular events over many years to evolve to the earliest dysplastic lesion or IEN. This multiyear process provides numerous opportunities to intervene with screening, early detection, surgical procedures, and chemoprevention (i.e., the use of specific nutrients and/or chemicals to treat IENs and/or delay their development) (Sporn 1976). Figure 1.4 presents

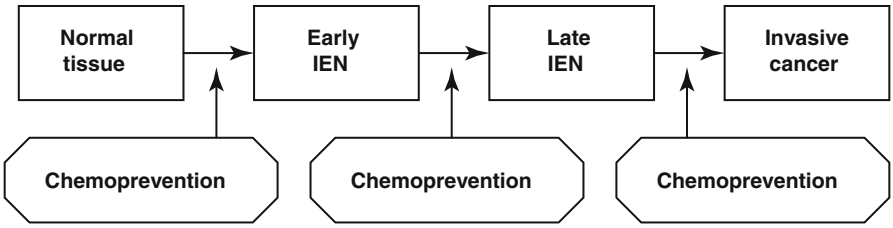

Fig. 1.4 Chemoprevention of intraepithelial neoplasia (IEN)

the concept that an effective chemopreventive agent could prevent IEN growth, progression, or, ultimately, invasion through the tissue basement membrane.

1.8 Cancer Prevention Research

The importance of conducting and participating in clinical trials cannot be understated. Every person is at risk of genetic mutations that may lead to cancer. Due to endogenous or exogenous factors, every human body has undergone genetic alterations. For many individuals, these initiating factors are the early steps to the development of IEN or cancer. The time period from the first initiated cell to the time of cancer is estimated to be approximately 20 years. As described earlier, the early steps towards cancer occur over time, which means that literally millions of individuals in the USA alone are currently in some phase of undetected cancer progression that will ultimately result in their death (Wattenberg 1993).

Cancer prevention trials are research studies designed to evaluate the safety and effectiveness of new methods of cancer prevention or screening. The focus of cancer prevention research can involve chemoprevention (including vaccination), screening, genetics, and/or lifestyle changes (e.g., diet, exercise, tobacco cessation). Cancer chemoprevention research differs from treatment research in several important ways as shown in Table 1.2. Cancer chemoprevention trials generally are performed in relatively healthy volunteers who have well-documented IENs (e.g., colorectal adenomas, bladder papillomas, breast ductal carcinoma in situ, actinic keratosis in the skin) or at increased risk due to genetic or other factors. These trials are usually double blind (i.e., both physician and participant do not know the assigned treatment) and placebo controlled and involve a few thousand to tens of thousands of randomized participants. As opposed to cancer treatment phase III trials, that rarely extend beyond 5 years in duration, cancer chemoprevention trials often take many years to complete and are extremely costly. The high cost of cancer prevention trials and the need to develop reliable and meaningful intermediate end points are significant barriers that must be overcome. Cancer prevention clinical trials take between 5 and 10 years (or more) to complete and require thousands of participants. In US dollars, the cost to complete large-scale trials (10,000 participants or more) is in the $100 to $200 million range and, of course, may not always result in the discovery of an effective prevention strategy.

Table 1.2 Cancer chemoprevention versus cancer treatment phase III trials

Characteristic	Cancer chemoprevention trials	Cancer treatment trials
Participants	Relatively healthy volunteers with IENs or at moderate/high risk	Patients diagnosed with invasive cancer
Trial design	Commonly double-blind, placebo-controlled	Unblinded to both patient and investigator
Dosage	Minimize dose, emphasize safety	Maximize dose, emphasize efficacy
Toxicity	Dosage changes with any toxicity, concern for long-term use of agent	Moderate toxicity acceptable, less concern with toxicity due to severity of disease
Adherence	Concern for "drop-ins" due to media or hype	Concern for "dropouts" due to toxicity
End point	Surrogate biomarkers; cancer incidence	Mortality
Sample size	A few thousand to several thousand participants	A few hundred to a thousand participants
Trial duration	Often 5–10 years	Several months to several years

Adapted from Alberts et al. (2004)

Research on developing and implementing effective cancer prevention and control interventions lags in funding relative to its potential impact on reducing the cancer burden. Despite the known cancer-causing effects of tobacco use, few non-nicotine medications are currently approved by the U.S. Food and Drug Administration (FDA) for smoking cessation, though others are in the pipeline, and these existing medications achieve smoking cessation quit rates that are 25 % at best. Since many health-care organizations do not include smoking cessation medications as a covered benefit, the incentive for pharmaceutical companies to prioritize the development of smoking cessation medications is not high – thus fostering a negative feedback loop that disincentivizes health-care organizations from covering medications because the effectiveness of those medications is low. Similarly, pharmaceutical companies have traditionally been unwilling to invest in the development of chemopreventive agents because of the required length of time, size, and cost of phase III confirmatory trials. Furthermore, companies are concerned about the uncovering of unexpected, life-threatening toxicities that may be observed with the long-term exposure required for many cancer prevention intervention strategies. This can have an extremely negative impact on safety profiles of approved drugs (e.g., COX-2 inhibitors increased cardiovascular events with twice-daily dosing in prospective randomized trials) (Baron et al. 2008).

The stages of investigation in cancer prevention research trials include a series of phases of clinical trials. Phase I trials take place after an agent has demonstrated activity with low toxicity in preclinical models. Phase I chemoprevention trials are relatively brief (i.e., 1–3 months), preliminary research studies in healthy humans to determine dose and safety of an agent. Phase II trials generally are randomized, double blinded, placebo controlled, and of longer duration (i.e., 6–12 months). The goals of phase II chemoprevention trials are to determine the activity of an agent in IEN and to further evaluate safety. Phase III trials generally are

large, double-blind, multiple-year, placebo-controlled randomized trials to evaluate the efficacy and safety of an agent in a sample of the target population. Often, cancer incidence is the primary end point in phase III prevention studies. For a chemopreventive agent to be used in a phase III research setting, it must meet several criteria. The agent must have strong data supporting its mechanistic activity, and there must be preclinical efficacy data from appropriate animal models. If the chemopreventive agent is a nutrient, there must be strong epidemiologic data supporting its potential effectiveness, and it must have demonstrated safety and activity in phase II trials. Phase III trials of novel chemopreventive agents should not be performed in the absence of a fundamental understanding of their mechanism of action. Finally, phase IV trials are focused on the dissemination of the phase III trial results into the population and the efficacy of these interventions in a real-world setting. Inadequate funding and insufficient attention have been given for these vitally important dissemination studies, leading to underutilization of effective chemoprevention strategies, such as tamoxifen or raloxifene to prevent the development of breast cancer in post-menopausal women (Fisher et al. 1998).

When the mechanism of action of a putative chemoprevention agent has not been explored in the setting of broad populations, the results of phase III trials can be alarming. Two examples of this include the results of the Finnish Alpha-Tocopherol, Beta-Carotene (ATBC) Trial and the University of Washington Carotene and Retinol Efficacy Trial (CARET). Both of these phase III trials used relatively high doses of beta-carotene as compared to placebo in heavy smokers to reduce the incidence of and mortality from lung cancer (Alberts et al. 1994; Omenn et al. 1996). Unfortunately, both trials found that the beta-carotene intervention was associated with an 18–28 % increase in lung cancer incidence and an associated increase in mortality. Perhaps the reason for these unexpected and extremely unfortunate results relates to the fact that at high beta-carotene concentrations in the setting of high partial pressures of oxygen (e.g., as achieved in the lung) and in the presence of heat (e.g., as achieved in the lung with cigarette smoking), beta-carotene can become an autocatalytic pro-oxidant (versus its usual role as an antioxidant) producing reactive oxygen species and DNA damage (Burton and Ingold 1984).

The design of chemoprevention phase III trials must be founded on a hypothesis that is soundly based on the mechanism of action of the agent, epidemiologic data, and its preclinical efficacy. The population to be enrolled to a phase III prevention trial must be relatively high risk, to assure that there will be a sufficient number of events (e.g., precancers or cancers) to compare the treatment to the control group. Phase III prevention trials should include both intermediate (e.g., IEN) and long-term (e.g., cancer) end point evaluations. Most importantly, the end point analyses should be planned in advance, including well-defined and well-powered primary and secondary analyses.

One example of a potentially high-impact phase III chemoprevention trial is the Breast Cancer Prevention Trial with Tamoxifen (BCPT) (Fisher et al. 1998). Healthy women at increased risk of breast cancer were randomized to either tamoxifen (20 mg/day) or placebo for up to 5 years. Tamoxifen was selected for this trial because of its well-documented mechanism of action (i.e., binding to the

estrogen receptor to prevent estrogen's effect on tumor cell proliferation), its strong safety profile in the setting of adjuvant breast cancer therapy, and its extreme activity in the prevention of contralateral breast cancer in patients with stage I/II breast cancer. After 69 months of follow-up, tamoxifen was found to be associated with an overall 49 % reduction in the risk of invasive breast cancer (Fisher et al. 1998). The benefit of breast cancer risk must be balanced with its toxicities, which include a greater than twofold increase in early-stage endometrial cancer and an increased incidence of deep vein thrombosis and pulmonary embolism. Since the publication of these results, much discussion has led to the identification of women who would most benefit from treatment with tamoxifen. Certainly, women who are at increased breast cancer risk have already undergone a hysterectomy and who at lower risk for thrombophlebitis (e.g., due to higher levels of physical activity, lack of obesity) would be good candidates for this intervention. Furthermore, there has been a relative lack of dissemination of this information to both primary care physicians and the population, resulting in limited tamoxifen usage (Freedman et al. 2003). More recently, the results of the phase III Study of Tamoxifen and Raloxifene (STAR) revealed equivalent activity of tamoxifen as compared to raloxifene for the reduction of breast cancer risk among postmenopausal women at moderately increased risk (Vogel et al. 2006). Raloxifene was associated with an improved safety profile (e.g., lower thromboembolic events and cataracts), leading to its approval as a chemopreventive agent with the FDA. Only time will tell if these results will lead to increased chemoprevention utilization. Currently, only a small fraction of eligible women at increased risk of breast cancer are taking advantage of the established efficacy of these chemopreventive strategies.

The translation of research findings to the clinic is the ultimate goal of cancer prevention research. Chemoprevention agents or screening modalities must be acceptable to the target population that would benefit from such interventions. For example, the ideal chemoprevention agent would have a known mechanism of action and would have no or minimal toxicity, high efficacy, be available orally or topically, have an acceptable treatment regimen, and would be inexpensive. Similarly, screening or early detection modalities should be minimally invasive, have high sensitivity and specificity, and be acceptable to the target population. Interventions that fail to maintain adequate adherence or that have high attrition rates during phase III trials will likely also not be acceptable to the patient in clinical practice.

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Assessing Human and Economic Benefits of Cancer Prevention

2

Stephen Joel Coons and Benjamin M. Craig

2.1 Introduction to Chapter

The consequences of the diagnosis and treatment of cancer are myriad and can include significant human and economic burdens on patients, their families, the health-care system, and society as a whole. It has been shown that cancer is the cause of more years of life lost than all other causes of death (National Cancer Institute [NCI] 2012) and that being a cancer survivor is associated with decreased physical health-related quality of life (Reeve et al. 2009; Weaver et al. 2012), increased psychological distress (Hoffman et al. 2009), changes in cognitive functioning (Phillips et al. 2011), higher out-of-pocket medical expenditures (Short et al. 2011), employment challenges (Short et al. 2005), and greater risk for personal bankruptcy (Ramsey et al. 2011). Hence, the avoidance of cancer and its consequences is paramount; where real change is possible in regard to known modifiable behavioral, environmental, and policy/regulatory risk factors for cancer, there is no doubt that "prevention is the cure" (Mukherjee 2010).

As will be described in much more detail in subsequent chapters, cancer prevention takes many forms. At the individual level, virtually all prevention activities involve (1) engaging in particular behaviors (e.g., following screening and immunization recommendations, taking tamoxifen for secondary prevention of breast cancer), (2) avoiding particular behaviors (e.g., sunbathing, smoking), or (3) changing particular behaviors once they have become habitual or routine (e.g., quitting smoking, lowering dietary fat). Each of these prevention behaviors, or the lack of them, can have short- and long-term health, quality of life, and/or economic consequences.

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Therefore, it is critically important to discuss and attempt to quantify the human and economic value of cancer prevention. The purpose of this chapter is to provide an overview of the ways in which this value can be defined and assessed.

2.2 Outcomes Assessment

In order to discuss the impact of cancer and the substantial benefits of preventing it, it is necessary to define *outcomes*. Death can be an outcome of cancer; however, "death rates alone do not provide a complete picture of the burden that deaths impose on the population" (NCI 2012). A more meaningful metric for measuring the impact of death (and the value of preventing it) is *person years of life lost* (PYLL). PYLL are the expected years of life lost due to premature death from a specific cause. Hence, PYLL can help to illustrate the magnitude of cancer's impact on shortening the length of lives. In 2008, each person who died in the USA as a result of cancer lost, on average, an estimated 15.5 years of life (NCI 2012). Overall, cancer-related deaths in the USA resulted in over 8.7 million PYLL in 2008. Lung cancer alone was responsible for almost 2.4 PYLL, which suggests that significant reductions in the number of life years lost to cancer can result from prevention. It is estimated that roughly 577,000 people in the USA died of cancer in 2012 (American Cancer Society 2012). Fortunately, death is not the only, nor most likely, outcome of cancer. Seigel and colleagues estimated there were 13.7 million cancer survivors in the USA at the beginning of 2012 and projected an increase to almost 18 million by 2022 (Siegel et al. 2012).

A conceptual framework articulated by Kozma and colleagues places outcomes into three categories: economic, clinical, and humanistic (Kozma et al. 1993). Economic outcomes are changes in the consumption and production of resources caused by disease or intervention, such as cancer prevention. The changes may be direct (e.g., cost of a medication) or indirect (e.g., early retirement due to reduced productivity). Clinical outcomes are the medical events that occur as a result of the condition or its treatment as measured in the clinical setting. This includes death, which will not be addressed further in this section. Humanistic, or patient-reported, outcomes include condition or intervention-related symptoms and side effects, treatment satisfaction, health status, and self-assessed function and well-being, or health-related quality of life. It is important to recognize that *progression-free survival*, which is the most commonly used measure of treatment benefit in cancer clinical trials, does not necessarily translate into quality of life improvements (Brettschneider et al. 2011).

The major cancer clinical trial cooperative groups in North America and Europe have recognized the importance of this outcomes triad in evaluating and improving the net benefit of cancer therapy (Bruner et al. 2004). Humanistic and economic outcomes, which are the focus of this chapter, are increasingly being incorporated into clinical trials (Lipscomb et al. 2004). In addition, the importance of outcomes assessment in cancer was reinforced with NCI's establishment of its Outcomes Research Branch in 1999 (Lipscomb and Snyder 2002) and the

Cancer Outcomes Measurement Working Group in 2001 (Lipscomb et al. 2005). According to the NCI, "outcomes research describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions on 'final' endpoints that matter to decision makers: patients, providers, private payers, government agencies, accrediting organizations, or society at large" (Lipscomb and Snyder 2002).

2.3 Humanistic Outcomes

As mentioned above, humanistic or patient-reported outcomes (PROs) include a wide range of health-related concepts or constructs. According to the U.S. Food and Drug Administration (2009), a PRO is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." PROs are on a continuum from the purely symptomatic (e.g., pain intensity) to more complex aspects of functioning (e.g., ability to perform activities of daily living) to much more complex concepts (e.g., quality of life). Since many cancer prevention activities are aimed at populations rather than individual patients, the term PRO in the context of this chapter may seem too narrow; however, the intent is to convey the importance of capturing individual's health and health-care perceptions and experiences through self-report. The PRO that has increasingly garnered the most attention, particularly in regard to drug therapy (Willke et al. 2004; European Medicines Agency 2005), is health-related quality of life, which will be a primary focus of this section.

Quality of life is a commonly used term that usually conveys a general feeling rather than a specific state of mind. A person's quality of life, or subjective well-being, is based on personal experience and expectations that affect and can be influenced by many factors, including standard of living, family life, friendships, and job satisfaction (Sirgy et al. 2006). Although health can impact these factors, health care is not directly aimed at enhancing them. Studies of health outcomes use the term *health-related quality of life* to distinguish health effects from the effects of other important personal and environmental factors. There is growing awareness that in certain diseases, such as cancer, or at particular stages of disease, health-related quality of life may be the most important health outcome to consider in assessing the effect of interventions (Staquet et al. 1992).

In much of the empirical literature, explicit definitions of health-related quality of life are rare; readers must deduce its implicit definition from the manner in which its measurement is operationalized. However, some authors have provided definitions. For example, Revicki and colleagues define health-related quality of life as "the subjective assessment of the impact of a disease and treatment across physical, psychological, social, and somatic domains of functioning and well-being" (Revicki et al. 2000, p. 888). Ferrans (2005) has provided a useful overview of various definitions and conceptual models of health-related quality of life. Definitions may differ in certain respects, but an important conceptual

characteristic they share is multidimensionality. Essential dimensions of health-related quality of life include:

- Physical health and functioning
- Psychological health and functioning
- Social and role functioning

In addition, disease- and/or treatment-related symptomatology (e.g., pain), general well-being, and spiritual well-being are sometimes assessed. The latter is more likely to be included in measures developed for conditions that have the potential to impact not only quality of life but length of life as well (e.g., cancer). For example, the four-dimensional model that provides the framework for the cancer-related quality of life questionnaires developed at the City of Hope National Medical Center includes spiritual well-being along with physical, psychological, and social well-being (Grant et al. 2004).

2.4 Measuring Health-Related Quality of Life and Other Patient-Reported Outcomes

Although PROs such as health-related quality of life are subjective, they can be quantified (i.e., measured) in a uniform and meaningful way. The quality of the data collection tool is the major determinant of the quality of the results. Psychometrics refers to the measurement of psychological constructs, such as intelligence, attitudes, and well-being. It is a field of study concerned with the proper development and testing of assessment tools (e.g., questionnaires) so that confidence can be placed in the measurements obtained. Two of the most commonly assessed psychometric properties are reliability and validity. Briefly, reliability refers to the consistency, stability, or reproducibility of scores obtained on a measure; validity reflects whether the instrument actually measures what it is purported to be measuring. More thorough discussions of these properties are provided elsewhere (Streiner and Norman 2008; Frost et al. 2007). Anyone planning to use PRO measures in cancer prevention research or clinical practice should confirm that there is adequate evidence to support the reliability and validity of the measures chosen.

Cullen and colleagues, in their review of the short-term quality of life impact of cancer prevention and screening activities, addressed ways in which outcomes have been assessed through the use of new and existing measures (Cullen et al. 2004). Since many of the outcomes were exclusively psychological states (e.g., anxiety, relief) or symptoms, they cannot be considered assessments of health-related quality of life. Measures of health-related quality of life should include, at a minimum, the three essential dimensions (i.e., physical, psychological, and social) recognized as comprising it. Nevertheless, the review by Cullen and colleagues and another by Mandelblatt and Selby (2005) provide important insight into the research that has been conducted to assess the short-term patient-reported consequences of clinical preventive services such as chemoprevention, genetic testing and counseling, and screening. Knowledge of these consequences is critical

in attempting to understand and act upon the factors that may affect participation in prevention-related activities.

Although it remains an empirical question, it appears that the predominantly transient negative consequences of participating in cancer prevention activities would be readily offset by the positive long-term outcomes (e.g., avoidance of quality of life losses resulting from cancer-related morbidity). As asserted by Badia and Herdman (2001), preventive interventions are unlikely to lead to immediate gains in quality of life, but should prevent or delay reductions in quality of life over time. For example, the human papillomavirus (HPV) vaccines marketed in the USA for primary prevention of invasive cervical cancer have a record of being safe and well tolerated (Einstein et al. 2009; Muñoz et al. 2009; CDC 2012), with the most common adverse events being brief and self-limiting occurrences of injection site reactions, fever, headache, nausea, and vomiting. There is a very low risk of serious adverse reactions with HPV vaccines and accepting transient side effects is a worthwhile investment in prevention for the vast majority of those vaccinated. HPV vaccination along with HPV-based screening has the potential to significantly decrease the incidence of invasive cervical cancer and the human and economic burden associated with it in the USA (Campbell et al. 2012).

A specific example of PRO assessment in the context of cancer prevention is provided by the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) P-2 Trial (Land et al. 2006). The STAR P-2 Trial was designed to evaluate the relative efficacy of the two study drugs in reducing the incidence of invasive breast cancer in high-risk postmenopausal women. The investigators used a number of measures to compare patient outcomes by treatment arm, including the Center for Epidemiological Studies Depression Scale (CES-D), the Medical Outcomes Study (MOS) Sexual Activity Questionnaire, a 36-item symptom checklist, and the MOS 36-Item Short-Form Health Survey (SF-36). This battery of multiple instruments and scales enabled the investigators to assess the PROs they felt were most relevant in the target population. The health-related quality of life end points were the physical (PCS) and mental component summary (MCS) scores of the SF-36. The SF-36 will be discussed in more detail below.

There are hundreds of PRO instruments currently available (Bowling 1997; McDowell 2006), some of which have been developed for use in people with cancer (Bowling 2001; Donaldson 2004) or for individuals undergoing cancer screening (Mandelblatt and Selby 2005). The Psychosocial Effects of Abnormal Pap Smears Questionnaire (PEAPS-Q) (Bennetts et al. 1995) and the Psychosocial Consequences Questionnaire for abnormal screening mammography (PCQ-DK33) (Broderson et al. 2007) are examples of PRO measures specifically developed for cancer-related clinical preventive services. However, the vast majority of available PRO measures were developed for use in people already experiencing disease and/or disability. The value of these measures in the context of cancer prevention is that they provide quantitative evidence of the losses in functioning and well-being that may be avoided by effective prevention strategies. A primary distinction among PRO instruments, particularly measures of health-related quality of life, is whether they are specific or generic.

2.5 Specific Measures

The pioneering work of Karnofsky and Burchenal in the 1940s that produced the Karnofsky Performance Scale recognized the need to assess the patient's functional status in the context of cancer chemotherapy (Karnofsky and Burchenal 1949). This tool, which was designed for clinician assessment of observable physical functioning, is still used today. It was one of the first steps in the development of patient-centered and, ultimately, patient-reported outcome measures. Since then, a considerable amount of time and effort has been invested in the development of cancer-specific instruments for use in clinical trials and routine patient monitoring. Another of these instruments is the Q-TWiST (Quality-Adjusted Time Without Symptoms and Toxicity), which addressed both quality and quantity of time following cancer treatment (Gelber et al. 1993). Other examples are the EORTC QLQ-C30 (Aaronson et al. 1993) and the Functional Assessment of Cancer Therapy-General (FACT-G) (Cella et al. 1993). The European Organization for Research and Treatment of Cancer (EORTC) has worked extensively in the area of instrument development (www.eortc.be/home/qol). In addition, the developers of the FACT-G have a broad array of cancer-specific instruments available (www.facit.org). Table 2.1 lists the dimensions covered by the EORTC QLQ-C30 and the FACT-G. Each of these instruments was designed to be supplemented with additional modules or scales aimed at specific cancer patient subgroups.

Cancer-specific instruments such as these are intended to provide greater detail concerning particular outcomes, in terms of functioning and well-being, uniquely associated with a condition and/or interventions to treat or prevent it. Disease- or condition-specific instruments may be more sensitive than a generic measure to particular changes in health-related quality of life secondary to the disease or its treatment. For example, the Functional Assessment of Cancer Therapy (FACT) subscales, such as the neurotoxicity subscale (FACT-NTX), address specific concerns (e.g., finger numbness, difficulty buttoning), which would not be addressed in a generic instrument. In addition, specific measures may appear to be more clinically relevant to patients and health-care providers since the instruments address issues directly related to the disease (Guyatt et al. 1993). However, a concern regarding the use of only specific instruments is that by focusing on the specific impact of a disease or its treatment, the general or overall impact on functioning and well-being

Table 2.1 Domains/dimensions addressed by the FACT-G and EORTC QLQ-C30

EORTC QLQ-C30	FACT-G
Physical functioning	Physical well-being
Role functioning	Social/family well-being
Cognitive functioning	Emotional well-being
Emotional functioning	Functional well-being
Social functioning	
Fatigue	
Global quality of life	
Nausea and vomiting	
Pain	

may be overlooked. Therefore, the use of both a generic and a specific instrument may be the best approach. This was the approach taken by the developers of the UCLA Prostate Cancer Index, which covers both general and disease-specific (e.g., sexual, urinary, and bowel function) concerns (Litwin et al. 1998).

2.6 Generic or General Measures

Since primary cancer prevention involves avoiding the occurrence of disease, general measures may be more applicable in that context. Generic, or general, instruments are designed to be applicable across a wide variety of populations, across all diseases or conditions, and across different medical interventions (Patrick and Deyo 1989). The two main types of generic instruments are health profiles and preference-based measures.

2.6.1 Health Profiles

Health profiles provide multiple outcome scores representing individual dimensions of health status or health-related quality of life. An advantage of a health profile is that it enables clinicians and/or researchers to measure the differential effects of a disease state or its treatment on particular dimensions. The most commonly used generic instrument in the world today is the SF-36 (www.sf36.org), which was used as a component of the STAR P-2 Trial discussed above. The SF-36 includes eight multi-item scales (Table 2.2) which address a wide array of dimensions (Ware and Sherbourne 1992). Each of the scale scores can range from 0 to 100, with higher scores representing better functioning or well-being. It is brief (it takes about 10 min to complete) and its reliability and validity have been documented in many clinical situations and disease states (Ware 2000). A means of aggregating the items into physical (PCS) and mental component summary (MCS) scores is available (Ware et al. 1994). However, the SF-36 does not provide an overall summary or index score, which distinguishes it from the preference-based measures.

2.6.2 Preference-Based Measures

For health-related quality of life scores to be most useful as an outcome in economic analysis, they need to be on a scale anchored by 0.0 (i.e., death) and 1.0 (i.e., perfect health). The values for the health states represented on the scale reflect the relative desirability or preference level for individual health states as judged by population- or patient-based samples. Although one can undertake direct preference measurement, a number of preference-based instruments are already available for which the health state preferences have been derived empirically through population studies. Examples include the Health Utilities Index (HUI) (www.healthutilities.com), the EuroQol Group's EQ-5D (www.euroqol.org), and the SF-6D (www.sf36.org).

Table 2.2 Domains included in selected generic instruments

SF-36	
Physical functioning	
Role limitations due to physical problems	
Bodily pain	
General health perceptions	
Vitality	
Social functioning	
Role limitations due to emotional problems	
Mental health	
Health Utilities Index (HUI)	
HUI2	*HUI3*
Sensation	Vision
Mobility	Hearing
Emotion	Speech
Cognition	Ambulation
Self-care	Dexterity
Pain	Emotion
Fertility	Cognition Pain
EQ-5D	
Mobility	
Self-care	
Usual activity	
Pain/discomfort	
Anxiety/depression	
SF-6D	
Physical functioning	
Role limitation	
Social functioning	
Mental health	
Bodily pain	
Vitality	

The SF-6D was developed to provide a preference-based overall summary or index score for data collected with the SF-36 (Brazier et al. 2002). The domains addressed by each of these instruments are listed in Table 2.2.

2.6.3 Quality-Adjusted Life Years (QALYs)

The preference-based instruments described above are administered to assess respondents' self-reported health status, which is then mapped onto the instrument's multiattribute health status classification system producing a health-related quality of life score on the 0.0–1.0 scale. Scores on this scale, which may represent the health-related consequences of disease or its treatment, can be used to adjust length

of life for its quality resulting in an estimate of quality-adjusted life years (QALYs). QALYs integrate in a single outcome measure the net health gains or losses, in terms of both quantity and quality of life. The metric of life years saved (LYS) is not sufficient since death is not the only outcome of concern; health-related quality of life changes can occur with or without changes in life years. The QALY approach assumes that 1 year in full health is scored 1.0 and death is 0.0. Years of life in less than full health are scored as less than 1.0 QALY. For example, based on a review by Tengs and Wallace, a year of life with small-cell lung cancer after the disease has progressed is equal to 0.15 QALY (Tengs and Wallace 2000).

QALYs can be a key outcome measure, especially in diseases such as cancer, where the treatment itself can have a major impact on patient functioning and well-being. Although the QALY is the most commonly used health outcome summary measure, it is not the only one (Gold et al. 2002). Other conceptually equivalent outcomes include *years of healthy life* (YHL), *well years* (WYs), *health-adjusted person years* (HAPYs), and *health-adjusted life expectancy* (HALE). As observed by Ubel, without an outcome measure such as QALYs, it would be impossible to compare the relative cost-effectiveness of life-prolonging versus life-enhancing interventions, much less interventions that do both (Ubel 2001).

2.7 Comparative Effectiveness Research

Although not a new concept, comparative effectiveness research (CER) has received increased focus and funding since the passage by the US Congress of the American Reinvestment and Recovery Act of 2009 (ARRA) and the Patient Protection and Affordable Care Act of 2012 (aka Affordable Care Act or ACA). As defined by the US Agency for Healthcare Research and Quality (AHRQ), CER "is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options" (AHRQ 2012). The National Institutes of Health has publicly expressed its continued commitment to CER (Lauer and Collins 2010). As stated by Lauer (2010) "Through CER, especially conflict-free CER supported by government, we answer a moral imperative to assure that the practice of medicine is a net social good."

The importance of the patient perspective and the role of PRO-based effectiveness measures in CER have been underscored (Wu et al. 2010; Basch et al. 2012). The Patient-Centered Outcomes Research Institute (PCORI), an independent, nonprofit organization, was authorized as part of the ACA. PCORI's statutory purpose is "To assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis that considers variations in patient subpopulations" (PCORI 2012). Through September 30, 2019, PCORI is projected to receive $3.5 billion for patient-centered outcomes research from congressional appropriations and a fee assessed on Medicare, private health insurance, and self-insured health plans.

One might think that this concerted effort to enhance evidence-based health-care decision making would be welcome and without controversy; however, as noted in a special issue of *Journal of Clinical Oncology* addressing CER in oncology, there is trepidation about the way in which the evidence will be used to control health-care costs (Pearson 2012). CER must be free of "commercial and political meddling" if its results are to be seen as credible evidence that can inform health-care decisions important to patients and their families rather than insurance firms and medical products companies (Selker and Wood 2009). In addition, although "Assessment of prevention, diagnosis, and treatment options" is one of the five priority areas adopted by PCORI's Board of Governors (PCORI 2012), there is little evidence that cancer prevention will be a primary focus of PCORI or CER efforts in general.

2.8 Economic Outcomes and Cancer

Prevention of cancer renders an economic benefit for society by reducing the amount of resources necessary for the treatment of cancer. The NCI reports that cancer treatment accounted for almost $125 billion in 2010 (NCI 2012), just under 5% of total US spending for medical treatments (Centers for Medicare and Medicaid Services 2012). By investing in cost-saving cancer prevention modalities, more resources may be available for the overall health-care system. Johnson and colleagues estimate that 53% and 13% of the medical expenditures for persons with lung cancer and chronic obstructive pulmonary disease, respectively, are attributable to smoking (Johnson et al. 2003). Substantial medical resources would become available, if smoking were reduced.

Economic benefits rendered by improving health go beyond the costs associated with medical treatments. The economic benefits of cancer prevention include decreases in the frequency of health-related disruptions in productive activity, such as lost workdays. By promoting health, cancer prevention reduces the need for assistance with personal care services and allows greater intangible benefits, like dignity, autonomy, and individuality. Simply put, prevention is better than cure because, as stated by Thomas Adams, a seventeenth-century physician, it saves the labor of being sick.

Although the economic benefits of cancer prevention are widely acknowledged, especially by NCI, there is a paucity of evidence regarding these benefits. The information regarding economic outcomes that is available is rarely translated for and applied to evidence-based medical decision making. As a result, cancer prevention is often inefficiently utilized. Researchers who study the economic outcomes of cancer prevention provide valuable information to individuals and institutions, who may fail to consider the full scope of the economic benefits (Fryback and Craig 2004). For example, the vaccination of girls against human papillomavirus (HPV) may be justified on grounds of improved health and cost savings; however, the case for boys, who may be future carriers of the cancer-causing virus, requires deliberation over whether the marginal benefits are worth the high cost in terms of cancer resources (Elbasha et al. 2007).

Decision makers at the individual, institutional, or governmental levels require evidence on economic outcomes of cancer prevention to improve their ability to make informed choices with regard to prevention activities, thereby maximizing limited resources. In this section, we describe core concepts in economic outcomes research and provide examples to illustrate their importance.

2.9 Defining and Measuring Economic Outcomes

Every cancer prevention strategy entails a change in the use of scarce resources, also known as an economic outcome. If we were to list the resources necessary to produce an intervention and the resources saved due to the intervention, we would have a description of the net bundle of resources attributable to the intervention. This bundle is known as the intervention's *opportunity cost*. Once the intervention is undertaken, the opportunity to use these resources differently is lost. Consideration of the economic outcomes associated with interventions is important for individuals and institutions that practice evidence-based medicine.

Economic outcomes, changes in resources due to an intervention, may be categorized by system, path, and flow. Resources from the medical system, such as physician time, medications, and hospital beds, are distinguished from nonmedical resources, such as community, familial, and personal goods. For example, fuel consumption by an ambulance is a medical outcome, whereas fuel for personal transportation to a clinic is a nonmedical outcome. Medical and nonmedical resources are differentiated, because each system faces different budgetary constraints.

Economic outcomes are also separated by their path, whether they are directly related to an intervention or indirectly related through a change in health caused by the intervention. For example, a nicotine patch may be consumed as part of a smoking cessation intervention, therefore a direct economic outcome of the intervention. The patch may change smoking-related behaviors, such as smoking breaks at work. Changes in productivity are indirect economic outcomes of the intervention. The direct and indirect outcomes are components of the smoking cessation program's opportunity cost. The concept of indirect and direct economic outcomes is unrelated to the accounting term "indirect costs" referring to overhead or fixed costs.

Economic outcomes represent an inflow of resources through consumption or an outflow of resources through production. Patients directly consume medical resources over the course of an intervention, but patients are also producers of resources. Smoking cessation programs change the consumption of resources, such as cigarettes, nicotine replacement medications, and counseling. These programs may also affect the productivity of individuals, either by making their lives more productive or by extending their productive lives. When considering the economic benefits of cancer prevention, the effect on the consumption of current resources may be small compared to the benefits in terms of productive activities. Economic outcomes can be characterized as medical or nonmedical, direct or indirect, and an inflow or outflow of resources.

2.9.1 Unit of Economic Outcomes

Economic outcomes are best measured in natural units. Natural units often appear in the form of number of hours, quantities of a specific medication, or distance traveled. Natural units describe the changes in the inflow and outflow of resources related to the intervention. Clinical-economic trials, which are randomized controlled trials that prospectively collect economic endpoint data, provide the strongest evidence on economic outcomes, because these trials randomly assign alternatives to participants to identify causality. In a prospective substudy of a randomized clinical trial, Sculpher and colleagues (Sculpher et al. 2000) evaluated alternative drug therapies, raltitrexed and fluorouracil with folinic acid, for advanced colorectal cancer based on the number of trips made to and from the hospital and the time lost from usual activity over the therapy period. In their study, they examined medical records for medical resource consumption data and self-report data to assess travel mode, distance, and time. This is an excellent example of a clinical-economic trial that collected economic endpoint data in natural units. These natural units can be translated into monetary values according to the perspective of the decision maker.

In economics, price is cost plus marginal profit, but outside of economics, price is often confused with cost and charges. Price represents the market value of a good, if sold. If the objective of the study is to predict revenue (or expenditure), natural units are to be translated using market values (i.e., prices). Market values fluctuate over time or region, according to market forces. If the objective is to predict cost of an intervention, natural units are to be translated according to the cost of producing those resources. The cost of producing resources may also depend upon market price of the inputs necessary for resource production. For example, a mammogram may cost a provider organization $50 to produce, but they set a price of $75 because that is what the market will bear. The difference between price and cost, $25, is the marginal profit for the health organization. The inclusion and extent of marginal profit in the translation of natural units into monetary values depends on the perspective of the decision maker. The reasonable amount of profit on a mammogram for a clinic is up for interpretation.

A charge is a payment of a claim, the rightful reimbursement for the provision of goods and services according to a contract. It is neither a price nor a cost because of its dependence on the contractual relationship between institutions. For example, managed care organizations often shift funds between services, overcharging for specialist visits to subsidize mammography under the same contract. Unlike prices, the charge for one resource may depend on the charges for other resources under the same contract. This dependent relationship makes it difficult to interpret end points measured through charges. However, it is well documented that charges exceed cost in most circumstances. The economic outcomes may be represented in monetary terms, such as costs, prices, and charges, depending on perspective. However, it is important that the perspective of the translation (i.e., unit of analysis) matches the perspective of the decision maker, so that they may practice evidence-based medicine.

2.9.2 Perspective of Economic Outcomes

The monetary value of an economic outcome depends on the perspective of the decision maker (e.g., individual, institutional, societal). Individuals face different prices (or costs) than institutions, so they translate natural units into monetary values differently. The societal perspective considers the economic outcome borne by all individuals and uses market value to translate natural units into monetary values. For example, the monetary value of an hour of a physician's time may be equal to a co-payment from a patient's perspective, an institution-specific wage from a managed care organization's perspective, or a market wage from the societal perspective.

Differing perspectives may lead decision makers to disagree on policies regarding cancer prevention. Smoking cessation programs have medical and nonmedical economic outcomes. Medical outcomes attributable to certain programs may entail a monetary loss from the perspective of a managed care organization. After incorporating the nonmedical outcomes, the programs may appear to save resources from the societal perspective. Disagreement between governmental and institutional decision makers over the economic consequences of smoking cessation programs is related to the translation of natural units into monetary values. Furthermore, societal and institutional perspectives often disagree about the inclusion of institutional profit in the translation.

2.10 Evaluative and Descriptive Analyses in Cancer Prevention

The economic benefits of cancer prevention are commonly described as a matter of investment in health (Wagner 1997). By investing medical resources in cancer prevention today, substantial economic benefits may accrue in the future. The purpose of evaluative analyses in cancer prevention is to examine the economic and health outcomes of alternative interventions so that decision makers may better understand the potential impact of cancer prevention. There are four forms for economic evaluation: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit. In addition, there are also descriptive studies that present economic outcomes of alternative interventions and disease, but do not directly compare health and economic outcomes. Descriptive analyses include cost-of-illness, cost-identification, and cost-consequence studies. In this section, examples of evaluative and descriptive analyses in cancer prevention are provided.

2.10.1 Economic Evaluations

To promote evidence-based medical decision making, economic evaluations present the economic and health outcomes of alternative interventions. If an intervention costs more and is less effective than another intervention, the choice between the two interventions is clear. However, in many cases, the dominance of one intervention

over another may depend on the relative importance of economic and health outcomes. For example, an intervention may cost more and be more effective or cost less and be less effective relative to another intervention. Economic evaluations verbally or quantitatively summarize the evidence to inform such difficult decisions.

The four types of economic evaluations (cost-minimization, cost-effectiveness, cost-utility, and cost-benefit) measure economic outcomes in monetary units, but each handles health outcomes in different ways. In cost-minimization studies, health outcomes are not measured, but assumed. For example, if two prevention interventions are known to have equivalent health outcomes, a study may examine which uses the least amount of medical resources to minimize the cost to the health-care system. Cost-effectiveness, cost-utility, and cost-benefit evaluations measure health outcomes, but using different units. Health outcomes in cost-effectiveness analyses are measured in natural units, such as number of life years saved. Cost-utility analyses use QALYs and cost-benefit analyses use monetary units, such as dollars. It can be difficult to translate health outcomes into QALYs or monetary units, so the typical form of economic evaluation is a cost-effectiveness analysis.

To summarize the evidence, cost-effectiveness and cost-utility analyses separate out the difference in cost and effectiveness between interventions and examine their ratio, known as an incremental cost-effectiveness ratio (ICER). This ratio measures the amount of resources required for each unit of health outcome (i.e., the amount of dollars required to increase life expectancy by 1 day). The ratios can be difficult to interpret because a positive value may signify an increase in cost and an increase in effectiveness, or a decrease in cost and a decrease in effectiveness. An intervention that saves money may have the same ratio as one that requires additional resources, so it is important to look at both the ratio and budgetary implications of the choice.

Cost-effectiveness analyses of cancer screening are commonplace, particularly in the cervical cancer literature (Eddy 1990; Kulasingam and Myers 2003; Goldie et al. 2004). Brown and Garber examined three cervical screening technologies (ThinPrep, AutoPap, and Papnet) among a cohort of 20- to 65-year-old women from the societal perspective (Brown and Garber 1999). Outcomes of interest, including life expectancy and lifetime direct medical cost, were compared among the three technologies and between each technology and conventional Pap at various intervals. The authors found that, depending on the technology and frequency of screening, these technologies increased life expectancy by 5 h to 1.6 days and increased cost by $30 to $257 (1996 US dollars) relative to conventional Pap. In this case, small increases in life expectancy are related to small increases in cost. When used with triennial screening, each technology produced more life years at a lower cost relative to conventional Pap used with biennial screening. In other words, conventional Pap used with biennial screening is dominated by each technology used with triennial screening. Among the new technologies, AutoPap dominated ThinPrep, but Papnet costs $43 more and produced 0.11 additional days of life expectancy. The incremental cost-effectiveness ratio, $391 ($43/0.11) per day of life saved, suggests that if society values a day of life more than $391 then Papnet may be preferred over AutoPap. The analysis does not account for

nonmedical or indirect costs and examines only life expectancy, excluding the potential burden of cancer in terms of quality of life.

Compared to cost-effectiveness analyses, cost-utility analyses have the advantage of being able to combine multiple health and clinical outcomes into QALYs. Two cost-utility analyses of cervical cancer screening have estimated health outcomes in terms of QALYs (Goldie et al. 1999; Mandelblatt et al. 2002). Goldie and colleagues assess alternative screening strategies in HIV-infected women, and Mandelblatt and colleagues examine combinations of conventional Pap and HPV testing at various intervals among a longitudinal cohort of women beginning at age 20 and continuing until age 65, 75, or death. In breast cancer screening, Tosteson and colleagues compared digital and film mammography and found that using all-digital mammography is not cost-effective (Tosteson et al. 2008).

Due to their complexity in measurement and modeling, economic evaluations may be difficult to interpret and assess in terms of study quality. Their summary of the evidence is similar to a quantitative literature review, yet they often involve the prospective collection of primary data, particularly use and cost outcomes (e.g., clinical-economic trials). Guidance for the *Journal of Clinical Oncology*, put forth by Levine and colleagues (2007), identifies five key questions, which readers may ask when reviewing a study: (1) Is the question being evaluated relevant? (2) Does the study compare the appropriate alternative interventions? (3) Is the quality of the data high (e.g., economic endpoints in a clinical trial)? (4) Does the study interpret both the efficiency (i.e., cost-effectiveness) and budgetary implications? (5) Lastly, was the study sponsored by organizations without potential conflicts of interest? Like with clinical trials, a negative response to any of these questions requires greater care in the interpretation of the evidence.

Evidence on economic outcomes is not meant to dictate the choice among alternative interventions. It is only one consideration among many possible considerations. Economic evaluations are conducted to assist policy makers in their deliberation over access to cost-effective cancer prevention strategies by providing evidence on the potential impact of the alternative strategies. In the absence of evidence-based policy, cancer prevention resources may not be allocated efficiently according to the perspectives of the decision makers.

2.10.2 Descriptive Studies

Cost-of-illness studies compare economic outcomes by disease, and cost-identification studies examine the difference in economic outcomes across alternative interventions. Taplin and colleagues (Taplin et al. 1995) conducted a cost-of-illness study and evaluated the direct cost of treating colon, prostate, and breast cancer. Their results suggest that the direct cost of cancer treatment increases with stage of diagnosis. Tsao and colleagues estimated that the cost of treating a patient with stage III or stage IV cutaneous melanoma is roughly 40 times the cost of treating a stage I patient (Tsao et al. 1998). Although increasing medical cost by stage may not be surprising, Ramsey and colleagues found that even after controlling for

stage, direct costs were lower among persons with screen-detected versus symptom-detected colorectal cancer in the 12 months following diagnosis (Ramsey et al. 2003). The findings of these cost-of-illness studies support the premise that primary and secondary cancer prevention may result in substantial economic benefits, potentially saving economic resources from the managed care perspective.

Cost-identification studies can improve medical decision making by dispelling perceptions of cost savings. Esser and Brunner reviewed 33 studies that examine economic outcomes of granulocyte colony-stimulating factor (G-CSF) in the prevention and treatment of chemotherapy-induced neutropenia (Esser and Brunner 2003). Contrary to conventional opinion, they found little evidence that G-CSF is cost saving as primary or secondary prophylaxis and only minor cost savings in patients undergoing bone marrow transplant. This tertiary prevention review is particularly notable because of reports that G-CSF expenses amount to 10 % of the total budget of US hospital pharmacies with limited observed clinical benefits.

Evidence from cost-identification studies may also emphasize the importance of cancer prevention as a cost containment strategy. Loeve and colleagues conducted a cost-identification study for endoscopic colorectal cancer screening and found that endoscopic colorectal cancer screening has the potential to be cost saving (Loeve et al. 2000). They stated that similar analyses of screening programs for breast and cervical cancer have not demonstrated potential cost savings under any reasonable assumptions.

Some cost-identification studies have focused on the travel and time costs of cancer prevention. O'Brien and colleagues estimated direct health service costs and the indirect cost of time off work among chemotherapy patients using patient and nurse survey data as well as administrative data from 107 participants (O'Brien et al. 1993). Houts and colleagues asked 139 patients receiving outpatient chemotherapy to keep diaries of nonmedical expenses resulting from their disease and its treatment and documented the economic experiences of these patients (Houts et al. 1984). These small, local cost-identification studies reveal a need to better understand the nonmedical economic outcomes using a patient-centered approach. Information on out-of-pocket savings in the long run due to cancer prevention might be useful to motivate individuals at risk and lead them to make more informed decisions regarding their health behaviors and use of medical services.

Cost-consequence studies entail a simple tabulation of health and economic outcomes of interventions. This rare and informal type of economic analysis is like a cost-identification analysis except that it includes health outcome information. The findings of a cost-consequence study are presented without summary statements about cost-effectiveness, which distinguishes it from economic evaluations.

Conclusion

The purpose of this chapter was to introduce the reader to ways of quantifying the human and economic value of cancer prevention activities. The human and economic costs of cancer to individuals, families, communities, and society are substantial (Brown et al. 2001). It is imperative that personal and financial investments in cancer prevention be made; however, since health-care resources are

limited, those available must be used efficiently and equitably. To justify investments in cancer prevention, it is essential to have data about the relative costs and outcomes of prevention activities. Resources should be used for programs that produce the greatest benefit for the greatest number of people. The lack of good information about input–output relationships in health care has led to enormous variations in costs and practice patterns. The creation of more useful data and the more informed use of data currently available can enhance the public's health, patient care, and the quality of health-care resource allocation decisions at many levels (e.g., individual, health plan, society).

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The Role of Diet, Physical Activity, and Body Composition in Cancer Prevention

3

Cynthia A. Thomson

3.1 Recommendations for Cancer Prevention: Body Weight, Diet, and Physical Activity

The association between diet, physical activity, and cancer has been well described in the scientific literature. In terms of primary prevention, current data support the need for improved food choices and increased physical activity to prevent several of the leading cancers diagnosed in the USA. Several organizations have provided guidance in terms of dietary recommendations to reduce cancer risk. Generally, the recommendations are similar across organizational groups, including the American Cancer Society, the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (Glade 1999; WCRF/AICR 2007) centers for disease control and prevention (CDC 2012), and the Committee on Medical Aspects of Food and Nutrition Policy of the United Kingdom. The recommendations are largely based on epidemiological evidence, much of which has been supported by plausible mechanisms of biological action. In forming such policy and recommendations, these organizations often give consideration to the plausibility that individuals or populations will be able to effectively achieve and maintain the cancer-preventive dietary pattern as recommended. Therefore, to some extent the recommended intakes may not be exact in terms of published literature, but instead reflect a positive change in intake toward an optimal level. While much of the evidence remains insufficient and further research is warranted, providing lifestyle guidelines (diet, physical activity, and body weight) is prudent in that there is a consistency in the evidence collected that supports lifestyle change in the American population. Importantly, these same guidelines, in a majority of the cases, also have the potential to reduce the rates of other chronic diseases including cardiovascular disease, hypertension/stroke, and diabetes.

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The WCRF/American Institute for Cancer Research (AICR) report published in hard copy in 2007 but continually upgraded on the AICR website represents recent and comprehensive reviews of the available evidence for diet-related behaviors to reduce cancer risk (WCRF/AICR Recommendations at http://www.aicr.org/reduce-your-cancer-risk/recommendations%20for%20cancer%20prevention). These recommendations currently include the following:

- Be as lean as possible without becoming underweight.
- Be physically active for at least 30 min every day.
- Avoid sugary drinks. Limit consumption of energy-dense foods.
- Eat more of a variety of vegetables, fruits, whole grains, and legumes.
- Limit consumption of red meats and avoid processed meats.
- If consumed at all, limit alcoholic drinks to two for men and one for women a day.
- Limit consumption of salty foods and foods with processed salt.
- Do not use supplements to protect against cancer.
- It is best for mothers to breast-feed exclusively for up to 6 months and then add other foods and liquids.
- Cancer survivors should follow the recommendations for cancer prevention.

The above advice for cancer prevention is also supported by the American Cancer Society recommendations for individual choices (Kushi et al. 2012):

- Achieve and maintain a healthy weight throughout life:
  - Be as lean as possible throughout life without being underweight.
  - Avoid excess weight gain at all ages. For those who are overweight or obese, losing even a small amount of weight has health benefits.
  - Engage in regular physical activity and limit consumption of high-calorie foods and beverages as key strategies for maintaining a healthy weight.
- Adopt a physically active lifestyle:
  - Adults should engage in at least 150 min of moderate-intensity physical activity or 75 min of vigorous intensity activity each week, or equivalent combination, preferably spread throughout the week.
  - Children and adolescents should engage in at least 1 h of moderate or vigorous intensity activity each day, with vigorous intensity activity at least three times per week.
  - Limit sedentary activity such as sitting, lying down, watching television, or other forms of screen-based entertainment.
  - Doing some physical activity above usual activity can have health benefits.
- Consume a healthy diet, with an emphasis on plant sources:
  - Choose foods and beverages in amounts that help maintain a healthy weight.
  - Limit consumption of processed meats and red meat.
  - Eat at least 2.5 cups of vegetables and fruits each day.
  - Chose whole grains instead of refined grain products.
- If you drink alcoholic beverages, limit consumption.
- ACS also expanded recommendations in 2012 to include a call for community action:
- Public, private, and community organizations should work collaboratively at national, state, and local levels to implement policy and environmental changes that:

- Increase access to affordable, healthy foods in communities, worksites, and schools and decrease access to marketing of foods and beverages of low nutritional value, particularly to youth.
- Provide safe, enjoyable, and accessible environments for physical activity in schools and worksites and for transportation and recreation in communities.

The 2006 ACS guidelines have been evaluated in relation to cancer risk reduction and suggest a substantial reduction in cancer risk as well as cardiovascular disease and all-cause mortality is demonstrated in individuals with higher guideline adherence scores (McCullough et al. 2011).

3.2 Body Weight and Body Composition and Cancer Prevention

Increasingly, evidence suggests that the primary driver of cancer risk in the near future will be our aging population in combination with the increasing rates of obesity in the population (Institute of Medicine 2012). Obesity is estimated to account for 14–20 % of the attributable cancer risk in US adults, and treatment of obesity appears to reduce cancer risk (Basen-Engquist and Chang 2011; Colditz and Wei 2012). These facts likely informed on recent modification in cancer prevention recommendations that have placed an increased emphasis on the importance of attaining and maintaining a healthy body weight in order to reduce cancer risk. And while not all cancers have been associated with obesity, a large number and most of the more common cancers have been. Table 3.1 provides an overview of evidence suggesting an association between overweight/obese status and risk for common cancers. Generally, obesity has been identified as a risk factor for several solid tumors as well as hormone-related cancers. Obesity has been consistently associated with greater risk for pre- and postmenopausal breast cancer (Anderson and Neuhouser 2012; Norat et al. 2008), colon and rectal cancer (Norat et al. 2010), and less consistently but generally related to pancreatic cancer (Aune et al. 2012a; Bracci 2012), renal cancer (Beebe-Dimmer et al. 2012), endometrial cancer (Reeves et al. 2011), bladder (Holick et al. 2007), and gallbladder cancer (Wang et al. 2012) with current evidence continuing to support earlier association estimates (WCFR/AICR, 2007). Of note, recent obesity rates have driven a rise in nonalcoholic fatty liver disease, a condition associated with marked increased risk for hepatocellular cancer (Chen et al. 2012; Shen et al. 2012). Further, obesity has been linked to higher prevalence of H. pylori infection, a well-known risk factor for gastric cancer (Li et al. 2012). Beyond hormone-related and solid tumors, obesity may also increase the risk for multiple myeloma, leukemia, and/or lymphoma (Lichtman 2010) particularly among men (Birmann et al. 2007). Abdominal fat has also been assessed in select populations and indicates an increased risk for pancreatic, colorectal (male and female), postmenopausal breast, and endometrial cancers (WCRF/AICR). Recent evidence also suggests that visceral obesity may also predict high-grade disease (Zhu et al. 2012), associations that will need to be explored in other cancer types and as imaging becomes more available to quantify visceral versus subcutaneous adiposity.

Table 3.1 Body weight and dietary factors associated with risk for select cancers

	Cancer type								
Lifestyle factor	Breast	Prostate	Colorectal	Gastric	Lung	Ovary	Pancreas	Skin	Oral
Obesity	+ (postmenopause)	+	+	±	O	±	+	O	+
Abdominal fat	+	+	+	unk	O	±	+	O	
Adult weight gain	+ (postmenopause)	+	+	unk	unk	±	unk	O	unk
Dietary factors associated with reduced cancer risk									
Low fat (<24 %)	+	+	±	unk	O	+	+	+	O
High omega 3	+	+	+	O	±	unk	unk	+	±
High fiber	+	+	+	+	O	O	O	O	O
High vegetable	±	±	±	+	+	+	unk	unk	+
Carotenoid-rich	+[a]	± Lycopene	+		+	+[c]		±	+
Cruciferous	±[a]	±	+		+	+[c]		±	unk
High fruit	±	+	±	+	+	unk	+	±	+
Citrus			±						
Green Tea	±	±	+	+	+	unk	unk	+	+
Lycopene	±	+	+	unk	+	unk	unk	+	+
Plant-based diet	+	+	+	+ Med diet	+	unk	unk	unk	+
Selenium	±	+	+	unk	+	unk	unk	O	unk
Calcium	O	O	+	unk	O	unk	unk	O	O
Vitamin D	+	+	+	unk	unk	unk	unk	unk	unk
Folic acid	±	unk	+[b]	unk	+	unk	+unk	unk	+
Dietary factors associated with increased cancer risk									
Saturated fat	+	+	+	±	±	unk	±	unk	unk
Red meat	unk	+	+	+	±	+	unk	unk	unk
Processed meat	O	+	+	+	+	+	unk	unk	unk

Animal fat	+	+	+	±	+	unk	±	O	O
Charred meat	+	+	+	O	+	O	unk	+	unk
Trans fatty acids	+	+	+	O	±	unk	unk	unk	±
Alcohol	+	+	+	+	+	±	+	±	+
Physical activity									
Protective	+	+	+	±	+	±	+	unk	unk

+ an association has been demonstrated, ± unequivocal, *O* no association shown, *unk* unknown association or lack thereof

[a]Intake post-diagnosis contributes to reduced risk for breast cancer recurrence

[b]Folic acid supplementation has been associated with increased risk for adenomas polyp recurrence and thus may be detrimental post-initiation

[c]Intake at time of diagnosis contributes to improved survival

Importantly, the relationship between obesity and cancer risk is not straightforward, in that numerous confounders or effect modifiers have been identified that may influence come complicated associations. As an example, gender-specific associations have also been shown to modify risk. A pooling project analysis assessing the relationship between body weight and colorectal cancer confirms earlier work that increased body mass index (BMI) is positively associated with risk, especially among males (Jacobs et al. 2007). Additionally, a meta-analysis of studies evaluating the role of obesity in relation to rectal cancer risk suggested that risk was significantly increased among males, but not females (Larsson and Wolk 2007). Similarly, data from the European Prospective Investigation into Cancer (EPIC) showed an increased risk for colon cancer related to BMI and body weight among males, but not females (Pischon et al. 2006). Interestingly, both genders were at elevated risk for this disease related to greater waist circumference or waist-hip ratio, suggesting that clinically we need to assess these parameters (and perhaps more exact adipose-quantifying imaging techniques) routinely rather than solely relying on body weight to evaluate risk associations. Other factors relevant to testing risk associations that will need to be more robustly exploited include age, race/ethnicity, weight change, and interactions with well-established risks including tobacco use, alcohol, and viral infections.

Excess adiposity drives cancer risk through a range of biological mechanisms, although the precise mechanisms have yet to be fully elucidated. Interrelated mechanisms are thought to contribute including the production of obesity-related hormones, alterations in insulin pathways, oxidant stress, and the subsequent state of chronic subclinical inflammation. Several substrates have been implicated including sex steroid hormones, cytokines, adipokines, growth factors, and insulin (Harvey et al. 2011). The relationship between obesity-associated metabolic disease and cancer risk is now clearly established (Faulds and Dahlman-Wright 2012). Inhibition of apoptosis and angiogenesis are additional avenues that are likely involved, and mounting evidence suggests mitogen-activated protein kinase and related downstream events are central to tumor promotion effects of excess adiposity (Chen 2011). One provocative hypothesis suggests that obesity-cancer risk associations may be largely influenced by the aging process. Specifically, with advanced age comes an increase in fat-to-lean mass that promotes an erosion of telomere length that in turn promotes chromosomal instability and metabolic dysregulation; obesity may accelerate these effects thus promoting earlier age of onset and/or more advanced disease (Tzanetakou et al. 2012).

Weight change over the lifespan has also been identified as a risk factor for select cancer, although the majority of research has focused solely on breast cancer risk. The EPIC study showed an eight percent increase in postmenopausal breast cancer risk among nonusers of hormone replacement therapy for every five kilograms of weight gain over adulthood (Lahmann et al. 2005). These results were supported by data from the Nurse's Health Study cohort, an analysis of which that also suggested a 57 % reduction in postmenopausal breast cancer risk among women who lost more than 10 kg of body weight in adulthood and who maintained this reduced body weight (Eliassen et al. 2006). The Iowa's Women's Health Study also tested these associations and provided additional evidence that weight loss even after menopause was beneficial to reducing breast cancer risk (Harvie et al. 2005). This same cohort has been used to

demonstrate a protective effect of intentional weight loss during adulthood among overweight women (e.g., women who lost more than 20 lb, resulting in normal weight status that was sustained) in terms of reduced risk for breast, colon, and endometrial cancers (Parker and Folsom 2003). Adult weight gain has also been associated with endometrial cancer risk (Hosono and Matsuo 2011), prostate cancer (Bassett et al. 2012), and colorectal cancer in women (Blake-Gumbs et al. 2012) as well as poorer prognostic tumor characteristics in breast cancer (Feigelson et al. 2006). Weight cycling, the process of intermittent reductions and regains in body weight, also has been associated with elevated cancer risk including renal, endometrial, and non-Hodgkin's lymphoma (Stevens et al. 2012; Thompson and McTiernan 2011).

The association between obesity, weight gain, and tumor characteristics may partially explain why in addition to the increased cancer risk, being overweight/obesity also appears to increase mortality risk among select cancer patients (Calle et al. 2003). This association was initially reported in the American Cancer Society (ACS) cohort in the late 1970s in which a "J-shaped" association between body weight and cancer was identified. This "J-shaped" association between body weight and cancer has been reported suggesting that extremes in body mass index (BMI) at both the lower and upper ends of the range were associated with increased mortality risk (Banegas et al. 2003; Kwan et al. 2012). Overall, the evidence to date is inconsistent and appears to differ by cancer type. For example, in cancers with high survival rates such as breast cancer, excess bodyweight is more consistently associated with poorer outcomes (Kamineni et al. 2013); cancers with poor overall prognosis such as pancreatic cancer (Gong et al. 2012) and ovarian (Tyler et al. 2012) show limited associations with mortality after disease, and finally, cancers with modest survival rates such as colorectal (Gribovskaja-Rupp et al. 2011) cancer provide inconsistent evidence. There is some evidence to suggest that overweight/obese status also increases the risk for secondary cancers among subjects previously treated for cancer. In one analysis the National Health Insurance Corporation Study, the relative risk (RR) for second primary tumors among overweight men was elevated for colorectal (RR = 3.45) and for genitourinary cancers (RR = 3.61) (Park et al. 2007), suggesting that males with these diagnoses should receive significant support to lower body weight as part of their primary cancer treatment plan.

The above evidence suggests that body weight should be a primary target for modifying risk not only for the primary prevention of cancer but also as a prognostic indicator after diagnosis with select cancers, primarily those with demonstrated responsiveness to current treatments. Weight should be monitored routinely including an individual's trajectory of weight change over time. Further, healthcare providers should be aware of known periods in the lifecycle when people are more vulnerable toward undesirable weight gain. These should serve as opportunities for primary prevention of cancer through weight control. These vulnerable periods include:

- Maternal weight gain – known to increase risk for postpartum obesity as well as infant obesity
- Infancy (especially first 24 months of life) – promotion of breast-feeding and avoidance of "catch-up" growth among small for gestational age or low birth weight infants

- Early childhood related to structured feedings versus eating to appetite, access to energy-dense foods, and uncontrolled screen time
- Adolescence/pre-pubertal especially in relation to decreased physical activity in girls
- Entry into college and/or the work force in young adults when sedentary time may increase significantly
- Marriage when spousal eating and activity behaviors may promote weight gain
- Childbirth where higher parity and lessened time between pregnancies is associated with weight gain
- Menopause when physiological and psychosocial as well as hormonal changes can promote weight gain
- Retirement where change in activity and/or intake above energy requirements of advancing age may promote undesirable weight gain
- Stressful life events, such as death of a significant other, divorce, and illness where mindless eating or inactivity may promote weight gain
- Activity-limiting illness (including cancer and even routine surgeries that restrict activity postoperatively and significantly increase loss of lean tissue mass)
- Select medication use (i.e., oral contraceptives, postmenopausal hormone therapy, anti-depressants, insulin, etc.)

Not only should research focus on these vulnerable time periods in life, clinicians should also be acutely aware of circumstantial changes in their patients' lives that may place them at risk of undesirable weight gain or shifts in body fat-to-lean mass ratio. In this way clinicians can act proactively to instruct patients regarding weight gain prevention during these vulnerable life circumstances.

3.3 Diet and Cancer Prevention: Review of Evidence

Historically, the majority of research indicating a cancer-protective effect for diet (Doll and Peto 1981) has largely focused on the importance of a diet high in intake of vegetables and fruit. Overall modest protective associations have been demonstrated (Key 2011; Aune et al. 2012a, b, c; Riboli and Norat 2003) although more consistently in association with plant-based eating patterns such as the Mediterranean diet pattern (Couto et al. 2011; Gonzalez and Riboli 2010; Kontou et al. 2011; Magalhaes et al. 2012) or vegetable/fruit variety (Buchner et al. 2010). Evidence for other dietary components such as fiber (protective) and fat or alcohol (harmful) is less consistent, but generally indicated a probable relationship (WCRF/AICR) for several cancers. Table 3.1 summarizes the relationship between diet and cancer prevention including protective as well as detrimental dietary components. As shown, vegetables and fruit, as well as select bioactive food constituents within these plant foods, continue to hold promise for reducing the risk of several cancers, while dietary fat/trans fats as well as animal fat and processed meats are commonly associated with increased risk. Importantly, evidence that energy imbalance leading to excess body weight modifies cancer risk continues to mount, suggesting that the current epidemic of excess body weight/obesity in children and adults in the USA

will result in a significant rise in incidence of disease over the next several decades unless dramatic efforts are undertaken to reverse this trend.

The evidence of a protective role of diet in primary cancer prevention is predominantly associated with protection against the development of solid, organ-specific tumors. Several of the most significant associations are shown for hormone-related cancers such as breast, prostate, and ovarian cancer or for cancers of the gastrointestinal tract including oral, esophageal, gastric, and colorectal cancers, where direct contact between food constituents and the tissue occurs. This direct contact likely contributes to alterations in epithelial cells that either reduce or increase the risk for cellular damage, leading to a modification of cancer risk.

Over the past several decades, evidence to describe the relationship between diet and cancer incidence has predominantly been from case–control and cohort studies. However, given the pronounced recall bias associated with case–control studies, prospective cohort analyses have gained greater scientific support in defining these associations. Ideally, the strongest evidence is afforded by well-controlled diet intervention trials. Though few in number, dietary intervention trials have been conducted, although those with cancer endpoints have generally not shown a protective or deleterious association. For example, adherence to a low-fat diet did not result in a reduction in risk for breast cancer among postmenopausal women enrolled in the Women's Health Initiative Dietary Modification (WHI-DM) trial (Prentice et al. 2006); although a significant reduction in risk was demonstrated in women randomized to the low-fat diet who reported the highest habitual dietary fat intake prior to study entry. A secondary analysis based on longer-term follow-up tested the hypothesis that a low-fat diet would result in significantly lower rates of ovarian cancer (Prentice et al. 2007). Two trials testing the hypothesis that increased intake of dietary fiber, with or without added fruit and vegetable intake, showed that the diet interventions did not reduce the risk for adenomas of the colon (Alberts et al. 2000; Schatzkin et al. 2000). Here again, in an analysis of strict adherers to the diet, there was a 35 % reduction in polyp formation in the Polyp Prevention Trial (Sansbury et al. 2009). Similarly, a low-fat intervention for a period of 8.1 years did not reduce colorectal cancer risk among postmenopausal women in the WHI-DM trial (hazard ratio, HR = 1.08, 95 % CI 0.90–1.29) (Beresford et al. 2006).

Similar null effects (or in some studies adverse outcomes) have been demonstrated in dietary supplementation trials. Starting with the early results of the CARET and Finnish smokers, beta-carotene supplementation trials wherein supplementation increased risk for lung cancer and also gastric cancer in smokers and asbestos workers (Druesne-Pecollo et al. 2010) efforts to identify effective supplementation regimes have largely gone unfulfilled. Calcium and vitamin supplementation did not modify colorectal cancer risk in the 18,176 WHI study subjects receiving supplementation (HR = 1.08, 95 % CI 0.85–1.34) (Wactawski-Wende et al. 2006), although the lack of efficacy may have been undermined by the high dietary intake of calcium reported in the study population overall. The more recent Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported an adverse effect of supplementation with vitamin E suggesting prostate cancer risk was increase by 17 % over the 7–12 years of follow-up (Klein et al. 2011). Risk was

increased nonsignificantly in the selenium alone and selenium plus vitamin E groups as well. In the Women's Antioxidant Cardiovascular Study, similar nonsignificant elevations in risk for cancer and overall cancer mortality were seen with vitamin C supplementation of 500 mg/day (Lin et al. 2009), while vitamin E and beta-carotene supplementation demonstrated nonsignificant protective associations for the same outcomes. Multivitamin use has not been shown to reduce cancer risk in postmenopausal women (Neuhouser et al. 2009), but long-term use was associated with reduced risk for cancer in men with a prior history of cancer (Gaziano et al. 2012). Overall, the lack of protective effects from supplementation trials and the concern for adverse effects have led to recent recommendations suggesting dietary supplementation should not be considered for primary prevention of cancer.

3.4 The Need for Improved Study Designs

The inconsistent findings have contributed to considerable discussion among cancer prevention scientists in an effort to explain why evidence from population studies suggesting a protective role for diet in reducing risk of select cancers seemingly has not been upheld in randomized, controlled clinical trials. These discussions have led to renewed emphasis on the need for improved study designs and analytical approaches, including dietary measurement error to better qualify and quantify these relationships. Design concerns such as the recruitment of healthy volunteers, inaccurate assessment of health-related behavior, time in lifespan of healthy behavior exposure, behavior and/or supplement "dose," point of activity in the carcinogenesis pathway where the behavioral intervention is being tested, and *a priori* hypotheses for subgroups including adherence measures are all relevant to accurate interpretation of findings to date.

Most diet or physical activity intervention trials attract volunteers who at the time of study entry, prior to randomization to healthy behaviors or to a control group, already demonstrate habitual adoption of healthy behaviors (nonsmokers, low-alcohol intake, higher physical activity, and lower-fat intake) than the general population. It has been suggested that if trials were to enroll "average" Americans, individuals who eat few vegetables, minimal fiber, and high amounts of dietary fat, a protective effect would be demonstrated in response to the dietary modification. This explanation of null study results recently was demonstrated in the WHI Diet Modification trial. In this study, a subgroup analysis among women consuming in the highest quartile of dietary fat at study entry demonstrated the greatest reduction in fat intake in response to the low-fat diet assignment. These women also showed a significantly reduced risk for breast cancer, while analysis of the total study population was unable to show a protective effect (Prentice et al. 2006).

Inaccurate assessment of dietary intake and patterns of intake, either cross-sectionally or over the study period or lifespan, continue to hinder the ability to accurately evaluate diet-cancer associations, partially because the associations are likely to be modest at best (Michels 2005). As an example, a comparison of two separate dietary methods for quantifying dietary fat intake showed important differences

in the relative risk of developing breast cancer. Food frequency questionnaire data resulted in a RR of 1.71 and the Seven-Day Food Record resulted in a RR of 2.09 (Freedman et al. 2006). Similarly, use of objective measures to calibrate self-reported dietary energy intake suggested that null associations from uncalibrated energy intake estimates revert to a significant increase risk for postmenopausal cancers (breast, colon, endometrial, and renal) in the WHI-DM comparison group (Prentice et al. 2009). Similar contradictory associations have been reported for diet versus circulating carotenoids and breast cancer (Zhang et al. 2012; Eliassen et al. 2012; Aune et al. 2012b) possibly related to underestimates of dietary exposure as well as diet versus serum vitamin D (Brinkman et al. 2011; Mondul et al. 2012), diet measurement error, or effect modification by vitamin D-binding protein. Additionally, food frequency questionnaire data may not provide sufficient detail to characterize intake of specific foods that may be associated with risk, and limited data on the bioactive compounds in the food supply also hinder quantification of these exposures in epidemiological research. The current state of dietary measurement error suggests efforts to expand objective measures of diet exposure are needed.

Many studies do not evaluate hard cancer endpoints simply because of the restricted time period for study implementation and analysis. Given this constraint most trials rely on intermediate or surrogate indicators of cancer risk. For example, the Legume Inflammation Feeding Experiment was designed to evaluate the effect of a legume-rich, low-glycemic diet could modify insulin resistance and inflammation, physiological states that have been theorized to increase cancer risk (Hartman et al. 2010). In this study, as with many reported in the literature, selecat measures were improved while others showed no change with diet intervention. Longitudinal trials that assess these measures over time are needed before a clear understanding of the relationship between these indices and risk can be assessed and/or evaluated in relation to the efficacy of lifestyle interventions.

Further, dietary intervention trials conducted in later adulthood may be ineffective in demonstrating efficacy in the setting of age-related risk. In other words, attempting behavior changes later in life may reflect an approach that is "too little, too late" or requires much higher "doses" of behavior change than would be considered reasonable longer term to demonstrate cancer-preventive effects. Efforts to overcome this shortfall through the study of earlier life exposure to reduce cancer risk are increasingly being sought by funding agencies.

In addition, there is increasing evidence that there is significant variability in individual responsiveness to select dietary manipulations, much of which is the result of polymorphisms in genes associated with metabolism of nutrients or bioactive food compounds, which are thought to play a role in cancer (Hunter 2006). Beyond genotypes, there is also strong suggestion of phenotypic variability in diet-cancer associations. This may include such variables as BMI, race/ethnicity, socioeconomic status, medication use, and others.

There also is concern that many of the dietary intervention trials that are conducted do not sufficiently test dose–response (e.g., do not have adequate data from phase I or II studies) prior to setting an intervention target dose for the initiation of

phase III randomized trials. A case in point, a review of cruciferous vegetable intake and breast cancer risk suggests the data are inconsistent (Thomson et al. 2007). This inconsistency may be explained, at least in part, by the wide variability in amount of cruciferous vegetable intake. Further, dose of raw versus cooked vegetables is seldom assessed despite the fact that raw cruciferous vegetables are known to have greater cancer-preventive activity.

The timing of dietary exposure in the pathogenesis of cancer may also contribute to inconsistent findings. Two key studies published in 2000 indicated that both daily consumption of a high-fiber, wheat bran cereal and daily intake of a high vegetable, fruit, and fiber diet were not associated with a reduction in polyp recurrence (Alberts et al. 2000; Schatzkin et al. 2000). Although these trials were well designed, researchers continue to speculate that once a premalignant lesion is identified and the gastrointestinal tissue is "initiated," an increase in daily fiber intake will not reduce the risk for polyp recurrence. The value of large-scale behavioral interventions can be significantly increased if investigators include *a priori* hypotheses to test intervention effects in select subgroups participating in the study. In order to do so, scientific integrity must be upheld meaning that subgroup analyses must be developed *a priori*. This can be challenging in that over the course of a study (more than 7 years in studies involving cancer endpoints), new information can become available that suggests the need for new hypotheses. For example, when the WHI was designed in late 1980s, our understanding of the role of dietary fat subtypes (i.e., trans fats, omega 3 vs omega 6, conjugated linoleic acid, etc.) in cancer etiology was minimal; yet testing these hypotheses with the current dataset holds significant promise in advancing knowledge.

Importantly, our ability to qualify tumors by subtypes affords an opportunity to reevaluate prior association studies to determine if select subtypes may have stronger associations with diet exposures than others. This is most apparent in breast cancer; a recent pooled analysis showed a reduction in estrogen receptor (ER)-negative and triple-negative disease in relation to high vegetable and fruit intake and association that is not apparent for ER-positive tumors that are highly responsive to current treatment regimens (Thomson and Thompson JNCI 2013). Our increasing awareness of the diversity in cancer subtypes (including tumor size and metastatic status, as well as hormone receptor status, immunohistology, molecular expression profiles, and responsive potential to select cancer therapies) will support tailored recommendations for dietary cancer prevention in the near future.

These realities support the need for a new approach to diet and cancer research and clinical recommendations to promote cancer prevention that considers the following: (1) cancer as a highly variable disease for which diet is likely to have differential effects not just based on cancer site but also stage, molecular signature, treatment, and many other factors; (2) an individual's habitual diet and physical activity pattern (including early life exposures) that will likely influence responsiveness to lifestyle interventions to reduce cancer risk; (3) genetic variability in metabolism of nutrients and bioactive food compounds that influence who is identified as a responder or nonresponder; (4) dose, which should be carefully and systematically evaluated; (5) the interaction between diet and physical activity and treatment in

order to evaluate potential improvements in treatment efficacy; and (6) accuracy in characterizing diet and physical activity exposures including specific foods and the bioactive constituents that may modulate cancer risk.

3.5 Physical Activity and Cancer Prevention

Physical activity can increase lifespan and quality of life. The biological plausibility that physical activity will reduce cancer risk is well accepted. Multiple epidemiological studies support the role of physical activity in reducing cancer risk (Kushi et al. 2012). The majority of available data support a relationship between physical activity and breast (Loprinzi et al. 2012; Slattery and Edwards 2007), advanced prostate (Nilsen et al. 2006; Littman et al. 2006; Johnsen et al. 2009), pancreatic (Berrington de Gonzalez et al. 2006), colon (Friedenreich et al. 2006; Mai et al. 2007; Wolin et al. 2007) including both distal and proximal disease (Boyle et al. 2012), and endometrial cancers (Friedenreich et al. 2007) with select evidence also suggesting a protective role in ovarian (Patel et al. 2006; Cust 2011) and in relation to lifetime physical activity and reduced colon cancer risk (Harriss et al. 2009). The Iowa Women's Health Study and EPIC cohort also suggest that lung cancer incidence may be reduced in physically active individuals (Sinner et al. 2006; Steindorf et al. 2006) The first suggestion of the protective role of physical activity dates to the early 1920s when the association between occupational physical activity and cancer prevention was first noted (Siverston and Dahlstrom 1922). Since that time, a fairly robust literature has developed that has further explored and defined this relationship. What is less well established is the specific dose of exercise required to significantly modify risk (Thune and Furberg 2001). The American Cancer Society (ACS) guidelines for physical activity and cancer prevention (Kushi et al. 2012) encouraged to "adopt a physically active lifestyle," defined as:

- Adults: Engaging in at least moderate activity for ≥30 min ≥5 days of the week; ≥ 45 min of moderate-to-vigorous physical activity (moderate-intensity physical activity) ≥5 days per week (may further enhance reductions in the risk of breast and colon cancer)
- Children and adolescents: Engaging in ≥60 min per day of moderate-intensity physical activity ≥5 days per week

These recommendations could be met in a variety of ways other than sports, to include leisure time physical activity (e.g., walking/hiking, swimming, resistance training), occupational physical activity (e.g., walking and lifting, manual labor), and home activities (e.g., lawn and house work). However, the pattern of association suggests that regular moderate activity lasting more than 30 min per day is likely more protective than frequent, sustained, and highly intense activity (Warburton et al. 2006).

Despite the supportive evidence, much remains unknown, including:

- Identification of the appropriate "dose" of physical activity
- Identification of the optimal time of life for intervention
- Determination of the "optimal" type of physical activity
- Mechanisms of action

It is probable that as cancer is a multifactorial disease, there will be no "one size fits all" explanation and that to some degree variations in providing physical activity prevention recommendations will exist. Nonetheless, the above-stated guidelines are a good starting point in moving individuals to a more active health-promoting lifestyle.

The associations identified in large epidemiological trials account for only small reductions in risk; however, the potential additive effects of several lifestyle modifications could be considerable. In addition, these are modifications that are achievable and cost-effective and have no or minimal side effects. Thus, pursuit of such changes in lifestyle is an appropriate strategy to reduce cancer risk.

3.6 Biological Mechanisms Driving Reduced Cancer in Relation to Physical Activity

Physical activity has been shown to promote healthy body weight, lower adiposity, reduce insulin resistance, regulate sex hormones, reduce inflammation, and promote activity immune response (Anzuini et al. 2011).

Weight Control. As discussed, obesity and fat distribution have been associated with increased rates of many cancers. Abdominal fat, specifically visceral or intra-abdominal fat, is the most metabolically active fat store. This relationship is mediated through variations in hormone levels, to include sex steroid hormones, insulin, and IGF-1. Physically active individuals are generally neither obese nor demonstrate central distribution of body fat (Westerlind 2003). Visceral fat is preferentially affected by aerobic exercise (Schwartz et al. 1991).

3.6.1 Immune Function

The effects of physical activity on the immune system have often been held as a primary link between physical activity and cancer, although it is believed that the majority of cancers are nonimmunogenic (Westerlind 2003). Regular, moderate exercise and physical activity have been noted to affect a number of immune parameters, both numerically and functionally, to include: macrophages, natural killer cells (NK), cytotoxic T lymphocytes, and lymphokine-activated killer cells (LAK) (Newsholme and Parry-Billings 1994). Aging-associated decreases in immune function (immune senescence) have been suggested as a possible explanation for the increased rates of cancer seen with aging. Conversely, regular physical activity has been noted to enhance T-cell function of elderly men and women (Mazzeo 1994). Therefore, overall immune enhancement and slowing of immune senescence may represent the physical activity-immunity relationship.

3.6.2 Oxidative Damage

Physical activity and exercise demonstrate varying degrees of oxidative damage and generation of free radicals. Whereas moderate activity causes no to minimal damage in young and/or trained athletes (Margaritis et al. 1997), strenuous exercise may

increase rates of oxidative stress (Poulsen et al. 1996). Free radicals may adversely affect DNA and may stimulate mutagenesis and tumor proliferation (Dreher and Junod 1996). Moderate physical activity and training effects may enhance the body's innate antioxidant system and scavenging of free radicals. Conversely, intense exercise may overwhelm the body's ability to manage oxidative stress, leading to increased oxidative damage.

3.6.3 Steroid Sex Hormones

Steroid sex hormones are associated with the development of reproductive cancers in both women and men. The varied effects of exercise on these hormones are believed to be responsible for this protective relationship. It also has been identified that chronic endurance activities may decrease levels of testosterone which may in turn reduce their risk for prostate cancer, although this effect has not been reported consistently (Lucia et al. 1996; Hackney et al. 1998). A relationship has been identified between sedentary occupations and increased risk of testicular cancer (Coggon et al. 1986), whereas 15 or more hours of vigorous physical activity per week have been noted to decrease the risk of this cancer. Concentrations of sex-hormone-binding globulin (SHBG) may be increased, thereby leading to depressed levels of free circulating testosterone. Likewise in women, SHBG levels may demonstrate a similar response to exercise. Additional mechanisms may lead to decreases of both estrogen and progesterone, in premenopausal women, causing increased menstrual irregularities, a shortened luteal phase, and increased anovulatory cycles (Westerlind 2003; Ballard-Barbash et al. 2012).

3.6.4 Bowel Function: Carcinogen Exposure

It is generally noted that physical activity decreases bowel transit time, possibly mediated by increased vagal tone and increased peristalsis. This may lead to decreased exposure time of toxins and/or carcinogens with the bowel mucosa and inhibit initiation and perhaps promotion of carcinogenesis.

In summary, physical activity modifies cancer risk through a range of biological mechanisms (Ballard-Barbash et al. 2012). Current epidemiologic evidence supports an inverse relationship between physical activity and the incidence of most cancers accounting for between 9 and 19 % of cancer cases (Friedenreich et al. 2010). Evidence is most consistent for colon, breast, and endometrial cancers but is mounting for ovarian, lung, and prostate cancers. The sum of the evidence is ample to suggest that current recommendations for physically active lifestyles will reduce the burden of cancer in the future (Kushi et al. 2012).

3.7 Lifestyle and Cancer Survivorship

As survival rates for cancer have steadily increased with current estimates suggesting there are over 14 million cancer survivors in the USA alone (Eheman et al. 2012), there has been substantial interest generated related to the role of lifestyle

modification in preventing cancer recurrence and enhancing the quality of life (QOL) for cancer survivors, both during and after treatment. Much of the literature surrounding cancer survivorship is presented in Chap. 20. Here we specifically focus on the role of diet and physical activity. Historically, clinicians and researchers have relied on the primary prevention model to direct patients regarding optimal diet and physical activity patterns to reduce cancer recurrence risk. This approach continues to be promoted among cancer organizations today (Rock et al. 2012).

Cancer survivors are a particularly appropriate population for assessing the role of lifestyle change in reducing cancer risk. This is because cancer survivors demonstrate a higher cancer incident rate than the general population (allowing for reduced study sample size and time for testing hypotheses prospectively). A survey of health behaviors of over 7,000 cancer survivors using the National Health Interview Survey showed that smoking and alcohol intake were similar for cancer survivors and controls, although survivors were nine percent more likely to meet physical activity recommendations (Bellizzi et al. 2005). Female breast cancer survivors frequently report and demonstrate high levels of motivation to improve diet-related behaviors on the personal level after cancer diagnosis (Thomson et al. 2002). However, physical activity levels measured at time of diagnosis and 6 months post-diagnosis appear to drop in some women while increasing in others (Andrykowski et al. 2007). This suggests that education may be needed to promote a physically active lifestyle post-diagnosis. There is also evidence that adolescents experience a significant reduction in physical activity following cancer treatment, which is sustained long term in approximately 14 % of youth, possibly related to ongoing fatigue (Keats et al. 2006).

3.8 Body Weight and Cancer Survival

As discussed above, body weight is a primary risk factor for select cancers and likely influences survival in obesity-related cancers. However, one should keep in mind that the magnitude and direction of the association between body weight and cancer survival vary and may depend upon the type of cancer. For example, increased body weight and body fat may negatively affect the prognosis of breast cancer, while survivorship in lung cancer patients is improved among those with stable weight or even weight gain. Using breast cancer as an example, there is limited evidence that weight loss after a cancer diagnosis changes prognosis (Protani et al. 2010), although modest weight loss is associated with improved metabolic health in breast cancer survivors (Thomson et al. 2010) and was associated with reduced ER-negative breast cancer recurrence in the Women's Intervention Nutrition Study (WINS) (Chlebowski et al. 2006). Several studies have been conducted to evaluate the role of weight control in cancer survivors and these are summarized in Table 3.2.

The relevance of weight control in the survival setting remains to be determined. This is particularly true given evidence that healthy behaviors, independent of body weight, may improve survival and overall mortality. In an analysis of diet and physical activity habits among over 1,500 breast cancer survivors, Pierce and colleagues

Table 3.2 Summary of weight loss studies in cancer populations of greater than 40 participants and greater than 6 weeks duration

Study	Target population	Sample size	Duration	Intervention	Outcome
Breast cancer					
Demark-Wahnefried et al. (2008)	Newly diagnosed premenopausal breast cancer survivors	90	6 months	Calcium rich diet vs exercise vs exercise plus low-fat, plant-based diet	No difference in weight change or adiposity except extremity adiposity greater in combination arm
Djuric et al. (2002)	Obese women diagnosed with breast cancer	48	12 months	One-on-one counseling or without Weight Watchers program participation in a 2×2 factorial design	Control – increased 0.85 kg; counseling alone decreased 8.0 kg; Weight Watchers alone – 2.6 kg; counseling with Weight Watchers decreased 9.4 kg
Djuric et al. (2009)	African-American breast cancer survivors	31; 24 completers	18 months	Weight loss counseling vs weight loss with spirituality	No significant change in body weight
Goodwin et al. (1998)	New diagnoses of locoregional breast cancer; BMI 20–35 kg/m^2 and on standard adjuvant therapies	61	12 months	Psychological supportive-expressive group weight loss intervention – goals, energy restriction, and physical activity	Exercise strongest predictor of weight loss; weight maintenance in normal weight women; weight loss in obese (−6.3 kg)
Irwin et al. (2009a, b)	Postmenopausal breast cancer survivors	75	6 months	Exercise – 150 min/week of moderate-intensity vs usual behavior	Significant reduction I percentage body; increase lean body mass
Pakiz et al. (2011)	Overweight breast cancer survivors	68; 44 intervention; 24 controls	16 weeks	Cognitive behavioral therapy for weight loss, physical activity, and energy restriction	Weight loss of −5.76 kg in intervention vs +0.2 kg in controls; modest improvements in inflammatory biomarkers

(continued)

Table 3.2 (continued)

Study	Target population	Sample size	Duration	Intervention	Outcome
Sedlacek et al. (2011)	Overweight and obese postmenopausal breast cancer survivors	370	6 months	Low-fat high-carbohydrate vs low-carbohydrate high-fat diet	Pending
Thomson et al. (2010)	Overweight and obese breast cancer survivors on hormone-modulating medications	40	6 months	Low-fat vs low-carbohydrate energy-restricted diet delivered by dietitian counseling	Significant weight loss with both diets, average 6.1 kg; marked improvements in most metabolic biomarkers
Breast and prostate and/or colorectal combined					
Ligibel et al. (2012)	Active After Cancer Trial (AACT); sedentary breast and colorectal cancer survivors	121	16 weeks	Telephone-based diet and activity counseling; ten calls	Physical activity increased by 54.5 min/week vs 14.6 min/week; improved 6-min walk and physical function
Christy et al. (2011)	FRESH START Breast and prostate cancer survivors	543	10 months	Sequentially tailored mailed print materials for diet and exercise behavior change vs publically available materials	Both arms decreased saturated fat and increased fruit and vegetables and improved diet quality score although tailored materials group had higher overall diet quality scores and lower saturated fat at year 2 follow-up
Demark-Wahnefried et al. (2012)	Long-term, sedentary, overweight/obese, US or UK, breast, colorectal, and prostate cancer survivors	641	12 months	Mailed print information on diet and exercise and telephone counseling	Improvements in diet quality score, physical activity; slight reduction in BMI (–0.56 kg/m^2); less loss of physical performance

Ligibel et al. (2012)	Active After Cancer Trial (AACT); sedentary breast and colorectal cancer survivors	121	16 weeks	Telephone-based diet and activity counseling; ten calls	Physical activity increased by 54.5 min/week vs 14.6 min/week; improved 6-min walk and physical function
Morey et al. (2009)	Older, overweight, long-term breast, colorectal and prostate cancer survivors	641	12 months	Weight loss diet – high vegetable, 10 % fat, strength training vs wait-list control	Weight loss of 2.06 kg in intervention vs 0.92 kg in control
Endometrial cancer					
Von Gruenigen et al. (2012)	Overweight/obese early stage endometrial cancer: the SUCCEED study	75	12 months	Diet and exercise; 10 weekly counseling sessions followed by 6 bi-weekly sessions	Intervention reduced weight by 3.5 kg vs 1.4 kg weight gain in control
Prostate Cancer					
Parson et al. (2008)	Prostate cancer survivors	43	6 months	Telephone-based diet counseling	Increase in vegetable intake; no change in body weight
Colorectal cancer					
Campbell et al. (2009)	Colorectal cancer survivors	266	9 months	Tailored print with telephone – based motivational interviewing counseling vs usual behavior	Significant increase in fruit and vegetables in intervention group; no change in physical activity or body weight

showed a significant increase in survival after breast cancer in women who reported being physically active at least 30 min a day, 6 days per week, and consuming greater than five servings of vegetables and fruits daily (Pierce et al. 2007). This finding was consistent even among survivors with BMIs over 25 kg/m^2.

3.9 Survivorship and Diet

Two large, longitudinal diet intervention trials conducted among breast cancer survivors to test hypotheses related to post-therapy diet modification and risk for disease recurrence and survival showed opposing results. The first, the Women's Intervention Nutrition Study (WINS), conducted between 1993 and 2003, enrolled 2,437 postmenopausal breast cancer survivors across 39 clinical sites throughout the USA (Chlebowski et al. 2006). Women were randomized, within 1 year of completion of primary treatment of breast cancer, to either 15 % energy from fat diet (40 % of subjects) or usual diet (60 % of subjects) for an average of 7 years. Results showed a statistically significant 42 % reduction in cancer recurrence among women diagnosed with ER-negative tumors randomized to the low-fat diet as compared to the usual diet group. These data suggest that women diagnosed with ER-negative tumors may benefit from dietary counseling to reduce dietary fat to less than 15 % of total energy intake. There was a small (six pounds over 7 years) reduction in body weight associated with this protective association. This finding will need to be explored further in future studies.

A second study, the Women's Healthy Eating and Living Study (WHEL) also targeted breast cancer survivors for participation in a 7.3-year dietary intervention trial testing the hypothesis that a plant-based diet (20 % energy as fat, five vegetables and three fruits daily, 16 oz fresh vegetable juice daily, and more than 30 g fiber daily) would significantly lower breast cancer recurrence among the 3,088 women enrolled between 1994 and 2000 (Pierce et al. 2002). In this study, despite significant and sustained changes toward a healthier eating pattern, breast cancer events were not reduced significantly among the plant-based diet as compared to the control diet (Pierce et al. 2007). One explanation for the null findings is the fact that study subjects reported relatively healthy eating habits at the time of study enrollment and also reported having improved the quality of their food selections shortly after breast cancer diagnosis and, on average, 2.3 years prior to study enrollment (Thomson et al. 2002). This explanation is further supported by an analysis of recurrence rates in the control subjects published by Rock and colleagues that showed a significant reduction in breast cancer recurrence among WHEL women who demonstrated the highest levels of plasma carotenoids at the time of study entry (Rock et al. 2005).

While these studies may appear to have conflicting results, several differences in study design likely contributed to differential diet-disease associations. First, the WINS study resulted in a significant decrease in dietary fat intake that brought intake to a level suggested to modify estrogen levels, an important risk factor for breast cancer, with a difference of 9 % versus 4 % across study groups. The extent of reduction in dietary fat (mean intake 28.6 % energy) in the WHEL study was not

as great as what was achieved in the WINS trial. Second, there is the possibility that the clinical timing of dietary intervention is of importance to efficacy. In the WINS trial the intervention was initiated within 1 year post-surgery, and in the WHEL study, women were recruited between 1 and 4 years post-diagnosis, and earlier analysis of self-reported dietary change showed that the WHEL study participants had already made significant changes in dietary intake (especially in terms of fat reduction and more fruit and vegetable intake) prior to enrollment in the study. Chemotherapy was an eligibility criterion for WINS participation, and a greater number received CMF rather than AC as the chemotherapeutic approach; in the WHEL study approximately 30 % of women did not receive any chemotherapy.

So while two large randomized dietary intervention trials may appear to suggest opposing results, close evaluation indicates that significant differences in study design, target populations, and clinical treatment as well as baseline dietary patterns at the time of study enrollment likely explain the variable results. Of importance, breast cancer survivors are in need of guidance on the issue of lifestyle change post-diagnosis. Based on these trials as well as related subgroup analyses from the same populations as well as other smaller intervention trials and epidemiological evidence, the current recommendations would be:

1. Reduce dietary fat intake to 15–20 % energy from fat daily (postmenopausal with ER tumors)
   WINS trial approach: *body weight in pounds/6* (i.e., *180 lb/6 = 30 g dietary fat daily*).
2. Maintain an intake of vegetables and fruit of 5–7+ servings/day.
3. Be physically active (≥30 min of moderate-to-vigorous activity daily).
4. BMI should be below 30 kg/m^2 and optimally between 19 and 25; slight weight loss (1–3 lb/year) may be beneficial in reducing recurrence risk and/or comorbidities associated with recurrence risk (Patterson et al. 2010) including diabetes (Erickson et al. 2011).

Dietary patterns may also inform on future health in cancer survivors. An analytical cohort of dietary patterns (Western vs prudent) reported among stage III colorectal cancer patients has been published. After a mean 5.3 years of follow-up, patients who reported consuming a Western type diet that was higher in fat and lower in vegetables, fruit, and fiber as compared to the prudent diet demonstrated a significantly poorer survival (Meyerhardt et al. 2007). The adjusted HR was 3.25 for disease-free survival, 2.85 for recurrence-free survival, and 2.32 for overall survival. Similar protective associations (prudent diet pattern) and elevated risk (Western diet pattern) profiles were seen in the HEAL (Health, Eating, Activity, and Lifestyle study) breast cancer survivor cohort (Kwan et al. 2009), although evidence is inconsistent (Thomson and Thompson 2009).

3.10 Physical Activity and Cancer Survivorship

The role of physical activity in reducing the risk for cancer recurrence has received increasing scientific attention in the past few years leading to the formation of physical activity guidelines by both the American Cancer Society (Rock et al. 2012) and

the American College of Sports Medicine (ACSM) (Schmitz et al. 2010a). Both groups strongly support physical activity and/or exercise after a cancer diagnosis, and these guidelines are also supported by the Australian Association of Exercise and Sport's Science (Hayes et al. 2009).

Briefly the guidelines from ACSM suggest:

- If able, cancer survivors should meet current activity guidelines for Americans including 150 min of moderate-intensity activity weekly.
- Clinicians should advise cancer patients to avoid inactivity.
- Exercise recommendations should be tailored to the individual.
- Progress should be closely monitored by clinicians and/or fitness professionals in order to avoid injuries.
- Strength training should be included in advice given to cancer survivors as it appears to be beneficial.

A comprehensive review of the literature in 2012 identified 45 studies that inform on the relationship between physical activity and cancer survival (Ballard-Barbash et al. 2012). The conclusion of the review was that only breast and colon cancer-specific mortality has sufficient evidence to support physical activity interventions. The majority of studies continue to be feasibility studies that look primarily at psychosocial outcomes or intermediate physiological measures such as insulin and inflammatory markers and are preliminary in nature. Additionally, a pooling project specific to women treated for breast cancer (n>13,000) showed those who met physical activity guidelines was associated with a 27 % reduction in all-cause mortality and a 25 % reduction in breast cancer mortality (Beasley et al. 2012). A separate review of evidence suggests that among patients *currently undergoing therapy*, increased energy expenditure in the form of regular physical activity provides benefits in biopsychosocial and physiological measures (Mishra et al. 2012).

Several review studies have evaluated exercise/physical activity in relation to functional capacity, body weight, and composition, as well as flexibility, nausea, physical well-being, functional well-being, mood states, anxiety and depression, satisfaction with life, and overall quality of life (Courneya et al. 2003; Speck and Courneya 2010; Wiggins and Simonavice 2010; Pekmezi and Demark-Wahnefried 2011). The studies evaluated have used a variety of exercise interventions (e.g., self-directed or home-based vs supervised exercise) for variable study lengths. Many have made use of the traditional "exercise prescription" guidelines with respect to frequency, intensity, type, and tempo with only a few studies looking at resistance training. Whereas methodologies have often differed, sample sizes have been small, and research vigor has been variable, thereby limiting interpretation of findings, the cumulative evidence supports the safety and the potential for benefit of physical activity for cancer survivors.

It is important to recognize that during the various phases of cancer treatment and posttreatment, people often experience significant limitations in their functional capacity. Fatigue, diminished exercise capacity, and decreased strength often exist. The decision how best to incorporate physical activity necessarily requires individualization based upon preexisting exercise levels, current physical status, and goals and expectations. For those with low preexisting physical activity levels, simple

stretching or a few minutes of walking performed regularly may be all that is tolerated. For those with more active backgrounds, maintenance of levels may be desirable. Physical activity levels may be increased as physical abilities are enhanced. Recently guidance was been published for clinicians interested in implementation exercise guidelines in the survivor population (Wolin et al. 2012). Overall evidence to date suggests exercise is well tolerated even in subgroups thought to be at risk for adverse side effects. In fact, a weight-lifting trial in breast cancer patients at risk for lymphedema suggested the program was protective and not associated with increased lymphedema risk (Schmitz et al. 2010b).

The combined findings of these trials, while limited, support the proposition that cancer survivors should adopt healthy behaviors for diet, physical activity, and weight control as soon as possible after cancer diagnosis in an effort to reduce their risk for disease recurrence but most likely to improve their overall survival.

3.11 Mechanisms of Carcinogenesis Modified by Lifestyle Factors

Although there are literally dozens of biological mechanisms by which diet and physical activity protect against the development of cancer, a few have been of particular biological relevance. These include insulin resistance, modulation of immunity, including the inflammatory response, and DNA damage repair. Each of these are described and discussed in more detail below.

3.11.1 Insulin Resistance

Insulin resistance has been described as the dysregulation of insulin response to elevations in blood glucose levels. Among individuals demonstrating insulin resistance, even moderate intake of low-fiber, high-carbohydrate food items (high-glycemic foods) can result in significant elevations of plasma insulin levels. Insulin is well known to be growth promoting, and thus, increased plasma insulin levels in the presence of precancerous or cancer cells are thought to provide the necessary microenvironmental stimulus for cancer development and growth. In other words, hyperinsulinemia is a compensatory response to control blood glucose levels within the normal range in people who demonstrate a blunted response to insulin. Evidence suggests that hyperglycemia and, in some cases, the corresponding insulinemia are associated with increased risk of several cancer types including colorectal, breast, and prostate cancers. Elevations in triglycerides, C-peptide (a marker of pancreatic insulin secretion) and insulin-like growth factor 1, and reductions in select insulin-binding proteins have also been associated with increased cancer risk in both animal models and human trials, thus further supporting the insulin resistance theory of carcinogenesis (Fig. 3.1).

In turn, dietary selections and eating patterns further augment this cancer-promoting process. It has been shown that diets high in refined sugars and

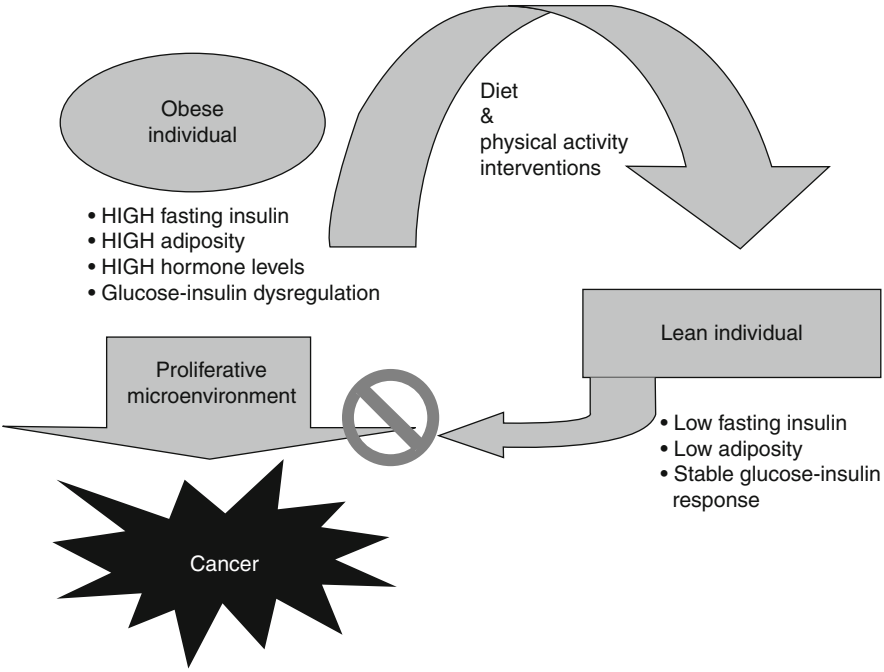

Fig. 3.1 Systematic factors modifying cancer risk in obese versus lean individuals

carbohydrates elevate blood glucose levels and insulin response more so than diets high in complex or high-fiber foods. Intake of protein- or fat-containing food items along with refined carbohydrates will reduce the maximal height on the insulin response curve as measured in peripheral blood over time but will not prevent the rise all together. In addition, the normal biological control of blood glucose and insulin response is significantly reduced in the presence of adiposity with aging. Certain populations, such as the Pima Indians, may have a genetic predisposition toward insulin resistance. Cell culture studies using a wide variety of cancer cell lines exposed to exogenous insulin and/or simple sugars, such as sucrose and high-fructose corn syrup, also indicate that carcinogenesis is promoted in such an environment.

Both optimal dietary selections and increased physical activity can modulate both the potential for developing insulin resistance as well as reverse the process in those previously demonstrated to have insulin resistance. Weight loss is pivotal to these protective effects. Significant reductions in energy intake (10–20 % of energy requirements) should be prescribed for weight loss of one kilogram weekly until weight is within normal acceptable limits. Concurrent with energy restriction, emphasis should be placed on increasing energy expenditure, starting with a goal expenditure of 1,000 kcal per week and increasing to 2,500–3,000 kcal/week. Weight loss is the single most effective intervention to prevent or reverse insulin resistance. Although the evidence does not currently exist regarding the specific macronutrient composition of the diet to prevent or control insulin resistance, the

biologic and pathophysiologic features of the insulin resistance syndrome indicate that a diet restricted in simple sugars, including high-fructose corn syrup and refined carbohydrates, is warranted. Efforts to increase high-fiber foods, which are low in sugars, and to consume a protein or fat food source, along with any carbohydrate-rich food, may also be of benefit. It is important to note that there are circumstances when a person of seemingly normal body weight may demonstrate increased adiposity and thus be prone to insulin resistance syndrome. In these cases, dietary modification as described above should be considered; however, optimizing physical activity levels will be central to reversing the adverse effects of hyperinsulinemia.

3.11.2 Immune Modulation

Cancer is thought to be a disease of the immune system. In fact, recent evidence from the Women's health initiative prospectively showed a positive association between elevated white blood cell count (an indicator of inflammation) and several cancers, including breast, colorectal, endometrial, and lung cancers (Margolis et al. 2007). Theoretically, if the immune system is functioning optimally, cancer should not occur. To this end, research has focused both on understanding the role of the immune system in cancer prevention as well as how lifestyle behaviors can modulate immune response. Several nutrients have been shown to play a role in immune function ranging from protein, the building block of immune cells, to numerous micronutrients, such as vitamins A, C, E, and zinc and copper. The role of select nutrients in immune modulation is summarized in Table 3.3. The appropriate level of nutrient intake for promoting optimal immune response has not been clearly established. For some nutrients it appears that there is a window; intake below or above this range may have immunosuppressive effects (e.g., zinc). For other nutrients, levels must be significantly depressed before immune suppression is shown (e.g., vitamin A). What is clear is that among immunosuppressed populations (such as HIV-infected individuals), the risk for cancer is increased. In addition, these same populations generally demonstrate improved immunity in response to nutrient-dense diets or supplementation. However, if the provision of nutrients to these high-risk individuals also reduces cancer occurrence has yet to be established.

As discussed earlier, obesity is a contributing factor in the development of several cancers. It has been demonstrated that obese individuals have suppressed immune response. Not only are the numbers of CD4- and CD8-positive T cells reduced, macrophage response is delayed in obese subjects as is natural killer cell cytotoxicity. It therefore appears that one plausible mechanism by which cancer risk is elevated in obese individuals may be related to the resultant immunosuppression, the onset of which is related to an accumulation of adipose tissue.

3.11.3 Inflammatory Response

One factor relevant to immune response and cancer risk theoretically identifies cancer as an inflammatory disease. In fact, inflammatory biomarkers have been

Table 3.3 Role of select nutrients in modulating immunity

Nutrient	Food sources	Demonstrated effects on immune response
Vitamins		
Vitamin A	Fortified dairy, yellow-orange vegetables	Improve mucosal integrity, increase T-cell function, increase antigen (AG)-specific immunoglobulin-G response
Vitamin C	Citrus, peppers, broccoli	Increase T-cell response, increase phagocytosis, increase epithelial integrity
Vitamin E	Seeds, almonds, oils, Raisin Bran	Increase cytokine production, increase B-cell function, increase T-cell cytotoxicity, increase phagocytosis
Minerals		
Copper	Beef liver, cashews, molasses	Increase B-cell function, increase T-cell response, increase phagocytic function
Iron	Fortified cereals, liver, clams	Increase B cells, increase Ab production, increase lymphoid tissue
Magnesium		Increase cytotoxic cells, increase cytokine production
Zinc	Oysters, wheat germ, dark meat, poultry	Increase B-cell function, increase cytokine production, increase cell-mediated immunity
Other nutrients		
Omega-3 fatty acids	Salmon, cold-water fish, flax	Decrease inflammatory response
Protein	Lean meat, low-fat diary, egg white	Increase total lymphocyte count/response to Ag, increase epithelial integrity

shown to be elevated in a variety of cancer patients before, during and after cancer therapy. Inflammation results in cellular damage and thus is thought to be a contributory factor in the multistep pathway to carcinogenesis. Inflammation is also characterized by an accumulation of macrophages that in turn release reactive oxygen species, another contributing factor in cancer development. This biological response may be of particular importance to the obese patient who not only demonstrates reduced macrophage-related response to antigens but also accumulates macrophages locally in adipose tissue thus elevating the level of localized oxidative damage in these cells.

There are several naturally occurring inflammatory response modifiers in the human diet. Of particular interest are the omega-3 fatty acids. Fatty acids have demonstrated effects on membrane fluidity and eicosanoid production that in turn alters signal-transduction pathways, membrane-bound receptors, and enzyme activity. The end result of these biological effects is an alteration in cytokine release and inflammatory response. Increasing omega-3 fatty acid intake results in a reduction in omega-6 fatty acid and in particular arachidonic acid, a proinflammatory compound. Fish oil, an abundant source of omega-3 fatty acids, when supplemented in the diet, results in a significant decrease in the omega-6 to omega-3 fatty acid ratio. Omega-3 fatty acids and foods high in omega-3 fatty acids, including alpha linolenic acid, are considered anti-inflammatory and thus may play a role similar to

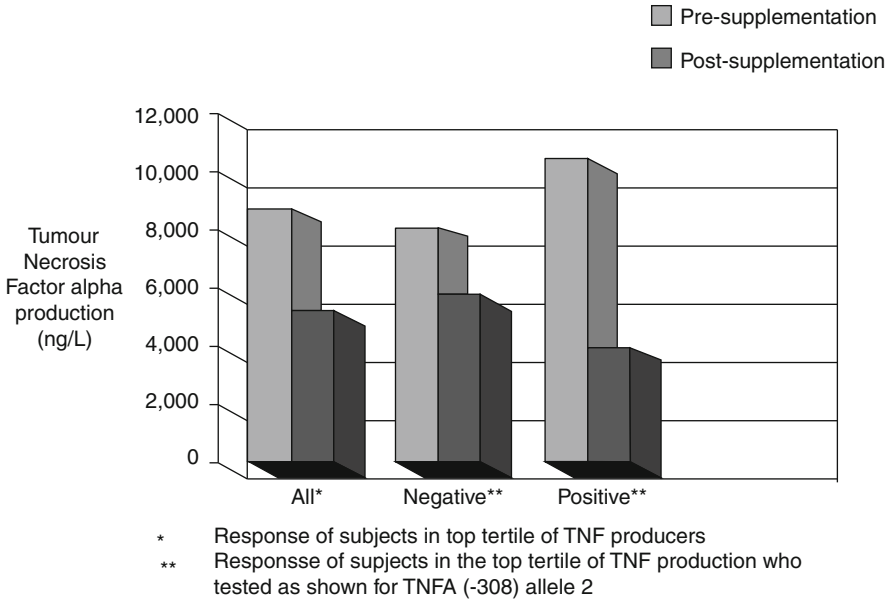

Fig. 3.2 Modulation of inflammatory response with omega-3 fatty acid supplementation (Adapted from Grimble et al. 2002)

prescribed cyclooxygenase inhibitors in reducing cancer risk. Recent evidence also suggests that responsiveness to omega-3 fatty acid supplementation may be modulated by genetic background (Fig. 3.2).

3.11.4 Oxidative Damage

Related to the inflammatory response is the role of oxidative DNA damage in cancer development and progression. All living organisms consuming oxygen experience oxidative damage to tissue on an ongoing basis. In turn, within the human, adaptive mechanisms exist to either reverse the oxidative damage inherent to our biological processes or minimize the effects by clearing by-products of oxidative damage from the body, thus reducing cancer risk. The role of antioxidants in reducing oxidative damage and promoting repair has been well described in the literature (Ames 1983; Halliwell 2002). Many clinicians fail to recognize that beyond the more well-known antioxidants (e.g., vitamins C and E and selenium) are several naturally occurring phytochemicals that also have significant antioxidant properties. These include carotenoids found in vegetables and fruits, polyphenols found in teas, resveratrol found in grapes, limonene from citrus peel, or isoflavones found in soy foods. The cancer-preventive role of vegetables and fruits likely stems in part from the high antioxidant content.

Several studies have been published over the past 5–10 years demonstrating the potential for vegetables and fruit to reduce oxidative damage. In a study by Thompson and colleagues (Thompson et al. 1999), a controlled feeding of vegetable (carrot) juice resulted in a significant reduction in oxidative damage biomarkers among healthy individuals. Another study showed a similar response using a high vegetable and fruit diet (Djuric et al. 1991). Similar results have been shown while feeding a variety of foods rich in antioxidant properties, not only to healthy individuals but also to smokers, people diagnosed with cancer, and long-term cancer survivors (Djuric et al. 1998; van Zeeland et al. 1999; Collins and Harrington 2002).

Reduction in oxidative damage through dietary modification seems an appropriate approach to reducing cancer risk. However, there is no direct evidence that such an approach will result in reduced cancer rates. A prudent diet should include a wide variety of vegetables and fruits with attention to a broad range of food colors. The diet should also include additional food selections that promote greater intake of dietary constituents that have demonstrated antioxidant properties such as green tea, citrus peel, onion, garlic, and soy foods.

3.11.5 Diet-Gene Interactions

Briefly, it is important to mention the role genetics is likely to play in the future of cancer-preventive diets and lifestyle interventions for individuals and subgroups at risk. A person's responsiveness to dietary intervention is increasingly being identified as being affected by the complexity of an individual's genotype and genetic polymorphisms. It is likely that many of the inconsistencies demonstrated in the epidemiological assessment of relationships between dietary constituents and specific cancer endpoints may be explained by genetic variability. In a given population, the interplay between an individual's genotype and dietary exposures throughout the lifespan may significantly influence whether or not that individual is diagnosed with cancer (Fig. 3.3). Understanding this relationship, future dietary interventions can be targeted to those at risk and can be adapted for individual likelihood of response.

Importantly, several trials are currently underway or have recently completed that will contribute significantly to our efforts to better define optimal lifestyle practices to promote health in the cancer survivor population. These include the ENERGY trial (Rock et al. 2013), the DIANA-5 trial (Villarini et al. 2012), and the CanChange study of colorectal cancer survivors (Hawkes et al. 2009) as well as the recently completed SUCCEED trial wherein weight loss was achieved in uterine cancer survivors (von Gruenigen et al. 2012), a study of weight loss in rural breast cancer survivors (Befort et al. 2012), and a study of weight loss in prostate cancer survivors (Bourke et al. 2011). A smaller trial in ovarian cancer (Paxton et al. 2012) and the recently initiated randomized controlled trial of over 1,000 ovarian cancer survivors (GOG-0225, Lifestyle Intervention in Ovarian Cancer Survival (LIVES)) also promise our first information for this specific cancer subgroup.

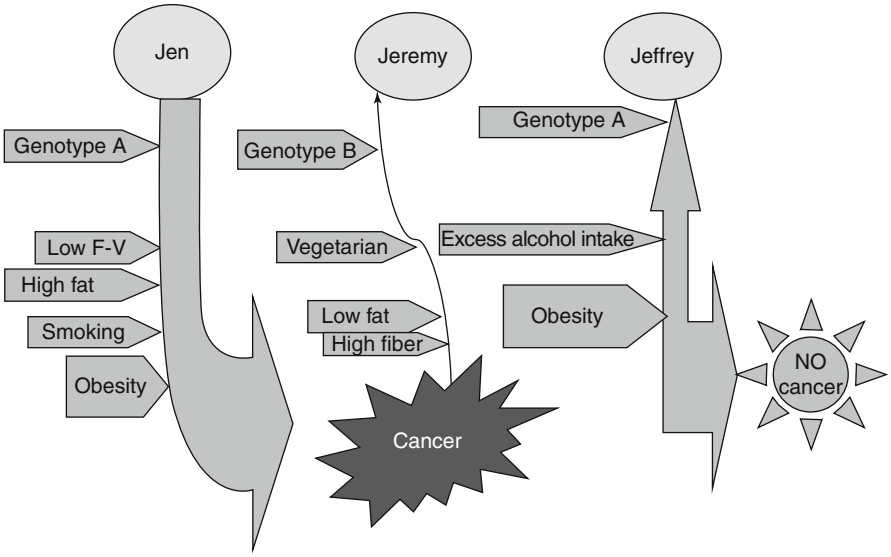

Fig. 3.3 Interplay between an individual's genotype and dietary exposures throughout the lifespan

3.12 Advancing the Guidelines for Cancer-Preventive Lifestyle

Currently, the guidelines provided by the American Cancer Society for primary cancer prevention and survival (Kushi et al. 2012; Rock et al. 2012) and from the WCRF/AICR report (WCRF/AICR, 2007 with web-based updates) should serve as the foundation of any recommendations provided to individuals to reduce their cancer risk. Individualization is essential, based upon the person's physical status, prior physical activity and exercise history, and goals and expectations.

The following is an expansion of current dietary and physical activity recommendations based on evolving scientific evidence. While prospective hypothesis-driven intervention trials are not available to support all of these recommendations, the risk-benefit ratio of available evidence suggests these recommendations should be considered in providing lifestyle advice to people seeking to reduce their cancer risk.

- Achieve and maintain a healthy body weight and body composition:
  - Be aware of small, incremental changes that over time result in excess adiposity.
  - Restrict energy intake.
  - Avoid energy-dense foods including sugary beverages, animal fats, and fast foods.
  - Control food portion sizes.
  - Increase energy expenditure.
  - Perform both aerobic and weight-bearing activities daily.

- Eat more vegetables daily:
  - Include a dark green leafy vegetable daily.
  - Include a dark orange-yellow vegetable daily.
  - Include cruciferous vegetables.
  - Include allium vegetables (onion, garlic, leeks).
  - Do not overcook vegetables or saturate in high-fat sauces/condiments.
- Eat at least three servings of fruit daily:
  - Consume fresh fruit over juice.
  - Include one serving of citrus daily.
  - Include berries, cherries, or other dark red-purple fruits daily.
- Eat at least 30 g of fiber daily:
  - Select both soluble and insoluble fiber sources.
  - Select only whole grain breads and cereals.
- Reduce intake or avoid processed or refined carbohydrates:
  - Select whole-grain breads.
  - Read labels and avoid foods with greater than 10 g of sugar per serving.
  - Avoid foods and beverages containing high-fructose corn syrup.
  - Prepare food at home more; reduce meals from fast food restaurants.
- Include foods rich in antioxidants:
  - Vegetables and fruits
  - Teas
- Avoid processed meat and limit red meat to less than 2 servings/week:
  - Do not overcook meat.
  - Select lean cuts.
- Include omega-3 rich foods daily:
  - Cold-water fish
  - Flax seed
  - Omega-3 oils
- Adopt a physically active lifestyle:
  - *Adults*: Engage in at least moderate aerobic physical activity for at least 150 min per week and muscle-strengthening activities on 2 or more days/week or equivalent. Recognition of the exercise continuum indicating that health and fitness gains are enhanced by greater volumes of activity should serve as a goal to achieve at least 20–60 min of continuous or intermittent (minimum of 10 min bouts accumulated throughout the day) moderate-to-vigorous aerobic physical activity regularly (US Department Health and Human Services 2008).
  - *Adults*: Engage in resistance training 2–3 days per week. A minimum of 8–10 exercises involving the major muscle groups should be performed that incorporate a minimum of one set of 8–15 repetitions.
  - *Youth*: Accumulate at least 60 min, and up to several hours, of age-appropriate, aerobic, moderate-to-vigorous physical activity daily and vigorous activity 3 days/week (US Department of Health and Human Services 2008). At least 3 days/week children should engage in bone-building and muscle-strengthening activities.

- All individuals should incorporate more physical activity into their daily lives. Simple measures such as the following can enhance regular activity and improve health:
  - Take the stairs rather than the elevator or escalator.
  - "Actively commute" by walking or bicycling where and when appropriate.
  - Schedule active family outings and vacations.
  - Engage in moderate housework and yard work where and when available.
  - Take 10-min minimum walk breaks at work.
  - Wear a pedometer to gauge daily activity level.
  - Get together regularly with friends and/or family members for hikes or walks.
  - Walk the dog.
  - Take the first available parking space and walk to the store entrance.
  - Carry bags of groceries in from the car one at a time.
  - Jump rope or run in place during television viewing.
  - Sit on a balance ball while working at your computer.

The American Cancer Society identifies specific issues for survivors of cancer that may preclude their participation in physical activity (Brown et al. 2003):

- Individuals with anemia should refrain from activity, other than that of daily living, until anemia improves.
- Individuals with compromised immune systems should avoid public gyms and other public venues; survivors post-bone marrow transplantation should avoid these spaces for 1 year following transplant.
- Persons experiencing significant fatigue should listen to their bodies and do as much as they feel able to do and are encouraged to do 10 min of stretching daily.
- Individuals should avoid chlorinated pools if undergoing radiation therapy.
- Persons with indwelling catheters should avoid water or other microbial exposures that may result in infections. They should also avoid resistance training that may cause dislodgement of the catheter.
- Persons who are experiencing significant peripheral neuropathy that may impede their ability to perform exercises and activities that make use of the affected limbs may consider using a recumbent bicycle or similar exercise equipment in controlled settings rather than performing activities outdoors.

As previously mentioned, it is important for clinicians to individualize physical activity and exercise recommendations as determined by the unique situation of the patient. An emphasis should be placed upon getting all individuals to limit their sedentary behavior and increase their activity as tolerated.

It is also imperative that the above lifestyle practices begin early in life and be sustained throughout life. Parents must become strong role models of healthy behavior for their children and communities must provide environments that are supportive of such behaviors.

3.13 Tools for Research and Clinical Practice

Researchers and clinicians can benefit from having the appropriate tools necessary to integrate diet and nutrition as well as physical activity and body composition assessment and behavior change instruments available. The remainder of this chapter focuses on key issues in measurement, assessment, and implementation of behavior change in this context. Some will have greater application to the researcher, while others will be most appropriately applied in clinical practice.

3.13.1 Measuring Diet

Dietary measurement is among the most challenging issues facing researchers and clinicians alike. Current dietary measurement tools rely heavily on self-report. It has been demonstrated that people have difficulty accurately recalling dietary intake and due to social desirability may have significant discomfort in reporting intake even when accurately recalled. This is particularly true for overweight persons and has been primarily described among women.

There are three major approaches to measuring diet reported in the scientific literature. These include the food frequency questionnaire (FFQ), where individuals recall intake of a specific list of foods (80–250 items), frequency of intake, and approximate serving sizes; dietary recalls, where individuals report their intake in terms of food items, amounts, and preparation methods for one or more 24-h periods; and the dietary record, where individuals record all food consumed, amounts, brands, and preparation methods for a predefined period of time. Each approach has both strengths and weaknesses. Correlations between these approaches generally range between 30 and 60 % supporting the concern for significant reporting error when it comes to dietary measurement. However, until more accurate approaches are developed, these approaches remain the basis for much of the dietary measurement reported in the literature. Several cancer centers across the USA (e.g., University of Arizona, Fred Hutchinson Cancer Research Center, University of North Carolina, and University of Minnesota) have shared services resources to assist clinicians and researchers in selecting the most appropriate instruments and approaches for use.

Generally, to best assess intake, researchers recommend that more than one approach be used and when possible, biological markers of intake also be measured. Presented in Table 3.4 are several biomarkers of dietary intake that can be employed in an effort to validate self-reported intake.

In addition, investigators have developed several focused food frequency questionnaires to more accurately capture intake of select foods that have been recognized for their chemopreventive properties. These include the Citrus Intake Questionnaire, the Arizona Tea Questionnaire, the Soy Foods Questionnaire, and most recently the Cruciferous Vegetable Questionnaire. Several of these instruments are available through the Dietary and Behavioral Measurements Service at the University of Arizona (Table 3.5). These focused instruments allow for more complete and valid assessment of intake of the designated foods,

Table 3.4 Biological markers (assays) used to validate self-reported dietary intake in cancer prevention research

Dietary constituents of interest	Biomarker/functional biomarker
Fiber	Fecal hemicellulose; fecal weight, short-chain fatty acid
Folate	Plasma folate; red blood cell folate; plasma homocysteine
Vitamin B12	Plasma B12
Vitamin C	Plasma vitamin C; urine deoxypyridinoline
Vitamin E	Plasma tocopherols; LDL oxidation
Calcium	Bone density; serum osteocalcin
Selenium	Plasma or whole-blood selenium; toenail selenium; plasma GSH peroxidase activity
Carotenoids	Plasma levels (alpha- and beta-carotene; lutein; lycopene)
Cruciferous vegetables/ isothiocyanates	Urinary dithiocarbamates
Citrus/limonene	Urinary perillylic acid
Tea polyphenols	Urinary polyphenols

thus supporting more reliable assessment of the association between these foods and cancer risk reduction.

Other clinical and research tools are available online. These include the National Cancer Institute FFQ, Block Fat Screener, and the NCI Fruit and Vegetable Screener. The US Department of Agriculture also has an online Healthy Eating Index; individuals can enter daily dietary intake and can receive an immediate assessment of specific macro- and micronutrients, a graphic comparison of how their intake compares to the Food Guide Pyramid, and a summary of individual intake versus national dietary goals. The Healthy Eating Index also affords the individual an opportunity to track progress over time as new dietary behaviors are adapted. A summary of diet and/or physical activity evaluation resources is listed in Table 3.5.

3.13.2 Assessment of Physical Activity and Energy Expenditure

Researchers should be familiar with the various methods of assessing physical activity and energy expenditure. The former term is broadly defined as any bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure. The latter specifically addresses the energetic cost associated with a specific physical activity and is dependent upon the numerous processes and personal characteristics (e.g., age, body mass, fitness level) associated with that activity (Montoye et al. 1996).

3.13.2.1 Physical Activity Questionnaires

Physical activity questionnaires are simple and inexpensive methods of obtaining data from participants. As they are dependent upon individual self-report, they are subject to recall and social bias. They are nonetheless useful and are often used in conjunction with more objective measures.

Table 3.5 Web-based resources for diet and/or physical activity measurement applications or instruments

Organization	Website address	Components
Arizona Cancer Center Diet and Behavioral Measurement Service	http://azcc.arizona.edu/research/shared-services/bmss/questionnaires	Food frequency questionnaires including FFQs for tea, citrus and cruciferous vegetables
Block, Gladys- Investigator	http://www.nutritionquest.com/fat-screener.html	Fat screener
Medical Research Council of UK	http://dapa-toolkit.mrc.ac.uk/	Toolkit for identifying and selecting measurement tools and instruments for diet and activity research
National Cancer Institute	https://www.gem-beta.org/public/Measure http://riskfactor.cancer.gov/tools/instruments/asa24	Fruit and vegetable screener NCI Energy from fat screener Self-report instrument for assessing 24-h dietary intake
National Cancer Institute Dietary Measurement Error webinar	http://riskfactor.cancer.gov/measurementerror/	Webinar of sources of measurement error in diet assessment and call to improved methodology
San Diego State University: Sallis inventory	http://www.drjamessallis.sdsu.edu/measures.html	Comprehensive listing of diet and physical activity measurement instruments, survey with hyperlink to individual items
US Department of Agriculture	http://www.cnpp.usda.gov/HealthyEatingIndex.html	Healthy eating index

Global short surveys (1–5 questions) that focus upon general aspects of physical activity provide limited information and lack specificity but provide an overview of physical activity patterns that may provide background information for more focused studies. Recall, or longer surveys (10–20 questions), are often used to obtain baseline data for comparison with post-intervention data. These instruments provide more detailed information about specific aspects of physical activity (e.g., frequency, amount) over a defined period of time (e.g., days, weeks, months). Quantitative history tools generally have more questions (greater than 20) and provide very detailed information about physical activity patterns over longer periods of time (e.g., past year, period in lifetime, entire lifetime). These instruments address the volume of activity and allow for the determination of dose–response effects on outcome measures of interest (e.g., kcal/week).

3.13.2.2 Physical Activity Logs, Records, and Recalls

Physical activity records provide an ongoing account of an individual's physical activity during a defined period of time in an attempt to capture all forms of activity. Physical activity logs are often used to determine adherence to specific protocols. They call for identifying specific aspects of physical activity over determined intervals (e.g., every 15 min). Physical activity recall is usually performed by telephone or personal interviews and attempt to catalogue an individual's physical activity patterns over a defined period of time (e.g., day, week).

3.13.2.3 Indirect Measures of Energy Expenditure

There are a wide variety of tools and methods that can be applied in either laboratory or field situations. They provide reliable and valid measures of free-living situations but vary in their logistical burden of performance. Doubly labeled water (DLW) provides an accurate assessment of energy expenditure based upon the volume of carbon dioxide (VCO_2) produced and oxygen uptake volume (VO_2). Stable isotopes of water are consumed, and then fractional excretion is calculated through urinary measures. Energy expenditure is calculated from determination of VCO_2 and VO_2. Although an accurate measure, it cannot provide specific information about the characteristics of physical activity that have contributed to the energy expenditure, such as intensity, frequency, or duration. VO_2 estimates energy intake based upon equations that provide a relationship between oxygen utilization by tissues and caloric utilization by activity (one liter O_2 approximately equals 5 kcal). These estimates are commonly determined by a treadmill or bicycle ergometer and are often used to provide an individual with an exercise prescription that defines the volume and intensity of activity to be performed (e.g., 60–90 % of maximum heart rate or 50–85 % of VO_{2max}).

Heart rate is a commonly used measure that provides an indirect estimate of workload or energy expenditure. It is based upon a linear relationship that may exist between heart rate and VO_2, but as it is significantly affected by a number of parameters, its accuracy is less than other measures. It nonetheless is easily measured and is a useful measure in interventions that provide an exercise prescription to participants.

Motion detectors are mechanical instruments that are worn to quantify a measure of physical activity. These instruments are based upon the premise that motion is related to energy expenditure. Accelerometers have commonly been utilized and provide researchers with an accurate assessment of activity intensity and volume over a determined time interval. Limitations, such as the inability to measure activities that may not cause trunk movement (e.g., resistance training), prevent them from accurately providing a measure of the wearer's total energy expenditure.

Pedometers are simple devices that have become increasingly popular for physical activity assessment. They measure the number of steps that are taken while worn but cannot differentiate characteristics of step-based activities, nor can they measure other forms of activity accurately (e.g., bicycling). Pedometers are inexpensive and have been associated with an increase in motivation toward behavior change, thus making them popular for clinical practice and research. In general, research studies are more likely to rely on accelerometers to measure physical activity because they have a higher correlation with actual energy expenditure [$r = 0.34–0.49$] (Freedson and Miller 2000).

3.13.3 Measurement of Body Composition

3.13.3.1 Anthropometric Measurements

Anthropometry has been used to predict body composition in laboratory and field situations. Some examples of anthropometric variables relevant to body composition are weight; trunk depth; stature; arm span; knee height; breadth of biacromial,

bi-iliac, knee, ankle, elbow, and wrist; circumference of waist, hip, thigh, calf, arm, and wrist; and skinfold thickness at the subscapular, midaxillary, suprailiac, triceps, and biceps. These variables can be used to predict percent body fat, body density, fat-free mass, total body muscle mass, and total body bone mineral content. A number of body composition predictive models with anthropometric variables have been developed and cross-calibrated. Because anthropometric procedures are noninvasive and the instruments used for anthropometric measurements are portable and relatively inexpensive, anthropometry tends to be used for large population-based studies. However, in comparison to other laboratory techniques for body composition measurements, anthropometric measurements may be less accurate.

3.13.3.2 Bioelectric Impedance Analysis (BIA)

BIA is often a substitute or supplement to conventional anthropometry in field research or epidemiologic studies on body composition. Impedance is the frequency-dependent opposition of a conductor to the flow of an alternating electric current and reflects both resistance and reactance. The use of BIA to estimate body composition is based on the assumption that different body tissue components have different conductive and dielectric properties at different frequencies of current. The conductive and dielectric properties can be measured through impedance. All BIA devices are composed of three essential parts: alternating electrical current sources; cables and electrodes to introduce the current into the body and to send the voltage drop due to impedance; and a system for measuring impedance. BIA is portable and easy to use. Predictive equations of impedance can be developed and calibrated for estimating total and regional body composition, including fat and fat-free mass. However, the general applicability of BIA is often limited by the availability of appropriately calibrated and cross-validated predictive equations in different populations who have different hydration status and thickness of subcutaneous fat. These factors may significantly affect the precision of BIA assessments. BIA does not provide reliable measurements of body composition for cancer patients with ascites (Sarhill et al. 2000). Until more research has been conducted, caution should be taken when applying general BIA predictive equations for body composition estimations among cancer patients.

3.13.3.3 Dual-Energy X-Ray Absorptiometry (DXA)

A new generation of bone densitometry not only measures bone density but also measures soft tissue mass. Body soft tissue measurements by DXA are derived from the assumed constant attenuation of pure fat and of bone-free lean tissue. The advantages of DXA in measuring body composition include its qualities as a noninvasive, highly precise and accurate instrument, and that it emits very low radiation (less than a standard x-ray). DXA scans may provide total body and regional measurements of bone mineral content, bone mineral density, soft tissue mass, lean soft tissue mass, and fat tissue mass as well as percent fat tissue mass. Hydration levels and body thickness have very small effects on the precision of DXA-derived body composition assessments. Hence, DXA can be used in both general and patient populations. With new developments in DXA hardware and software, the

total body scan time has been significantly shortened, and body composition analyses can be conducted for any defined regions by the investigator. However, the high cost of DXA units and the need of special radiologic training for DXA operators limit the application of DXA for body composition measurements in standard research and clinical practice. Nevertheless, given the growing numbers of DXA instruments, and especially DXA-mobile units, the utility of DXA in field and epidemiologic and clinical studies of body composition will increase. Body composition measurement will likely have an increasing role in the supportive care of the patient, specifically to evaluate nutritional status and treatment effects on health.

3.13.3.4 Other Techniques

Hydrodensitometry, hydrometry, whole-body counting, neutron activation analysis, ultrasound, and imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are other techniques for body composition assessments. The hydrodensitometry method, which measures percent body fat, requires that the subject completely submerges in water and assumes consistent densities of the constituents of the body from person to person. The hydrometry method measures total body water, as well as intracellular and extracellular water, based on the distribution of isotopic tracers in different water compartments. Whole-body counting and neutron activation analysis can be used to measure skeletal muscle mass and other body composition through assessing natural potassium concentration or assessing selectively activated atoms in the body. Ultrasound has been used to measure regional body composition for over 30 years. However, the precisions of ultrasound-derived body composition measurements are less satisfactory in comparison with DXA measurements.

Most previous studies have used body mass index or weight and waist-to-hip ratio as proxies for obesity and fat distribution. Measurement errors due to improper anatomical placement of the measuring tape and other technician operation errors, particularly with repeated measures, may limit the ability to detect an association of obesity or fat distribution with cancer.

Conclusion

Success usually comes when behavior change is made using small, positive, and incremental steps that are frequently reinforced. Food and other lifestyle choices are influenced by several factors including perceived risk, cost, convenience, taste (e.g., food), social support, self-efficacy, and environment. Table 3.6 provides examples of behavior strategies or "prescriptions" that can be employed to promote behavior change and, as a result, achieve the desired health outcome.

The role of diet, physical activity, and body composition continues to be an area of active research both in terms of primary prevention and in terms of reducing morbidity and mortality among those previously treated for cancer. Evidence to date supports efforts to improve dietary selections toward a more plant-based, low-fat, complex carbohydrate-rich diet along with daily, regular, and varied

Table 3.6 Desired health outcomes in cancer prevention and survival and applicable behavioral strategies to achieve desired outcomes

Health or behavioral outcome sought	Behavioral strategy
Weight loss	Cut all portions in half Use a salad plated to serve food Restrict fast food restaurants to once/week Record intake Substitute calcium chews for dessert
Increased fruit and vegetable intake	Select new fruit or vegetable from the produce department each week Purchase a 5-a-day cookbook and try three new recipes each week Keep a fruit bowl readily available at work and home Select at least five different colors of produce at the market each week Visit the farmers' market weekly – bring a friend Add fresh fruit to cereal Have a fruit smoothie for breakfast Put blended vegetables into your pasta sauce Make salads a meal
Increased fiber intake	Select and eat cereal with at least 6 g of fiber per serving Try oatmeal again Purchase the heaviest bread on the shelves Eat five to nine servings of vegetables and fruits daily Add seeds to cereal, salads, etc. Snack on air-popped popcorn
Normal glucose-insulin levels	Avoid any food with great than 10 g sugar/serving Switch from soda to fresh lemonade or tea with no added sugar Consume protein-carbohydrate combined meals Replace white bread with whole grain; replace white potato with sweet potato
Daily physical activity	Wake up 30 min early and walk Find a friend to walk with Jump rope during television commercials Garden Ride a bike to work or on errands Try a new sport Train for a charity walk/run Keep an active log-reward yourself when goals are met

physical activity. Maintenance of a healthy body weight throughout life is strongly recommended to reduce cancer risk. Measuring diet, physical activity, and body composition is both plausible and challenging. Practitioners should develop strategies to routinely evaluate the diet, physical activity, and body composition of each patient to promote early and effective behavior change to reduce cancer risk.

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Innate and Adaptive Immune Responses to Cancer

4

Karen Taraszka Hastings and Matthew P. Rausch

Together innate and adaptive immune responses are capable of recognizing and destroying cancer. As part of the innate immune response, natural killer cells and gamma delta T cells are capable of specifically recognizing and killing tumor cells. As part of the adaptive immune response, cancer patients generate CD4+ and CD8+ T lymphocytes and B lymphocytes specific for tumor antigens, which have been identified from many cancers. Tumor-specific lymphocytes are found infiltrating tumors and in the peripheral blood of cancer patients. The presence of brisk tumor-infiltrating lymphocytes in primary melanoma portends a survival advantage compared to tumors where tumor-infiltrating lymphocytes are absent. In some instances, the immune system can cause spontaneous regression of tumors. For example, partial regression is a common finding in primary melanoma lesions, and there are rare reports of complete regression of metastatic melanoma. The importance of the immune system in preventing cancer is reflected in the increased frequency of malignancies in immunosuppressed and immunodeficient patients. Under the selective pressure of the immune response, tumors evolve to escape immune-mediated destruction.

4.1 Importance of the Immune System in Cancer Prevention

The concept of cancer immunosurveillance was first proposed by Burnet in 1957 (Burnet 1957) and has been refined into a three-step cancer immunoediting process of elimination, equilibrium, and escape (Schreiber et al. 2011; Teng et al. 2008) (Fig. 4.1). Elimination refers to cancer immunosurveillance and the ability of the innate and adaptive immune responses to detect and destroy a developing tumor.

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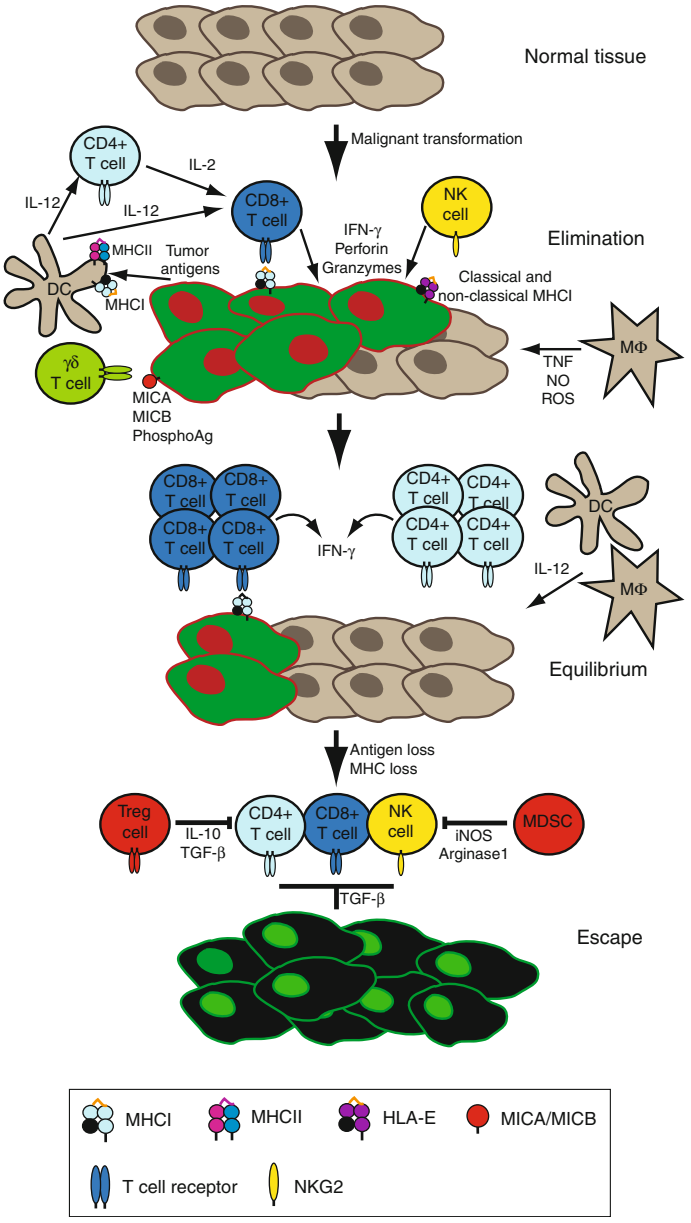

Fig. 4.1 Cancer immunoediting can be broken down into three phases: elimination, equilibrium, and escape. In the elimination stage, cells of the innate and adaptive immune system infiltrate and destroy newly transformed cells. During the equilibrium stage, cells of the adaptive immune system (primarily CD4+ and CD8+ T cells) hold transformed cells in a state of dormancy, preventing their outgrowth. The selective pressure exerted by the immune system on genetically unstable tumor cells can lead to the emergence of poorly immunogenic tumor cell variants due to antigen loss, defects in antigen processing and presentation, and the immunosuppressive state of the tumor microenvironment. At this point, tumor cells have entered the escape stage which ultimately leads to clinically detectable cancer (Adapted from Schreiber et al. (2011))

In mouse models, the absence of the cytokine interferon (IFN)-γ or IFN-γ signaling (IFN-γ receptor knockout or signal transducer and activator of transcription 1 (STAT1) transcription factor knockout) results in enhanced formation of transplanted tumors and chemically induced and spontaneous tumors (Dighe et al. 1994; Kaplan et al. 1998). IFN-γ is produced by natural killer (NK) cells as part of the innate arm and by T lymphocytes as part of the adaptive arm of the immune response and will be discussed in detail later. In addition, perforin-deficient mice are more prone to develop chemically induced and spontaneous tumors than wild-type mice (Smyth et al. 2000; Street et al. 2001, 2002; van den Broek et al. 1996). Perforin is a component of the cytolytic granules of both NK cells and CD8+ cytotoxic T lymphocytes and, thus, is a mediator of target cell killing for both the innate and adaptive immune responses. Recombination activating gene (RAG) 1 and 2 are essential for rearrangement of the B and T cell receptors, and deficiency of either enzyme results in the complete absence of B and T cells. RAG-deficient mice have an increased frequency of chemically induced and spontaneous tumors (Shankaran et al. 2001). Mice with combined deficiencies in the lymphocyte pool (RAG knockout or perforin knockout) in addition to IFN-γ have a modest increase in tumor formation (Shankaran et al. 2001; Street et al. 2001). In addition, mice with deletions of NK cells and T cells expressing the γδ T cell receptor (TCR) have increased susceptibility to chemically induced tumors (Girardi et al. 2001; Smyth et al. 2001).

There is corresponding evidence for the role of the immune response in elimination of tumors in humans (Schreiber et al. 2011). Immunodeficient or immunosuppressed patients have an increased incidence of cancer. Many of these cancers have a viral etiology such as Epstein-Barr virus (EBV)-induced lymphomas, human herpesvirus 8 (HHV8)-induced Kaposi sarcoma, and human papillomavirus (HPV)-induced cervical, anogenital, and skin cancers. However, the incidence of cancers without an apparent viral etiology is also increased. A two- to tenfold increase in the incidence of melanoma has been observed in transplant recipients (Penn 1996; Sheil 1986) as well as an increased incidence of colon, lung, pancreatic, endocrine, bladder, and kidney cancer (Birkeland et al. 1995; Pham et al. 1995). The presence of lymphocytes within a tumor correlates with increased patient survival. For example, in primary cutaneous melanoma there are three categories of tumor-infiltrating lymphocytes (TILs): brisk, nonbrisk, and absent. Figure 4.2 demonstrates the histopathology of a primary cutaneous melanoma with brisk TILs defined as lymphocytes forming a continuous band beneath the tumor or diffusely distributed throughout its substance. Several studies have shown that patients with brisk TILs have a better prognosis and survive longer than patients with absent TILs (Azimi et al. 2012; Burton et al. 2011; Clark et al. 1989; Clemente et al. 1996; Tuthill et al. 2002; Venna et al. 2013). Similar positive correlations between TILs and patient survival are seen in breast, bladder, colon, prostate, ovarian, rectal, and neuroblastoma cancers.

Equilibrium, or immune-mediated tumor dormancy, refers to the immune response controlling the expansion of fully transformed tumor cells (Schreiber et al. 2011; Teng et al. 2008) (Fig. 4.1). Equilibrium can be demonstrated in mouse models, in which chemically induced sarcomas that are maintained in equilibrium in wild-type mice grow when transplanted into immunodeficient mice, but tumors from immunodeficient mice are rejected by naïve, wild-type mice. In mouse models of chemical carcinogenesis, ultraviolet radiation, and spontaneous melanoma, the

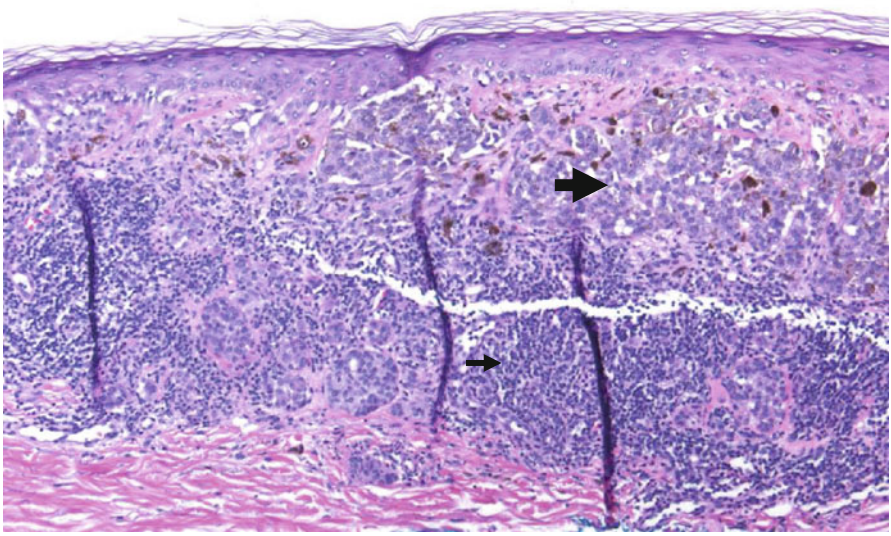

Fig. 4.2 Tumor-infiltrating lymphocytes in a malignant melanoma. Punch biopsy specimen of a cutaneous malignant melanoma demonstrating epidermal and dermal nests of melanoma cells (*large arrow*) and the presence of brisk tumor-infiltrating lymphocytes forming a band at the base of the tumor (*small arrow*) (hematoxylin-eosin stain; 100× magnification) (Photo courtesy of Christine J. Ko, M.D., Yale University)

adaptive immune response (CD4+ and CD8+ T cells, IFN-γ, and IL-12), but not innate immunity, is responsible for equilibrium. Evidence also suggests that the immune system may play a role in the maintenance of equilibrium in humans, as some patients remain in remission despite the presence of circulating tumor cells and cancer recurrence in patients who have been in remission for several years is associated with immunosuppressive treatments. Escape refers to tumor cell variants that expand in an uncontrolled fashion and grow into clinically apparent tumors (Fig. 4.1). Immune escape may be mediated by changes in the tumor cells in response to selective pressure from the immune response and/or by the tumor cells inducing immunosuppression. Loss of tumor antigen presentation, through selective loss of tumor antigen, MHC class I, or antigen-processing machinery, is the most well-characterized escape mechanism. In addition, tumor cells promote immunosuppressive leukocyte populations including myeloid-derived suppressor cells (MDSCs) and regulatory T (Treg) cells (discussed below). Taken together, this evidence demonstrates a role for the immune response in preventing and controlling tumor growth and in selecting tumor cells variants with decreased immunogenicity for escape.

4.2 Innate Immune Responses to Cancer

The innate immune response represents the first line of defense against cancer and infection. Cells of the innate immune response recognize patterns as opposed to the antigen-specific immune responses of adaptive immunity. Innate immunity has the

ability to recognize tumors and contributes to immunosurveillance and destruction of tumors. In the first step of the elimination process, tumors begin to require increased blood supply, and invasive growth induces inflammatory signals that lead to the recruitment of cells of the innate immune response including NK cells, γδ T cells, macrophages, and dendritic cells (DCs) (Fig. 4.1). NK cells and γδ T cells secrete IFN-γ and are able to kill tumor cells. In the next phase of the elimination process, IFN-γ induces a limited amount of tumor death through antiproliferative and proapoptotic mechanisms and induces the production of chemokines and adhesion molecule expression resulting in enhanced leukocyte infiltration and tumor killing. DCs which have ingested tumor cell debris travel to the draining lymph node to stimulate naive, tumor-specific CD4+ and CD8+ T lymphocytes. In the final stage of elimination, activated, tumor-specific T cells home to the tumor site secrete IFN-γ and destroy tumor cells.

4.2.1 Natural Killer Cells

NK cells destroy malignantly transformed cells but usually do not damage healthy cells (Vivier et al. 2011, 2012). NK cells distinguish dangerous targets from normal cells using a combination of inhibitory and activating receptors. The inhibitory receptors share the presence of immunoreceptor tyrosine-based inhibition motifs (ITIMs) in their cytoplasmic tails. Upon engagement of the receptor, the ITIM is phosphorylated and recruits phosphatases such as SHP-1, SHP-2, or SHIP which counteract the effect of kinases in the signaling pathway initiated by activating receptors. Activating receptors lack ITIMs in their cytoplasmic tail and are generally associated with CD3ζ, FcRγ, or DAP12, which bear immunoreceptor tyrosine-based activation motifs (ITAMs) on their cytoplasmic tails. The balance of signals from inhibitory and activating receptors determines NK cell activation and target cell killing. Similar to CD8+ T cells, NK cells kill target cells using granzymes, perforin, CD95L (FasL), and TNF-related apoptosis-inducing ligand (TRAIL). NK cells also express the low-affinity Fc receptor for IgG (CD16) which enables NK cells to kill target cells coated with IgG via antibody-dependent cell-mediated cytotoxicity.

Human NK cell major histocompatibility complex (MHC) class I-specific inhibitory receptors include members of at least three families: killer cell immunoglobulin-like receptor (KIR), leukocyte immunoglobulin-like receptors (LILR) (also known as LIR, ILT, and CD85), and CD94/NKG2 families (Vivier et al. 2011, 2012). Yet each of these families has some members which can serve as activating receptors. The polymorphic KIR family recognizes different alleles of MHC class I molecules HLA-A, HLA-B, and HLA-C. KIRs bind both the MHC class I molecule and its bound peptide. Some KIRs have short cytoplasmic tails without ITIMs. These activating KIRs either do not bind MHC class I or bind with much lower affinity. The LILR family recognizes many MHC class I alleles. LILRB1 is an inhibitory receptor with four ITIMs in its cytoplasmic tail and is variably expressed on NK cells and a subset of T cells and highly expressed on B cells and monocytes. LILRB1 binds with low affinity to a conserved region of the α3 domain of essentially all MHC

class I alleles (HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G). The CD94/natural killer group 2 (NKG2) family of receptors consists of a disulfide-linked heterodimer of C-type lectin NKG2 with CD94. The most well-characterized receptors are the CD94/NKG2A inhibitory receptor and the CD94/NKG2C-activating receptor. NKG2A has an ITIM in its cytoplasmic domain. In contrast, NKG2C/CD94 acts as an activating receptor and associates with the DAP12 adapter protein for stable cell surface expression and signaling. CD94/NKG2 receptors are expressed on most NK cells and γδ T cells and a subset of CD8+ T cells. Both CD94/NKG2A and CD94/NKG2C bind HLA-E, a nonclassical MHC class I molecule. Since stable surface expression of HLA-E requires peptide binding and the most abundant peptides bound to HLA-E are the signal peptides from HLA-A, HLA-B, HLA-C, or HLA-G, the CD94/NKG2 receptors monitor the presence of classical (HLA-A, HLA-B, HLA-C) and nonclassical (HLA-E, HLA-G) MHC class I molecules. MHC class I molecules are constitutively expressed on essentially all nucleated cells. Thus, inhibitory receptors grant NK cells the capacity to attack cells that have lost or downregulated MHC class I expression. Tumor cells frequently have lowered or absent MHC class I expression possibly due to selective pressure to escape lysis by CD8+ T cells.

NKG2D, NKp46, NKp44, and NKp30 are activating receptors that recognize self-ligands that are poorly expressed on normal cells and are upregulated on cancer and infected cells (Vivier et al. 2011, 2012). The NKG2D receptor is encoded by a single, non-polymorphic gene. The name is a misleading because the *NKG2D* gene has very little homology to the *NKGA, NKGC, NKGE*, and *NKGF* genes, and the NKG2D protein does not form dimers with CD94. NKG2D is expressed as a disulfide-linked homodimer on the surface of all NK cells, all CD8+ T cells, and most γδ T cells. Stimulation of NK cells through NKG2D triggers cell-mediated cytotoxicity and in some cases cytokine secretion. NKG2D binds molecules with structural homology to MHC class I: MHC class I chain-related A (MICA), MICB, and UL16-binding proteins (ULBP1, also called Raet1), ULBP2, ULBP3, and ULBP4. MIC and ULBP proteins are expressed in response to activation of the DNA damage response and are found on tumor cell lines, precancerous cells, cancer cells, and cells infected by some viruses. However, tumors have ways to evade NKG2D-mediated detection. Although tumors frequently express NKG2D ligands, some tumors secrete these ligands. Secreted ligands can serve as decoys to subvert NK cell and T cell immune responses. For example, soluble MICA and ULBP proteins have been detected in the sera of cancer patients, and these individuals have significantly decreased levels of NKG2D expression and impaired activation of NK and T cells. In addition, transforming growth factor (TGF)-β, which is frequently produced by tumors, downregulates expression of NKG2D on lymphocytes (see below). While it is known that NKp46, NKp44, and NKp30 are important in NK cell activation, the ligands for this family of receptors on tumor cells are poorly understood. B7-H6, a member of the B7 immunoreceptor family, was recently identified as a ligand for NKp30 (Brandt et al. 2009; Li et al. 2011). B7-H6 is absent from normal cells but is present on tumor cells and capable of inducing NK cell activation and cytotoxicity.

4.2.2 Gamma Delta T Cells

The majority of T cells express a TCR composed of an α- and β-chain. A subset of T cells, 2–5 % of peripheral blood T cells, express a TCR composed of a γ and δ chain (Kabelitz et al. 2007; Morita et al. 2007). These γδ T cells have similar effector functions to T cells expressing αβ TCRs, such as cytokine secretion (tumor necrosis factor (TNF)-α and IFN-γ) and cytotoxic activity. However, these cells recognize a distinct subset of ligands and may play a role in tumor immunosurveillance and destruction.

γδ T cells bearing the variable region gene Vδ1 can exhibit antitumor activity through recognition of MICA, MICB, and ULBPs via the NKG2D receptor. There is also evidence that the Vδ1 TCR can directly bind MICA (Wu et al. 2002; Zhao et al. 2006). MICA and MICB are not usually expressed on normal tissue. The intestinal epithelium is an exception, presumably due to constant microbe exposure. Expression of MICA and MICB corresponds with increased frequencies of Vδ1 T cells at this site. Similarly, MICA and MICB expression has been identified in lung, breast, renal cell, ovarian, prostate, and colon carcinoma and corresponds to an increased frequency of Vδ1 T cells relative to all γδ T cells (Groh et al. 1999). Vδ1 T cell clones, including those derived from tumors, recognize MICA and MICB on both autologous and allogeneic tumor cells. Vδ1 T cells are increased in chronic lymphocytic leukemia of B cell type (B-CLL) patients with low-risk stage compared to high-risk stage and healthy donors (Poggi et al. 2004). Vδ1 cells produce TNF-α or IFN-γ in response to autologous B-CLL cells but not normal lymphocytes. Incidentally, patients with high numbers of Vδ1 T cells and detectable or inducible ULBP have a better prognosis. Vδ1 T cells have also been shown to have anti-melanoma activity (Lozupone et al. 2004). In addition to antitumor activity, recent work in breast cancers has identified a large number of tumor-infiltrating Vδ1 T cells with suppressive activity mediated through soluble factors other than TGF-β or interleukin (IL)-10 (Peng et al. 2007).

γδ T cells bearing the variable region gene Vδ2 recognize non-peptidic phosphorylated isoprenoid pathway metabolites referred to as phosphoantigens (Bonneville and Scotet 2006; Morita et al. 2007). The population of Vγ2Vδ2 (also called Vγ9Vδ2) T cells makes up the largest proportion of peripheral blood γδ T cells. The most potent Vγ2Vδ2 antigens, such as hydroxy-methyl-butyl-pyrophosphate (HMBPP), are produced through the 1-deoxy-D-xylulose-5-phosphate pathway found in microorganisms (Begley et al. 2004; Jomaa et al. 1999). In contrast, eukaryotic cells use the mevalonate pathway for isoprenoid biosynthesis and produce isopentenyl pyrophosphate (IPP) which activates Vγ2Vδ2 T cells but only at supraphysiologic concentrations. Unlike peptide antigens recognized by γδ T cells, recognition of phosphoantigens does not require antigen uptake and intracellular antigen processing. Phosphoantigen activation of Vγ2Vδ2T cells requires cell-cell contact, and the phosphoantigen does not bind directly to the γδ TCR (Lang et al. 1995; Morita et al. 1995), suggesting the presence of an antigen-presenting molecule. MHC class I, MHC class II, or CD1 molecules are not required, and F1 ATPase has been shown to bind phosphoantigen and promote γδ T cell

activation (Mookerjee-Basu et al. 2010; Morita et al. 1995). Vγ2Vδ2 T cells recognize phosphoantigens via the TCR, but their activity can be modulated via activating receptors such as NKG2D and NKp44 and inhibitory receptors including CD94/NKG2A and KIRs. Therefore, Vγ2Vδ2 T cells, like NK cells, can recognize tumor cells that have upregulated MICA/B and ULBPs or have downregulated MHC class I. In addition, Vγ2Vδ2 T cells are reported to present peptide antigens in the context MHC class II for the stimulation of CD4+ αβ T cells (Brandes et al. 2005).

Vγ2Vδ2 T cells are likely to be important in the antitumor immune response. Vγ2Vδ2 T cells are increased in patients with hematopoietic and solid tumors (Bonneville and Scotet 2006). Some patients with lymphoid malignancies have dramatic expansions of γδ T cells in the peripheral blood (McClanahan et al. 1999). In vitro human Vγ2Vδ2 T cells show broad tumor cytotoxicity including bladder cancer (Kato et al. 2001), breast cancer (Guo et al. 2005), colon carcinoma (Corvaisier et al. 2005), B cell lymphoma (Fisch et al. 1997; Sicard et al. 2001), melanoma (Kabelitz et al. 2004), myeloma (Kunzmann et al. 2000; Mariani et al. 2005; von Lilienfeld-Toal et al. 2006), nasopharyngeal carcinoma (Zheng et al. 2001), neuroblastoma (Otto et al. 2005), pancreatic adenocarcinoma (Kabelitz et al. 2004), prostate cancer (Liu et al. 2005), renal cell carcinoma (Kobayashi et al. 2001; Viey et al. 2005), and small cell lung cancer (Sato et al. 2005b) and are not limited by MHC restriction like γδ T cells. Human Vγ2Vδ2 T cells transferred into severe combined immunodeficiency (SCID) mice have antitumor activity against B cell lymphoma (Malkovska et al. 1992), nasopharyngeal carcinomas (Zheng et al. 2001), pancreatic adenocarcinoma (Kabelitz et al. 2004), melanoma (Kabelitz et al. 2004; Lozupone et al. 2004), and neuroblastoma (Otto et al. 2005). γδ T cells have the ability to lyse a wide variety of tumors due to recognition of ligands by NK-activating receptors such as NKG2D (Das et al. 2001). Vγ2Vδ2 T cells can recognize some malignant B cells, such as a B cell lymphoma line and plasmacytoma line, directly via the TCR (Bukowski et al. 1995; Fisch et al. 1990; Selin et al. 1992). Of interest, some tumors overexpress hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase. Endogenous or induced overexpression of HMG-CoA reductase or treatment with farnesyl pyrophosphate synthase inhibitors leads to accumulation of isoprenoid pathway metabolites such as IPP which can be detected by Vγ2Vδ2 T cells (Gober et al. 2003). Both pathways likely contribute to T cell activation and tumor cell lysis, as shown by Vγ2Vδ2 T cell recognition of colon carcinoma that is dependent on both the TCR and NKG2D (Corvaisier et al. 2005). The ability of γδ T cells to recognize a broad range of tumors without MHC restriction and without reactivity to non-transformed cells makes them candidates for the prevention and treatment of cancer.

4.2.3 Phagocytes

4.2.3.1 Dendritic Cells

Dendritic cells (DCs) reside in the tissues and play a key role in initiating and controlling the magnitude and quality of the adaptive immune response (Palucka and Banchereau 2012; Ueno et al. 2007). Immature DCs act as sentinels for potentially

dangerous signals from cancer cells or microbes and have strong phagocytic antigen-capturing abilities. Upon receiving maturation stimuli, immature DCs lose adhesion molecule expression, undergo cytoskeleton reorganization, and migrate to the draining lymph node. In the maturation process, they lose their endocytic and phagocytic receptors and, in turn, become adept at processing previously captured antigens and presenting these antigens in the context of MHC molecules for the stimulation of naive T cells. Mature DCs are professional antigen-presenting cells and have increased MHC class II and costimulatory molecule expression on their cell surface. In addition, mature DCs acquire the expression of the chemokine receptor CCR7 which allows them to migrate to the T cell zones of the draining lymph nodes.

The innate immune response detects microbes using pattern recognition receptors that are germline encoded to recognize a limited number of microbial patterns. These receptors include Toll-like receptors (TLRs), cell surface C-type lectin receptors, and intracytoplasmic nucleotide oligomerization domain (NOD)-like receptors. Microbes directly activate DCs through their pattern recognition receptors. There is evidence the DCs can also be activated by products of dying cells, the tissue microenvironment, and innate immune cells. Mature DCs can assume a range of phenotypes depending upon the particular set of activating signals present in the microenvironment. Distinct DC phenotypes are capable of stimulating different subsets of immune cells ultimately shaping the type of immune response that is initiated. Thus, DCs have a critical function in the activation of the adaptive immune response by bridging the gap between innate and adaptive immunity.

DCs can play a role in immune evasion (Palucka and Banchereau 2012). DCs are important in generating peripheral tolerance. Immature DCs are believed to continuously present self-antigens sampled from the environment. Engagement of the TCR on an autoreactive T cell in the absence of costimulation results in anergy or deletion of the autoreactive cell. However, tumor antigens that are presented by immature DCs, that have not been activated, will result in anergy or deletion of tumor-specific T cells. In addition, tumors have a number of mechanisms to block DC differentiation and maturation. STAT3 is constitutively activated in a diverse group of hematologic and epithelial cancers inhibiting tumor production of proinflammatory cytokines and promoting release of soluble factors that inhibit DC function. Cytokines in the tumor microenvironment such as IL-10 interfere with DC maturation and yield tolerogenic DCs that induce tumor-specific anergy. Growth factors in the tumor microenvironment such as vascular endothelial growth factor (VEGF) also inhibit DC maturation. Tumor antigens such as MUC-1 evade efficient MHC class II-restricted processing in DCs and block DC secretion of IL-12 skewing the CD4+ helper T (Th) cell response to the Th2 subset (see below).

4.2.3.2 Macrophages

Tumor-associated macrophages are derived from peripheral blood monocytes and can comprise up to 50 % of the tumor mass (Knowles and Harris 2007). Classically activated M1 macrophages, in response to IFN-γ and microbes, have strong antigen processing and presenting capability and cytotoxic activity and secrete high levels

of the proinflammatory cytokines IL-12 and IL-23 (discussed below) (Hao et al. 2012). Macrophages are capable of killing tumor cells in the same ways that they kill microbes including the release of lysosomal enzymes, nitric oxide (NO), and reactive oxygen species (ROS). Activated macrophages also secrete TNF, which as the name implies, has antitumor activities (discussed below). Alternatively, activated M2 macrophages promote tumor growth and metastasis. They promote angiogenesis, matrix remodeling, and suppression of effective adaptive immunity. Furthermore, they lack tumor cell lytic ability and have poor antigen processing and presenting capability. M2 macrophages secrete matrix metalloproteinases (MMPs), some of which are induced by the hypoxic tumor environment, that digest the tumor extracellular matrix and facilitate endothelial cell migration. The M2 phenotype is promoted by secretion of prostaglandin E_2, TGF-β (discussed below), IL-4, IL-6, and IL-10 within the tumor microenvironment. Overactivation of STAT3 can also contribute to the macrophage's immunosuppressive phenotype. Therefore, M1 macrophages are generally thought to offer tumor protection while M2 macrophages are considered to promote tumor progression.

The prognostic benefit of tumor-associated macrophages in human tumors has been controversial. In many cancers, a high number of tumor-associated macrophages correlate with poor prognosis (Hao et al. 2012). In a study of patients with HPV-induced cervical neoplasia, high numbers of infiltrating macrophages correlated with disease progression (Hammes et al. 2007). Similarly, high numbers of IL-10+ macrophages are associated with poor survival in lung cancer patients (Zeni et al. 2007). However, some studies have shown a beneficial effect of tumor-associated macrophages. Increased numbers of tumor-associated macrophages correlate with enhanced tumor cell apoptosis and improved disease-free survival in gastric and esophageal cancer (Ohno et al. 2003). One potential reason for this discrepancy is that many human studies do not differentiate between M1 and M2 polarization in the tumor-associated macrophage infiltrate. In a study of non-small cell lung cancer patients where tumor-associated macrophage polarization was analyzed, a high M1/M2 macrophage ratio in malignant tissue was associated with improved survival (Ohri et al. 2009). Thus, it is important to assess both the number and type of macrophage population within the tumor microenvironment.

4.2.3.3 Myeloid-Derived Suppressor Cells

MDSCs are a heterogeneous population of immature myeloid cells with an immunosuppressive phenotype that expands in both tumor-bearing animals and cancer patients (Gabrilovich and Nagaraj 2009). Under normal conditions, immature myeloid cells differentiate into mature granulocytes, macrophages, or DCs. However, during certain disease states including cancer, the differentiation of immature myeloid cells is suppressed leading to an increased population of immature myeloid cells. In humans, MDSCs are usually identified based upon the expression of CD11b and CD33 and a lack of CD14 and other markers of more mature myeloid and lymphoid cells.

A number of soluble factors secreted by tumor cells have been shown to induce the expansion of MDSCs in both tumor-bearing mice and humans including prostaglandins, stem cell factor (SCF), macrophage colony-stimulating factor,

granulocyte-macrophage colony-stimulating factor (GM-CSF), VEGF, and IL-6 (Gabrilovich and Nagaraj 2009). Most of these tumor-derived factors induce signaling pathways that involve the transcription factor STAT3 which is considered the primary transcription factor controlling MDSC expansion. MDSCs also require activation signals in order to attain their full suppressive phenotype. These signals are provided by T cells and stromal cells in the tumor microenvironment and include IFN-γ, IL-4, IL-13, TGF-β, and certain Toll-like receptor ligands.

The tumor-promoting effects of MDSCs are mediated primarily by their ability to suppress T cell-mediated immunity through several mechanisms that require direct cell-cell contact (Gabrilovich and Nagaraj 2009). MDSCs express high levels of the enzymes inducible nitric oxide synthase (iNOS) and arginase 1. iNOS generates NO which suppresses T cell function by disruption of JAK3/STAT5 signaling, inhibition of MHC class II expression on antigen-presenting cells, and the induction of T cell apoptosis. Arginase 1 mediates the catabolism of L-arginine which is an essential amino acid required for T cell proliferation. The increased activity of arginase 1 in MDSCs creates a shortage of L-arginine in the tumor microenvironment that suppresses T cell proliferation. MDSCs also produce ROS that inhibit T cell proliferation and function. In addition, MDSCs have been shown to induce the expansion of Treg cells. Furthermore, MDSCs contribute to tumor growth and progression through nonimmunological mechanisms including the promotion of tumor angiogenesis and metastasis.

Evidence from animal and human studies has demonstrated that MDSC levels can be used as a prognostic marker in a number of cancer types. Increased numbers of MDSCs have been shown to correlate with tumor growth, clinical stage, and progression in non-Hodgkin lymphoma, breast, colorectal, pancreatic, gastric, and esophageal cancer patients (Diaz-Montero et al. 2009; Gabitass et al. 2011; Solito et al. 2011). Elevated MDSC numbers are associated with diminished overall survival in patients with breast and various gastrointestinal cancers (Gabitass et al. 2011; Solito et al. 2011). Furthermore, MDSC levels may also be an important biomarker in patients undergoing immunotherapy as low circulating numbers of MDSCs were able to distinguish responders from nonresponders in a cohort of kidney cancer and melanoma patients undergoing IL-2 immunotherapy (Finkelstein et al. 2010).

4.2.4 Cytokines

Cytokines are polypeptides that are produced in response to microbes and other antigens, such as tumor antigens, and regulate inflammatory and immune reactions. Cytokine secretion is a brief, self-limited event, and cytokines exert their function by binding cytokine receptors on target cells and altering gene expression. The majority of cytokines act locally in an autocrine or paracrine fashion. However, some cytokines may be produced in large amounts, enter the bloodstream, and have systemic or endocrine effects, such as TNF in gram-negative bacterial sepsis. Cytokines may be divided into those that are produced by cells of the innate

immune response, such as DCs and macrophages, and those that are produced by cells of the adaptive immune response, namely, T lymphocytes. TNF, type I IFNs, and IL-12 are key cytokines that mediate and control the innate immune response. Key cytokines that regulate the adaptive immune response include IL-2, IL-15, IL-17, IFN-γ, and TGF-β and will be discussed in the following section on the adaptive immune response.

4.2.4.1 Tumor Necrosis Factor (TNF)

TNF, also called TNF-α, is primarily produced by macrophages that have been activated by TLR engagement (Balkwill 2009). TNF enhances leukocyte homing to sites of inflammation by inducing vascular endothelial cell expression of adhesion molecules that are responsible for leukocyte homing, stimulating chemokine secretion by endothelial cells and macrophages that enhance the affinity of leukocyte integrins for their ligands and promote leukocyte homing and chemotaxis, and decreasing endothelial cell intercellular adhesion. TNF increases endothelial cell synthesis of NO and MMPs and increases surface thrombogenicity of endothelial cells. TNF also induces production of other cytokines (such as IL-1 and IL-6) by macrophages and activates macrophages and neutrophils to induce production of NO and ROS.

TNF can mediate selective destruction of tumor cells through two mechanisms (Balkwill 2009). TNF is capable of direct cytotoxicity. TNF binding to TNF receptor-1 (TNFR1) leads to the association of adaptor protein TNF receptor-associated death domain containing protein (TRADD) which ultimately leads to apoptosis through caspase activation. TNF may also disrupt tumor vasculature and is responsible for hemorrhagic necrosis of tumors. In animal models, the absence of TNF diminishes tumor rejection.

In contrast, TNF can promote cancer development and metastasis (Balkwill 2009). Association of TNFR1 with other adaptor proteins such as TNF receptor-associated factors (TRAFs) stimulates degradation of the inhibitor of NF-κB resulting in activation of NF-κB and promotion of cell survival. Chronic inflammation with persistent low-dose TNF results in an increase in positive cell cycle regulators (Ras, c-myc) and a decrease in cyclin-dependent kinase inhibitors. This pathway has been shown to be important in the progression of Barrett esophagus to mucosal dysplasia to esophageal adenocarcinoma. TNF is also involved in the pathogenesis of inflammatory bowel disease which can develop into colon cancer. In addition, TNF is implicated in hepatitis B- and C-associated chronic liver inflammation that can ultimately lead to hepatocellular carcinoma. Release of genotoxic substances, such as NO and ROS that are induced by TNF, into the environment can promote DNA damage. Chronic low doses of TNF promote angiogenesis required for tumor growth and production of MMPs which contribute to tumor invasion. In animal models, exogenous TNF or tumor-induced TNF produced by tumor-infiltrating macrophages promotes metastasis. Furthermore, in a murine model of spontaneous melanoma, TNF has been shown to promote immune escape by promoting the dedifferentiation of melanoma cells and downregulation of several melanoma-associated antigens (Landsberg et al. 2012).

The pleiotropic nature of TNF can be explained by the fact that TNF can stimulate multiple intracellular pathways that mediate opposing effects (Balkwill 2009; Mocellin and Nitti 2008). In addition, the effect of TNF on tumors depends on the tumor microenvironment: the degree of vascularization, the presence of an MMP family member which cleaves TNF, and the amount of NO produced by tumor endothelial cells. In general, chronic low doses of TNF favor angiogenesis and tumor development and progression, and single, high doses cause destruction of newly formed blood vessels and tumor regression. Clinical trials with TNF alone or as an adjuvant have not demonstrated a survival benefit.

4.2.4.2 Type I Interferons (IFNs)

A principal function of type I IFNs, including IFN-α and IFN-β, is to mediate the early innate immune response to viral infections through inducing the expression of proteins that inhibit viral replication (Rizza et al. 2011; Trinchieri 2010). In addition, type I IFNs stimulate a number of functions important for the recognition and destruction of cancer and infected cells. The major source of IFN-α is plasmacytoid DCs, and the most potent stimuli for type I IFN synthesis are viral nucleic acids which bind to cytoplasmic sensors, caspase activation and recruitment domain (CARD)-containing proteins called retinoic acid inducible gene-1 (RIG-1), or melanoma differentiation-associated gene 5 (MDA5). Macrophages are also a source of type I IFNs, and IFN production is stimulated through the interaction of CD40L on activated T cells with CD40 on macrophages. TLR ligation can also stimulate type I IFN production. IFN-β is produced by many cell types, including fibroblasts.

Type I IFNs promote innate and adaptive immune responses (Rizza et al. 2011; Trinchieri 2010). Type I IFNs serve as an important signal for differentiation and maturation of DCs for antigen presentation to CD4+ and CD8+ T cells. Despite their mature phenotype, DCs generated in the presence of IFN-α retain their ability to readily take up antigen from apoptotic tumor cells for cross-presentation on MHC class I to activate naïve tumor-specific CD8+ T cells (see below). Type I IFNs upregulate IFN-γ production by DCs and T cells favoring the differentiation of CD4+ T cells into the Th1 subset (see below). Type I IFNs promote the generation and activity of CD8+ T cells as well as enhance the lytic activity of activated CD8+ T cells for targets, including tumor cells. Type I IFNs promote the survival and proliferation of CD8+ and CD4+ T cells though expression of antiapoptotic genes and induction of IL-15 by antigen-presenting cells. Type I IFNs also increase the cytotoxicity of NK cells and promote the development of, activation of, and NO production in macrophages.

Type I IFNs also exert effects on tumor cells and infected cells to promote their destruction (Rizza et al. 2011; Trinchieri 2010). All IFNs increase the expression of MHC class I molecules and thus increase recognition of and killing by CD8+ T cells. This effect is important not only for destruction of virally infected cells but also for destruction of tumor cells. Type I IFNs have an antiproliferative effect inhibiting cell growth by targeting components of the cell cycle and are important in the suppression of cancer and infection. A distinct type I IFN-mediated pathway controls apoptosis exerting either anti- or proapoptotic effects depending on the state of cell differentiation.

IFN-α augments the immune response and can inhibit tumor cell proliferation, downregulate oncogene expression, induce tumor suppression genes, and increase MHC class I expression to improve immune recognition (Rizza et al. 2011; Trinchieri 2010). Tumor cells transfected with IFN-α are rejected more effectively. These antitumor effects of IFN-α are taken advantage of by using it as a cancer treatment. IFN-α is used clinically in the treatment of cutaneous T cell lymphoma, multiple myeloma, malignant melanoma, renal cell carcinoma, and HHV8-associated Kaposi sarcoma.

4.2.4.3 Interleukin 12 (IL-12)

IL-12 is a key inducer of the innate immune response and the adaptive immune response for defense against cancer and intracellular microbes (Lyakh et al. 2008). IL-12 is a heterodimer composed of p35 and p40 subunits and is produced primarily by activated DCs and macrophages. IL-12 induces the differentiation of naïve CD4+ T cells into Th1 cells (see below) and maintains Th1 responses which promote cell-mediated immunity. IL-12 stimulates production of IFN-γ from NK cells and T cells and enhances the cytotoxic functions of activated NKs cells and CD8+ T cells.

IL-12 production is initially induced during antigen-presenting cell maturation by TLR stimulation (Lyakh et al. 2008). However, additional signals are required to stimulate optimal IL-12 production by mature antigen-presenting cells. The Th1 cytokine IFN-γ has been shown to enhance the production of IL-12 by antigen-presenting cells, and this is thought to serve as a positive feedback mechanism during Th1 responses (see below). Additionally, T cells further enhance IL-12 production through a cell-cell contact mechanism involving the ligation of CD40 on the surface of mature DCs or macrophages with CD40L on the surface of activated T cells.

The antitumor effect of IL-12 depends on CD4+ and CD8+ T cells as well as a contribution from suppression of angiogenesis (Del Vecchio et al. 2007). Tumor cells transfected with IL-12 are rejected by CD8+ T cells and accompanied by macrophage infiltration, vascular damage, and necrosis. Treatment with IL-12 induces IFN-γ production within the tumor microenvironment, and IL-12's antitumor properties are dependent on the ability to induce IFN-γ expression and intact signaling through IFN-γ receptors (see below). Furthermore, recent studies in mice have demonstrated that IL-12 improves the ability of CD8+ T cells to eradicate melanoma tumors by enhancing the immunostimulatory capacity of dysfunctional antigen-presenting cells in the tumor stroma (Kerkar and Restifo 2012). Systemic delivery of IL-12 has remarkable efficacy not only in tumor prevention but in the treatment of well-established tumors in animal models. In light of IL-12's antitumor effect in preclinical studies, IL-12 has been investigated as a monotherapy or as an adjuvant. Clinical trials of systemic IL-12 for the treatment of cutaneous T cell lymphoma, acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma, and non-Hodgkin lymphoma have an objective response rate of 21–56 %. The efficacy is minimal in the remainder of the clinical trials using IL-12 for the treatment of other advanced solid tumors.

4.3 Adaptive Immune Response

4.3.1 Recognition of Tumor Antigens

A large number of tumor antigens recognized by T and B cells have been identified. Antibodies have tremendous diversity, specificity, and affinity for the antigens that they recognize. Antibodies can recognize proteins/peptides, nucleic acids, polysaccharides, lipids, and small chemicals. Antibodies can recognize conformational or linear epitopes, and antibodies can bind soluble or cell-associated antigens. The antigen specificity of antibodies generated by cancer patients has been determined using serologic analysis of recombinant complementary DNA expression (SEREX). In SEREX, the patient's tumor RNA is used to generate a complementary DNA (cDNA) expression library, and the patient's serum immunoglobulins are used to screen the library and determine the gene sequence and predicted protein product recognized.

The majority of T cells recognize linear peptides presented by cell surface major histocompatibility complex (MHC) class I or class II molecules. Epitopes recognized by T cells have been identified by cloning T cells derived from cancer patient's peripheral blood, tumor-draining lymph node, or TILs. A cDNA library is prepared from the tumor cells, pools of DNA from the library are transfected into syngeneic cells, and the T cell clones are tested for reactivity against the transfected cells. Smaller pools of DNA can be transfected until a single gene is identified. Similarly, synthetic peptide fragments can be used to isolate the T cell epitope. A comprehensive database of known T cell epitopes of tumor antigens is available at http://cancerimmunity.org/peptide/. In addition, a subset of T cells recognize lipid antigens presented via CD1 or phosphoantigens.

Nearly every nucleated cell including tumor cells expresses MHC class I and can present antigens derived from the cytoplasmic compartment for recognition and lysis by CD8+ T cells (Cresswell et al. 2005). The proteasome degrades cytosolic proteins, and the resulting peptides can be transported into the endoplasmic reticulum (ER) via the transporter associated with antigen processing (TAP). Assembly of MHC class I heavy chain with β_2-microglobulin (β_2M) and a cytosolically generated peptide occurs in the ER and is assisted by several chaperones. The MHC class I-β_2M-peptide complex is transported to the cell surface where it can be recognized by the TCR on CD8+ T lymphocytes. A tumor cell uses this classical MHC class I pathway to present its antigens to CD8+ T cells. However, naive CD8+ T cells must first be stimulated by a professional antigen-presenting cell and receive signals from costimulatory molecules and cytokines to become activated. Cross-presentation or cross-priming refers to the ability of professional antigen-presenting cells such as DCs to present material derived from the extracellular space, such as tumor cell debris, on MHC class I for the stimulation of naive CD8+ T cells. Phagocytosed proteins reach the cytoplasmic compartment, are degraded by the proteasome, translocated into the ER via TAP, and loaded onto MHC class I. Tumors can evade immune recognition through disrupting MHC class I-restricted antigen processing through loss of class I itself or components in the class I pathway (Algarra et al. 2004).

For example, some melanomas lose cell surface expression of MHC class I through defective expression of β_2M or TAP or expression of a splice variant of tapasin (Belicha-Villanueva et al. 2010; Wang et al. 1996).

MHC class II is expressed primarily by professional antigen-presenting cells, can be upregulated by IFN-γ on other cells types, and can be aberrantly expressed on some tumors such as melanoma, lung cancer, breast cancer, and osteosarcoma. The MHC class II pathway produces cell surface MHC class II-peptide complexes for the activation of CD4+ T lymphocytes (Neefjes et al. 2011). MHC class II αβ heterodimers are formed in the ER and associate with invariant chain (Ii). The C-terminal portion of Ii contains class II-associated Ii peptides (CLIP), which protects the MHC class II peptide binding groove from acquiring peptide in the ER like MHC class I, and the N-terminal cytoplasmic domain of Ii targets the MHC class II-Ii complex to endosomes and lysosomes. Exogenous proteins enter the endocytic pathway via pinocytosis, phagocytosis, and receptor-mediated endocytosis. Endogenous proteins normally located in the endocytic compartment are also presented on MHC class II. In the late endosomes and lysosomes, gamma-interferon-inducible lysosomal thiol reductase (GILT) reduces disulfide bonds of proteins in the endocytic compartment exposing additional epitopes for MHC class II binding (Hastings and Cresswell 2011). GILT is of particular importance to anti-melanoma immunity as GILT is required for efficient processing and presentation of the melanoma antigens tyrosinase (Haque et al. 2002) and tyrosinase-related protein 1 (Rausch et al. 2010). Proteases further breakdown protein antigens for presentation by MHC class II. The MHC class II-related molecule HLA-DM facilitates the exchange of CLIP for an antigenic peptide, and the MHC class II-peptide complexes are directed to the cell surface.

4.3.2 Tumor Antigens

Tumor antigens can be classified based upon their molecular structure and expression.

4.3.2.1 Tissue-Specific Differentiation Antigens

Tumor cells express lineage-specific differentiation antigens that are also expressed in the cells of origin (Abeloff 2008). For example, melanocyte differentiation antigens including tyrosinase, tyrosinase-related protein-1 and tyrosinase-related protein-2, gp100, and melan-A/MART-1 are expressed by both benign and malignant melanocytes. These melanoma antigens are melanosomal proteins involved in melanin biosynthesis and melanosome structure. Since these antigens are self-antigens also expressed in normal tissues, they tend to elicit tolerance. Overexpression in melanoma cells may contribute to the ability of the immune system to mount a response to these self-antigens. Melanoma patients generate CD4+ T lymphocytes, CD8+ T lymphocytes, and B cells specific for these antigens. Since these antigens are not essential for tumor growth or survival, immune responses to these tumor antigens exert selective pressure that results in the survival and outgrowth of tumor cells that have lost expression of tissue-specific differentiation antigens. This

mechanism of immune evasion is observed in melanomas through the loss of melanocyte differentiation antigen expression and escape from melanocyte differentiation antigen-specific CD8+ T cells (Trefzer et al. 2006).

Prostate-specific antigen (PSA) is an example of a tissue-specific differentiation antigen that is useful in cancer diagnosis. PSA is a serine protease expressed at a high level in luminal epithelial cells of the prostate and is absent or present at low levels in other tissues (Abeloff 2008). Expression is regulated by androgens. Serum levels increase with age and are higher in African-American men compared to Caucasian men. Serum levels of PSA are elevated in prostate cancer and can also be seen in benign prostatic hypertrophy. PSA levels along with digital rectal examination detect prostate cancer at very early stages; PSA levels are also helpful in management after diagnosis. Two MHC class I-restricted peptides from PSA have been shown to stimulate CTL activity.

Other examples of tissue-specific differentiation antigens are CD10 and CD20, which are expressed on B cell precursors, mature B cells, and B cell-derived lymphomas (Abeloff 2008). These cell surface antigens help identify the cell of origin and are useful targets in immunotherapy. Rituximab is an anti-CD20 monoclonal antibody approved for the treatment of non-Hodgkin lymphoma and other B cell malignancies. Although tissue-specific differentiation antigens are usually not tumor-specific, tumor-specific examples are the idiotypic determinants of the B cell receptor (immunoglobulin) and T cell receptor (TCR). Each B and T cell receptors has a unique antigen recognition site which is specific to that B or T cell clone.

4.3.2.2 Tumor Antigens Resulting from Mutations

Many tumors express mutated gene products that are required for malignant transformation or maintenance of the malignant phenotype. These antigens represent excellent targets for the immune response, because the mutated gene products are tumor-specific and therefore not subjected to immune tolerance. In addition, since many of these mutations are required for continued growth of the cancer, the cancer cells are not able to evade immune-mediated destruction through loss of these antigens.

Mutations in oncogenes essential for tumorigenesis are important tumor-specific targets of the immune response. The *Ras* proto-oncogene is a guanosine triphosphate (GTP)-binding protein with a low level of GTPase activity that is active when bound to GTP and inactive when bound to guanosine diphosphate (GDP) (Schubbert et al. 2007). Ras proteins are negatively regulated by GTPase-activating proteins (GAPs) which markedly increase the intrinsic GTPase activity. Ras-GTP regulates a signal transduction network resulting in increased transcription due to alterations in nuclear transcription factors. The most well-characterized Ras effector pathway is Raf-mitogen-activated and extracellular signal-regulated kinase (MEK)-extracellular signal-regulated kinase (ERK) cascade leading to formation of the activator protein 1 (AP1) transcription factor. Activating *Ras* mutations impair the intrinsic GTPase activity and response to GAPs, such that Ras accumulates in the active form. Activating *Ras* mutations are found in approximately 30 % of human cancers. The *Ras* family contains *KRAS*, *NRAS*, and *HRAS*. *KRAS* mutations are common in pancreatic, colorectal, endometrial, biliary tract, lung, and cervical

cancers. A mutated K-Ras peptide recognized by CD8+ T cells has been identified in pancreatic cancer (Gjertsen et al. 1997). *KRAS* and *NRAS* mutations are seen in myeloid malignancies. Mutated *NRAS* and *HRAS* are prevalent in melanoma and bladder cancer. A mutated N-Ras peptide is recognized by CD8+ T cells in melanoma (Linard et al. 2002).

BRAF a member of the *Raf* family of serine/threonine kinases has recently been described as an important target in melanoma immunity. The *Raf* family of kinases includes *ARAF*, *BRAF*, and *CRAF* and is involved in the RAS-RAF-MEK-ERK signaling pathway. *BRAF* is mutated in about 50 % of melanomas and CD4+ and CD8+ T cells specific for mutated B-Raf peptides have been found in melanoma patients (Sharkey et al. 2004; Somasundaram et al. 2006).

Chronic myelogenous leukemia (CML) is characterized by a balanced translocation between Abelson (*ABL*) proto-oncogene on chromosome 9 and breakpoint cluster region (*BCR*) on chromosome 22 (Abeloff 2008). The 210 kD chimeric protein product (p210) exhibits constitutive tyrosine kinase activity compared to the tightly regulated tyrosine kinase activity of the normal *ABL* product. The junctional region of the BCR-ABL chimeric protein represents a novel, CML-specific antigen that is recognized by both CD4+ and CD8+ T lymphocytes (Bosch et al. 1996; Makita et al. 2002; Yotnda et al. 1998).

Mutations in tumor suppressor genes also represent important tumor-specific antigens. The p53 tumor suppressor gene is mutated in approximately 60 % of cancers, and mutations of upstream or downstream signaling molecules are found in the remainder (Bourdon 2007). The p53 gene encodes nine different isoforms which function as transcription factors that stop cell cycle progression for DNA repair or promote apoptosis of damaged cells. It is interesting to note that 60 % of p53 mutations do not affect transcriptional activity, 15 % lead to completely inactive transactivation, and 25 % have differential transcriptional activity. CD4+ and CD8+ T cell epitopes have been identified from p53, but they do not involve mutations (Azuma et al. 2003; Fujita et al. 1998).

Tumor suppressor *CDKN2A* encodes two separate gene products, p16 and p14 alternate reading frame (ARF), which are both involved in negative regulation of cell cycle progression (Abeloff 2008). The p16 protein is a competitive inhibitor of cyclin-dependent kinase 4 (CDK4). CDK4 interacts with cyclin D and phosphorylates the retinoblastoma (Rb) protein which leads to S phase progression. *CDK2NA* mutations leading to loss of p16 function increase the probability that mutated DNA is not repaired prior to cell division. The p14ARF protein binds to MDM2 resulting in stabilization of p53 and G_1 arrest. Loss of p14ARF function leads to increased destruction of p53 and enhanced growth of mutated cells. p16 is mutated in 30–50 % of familial melanoma and 25–40 % of sporadic melanomas, and p16 mutations have been identified in other solid tumors and hematologic malignancies (Ruas and Peters 1998). A novel peptide epitope caused by a two base pair deletion in *CDK2NA* exon 2 is recognized by CD8+ T cells from a melanoma patient (Huang et al. 2004). Less frequent mutations in melanoma are observed in *CDK4*, and a mutated CDK4 peptide was identified as a tumor-specific antigen in melanoma recognized by CD8+ T cells (Wolfel et al. 1995). This mutation was found in two out of 28 melanomas tested.

The *wnt-1* proto-oncogene activates β-catenin signaling by reducing the rate of β-catenin degradation, whereas *adenomatous polyposis coli* (*APC*) tumor suppressor gene (mutated in colon cancer) enhances β-catenin degradation. A mutated β-catenin epitope that enhances stabilization is recognized by CD8+ T cells and present in tumors isolated from multiple melanoma patients (Rubinfeld et al. 1997). Mutations in genes that are not involved in tumorigenesis have also been identified. Multiple-mutated proteins have been identified in melanomas that are recognized by CD8+ T cells including *ARTC1*, *FN1*, *GPNMB*, *MART-2*, *MUM-1,2* and *3*, *neo-PAP*, *myosin*, *PRDX5*, *PTPRK*, *RBAF600*, *SIRT2*, and *SNRPD1* (Baurain et al. 2000; Chiari et al. 1999; Coulie et al. 1995; Kawakami et al. 2001; Lennerz et al. 2005; Novellino et al. 2003; Sensi et al. 2005; Topalian et al. 2002; Wang et al. 2002, 2005; Zorn and Hercend 1999).

4.3.2.3 Abnormally Expressed Cellular Proteins

Cancer/testis antigens, which are normally expressed in gametes and trophoblasts, are found in many types of cancer but not in normal somatic tissues (Nicholaou et al. 2006; Scanlan et al. 2002). Approximately 20 cancer/testis antigens or antigen families have been identified. In general, these antigens are not required for the malignant phenotype and are not mutated. Instead, they are distinguished by abnormal expression. They are expressed on a wide variety of cancers including bladder, breast, hepatocellular carcinoma, melanoma, multiple myeloma, neuroblastoma, non-small cell lung, ovarian, prostate, and thyroid. The X chromosome contains a disproportionately high number of the cancer/testis antigens. In fact, up to 10 % of the genes on the X chromosome are cancer/testis antigens. Expression of these antigens appears to be due to demethylation of the promoter regions and/or histone acetylation. The function of the majority of these antigens is not known. The first cancer/testis antigen was identified as an antigen recognized by patient-derived melanoma-specific CD8+ T cells and termed melanoma antigen-1 or MAGE-1. MAGE-1 was subsequently renamed as MAGE-A1 with the discovery of the MAGE-A and MAGE-B families each with at least 15 members. Cancer/testis antigen NY-ESO-1 was identified by SEREX from the serum of a patient with esophageal squamous cell carcinoma. LAGE-1, the second member of the NY-ESO-1 family with approximately 85 % amino acid sequence homology, was cloned by mRNA expression profiling. Cancer patients generate antibodies, CD8+ T cells, and CD4+ T cells specific for MAGE and NY-ESO-1 family members.

The proto-oncogene *ERBB2 (Her-2/neu)* encodes a transmembrane receptor tyrosine kinase (Abeloff 2008). *ERBB2* gene amplification or protein overexpression is found in 20–30 % of breast cancers and is the basis for treatment with trastuzumab, a humanized monoclonal antibody that blocks ERBB2 signaling. Multiple Her-2/neu MHC class I-binding epitopes recognized by CD8+ T cells have been identified (Fisk et al. 1995; Scardino et al. 2002).

4.3.2.4 Antigens of Oncogenic Viruses

Products of oncogenic viruses function as tumor-specific antigens and elicit T cell responses that help to eliminate tumor cells (Abeloff 2008). EBV-associated lymphomas, HPV-associated squamous cell carcinomas of the skin, HPV-associated

cervical and anogenital cancers, and HHV8-associated Kaposi sarcoma arise more frequently in immunosuppressed individuals such as allograft recipients on immunosuppressive therapy and patients with AIDS. HPV E6 and E7 proteins are expressed in infected cells, and they inactivate tumor suppressors p53 and pRB, respectively, contributing to carcinogenesis. The development of lymphoma in mice transgenic for the *EBNA-1* gene of EBV, requirement for EBNA-1 for the malignant phenotype of a Burkitt lymphoma cell line, and association of *EBNA-1* mutations with Burkitt lymphoma suggest that the EBNA-1 may contribute to lymphomagenesis.

4.3.2.5 Oncofetal Antigens

Oncofetal antigens are expressed in fetal development and cancer cells; however, they are present at lower levels in normal adult tissues and in nonneoplastic conditions. The two most characterized oncofetal antigens are carcinoembryonic antigen (CEA) and α-fetoprotein (AFP). CEA (CD66) is a highly glycosylated transmembrane protein that is a member of the immunoglobulin superfamily (Abeloff 2008). CEA functions as a homophilic intercellular adhesion molecule. CEA is normally expressed at high levels in the gastrointestinal tract, pancreas, and liver during the first 2–6 months of fetal development. CEA is expressed at low levels in normal adult colonic mucosa and the lactating breast. CEA expression and serum levels can be elevated in many epithelial-derived carcinomas including colon, pancreas, stomach, and breast. Although serum levels of CEA are not useful for the diagnosis of primary tumors, when serum levels of CEA are elevated initially, they are useful for monitoring tumor progression during treatment. CEA levels can be modestly elevated (usually less than 10 ng/ml) in smokers and patients with benign gastrointestinal and hepatic disorders (Loewenstein and Zamcheck 1978).

AFP is a circulating glycoprotein that is normally synthesized and secreted by the yolk sac and liver during fetal development (Abeloff 2008). AFP is the major serum protein in fetal development. In adults, it is replaced by albumin and only present at low levels in the serum. Elevated serum levels of AFP are found in patients with nonseminomatous germ cell tumors, hepatocellular carcinoma, and pregnant women due to fetal hepatic production. Lower level elevations sometimes accompany cirrhosis and hepatitis. An elevated serum AFP level is a useful indicator of advanced liver or germ cell tumors or of recurrence of these tumors after treatment. Furthermore, the detection of AFP in tissue sections by immunohistochemistry can aid the pathological diagnosis of unknown primary carcinoma.

4.3.2.6 Altered Glycolipid and Glycoprotein Antigens

Tumor cells often express higher levels or abnormal forms of surface glycoproteins and glycolipids such as mucins, including blood group-related markers, and gangliosides (Baldus et al. 2004). Mucins are high-molecular-weight glycoproteins with dense O-glycosylation expressed by epithelial tissues. MUC1 is normally expressed on the apical cell surface of glandular and ductal epithelia, including the mammary gland, pancreas, lung, and gastrointestinal tract. Tumor-associated MUC1 differs in the pattern of expression and glycosylation profile and, thus, has new carbohydrate and peptide epitopes that can be recognized by the adaptive immune response. Restriction to the apical surface is lost, and MUC1 is expressed at higher levels on the entire cell surface. Differences in O-linked

glycosylation are tissue specific. In general, the core glycans are shorter such that the peptide core is more exposed, and the degree of sialylation increases altering expression of blood group antigens. Membrane-bound MUC1 is involved in cell-cell adhesive and anti-adhesive functions. Adhesion may be mediated by oligosaccharide chains bound to the core protein or the core protein itself. For example, sialyated Lewis blood group antigen sialyl-Lewis x is recognized by members of the selectin family involved in leukocyte homing, and the core protein which is exposed on tumor cells binds to intercellular adhesion molecule (ICAM)-1. Overexpression of MUC1, as seen in tumor cells, can block cell-cell (such as E-cadherin homophilic interactions) and cell-matrix (such as integrin-extracellular matrix) interactions. All of these interactions may enhance the metastatic potential of tumor cells. MUC1 core protein-specific B cell, CD4+ T cell, and CD8+ T cell epitopes have been identified in cancer patients. Recent studies in mice have demonstrated that immune responses against MUC1 are dependent on its glycosylation status (Lakshminarayanan et al. 2012). Vaccination of mice with unglycosylated MUC1 peptides results in defective immune responses that fail to control tumor growth, and heavy glycosylation impairs MUC1 processing and presentation. Optimal immune responses against MUC1-expressing tumors are only observed when animals are vaccinated with aberrantly glycosylated MUC1 peptides. However, MUC1 also contributes to immune evasion. MUC1 can decrease susceptibility to NK cell and CD8+ T cell cytotoxicity. Tumor-associated MUC1 is unable to efficiently activate CD4+ T cells in vitro. In DCs, the mannose receptor traps MUC1 in early endosomes resulting in impaired trafficking to late endosomes where MHC class II antigen processing and loading occurs and results in a lower frequency of MUC-1-specific CD4+ T cells. In addition, MUC-1 inhibits the capacity of DCs to secrete IL-12 and thus skews CD4+ T cell differentiation to Th2 cells. MUC1 is shed from the surface and increased in the sera of cancer patients. Several mucins are used in cancer management, such as CA-125 (MUC16) in ovarian cancer and CA-19-9 in ovarian, gastrointestinal, and pancreatic cancers. Gangliosides GM2, GD2, and GD3 are glycolipids expressed at high levels in tumors such as melanoma, neuroblastoma, and breast cancer. Clinical trials exploring the use of ganglioside-specific monoclonal antibodies and immunization with ganglioside-containing vaccines are ongoing (Durrant et al. 2012).

4.3.3 T Lymphocytes

4.3.3.1 CD8+ Cytotoxic T Lymphocytes (CTLs)

CD8+ T cells are principal mediators of tumor killing (Arens and Schoenberger 2010). Tumor-specific CD8+ T cells can be isolated from cancer patients with established tumors. In the case of ovarian and colorectal cancer, CD8+ T lymphocytes have been identified as the lymphocyte population with the TILs that affect survival (Naito et al. 1998; Sato et al. 2005a; Zhang et al. 2003). CD8+ T cell activation requires signals from the TCR, costimulatory molecules, and a third signal provided by cytokines IL-12 or IFN-α (Arens and Schoenberger 2010). In the

absence of this third signal, CD8+ T cells weakly proliferate, fail to develop effector functions, and are tolerant long term. CD4+ Th cells stimulate DCs to effectively present antigen to CD8+ T cells along with costimulation and the appropriate cytokines. After becoming fully activated, CD8+ T cells develop activation-induced nonresponsiveness, an anergic state characterized by the inability to produce IL-2 needed for further expansion. Nearby antigen-activated CD4+ Th cells can produce IL-2 that can overcome the anergic state and lead to further expansion and development of memory cells. If IL-2 or other proliferative signals are not present, persistent antigen maintains the CD8+ T cells in the anergic state. CTL killing is antigen dependent via the TCR and requires cell-cell contact. Granules containing granzyme and perforin are released at the site of contact. Granzymes are serine proteases that can induce apoptosis in both a caspase-dependent manner and caspase-independent manner. Perforin forms pores within the plasma membrane of the target cell and facilitates the action of granzymes. CD8+ T cells can also induce apoptosis of target cells via membrane-bound death ligands CD95L (FasL) and TRAIL which activate death receptors CD95 (Fas) and TRAILR1 or TRAILR2 on the target cell.

4.3.3.2 CD4+ T Helper Lymphocytes

Given that the majority of tumors express MHC class I and that CD8+ T cells have cytotoxic capability, tumor immunology research initially focused on CD8+ T cells. However, it has become clear that CD4+ Th cells are critical for effective and durable antitumor immunity (Knutson and Disis 2005). Tumor-specific CD4+ Th cells are present in cancer patients. CD4+ Th cells are activated by TCR engagement by peptide-MHC class II complex and costimulatory molecules such as CD28 on the T cell interacting with CD80 (B7-1) or CD86 (B7-2) on activated antigen-presenting cells. CTLA-4, an inhibitory member of the CD28 family, has a higher affinity for B7-1 and B7-2, and engagement inhibits T cell activation. Th cell differentiation is regulated by the environment (cytokines, TCR stimulation, costimulatory molecules) present at the activation of CD4+ T cells. A number of different Th cell lineages have been described, but, in the context of cancer, the three major categories are Th1 cells, which produce IFN-γ and TNF; Th2 cells, which secrete IL-4, IL-5, and IL-13; and recently described Th17 cells which secrete IL-17.

4.3.3.3 Th1 Lymphocytes

Th1 cells are responsible for activating cell-mediated immunity and are especially adept at fighting cancer and intracellular organisms (Amsen et al. 2009). Th1 cells are also responsible for activating and regulating the development and persistence of CTL. They improve the antigen processing and presenting function of antigen-presenting cells, induce production of antibody isotypes that facilitate Fc receptor-mediated endocytosis, and activate the killing ability of macrophages through production of NO and ROS. Th1 differentiation depends on high antigen density on the antigen-presenting cell, high TCR avidity, and the presence of antigen-presenting cell-derived IL-12 during antigen presentation. Th1 lineage commitment is directed by the transcription factor T-bet which is induced by TCR engagement and activation of STAT1. T-bet enhances

IFN-γ production by binding to promoter and enhancer sequences in the IFN-γ gene, inhibits IL-4 production by binding to a silencer sequence in the IL-4 gene, and boosts sensitivity to IL-12 by promoting expression of the IL-12 receptor β chain.

4.3.3.4 Th2 Lymphocytes

In contrast, Th2 cells are required for optimal antibody production and effective elimination of extracellular pathogens particularly helminths but are not effective in antitumor activity (Amsen et al. 2009). Th2 differentiation is promoted by IL-4 and blocked by IL-12. Th2 lineage commitment is controlled by the transcription factor GATA-3. GATA-3 serves as a transactivator for the IL-4 gene and inhibits the expression of the IL-12 receptor β chain and STAT4, which is an important downstream mediator of IL-12 signaling.

4.3.3.5 Th17 Lymphocytes

Th17 cells are defined by the production of the cytokine IL-17 (Korn et al. 2009; Peters et al. 2011). In addition, Th17 cells produce IL-21 and IL-22. Th17 cells mediate the host response to extracellular microbes due to the ability of IL-17 to induce neutrophil recruitment (see below). Th17 cell differentiation requires a combination of TGF-β and IL-6. IL-23 also plays an important role in maintaining Th17 cell survival and function. Th17 lineage commitment is directed by the transcription factor RORγt.

Recent studies in mice and humans have identified an important role for Th17 cells in tumor immunity (Wilke et al. 2011). In a murine model of melanoma, melanoma-specific CD4+ T cells polarized in vitro toward a Th17 phenotype were more effective at eradicating large established tumors than Th1 polarized CD4+ T cells. In humans, increased Th17 cells levels at the tumor site correlate with improved survival in patients with ovarian and lung cancer. In addition, Th17 cell differentiation is associated with slower disease progression in prostate cancer patients. However, Th17 cells may also promote tumor development and progression in some situations. For example, Th17 cells promoted colitis and subsequent development of colonic tumors in a mouse model of spontaneous colon cancer. Furthermore, Th17 cells may facilitate tumor growth in certain murine tumor models due to the ability of IL-17 to stimulate angiogenesis (see below).

4.3.3.6 Regulatory T Cells

An advantage of the adaptive immune response is the extreme diversity and specificity of T and B cell receptors generated by recombination of receptor gene segments. However, the random process also creates T and B cell receptors that recognize self-antigens. Since tumors are derived from self, generating an effective antitumor response requires avoiding tolerance mechanisms, which delete or suppress the immune response to self-antigens. Central tolerance occurs in the thymus during T cell development. T cells that recognize self-antigens too strongly are negatively selected and deleted before exiting the thymus. Deletion of high-affinity self-reactive lymphocytes during development creates a peripheral repertoire that primarily recognizes nonself-antigens. However, autoreactive T cells that escape deletion in the thymus require mechanisms of peripheral tolerance, such as Treg

cells, which suppress the function of other immune effector cells through direct cell-cell contact or secretion of cytokines such as IL-10 and TGF-β (discussed below) (Byrne et al. 2011; Josefowicz et al. 2012). Treg cells were initially described by the expression of CD4 and CD25. However, CD25, the α-chain of the high-affinity IL-2 receptor, is expressed on activated effector T cells, and its expression does not necessarily correlate with a suppressive phenotype. A better marker of Treg differentiation is the nuclear transcription factor forkhead box P3 (FoxP3). In addition to being a specific marker of Treg cells, FoxP3 is also required for their development and maintenance.

Two populations of Treg cells exist: natural Treg cells which originate from the thymus and induced Treg cells which arise in the peripheral tissues (Byrne et al. 2011; Josefowicz et al. 2012). Studies in mice have revealed that CD4+ T cells with TCRs that bind peptide MHC complexes in the thymus with intermediate avidity preferentially develop into natural Treg cells. In contrast, induced Treg cells arise from effector CD4+ T cells that undergo defective stimulation in the periphery and acquire FoxP3 expression and an immunosuppressive phenotype. Peripheral induction of induced Treg cells occurs in the absence of costimulation or under conditions of suboptimal TCR stimulation including low antigen dose, low TCR affinity, and low TCR ligand density. MHC class II-expressing tumors, such as melanoma, may preferentially stimulate CD4+ induced Treg development given the absence of costimulatory molecule expression on tumor cells. In addition, the tumor itself and the tumor microenvironment, including DCs, induce the differentiation of Treg cells by various mechanisms such as TGF-β secretion and expression of B7-H1 (Curiel et al. 2003).

Treg cells may explain why tumors with intact antigen-processing machinery and displaying ample tumor antigens are not eradicated by the immune response. Elevated proportions of Treg cells in relationship to total CD4+ T cells have been identified in lung, breast, ovarian, and melanoma tumors (Ascierto et al. 2010; Erfani et al. 2012; Redjimi et al. 2012; Wang et al. 2012), and tumor-specific Treg cells have been described (Wang et al. 2004, 2005). For example, tumor antigen (LAGE1 and ARTC1)-specific Treg cells have been cloned from TILs in melanoma (Wang et al. 2004, 2005). Increased Treg cells in melanoma patients are associated with recurrence, tumor progression, inhibition of tumor-infiltrating T cell function, and death (Ascierto et al. 2010; Fujii et al. 2011; Miracco et al. 2007; Viguier et al. 2004). In ovarian cancer (Wolf et al. 2005), breast cancer (Yan et al. 2011), and hepatocellular carcinoma (Mathai et al. 2012), the presence of FoxP3+ Treg cells inversely correlates with clinical outcome. The frequency of Treg cells is increased in the peripheral blood of patients with CLL and decreases following treatment (Beyer et al. 2005).

Several Treg cell-depleting strategies have been developed to overcome immune suppression mediated by Treg cells (Byrne et al. 2011). Several anti-CD25 monoclonal antibodies including daclizumab and basiliximab have been developed that deplete Treg cells by depriving them of IL-2. Results from clinical trials have shown that daclizumab depletes Treg cell numbers and enhances T cell responses to tumor vaccines. Another Treg cell-depleting strategy involves the use of denileukin diftitox which is a recombinant fusion protein composed of a diphtheria toxin

fragment coupled to IL-2. Denileukin diftitox targets the cytocidal action of diphtheria toxin to cells expressing CD25. It is approved for the treatment of cutaneous T cell lymphoma and has been investigated in the treatment of several different types of cancer including melanoma and renal cell carcinoma where it has been shown to reduce Treg cell numbers However, the clinical benefit of denileukin diftitox thus far has been limited. Since CD25 is also expressed by activated effector T cells, targeting Treg cells with these agents may also deplete effector T cells required for tumor protection.

4.3.4 B Lymphocytes

Although not the dominant effector in the antitumor immune response, B cells generate tumor-specific antibodies, and tumor-specific antibodies have been identified in many cancers (Cassard et al. 2006). These antibodies can coat tumor cells and trigger tumor cell destruction by antibody-dependent cell-mediated cytotoxicity or by activating complement. In antibody-dependent cell-mediated cytotoxicity, antibody-coated target cells engage the Fc receptors on NK cells, macrophages, and neutrophils and trigger cytokine secretion and release of toxic granules which mediate killing. In complement-dependent cytotoxicity, the antibody-coated target activates the complement pathway and results in the formation of the membrane attack complex, which forms a pore in the target cell causing death. Antibodies also increase the afferent arm of adaptive immunity. Fc receptor engagement by antibody-coated targets mediates activation of phagocytes and improved efficacy of phagocytosis and antigen processing and presentation. The therapeutic efficacy of monoclonal antibodies, such as rituximab and trastuzumab (discussed above), supports a role for antibodies in antitumor defenses. In addition, induction of antibodies by vaccination can prevent infection by oncogenic viruses and, thus, prevent virally induced tumors (see below). Interestingly, in some mouse models B cells can inhibit the antitumor immune response through diminished IFN-γ production, which may result from IL-10 secretion by B cells (Inoue et al. 2006; Shah et al. 2005). IL-10 is a cytokine that downregulates immune responses by decreasing macrophage and DC production of IL-12 and thus decreasing IFN-γ production by NK cells and T cells. IL-10 also inhibits expression of costimulatory molecules and MHC class II expression on antigen-presenting cells.

Antibodies to tumor-associated antigens may also represent a powerful biomarker for the early detection of cancer. Current cancer diagnostic methods such as imaging and assays to detect tumor proteins in serum have limited ability to identify tumors during the earliest stages of development where they are often easiest to treat. Patients generate humoral immune responses to tumors months or even years before they receive a clinical diagnosis. Thus, antibodies in the serum of these patients can be used as a tool for early detection (Chapman et al. 2007). This approach has shown promise in the early detection of breast (Anderson et al. 2011a; Desmetz et al. 2009), ovarian (Anderson et al. 2010), lung (Pereira-Faca et al. 2007), and HPV-associated head and neck tumors (Anderson et al. 2011b).

4.3.5 Cytokines

4.3.5.1 Interleukin 2 (IL-2)

The principal function of IL-2 is to promote the growth, survival, and differentiation of T cells. IL-2 is produced by CD4+ T cells and can serve as an autocrine or paracrine growth factor (Waldmann 2006). The high-affinity IL-2 receptor (IL-2R) is made up of three subunits, namely, an α (CD25)-, β (CD122)-, and γ (CD132)-chain, and is expressed on antigen-activated T cells, Treg cells, and malignant cells of various B and T cell malignancies. Thus, IL-2 supports the survival, proliferation, differentiation of antigen-activated T cells as well as the survival and function of Treg cells. IL-2 also functions to generate peripheral tolerance through activation-induced cell death, a mechanism of eliminating self-reactive, peripheral T cells. IL-2 induces the proliferation of B cells and immunoglobulin synthesis. Furthermore, it stimulates the generation of CD8+ T cells and promotes the differentiation, proliferation, and activation of NK cells. The antitumor activity of IL-2 likely stems from stimulating the proliferation and activity of NK cells and CD8+ T cells.

Recombinant IL-2 (aldesleukin) is used in treatment of metastatic melanoma and metastatic renal cell carcinoma as well as some settings of acute myelogenous leukemia, non-Hodgkin lymphoma and cutaneous T cell lymphoma. In metastatic melanoma, IL-2 alone results in an objective response rate of five to 27 % and a complete response rate of zero to four percent (Petrella et al. 2007). When administered together with lymphokine-activated killer cells or TILs, the complete response rate is 11 or 20 %, respectively, with the possibility of achieving long-term responses (Petrella et al. 2007; Rosenberg 2012). Similar response rates are observed in the treatment of renal cell carcinoma (Klapper et al. 2008). Systemic use of IL-2 is limited by capillary leak syndrome and the ability of this cytokine to induce Treg cell expansion.

4.3.5.2 Interleukin 15 (IL-15)

The receptor for IL-15 shares the β- and γ-subunits with the IL-2R but has a unique α-subunit (Steel et al. 2012; Waldmann 2006). Therefore, these cytokines share several functions. Like IL-2, IL-15 stimulates the proliferation of T cells, induces the generation of CD8+ T cells, facilitates the proliferation of B cells and immunoglobulin synthesis, and induces the generation and survival of NK cells. In contrast to IL-2, IL-15 inhibits activation-induced cell death and does not support Treg cell survival or expansion. Unique to IL-15, it supports the survival of CD8+ memory T cells. IL-15 has the potential to be a better candidate than IL-2 for inhibiting tumor growth. In the presence of IL-2, CD8+ T cells might recognize the tumor antigen as self and undergo activation-induced cell death, or the antitumor immune response may be inhibited by IL-2-dependent Treg cells. In contrast, IL-15 has the ability to activate T cells and NK cells and has the advantage of inhibiting activation-induced cell death and promoting the persistence of CD8+ memory T cells. IL-15 can also stimulate IL-12 and TNF production by macrophages and costimulatory molecule expression and IFN-γ production by DCs. IL-15 is effective in preventing tumor growth and producing long-lasting cellular immunity in mouse models and is

currently being tested in several human clinical trials either alone or in combination with TILs.

4.3.5.3 Interleukin 17 (IL-17)

IL-17 is the principal cytokine produced by CD4+ Th17 cells and plays an important role in the immune response against extracellular bacterial and fungal pathogens (Iwakura et al. 2011). The IL-17 cytokine family consists of six structurally related family members (IL-17A–F) that appear to exhibit some degree of functional specialization that is not fully understood. Il-17A is the most fully characterized family member. In addition to Th17 cells, IL-17A is produced by CD8+ T cells and innate immune cells including γδ T cells and natural killer cells. IL-17 has several functions including the promotion of neutrophil migration, antibody production, and the secretion of the proinflammatory cytokines TNF and IL-1β. In addition, IL-17 and Th17 cells play a critical role in the pathogenesis of a number of autoimmune diseases.

IL-17 plays a complex role in cancer, exhibiting both anti- and pro-tumor effects (Iwakura et al. 2011). Studies in mice suggest that this cytokine may play an important role in antitumor immunity. For example, colon and melanoma tumor growth and metastasis is enhanced in IL-17A-deficient mice (Kryczek et al. 2009b; Martin-Orozco et al. 2009). IL-17-producing CD8+ T cells have been shown to control the growth of melanoma tumors in mice by recruiting T cells, neutrophils, and macrophages to the tumor (Garcia-Hernandez Mde et al. 2010). In addition, high levels of IL-17 in ascites from ovarian cancer patients are also associated with improved survival (Kryczek et al. 2009a). However, IL-17 has been shown to promote tumor growth by stimulating angiogenesis (Iwakura et al. 2011). In murine models IL-17 can stimulate the production of proangiogenic factors including VEGF and IL-8. In patients with hepatocellular, non-small cell lung, and gastric cancer, IL-17 expression within the tumor correlates with microvessel density and poor survival (Chen et al. 2010; Meng et al. 2012; Zhang et al. 2009). IL-17 is also associated with invasion and metastasis in non-small cell lung cancer in mice and humans (Li et al. 2012). Furthermore, IL-17 can promote the development of certain types of cancer that are associated with inflammation. In mouse models IL-17-stimulated colitis directly contributes to colon tumorigenesis (Wilke et al. 2011).

4.3.5.4 Interferon γ (IFN-γ)

IFN-γ, also called type II IFN, plays a critical role in augmenting both innate and adaptive immunity (Schroder et al. 2004). IFN-γ is produced by NK cells in response to IL-12 or by CD4+ Th1 cells and CD8+ T cells in response to antigen activation. IFN-γ activates macrophages to generate NO and ROS and improve killing of intracellular organisms. IFN-γ promotes the differentiation of naïve CD4+ T cells into Th1 cells generating effective cell-mediated immunity for attack of intracellular microbes and cancer cells. IFN-γ promotes Th1 differentiation by enhancing synthesis of IL-12 by antigen-presenting cells and blocking differentiation of Th2 cells by inhibiting production of IL-4. Similar to type I IFNs, IFN-γ enhances expression of MHC class I. IFN-γ also induces expression of proteasome subunits that make up

the immuno-proteasome in antigen-presenting cells, as well as TAP subunits further enhancing MHC class I-restricted processing and presenting and thus promoting recognition and killing of malignant or infected cells by CD8+ T cells. In addition, IFN-γ uniquely induces MHC class II expression on a wide variety of cell types via the class II transactivating (CIITA) factor. Together with increased MHC expression, IFN-γ increases costimulatory molecule expression enhancing antigen processing and T cell activation. IFN-γ promotes B cell class switching to complement fixing IgG subclasses and inhibits switching to IgE. IFN-γ promotes leukocyte trafficking to sites of inflammation and cancer by increasing the expression of adhesion molecules and chemokines involved in leukocyte homing.

IFN-γ promotes an antitumor immune response when expressed in the tumor microenvironment but has limited efficacy as a systemic agent (Tannenbaum and Hamilton 2000). Tumor cells transfected with IFN-γ have a poor capacity to form tumors and induce potent antitumor immunity. Systemic delivery of IL-12 causes a strong antitumor effect by inducing IFN-γ expression in the tumor microenvironment that cannot be achieved with systemic treatment using IFN-γ even at high doses. The antitumor response often depends on the tumor cells being responsive to IFN-γ. Indeed, under the selective pressure of the immune response as many as one third of human tumors have lost sensitivity to IFN-γ through loss of IFN-γ receptor chains, IFN-γ signaling pathway kinases, or transcription factors. Although IFN-γ can display proapoptotic and antiproliferative activity on tumor cells, its primary antitumor effect derives from its immunomodulatory properties discussed above.

4.3.5.5 Transforming Growth Factor β (TGF-β)

Whereas cytokines like IL-2 and IFN-γ promote the antitumor response, TGF-β is involved in negatively regulating immune responses and can be produced in the tumor microenvironment to contribute to immune evasion (Flavell et al. 2010). TGF-β is produced by a variety of cells including activated T cells, macrophages, DCs, NK cells, tumor cells, and some Treg cells. TGF-β maintains peripheral tolerance via regulation of lymphocyte proliferation, differentiation, and survival. It exerts an antiproliferative effect on T cells by inhibiting expression of T cell growth factor IL-2. In addition, TGF-β blocks expression of cell cycle-promoting factors, including c-myc, cyclin D2, cyclin E, and cyclin-dependent kinase 4 and upregulates cyclin-dependent kinase inhibitors. TGF-β promotes the differentiation of Th17 cells and decreases the differentiation of naïve CD4+ T cells into Th1 and Th2 cells as evidenced by decreased T-bet (Th1-specific transcription factor) and GATA-3 (Th2-specific transcription factor), respectively. TGF-β also inhibits the differentiation of CD8+ T cells via decreased T-bet expression and reduces the cytolytic function of CD8+ T cells through inhibition of perforin and FasL expression. TGF-β is also involved in the survival and differentiation of Treg cells which actively suppress immune responses and maintain immunologic tolerance. Studies from mice suggest that TGF-β may play a role in the maintenance of natural Treg cell survival in peripheral tissues. Furthermore, in the absence of proinflammatory cytokines, TGF-β promotes the differentiation of effector CD4+ T cells into induced

Treg cells. Interestingly, the involvement of TGF-β in the differentiation of both CD4+ Th17 and induced Treg cells suggests that an early developmental connection may exist between these two T cell lineages.

TGF-β's regulatory activity is modulated by the state of cell differentiation and the presence of inflammatory cytokines and costimulatory molecules. In the absence of CD28 costimulation, TGF-β inhibits TCR-stimulated proliferation of naïve T cells. Since tumor cells express MHC class I but tend to lack costimulatory molecules, TGF-β blunts the antitumor response. Conversely, in the presence of CD28 costimulation, TGF-β promotes T cell proliferation and inhibits apoptosis. In addition, TGF-β promotes the survival of effector memory T cells and inhibits Fas-induced T cell apoptosis through decreased c-myc expression and decreased levels of FasL. TGF-β blocks B cell activation and class switching, except for IgA, and induces apoptosis of naïve B cells.

TGF-β controls initiation and resolution of inflammatory responses through regulation of chemotaxis, activation, and survival of lymphocytes, NK cells, DCs, macrophages, and neutrophils (Flavell et al. 2010). TGF-β is a potent inhibitor of NK cell function by diminishing NK cell cytolytic activity and IFN-γ production and promoting NK cell homeostasis. TGF-β antagonizes IL-12-induced IFN-γ production that is essential to Th1 differentiation. TGF-β blocks the cytolytic function of NK cells by inhibiting expression of NKp30 and NKG2D receptors. TGF-β inhibits DC maturation and in the presence of TGF-β DCs has decreased MHC class II and costimulatory molecule cell surface expression. On the other hand, TGF-β is required for the differentiation and survival of Langerhans cells, resident DCs within the epidermis. TGF-β acts as a chemoattractant for monocytes, induces the expression of adhesion molecules such as LFA-1 on monocytes, and induces production of MMPs that facilitate transmigration. Once monocytes differentiate into tissue macrophages, TGF-β is mostly inhibitory. It downregulates scavenger receptors involved in phagocytosis, downregulates expression of FcγRI and FcγRIII which results in decreased phagocytosis of IgG-coated particles, decreases expression of inflammatory mediators (TNF-α and MMP-12) and chemokines (MIP-1α and MIP-2), downregulates production of NO and ROS, and blocks IFN-γ-induced expression of MHC class II via attenuation of CIITA.

Tumors that produce increased TGF-β or promote TGF-β production by surrounding cells advance tumor progression and allow immune evasion (Flavell et al. 2010; Li and Flavell 2008). In mouse models, overexpression of TGF-β suppresses the antitumor immune response, and inhibition of TGF-β expression is associated with decreased tumor growth. TGF-β's inhibition of the antitumor immune response is due to decreased NKG2D expression on NK and CD8+ T cell, decreased MICA expression on tumor cells, inhibition of CD8+ T cells, and induction of Treg differentiation. Elevated levels of TGF-β are associated with downmodulation of NKG2D surface expression on NK cells in lung and colorectal cancer patients (Lee et al. 2004). As discussed earlier, the frequency of TGF-β-induced Treg cells is increased in cancer patients and portends a poorer prognosis. Additionally, Smad3 protein, an intracellular transcription factor activated by phosphorylation by the TGF-β family of serine/threonine kinase receptors, is absent or reduced in several

cases of human T cell acute lymphoblastic leukemia suggesting the importance of TGF-β signaling in preventing lymphoproliferative disease.

4.4 Immunotherapy for Cancer Prevention

Much cancer immunotherapy research has focused on the difficult challenge of treating metastatic disease. To date, only one therapeutic tumor vaccine has shown an improvement in overall survival and received approval by the Food and Drug Administration (FDA). Provenge® (sipuleucel-T), which consists of an autologous infusion of a patient's own antigen-presenting cells loaded with the prostate cancer antigen prostatic acid phosphatase, demonstrated a 4.1 month improvement in overall survival in prostate cancer patients compared to a placebo (Kantoff et al. 2010). However, none of the patients in this trial achieved a complete response. Two separate reviews of patients with solid tumors treated with immunotherapy prior to 2010 including 936–1,306 patients revealed an overall objective response rate of 3.3–3.6 %, underscoring the important need for new strategies in immunotherapy (Klebanoff et al. 2011; Rosenberg et al. 2004). Analogous to the situation with infectious disease, it is immunologically more feasible to use vaccines to boost the immune response and prevent cancer than to use vaccines to treat advanced disease. Therefore, the prospect of developing of vaccines to prevent cancer is exciting. Tumors that have tumor-specific antigens shared by the vast majority of individuals with that tumor are candidates for preventive vaccines. Virally induced tumors are primary examples of tumors that may be prevented by vaccination.

HPV types 16 and 18 cause approximately 68 % of cervical squamous cell cancer and 83 % of cervical adenocarcinoma (Future II Study Group 2007; Lehtinen et al. 2012; Paavonen et al. 2009; Palefsky et al. 2011; Wheeler et al. 2012). A large percentage of anogenital cancers involving the anus, vulva, vagina, and penis and a smaller percentage of oral cavity and pharyngeal cancers are also attributable to HPV, especially HPV type 16. The quadrivalent (HPV types 6, 11, 16, and 18) and bivalent (HPV types 16 and 18) HPV vaccines were FDA-approved in 2006 and 2009, respectively, for the prevention cervical cancer and cervical cancer precursors in females aged 9–26 years. The quadrivalent vaccine is also indicated for prevention of vaginal, vulvar, and anal cancer precursors in women and prevention of anal cancer and genital warts in males 9–26 years of age. Both vaccines have been shown to prevent the development of precancerous lesions of the cervix, including HPV types 16 and 18, related cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3), and adenocarcinoma in situ. In addition, the quadrivalent vaccine has been demonstrated to prevent vulvar, vaginal, and anal intraepithelial neoplasia grade 2 or 3. There is evidence of cross-protective efficacy against CIN 2 or greater for non-vaccine HPV types. However, there is no evidence of cancer prevention or treatment of disease caused by HPV types for which the subject was positive prior to vaccination. It is currently unknown whether HPV vaccination results in prevention of HPV-related head and neck and cutaneous squamous cell carcinomas.

In addition, hepatitis B virus (HBV) vaccination has the potential to prevent HBV-related hepatocellular carcinoma. Since the introduction of the HBV vaccine in 1982, a comprehensive strategy to eliminate HBV transmission and prevent its consequences has been implemented in the USA. This strategy includes universal vaccination of neonates, routine screening of pregnant woman and postexposure prophylaxis for neonates, vaccination of children and adolescents not previously vaccinated, and vaccination of at risk adults (Mast et al. 2006). Approximately 50 % of hepatocellular carcinoma cases are associated with HBV, and the association is stronger in children, who are more likely to have chronic infection than adults. In Taiwan, the incidence of childhood hepatocellular carcinoma has significantly decreased since the institution of a universal HBV vaccination program (Chang et al. 1997). Since the incidence of hepatocellular carcinoma peaks in the sixth decade of life, it will take more than 40 years for the full impact of HBV vaccination on the prevention of hepatocellular carcinoma to be observed.

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Hereditary Risk for Cancer

5

Katherine S. Hunt, Jessica A. Ray, and Joanne M. Jeter

5.1 Introduction

Approximately 5–10 % of all cancers are thought to be due to an inherited predisposition or hereditary cancer syndrome. One hallmark of hereditary cancer is an unexpectedly early age of cancer diagnosis. Hereditary cancers may occur up to 20 years earlier than the usual age of diagnosis for a given cancer type. Individuals with multiple separate primary cancers or bilateral cancers in paired organs such as the breasts or the kidneys also are more likely to have an inherited cancer predisposition. The presence of the same or related cancer types in two or more generations of a family is another indication of possible hereditary risk (with the important caveat that the individuals with cancer must be from the same side of the family and "blood relations").

Perhaps the most important characteristic of hereditary cancer syndromes is the potential for increased risk to the relatives of the affected individual who is found to carry a hereditary predisposition gene. Over 200 hereditary cancer syndromes have been described in the literature (Schneider 2001); however, many of these are extremely rare. The scope of this chapter is not to describe all hereditary cancer syndromes, but to review the characteristics of the hereditary cancer syndromes most frequently observed and to provide the tools to identify a hereditary cancer syndrome in a family and describe the process individuals and families undergo to determine a hereditary susceptibility towards cancer. The more common hereditary breast, ovarian, and colon cancer syndromes will be described, along with

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recommended screening and surveillance and prophylactic and chemoprevention options currently available to those at increased risk.

5.2 Cancer as a Genetic Disorder

Cancer is the outcome of an evolution of genetic mutations and epigenetic effects on deoxyribonucleic acid (DNA) over time. Therefore, cancer is always a genetic disease; however, not all cancer is hereditary or due to inherited genetic alterations.

Mutations can be classified in three groups: *genome mutations* are those that change the total number of chromosomes in the cell, *chromosomal mutations* change the structure of the individual chromosomes, and *genetic mutations* change the sequence of amino acids within the gene (Nussbaum et al. 2001). By this definition, this discussion will focus on genetic mutations, as they are the primary causes of hereditary cancer syndromes. Another important distinction is the difference between germline and somatic mutations. Mutations occurring in germline cells (sperm or ova) will manifest in all cells of the resulting offspring and will be present in those offspring from the time of conception. Mutations occurring in non-germline cells over the course of an individual's life are considered somatic mutations and are not passed on to the offspring of that individual. The majority of cancers in the general population are caused by the occurrence of multiple somatic mutations; however, individuals with an inherited germline mutation will also develop cancer after additional somatic mutations occur.

5.2.1 Tumor Suppressor Genes

Most hereditary cancer syndromes are caused by mutations in tumor suppressor genes (Schneider 2001). The function of the proteins expressed from tumor suppressor genes is negative regulation of cellular growth, especially in damaged cells (Schneider 2001). Tumor suppressor genes are inherited dominantly in hereditary cancer syndromes, but behave recessively on the cellular level (Franks and Teich 1997). When an individual inherits a mutation on one copy of a tumor suppressor gene, the protein produced from the working gene will maintain cell growth and suppress proliferation (Schneider 2001). If this individual were to lose the working copy of the same gene, tumor growth can occur in the target cell. Mutations in tumor suppressor genes do not always begin with a germline mutation followed by a somatic mutation. Cancer may also result from two somatic mutations. This form of cancer initiation is thought to represent the majority of sporadic cancer occurrences (Schneider 2001).

One of the classic explanations of hereditary cancer is Alfred Knudson's "two-hit" model of retinoblastoma. He compared the inherited form of retinoblastoma, occurring in 9 out of every 10 children with an inherited germline mutation, to the sporadic form of the disease, which occurs in 1 of every 20,000 children in the USA (Knudson 1971). Children with the inherited mutation were much more likely to be affected

with cancer because they were born with "one hit" or a germline mutation, as compared to the children with sporadic cancer, who acquired two mutations in somatic cells in order for the disease to occur.

Vogelstein furthered the two-hit theory with his model of carcinogenesis in 1990 (Fearon and Vogelstein 1990). Vogelstein's model described multiple genetic mutation "hits" occurring in normal colon cells causing increasing dysplasia and ultimately resulting in carcinoma. His model was based on the adenomatous polyposis coli (*APC*) tumor suppressor gene, which is mutated in the germline cells in familial adenomatous polyposis (FAP), one of the classic hereditary colon cancer syndromes. The *APC* gene can be thought of as the "gatekeeper" gene (Schneider 2001). A mutation in this gene allows for additional gene mutations, such as activation of the *K-RAS* oncogene and loss of other tumor suppressor genes, to occur more readily. The succession of genetic mutations and the order in which these mutations occur are important in determining stages of development of adenomas.

5.2.2 Oncogenes

Few hereditary cancer syndromes occur as a result of oncogenes (Schneider 2001). Oncogenes arise from proto-oncogenes, which are responsible for regulating cellular signaling pathways. A mutation in the proto-oncogene activates the oncogene, causing either increased expression of the proto-oncogene protein or a change in the protein's structure and function (Schneider 2001). Most mutations occur on the somatic level and behave dominantly, requiring only one mutation to cause abnormal cell growth. As is described in Vogelstein's cancer progression model, more than one activated oncogene in a target cell or cells is necessary for cancer to occur.

5.2.3 DNA Repair Genes

DNA repair genes identify and repair errors made in the nucleotide sequence during replication. DNA repair involves several steps, including identification of the error in the DNA strand, collection of proteins for repair, incision of the DNA, excision of the erroneous nucleotide sequence, synthesis of the correct nucleotides, and reattachment of the correct sequence (Schneider 2001). Mutations in the genes involved in the repair process can lead to accumulations of DNA errors within a cell. A defective DNA repair gene has a secondary effect on cancer progression, whereas mutations in oncogenes and tumor suppressor genes cause a primary effect (Schneider 2001).

Several DNA repair genes, called mismatch repair (MMR) genes, have been implicated in hereditary nonpolyposis colorectal cancer syndrome (HNPCC), another inherited colon cancer predisposition syndrome that is also known as Lynch syndrome. Cells with mutated mismatch repair genes demonstrate microsatellite instability (MSI). Microsatellite sequences (short repeats of six or fewer base pairs)

become unstable and result in a long series of the same repeated sequence. The presence of MSI results in the progression of additional somatic mutations in the cell (Offit 1997).

5.2.4 Epigenetic Mechanisms

Epigenetic effects change gene expression through the activation or silencing of growth regulatory genes. Genomic imprinting and methylation are two examples of epigenetic mechanisms causing gene silencing. When growth regulation genes are silenced by this mechanism, cells may receive a potential hit (Schneider 2001). Epigenetic effects are important because these changes may be the most common alteration seen in human cancer. Because epigenetic mechanisms are not thought to be the result of DNA changes, the process may be reversible, leading to better targeted treatment options for patients in the future (Schneider 2001).

Cancer occurs as a multistep model in which a succession of events, genetic mutations, environmental agents, and epigenetic agents leads to cancer progression. Learning the molecular changes in cells and following the sequential progression of cancer may allow the development of effective interventions that will stop cancer progression on the molecular level.

5.3 Cancer as a Hereditary Disease

Identifying a sporadic occurrence of cancer versus a familial or hereditary form is the first step in locating patients at higher cancer risk and thus providing appropriate screening and prevention recommendations. Differentiation between sporadic and hereditary cancer is often obvious, whereas elucidating a hereditary versus familial form of cancer can be more nuanced.

A sporadic cancer characteristically manifests as a single individual with cancer, with an age of onset typical for that cancer type and no known cancers in first-, second-, or third-degree relatives. An example would be a 70-year-old woman recently diagnosed with breast cancer and with no known family history of cancer. In this case, her cancer would be classified as a sporadic incidence of cancer with no concern of inherited susceptibility.

Familial forms of cancer are clusters of cancer in a family that are not consistent with a pattern caused by high-penetrance cancer risk genes. These findings may be due to shared environmental causes, gene-environment interactions, or low-penetrance genetic polymorphisms. Familial cancer syndromes are more difficult to differentiate from hereditary cancer due in large part to the variability in gene expression exhibited by hereditary cancer syndromes. Familial forms of cancer typically present with at least two relatives who are affected with similar cancers, often at usual ages for diagnosis for these cancers. A typical presentation would be a woman diagnosed with breast cancer at age 68 who has a maternal aunt who was also diagnosed with breast cancer in her 80s. Her mother does not have a diagnosis

of breast cancer, and therefore there is no evidence of an autosomal dominant pattern. Due to incomplete penetrance of the gene or competing causes of mortality, her mother could be the carrier of a gene predisposing to breast cancer; however, with the late ages of diagnosis, this scenario is more likely to represent familial clustering rather than a true inherited cancer susceptibility.

As noted above, cancers occurring at earlier ages than would be expected, similar cancers in multiple relatives in an autosomal dominant pattern, and multiple cancers in one individual are hallmarks for hereditary cancer syndromes. Both males and females may inherit these cancer susceptibility genes, and both men and women may pass them on to their offspring. For an autosomal dominantly inherited hereditary cancer syndrome, there is a 50 % risk of passing down a genetic mutation from the carrier to an offspring. In a typical family history with a hereditary cancer gene mutation, there tends to be at least one affected relative in each generation. However, there are many families in which an individual carries one of the gene mutations for an autosomal dominant cancer syndrome, yet they do not express the phenotype of the mutation and are not affected with cancer. This phenomenon is observed because hereditary cancer syndromes demonstrate variable expression of the disease phenotype. In addition, most hereditary cancer genes exhibit incomplete penetrance, meaning that not all individuals with an inherited mutation will develop cancer.

There are only a few hereditary cancer syndromes inherited in an autosomal recessive manner. Autosomal recessive disorders occur when an individual inherits the same genetic mutation on each chromosome. A carrier for an autosomal recessive gene is not affected with the disease. When parents carry the same autosomal recessive gene mutation, the risk to have an affected child is 1 in 4, or 25 %.

5.4 Common Hereditary Cancer Syndromes

5.4.1 Hereditary Breast and Ovarian Cancer

Genetic predisposition provides one of the most significant risk factors for women to develop breast or ovarian cancer. Genetic testing became available for the breast and ovarian cancer syndrome in the mid-1990s. Currently, there are two genes described for the hereditary breast and ovarian cancer syndrome. The first gene described, *BRCA1*, was identified in 1989 and sequenced in 1994 (Hall et al. 1990; Miki et al. 1994). The second gene, *BRCA2*, was sequenced in 1995 (Wooster et al. 1995).

Similar to other hereditary cancers, between 5 and 10 % of all breast cancers and 10–15 % of all ovarian cancers are thought to be due to inherited susceptibility (Malander et al. 2004; Pennington and Swisher 2012). The *BRCA1* and *BRCA2* genes are thought to account for approximately 80–90 % of all hereditary breast and hereditary ovarian cancers (Thull and Vogel 2004).

The incidence of a *BRCA1* or *BRCA2* gene mutation in individuals of Northern European descent is between 1 in 800 and 1 in 2,500 (Schneider 2001). In North

America, 1 in every 300–500 people is estimated to harbor a germline BRCA mutation (Nelson et al. 2005). Several founder mutations specific to geographically isolated populations have been identified in hereditary breast and ovarian cancer. The best-described founder mutations are found in the Ashkenazi Jewish population, in which the carrier frequency for a *BRCA1* or *BRCA2* gene mutation is 1 in 40, or approximately 2.5 % (Tonin et al. 1996). *BRCA1* contains two of the three founder mutations for the Ashkenazi Jewish population. Approximately 1 % of the Ashkenazi Jewish population carries the mutation, 185delAG, and 0.1 % of the Ashkenazi population carries the founder mutation, 5382insC (Peelen et al. 1997). There is one Ashkenazi Jewish founder mutation on *BRCA2*, 6174delT. This mutation is seen in approximately 1 % of individuals of Ashkenazi Jewish descent (Peelen et al. 1997). Other founder mutations have been identified in the Dutch, Icelandic, and French Canadian populations (Johannesdottir et al. 1996; Tonin et al. 1996, 1998; Peelen et al. 1997; Petrij-Bosch et al. 1997).

The *BRCA1* gene is large, with 24 exons. It encodes a protein of 1,863 amino acids and works as a tumor suppressor gene (Miki et al. 1994). The function of a normal *BRCA1* protein is to recognize DNA damage (Couch et al. 1996). Referring back to the model of carcinogenesis, the inherited mutation of one *BRCA1* gene leads to increased susceptibility to mutations in the remaining somatic copy of the *BRCA1* gene, beginning the pathway to carcinogenesis.

The 800 hereditary mutations identified on the *BRCA1* gene are found throughout the gene sequence. The majority of these mutations lead to premature protein termination and are frameshift (insertion or deletion of nucleotides causing a shift in the DNA reading frame) or nonsense (insertion or deletion of nucleotides causing a premature stop codon) mutations (Barnes-Kedar and Plon 2002). Testing for a *BRCA1* gene mutation is complex, due in part to the fact that the majority of gene mutations described to date have been identified as private mutations that are unique to each family undergoing testing (Tirkkonen et al. 1997). Tumors from *BRCA1* mutation carriers are classically of the basal subtype, which corresponds to the triple-negative phenotype (i.e., negative for estrogen receptor, progesterone receptor, and HER2Neu overexpression) (Turner and Reis-Filho 2006). This tumor subtype underlies the poor prognosis of breast cancer in *BRCA1* mutation carriers.

The *BRCA2* gene is larger than the *BRCA1* gene with 27 exons, encoding a protein of 3,418 amino acids (Tirkkonen et al. 1997). The *BRCA2* gene, like *BRCA1*, is also a tumor suppressor gene with a protein product that is also involved in DNA repair (Couch et al. 1996). There have been approximately 100 mutations reported in the *BRCA2* gene, and most of these mutations also play a role in premature chain termination (Tirkkonen et al. 1997). Unique to the *BRCA2* gene is a region identified as the ovarian cancer cluster region (OCCR). Mutations found in this region confer lower risks for women to develop breast cancer and increased risks for developing ovarian cancer (Thompson et al. 2001). Characteristically, most tumors that develop in *BRCA2* carriers are of the luminal subtype (i.e., positive for estrogen and progesterone receptors and negative for

Her2Neu overexpression) (Bane et al. 2007). The luminal subtype generally has a good prognosis. Interestingly, neither the *BRCA1* nor *BRCA2* genes exhibit mutations in truly sporadic breast cancer.

In addition to increased susceptibility to breast and ovarian cancer, mutations in the *BRCA1* and *BRCA2* genes confer risks for other cancers as well. Males who carry the *BRCA1* gene mutation may also have an increased risk for prostate cancer (Liede et al. 2004). It is likely that women with a *BRCA1* or *BRCA2* mutation have an increased risk for developing cancer of the pancreas, or stomach, or primary peritoneal serous carcinoma; however, the risk is rather small (Nelson et al. 2005). Although early studies reported an increased risk for colon cancer in carriers of the *BRCA1* gene mutations (Ford et al. 1994), follow-up studies failed to duplicate these risks (Peelen et al. 2000).

Male breast cancer has also been correlated with a *BRCA2* gene mutation. There are a variety of other cancers also associated with the *BRCA2* gene mutations, including prostate, pancreatic, gallbladder, bile duct, and stomach cancers, as well as malignant melanoma (Risch et al. 2001).

Current estimation of cancer risks for carriers of a *BRCA1* or *BRCA2* mutation indicates the lifetime risk for breast cancer is between 50 and 87 %. As a basis for comparison, the risk of breast cancer in the general population is approximately 12 %. The risk for ovarian cancer in women who carry a *BRCA1* gene is estimated to be 15–40 %, whereas the risk for ovarian cancer in women who carry a *BRCA2* gene is 14–27 % (Struewing et al. 1997; Risch et al. 2001). In the general population, about 2 % of women will develop ovarian cancer. Primary peritoneal and fallopian tube cancers are also increased for carriers of mutations in either the *BRCA1* or *BRCA2* genes.

The risk of breast cancer in men who carry a *BRCA2* mutation is between 2.8 and 6.3 % (Thompson et al. 2001), which, although a low absolute risk, is markedly increased relative to that of the general population. The risk of prostate cancer in men who carry a *BRCA1* gene mutation is between 8 and 16 % based on one study (Ford et al. 1994). The risk of prostate cancer in men who carry the *BRCA2* gene mutation has been estimated to be as high as 20 % before age 80, with the relative risk greater for men younger than 65 (Struewing et al. 1997; The Breast Cancer Linkage Consortium 1999). Pancreatic cancer was also found in studies to be modestly increased in *BRCA2* mutation carriers, with a 2.1 % cumulative risk by age 70; average incidence of pancreatic cancer in the general population is less than 1 % (The Breast Cancer Linkage Consortium 1999).

The wide range of cancer risks described from mutations in the *BRCA1* and *BRCA2* genes can be explained by inadequate study designs with potential for biased ascertainment as well as variable expressivity of the gene, environmental factors, and other gene modifiers. A report on risks for breast and ovarian cancer in Ashkenazi Jewish women with inherited *BRCA1* and *BRCA2* mutations identified physical exercise and lack of obesity in adolescent as modifiable risk factors, delaying the age of breast cancer onset (King et al. 2003). Further studies are under way to determine effects of environmental factors and other modifier genes on the expression of these gene mutations.

5.4.2 Cowden Syndrome

Cowden syndrome, also called multiple hamartoma syndrome, accounts for less than 1 % of hereditary breast and ovarian cancer. The incidence of Cowden syndrome is approximately 1 in every 200,000–250,000 individuals (Schneider 2001), although this syndrome is likely underreported due to lack of awareness. Cowden syndrome is inherited in an autosomal dominant pattern. Penetrance of Cowden syndrome may be as high as 100 % (Nelen et al. 1996). The gene mutated in Cowden syndrome, *PTEN*, is a tumor suppressor gene. The role of the protein product is to control cell cycle arrest and apoptosis (Schneider 2001). As many as 80 % of individuals with clinical findings suggestive of Cowden syndrome will have a gene mutation identified with clinical testing (Eng 2000).

Individuals with Cowden syndrome often have unique physical findings associated with this syndrome. The pathognomonic features of Cowden syndrome are facial trichilemmomas, acral keratoses, oral papillomatous papules, and mucosal lesions (Eng 2000). Major criteria used to establish a clinical diagnosis include breast cancer, thyroid cancer, especially papillary carcinoma, macrocephaly, Lhermitte-Duclos disease or cerebral dysplastic gangliocytoma, and endometrial cancer. The minor criteria include other thyroid lesions, mental retardation, gastrointestinal hamartomas, fibrocystic breasts, lipomas or fibromas, genitourinary tumors (renal cell carcinoma, uterine fibroids), and genitourinary malformations. Diagnosis is confirmed clinically when the affected individual presents with either six facial papules listed in the pathognomonic criteria, two major criteria that must include macrocephaly or Lhermitte-Duclos disease, one major criteria and three minor criteria, or four minor criteria (Eng 2000).

The lifetime risk for breast cancer in women who are identified with Cowden syndrome is between 25 and 50 % (Brownstein et al. 1978). Male breast cancer has also been identified in men who carry a *PTEN* mutation, but the specific risks are not documented (Fackenthal et al. 2001). Endometrial cancer is also considered in Cowden syndrome, with risks reported between 5 and 10 % (Eng 2000). Lifetime risk for thyroid cancer (usually follicular, rarely papillary, and never medullary) is around 10 % (Eng 2000).

5.4.3 Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is another rare syndrome conferring increased risk for breast cancer in affected women. LFS accounts for less than 1 % of hereditary breast cancer. The inheritance of LFS, similar to the other hereditary breast cancer syndromes, is autosomal dominant. The majority of families who meet diagnostic criteria for LFS are found to carry an identifiable genetic mutation. The gene for LFS, *p53*, is also a tumor suppressor gene and is involved in cell repair, the apoptosis pathway, and maintaining genomic stability (Schneider 2001).

Classic criteria for the diagnosis of Li-Fraumeni syndrome include an individual with sarcoma diagnosed prior to the age of 45 and a first-degree relative with cancer diagnosed prior to the age of 45 and another first- or second-degree relative with

cancer diagnosed prior the age of 45 or with a sarcoma diagnosed at any age (Li et al. 1988). The Chompret criteria expanded this definition to include individuals with a Li-Fraumeni-associated cancer diagnosed before age 46 and at least one first- or second-degree relative with a Li-Fraumeni-associated cancer diagnosed prior to 56 or with multiple primary cancers, individuals with two tumors in the Li-Fraumeni spectrum with the initial cancer diagnosed prior to 46, or individuals with adrenocortical cancer or choroid plexus tumors at any age (Chompret et al. 2001; Tinat et al. 2009). For these criteria, Li-Fraumeni-associated tumors included breast cancer, soft tissue sarcomas, osteosarcoma, brain tumors, adrenocortical cancers, leukemia, or bronchoalveolar cancer of the lung. Other cancers associated with LFS include malignancies in the stomach, colon, and lung as well as childhood neuroblastomas and melanoma (Schneider 2001).

The risk of all cancers in individuals with LFS is estimated to be 50 % by age 30 and 90 % by age 70. Mutations in *p53* also place a carrier at a 50 % risk of a second primary tumor (Schneider 2001; Thull and Vogel 2004).

5.4.4 CHEK2

Genes with low to moderate penetrance have been proposed to play a role in hereditary breast and ovarian cancer. *CHEK2* acts as a tumor suppressor gene and is a cell cycle regulator. The full range of cancers associated with *CHEK2* mutations has not been determined; however, studies suggest increased risks for prostate, kidney, lung, colon, thyroid, and ovarian cancers. These mutations have also been found in some brain tumors and in osteosarcomas. Women with the *CHEK2**1100delC germline mutation have a twofold increased risk of developing breast cancer compared to women in the general population (Meijers-Heijboer et al. 2002; Walsh et al. 2006; Weischer et al. 2007).

5.4.5 Ataxia-Telangiectasia

Ataxia-telangiectasia (A-T) is one of the few hereditary cancer syndromes inherited in an autosomal recessive manner. This rare syndrome, affecting between 1 in 30,000 and 1 in 100,000 individuals, is characterized by cerebellar ataxia, immune defects, telangiectasias, radiosensitivity, and predisposition to malignancies, especially leukemias and lymphomas (Izatt et al. 1999; Schneider 2001). While the syndrome itself places the affected individuals at a substantial increased risk of dying from cancer, the carriers of the gene for A-T are also at an increased risk of breast cancer.

The gene for A-T, *ATM*, is believed to be involved in maintaining genomic stability (Savitsky et al. 1995). The increased risk of breast cancer in carriers of an *ATM* mutation is not well established. Earlier data indicated that a female carrier could have a five- to sevenfold increased relative risk of breast cancer (Schneider 2001). Breast cancer caused by mutations in the *ATM* gene accounts for approximately 8 % of all breast cancer cases (Swift et al. 1991).

5.4.6 Hereditary Nonpolyposis Colorectal Cancer

Hereditary forms of colorectal cancer (CRC) account for between 10 and 20 % of the cases of colorectal cancer. The most common form of inherited colorectal cancer is hereditary nonpolyposis colorectal cancer (HNPCC), also called Lynch syndrome. The prevalence of HNPCC is 1 in 200 to 1 in 1,000 and accounts for approximately 1–6 % of colon cancers (Hampel and Peltomaki 2000). HNPCC is inherited in an autosomal dominant pattern. The penetrance of the involved genes is as high as 90 % (Lynch and Lynch 1998).

The genes implicated in HNPCC are involved in mismatch repair. As a result of mutations in the MMR genes, MSI is a characteristic of HNPCC tumors. Ninety-five percent of the tumors in individuals with HNPCC exhibit MSI (Hampel and Peltomaki 2000). There are four genes responsible for the mismatch repair pathway associated with HNPCC: *MLH1*, *MSH2*, *MSH6*, and *PMS2* (Wooster et al. 1995). *MLH1* and *MSH2* mutations are found in the majority of families with an identifiable mutation (Peltomaki and Vasen 1997). There have been over 400 different mutations reported in these genes, with *MLH1* accounting for 50 % of the mutations and *MSH2* accounting for 40 % (Umar et al. 2004). In addition, mutations in the *EPCAM* gene have recently been shown to silence *MSH2* through hypermethylation, leading to an HNPCC phenotype (Kempers et al. 2011; Rumilla et al. 2011).

Individuals with HNPCC have up to an 80 % lifetime risk of colorectal cancer. Colorectal cancer typically occurs at an earlier age (in the 40s on average), with an increased incidence of tumors in the proximal colon. Individuals with HNPCC also have an increased risk of synchronous or metachronous colon cancer (Hampel and Peltomaki 2000). The colonic adenomas in HNPCC occur with the same frequency and in the same location within the colon as in the general population; however, the adenomas are larger, occur earlier in life, and have a higher grade of dysplasia and villous features. The characteristics of carcinomas of the colon in HNPCC patients include poor differentiation, tumor infiltrating lymphocytes, mucin, and signet ring histology (Lynch and Lynch 2000).

While the average age of cancer diagnosis is 44 years, patients with HNPCC are reported to have a better survival than age- and stage-matched sporadic patients (Lynch and Lynch 1998). Studies have suggested this survival difference can be explained by the response to chemotherapy in HNPCC as compared to sporadic tumors (Watanabe et al. 2001). Gender differences are a possible factor in HNPCC tumor expression; the male risk of colon cancer is reported to be 91 %, and female risk is 69 % (Dunlop et al. 1997). Women affected with HNPCC have up to a 60 % lifetime risk of endometrial cancer, with the average age at diagnosis of 46 years (Aarnio et al. 1999). Improved survival in women affected with HNPCC-related endometrial cancer versus sporadic occurrence is also observed (Solomon and Burt 2004).

Stomach or gastric cancers have been described, but perhaps because of changes in Western diets and gene-modifying events, the incidence of stomach cancer in HNPCC has declined in the USA. The risk of stomach cancer is reported to be as high as 13 %, with the average age at diagnosis being 56 years. Women are also at 12 % lifetime risk of ovarian cancer, with the mean age at onset of 42.5 years

(Solomon and Burt 2004). Incidence of cancers of the hepatobiliary tract, urinary tract, small bowel, and central nervous system are also mildly increased in HNPCC patients.

The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) created the Amsterdam Criteria in an attempt to standardize the diagnostic criteria for families suspected of having HNPCC. These criteria stated that at least three relatives with colorectal cancer should be present in the family; one should be a first-degree relative of the other two; two successive generations should be affected; and at least one relative should have been diagnosed with colon cancer prior to the age of 50. In addition, FAP must be excluded. Subsequently, the Amsterdam Criteria II was proposed by the ICG-HNPCC to include HNPCC-associated cancers in addition to colon cancers (Thull and Vogel 2004). In 1996, the National Cancer Institute developed the Bethesda Guidelines that described criteria for identifying colorectal tumors that should be tested for MSI. These guidelines were revised in 2002 in an attempt to increase sensitivity in identifying HNPCC-related tumors (Umar et al. 2004). The updated Bethesda Guidelines are outlined below under genetic testing for HNPCC. It is important to realize that families who do not meet Amsterdam Criteria I or II are not to be excluded from a diagnosis of HNPCC.

5.4.7 Familial Adenomatous Polyposis

Although familial adenomatous polyposis (FAP) is responsible for only about 1 % of all hereditary colorectal cancers, it has played a large role in understanding the multiple gene model of cancer progression. The prevalence of FAP is 1 in 30,000 to 50,000 individuals. Similar to HNPCC, FAP is inherited in an autosomal dominant manner, with 75–80 % of individuals reporting an affected parent. The remaining cases result from *de novo* mutations (Amos et al. 2007). The gene responsible for FAP is called adenomatous polyposis coli (APC). The APC gene is a tumor suppressor and works to maintain apoptosis and decrease cell proliferation in addition to participating in many other important cellular functions. As with other cancer predisposition genes, mutations in the APC gene result in truncated protein products. The penetrance of the APC gene is close to 100 % (Schneider 2001).

FAP is characterized by hundreds to thousands of precancerous colon polyps that begin to develop at a mean age of 16 years (range of 7–36 years) (Solomon and Burt 2004). By age 35, 95 % of individuals with FAP have colorectal polyps. Colon cancer risk is 100 % by the mean age of 40 without intervention (Hampel and Peltomaki 2000). Clinical diagnosis of FAP is made in an individual with more than 100 colorectal adenomatous polyps or in any individual with less than 100 adenomatous polyps who had one relative affected with FAP (Solomon and Burt 2004).

Associated extracolonic findings include polyps of the upper gastrointestinal tract, osteomas, dental anomalies, congenital hypertrophy of the retina pigment epithelium (CHRPE), soft tissue tumors, desmoid tumors, and brain cancer. Increased risks for papillary thyroid carcinoma in younger women and hepatoblastoma in

affected children have also been documented (Hampel and Peltomaki 2000). Variability in clinical symptoms is quite extensive between affected family members. Gardner syndrome, a variant of FAP, is also associated with extracolonic features, osteomas, dental abnormalities, desmoid tumors, and sebaceous cysts (Hampel and Peltomaki 2000).

5.4.8 Attenuated Familial Adenomatous Polyposis

Attenuated FAP (AFAP) is described as a form of FAP with fewer colorectal polyps (e.g., between 50 and 100 with average number of 30) that are found more proximally in the colon and at a later age than classic FAP (Lynch and Lynch 1998). AFAP is more likely to be confused with HNPCC than classic FAP for this reason. The colon polyps take on a polypoid shape in AFAP (Hampel and Peltomaki 2000). The average age for colon cancer in individuals with AFAP is 50–55 years (Solomon and Burt 2004). Multiple extracolonic polyps, such as fundic gland polyps and duodenal polyps, are detected, but individuals with AFAP do not typically exhibit CHRPE characteristics. AFAP has an autosomal dominant inheritance pattern, and the mutations for AFAP are also located on the APC gene. Mutations are characteristically located on either the extreme 5′ region of the first four exons or the 3′ region of the APC gene (Hampel and Peltomaki 2000).

5.4.9 MYH-Associated Polyposis (MYH, MAP)

MYH-Associated Polyposis (*MYH*, MAP) is a fairly recently described autosomal recessive hereditary cancer syndrome associated with multiple adenomas and a phenotype similar to AFAP. A study by Jenkins and colleagues in 2006 found that monoallelic carriers had a threefold increased risk for colorectal cancer, whereas biallelic carriers had a 50-fold increased risk for colorectal cancer (Jenkins et al. 2006).

5.4.10 Peutz-Jeghers Syndrome

Another rare colorectal cancer syndrome characterized by polyposis is Peutz-Jeghers syndrome (PJS). This syndrome occurs in 1 of every 120,000 individuals. PJS exhibits an autosomal dominant inheritance pattern of the implicated gene, *STK11* (Hemminki et al. 1998). The gene product of the PJS gene is involved in a signaling pathway for cellular apoptosis (Amos et al. 2007). In a study of 56 individuals with a clinical diagnosis of PJS in which a combination of sequence analysis and multiple ligand-dependant probe assay (MLPA) was used, the *STK11* mutation detection rate was 94 % (Aretz et al. 2005).

PJS is clinically diagnosed in an individual with two or more Peutz-Jegher-type hamartomatous intestinal polyps and hyperpigmented macules on the lips and buccal mucosa. These macules also occur on the eyes, genitalia, anus, hands, and feet

(Hampel and Peltomaki 2000). Individuals affected with PJS are at increased risk of multiple hamartomatous polyps in the small bowel, stomach, colon, and rectum, causing intussusception and obstruction (Hemminki 1999). Individuals affected are 10–18 times more likely to be diagnosed with intestinal and other cancers during their lifetime. Breast and cervical cancers are also described in individuals with PJS (Boardman et al. 1998).

5.4.11 Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome associated with increased risks for diffuse gastric cancer and lobular breast cancer due to mutations in the E-cadherin (*CDH1*) gene. The estimated lifetime risk (by age 80) for gastric cancer for individuals with *CDH1* mutations is 67 % in men and 83 % in women. Women also have a 39 % risk of lobular breast cancer (Brooks-Wilson et al. 2004).

5.5 Genetic Counseling

Given the complexities involved in genetic testing and the clinical diagnosis of hereditary cancer syndromes described above, the clinician must be prepared to understand basic Mendelian inheritance as it is applied to hereditary cancer in the family, explain the hereditary components of a cancer syndrome, and understand the complexities of genetic testing. An increase in the number of syndromes identifiable through mutational analysis coupled with the complexities inherent in testing and the potential psychological impact on affected individuals has created the need for specialized cancer genetics and high-risk clinics.

In order to accurately address patient concerns related to cancer risk, the American Society of Clinical Oncology (ASCO 2003), the American Society of Human Genetics (ASHG 1994), and the American College of Obstetricians and Gynecologists (ACOG 1997) have issued the recommendation of pre- and post-testing counseling by appropriately trained individuals with knowledge of the complex genetic issues related to hereditary cancer syndromes.

In order to meet this recommendation, genetic counseling is now offered in cancer centers and other institutions throughout the country. Genetic counseling is defined as a communication process that deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family (Ad Hoc Committee on Genetic Counseling 1975). Genetic counseling is offered by individuals with an MD, PhD, or MS degree who are certified by either the American Board of Medical Genetics or the American Board of Genetic Counseling (Peters and Stopfer 1996). A national list of genetic counselors is available through the National Society of Genetic Counselors website (NSGC 2004).

A pedigree analysis is perhaps the most critical tool for defining a high-risk candidate and the need for further evaluation in a cancer genetics or high-risk clinic.

Once completed, the pedigree allows for the identification of patterns of clinical clues, based on the phenotypic expression of cancer, to determine a hereditary cancer syndrome diagnosis. Documentation of cancers through medical records and pathology reports, when possible, increases the accuracy of the risk assessment.

5.5.1 Cancer Risk Assessment Models

After a family history has been evaluated thoroughly, the patient may be provided with a risk assessment for being affected with cancer or, if they have already been diagnosed with a cancer, for carrying a germline mutation for a hereditary cancer syndrome. This discussion will focus on the cancer risk assessment models that may be utilized during this portion of the evaluation.

5.5.2 Epidemiologic Models of Breast Cancer Risk

There are two well-known models used to predict breast cancer risk in women: the Gail model and the Claus model. The Gail model is a statistically validated model that was developed using risk factors for breast cancer identified in the Breast Cancer Detection Demonstration Project (Baker 1982). The model asks women to report age at menarche, age at first birth of a live child, number of breast biopsies and pathologic results, number of first-degree relatives with breast cancer, and current age. Using this data, the Gail model provides women with both 5-year and lifetime risk of developing breast cancer. An updated version of the Gail model can be downloaded from the National Cancer Institute website (NCI 2007). The updated version provides risks for invasive breast cancer only, derives baseline incidence rates from SEER data, and includes a separate baseline incidence for black women (NCI 1998). Results have been extrapolated for Asian and Hispanic populations, but no validation studies have been done for the model in these populations to date.

The Gail model was developed prior to the discovery of the *BRCA1* and *BRCA2* genes, and the family history is limited to first-degree relatives only. This shortcoming leads to underestimation of cancer risks in women with a more extensive family history of early-onset breast cancer, ovarian cancer, male breast cancer, or paternal relatives with breast cancer. Therefore, the Gail model is not recommended for use in high-risk families (Barnes-Kedar and Plon 2002).

The Claus model consists of published tables to estimate risk of breast cancer over time. This model requires family history information, including paternal history and occurrences of ovarian cancer to calculate cancer risk (Domchek et al. 2003). Individuals receiving risk values from this model are encouraged to remember that the model can be imprecise since it does not account for subtle features of hereditary cancer. Like the Gail model, Claus should also be avoided in individuals with a strong family history of cancer. New models are under development that will incorporate both family history and individual risk factors (Tyrer et al. 2004).

5.5.3 Genetic Testing Models

During genetic counseling, genetic testing models may be used to offer the patient an estimation of the prior probability of an individual to carry a mutation in one of the hereditary cancer susceptibility genes. Prior probability models are available for hereditary breast and ovarian cancer and for HNPCC.

Models for predicting breast cancer mutation probability include the Couch, Shattuck-Eidens, Frank, and the Berry-Parmigiani-Aguilar or BRCAPRO models (Claus et al. 1994; Shattuck-Eidens et al. 1997; Frank et al. 1998; Parmigiani et al. 1998). In addition, a computer program has been developed (CaGene) that calculates risk by incorporating the Couch, Shattuck-Eidens, and BRCAPRO models. It also provides mutation prevalence estimates from Myriad Genetic Laboratories. This program is offered as a free service on the Internet (Parmigiani and Wang 2004). For a more extensive review of each of these models, see Domchek et al. (2003).

A calculator for the probability of a *PTEN* mutation is available from the Cleveland Clinic at www.lerner.ccf.org/gmi/ccscore/index.php.

The Wijnen model predicts prior probability for a HNPCC-causing mutation in either the *MLH1* or the *MSH2* genes. The average age of diagnosis of colorectal cancer, presence of endometrial cancer in the family, and the Amsterdam Criteria are entered into the program to calculate prior probability risk. If an individual's prior probability for carrying a mutation on one of these two genes is calculated to be equal to or greater than 20 %, Wijnen suggests clinicians first offer germline testing without MSI testing (Wijnen et al. 1998). One shortcoming of this model is that it does not account for less-prevalent HNPCC genes such as *MSH6* or *PMS2*. CRCAPRO is a statistical model that assesses the probability that an individual carries a germline deleterious mutation of the *MLH1*, *MSH2*, and/or *MSH6* genes. It is based on personal and family history of colon and endometrial cancer and uses a Mendelian approach assuming autosomal dominant inheritance. Age-dependent penetrance and prevalence data are based on review of the literature. It is available as part of the CaGene program by David M. Euhus mentioned above. Newer models for calculation of risk of carrying a mutation in a mismatch repair gene include the PREMM1,2,6 model (available at http://dana-farber.prod.dfcidev.org/pat/cancer/gastrointestinal/crc-calculator/default.asp) and the HNPCC predict model at http://hnpccpredict.hgu.mrc.ac.uk.

5.5.4 Informed Consent Prior to Genetic Testing

The issues surrounding genetic testing for hereditary cancer syndromes have been debated extensively. The conclusion of these debates is that the decision to undergo genetic testing should remain a personal choice. Therefore, proper informed consent requires a thorough discussion with the patient prior to genetic testing. A comprehensive informed consent should be documented and should include a discussion of the purpose of the test; costs; turnaround time; documentation of results; the

predictive value of a positive, negative, or indeterminate result; and corresponding cancer risk information. It should also include options for cancer risk management if the test is positive, negative, or indeterminate, the possible psychological implications of testing, individualized assessment of insurance coverage, discrimination risks, and alternatives to genetic testing, such as the possible delay of decision making to a future date (Geller et al. 1997).

The importance of adhering to this informed consent process was demonstrated in a study that examined the use and interpretation of genetic testing for mutations on the APC gene. The study found that 20 % of physicians ordered testing erroneously for FAP; only 18.6 % of individuals in this study received genetic counseling before the test, and in 31.6 % of the cases, the physicians misinterpreted the results (Giardiello et al. 1997).

In direct response to the complexity of genetic testing issues, as well as in an attempt to define those who would most benefit from genetic testing, the American Society of Clinical Oncology (ASCO) recommends genetic testing be offered when personal or family history is representative of a possible hereditary cancer syndrome; the test is able to be adequately interpreted; and the results from the genetic test will assist with medical management decision for the individual and their family. ASCO guidelines also state that clinicians offering genetic testing must include pre- and post-test genetic counseling, documentation of a family history of cancer, and must provide a risk assessment as well as discuss options for prevention and early detection (ASCO 2003).

5.6 Genetic Testing

5.6.1 Genetic Testing for Hereditary Breast and Ovarian Cancer

Although there is no recommended numerical "prior probability" to indicate when to offer gene testing for the *BRCA1* and *BRCA2* genes, responsibility of when to offer genetic testing is based on the judgment of the clinician. Once an individual has undergone a family history evaluation, provided with risk assessments, demonstrated to meet the criteria outlined by ASCO guidelines, genetic testing is typically offered. Eighty to ninety percent of hereditary breast and ovarian cancer is caused by *BRCA1* and *BRCA2* mutations. A recent study from Sweden reported that 1 in 10 ovarian cancer patients carries a *BRCA1* or *BRCA2* mutation (Malander et al. 2004).

The standard protocol for initiating genetic testing is to test for the *BRCA1* and *BRCA2* genes on the affected individual in a family before offering testing to the at-risk relatives. Given the high incidence of "private mutations," and the likelihood of other hereditary breast cancer genes yet to be discovered, the results will be most definitive in an individual already affected with cancer. If no living affected relatives are available, testing close family members may be considered; however, this strategy is suboptimal.

Genetic analysis of the *BRCA1* and *BRCA2* genes includes complete sequencing of both genes. Most insurance companies will cover at least a portion of the cost of

this test. Individuals of Ashkenazi Jewish descent can elect to undergo the ethnicity panel, screening for the three common founder mutations. Further testing for large deletions and duplications can be done with BART testing in individuals at high risk of having a mutation if complete sequencing of the BRCA genes does not identify a mutation.

Issues related to health insurance discrimination are uncommon. Most states currently have legislation to prohibit health insurers from using the results from a genetic test to deny coverage, set premiums, or drop coverage. Additionally, the Genetic Information Nondiscrimination Act (GINA) was passed in 2008 to prohibit health insurance and job discrimination on the basis of genetic information.

A positive result from a *BRCA1* or *BRCA2* genetic test identifies a deleterious mutation in the individual tested. Relatives of the BRCA-positive individual can then be offered single-site analysis for the identified mutation. Rarely, more than one deleterious mutation is identified, complicating the testing protocol. In these situations, it is recommended that all at-risk relatives undergo genetic counseling prior to undergoing genetic testing.

A negative result indicates no deleterious mutations were identified in the examined gene. Negative results are may be either a true negative or uninformative. A true negative occurs when a mutation has already been identified in an affected family member. Therefore, the individual who tested negative did not inherit the mutation in their family history. A recent study by Smith and colleagues (Smith et al. 2007) found that in these identified high-risk families, even women who test negative for the familial *BRCA1*/*BRCA2* mutation have a two- to threefold increased lifetime risk (by age 70) of breast cancer consistent with genetic modifiers.

A result is uninformative when an affected individual tests negative, yet their family history is suggestive of the breast and ovarian syndrome. In families in which a true autosomal dominant cancer syndrome is present, but no mutation has been located, either the family carries a mutation in a different susceptibility gene or there is a mutation on the *BRCA1* or *BRCA2* gene that is not detectable by current testing methods. In families for which no mutation is identified, yet there is a pedigree suggestive of hereditary cancer, risk assessment and management of cancer risk must be based on the family history.

A negative test result in an individual not affected with cancer may also be uninformative when they are tested before an affected relative. Until the affected relative is tested, it is impossible to know whether the results were negative because they did not inherit the cancer susceptibility gene or because there is no such mutation in the family. If affected relatives are unavailable to clarify the results, risk assessment should again be based on the family history of cancer.

The final possible result for individuals undergoing *BRCA1* and *BRCA2* analysis is a variant of uncertain significance. Variants occur in 10 % of the samples that are analyzed at Myriad Genetics, Inc. (Salt Lake City, UT) (Frank et al. 1998). This result is most commonly reported when a missense mutation is identified. Missense mutations, or mutations in which a change in a nucleotide results in the substitution of one amino acid for another, may or may not affect the protein function of the gene product.

Until a protein assay is developed to determine the effect on protein expression, interpretation of this result is based on clinical observation. All affected relatives in a family are offered testing to determine if the variant tracks with cancer in the family. Receiving a result of a variant of unknown significance leaves the clinician with limited information about cancer risks, and medical decision making must be individualized in these situations.

5.6.2 Genetic Testing for Hereditary Nonpolyposis Colon Cancer

Genetic evaluation for HNPCC usually originates with testing of the tumor using immunohistochemistry (IHC) to assess the expression of four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and/or evaluation for microsatellite instability within the tumor. Lack of expression of an MMR protein on IHC can be helpful in diagnosis but is not pathognomonic in and of itself, as epigenetic somatic changes can also lead to this result in about 10–15 % of sporadic tumors. Although IHC can be nonspecific for HNPCC, MSI can lack sensitivity to detect this condition, as it has a false-negative rate of 5–10 %.

Given that 95 % of tumors in individuals with HNPCC are MSI positive, testing the tumor for MSI is recommended prior to genetic testing (Hampel and Peltomaki 2000). The Bethesda Guidelines have been developed to identify individuals affected with colon cancer who would be appropriate candidates for MSI testing. The revised Bethesda Guidelines recommend testing tumors for MSI in individuals who meet one or more of the following criteria:

1. Colorectal cancer diagnosed before age 50
2. Presence of synchronous, metachronous colorectal or the HNPCC-associated tumor irrespective of age at diagnosis
3. Colorectal cancer with microsatellite instability and the presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor and one cancer diagnosed less than 50 years old
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, irrespective of age at diagnosis (Umar et al. 2004)

If the tumor is MSI positive, germline testing is offered. The probability of detecting a germline mutation when an individual meets Amsterdam Criteria I is 40–80 %. When the Bethesda Guidelines are met and a tumor is MSI positive, the probability of detecting a mutation nears 50 % (Kohlman and Gruber 2004). Since 5 % of tumors from verified HNPCC cases do not exhibit MSI, screening negative for this feature does not rule out the diagnosis of HNPCC. In addition, many individuals with colon cancer have MSI but do not have HNPCC. Currently, clinical testing for mutations in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes is available.

Universal screening of all colorectal and endometrial cancers with IHC and/or MSI has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the US Center for Disease Control

as a cost-effective measure, and many centers are starting to adopt this practice (EGAPP 2009). However, an appropriate infrastructure for managing these results should be in place prior to implementation of such a program.

5.6.3 Genetic Testing for Familial Adenomatous Polyposis

Germline testing in individuals with a clinical diagnosis of FAP is typically performed to identify a mutation in the family so that at-risk relatives can undergo genetic testing. Molecular testing is also offered to confirm the clinical diagnosis in patients with FAP who may have less than 100 adenomatous polyps. Full gene sequencing will detect up to 90 % of mutations on the APC gene. A protein truncation test, when performed alone, will be positive in about 80 % of individuals affected with FAP. If there are at least two affected individuals available for testing, linkage analysis can also be attempted and is informative in 95 % of families tested (Solomon and Burt 2004).

Because screening begins in childhood for hepatoblastoma and colon cancers, molecular genetic testing is offered to children at risk for FAP who are under the age of eight. While there is no evidence of psychological problems when testing is performed this early, some recommend that long-term psychological counseling be provided to these individuals (Solomon and Burt 2004).

Genotype-phenotype correlations are predicted to be available in the future allowing for individualized preventative screening and medical management recommendations.

5.6.4 Genetic Testing for Attenuated FAP and MYH (MAP)

Because the APC gene is responsible for both FAP and AFAP, the recommendation for genetic testing is the same. The mutations for attenuated FAP are located on the far ends, the 3′ or 5′ ends of the gene. Since AFAP and HNPCC can present in a similar manner, molecular testing may be used to confirm or rule out a diagnosis. Molecular testing is offered to individuals 18 and older for AFAP given the later age of onset of symptoms (Solomon and Burt 2004). Genetic testing is also available for *MYH*-associated polyposis, with both common mutations and founder mutations already described.

5.6.5 Next-Generation Genetic Testing Panels

Panels have recently been developed for commercial testing for multiple cancer susceptibility genes simultaneously. Currently, panels are available for genes associated with risk of breast cancer, colon cancer, ovarian cancer, and cancers in general. Of note, at this time, *BRCA1* and *BRCA2* are not included in these panels. Data are pending on the use of this new strategy, which may prove more efficient than genetic testing done in the usual stepwise manner. However, the variety of genes

being tested provides challenges for genetic counseling associated with the testing, and the risk of having variants of uncertain significance is increased with testing multiple genes. The role of these panels in the risk assessment process is still being determined.

5.7 Cancer Screening, Surveillance, and Prophylactic Management for Hereditary Cancer Syndromes

The purpose of offering a risk assessment evaluation and genetic testing is to identify individuals at increased risk for cancer prior to cancer initiation so that screening and prevention strategies can be implemented. Medical management guidelines have already been published for hereditary breast and ovarian cancer as well as hereditary colorectal cancer syndromes.

5.7.1 Prevention Strategies for Hereditary Breast/Ovarian Cancer

The manner in which individuals incorporate positive genetic test results for a *BRCA1* or *BRCA2* mutation is the initial step in understanding the effect genetic testing has on screening and surveillance and other prophylactic options. Behavioral modification, when necessary, is the first line of defense towards this effort. Currently several studies are working to identify the long-term effects of learning genetic predisposition to cancer prior to a cancer diagnosis (Risch et al. 2001). Early results indicate that fewer women than expected opted for prophylactic surgery after testing positive for a *BRCA1* or *BRCA2* mutation (Lerman et al. 2000). More research is necessary to understand the psychological effects of identifying a positive mutation. The findings of these studies will aid in developing behavioral interventions to increase understanding of, and adherence to, available options for this at-risk population.

The options available to women who are at an increased risk of breast and ovarian cancer can be divided into three categories: screening and surveillance, prophylactic surgery, and chemoprevention. Screening recommendations for women positive for a *BRCA1* or *BRCA2* mutation from the National Comprehensive Cancer Network (R) (NCCN(R)) Clinical Practice Guidelines in Oncology (NCCN Guidelines (R)) for Genetic/Familial High Risk Assessment: Breast and Ovarian V.4.2013 are summarized below:

- Breast cancer screening: Education regarding breast awareness and periodic self-examination starting at age 18, clinical breast exam every six to twelve months starting at age 25, and annual mammograms and annual breast MRI beginning at age 25 or individualized based on earliest age of onset in the family.
- Ovarian cancer screening: Transvaginal ultrasounds and serum CA125 levels every six months, starting at age 30 or 5-10 years prior to earliest age of diagnosis of ovarian cancer in the family.

It should be noted that the information on ovarian cancer screening is based on expert opinion with no data indicating that these screening methods will reduce

mortality from ovarian cancer in women who test positive for a *BRCA1* or *BRCA2* mutation (Madalinska et al, 2007; Risch, McLaughlin et al 2001).

Studies are not yet complete, so there is no known proven benefit of surveillance on cancer-related mortality in women who are *BRCA1* or *BRCA2* mutation carriers. These recommendations are therefore based on expert opinion only. Some practices avoid the use of mammograms until the age of 30 in order to avoid radiation to the breasts at a young age, as this may increase cancer risk in this population. Magnetic resonance imaging (MRI) of the breasts has been shown to have an increased sensitivity of detection of breast cancer compared to standard mammography (Kriege et al. 2004; Warner et al. 2004). While MRI has shown to be more sensitive than mammography, the specificity is lower for MRI versus mammography (Kriege et al. 2004; Warner et al. 2004). In addition, these studies still have not proven benefit of MRI surveillance on cancer-related mortality in women who carry a *BRCA1* or *BRCA2* mutation. For individuals who are unable to have breast MRI due to metal implants or claustrophobia, whole-breast ultrasound is emerging as an alternative.

Male carriers of mutations in *BRCA1* or *BRCA2* should also be offered appropriate screening and surveillance. Currently there is no standard recommendation for breast cancer screening in male carriers. Men can be advised to perform breast self-examination and contact their physician if any changes are detected. Screening with mammography is not typically recommended for males. Prostate cancer screening includes an annual prostate-specific antigen (PSA) test and a digital rectal examination for men over the age of 40 (Liede et al. 2004).

5.7.2 Prevention Strategies for Hereditary Colorectal Cancer Syndromes

Three groups have published screening guidelines for individuals with HNPCC. The ICG-HNPCC first published their guidelines in 1996, which were reviewed by a task force from The Cancer Genetics Studies Consortium in 1997 (Weber 1996; Burke et al. 1997). In general, both groups recommended colonoscopy every 1–3 years, starting at age 20–25, for all at-risk relatives. For *MLH1* and *MSH2* mutation carriers, NCCN (R) recommends colonoscopy every 1–2 years starting at age 20–25 or 2–5 years before the earliest age of colon cancer diagnosis, whichever is earlier; if the patient has adenomas with high-grade dysplasia or is otherwise difficult to manage with endoscopic surveillance, they recommend total abdominal colectomy with ileorectal anastomosis (Burt et al 2013, NCCN Guidelines (R) for Colorectal Cancer Screening V 2.2013). Screening may be started later for *MSH6*/*PMS2* mutation carriers: according to NCCN, colonoscopy should start at age 30–35 for *MSH6* carriers and age 35–40 for *PMS2* carriers, and may be continued every 2–3 years. Once *MSH6* carriers reach 40 and *PMS2* carriers reach 50, the frequency of colonoscopy should increase to every 1–2 years. Several studies have reported on the efficacy of such screening strategies in HNPCC families and conclude a decrease in incidence and mortality from colorectal cancer (Vasen et al. 1998).

Initial recommendations for endometrial cancer screening were changed by the task force in 1997. Currently, screening for endometrial cancer is recommended beginning from age 25–35. Screening methods include either annual endometrial

aspirate (in premenopausal women) or transvaginal ultrasound with biopsies of suspicious areas. NCCN Guidelines state that annual endometrial biopsy is an option for *MLH1* and *MSH2* mutation carriers, although no clear evidence supports this practice. Data do not support ovarian cancer screening with transvaginal ultrasound or CA125 in this population due to lack of sensitivity and specificity, but in the absence of more effective measures, these studies are commonly used in this population. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a consideration for these women once their families are complete. NCCN Guidelines mention esophagogastroduodenoscopy with extended duodenoscopy every 3–5 years, starting at age 30–35 to screen for gastric and small bowel cancer in selected *MLH1* and *MSH2* mutation carriers; however, these studies have not been proven to have clear clinical benefit in this population to date. Some clinicians also screen for urothelial cancers with annual urinalysis, but this practice remains controversial as well.

Guidelines for individuals with FAP have been updated and published by the Mayo Clinic. Screening for FAP begins as early as age ten, with prophylactic colectomy recommended between 17 and 20 years of age. An individual who does not undergo a proctocolectomy will require surveillance of the rectal stump every 6–12 months. Individuals with FAP are also encouraged to undergo baseline endoscopic screening for adenomas in the stomach and duodenum and a follow-up every 3–5 years after colectomy (Hampel and Peltomaki 2000). Surveillance for colon cancer in individuals with AFAP is similar, but typically begins at age 20 with annual colonoscopy.

In order to screen for hepatoblastoma, liver palpation, serum alpha-fetoprotein measurement, and ultrasound are recommended for children with FAP until age six (Hampel and Peltomaki 2000). Annual clinical examination is recommended for surveillance for thyroid, central nervous system, and abdominal desmoid tumors.

5.7.3 Prophylactic Surgery

Early studies have indicated a 90 % risk reduction in breast cancer incidence and mortality after prophylactic mastectomy in women at increased risk (Hartmann et al. 1999). A recent study reported a 95 % reduction in breast cancer in *BRCA1* and *BRCA2* mutation carriers after prophylactic mastectomy with prior or concurrent bilateral prophylactic oophorectomy (Rebbeck et al. 2004). Bilateral prophylactic salpingo-oophorectomy (BPO) is recommended between the ages of 35 and 40 or upon completion of childbearing for women at increased risk for ovarian cancer. In addition to reducing risk of ovarian cancer to nearly negligible levels, Rebbeck and colleagues studied the effects of BPO in carriers of a *BRCA1* mutation and reported a 50 % reduction in risk of breast cancer (Rebbeck et al. 2004). Early studies have suggested increased life expectancy in *BRCA1* and *BRCA2* carriers who undergo prophylactic mastectomy and oophorectomy (Schrag et al. 1997). However, issues such as menopausal symptoms and decrease in bone density must be addressed in individuals who have oophorectomy prior to menopause. Two groups have demonstrated that a short course of hormone

replacement therapy after prophylactic oophorectomy does not increase breast cancer risk, but the effects of longer-term use are not known (Rebbeck et al. 2005; Eisen et al. 2008).

Prophylactic colectomy is the standard of care for individuals with FAP once their polyposis is not manageable by endoscopic methods. In individuals with classic FAP, surgery is often performed in the mid- to late teens. Prophylactic surgery has not been proven to be effective in individuals affected with HNPCC, but the option for either subtotal colectomy (or proctocolectomy) with ileorectal anastomosis should be given to the patient after the first colon cancer diagnosis is made or when adenomas are diagnosed. In addition, women should be offered total abdominal hysterectomy and bilateral salpingo-oophorectomy (King et al. 2000).

5.7.4 Chemoprevention

In the primary prevention setting, use of tamoxifen for 5 years has reduced breast cancer incidence in high-risk women by approximately 50 % (Fisher et al. 2005). As a result, tamoxifen became the first drug to be approved by the FDA for use as a preventive agent against cancer in women at very high risk. Subgroup analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial found that tamoxifen reduced breast cancer incidence by 62 % in *BRCA2* carriers but failed to do so in *BRCA1* carriers when started at age 35 or older (King et al. 2001). Prophylactic use of tamoxifen is also beneficial for *CHEK2* mutation carriers, who are more likely to develop hormone-receptor-positive tumors (Schmidt et al. 2007). Tamoxifen chemoprevention is reserved for women at high risk because of the associated adverse effects, such as endometrial cancer and thromboembolic events (Fisher et al. 2005). A second prevention trial conducted by the NSABP (P-2) compared tamoxifen with raloxifene and showed that raloxifene was equivalent to tamoxifen in the prevention of invasive breast cancer (Vogel et al. 2006). Raloxifene use was studied only in the postmenopausal population in this study. Patients on raloxifene had a lower rate of thromboembolic side effects and did not have an increased risk of endometrial cancer; however, raloxifene did not provide the protection against noninvasive breast cancer that was observed with tamoxifen. More recently, exemestane, an aromatase inhibitor, was also shown to reduce breast cancer risk by 65 % in a population of postmenopausal woman at high risk of breast cancer; however, data specific to the BRCA mutation carrier population have not been published to date (Goss 2011).

Investigators have explored the possible prevention effects of oral contraceptive use in women who carry a *BRCA1* or *BRCA2* mutation. Initial studies have suggested a reduction in the risk of ovarian cancer in *BRCA1* or *BRCA2* carriers after oral contraceptive use for an average of 4 years (Narod et al. 1998).

Several chemoprevention trials are under way to test sulindac and other nonsteroidal anti-inflammatory drugs to prevent the development and advancement of polyps in FAP individuals (Hampel and Peltomaki 2000). Aspirin has been investigated to prevent colon cancer in HNPCC patients. The CAPP2 trial randomized 861

HNPCC patients to aspirin or placebo. Those who took aspirin for at least 2 years had a 59 % reduction in colon cancer incidence (HR 0.41; 95 % CI 0.21–1.06; $p = 0.07$) (Burn et al. 2011).

Conclusion

Cancer genetics and hereditary cancer syndromes are opening up an entirely new arena for cancer prevention. Education is the first step in the process of cancer prevention for hereditary cancer syndromes. Understanding the concepts of cancer genetics and inheritance of hereditary cancer allows the clinician to properly identify those at increased risk. Educating the general population on the importance of maintaining accurate family records, especially of diagnosis and age of onset, is also necessary. Educating individuals and families and helping them appreciate the role of heredity in cancer will empower patients to learn more about their family history.

Understanding the genetic risks conferred to patients who carry hereditary cancer gene mutations allows for more personalized medical management strategies. Information provided through the genetic test results may serve to increase an individual's life span and to prevent cancer occurrence.

Our continued understanding of the molecular genetics of cancer at the cellular level is leading to better targeted therapies and chemoprevention options. Learning how the environment can affect a gene's function will allow individuals to modify lifestyle choices and play a part in their own cancer prevention.

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Cancer Health Disparities

6

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6.1 Introduction

Many improvements in health and health outcomes have occurred in recent years; however, there are segments of the United States (US) population that have not seen the same improvements. Among the group that has not seen equitable progress are racial and ethnic minorities, who comprise 36 % of the US population (U.S. Census Bureau 2010).

Minority groups in the USA have worse overall health and often receive lower standards of health care. This trend also applies to those who have lower incomes, are less educated, and those who live in poor neighborhoods (Health Affairs 2011). In some cases the health of these populations has declined. For more than 25 years, researchers have documented the differences and gaps in health between individuals from specific racial and ethnic groups (Braveman and Gruskin 2003). In 2000, these gaps (health disparities) were given a legal definition via the United States Public Law 106–525, also known as the "Minority Health and Health Disparities Research and Education Act," which was authorized by the National Institute for Minority Health and Health Disparities. This definition reads "a population is a health disparity population if there is a significant disparity in the overall rate of disease

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incidence, prevalence, morbidity, mortality or survival rates in the population as compared to the health status of the general population" (Minority Health and Health Disparities Research and Education Act 2000). Health disparity populations, specifically racial/ethnic minorities, also have lower life expectancy, higher mortality, and morbidity compared to Whites. In addition to overall health, individuals from these groups experience lower quality of care and have more problems accessing health care. In some cases these differences appear regardless of income or coverage by health insurance (Smedley et al. 2003; Bulatao and Anderson 2004). The goal of researchers and scientists is to identify why these differences exist and to determine strategies to reduce or eliminate them (Haynes and Smedley 1999).

Causes of health disparities are varied and complex but include factors such as the physical environment (where we work, live, and play), social environment (i.e., interactions with family, community, schools, places of worship), behavior (i.e., health choices—diet, exercise, smoking, alcohol use), and biology (genetic profile). The complex nature of health disparities necessitates multilevel, comprehensive plans and programs that involve multiple disciplines to address the aforementioned etiological factors (Carter-Pokras and Banquet 2002; Eberhardt and Pamuk 2004; Farmer and Ferraro 2005; House 2002).

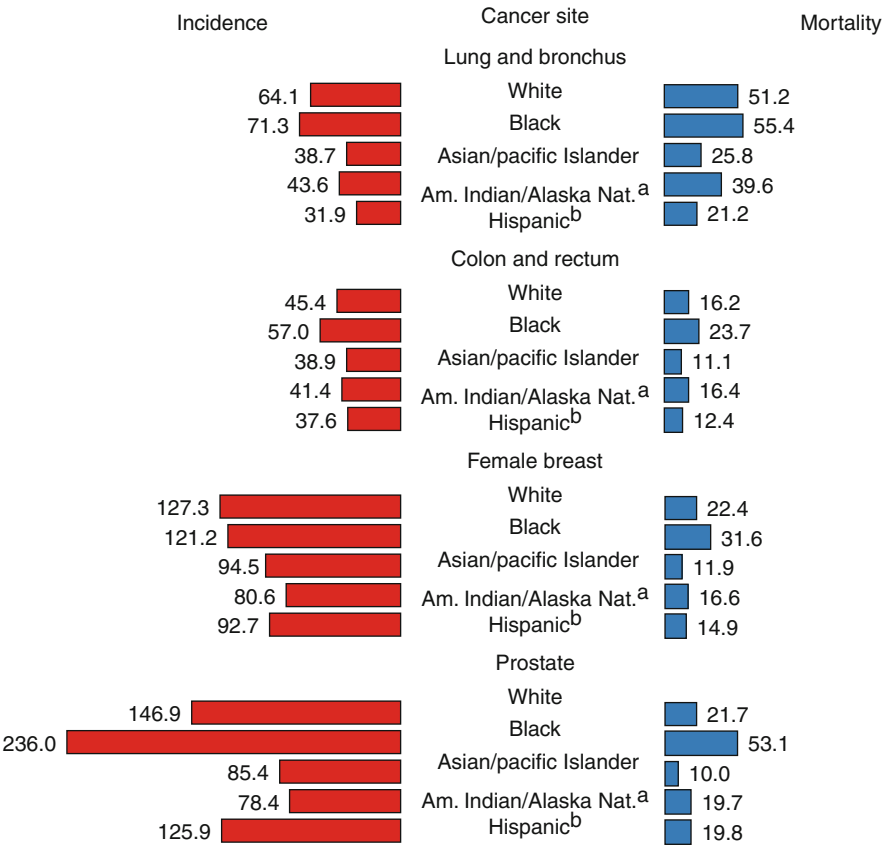
Based on emerging trends in the Census data, it is evident that the US population is becoming increasingly racially and ethnically diverse. From 2000 to 2010, every racial or ethnic minority group either increased in population or remained the same; Whites are the only racial group who decreased in population (Humes et al. 2011). Given this continuing demographic shift, and because of the evidence of poorer health outcomes in these groups, there is an urgency to understand the magnitude of disparities across various disease states, such as cancer. In order to reduce and eliminate health disparities, it is important to understand how, where, why, and for whom they arise. The purpose of this chapter is to provide information that can address these questions regarding cancer health disparities.

6.2 Cancer Health Disparities

Cancer health disparities are defined by the National Cancer Institute (NCI) as adverse differences in cancer incidence (new cases), cancer prevalence (all existing cases), cancer death (mortality), cancer survivorship, and burden of cancer or related health conditions that exist among specific population groups in the USA (NCI 2008). This chapter will discuss in more detail disparities in breast (female), cervical, colorectal, prostate, and lung cancers. These five cancers provide the best overall picture of how and for whom cancer disparities exist.

6.3 Epidemiology

Although cancer's detrimental effects are felt across all demographic groups, some groups are more affected than others regarding incidence, survival, and mortality rates. Incidence and mortality rates for all cancer types have steadily decreased or



Source: SEER 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose Monterey, Los Angeles, Alaska Native Registry, Rural Georgia California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG) and US Mortality Files.
National Center for Health Statistics, Centers for Disease Control and Prevention.
[a]Rates for American Indian/Alaska Native are based on the CHSDA (Contract Health Service Delivery Area) countries.
[b]Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/ Alaska Natives.
Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry.
Mortality data for Hispanics exclude cases from the District of Columbia. North Dakota and South Carolina.

Fig. 6.1 SEER cancer incidence and US death rates, 2005–2009 by cancer site and race/ethnicity

remained stable since 1975. Blacks or African Americans (Blacks) have the highest incidence and mortality rates for all cancer sites combined compared to any other racial/ethnic group (NCI 2008). Figure 6.1 illustrates the incidence and mortality rates for breast (female), colorectal, prostate, and lung cancers by racial/ethnic group from 2005 to 2009 according to the Surveillance Epidemiology and End Results (SEER) data (Howlader et al. 2012).

White, non-Hispanic women have the highest incidence rate of breast cancer (127.3 per 100,000 women) and have for the last two decades. However, Black

women's breast cancer mortality rates (31.6 per 100,000 women) are astonishingly higher than women of all other races and ethnicities. Interestingly, from the 1950s through the 1980s, both incidence and mortality rates were lower for Black women compared to White, non-Hispanic women. Beginning in the 1990s, this trend changed and the mortality rates for Black women are now staggering compared to other racial/ethnic groups.

Overall, colorectal cancer incidence in the USA has decreased over the last 30 years, yet it has increased in patients younger than 50 years of age. The most significant increase in colorectal cancer has occurred in patients aged 40–44 years old. Since 1985, colon cancer rates have dipped 20–25 % for Whites, while rates have gone up for Black men and stayed the same for Black women. The overall increase in colorectal cancers seems to derive largely from a higher increase in cancers located in the rectum. Patients between the ages of 20 and 45 have an increasing incidence in each 5-year interval for both colon and rectal cancer.

The disproportionate impact of prostate cancer among Black men in the USA has persisted over the past two decades. Prostate cancer accounts for nearly 40 % of the overall disparity in cancer mortality between Black and White men (American Cancer Society [ACS] 2009). In comparison to Whites, prostate cancer afflicts Black men at an earlier age, higher grades, and more advanced stages (ACS 2010b). Black men experience a 60 % higher incidence and are twice as likely to die in comparison to Whites (ACS 2011b). Due to late stage presentation at the time of clinical diagnosis, the rates of cure and survival are low for Blacks as compared to Whites (ACS 2010b). However, strides are being made as it relates to this disparity. From 1999 to 2008, the incidence of and mortality from prostate cancer decreased significantly among Black men. In spite of the declines in incidence and mortality, the disparity remains.

For both men and women, lung cancer is the second most commonly diagnosed cancer and is the leading cause of cancer-related mortality in the USA (Jemal et al. 2009). An examination of lung cancer rates shows that it affects some races more than others. There has been a decrease in overall lung cancer death rates for Blacks and other racial and ethnic groups; however, the disparity continues to persist. Blacks suffer from lung cancer more than any other population group in the USA. Blacks have higher mortality and incidence rates as compared to Whites and lower survival rates (Gadgeel and Kalemkerian 2003; Bach et al. 1999). Black men are 37 % more likely to develop lung cancer compared to White men even considering that their overall exposure to cigarettes, a proven risk factor, is lower (Howlader et al. 2012). An examination of SEER data indicate that Blacks tend to present with lung cancer at a later stage and were 66 % less likely to receive appropriate therapy and timely care compared to their White counterparts, thus partially contributing to lower survival rates.

As of 2009, there were over 247,000 women in the USA living with a diagnosis of cervical cancer. From 2005 to 2009, the cervical cancer age-adjusted incidence rate for all races was 8.1 per 100,000 women and the mortality rate was 2.4 per 100,000 women (Howlader et al. 2012). Hispanics have the highest incidence at 11.8 per 100,000 women, followed by Black women. Black women have the highest

mortality at 4.3 per 100,000 women and American Indian/Alaskan Native women have the second highest mortality (Howlader et al. 2012). More than 60 % of cervical cancer cases occur among underserved and under-screened populations of women (Scarinci et al. 2010).

6.4 Potential Causes of Cancer Health Disparities

6.4.1 Social Determinants

Cancer health disparities are a very complex set of issues that includes a myriad of potential causes. One contributor gaining increasing attention is social determinants and their impact on health disparities. According to the World Health Organization, social determinants of health are "complex, integrated, and overlapping social structures and economic systems that include the social environment, physical environment, and health services; structural and societal factors that are responsible for most health inequities. Social determinants of health are shaped by the distribution of money, power, and resources at the global, national, and local levels, which are themselves influenced by policy choices" (Commission on Social Determinants of Health 2008). More specifically, social determinants include areas such as discrimination, child development, social support, transportation, working conditions, housing, food security, health-care services, culture, and socioeconomic status (Kreiger 2005).

Socioeconomic status (SES) is a term that is used to describe one's place in society related to education, income, employment, and insurance status. All of these factors potentially affect the risk of developing and surviving cancer. It is well documented that Blacks score lower on measures of SES compared to the White population. About 13 % of the US population lives in poverty. Of this group 8 % are White and 24 % are Black. SES plays a major role in access to health care, health services, and health insurance. There are studies that have shown that health disparities track more closely with SES than race or ethnicity. Low SES, lack of health-care access, and lack of health insurance tend to be fairly prominent causes of health disparities. These individuals are also often diagnosed at later stages of disease. Many of these cancers can be prevented or treated effectively if diagnosed early (House and Williams 2000; Kaplan 1999; Keppel et al. 2005).

6.4.2 Disparities in Access to Care and Insurance Coverage

Access to care is critical in addressing an individual's health needs. Having access means that the patient has a doctor or health-care provider, hospital or clinic that is available, has the means to get there, and has the financial ability to pay for the cost of the visits and treatment if necessary (Mulligan et al. 2006). When all minority communities are compared to Whites, they are less likely to have health insurance, have more difficulty in getting care, and have fewer choices in which to receive

needed care. One clear example is that Blacks tend to receive the majority of their care in emergency rooms and are less likely to have a regular primary care doctor (Smedley 2006).

Significant data supports the fact that lack of health-care insurance significantly contributes to health-care disparities. Lack of insurance often impacts when and where individuals get treated for a medical condition. This has a direct impact on health outcomes, including cancer (Flenaugh and Henriques-Forsythe 2006). Furthermore, minorities are much more likely than Whites to be uninsured or underinsured. Thirty-seven percent of Hispanics are uninsured, which is the highest rate among all ethnic groups and 2½ times the rate of Whites. Blacks fare slightly better with approximately 25 % being uninsured. The data for Asian-Americans, Pacific Islanders, and American Indians indicate an uninsured rate of about 20 % (DeNavas-Walt et al. 2011). The rates tend to be connected to lower rates of employment-based insurance.

Underserved and low-income communities are placed at a disadvantage for receiving necessary screenings because those with health insurance are more likely to have a usual source of care than those who are uninsured (Williams 2002), and underserved communities are considerably less likely to have health insurance (DeNavas-Walt et al. 2011). For example, lacking access to care because one is uninsured greatly affects participating in cancer screenings. Not being routinely screened increases the chances of presenting with cancer at later stages when it is harder to treat, increasing the disparities in cancer mortality. Disparities in cancer screening participation exist among various population groups. For instance, in 2010, White (77.7 %) and Black women (77.8 %) were more likely to have had a Pap test within the last 3 years compared to Asian (66.1 %) and Hispanic women (73.4 %) (Smith et al. 2012). Additionally, women with higher education and access to health care are more likely to have had a Pap test within the last 3 years (Smith et al. 2012).

6.4.3 Disparities in Quality of Care

In 2003, the Institute of Medicine published a landmark report entitled "Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare" (Smedley et al. 2003). The report examined the notion that racial and ethnic minorities receive lower quality health care compared to nonminorities, even when access-related factors such as insurance status, income, and education are controlled. The report contends that these disparities are complex, rooted in historic and contemporary inequalities, and involve many participants at different levels including health systems, the processes within the health systems, managers who oversee utilization, health-care professionals, and patients. Since 2003, general improvements in the quality of care that individuals receive have occurred; however, for minorities the poor quality of care seems to persist at unacceptably higher levels compared to Whites (Agency for Healthcare Research and Quality 2011a, b). It is believed that because of the nature and complexity of this issue, a comprehensive and multilevel strategy is needed to eliminate these quality-of-care disparities.

6.4.4 Behavioral Risk Factors

Many forms of cancer can be attributed, in part, to behavioral risk factors such as smoking and tobacco use, diet, exercise, and obesity. SES plays a role in behavioral aspects of cancer risk (Kawachi et al. 2005). Those who are at lower SES tend to engage in riskier health behaviors such as smoking and tobacco use, lack of exercise, increased alcohol intake, and lower uptake of screening recommendations for most cancers. Over the past four decades, there has been tremendous progress in the reduction of individuals who use tobacco in the USA (Dube et al. 2009). Despite these efforts, one in five adults in the USA continues to smoke with some groups having higher rates of smoking. Blacks, for example, have rates that usually exceed those of other populations. Blacks initiate smoking at a later stage but continue to smoke later in life (Williams and Jackson 2005).

Obesity, exercise, and diet are well-known risk factors for cancer. According to data collected by the National Health and Nutrition Examination Survey (NHANES), Black and Hispanic men and women have higher rates of obesity (over 34 %) (National Center for Health Statistics [NCHS] 2010). An examination of exercise levels revealed White men and women report higher levels of exercise compared to all other minority groups. A correlation also exists between physical activity and education. For example, 57 % of individuals with less than an 8th grade education report no physical activity. Regarding diet, there are differences in reported nutrition intake between populations. It has been found, with the exception of Asians, that all racial and ethnic groups show low-prevalence levels of fruit and vegetable intake. These rates tend to be even lower among individuals with less education and higher levels of poverty.

Most of these behavioral differences can be attributed to being poorer and living in minority communities. Within these communities there are fewer resources, inadequate housing, fewer safe recreational facilities, less access to grocery stores that sell fresh fruits and vegetables, greater exposure to carcinogens, and marketing strategies that target this community for tobacco products. It is also believed that culture, health literacy, attitudes, and beliefs also play a role in health behaviors within minority communities.

6.4.5 Patient-Level Causal Factors

There are several patient-level factors that are believed to impact some of the observed cancer health disparities. These include patients' preferences, provider concordance, patient mistrust and experiences with discrimination, and patient refusal of recommended treatment.

6.4.5.1 Patient Preferences

Patients' preferences play a critical role in how they interact with the health-care system and their health-care providers. Patients approach the clinical encounter with different fears, beliefs, hopes, and cultural factors which may influence the

level and type of care that they receive. Patients also enter the clinical encounter with a certain level of comfort concerning the effectiveness of recommended treatment plans. This comfort level may have a direct impact on their decision to accept the recommendation from their health-care provider concerning the most appropriate cancer treatment. If there are high levels of reluctance to accept the recommendations of the health-care provider, the chances of health-care disparities increase significantly. This reluctance may stem from a lack of trust resulting from racial discrimination and a long-held history of inferior care for minorities. The negative experiences with the health-care system and providers might decrease the likelihood that minorities would participate in more robust treatments—thus directly impacting cancer outcomes and disparities (Smedley et al. 2003).

6.4.5.2 Provider Concordance

The relationship between a provider and a patient potentially impacts cancer disparities. Studies demonstrate that Black and Hispanic patients are more likely to report dissatisfaction with their provider, tend to receive poorer quality of care, and report that care is disjointed. These findings have introduced the importance of physician/patient concordance, which occurs when the physician and patient have shared identities or similarities such as race, ethnicity, gender, or age. It has been found that concordance increases trust, satisfaction, utilization of services, and informed and shared decision making among those patients. This is an area that needs further investigation regarding cancer diagnosis and treatment (Smedley et al. 2003).

6.4.5.3 Patient Mistrust and Experiences with Discrimination

Minority patients have shown higher levels of mistrust of the health-care system and health-care providers compared to other populations due to historical breaches of trust within the research enterprise and the medical encounter (Ard et al. 2003). Numerous studies have reported higher levels of perceived racial and ethnic discrimination in the health-care setting for minorities compared to nonminorities (Williams 1999; Corbie-Smith et al. 1999). More Blacks as reported by LaVeist et al. (2000) endorse the notion that racial discrimination is a common practice in health-care settings and doctors' offices. A study by Lillie-Blanton and LaVeist (1996) found in a nationwide study that 30 % of Hispanics and 35 % of Blacks believe that racism is a major problem in health care compared to only 16 % of Whites. More than half of the sample of minorities, compared to 22 % of Whites, indicated that they are very or somewhat concerned that they or a family member could be treated unfairly while seeking medical care because of their race or ethnicity.

6.4.5.4 Patient Refusal of Recommended Treatment

Multiple studies have examined how patient refusal of treatments has had an impact on health-care disparities. Black and other ethnic minorities may be more likely to refuse more invasive treatments and procedures. Given the invasive nature of some cancer treatments, more research needs to be conducted to better understand the role of patient refusal (Smedley et al. 2003). Additionally, recommendations for diagnosis, treatment, and pain management vary. For example, significant

health-care disparities occur in the receipt of appropriate cancer diagnostic tests as well as analgesics. These differences remain even after controlling for stage of the cancer and other key clinical factors (Smedley et al. 2003).

6.4.6 System-Level Causal Factors

6.4.6.1 Lack of Diversity in Medicine

The lack of diversity in medicine, research, and health care has been postulated to assume a role in cancer health-care disparities. It is believed that increasing the racial and ethnic diversity of medical providers is essential in providing care that is culturally and linguistically appropriate, especially within a nation that is becoming increasingly diverse (Kington et al. 2001). A more diverse and representative workforce will help to advance cultural competency, increase overall access to high-quality health care, help strengthen the research agenda that impacts minority communities, and address diverse management of our health-care system (Kington et al. 2001).

Another reason for diversity in the health-care workforce is to help provide access to high-quality health care for individuals who are underserved. Minorities disproportionately populate designated health professional shortage areas. Physician shortages exist in those areas; therefore, it is likely that access to high-quality care will be compromised because there are fewer places to go for care (Smedley et al. 2004; The Sullivan Commission 2004). Similarly, there is a lack of minority scientists who can help to broaden the conversation or agenda surrounding cancer health disparities. Without minority scientists, many research questions may go unstudied, and research agendas may not include issues that impact minority communities, who are disproportionately impacted by cancer (The Sullivan Commission 2004).

Equally important to the discussion of a diverse health-care workforce is the preparing and hiring of health-care executives from diverse backgrounds. The success of a health-care organization hinges on the management and leadership team. Individuals in management roles make key decisions that greatly impact the community in general and minority communities specifically. Diverse management teams, who represent the community, provide varied perspectives which often lead to tactical and strategic advantages. These advantages help position health-care organizations for success (Perez et al. 2007).

6.5 Cancer Site-Specific Disparities

As mentioned previously, this chapter delves into disparities that exist among five cancer sites. These five cancer sites demonstrate the greatest evidence of cancer disparities among segments of the US population. The information given will highlight epidemiology, causes of disparities, and strategies for reducing and eliminating each site-specific cancer.

6.5.1 Breast Cancer Disparities

Cancer is the second leading cause of death for women in the USA, and breast cancer is the most commonly diagnosed form of cancer (Eheman et al. 2012). Over the past decade, breast cancer mortality has decreased. While decreases in mortality rates are apparent, incidence rates are stagnant (Eheman et al. 2012). Given the devastating impact of breast cancer on individuals, families, and communities, many efforts and initiatives have been established to research, treat, and ultimately eradicate this disease.

6.5.1.1 Epidemiology of Breast Cancer Disparities

Breast cancer mortality has decreased; however, racial and ethnic disparities persist. Black women's breast cancer mortality rates (31.6 per 100,000 women) are higher than women of all other races and ethnicities. Overall, White, non-Hispanic women have the highest incidence rate of breast cancer (127.3 per 100,000 women) and have for the last two decades. However, when stratified by age, Black women have higher incidence rates among women that are age 40 and younger (Baquet et al. 2008). The aforementioned represents a shift that has occurred over the last three decades. According to Menashe et al. (2009), a racial mortality gap was noted in the 1980s and has increased since then. Currently, mortality rates for Black women are higher, with lower survival rates (Baquet et al. 2008). Additionally, Black and Hispanic women are diagnosed at more advanced stages, partially contributing to a poorer prognosis (Vona-Davis and Rose 2009). Native Hawaiians and Native Americans also have worse prognosis than White women, while Japanese-American women's breast cancer outcomes are better than those of Whites (Maskarinec et al. 2011). In addition to stage of diagnosis, other contributing factors are also apparent.

6.5.1.2 Causes of Breast Cancer Disparities

The existence of breast cancer health disparities has been documented for over 30 years. However, causes of disparities in breast cancer prognosis, incidence, mortality, and survival rates are not yet conclusively understood. At a basic level, evidence suggests that the risk profile for Black women, in particular, may differ from that of White women (Bernstein et al. 2003). Existing socioeconomic disparities have been identified as a major contributor to observed differences in breast cancer mortality (Vona-Davis and Rose 2009), specifically regarding the increased mortality among Hispanic and Black women. Similarly, other social determinants such as culture, poverty, and social injustice have been identified (Gerend and Pai 2008). Within the broad category of culture are more nuanced contributors such as folk beliefs, a mistrust of the health-care system, and perceived invulnerability. The role of poverty is demonstrated via less access to quality health care, the absence of a primary care physician, and inadequate or no health insurance. Health insurance often influences a woman's decision regarding when, where, and what type of care to seek—perhaps resulting in the delay of care due to the costs of testing and treatment. This delay can exert detrimental effects on timely diagnosis and treatment.

Unfortunately, Black and Hispanic women delay treatment longer than White women (Fedewa et al. 2011). However, when Black women do seek treatment, disparities in the prescribed treatment have been noted. Specifically, Black women are less likely to receive surgery as the recommended treatment (Baquet et al. 2008). Racial profiling and discrimination have been identified as social injustice barriers. However, according to Gerend and Pai (2008), many of these factors can be modified. Practically, modification of these factors will take substantial commitment and action at both the patient and system levels.

Biological factors such as family history/genetics certainly assume a role (Spector et al. 2011; Nemesure et al. 2009), with the area of genetic testing gaining prominence as women desire to make more informed decisions based upon their family history. However, there are marked disparities in genetic counseling participation, with significantly fewer Black women (with a family history of breast or ovarian cancer) receiving genetic counseling compared to White women with a similar family history (Armstrong et al. 2005). Information derived from genetic tests has prompted some women to elect mastectomies or in some cases double mastectomies based upon their risk.

The disparities that are observed with breast cancer are also due, in part, to behavioral factors such as nutrition, physical activity, and screening behaviors. According to Eheman et al. (2012), overweight individuals and those who do not engage in the recommended amount of physical activity are at a higher risk of cancer. Indeed, physical activity has been associated with a 64 % decrease in breast cancer risk among Black women (Sheppard et al. 2011). However, in a study of sisters of women with breast cancer, results indicated that Black women consumed less fruits and vegetables and were less likely to meet the ACS recommended body mass index and amount of physical activity compared to White women. Moreover, as a group, these women were no more likely to engage in healthy eating and physical activity behaviors than the general population, despite being at a higher risk for breast cancer due to their family history (Spector et al. 2011). The higher BMI, lower physical activity, and less healthy diet among Black women has also been previously observed (Forshee et al. 2003). Even Black female breast cancer survivors engage in less physical activity compared to female survivors of other races and ethnicities (Paxton et al. 2012). Screening participation is also integral to early detection, which is oftentimes dependent upon individual and system-level factors, such as pain from mammograms and cost (Mishra et al. 2012). Unfortunately, Black women are more likely to have received inadequate mammographic screening, compared to White women (Smith-Bindman et al. 2006), except in rural areas where they are more likely to be screened compared to Whites and Hispanics (Bennett et al. 2012). Inadequate screening increases the propensity for more advanced stage diagnosis, thus contributing to health disparities.

An emerging area of study is investigating causal differences among racial and ethnic subgroups. For example, in a comparative study of African-Barbadian and African American women, differences in reproductive patterns were discovered. Preliminary results suggest that this may partially account for the lower breast cancer incidence among postmenopausal African-Barbarian women (Nemesure et al.

2009). Given the influx of various subpopulations in the USA, it is necessary to understand contributors among these groups and how they may differ from those born in the United States.

6.5.1.3 Strategies to Reduce and Eliminate Breast Cancer Disparities

Strategies in research, practice, and mainstream communications have been developed to address contributors to breast cancer disparities. There are a variety of approaches designed to predict risk for breast cancer as well as to better understand environmental and behavioral factors. The Gail and Contraceptive and Reproductive Experience (CARE) models are two of the more commonly accepted breast cancer risk assessment models. As with many models, these two were initially developed for White women. The Gail model was not validated among Black women (Bondy and Newman 2003) and consequently underestimated risk among this population (Adams-Campbell et al. 2009). Therefore, the CARE model was developed with an aim to supplant the Gail model (Adams-Campbell et al. 2009).

Risk models may assist with early detection, which has contributed to the overall decrease in cancer mortality and cannot be over emphasized. Women are also encouraged to get mammograms, beginning as early as age 40 depending upon whose recommendations are followed. In 2009, mammography recommendations by the U.S. Preventive Services Task Force changed. Its current recommendations are for women from 50 to 74 to get a mammogram every 2 years, while the American Cancer Society recommends that women over 40 get a mammogram annually. In 2010, a greater percentage of American Indian/Alaska Native women (71.2 %) reported receiving a mammogram in the past 2 years, followed by Black, White, and Hispanic women (67.9, 67.4, and 64.2 %, respectively). Between 2000 and 2010, mammography use within the past 2 years was stable among all age groups of women 40 years of age and over (NCHS 2012). However, there are nuances within that recommendation that are not as frequently discussed, such as when a woman with a family history of breast cancer should begin getting mammograms. Because mortality rates are higher among Black women and disparities persist, better understanding of this subgroup's screening needs is necessary. Also, the limitations of mammograms have been stated and some endorse ultrasound techniques, in lieu of or in combination with mammograms, because they are thought to be more sensitive (Berg et al. 2008). Consensus needs to be reached and recommendations must be clearly articulated and disseminated to women, so that they can make the best health decision possible. Research can also augment efforts to understand perceptions regarding mammograms.

Community-based participatory research (CBPR) is a research orientation that has been commonly implemented to engage the affected populations as equal partners in the research process. This opens an avenue to better understand breast cancer disparities and its determinants from the target population's perspective. CBPR has been used to further delve into screening participation (Mishra et al. 2012). Theoretical models, such as the health belief model, have been employed to assess and improve individual-level factors such as Black women's understanding of breast cancer (Doughty 2012). Other interventions have utilized multiple methods to

modify screening behaviors, within the clinical encounter, by engaging the patient and providers. Results indicate that such multifaceted interventions are promising for enhancing mammography participation (Fiscella et al. 2011). Additionally, patient navigation interventions have been widely used to improve screening and are also found to increase adherence to breast cancer care regimens (Robinson-White et al. 2010).

Although genetics is considered a non-modifiable risk factor, gene expression profiling of breast tumors is a currently proposed technology for increasing survival and quality of life for diagnosed individuals. However, there are concerns that this available procedure will potentially *increase*, not decrease, breast cancer health disparities. In essence, this procedure has not been well tested and validated using minority samples (Odierna et al. 2011). Therefore, its utility among and benefit for these groups is questionable.

Marketing campaigns have also been launched which have garnered widespread attention, raised awareness, and placed breast cancer in the mainstream spotlight. Such campaigns include American Cancer Society branding itself as the "official sponsor of birthdays." Nationally televised programs and fundraisers such as "Stand Up 2 Breast Cancer" have also spurred national interest. The month of October has been widely embraced as breast cancer awareness month. Organizations such as Susan G. Komen and American Cancer Society have launched major initiatives to bring attention to this serious health issue. These corporate efforts have given breast cancer and breast cancer research greater visibility, as well as raised millions of dollars to support much needed research. It is hoped that this research will help to reduce and eliminate cancer health disparities.

Despite current initiatives, culturally appropriate efforts are still needed which focus on groups with lower survival and higher mortality rates, such as Black women. While some individual-level interventions may be helpful, it has become evident that efforts which address social determinants must be enacted to make larger leaps toward eliminating disparities and ultimately finding a cure.

6.5.2 Cervical Cancer Disparities

6.5.2.1 Introduction to Cervical Cancer Disparities

Prior to the 1950s, cervical cancer was one of the major causes of cancer deaths in women (NCI 2010). Since then, there has been a decrease in cervical cancer incidence and mortality rates, which can be attributed to advancements in the early detection of cervical cancer via the Papanicolaou (Pap) smear test (NCI 2010). For women in whom precancerous lesions have been detected through Pap tests, the likelihood of survival is nearly 100 % with appropriate evaluation, treatment, and follow-up care (ACS 2010a). The human papillomavirus (HPV) causes almost all cervical cancer cases. Specifically, two strands of HPV (HPV-16 and HPV-18) cause 70 % of cervical cancer cases (NCI 2010). The Federal Drug Administration has approved two vaccines for girls and boys ages 9–26 years old to prevent HPV infections caused by these two strands.

Even with the advancements of cervical cancer screening and prevention, there still remain groups of the population that suffer disproportionately from cervical cancer (Downs et al. 2008). Minority women, women living in certain geographical regions of the USA, and low-income women are more prone to be diagnosed with and/or die from cervical cancer (Downs et al. 2008). To address these disparities in cervical cancer, researchers and health professionals are strategically working to promote prevention through HPV vaccinations and early detection through Pap smear testing.

6.5.2.2 Epidemiology of Cervical Cancer Disparities

As previously noted, Hispanics have the highest incidence rate of cervical cancer. Black women have the second highest incidence rate and the highest mortality rate (Howlader et al. 2012). Higher cervical cancer rates are associated with low income, lower education levels, and medically underserved populations (Freeman and Wingrove 2005; Scarinci et al. 2010). Disparities in cervical cancer mortality also exist within different geographical areas. White women living in largely rural counties within the Appalachia area, Black women in the Deep South, Hispanic women along the Texas-Mexico border, American Indians in the Northern Plains, and Asian women in parts of the Central Valley of California have higher rates of cervical cancer mortality than do women in other parts of the country (Freeman and Wingrove 2005). For example, women living in Appalachia have an incidence rate of 15 per 100,000 women for invasive cervical cancer (Hopenhayn et al. 2005).

Differences in cervical cancer screening rates also exist among certain population groups. Asian and Hispanic women are less likely to report being up-to-date on Pap test screenings (Smith et al. 2012). Additionally, women with higher education and access to health care are more likely to have had a Pap test within the last 3 years compared to those with a high school degree or less and uninsured women (Smith et al. 2012). Women aged 65 years and older are less likely to be adherent to Pap testing recommendations (Akers et al. 2007; ACS 2012b). Foreign-born women are less likely to get screened for cervical cancer, regardless of race/ethnicity (Goel et al. 2003; Singh and Miller 2004). It was found that foreign-born Whites, Hispanics, and Asian-American/Pacific Islanders had lower odds of reporting a Pap smear than US-born Whites (Goel et al. 2003).

6.5.2.3 Causes of Cervical Cancer Disparities

Even though cervical cancer is nearly a preventable disease, there are underlying environmental, social-behavioral, as well as cultural issues causing disparities among portions of the US population. Cervical cancer screening, incidence, and mortality rates vary widely according to sociodemographic factors and access to health-care services (Akers et al. 2007). Major factors contributing to cervical cancer disparities consist of lacking access to care and experiencing cultural barriers that lead to screening nonadherence, low knowledge levels of HPV infection/vaccination and cervical cancer risk, and inappropriate follow-up for abnormal Pap smears (Akers et al. 2007).

Socioeconomic barriers affect access to and affordability of care and of screening services. Poverty is a strong predictor of cervical cancer screening, diagnosis, treatment, and survival odds regardless of other variables (Newmann and Garner 2005). Women living below the poverty line are three times more likely to be infected with a high-risk strain of HPV than those who are not poor (Kahn et al. 2007). Further, the factors that usually measure socioeconomic status (income, poverty level, and educational level) have all strongly been associated with cervical cancer screening, resulting in the lower the socioeconomic position, the less likely a woman will be screened for cervical cancer (Akers et al. 2007). Lacking access to health-care services is strongly correlated to low cervical cancer screening rates and receiving appropriate treatment (Akers et al. 2007; Freeman and Wingrove 2005). A usual source of care (Akers et al. 2007; O'Malley and Forrest 2002) and a physician's recommendation (Coughlin et al. 2005) has been shown to be strong predictors of Pap testing in many populations. Therefore, uninsured women are less likely to have had a recent Pap test, compared to women who have health-care coverage because they are not receiving a physician's recommendation nor do they have a usual source of care (Freeman and Wingrove 2005).

Cultural barriers affecting screening participation also exist (Downs et al. 2008). For example, Hispanic and Asian women's nonadherence to cervical cancer screening is associated with low acculturation, limited English proficiency, and being born outside the USA (Coronado et al. 2004; De Alba and Sweningson 2006; Nguyen et al. 2002; Rodriguez et al. 2005; Newmann and Garner 2005). Other cultural barriers include stigmas of sexually transmitted diseases and fears or fatalistic beliefs of cancer (Cain et al. 2007; Akers et al. 2007; Kim et al. 2008; Johnson et al. 2008).

A lack of knowledge or awareness of cervical cancer risk, screening, and HPV vaccination contributes to cervical cancer disparities as well (Behbakht et al. 2004; Cain et al. 2007). Among studies involving females ages 13 years and older, only about 15–31 % heard of HPV (Klug et al. 2008). Approximately 50 % of adolescent girls and 2 % of boys have been vaccinated (Etter et al. 2012), whereas only 32 % of age-eligible females have received all three recommended doses (Pierce Campbell et al. 2012). The Centers for Disease Control and Prevention (CDC) explored HPV awareness in a sample of diverse women and found most women did not know HPV was linked to cervical cancer (Friedman and Shepeard 2007). One study examining Haitian women's knowledge and perceptions of HPV found that they had generally low knowledge levels of HPV and had some misconceptions about viral transmission and the role of HPV in cervical cancer (Kobetz et al. 2011). Similarly, low knowledge levels of HPV infection and vaccine exist among Hispanic and Black women (Luque et al. 2010; Cates et al. 2009). The aforementioned is critically important, considering that women with low health literacy are less likely to seek medical attention for an abnormal Pap smear compared to those with adequate health literacy (Norman et al. 1991).

Another contributing factor to cervical cancer disparities is timely follow-up of an abnormal Pap test. Adherence for a follow-up test ranges considerably from 20 to 74 % (McKee 1997). The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) reported that about 56 % of women with an abnormal Pap

test who were enrolled in the program did not receive the necessary follow-up care (Downs et al. 2008). Minority women seemingly have inconsistent follow-up care after an abnormal Pap test (Engelstad et al. 2001; Cardin et al. 2001). Specifically, Black women tend to have a higher percentage of no follow-up care for an abnormal test compared to other races and ethnicities (Benard et al. 2005). Untimely follow-up care may lead to diagnosis of cervical cancer at later stages when it is harder to treat, perhaps partially accounting for observed disparities.

6.5.2.4 Strategies to Reduce and Eliminate Cervical Cancer Disparities

Key strategies for reducing and eliminating cervical cancer disparities should focus on increasing access to care and improving information and communication (Freeman and Wingrove 2005). In particular, community-based education and outreach efforts are crucial for promoting prevention/early detection and increasing knowledge and awareness of cervical cancer. Community health workers (CHWs; also called promotoras, patient navigators, or lay health advisors) have successfully provided cancer education, helped minority women navigate screening services, and drastically increased participation in Pap testing (Partridge et al. 2005; O'Brien et al. 2010). In the Appalachian region, patient navigators have been utilized to increase access for abnormal Pap smear follow-up care among underprivileged women (Scarinci et al. 2010). Strategies to address disparities in the Asian community have sought to educate and inform women on the importance of cervical cancer screening, explore the relationship between cultural factors and screening behavior, and connect women to low-cost providers or providers who do not require health insurance in the local community (Nguyen et al. 2011). A CBPR approach was implemented to address cervical cancer disparities in Haitian women. Several facilitators/barriers for receiving the vaccine were identified, which highlights the importance of culturally tailored education to address gaps in knowledge of HPV and cervical cancer (Kobetz et al. 2011).

Other vital strategies in reducing cervical cancer disparities exist within local and national programs that seek to increase access to screening services for women. For example, at the local level, the Los Angeles County Office of Women's Health implemented a Cervical Cancer Prevention and Education Initiative. This initiative is a comprehensive, multifaceted outreach and education campaign to increase awareness among high-risk, low-income, underserved minority women about the importance of Pap tests and to increase the number of screenings and treatment services provided to them (Stone-Francisco et al. 2004).

Two federal laws (Breast and Cervical Cancer Mortality Prevention Act of 1990 and Breast and Cervical Cancer Prevention and Treatment Act of 2000) have led to the creation and funding for the CDC's National Breast and Cervical Cancer Early Detection Program (CDC 2012a). NBCCEDP provides low-income, uninsured, and underserved women access to timely cervical cancer screening and diagnostic services. From 2006 to 2011, NBCCEDP screened over one million women for cervical cancer: 46 % White, 27 % Hispanic, 14 % Black, 6 % Asian/Pacific Islander, and 5 % American Indian/Alaskan Native (CDC 2012b).

Advancements in cervical cancer research, screening methodology, and vaccinations have led to decreased incidence and mortality rates, producing an almost preventable disease (Freeman and Wingrove 2005). Unfortunately, individuals still suffer disproportionately from cervical cancer in the USA due to lack of screening, HPV vaccine uptake, and not having access to care. The national endeavors to address cervical cancer disparities are valuable because individuals are being motivated to take action in the form of health-promoting behaviors, resulting in better health outcomes and reduced disparities within the community (Smedley and Syme 2000).

6.5.3 Colorectal Cancer Disparities

6.5.3.1 Introduction to Colorectal Cancer Disparities

Colorectal cancer is one of the few cancers that is considered largely preventable due to effective screening and removal of polyps. Early stage colorectal cancer may not present any symptoms; thus, screening is key. A colonoscopy every 10 years is the preferred screening strategy as it has the potential to image both cancer and polyps, thus increasing the chances of removing any polyps and preventing cancer (ACS 2011a). The average-risk man and woman should be screened starting at age 50. Those who are high risk should be screened sooner. Blacks are at increased risk of developing colorectal cancer and should be screened beginning at age 45 (Rex et al. 2009).

The general risk factors for colorectal cancer include obesity, physical inactivity, long-term smoking, a diet high in red or processed meat, alcohol, and very low fruits and vegetables intake. Also, a personal/family history of colorectal cancer or polyps, chronic inflammatory bowel disease, or inherited genetic conditions, such as Lynch syndrome, is also a risk factor. Heavy cigarette smoking and obesity are linked to an increased risk and the development of colorectal cancer at an earlier age (ACS 2011a).

Colorectal cancer risk can be decreased by increasing intake of milk, calcium, and high blood levels of Vitamin D. Also nonsteroidal anti-inflammatory drugs, such as aspirin and menopausal hormone therapy (among high-risk populations), have been found to lower ones risk of colorectal cancer (ACS 2011a).

Colorectal screening is lowest among underserved populations, including minorities and the poor, resulting in high mortality. A possible rationale for the low screening rates is that colorectal screening tests depend on a clinician referral, unlike screening exams for breast or cervical cancer. Thus, many postulate that effective communication between providers and patients is needed. This is especially true in the case of discordant race relations between doctors and patients when their differences in culture might impact their discussions and ability to convey meaning and significance of screening (Gao et al. 2009).

6.5.3.2 Epidemiology of Colorectal Cancer Disparities

Colorectal cancer is the third most common cancer diagnosis for men and women, following prostate (men) and breast (women). About 91 % of colorectal cancers are diagnosed at age 50 or older. Approximately, 143,000 new cases of colorectal

cancer will be diagnosed in 2012, and more than 51,000 colorectal cancer patients will die in 2012. Colorectal cancer is the second most common cause of cancer death. Fortunately, incidence and mortality has declined in the past 20 years; however, many preventable cases of colorectal cancer still arise. About 91 % of colorectal cancers are diagnosed at age 50 or older. Colorectal cancer is more frequent in Blacks. Overall, Blacks are 38–43 % more likely to die from colon cancer than Whites. Blacks tend to be diagnosed at a later stage, to suffer from better differentiated tumors, and to have worse prognosis when compared with Whites. Blacks are more likely to develop colorectal cancer overall, at a younger age, be diagnosed at advanced stage, and have higher colorectal cancer-related mortality (Hou et al. 2012; Dimou et al. 2009).

6.5.3.3 Causes of Colorectal Cancer Disparities

Numerous patient, provider, and health-care system barriers impede appropriate screening and early detection among minorities (Gao et al. 2009). For example, patients often lack awareness about screening recommendations, lack a regular doctor or doctor's recommendation for screening, and are burdened by the cost of co-pays or deductibles. Minority cancer patients often lack health insurance, need assistance with transportation, or cannot afford to take time off work. Some fear the screening test or test results and experience language or cultural barriers in the medical encounter. Additionally, providers often lack knowledge about current regulations or do not follow current best practices. Some providers lack office reminder systems for screenings and have an inability to meet the needs of a multicultural practice. In general the health-care system offers a lack of medical care or medical homes for patients. There is a lack of funding for uninsured patients with a colorectal cancer diagnosis and too few primary care doctors perform screenings. The high co-pays and deductibles for the insured pose a financial burden, and the lack of medical providers who accept uninsured, medical assistance, or Medicare patients also poses a challenge.

Given such factors, more than 40 % of the disparity in incidence and approximately 20 % of the disparity in mortality between Blacks and Whites can be explained by differences in screening uptake. Blacks tend to receive significantly less frequent screening than Whites. Among people with multiple affected first-degree relatives, or relatives diagnosed before age 50 years, Blacks were less likely than Whites to follow the screening guidelines. Blacks who have a family history are less likely to be screened compared with their White counterparts and when compared with Blacks who are at average risk for colorectal cancer. Ensuring access to care could dramatically reduce the disparities burden (Lansdorp-Vogelaar et al. 2012).

6.5.3.4 Strategies to Reduce and Eliminate Colorectal Cancer Disparities

A number of strategies have been enumerated as ways to curb colorectal cancer disparities, including patient-provider communication and access to care. Provider recommendation is essential to patients' adherence to colorectal cancer screening. Such recommendations should be consistent with the preferences of individual

patients. In 2002, U.S. Preventive Services Task Force (USPSTF) recommended that "the choice of specific colorectal cancer screening strategy should be based on patient preferences" (USPSTF 2002). It is possible that continually low screening rates are due in part to the complexity of the screening recommendations. Primary care patients have distinct preferences for different screening tests preferring either fecal occult blood test or colonoscopy. For example, Blacks prefer colonoscopies. Patient choice is an important factor in improving screening adherence in studies reporting improved screening rates (Hawley et al. 2008).

Additionally, efforts should be taken to address the financial factors that significantly contribute to receipt of services such as providing insurance that will improve the likelihood of receiving services and prevent deferring care due to cost of screening (Bennett et al. 2012).

Given colorectal cancer's largely preventable nature, it is paramount that widespread screening efforts ensue to halt the progression of this disease. Patients, providers, and health systems can work together to reduce the barriers and burden of colonoscopy screenings, while simultaneously promoting the benefits of early detection and treatment. By employing culturally and linguistically appropriate education and outreach efforts, those who are at highest risk for colorectal cancer will understand the relevance of disease detection and appreciate the urgency in participating in screening behaviors as well as practicing healthy lifestyles that reduce the risk of colorectal cancer.

6.5.4 Prostate Cancer Disparities

6.5.4.1 Introduction to Prostate Cancer Disparities

Over the past decade, there has been a tremendous investment in the identification of effective intervention strategies to reduce and eliminate prostate cancer disparities. When compared to men of other racial and ethnic groups, prostate cancer has affected Black men at an unmatched rate. Despite declines in prostate cancer incidence and mortality, Black men continue to have the highest incidence rates for prostate cancer in the USA and are more than twice as likely as White men to die of the disease (ACS 2010b). With the only well-established risk factors for prostate cancer being age, race, and family history, there has been an increased focus on better understanding the genetic basis of this disease, the interplay with the social and environment context, and individual behavior. In the following sections, we discuss the epidemiology and postulated causal factors for prostate cancer disparities and potential intervention strategies for reduction and elimination.

6.5.4.2 Epidemiology of Prostate Cancer Disparities

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related death among US men. The disproportionate impact of prostate cancer among Black men in the USA has persisted over the past two decades. Black men experience a 60 % higher incidence rate and are twice as likely to die in comparison to Whites (ACS 2011b). However, strides are being made as it relates to

this disparity. From 1999 to 2008, the incidence of prostate cancer has decreased significantly by 1.7 %/year among Black men. During this same time period, deaths from prostate cancer have decreased significantly by 3.7 %/year among Black men. From 2004 to 2008, the age-adjusted incidence rate for prostate cancer was 228.6 and 142.5 per 100,000 for Black and White men, respectively (U.S. Cancer Statistics Working Group 2012). The age-adjusted death rate for the same time period was 54.9 and 22.4 per 100,000 for Black and White men, respectively (U.S. Cancer Statistics Working Group 2012). Although we are seeing declines in incidence and mortality, the disparity remains. Prostate cancer is thought to account for nearly 40 % of the overall disparity in cancer mortality between Black and White men (ACS 2009). In comparison to Whites, prostate cancer afflicts Black men at an earlier age, higher grades, and more advanced stages (ACS 2010b). As a result of late stage presentation at the time of clinical diagnosis, the rates of cure and survival are low for Blacks compared to Whites (ACS 2010b). About 60 % of all prostate cancer cases are diagnosed in men 65 years of age and older, and 97 % occur in men 50 and older (ACS 2010b).

6.5.4.3 Causes of Prostate Cancer Disparities

While the disparity in prostate cancer mortality is well documented, examination of the causes is recent. As noted previously, the non-modifiable risk factors for prostate cancer are being Black, age, and family history. For men whose father, brother, or son has had prostate cancer, they have a higher-than-average risk of prostate cancer. In addition to these risk factors, to better understand the etiology of prostate cancer disparities, there are studies in progress examining the role and impact of other potential contributing factors. Such factors that have been postulated and are currently being examined include access to care, patient-centered communication, concordance of patient and physician race, level of prostate cancer knowledge, attitudes toward and perceptions of care, socioeconomic differences, differences in biological manifestation, type and aggressiveness of treatment, diet, genetics, lifestyle, and environmental factors (Bennett et al. 1998; Conlisk et al. 1999; Cooper et al. 2003; Freedland and Isaacs 2005; Howard et al. 2000; Odedina et al. 2004; Roetzheim et al. 1999; Tarman et al. 2000; Vijayakumar et al. 1996). While the examination continues, evidence of these factors being modifiable risk factors to support the exact etiology of prostate cancer disparities remains inconclusive.

Although screening and early detection, a secondary preventive strategy, have contributed to the decline in prostate cancer mortality, the scientific evidence to date has not definitively shown that screening with the PSA test reduces deaths (Andriole et al. 2009). The uncertainty with the biomarker PSA has led to much contention between clinicians, researchers, advocates, and policy makers. The contention relates in part to the biology of prostate cancer. Prostate cancer is biologically heterogeneous, where some prostate cancers grow slowly and never cause symptoms, while other prostate cancers are fast growing and metastasize quickly. The PSA is currently used as the clinical standard to detect prostate cancer. The PSA is secreted by prostate cells and when a large amount of this protein is seen in the blood, further evaluation is administered. An elevated amount of PSA does not mean cancer is

present but could be the result of an enlarged prostate or an infected prostate. Thus, the PSA is not a good predictor of detecting cancer and is likely to contribute to increased false positives and overtreatment.

From a behavior perspective, prior research has indicated that Black men know little about prostate cancer, which may serve as a primary barrier to participation in the preventive care strategies (Agho and Lewis 2001; Barber et al. 1998; Collins 1997; Wahnefried et al. 1995; Forrester-Anderson 2005; Fowler and Christie 1996; Price et al. 1993; Robinson et al. 1996; Smith et al. 1997; Steele et al. 2000; Weinrich 2001; Weinrich et al. 1998). While prostate cancer knowledge has not been correlated with increased screening behavior as some men decide to be screened after learning of the controversy surrounding the PSA test, lower knowledge levels among Blacks have been correlated with inability to recognize cancer symptoms, less access to cancer screening services, late stage presentation, lack of participation in screening activities for prostate cancer, and delays in seeking care after diagnosis, all of which ultimately impacts morbidity and mortality (ACS 2010b; Richardson et al. 2004; Smith et al. 1997; Targonski et al. 1991).

Genetic studies suggest that strong familial predisposition may account for 5–10 % of prostate cancers. Recent studies from the NCI's Cancer Genetic Markers of Susceptibility program and other investigations have identified variants in human DNA that are associated with the risk of developing prostate cancer. Different combinations of these variants have been found in men from different racial/ethnic backgrounds, and each combination is associated with higher or lower risk for prostate cancer. Nearly all of the variants associated with increased risk of developing prostate cancer were found most often in Black men, and certain combinations of these variants were associated with a five-fold increased risk of prostate cancer in men of this racial/ethnic group (Agalliu et al. 2009; Foulkes 2008; Amundadottir et al. 2006; Gudmundsson et al. 2007).

6.5.4.4 Strategies to Reduce and Eliminate Prostate Cancer Disparities

Over the last decade, there has been a host of strategies employed to address prostate cancer disparities. These strategies include the use of decision aids for prostate cancer screening and treatment in clinical and non-clinical settings, the use of lay health advisors through the community-based participatory research model, changes in public policy, addressing health literacy, and advancing models of health communication in community-based settings. While most of these aforementioned strategies focused on increasing education and awareness, the processes allowed for the examination of other etiological factors related to prostate cancer disparities. The goal to increase the knowledge levels of patients to a level which allows them to make an informed decision was found to be a unique challenge. However, Yarnall et al. (2003) concluded that due to the time constraints of the physician, they are limited in regards to being able to fully educate their patients. Educational efforts must continue at the patient level, but a change must take place in the source and method of administering such information. Myers et al. (1999) found men were more likely to participate in the informed decision-making process by the provision

of health education messages that emphasize the salience and coherence of early detection and elevation population risk. For many of the men in their study, their knowledge levels of prostate cancer treatment options were very low to nonexistent. Wilkinson et al. (2003) demonstrated prostate cancer awareness and knowledge could improve dramatically after a 1-hour seminar on the topic of treatment options for prostate cancer. Similar to the Wilkinson study, researchers are increasingly turning to decision aids as a primary source of education regarding prostate cancer treatments. Schapira et al. (1997) concluded that a videotape decision aid would benefit clinical practice by conveying knowledge to patients regarding treatment options and outcomes and encourage them to participate with their physicians in medical decision making. Onel et al. (1998) concluded standardized video presentations of treatment alternatives for prostate cancer could be incorporated into busy office practices. Both patients and physicians benefit from the increased level of understanding that allows physician/patient discussions to focus on the critical risk/benefit trade-offs rather than simply describing treatment alternatives. Similar studies assessing the role of videos in the shared decision-making process have led to similar conclusions. Besides videos, researchers have also concluded brochures and pamphlets have a significant role in the decision-making process. Schapira and VanRuiswyk (2000) concluded when used in a primary care setting, an illustrated pamphlet decision aid was effective in increasing knowledge of prostate cancer treatments. These findings were echoed by Cegala et al. (2000) who highlighted the role of brochures of enabling patients to communicate effectively. Thus, we see decision aids as a promising source in the future for educating patients regarding health matters, in our case prostate cancer treatments, enabling them to eventually make an informed decision. Decision aids may hold promise toward taking the burden of fully educating patients of such matters.

Based on these studies, it is apparent that educational efforts must not be limited to the patient level. Due to the psychological and other mental effects a person diagnosed with such a disease undergoes, it is improper to assume they fully understand the benefits, harms, or treatment outcomes and how they may affect their lives. Thus, educational efforts to increase their understanding must extend beyond the patient to their social support, which may include spouses, siblings, extended family, or friends.

The literature examining the preferences of men and spouses regarding trade-offs involved in prostate cancer treatment decisions reflect similar attitudes. Volk et al. (1999) found that women opted for more radical treatment choices than did their husbands when presented with hypothetical scenarios regarding prostate cancer treatment. Women were largely motivated by their desire to prolong time together as opposed to concern regarding the degree of burden of treatment side effects. When men were presented with similar scenarios, they were more conservative in their choices and rated potential side effects as more burdensome than their wives. Thus, we see a difference in viewpoints among patients and their spouses. Educational efforts should be targeted to increase the knowledge levels of couples with the focus on beliefs. O'Rourke and Germino (1998) found beliefs about cancer and cure were identified as major influential factors in the prostate cancer treatment

decision-making process among men and their spouses. Methods of education rendered to couples and patients' other social support include videotapes, brochures/pamphlets, hypermedia programs integrating CD-ROM and Internet technology, and the desire to discuss the cancer experiences of friends and relatives and compare it to their own. While the idea of incorporating spouses and other social support in the informed decision-making process is in the developmental stages, researchers must continue to build on the present work to identify patient and spousal/partner needs to ensure an informed decision is made based upon sufficient understanding. While steady progress has been made through educational campaigns, a plethora of studies indicate that Black men are not receiving or processing the information. Further research is needed to identify culturally appropriate communication channels to more effectively reach Black men. The disparity in knowledge about different aspects of prostate cancer illustrates the need to develop targeted and tailored information based on the sociodemographic characteristics of minority populations, such as age, educational attainment, income level, employment, marital status, and theoretically tested constructs of knowledge (Myers et al. 1994, 1999, 2000). It is also imperative that our level of inquiry begin to extend beyond the individual level to incorporate institutions, community, and policy factors. These structural and systemic improvements will help to address prostate cancer disparities in health and health care comprehensively.

Prostate cancer continues to disproportionately impact Black men when compared to men of other racial and ethnic groups. While tremendous progress has been made in the context of health promotion and education, there is an imperative to address those multilevel factors that impacts individual behavior. These include the built environment, health-care system, and policy. Comprehensive and systematically addressing these factors would allow for the reduction and elimination of prostate cancer disparities.

6.5.5 Lung Cancer Disparities

6.5.5.1 Introduction to Lung Cancer Disparities

Lung cancer is the leading cancer killer in the USA and is considered a highly preventable disease. It has been the leading cause of cancer death among men since the early 1950s and in 1987 passed breast cancer as the leading cause of cancer deaths among women (ACS 2008).

Lung cancer is the uncontrolled growth of abnormal cells in one or both of the lungs. While normal cells reproduce and develop into healthy lung tissue, the abnormal cells reproduce at a faster rate and never grow into healthy lung tissue. These growths cause tumors and eventually interfere with the normal functioning of the lungs. The tumor can eventually spread into other systems of the body and cause other damage and eventually death (Alberg et al. 2007).

Cigarette smoking is by far the primary risk factor for lung cancer, with the risk increasing based on the number of cigarettes smoked and the years of smoking. The US Surgeon General estimates that cigarette smoking causes 80 % of lung cancer

deaths in women and 90 % of lung cancer deaths in men. Individuals who are non-smokers who are exposed to cigarette smoke have a 20–30 % greater chance of developing lung cancer (U.S. Department of Health and Human Services 2004, 2006). The survival rates for lung cancer tend to be much lower than those for other common cancers. For example, the 5-year survival rate for all patients with lung cancer is approximately 15 % compared to 64 % for colon cancer, 89 % for breast cancer, and 99 % for prostate cancer (SEER 2008). Black men have higher lung cancer incidence and mortality despite the fact that Blacks have later onset of smoking and smoke fewer cigarettes per day compared to Whites (Muscat et al. 2005). Education and awareness efforts that are culturally competent are needed to help address this issue.

6.5.5.2 Causes of Lung Cancer Disparities

To date, there are no consensus guidelines for lung cancer screening, even for high-risk individuals and groups (Flenaugh and Henriques-Forsythe 2006; Smith et al. 2009). However, the causal factors that have been investigated regarding lung cancer disparities can be categorized as tobacco use, prevention/awareness, environmental exposures, and genetics.

Smoking has been well documented as the major risk factor for lung cancer among all races and ethnicities. Smoking tobacco tends to be concentrated in populations that have limited resources, low incomes, and are minorities as a coping strategy that addresses issues around stress, violence, and unemployment (Irvin Vidrine et al. 2009). Smoking tobacco is a particularly concerning issue within the Black community. Research has demonstrated that Blacks have higher serum cotinine levels per cigarette smoked, resulting in a higher intake of nicotine per cigarette smoked and slower cotinine clearance (Pérez-Stable et al. 1998). Additionally, it has been suggested that a difference in the use of menthol cigarettes may be the differences that are noted between Black and White smokers. The effects of menthol cigarettes are still not very well understood, but it is believed that these cigarettes provide higher levels of cotinine (a by-product of nicotine) in the blood, and these rates may be linked to increased levels of addiction. Menthol smokers are less likely than non-menthol smokers to feel that they can quit smoking, less likely to attempt smoking cessation, and more likely to relapse after successfully quitting (Okeuyemi et al. 2007; Gundersen et al. 2009). The higher usage of menthol cigarettes has been linked to decades of marketing that specifically target the Black community, brand choice among Blacks, and difficulty with smoking cessation. Intense marketing of cigarettes to Blacks has occurred since the 1960s. Referred to as the "African Americanization of menthol cigarettes," the tobacco industry marketed menthol cigarettes to the Black community as "smooth," "cool," and "healthier" than non-menthol cigarettes. Cigarette advertising in Black magazines was ten times more likely than magazines for the general population. It was also noted that 70 % of those ads were for menthol cigarettes (Connolly 2007). The concerted marketing efforts were seemingly successful given a report from the Substance Abuse and Mental Health Services Administration (SAMHSA) which indicates that 83 % of Black

smokers aged 12 and older choose menthol cigarettes. This compares to only 32 % of Hispanic and only 24 % of White smokers choosing menthol cigarettes (SAMHSA 2009).

The Black community is disproportionately affected by lung cancer compared to other communities, where the prevalence rate of smoking in Black men is estimated to be approximately 28 % and disparities in incidence and mortality are significant. Knowledge has emerged as a potentially causal factor. Specifically, there has been a reported difference in knowledge related to tobacco utilization. Data from the National Cancer Institute's Health Information National Trends Survey (HINTS) indicates that knowledge related to lung cancer mortality was lower among women, older adults, and non-Hispanic Blacks (Finney Rutten et al. 2008). Another study found that Hispanics and Blacks were less likely to be asked about their tobacco use, less likely to be advised to quit smoking, and less likely to have used a smoking cessation program or aid in the past year (Cokkinides et al. 2008).

Environment plays an important role in one's exposure to pollutions in the air. Exposures to secondhand smoke, asbestos, certain metals, and paints are associated with increased risk of lung cancers (ACS 2012a). Race and income has an effect on one's ability to choose where they live and or work. This in turn may expose them to higher levels of pollutions that are in their communities. Blacks have historically faced higher levels of pollutants in their communities because of racial segregation, which limit choices of where they could live. According to a recent study, Black neighborhoods face an average of 1.5 times higher levels of air pollutants than any other communities. Interestingly higher levels of pollutants are found as the SES of the residents goes down (Downey and Hawkins 2008). Another key exposure to consider is occupational exposures. It is also well documented that Blacks tend to be exposed to more toxins on the job compared to other populations. Blacks tend to have jobs that require them to work closely to toxins, such as transportation jobs. Blacks also tend to be overrepresented in the service jobs area, which leads to more exposure to environmental hazards (U.S. Environmental Protection Agency 2002).

A genetic connection to lung cancer is a young but emerging area of study. Researchers continue to look for specific types of genes that may increase risk among individuals or discover whether certain racial and ethnic populations have classes of genes that increase risk. Preliminarily analysis reveals there may appear to be a genetic association with nicotine dependence and an increased risk of lung cancer (Schwartz et al. 2009). Blacks are less likely to carry this particular gene but have a greater risk for lung cancer than Whites when the gene is present (Schwartz et al. 2009). Another study examining genes and the impact on lung cancer found a specific gene that is linked to cotinine levels (Hamidovic et al. 2012). Black smokers tend to have higher levels of cotinine in their blood compared to Whites. Cotinine is important because it is a by-product of nicotine that stays in the bloodstream after smoking. This higher level of cotinine may also suggest that Blacks might have higher levels of other carcinogens related to tobacco in their system. Some studies have examined how genetic differences impact how individuals respond to lung cancer drugs. Some of the newer lung cancer drugs have been designed to target

specific characteristics of lung cancer cells. A study of Blacks determined that they did not respond well to this new drug because they were missing the genetic characteristic that is targeted by one of the more common lung cancer drugs (Leidner et al. 2009). The progress in this area continues to be slow because of the low levels of Black patients who participate in clinical trials. This issue is elaborated upon in another section of this chapter.

6.5.5.3 Strategies to Reduce and Eliminate Lung Cancer Disparities

There have been many advances made in addressing lung cancer rates and risk factors. There is still work to be done to close the gap in lung cancer disparities between populations. In order for this gap to be closed, special attention will need to be paid to this issue and more dedicated resources focused on lung cancer disparities. Much like the strategies for other cancers, more emphasis on education and awareness of the risk factors associated with lung cancer is essential. There are many public and private organizations and agencies that have developed effective interventions to address this issue. It will be important to identify and replicate these efforts on a more national level. Many of these interventions have focused on advocacy work that includes tobacco control efforts; healthy air legislation; increased funding for research, prevention, and treatment; and finally improving the treatments for locally advanced lung cancers. A part of that effort would be to ensure that high-risk individuals are screened and treated as early as possible. It is clear that in order to see the improvements in this area, governments, health-care providers, community advocates and leaders, and individuals must understand their role and work together.

The differences that are observed in lung cancer incidence among racial and ethnic groups tend to be influenced by genetic susceptibility to lung cancer, environmental exposures, and smoking prevalence differences. Many organizations, such as the CDC, recommend an approach that is comprehensive and takes into account the factors that increase risk of lung cancer. The approach must also be evidence-based prevention and cessation strategies. Given that smoking is the most prevalent risk factor, there must be a focus on comprehensive tobacco control. From a policy perspective, enhanced smoke-free laws may have an impact on smoking rates across populations. Finally, there must be continued surveillance of smoking prevalence and lung cancer incidence within racial and ethnic groups and between groups. This surveillance will be critical in determining the impact of evidence-based interventions.

6.6 Strategies for Reducing and Eliminating Cancer Disparities

There are multiple, interrelated factors that contribute to disparities. Therefore, strategies to reduce disparities should aim to address several of these causal factors in order for groups and/or individuals to truly benefit.

6.6.1 Community-Based Outreach and Education

Community-based methods provide an imperative approach for reaching high-risk groups through education, research, and access to services and allow for community involvement in an effort to reduce health disparities (Wallerstein and Duran 2006). In particular, community health workers (CHWs) are useful in increasing access to screening services, improving the quality of care, and leading to broader social contributions, such as educational opportunities for underrepresented groups (Wells et al. 2011). CHWs are lay members of the community, who usually share ethnicity, language, socioeconomic status, and life experiences with the community members in which they serve (Health Resources and Services Administration 2007). Typical roles of CHWs consist of (1) providing an effective link between vulnerable populations and the health-care system, (2) managing care for vulnerable populations, (3) ensuring cultural competence among health-care professionals, (4) delivering culturally appropriate health education, (5) advocating for underserved individuals to receive appropriate services, (6) providing informal counseling, and (7) building community capacity to address health issues (Health Resources and Services Administration 2011).

6.6.2 Access to Health Services

An important opportunity for eliminating cancer disparities is increasing access to care, including regular, age-appropriate cancer screening participation. Early detection, via screening, has contributed to the overall decrease in cancer mortality. Providing or expanding insurance coverage for preventive services could minimize out-of-pocket expenses, which may decrease the likelihood of deferring care due to cost (Bennett et al. 2012). Anhang Price et al. (2010) suggest that to improve cancer screening rates, strategies should include (1) limiting the number of interfaces across organizational boundaries and provide on-site, same-day screenings; (2) recruiting patients, promoting referrals, and facilitating appointment scheduling; and (3) promoting continuous patient care.

National programs to increase access to screening services have been implemented such as the CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) and the Screen for Life: National Colorectal Cancer Action Campaign. The NBCCEDP provides low-income, uninsured, and underserved women access to timely breast and cervical cancer screening and diagnostic services (CDC 2012a). From 2006 to 2011, over one million women were screened for breast cancer and for cervical cancer.

The Screen for Life: National Colorectal Cancer Action Campaign began in 1999 to encourage men and women 50 years of age and older to regularly be screened for colorectal cancer. This program also provided public education, outreach, diagnostic follow-up care, and means to evaluate the program's effectiveness (CDC 2012c).

6.6.3 Health-Care Providers

Another important strategy for reducing disparities is to consider the role of the health-care provider and the need to reduce structural barriers to individual health-seeking behaviors (Shavers et al. 2002). A report by the Institute of Medicine (IOM) concluded that, based on a large body of published research, racial and ethnic minorities, in particular Blacks, experience lower quality health services and are less likely to receive even routine medical procedures than are Whites (Smedley et al. 2003). For example, Bartlett (1999) discovered that, under the existing managed care system, many Black patients complained that their health-care providers failed to provide complete information, are hurried in providing their care, and do not spend sufficient time with them. In a study by Baldwin (1996), Black patients complained that doctors do not listen to their concerns and believed their insensitivity was the result of racial bias and discrimination.

The IOM report (Smedley et al. 2003) additionally stresses the need for health-care providers to understand cultural variations. Communication is commonly linked to culture and belief systems (Roter 1987); terminology and jargon depend primarily on the culture in which individuals are reared. Post et al. (2001) concluded that taking patient characteristics, such as race and culture, into account could enhance the benefits of physician communication. To understand the attitudes and values of their patients, health-care providers must become familiar with their socioeconomic and demographic characteristics, belief systems, and health behaviors. Once they attain sufficient knowledge, they can progress to a level of cultural competency, which is the application of cultural knowledge, behaviors, and interpersonal and clinical skills that enhances effectiveness in managing patient care. Health professionals must receive education about culturally competent care and learn the role and impact of sociocultural factors on health-seeking behaviors among racial and ethnic groups, such as Blacks, early in their formal training and education (e.g., medical school, nursing school) and frequently thereafter through continuing education (Green et al. 2006).

Additionally, an increase in the number of minority providers will help in overcoming health-care barriers. Minorities continue to be severely underrepresented in health professions schools and the health-care workforce (Smedley et al. 2003, 2004; The Sullivan Commission 2004). This shortage has been established as a causal link between unequal treatment and unequal health status. The Sullivan Commission (2004) reports that (1) diversity is critical to increasing cultural competence and thus improving health-care delivery, (2) increasing diversity in the workforce improves patient satisfaction, and (3) underrepresented minority health-care providers tend to practice in underserved areas, thus improving access for the most vulnerable. The diversity of our society demands that our health-care system reflect and respond to changing demographics.

Health-care providers also play a key role in encouraging their patients to participate in cancer screenings. While uncertainty about the effectiveness of prostate cancer screening persists, patients are encouraged to make an informed decision with their health-care provider (U.S. Preventive Services Task Force [USPSTF] 2008). The underlying assumption is that adherence will increase if the patient trusts his health-care provider and has enough knowledge about prostate cancer to make a decision reflecting his

personal values. It is further anticipated that health professionals can effectively engage in discussions with patients, providing informative, unbiased health information and delivering it in a culturally sensitive manner (Nguyen and McPhee 2003). The extent of patient interaction with the health-care provider has been established as a possible facilitator or barrier to securing health information and adequate health care among racial and ethnic groups. These structural and systemic improvements will help to address cancer disparities in health and health care comprehensively.

6.6.4 Knowledge and Awareness

Strategies to increase knowledge and awareness of cancer and cancer disparities are critical to empowering individuals to take proactive measures regarding their health. Individuals need to understand ways to help prevent cancer through healthy lifestyles and know the importance of early detection through routine cancer screenings. The interventions developed and utilized by health professionals and researchers to increase knowledge and awareness desperately need to be linguistically and culturally appropriate.

It is essential to account for culture, literacy, and communication issues among populations at higher risk for disparities when implementing message interventions (Meade et al. 2007). The effectiveness of disseminating generic cancer messages through the usual channels (e.g., health-care providers and educational materials, such as CD-ROMs and DVDs) must be further evaluated with minority populations. Targeted and tailored messages must be developed and disseminated through culturally appropriate channels to ensure reception and retention.

6.6.5 Health Policy

The inclusion of health policies as a strategy for reducing health disparities is extremely effective and necessary. Policy decisions have the ability to affect the health of individuals in the greatest numbers. In particular, policies that focus on social determinants of health can have the most profound impact on disparities because they address the social conditions that contribute to the complexity of health disparities (Carter-Pokras et al. 2012). It is of even greater importance that the effectiveness of health policies be measured by a progression toward achieving health equity (Marmot 2012).

System and policy changes, although daunting, are achievable. Increasing access to quality-improved facilities, collection and reporting of health status data, as well as federal funding and policies that support American Recovery and Reinvestment Act (ARRA)-funded comparative effectiveness programs and implementation of the health reform provisions within the Affordable Care Act, are a few of the current initiatives to impact social determinants of health at the system and policy levels. Each of these efforts helps move beyond an individual-level, medical-model approach to systems and population changes that improve overall health by more readily adopting evidence-based practices and practice-based evidence (Green and Glasgow 2006).

Additionally, the Patient Protection and Affordable Care Act addresses disparities by improving access to quality health care for all Americans, with the anticipation of assisting with the reduction of disparities. Specifically, through this landmark legislation, the following improvements in the nation's health-care system will take place:

- *Preventive care*. Medicare and some private insurance plans will cover recommended regular check-ups, cancer screenings, and immunizations at no additional cost to qualifying individuals and families. The cancer screenings include mammograms and colonoscopies (U.S. Department of Health and Human Services n.d.; Patient Protection and Affordable Care Act 2010).
- *Coordinated care*. The law calls for new investments in community health teams to manage chronic disease. This is particularly relevant for minority communities as they experience higher rates of illness and death for chronic diseases such as diabetes, kidney disease, heart disease, and cancer (U.S. Department of Health and Human Services n.d.; Patient Protection and Affordable Care Act 2010).
- *Diversity and cultural competency*. The legislation expands initiatives to increase racial and ethnic diversity in the health-care professions. It also strengthens cultural competency training for all health-care providers. Health plans will be required to use language services and community outreach in underserved communities. Improving communications between providers and patients will help address health disparities particularly in Hispanic communicates, which currently have high numbers of uninsured people (U.S. Department of Health and Human Services n.d.; Patient Protection and Affordable Care Act 2010).
- *Health-care providers for underserved communities*. The law increases funding for community health centers, which provide comprehensive health care for everyone regardless of their ability to pay. It is estimated, health centers serve an estimated one in three low-income people and one in four low-income minority residents. The new resources will enable health centers to increase the number of patients they serve (U.S. Department of Health and Human Services n.d.; Patient Protection and Affordable Care Act 2010).
- *Ending insurance discrimination*. Through the legislation, insurance discrimination will be banned; thus people with preexisting conditions or who have been sick cannot be excluded from coverage or charged higher premiums. Women will no longer have to pay higher premiums because of their gender. New funding will be available to collect information on how women and racial and ethnic minorities experience the health-care system, leading to improvements that will benefit these groups (U.S. Department of Health and Human Services n.d.; Patient Protection and Affordable Care Act 2010).
- *Affordable insurance coverage*. A new health insurance marketplace will be created in 2014. These new health insurance Exchanges will offer one-stop shopping so individuals can compare prices, benefits, and health plan performance on easy-to-use websites. The Exchanges will guarantee that all people have a choice for quality, affordable health insurance even if a job loss, job switch, move, or illness occurs. The new law also provides tax credits to help more Americans pay for insurance (U.S. Department of Health and Human Services n.d.; Patient Protection and Affordable Care Act 2010).

6.6.6 Clinical Trials Participation

Cancer clinical trials are instrumental to developing new methods to prevent, detect, and treat cancer (NCI 2012). It is through clinical trials that researchers are able to make the determination whether new treatments are safe and effective and work better than current treatments (NCI 2012). There are several types of cancer clinical trials, including treatment trials, prevention trials, screening trials, and supportive and palliative care trials (NCI 2012). A key strategy to increasing the effectiveness of health care is the development of applicable prevention, therapeutic, and supportive care strategies for the American population, respective of their biological, social, and environmental differences. However, to achieve such participation and ensure the generalizability of research results, participation by all populations is needed in clinical trials. Racial and ethnic minority groups historically tend to be underrepresented in health research studies. Minorities' unwillingness to participate in research is believed to be a result of distrust originating from past research abuses, such as the U.S. Public Health Service Syphilis Study at Tuskegee (Shavers et al. 2001; Green et al. 2000; Thompson et al. 1996; Dennis and Neese 2000; Shavers-Hornaday et al. 1997; Gauthier and Clarke 1999; Svensson 1989; Williams et al. 2001; Shavers et al. 2002; Wendler et al. 2006). More recently, several studies have found other predictors to be more salient to minorities' participation in clinical trials. These include minority access to research participation, utilization of locales accessible to minority groups, knowledge and awareness of minorities' participation in research, cost, lack of insurance, study design eligibility criteria, cultural barriers, low literacy, and practical obstacles (Wendler et al. 2006; Stallings et al. 2000; Corbie-Smith 2004; Corbie-Smith et al. 2003; Katz et al. 2006, 2008; Green et al. 2011).

Several national initiatives have been implemented to address many of the aforementioned issues. Given the vast array of issues, only two will be discussed in this section. In response to the lack of insurance coverage for patients who participate in a clinical trial, a growing number of states have passed legislation or instituted special agreements requiring health plans to pay the cost of routine medical care participants receive in a clinical trial. While coverage varies by state, in 2014, the Patient Protection and Affordable Care Act will require health insurers to pay for routine cost of care in approved clinical trials for cancer and other life-threatening diseases (Phillips 2010). Out of concern with the lack of minority representation at all levels of biomedical research and to increase access to clinical trials through physicians, the National Medical Association developed the program Project Increase Minority Participation and Awareness of Clinical Trials (I.M.P.A.C.T.), which is purposed to increase the awareness, knowledge, and participation of Black physicians and consumers/patients in all aspects of biomedical research and clinical trials. Key activities through this initiative include the education of Black physicians and facilitation of their participation in clinical and biomedical research, development and distribution of culturally and contextually appropriate clinical trial materials, governance of a database of minority physician investigators interested in participating in clinical trials, dissemination of information regarding biomedical research involving Blacks to members of the National Medical Association, and

collaboration and partnerships with other organizations and entities to increase minority awareness and participation in biomedical research and clinical trials (Powell et al. 2008). Similar initiatives may prove successful with other racial and ethnic minority groups.

Conclusion

There is ample evidence to support the notion that cancer health and health-care disparities do exist in this country. These differences are consistent across the range of cancers. Disparities in cancer have a critical impact on society. Inequalities in health are simply unfair, and the notion that individuals have to suffer due to reasons primarily beyond their control is unjust (Woodward and Kawachi 2000). In a study assessing Americans' perceptions of fairness in health, those who perceived health care as an important social good believed that everyone has a right to decent health not just because health offers equal opportunities (Lynch and Gollust 2010). Health disparities affect everyone, not just the ones experiencing the inequality, resulting in a "spill over" effect (Brott et al. 2011; Woodward and Kawachi 2000). Those who are disadvantaged may lack the resources to participate in the social and economic mainstream of society, which in turn will affect the health of everyone in the community.

Healthy People 2020 established a goal of achieving health equity and thereby eliminating health disparities, in order to improve the health of all groups (U.S. Department of Health and Human Services 2012). Eliminating cancer disparities would, in essence, result in better survival rates, enhanced health-related quality of life, decreased medical costs, and perhaps in some cases the prevention of cancer altogether (NCI 2007). Promoting routine cancer screenings would result in early detection and therefore, less intensive treatment for the patient, helping to reduce the overall costs of cancer. It has been estimated that about one-third of cancer deaths can be attributed to preventable behaviors (ACS 2012a). Therefore, increasing health-promoting behaviors among individuals experiencing inequities in health can contribute to the prevention of cancer and would decrease cancer mortality rates across communities. The term "healthy community" was coined as a community that is "continuously creating and improving those physical and social environments and expanding those community resources that enable people to mutually support each other in performing all the functions of life and in developing to their maximum potential" (Duhl and Hancock 1988).

However, the realization of such a community will require interventions at multiple levels and within the complex nature in which health and health-care disparities exist. Strategies to eradicate inequities will require (a) additional research, (b) enhancements of clinical practice, and (c) system and policy changes that recognize and address past injustices and preclude future abuses. Future research must clearly articulate best practices and efficacy. Thereby, behavioral and clinical interventions can and will be more likely augmented by community-directed programs and integration of multiple professional and civic organizations in the work of improving the health of disparate populations. As well, clinical research will lead to health-care system changes and provider

practices that involve the patient, caregivers, and communities involved in finding remedies. Additionally, funding agencies will do well to tie grant and foundation funding to interventions that demonstrate both cost and practical effectiveness. Evidence-based clinical care should be the standard of care. Patients should be educated and empowered to contribute to the improvement of their clinical care experience. As well, technology and informatics should be utilized to bolster the clinical experience. Finally, institutional and insurance payer policies should be tied to evidence-based, cost-effective, improved patient health outcomes.

Eliminating cancer health disparities will not only benefit individual's health but will essentially create healthier communities. Understanding the unfortunate burden cancer health disparities causes on individuals and society, implementing effective strategies for research, policy and practice, and having hope for a better tomorrow may be the driving force for a national commitment to eliminating cancer disparities.

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Human Categories and Health: The Power of the Concept of Ethnicity

7

Kathryn Coe and Craig T. Palmer

7.1 Introduction and Background

In 2011, it was reported, based on SEER data, that cancer incidence and mortality rates were lower in other racial and ethnic groups than in Whites and African Americans, for all cancer sites combined and for the four most commonly diagnosed cancers (Siegel et al. 2011). Deaths due to cancer, between 1998 and 2007, declined in all racial/ethnic groups, with the exception of American Indian/Alaska Native (AIAN) women, where the cancer death rates remained stable (Siegel et al. 2011). Once certain cancers are diagnosed, members of racial and ethnic groups can experience a greater risk of death. African Americans (AA) compared with Whites have poorer rates of survival once cancer is diagnosed, with a 5-year relative survival rate being lower for every stage of diagnosis for nearly every cancer site. Although the causes of these disparities are not completely understood, cancer disparities continue to be evident across the continuum of cancer, from survival, to prevention and early detection, to treatment quality (Mohammed et al. 2012).

7.1.1 Cancer Screening and Stage at Diagnosis

As discussed in Chap. 6 in detail, cancer screening rates are lower in minority populations than in Whites (Walsh et al. 2004). Substantial subgroups of American women, specifically those of ethnic minorities, have not been screened for cervical

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cancer nor are they screened at regular intervals. Hispanic women are less likely to receive screening mammograms than are White or African American women (Bazargan et al. 2004). Warner et al. (2012) conducted study of 21,427 non-Hispanic White (White), Hispanic, non-Hispanic Black (Black), and non-Hispanic Asian/Pacific Islander (Asian) women diagnosed between January 1, 2000, and December 31, 2007, at a comprehensive cancer center with stage I to IV breast cancer. They found that Blacks had the highest proportion (26 %) of stage III or IV tumors. While unable to fully account for this higher proportion of late-stage tumors among Blacks, they did find that Blacks and Hispanics experienced longer time to diagnosis than Whites, and Blacks were more likely to be diagnosed with late-stage tumors. Longer time to diagnosis, however, did not fully explain differences in stage between racial and ethnicity groups.

7.1.2 Access to a Primary Care Physician and Quality Care

Cancer disparities may result from inequalities in access to and receipt of quality health care (Siegel et al. 2011). Supporting this thinking are studies suggesting that African Americans who receive cancer treatment that is similar to the treatment that Whites receive do experience similar outcomes (Bach et al. 2002). Having a regular primary care physician is associated with such things as more frequent screenings (Fox et al. 1991; Zapka et al. 1989). In a recent study of prostate cancer, racial/ethnic minorities were found to be less likely to receive definitive therapy for the treatment of disease (Underwood et al. 2004). Smith et al. (2011), in their study of patients identified in the SEER 1988–2006 registry as having been diagnosed with potentially resectable (stages 1-111A) non-small cell lung cancer, found that American Indians had survival rates that were worse than those of Whites but comparable with those of other minority groups. They argued that these survival differences could be partly explained by advanced stage at diagnosis and lower rates of treatment. Researchers have found that even among those populations in which cancers incidence rates are lower, the mortality may be higher. Dwojak et al. (2012) conducted a study of survival differences among American Indians/Alaska Natives with head and neck squamous cell carcinoma. They identified all cases of HNSCC among American Indiana/Alaskan Native and White patients from 1996 to 2007 using the SEER database. They found that AI/AN experienced decreased survival for oropharyngeal cancer (hazard ratio [HR] = 1.4; $p = .008$). After adjusting for demographic factors, survival was decreased for oral cavity cancer (HR = 1.3; $p = .05$) and hypopharyngeal/laryngeal cancer (HR = 1.6; $p = .04$). American Indians/Alaska Natives received less surgery for oral cavity cancer (78 % vs 85 %; $p = .02$). They concluded that disparities in survival did exist among American Indian/Alaskan Native patients with HNSCC and that those disparities were related to stage and differential treatment patterns.

7.1.3 The Environment and Social Determinants

Poverty, as W.E.B. DuBois noted in 1906, appears to play a dominant role in cancer disparities. Poverty is associated with the level of education received. Cancer death rates in 2007 were 2.6 times higher in the least educated than they were in the most educated. In the case of lung cancer, the death rate for men was 5 times higher for the least educated than the most educated. This difference may reflect the striking gradient in smoking by level of education (Siegel et al. 2011). Poverty also is associated with risk-promoting lifestyles (e.g., poor nutrition, physical inactivity, and obesity) that can contribute to morbidity and mortality from chronic diseases (Freeman and Chu 2005). It is perhaps for these reasons that comorbidities, including things as hypertension, diabetes, and cardiovascular disease, are more likely to be experienced by certain minority women, including AA women. Comorbidities are likely to affect survival through differences in physician recommendations related to the comorbid condition and patient's ability to receive treatment (Siegel et al. 2011). Kidney cancer incidence and death rates are highest among American Indians (AIAN). This higher incidence and mortality can perhaps be explained by the higher prevalence of obesity and smoking (Siegel et al. 2011). When cancer sites (e.g., uterine cervix, stomach, and liver) are associated with infectious agents, which are related to environment and exposure, incidence and mortality rates are generally higher in minority groups than in Whites. Stomach and liver cancer incidence and death rates are at least twice as high in Asian Americans/Pacific Islanders, compared with Whites, perhaps reflecting a prevalence of chronic infection with such things as *Helicobacter pylori* and hepatitis B and C viruses.

7.1.4 Genetics

A number of studies seem to point to the role genetic factors in disparities. Certain women may have a greater probability of inheriting genetic risk (e.g., Ashkenazi Jewish women) than do others. Breast cancer in AA women tends to be a more biologically aggressive disease (Gerend and Pai 2008). Bailes et al. (2012) found in their study of 1902 patients diagnosed with cancer-ductal carcinoma in situ (DCIS) that there was variation by self-reported race/ethnicity and age at presentation, biologic features, and treatment. Asian women were significantly younger than White or African American patients ($p < .001$), and African American patients aged >70 years and Hispanic women aged <50 years were significantly more likely to have estrogen receptor-positive DCIS than patients of other races in the same age categories ($p < .001$). Further, breast cancers in African American women often have unfavorable characteristics, with 32 % of the tumors in African American women, but only 10 % in White women, being both high grade and estrogen receptor negative (adjusted OR = 4.70, 95 % CI = 3.12–7.09) (Chlebowski et al. 2005). Men of African descent have a higher incidence of prostate cancer compared to white men (238.8 per 100,000 vs 149.7 per 100,000 for the period 1979–2009) (Howlader et al. 2011).

The link between cancer and genes may be indirect. Differential mortality in the case of prostate cancer in African American men may be related to genetic differences in the androgen pathway (Howlader et al. 2011). Yao et al. (2012) conducted a case-control study of African American (AA) women who are more likely than White (European American, EA) women to have estrogen receptor (ER)-negative breast cancer. Focusing on the fact that 25-hydroxyvitamin D (25OHD) is low in African Americans and also was associated with ER-negative tumors in EAs, they hypothesized that racial differences in 25OHD levels, as well as in inherited genetic variations, may contribute, in part, to the differences in tumor characteristics. In their case ($n=928$)-control ($n=843$) study of breast cancer in AA and EA women, they found that AAs had severe vitamin D deficiency (<10 ng/ml) than EAs (34.3 % vs 5.9 %), with lowest levels among those with the highest African ancestry. Associations for single-nucleotide polymorphisms (SNPs) also differed by race. They concluded that genetic variants in the vitamin D pathway may be related to the higher prevalence of ER-negative breast cancer in AA women.

Teasing out the relative contribution that genes versus the environment make in cancer risk is not an easy task. A number of studies have postulated that disparities in triple-negative breast cancer (TNBC), a cancer that demonstrates unique clinicopathological characteristics and survival outcomes, was more common in Hispanic women than in women from other racial/ethnic groups. Tested this possibility in a study of Puerto Rican females with TNBC residing in Puerto Rico. They identified 54 patients in the electronic medical records database and found that the median age at diagnosis was 55 years. Of the 54 cases, 51 had stage I–III presentation. T1/T2 tumors were found in 88.9 % and absence of nodal involvement in 68.5 %. Prognostic factors for progression-free survival (PFS) that were statistically significant were lymph node involvement ($p=0.02$), tumor size >2 cm ($p=0.037$), and stage IV ($p=0.00002$). The 5-year overall survival and PFS were 81 and 80 %, respectively. They concluded that as these results are very similar to published data on females from North America and Europe, differences in clinical outcome and stage at diagnosis in Hispanic women with TNBC are more likely explained by socioeconomic status and adequate access to care, rather than biological/genetic differences.

7.1.5 Epigenetics

It is possible that links between cancer disparities and race and ethnicity are related to epigenetic processes, which are affected by socioeconomic status, culture, diet, stress, the environment, and biology. Epigenetic research, to date, has helped identify biomarkers, therapeutic targets, and understand cancer causation in the general population (Mohammed et al. 2012). DNA methylation may play a role in the induction of phenotypes with increased cancer risk due to exposure to these multiple factors (Mohammed et al. 2012). DNA methylation is known to cause changes in gene expression of key regulatory genes in cancer. The few studies that have focused on epigenetic changes have reported significant epigenetic differences in various racial and ethnic groups that could account for the differences seen in tumor

initiation, progression, aggressiveness, and cancer outcome. Genes differentially methylated among these racially and ethnically diverse populations were involved in important cellular functions, such as tumor growth, tumor suppression, hormone receptors, and genes involved in tumor metastasis (Mohammed et al. 2012).

In sum, there is clear evidence that a large number of cancer disparities exist by race/ethnicity; the factors underlying these disparities are not well understood. We turn now to a discussion of the definitions of race and ethnicity because the answer to questions regarding disparities, we argue, lies in a deeper understanding of the meaning of these concepts. Definitions are inconsistent and unclear; researchers employ the concept of race and ethnicity to measure every important indicator associated with inequality or difference: socioeconomic status, cultural lifestyles and values, and genetic predispositions are all being measured by the race/ethnicity variable.

7.2 The Meaning of Race and Ethnicity

A discussion of the multifactorial elements, implicit or explicit, in the use of the terms race, ethnicity, and culture can be used to point out the elements that are fundamental to these terms and that may influence health behaviors and outcomes. While we discuss the meanings attributed to the concept of race, we will argue that the concept of ethnicity is more useful for understanding health because it has, since the origins of the term, focused on the role of traditions while acknowledging that genetics are involved. Ethnicity is best understood when we adopt the interactionist view that specifies that both genes and environmental factors interact in human development and over the life course and play a role in health and illness.

Due to the scientifically verifiable robust relationships that exist between ethnic groups and health outcomes (Kato 1996; Patrinos 2004), the term "ethnicity" is increasingly being used as categorical variables in social research related to cancer and its prevention. While an association between ethnicity and health outcomes does exist,

> …the use of ethnicity as a grouping variable in health research is disturbing to scientists. It is poorly defined, is not objectively measured, and cannot be studied in a true experiment. Thus, scientific conclusions about the causal relationship between ethnicity and health are difficult to make (Kato 1996).

The failure of scholars to agree on the traits necessary or sufficient for ethnic membership has led to controversy, with some researchers dismissing the term as a political category that is otherwise meaningless. The strong association between ethnicity and health indicates that we should not consider abandoning the term but rather suggest that it deserves careful study (Kato 1996). This is true not only for the study of health and ethnicity but for the study of ethnicity in general because "the academic specialty usually called 'race and ethnic relations' is rich in literature but poor in theory" (Van den Berghe 1981). Much of the confusion related to the term ethnicity is the result of attempts to equate ethnicity with either the biological or

genetic concept of race or the environmental concept of culture. These attempts have failed because, we argue, ethnicity incorporates both genetic and environmental factors.

7.2.1 The Problem of Race

Race originally was a taxonomic term coined by biologists to refer to a subspecies, and today, in biology, a race is a recognizably distinct division (e.g., subspecies) of a species, which is considered to be the fundamental classificatory unit. A race, thus, encompasses the dual attributes of resemblance and common ancestry and is a consequence of such things as geographic isolation, genetic drift, natural and sexual selection, and genetic mutation (Hamilton 2008).

When applied to human populations, the definition of the term race changed over time. Early explorers used the term race to refer to groups of geographically isolated human populations that seemed to be distinguishable in terms of phenotypic characteristics. Francois Bernier (1684), in his *Nouvelle division de la terre par les différents espéces ou races qui l'habitent* ("New division of Earth by the different species or races which inhabit it"), published one of the earliest human racial classifications.

In the Middle Ages, the major term used to refer to these different groups was *gens*, which is a Latin word meaning people or nation generally assumed to share common ancestry based on shared descent or lineage. Throughout the seventeenth through the eighteenth century, race continued to be identified based on similarity in appearance and was generally measured by skin color and other obvious morphologic characteristics. Linnaeus placed man as an animal into his classificatory system (Thirteen editions, 1735–1770) and divided this species into four subspecies.

In the nineteenth century, John Hall, in the preface to Charles Pickering's 1848 volume, *The Races of Mankind*, wrote that "the physical particularities and geographic distribution of the human family" were felt to "furnish one of the most interesting problems in history" (p. ix). While various and distinct classifications were compiled, at no point did scientists agree on the number of races or even on what criteria should be used to distinguish one race from another.

During the twentieth century, however, scientists began to change their minds about the importance of racial classification. Even Kroeber (1923, p. 75), who wrote that a race "is a group united by heredity, a breed or genetic strain or subspecies," that corresponded "to a breed in domestic animals," came to argue that in terms of gross physiology, all human races were much alike. Although a great many distinct characteristics distinguished different categories of humans (e.g., skin and hair color, stature, cephalic index, nasal index, texture of the hair, hairiness of the body, prognathism), other characteristics were shared, and it still was not clear which of these markers might be the most important in classifying races.

While heredity was involved (in that children resembled their parents and kin resembled one another), scientists explain these physical similarities as associated with a common geographic place of origin and reproductive isolation: the white

race, with its origin in the Caucasus; the yellow race, with its origin in Mongolia; and the black race, with its origin in Ethiopia or Africa (Gould 1981). Racial categories were seen as typologies; one of such types (black) differed from another (white, yellow, or red) (Crews and Bindon 1991).

Hoebel was yet more explicit. "A race is a biologically inbred group possessing a distinctive combination of physical traits that tend to breed true from generation to generation" (p. 69). The assumption that race was defined by genetic differences between races, often mislabled as biologic differences, is illustrated by the fact that such a grouping is at times called a Mendelian population (Zuckerman 1990). The genetic differences responsible for the physical and behavioral similarities (e.g., phenotypes) found among individuals in Mendelian populations occur because all individuals in this small population share relatively recent common ancestry.

By the twentieth century, the conditions once considered to be necessary or sufficient for membership in a particular human race were beginning to be seen as problematic. Although the characteristics that determined racial membership were due to genetic similarities resulting from common ancestry and reproductive isolation, these characteristics were beginning to appear to be arbitrary. Researchers began to argue that the term race might not be an appropriate term for human groups. In fact, a long tradition of scholarly research has argued that race is an arbitrary system of visual classification that fails to and, indeed cannot, "demarcate distinct subspecies of the human population" (Fullilove 1998).

Similarity in physical and behavioral features may be a product of genetic admixture brought about by the migrations that began to occur early in human prehistory or may be due to convergent evolution, with similar environmental pressures selecting for similar responses, including both physical and behavioral characteristics. People in Africa and in India, while perhaps sharing a dark skin, are not closely related; their dark skin may be an adaptation to particular environmental pressures. Among humans, as among other species, physical appearance is neither a reliable nor a valid indicator of relatedness or shared descent. "We are genetically far more nuanced and variable than is reflected in just skin coloration" (Patrinos 2004).

While some of the debate was related to the concerns about the concept of humans being considered as animals, there was ample reason to reject the idea of race. While subspecies and Mendelian populations are usually small, races are often large. In addition, as races were identified by ideal type, intermediate types that failed to match the ideal, such as brown as opposed to black skin, led to the breakdown of the typology. These variants could neither be forced into one of the ideal types nor ignored (Crews and Bindon 1991).

Particular mate choices, including a long history of arranged marriages and tribal endogamy can lead to rapid selection for certain morphological characteristics. As Crews and Bindon (1991) explained, cultural rules governing mate choice can lead to a rapid differentiation of such things as skin, eye, or hair color while leaving out important aspects of basic biology. Visual differences, in sum, were superficial and the racial categories based on those distinctions did not typically reflect the factors that actually were important for human classification. Most importantly, studies of actual genetic clinal distributions found that the vast majority of genetic

differences occur within any given racial category, with only a very small percentage of the variation occurring between racial classifications (Lewontin 1972). As early as 1923, Kroeber argued that "variations between individuals of the same race are often greater than differences between the races" (Kroeber 1923, p. 126). These studies led to the realization that phenotypic differences do not necessary indicate that there are dramatic genotypic differences. In addition, as there was the real fear that a clear designation of racial categories would contribute to racism, the concept of race fell into disfavor in fields such as anthropology. As all human beings were said to belong to a single species, the term race was now seen as truly inappropriate.

The rejection of the concept of race by the scientific community led to the popularity of ethnicity as a replacement in both the scientific and nonscientific literature (Bhopal and Donaldson 1998). The roots of the term ethnic are Greek (as well as Latin *ethnicus*, German *ethnikos*, and French *ethnique*), meaning a nation or people and its cultural practices. Initially, ethnicity was a term used to refer to nations or groups that were neither Christian nor Jewish but heathen (Cornell and Hartman 2007). Ethnicity was used to distinguish "them" from "us," with us being the explorers and scholars writing about exotic peoples. The second meaning of ethnic referred to "any of the basic divisions or groups of mankind, as distinguished by customs, characteristics, (or) language" (Webster's New World 1959). Ethnic groups were identifiable and distinguishable on the basis of cultural traits, which included not only the shared language and cultural practices but also the knowledge, attitudes, and beliefs shared by members of a cultural group.

At its origin, ethnicity was used to distinguish cultural homogeneity (ethnic group) from biological homogeneity (race) (Damon 1969). The use of the term "ethnic group" was promoted, based at least partially on the idea that it would stimulate discussion as to its meaning and thus clarify the meaning of race (Montagu 1962). Attempts to replace the term race with the term ethnicity, and thus shift from genetic racial categories to cultural ethnic categories, have not proven to be successful (Crews and Bindon 1991).

Ethnicity is not simply a synonym for culture. Although researchers often deny that there is a genetic component to ethnicity (Amick 1995), ethnicity does in fact have a genetic aspect. While ethnicity has been tied to cultural behavior since its origin, there is an association with other traits that are not necessarily cultural. The realization that ethnicity is not just cultural has lead to the persistence of attempts to equate ethnicity with race. For example, the terms race and ethnicity are still often found together and at least implicitly are often used as synonyms (Bulmer and Solomos 1999; Kromkrowski 2002; Scupin 2003).

Ethnic groups are also often described as being subgroups of races, and to the extent that ethnicity is seen as a subgrouping of race, it has an implied genetic component (Miranda 1997). While physical appearance may be due to convergent evolution, it can be related to genetic differences (Crews and Bindon 1991). Looking like the other members of your ethnic group was important (Westermarck 1921). Noncultural phenotypes are the most reliable markers of ethnicity (Van den Berghe 1981). For example, an individual who looks Asian is classified as Asian, even if he or

she follows no Asian cultural practices (Kato 1996). Despite attempts to define ethnicity in purely cultural terms, ethnicity is popularly seen as biological, as related to ancestry and genetics (Nagel 1996). The failure of the term ethnicity to completely replace race indicates that there is a clear sense that something important would be lost by a complete shift from a biological or genetic to a cultural definition.

There are contradictions encountered when ethnicity is used interchangeably with race. It is recognized that racial categories "are not co-extensive with any existing ethnic group" (Crews and Bindon 1991). The Serbians and Croatians are classified as White; however, few would argue that they represent a single ethnic group (Crews and Bindon 1991). As a result, many researchers have returned to using the term race but have redefined it in an attempt to make it more applicable to human categories (Bhopal 1999). Some researchers use the term race but assert that there are no identifiable innate genetic differences between races that can explain disparities in health (Fullilove 1998). If no innate genetic differences exist, it is unclear why race should be used at all instead of simply using cultural differences for these categorizations. Despite all of the problems with the term race, it has neither been abandoned nor replaced with culture because of the view that ignoring race in health statistics could lead us to ignore the disparities these statistics bring to light (Buehler 1999).

Instead of attempting to redefine race, the best solution may be to more clearly define ethnicity. The inability to define ethnicity in exclusively genetic or cultural terms implies that both factors need to be incorporated. Ethnicity must be understood within the context of the interactive view of human development.

7.3 The Interactive View of Human Development

An accurate understanding of the relationships among race, ethnicity, and culture requires an understanding of the interactive theory of human development (Alcock 2001). According to the interactive theory, the development of humans and all living organisms involves an incredibly complex interaction of both genetic and environmental factors. This requires an understanding of the terms biologic, genetic, environmental, innate, learned, culture, and tradition as well as an understanding of their interactions.

7.3.1 Biologic, Genetic, and Environmental

Much of the confusion over the meaning of ethnicity stems from the meaning of biological difference. This can be avoided by simply remembering that biology is the study of life (Thornhill and Palmer 2000). Hence, to describe something as biological is simply to declare that it is living. Often, biological is incorrectly interchanged with the term genetic. These terms, however, are not interchangeable; the traits of living, biological things (e.g., organs, limbs, skin, eye color,

behaviors) are all phenotypes. In contrast, the genes within any individual organism are merely its genotype. Phenotypes are not the same as genotypes. Any part of an organism's phenotype is the result of an interaction between genes and environmental factors.

To understand this point it is crucial to recognize that environmental factors include more than just those things normally associated with the environment. To a biologist, the environment includes all exogenetic factors, that is, everything that the genes of an organism interact with during the development of an organism, both before and after birth. Such factors include not only the air, water, nutrients, and other chemicals the organism consumes but the other living things, including humans, the organism encounters. Further, the environment includes not only things external to the organism but also chemicals within the organism that interact with genes. Hence, everything biologic is the product of both genes and environmental factors. Even an individual cell, the most fundamental building block of any larger organism, is a product of genes and certain aspects of the environment. The constant intertwining of genetic and environmental factors continues throughout the life of the organism. This is true even for behavior, the muscular-induced movements of organisms.

7.3.2 Learned and Innate

Because behavior is part of the phenotype of an organism, it is a product of the interaction of both genetic and environmental factors. This fact makes the distinction between learned and innate behaviors untenable. A behavior is learned when a specific environmental factor has been identified as necessary for the behavior's occurrence. For example, when it is identified that a person must get on a bicycle and fall off several times before they are able to ride successfully, riding a bicycle is claimed to be a learned behavior. However, focusing on only this particular necessary environmental factor causes people to overlook all of the other factors that are also necessary for a human to ride a bicycle. These include all kinds of other environmental factors during the development of the child such as oxygen, water, and nutrients, as well as certain genes that enable physical functioning to interact with environmental factors. Remove any of these necessary environmental or genetic factors and bicycle riding will never occur. All behaviors that we call learned are the result of many environmental factors and genes.

A behavior is considered to be innate when environmental factors cannot be identified as being necessary for a behavior to occur. For example, the sucking behavior of infants occurs before the infant ever sees another infant making the motion or is even exposed to a nipple. Suckling, thus, is claimed to be an innate behavior. However, there are many other factors that occur during development that are necessary if an infant is to perform the sucking motion. These include not only certain genes but the interaction of those genes with such environmental factors in utero, including maternal nutrition. Even behaviors that we call innate, in sum, are also the result of many environmental factors and genes.

Since all behavior, whether it is claimed to be learned or innate, is the result of an interaction between genes and numerous environmental factors, the distinction between learned and innate behavior has no meaning. The debate between whether a behavior is learned or innate should be replaced with attempts to identify what genes and what environmental factors are necessary to produce a given behavior or for that matter, disease.

7.3.3 Heritability and Inheritable

It is crucial to understand the term heritability and how it differs from the term inherited. Heritability is the degree to which differences between individuals are due to differences in genes. Heritability is expressed as the proportion of the variation among individuals with regard to a certain trait that is attributable to genetic rather than environmental variation (Falconer 1981). For example, differences between individual humans in height have a heritability index as high as 0.9 in some human populations (Bodmer and Cavalli-Sforza 1976). This means that about 90 % of the difference in height between individuals is due to genetic differences and about 10 % to differences in environment (e.g., nutrition, disease). However, this does not mean than any given individual's height is 90 % genetic. The height of any individual is the result of an inseparable interaction of genes and environmental factors (Alcock 2001).

The difference between heritability and inheritable is crucial because a trait can be inherited regardless of its heritability. Highly heritable traits may be inherited; for example, a tall parent can have a tall offspring. However, a highly heritable trait also might not be inherited. The offspring of a tall parent may be short because of the environment in which the offspring develops (e.g., an environment lacking nutrition or containing disease). On the other hand, inheritance often occurs in the absence of heritability. Although two hands are normally inherited from one's parents, hand number is not a heritable trait—that is, there is essentially no genetic variance underlying hand number. In times past, hand number in humans was under strong selection and that greatly reduced variation affecting the development of this trait.

7.3.4 Culture

Although culture often is asserted to involve mental states, and sometimes to involve only mental states, culture becomes important in scientific studies when certain kinds of behavior or their consequences are observed. Most social scientists refer to culture when describing socially learned behavior (Flinn 1997), but what may appear to be essential to culture is not just that it is learned and shared, but that it is acquired from another individual and potentially transmittable to a third (Palmer and Steadman 1997; Thornhill and Palmer 2000; Coe 2003). To say that culture is socially learned behavior means only that the developmental causes of the behavior include, not that they are limited to, learning experiences involving other human beings. Speaking a language, for example, is clearly a cultural behavior, because the

environmental influences leading to its occurrence include social learning. But the presence of another person is far from sufficient. Speaking a language only occurs when certain necessary genes have interacted with numerous environmental factors in addition to other people speaking the language.

If cultural is a term used to refer to socially learned and transmitted behaviors, then a culture would include a set of people who share a vast amount of socially learned behaviors. That is, the members of a culture share more socially learned behaviors with other members of that culture than they do with members of other cultures. If two cultures are geographically isolated, the cultural behaviors tend to be fairly distinct. However, in most cases, human cultures have been in contact and cultural behaviors are exchanged. Today it is probably more often likely to be true that the boundaries between cultures are at least somewhat arbitrary because of cultural behaviors being shared between what are designated as distinct cultures. The term subculture is often used because within a culture some sets of individuals share more cultural behaviors with each other than they do with other individuals in their culture.

7.3.5 Tradition

Traditional behaviors refer to only those behaviors that are socially learned from a parent or other ancestor. Thus, traditional behavior is a subset of cultural behavior and occurs when genes interact with many environmental factors, including a parent or other ancestor engaged in the behavior. Speaking a language, for example, is always cultural, but it may or may not be traditional. An individual may have learned French at school, not from parents or grandparents. Speaking a language learned from someone other than an ancestor is not traditional; learning a language from an ancestor is traditional. Until recently, not only language but nearly all other cultural behaviors were traditional.

Until recently, most shared socially learned behaviors, which were seen as characteristic of and as distinguishing a particular culture, were a consequence of social learning from common ancestors. The shared socially learned behaviors defining a culture were traditional behaviors, and the members of the culture tended to be co-descendants, all of whom inherited culture from a common ancestor through grandparents and parents. While this continues to be the case in many parts of the world in what we have come to call ethnic groups, the shared socially learned behaviors in other areas, such as in much of the USA, are primarily due to social learning from people other than ancestors. In such areas, the shared socially learned behaviors defining a culture are often not traditional.

7.4 The Interactive View of Development and Health

The view that race correlates with health assumes that genes alone produce aspects of a phenotype that is correlated in some way with health. Race may be useful in studying health issues occurring in environments in which the health issues are

highly heritable as well as inheritable but only to the extent that the racial categories used correlate with the particular genetic differences related to the health issue. The fact that such correlation is often absent, because most genetic variation is found within a given racial category instead of between racial categories, weakens the relation between race and health. This approach is further weakened by the fact that genes alone do not create aspects of a phenotype that affect health. Even if certain genes are found to correlate with a racial category and the racial category correlates with a health issue, the health issue may not be causally related to those genes. The health issue may actually be related to some aspect of the environment (e.g., diet or exposure to pollutants) that also correlates with the racial category in that particular setting. These factors severely weaken the use of race as a variable in health research.

The typical view of culture is also limited because of its focus in the development of cultural behavior. By focusing only on the necessity of interaction with other people, the other factors, including genes, tend to be ignored. These other factors may also be necessary for the development of cultural behaviors and that might be related to health conditions. A focus on only cultural variables limits our ability to explain highly heritable health conditions. For example, without an understanding of the heritability of a health condition, merely detecting a correlation between a certain cultural practice and a health issue would not indicate whether or not the health issue was likely to be inherited. This is because the inheritance of the health condition by offspring might depend on inheriting both certain genetic factors and certain environmental factors (e.g., diet) from the parents. To provide a clear example, a study conducted in Brazil of Leber's hereditary optic neuropathy (LHON) began by identifying four index cases from a remote area. Molecular analysis of blood showed that they were LHON, homoplasmic 11778, J-haplogroup. As these four individuals had an extensive family living in that rural area, 273 of the 295 family members were investigated (Sadun et al. 2002). The team conducted epidemiological interviews attempting to identify possible environmental risk factors and conducted comprehensive neuro-ophthalmological examinations, psychophysical tests, Humphrey visual field studies, fundus photography, and blood testing for both mitochondrial genetic analysis and nuclear gene linkage analysis. They found that the individuals were all descendants of an immigrant from Verona, Italy, and that subsequent generations of his descendants demonstrated penetrance rates of 71, 60, 34, 15, and 9 %. Age at onset ranged from 10 to 64 years of age. Current visual acuities varied from light perception to 20/400. The team was left unable to answer the question of why only some of the genetically affected individuals manifested the disease (Sadun et al. 2002). The obvious answer is that the expression of a disease is a consequence not only of the genes but of complex environmental factors.

Ethnicity is better able to explain health issues than are either race or culture because it incorporates both genetic and environmental (including cultural) factors. This is because ethnicity is defined by descent from common ancestors and involves the inheritance of both genes and culture. This is also why attempts to equate ethnicity with either genetic race or environmental culture have failed.

> (T)he notion that ethnicity has something to do with kinship or 'blood' is not new. Indeed descent seems to be, implicitly and very often explicitly, the essential element of the definition of those groups of 'significant others' that go under a wide variety of labels: tribe, band, horde, deme, ethnic group, race, nation, and nationality (Van den Berghe 1981).

Ethnicity, when defined by descent, incorporates both genetic and cultural factors, including those factors related to health. The key to such an understanding is an appreciation of the importance of cultural traditions and an understanding of how they are inherited. Inheritance occurs "when and only when both genetic and environmental influences are repeated between generations" (Thornhill and Palmer 2000). Traditions are a form of culture that is transmitted vertically, across generations from ancestors to descendants, parent to child. Traditions make up a significant amount of human behavior and distinguish the sets of co-descendants referred to as ethnic groups. Ethnic groups are distinguished by both genetic and environmental factors because traditions are inherited from one's ancestors when both the necessary genes and environmental factors are present.

In contrast to a race, an ethnic group is a set of co-descendants that cannot be identified solely by noncultural phenotypes. Ethnicity is a category of co-descendants often identifiable only through particular traditional cultural traits. Typically these include language, clothing, tattooing, hairstyles, dance, art, and other traits. In contrast to a race, an ethnic group is a set of people perceived to be co-descendants of a recent common ancestor (i.e., members share a more recent common ancestor with other members of the ethnic group than with nonmembers). An ethnic group is perceived to be identifiable through traditional cultural markers.

The realization that ethnicity is a combination of genetic and cultural factors does not simplify the concept of ethnicity. Although ethnicity incorporates both genetic and cultural factors, it does not perfectly correlate with either. Descent from a common ancestor predicts that members of an ethnic group may be more likely to have a certain gene, but a correlation between genes and ethnicity is far from perfect. Each child inherits only 50 % of our genes. While traditional behaviors identify one's ethnicity, not all members of an ethnic group will share all traditional behaviors. The amount of correlation between ethnic groups and both genes and traditions is also likely to vary from one ethnic group to another.

In the twenty-first century, we are less likely to find individuals who share genes due to common ancestry and who have maintained ancestral traditions. However, in the past, traditions remained unchanged for centuries or even millennia (Coe 2003). Although all forms of culture imply social interaction, traditions imply enduring social interactions between individuals sharing ancestry. The transmission of a tradition, such as learning how to make pottery, can require decades of social interaction during which strong social ties were formed and the history of the people was learned (Coe 2003). It is for this reason that anthropologists have seen traditions as embedded in social support (Corin 1995), as identifiers of group membership, and as very difficult to change without damaging important social ties (Coe 2003). Ethnicity is often communicated by using such things as distinctive cuisine and body decoration. Many ethnic groups have had explicit rules specifying that clan or tribal "brothers" or "sisters" or "siblings" were to be treated preferentially;

outsiders (e.g., those of another clan or tribe) were not to be given the same consideration. One function of ethnic costumes and outfits seems to have been to identify, continuously and unambiguously, cooperative units—the ethnic groups. For much of human history, it would have been important to identify one's affiliation with certain others and dangerous to point out one's distinctiveness or lack of membership. Farley recognized this separation when he wrote, "we are all ethnics; we represent some groupings of people who are or have been separate or different from other groupings of people" (Farley 1988, p. 2). Others have emphasized the importance of the we-they component of ethnicity when describing the "… unity that characterizes all ethnic groups… Despite differences, there is an overarching sense of 'we' (and of 'they') that emerges when collective fates and interests are at stake and when the larger group confronts outsiders" (Nagel 1996).

The failure to understand the vertical nature of culture led many sociologists to see culture as a product of horizontal social conformity acquired through proximity and readily subject to change. For this reason, sociologists predicted, especially in the decades after World War II, the demise of ethnicity. They felt that the horizontal social conformity they thought essential to ethnic identification would break down in industrialized, urban societies such as the USA (Park 1950; Wilson 1967; Bonacich 1980; Keefe et al. 1987). It was believed that ethnic groups would eventually disappear because technology is associated with urbanism that is, in turn, associated with mobility and the loss of community. Individualism (refusing to conform to others around you) and growing alienation (implied by this lack of conformity) would thus result in the loss of ethnicity.

While many of the traditional behaviors associated with ethnic groups have disappeared, it is important to recognize that identification with ethnic groups has not. A number of studies conducted in the second half of the twentieth century have shown maintenance of or increase in ethnic identification despite a historical loss of traditions and weakening of mechanisms that protected ethnic boundaries (e.g., rules of endogamy; loss of ancestral language) (Scupin 2003). For example, American individuals of Irish descent continue to identify with their ancestry despite the fact the family may have been in America for generations and the descendants have never traveled to Ireland. While many traditional behaviors that once distinguished ethnic groups have disappeared, the ethnic wars now occurring around the world demonstrate that ethnicity, including the strong passions associated with in-group membership and the antagonism directed against outsiders, remains (Coe 2003; Scupin 2003).

Ethnicity is further complicated by the fact that there are nearly an infinite number of common ancestors that could be used to delineate an ethnic group. A focus on more distant common ancestors identifies a larger ethnic group because it implies a larger set of co-descendants, while a focus on a more recent common ancestor identifies a smaller ethnic group (Palmer and Steadman 1997). All mammals, for example, share a common ancestor, although that ancestor is quite distant. All humans share a closer common ancestor with each other than with other mammals. A Hopi shares a more recent common ancestor with other Hopi than with members of other Pueblo tribes. However, a Hopi shares a more recent common ancestor with

members of other Pueblo tribes than with members of Athabascan tribes, such as the Navajo and Apache. A Hopi may share a more recent common ancestor with other American Indians, including the Athabascans, than with those of European descent (Dillehay 2001). Humans routinely expand or contract their ethnic category by focusing on more distant or nearer common ancestors in different situations. For example, a person may be a Lakota in one situation and a Native American in another.

The use of cultural behaviors and their products to identify ethnicity also complicates the concept of ethnicity. Individuals can manipulate their ethnicity by manipulating their cultural behaviors. Sociologists have noted that the ethnicity claimed by an individual could change depending on the social situation (Nagata 1974; Cohen 1978; Okamura 1981; Nagel 1996). Individuals, particularly given the mixed ancestry of most Americans, can identify with different ethnic groups at different times; there are limitations. As Van den Berghe points out, "the fiction of kinship, even in modern industrial societies, has to be sufficiently credible for ethnic solidarity to be effective. One cannot create an instant [ethnic group] by creating a myth. The myth has to be rooted in historical reality to be accepted. Ethnicity can be manipulated but not manufactured" (Van den Berghe 1981). The tie of ethnicity to at least a plausible approximation of ancestry is what makes ethnicity a more powerful concept than culture.

The importance of the interactive view of development when applied to health and ethnicity is illustrated by Alcock, who writes:

> … every visible attribute of every organism is the product of a marvelously complex and all-pervasive interaction between genes and environment. The evidence for the interactive theory of development is overwhelming, but a nice illustration of the point comes from work showing that persons with different genes can develop similar traits given the appropriate environments. A famous example of this sort comes from studies of a human gene we will label PAH. … [with certain alleles of the PAH gene make forms of phenylalanine hydroxylase that may fail to do their job properly. Persons carrying these variant genes are generally unable to convert phenylalanine to tyrosine and therefore phenylalanine typically builds up in their cells. The extra phenylalanine [in the formation of considerable amounts of… [acid], which happens to be developmentally damaging in large quantities… [the sad result [a child who suffers from severe mental retardation. (Alcock 2001)

This form of mental disability is influenced by a particular gene; therefore, individuals unaware of the interactive view of development tend to only focus on this particular factor, calling it a genetic disease that is innate in those who have it. This view is inaccurate because it ignores the other factors involved in the development of this problem.

Due to our recently acquired understanding of the interactive view of development, "today any newborn testing positive for phenylketonuria is immediately placed on a highly restrictive diet very low in phenylalanine. This intervention does not change the genes of the babies, but it does change the chemical environment of the brain cells, and thereby helps prevent the buildup of phenylalanine and its devastating by-product, phenylpyruvic acid. As a result, brain cell development usually

proceeds more or less normally, as does intellectual development. Thus, having certain alleles of the PAH gene does not condemn one to be mentally retarded. The disease is not genetically determined" (Alcock 2001).

7.5 Identifying Ethnicity Using Proxy Measures

Another advantage to a clear understanding of ethnicity is that it reveals limitations to some of the various ways that are currently used to identify a person's ethnicity. Based on the assumption that culture is acquired horizontally, general geographic origin (e.g., Cuban American, Asian American) was assumed to be a good proxy measure for ethnicity (Ortiz and Arce 1984; Kato 1996). We often continue to see geography associated with ethnicity and race. Patrinos (2004) wrote in *Nature Genetics*:

> With very rare exceptions, all of us in the U.S. are immigrants. We bring with us a subset of genes from our homelands, and for many Americans, often first-generation but more commonly second-generation, the plural noun 'homelands' is appropriate.

However, a general geographic place, such as a country, often contains numerous ethnic groups with distinct traditions. For example, the category of Native American contains hundreds of distinct tribes. Limiting geographic origin to a smaller area is helpful, although it does not solve the problem in the case of multiple ethnic groups who inhabit a geographic area.

Other proxy measures for ethnicity are language and surname, but these are also problematic. In the 1930s, the US Census Bureau began to look at Hispanics, persons of Spanish/Hispanic origin, as a separate group (Miranda 1997). An early policy in the southwestern states was to group together individuals with Spanish surnames. This practice was abandoned when a study conducted by the US Census Bureau indicated that about one-third of those who claimed Spanish descent did not have Spanish surnames, and around a third of those with Spanish surnames did not claim Spanish descent (United States, Bureau of the Census 1973). While in the USA individuals frequently inherit the last name of their fathers, those individuals may be likely to identify with maternal traditions and ethnic identity. Some surnames are shared with other ethnic groups, such as the Spanish surname Miranda, which is shared by Italians, Portuguese, Filipinos, and Brazilians (Miranda 1997). Language as a proxy measure for ethnicity would lead us to omit individuals who do not speak the language of their ethnic group. For example, a Hispanic individual may or may not speak Spanish. Many entire ethnic groups in the USA have lost their traditional language but continue to identify with the ethnic group.

Failure to define the term ethnicity explicitly and empirically has led to an inability to identify why and how ethnicity might be related to differential health outcomes and even to the argument that ethnicity may not be an important variable in health research. It is crucial to remember that ethnicity is based on ancestry and that

any number of traditional cultural behaviors may be used to identify a person with that ancestry. This approach facilitates the identification of correlations between ethnicity and health as it focuses attention on any number of possible traditions that might influence health.

7.6 Ethnicity and Health

The realization that ethnicity is a combination of genetic and cultural factors does not simplify the relationship between ethnicity and health. It does, however, direct research toward better ways to deal with the complexities of this relationship due to the focus on the inheritance of both genes and traditions that occur in the development of offspring. This makes the concept of ethnicity extremely powerful in sorting out the various genetic and environmental factors that influence individuals and their health. Consider a population where there is a correlation between a health issue and ethnicity. An understanding of what ethnicity is, and of the interactive theory of human development, allows an efficient approach to identifying the genetic and environmental factors involved in the health condition.

If there is a correlation between ethnicity and the health condition, that could mean that the condition is more common within the ethnic group for a number of reasons. The correlation could be due to genes inherited by the recent common ancestry of the ethnic group, the cultural traditions inherited by the recent common ancestry of the ethnic group, or due to some other variable that just happens to correlate with the ethnic group (e.g., residence near a toxic waste dump, socioeconomic class). Differences in health outcomes and in the behaviors that influence those outcomes may be artifacts of the tendency for certain ethnic groups to share a common socioeconomic status (Landry 1987). This realization directs investigators toward the tests needed to determine exactly which factors are related. In addition to genetic testing, variation in traditions within the ethnic group could be examined to determine which factors may be causal.

A number of anthropologists have identified traditions that are important to the persistence and well-being of groups and, hence, likely to be related to some aspect of health.

> Cultural influences on health and medical care involve such basic aspects of human behavior and belief systems as religious practices, language, folk medicine, diet, dress, norms and values, and help seeking behavior. These cultural practices in turn have an impact on perceptions of symptoms, definitions of illness, delivery of health services, disease prevention, health promotion, medical practice and patient adherence. (King and Williams 1995)

Health outcomes are influenced not only by culture but also by discrimination by the dominant culture, self-imposed isolation, physical environment, resources available, socioeconomic and political factors, limitations of health care (including provider ignorance of the sociocultural determinants of health and disease), or genetic factors (Farley 1988).

People of persistence are those ethnic groups around the world that maintain a unique group identity despite intense contact with other cultures. Anthropologists

have argued that the cultural features crucial to persistence include common "language, style of dress and adornment, religion, patterns of social interaction, and food habits" (Crews and Bindon 1991), as well as the close kinship ties that are necessary for and resulting from the transmission of traditions (Coe 2003). Ethnic clothing often functions to continuously and unambiguously identify ethnic or ancestral groups. We know that a member of the Tsachila tribe is a Tsachila by the manner of their dress, body paint, and even their hair arrangement (Coe 2003). This body decoration is inherited from one's ancestors, identifies one as a descendant of that ancestor, and identifies others who share that ancestry and with whom each must cooperate. Even today in the USA, individuals who cooperate (e.g., sorority sisters, gang members) tend to dress similarly and often claim metaphorical ancestry. Dietary traditions have been promoted as an important tradition that persists long after other aspects of culture are no longer evident (Van den Berghe 1981). Food-sharing rituals persist because they involve family and reinforce the important kinship ties that form the basis of social support (Van den Berghe 1981).

The importance of tradition is evident in the American Indian populations of the USA. American Indian tribes, as members of unique and diverse ethnic groups, tend to each have rules encouraging respect for elders (e.g., honor your elders who are the bearers of traditions) and ancestors, who are the creators of tradition. Such respect may be necessary for the successful transmission of tradition, including those related to health, and for building strong social relationships. Mothers are important in Native American societies, as families and extended families revolve around them and their children (Coe 2003). "So important are mothers that even very ferocious people…would never hurt a mother because the mother is considered the fountain of kinship" (Briffault 1931).

Religion, which in the past was often inherited from one's ancestors through one's grandparents and parents, is also often associated with rules specifying appropriate kinship behavior. Of importance to the field of cancer prevention, religion and beliefs "are at the core of preventive and curative health practices" (Airhihenbuwa 1995). Healthful behaviors are learned from ancestors via close kin and result in an obligation owed to one's ancestors. Religions around the world promote kinship behaviors that make the transmission of traditions possible. Christians, as one example, encourage individuals to honor their parents and care for their children. This rule, however, is not unique to Christianity. Kinship is the informal hierarchy used for teaching the young and reminding adults of culturally appropriate behavior. Storytelling, along with modeling and guided learning, is the method most often used to teach traditions. Humans respond to stories and they influence behavior (Coe 2003).

Some of the evidence of the relationship between traditions and health are the consequences of losing these traditions. Rapid loss of cultural traditions, whatever the cause, can leave populations vulnerable to certain health problems (Swedlund and Armelagos 1990; Corin 1995; Coe 2003). A loss of traditions, particularly those encouraging kinship behavior, may be associated with an increase in high-risk behaviors, including substance abuse and failure of a pregnant woman to protect her health and the fetus (Coonrod et al. 2004).

7.7 Applications to Disparity Research

Cancer health disparities in ethnic minorities are a serious problem in the USA. If we recognize that ethnicity is inherited and refers to categories of individuals who are co-descendants of a common ancestor, we may begin to understand its importance and the role it may play in both health and research. Ancestors are a key to understanding ethnicity, yet it is important to determine the breadth of how ancestry is defined. The guidelines of the 1990 census already recognized the importance of ancestry and inheritance of ethnicity. "A person is of Spanish/Hispanic origin if the person's origin (ancestry) is Mexican, Mexican-American, Chicano, Puerto Rican, Cuban, Argentinean, Colombian, Costa Rican, Dominican, Ecuadorian, Guatemalan, Honduran, Nicaraguan, Peruvian, Salvadorian, from other Spanish-speaking countries of the Caribbean or Central or South America, or from Spain" (United States, Bureau of the Census 1990).

Although ancestry is included in this definition, the term Hispanic refers to a very heterogeneous population. Hispanics share only very distant ancestors, perhaps one that lived tens of thousands of years ago, because the ancestors of Hispanics came from indigenous populations spread across the Americas, as well as from populations living in Europe, Asia, and Africa. Some Hispanic ancestors, like those of American Indians, came hundreds or even thousands of years ago from different and diverse ecological habitats. These ancestors brought distinct cultural behaviors that underwent unique adaptations in response to the environment encountered in the New World. These practices were blended with older ones to produce a rich and highly diverse cultural fabric. Today, through the process of acculturation to a more western lifestyle, many of these traditions are rapidly disappearing. Hispanic is an extremely complex term that has historical, social, cultural, legal, and political connotations and ramifications.

It is not clear how much of the variance in health outcomes can be explained by unique genetics and cultural practices attributed to such a diverse ethnic category. There are regional patterns and socioeconomic patterns to disease incidence that may or may not be associated with ethnicity. Lack of access to health-care providers means not only that diagnoses are underreported but also that diseases are diagnosed at later and more serious stages. Nevertheless, by recognizing that ethnicity is related to descent, we gain a great deal of understanding. The proper focus on individuals sharing common descent has a genetic component (genes are inherited from ancestors) as well as cultural components (traditions are inherited from ancestors).

Many of the problems currently faced in health research disparities are related to our current inability to understand ethnicity and its importance. Researchers have often used the wrong frame of reference. In so doing, researchers have placed themselves in the position of trying to understand ethnicity from the standpoint of a period of time in which intermarriage, migration, and westernization have led to ethnic groups in which the members have few, if any, cultural traits in common.

For this reason that Fullilove criticized health research for focusing on "small periods of time… [e]ven longitudinal studies are limited to 40 or 50 years. The evolution of human behavior and ecosystems within which it is located must be

understood from the perspective of much longer time frames" (Fullilove 1998). Ethnicity, as van den Berge explains, has to be validated by several generations of common historical experience (Van den Berghe 1981, p. 16).

By focusing on ethnicity as a descent category that develops over time, we can turn this complex concept into a powerful means of identifying both the genetic and environmental (including cultural) factors influencing health. However, this will only be possible if political agendas are kept separate from the scientific study of ethnicity and health. This represents a considerable challenge because as ethnicity is associated with in-group and out-group identity, it has always been political, associated with judgments of good and bad, appropriate and inappropriate. In 1923, Kroeber cautioned anthropologists, warning them that discussions of race were very likely to be guided by "feeling, usually of considerable strength, which tends to vitiate objective approach" (Kroeber 1923, p. 205). For some researchers and many laypeople, ethnicity is pejorative, a name given to minority populations by a "dominant" society. For these individuals, the established race and ethnic classifications or taxonomies in American societies evolved from systems of stratification, power, and ideology (Amick 1995). In this setting, certain populations are seen as marginal, dismissed as "ethnics" because they lack political power and have a low social status (Amick 1995). For others, ethnicity is a positive, "Diversity and ethnicity are basic to our species. Many of us want to be different in belief, looks and actions from others…" (Farley 1988, p. 1). The positive nature of ethnicity may be implied in the way people continue to identify with ethnic groups, long after identifying features have been lost and boundaries erased and even when faced with prejudice for such an identification.

Both of these positions, however, may be guilty of the naturalistic fallacy. From a scientific point of view, ethnicity is neither good nor bad, it just is. Cross-cultural judgments that conclude that some ethnic groups are somehow less or better than others are simply judgments. To the extent that such judgments affect health and access to health services, they are examples of racism or ethnocentrism. Clearly, while this political aspect of ethnicity should be the focus of study, we should recognize that if we are to understand the fundamental meaning of ethnicity, we have to appreciate that there are, inherently, no differential values related to ethnic group membership. All of our ancestors, evolutionarily speaking, were equally successful. They all left behind them a line of descendants that began with the origins of life on earth and continues until today. Ethnicity and race as a political category have unfortunately led to claims that current racial and ethnic designations have little relevance to science and are essentially pragmatic or politically expedient categories (Weissman 1990; Hahn 1992; Hahn et al. 1992). Ethnicity, however, is much more.

Conclusion

Ethnicity cannot be understood as a term useful in scientific study until its necessary elements (genes, environment, heritability, inheritability, culture, and traditions) are understood. Once we understand that all these elements play a role in the disease process, we can begin to move forward in the study of the relationship between ethnicity and disease. Both the genetic and environmental

backgrounds are important. The field of genomics now makes it possible to study the underlying mechanisms of human health in relation to diet and other environmental factors (Desiere 2004). However, the environment is more than drugs and toxic pollutants; it is complex and involves social relationships and traditional behaviors.

Traditions do not only serve as in-group and out-group identification. The process of transmitting a tradition from one generation to the next builds the social relationships that are crucial to health. Health behaviors, today as in the past, are by and large taught in families. Family members are present to reinforce these behaviors. Kinship is centered on a maternal-child relationship that is characterized by the responsibilities the one at the top of the hierarchy, the mother, has to those beneath. Many health programs, utilizing indigenous health-care workers, are based on this model. However, more than a benevolent hierarchy is implicated in promoting health behaviors. We ignore families in our health promotion efforts at our peril because families reinforce behaviors in a myriad of ways.

Finally, programs that interest ethnic minorities and nonminorities should be developed based on the methods used in traditional societies to educate the young and to reinforce beliefs among adults. Cultures are holistic; education takes place during all activities of daily living. Learning incorporates the humanities, the spiritual, and the pragmatics of subsistence strategies for procuring food. Those from whom we learn are those we trust. Learning traditionally has not been done in a classroom setting but involves modeling and guided practice. A lecture approach to health will never be attractive to people who have been raised in a rich cultural environment nor will it be an effective teaching method.

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Complementary and Alternative Approaches to Cancer Prevention

8

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8.1 CAM and Cancer Prevention Research

Although there are no proven methods to definitively prevent cancer in either conventional medicine or CAM, many cancer prevention approaches currently under investigation focus on dietary changes, nutritional supplements, lifestyle modifications (e.g., increasing exercise, decreasing sun exposure), and decreasing environmental exposures, many of which fall into the field of CAM research. Although the field of research on CAM in treatment of diseases, including cancer, has exploded in the past few years, there is a notable lag in the development of research protocols in the area of cancer prevention. Research on treating disease generally progresses through systematic phases of theory development, lab and animal testing, followed by small pilot trials to large population studies (see Chap. 1). However, prevention research may follow a less convenient trajectory. Theories of cancer prevention often originate from correlational, longitudinal databases or observations of populations, national or cultural patterns of diet, or lifestyle that might impact cancer rates (Krishnaswamy 1996).

Following epidemiologic investigation, potential mechanisms for affecting the precursors or biomarkers of cancer development (and those associated with prevention of recurrence when applicable) are studied. Although identification of biomarkers indicating a cancer diagnosis is still a challenge (Diamandis 2010), there are a number of precursors, mostly related to stress and inflammation, that suggest higher risk for cancer and may be useful targets for early intervention for prevention. Trials to investigate

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the effects of manipulating such variables and eventually measuring cancer outcomes in CAM have yet to take a prominent role in the USA. Large-scale national trials in conventional chemoprevention and in nutritional interventions (see Chap 3) show promise for teasing out factors that might make a difference. A recent trend in NCCAM priority funding has been to explore mechanisms of action of CAM practices such that biological changes and biomarkers can be identified that may eventually produce CAM candidates ready for examination in larger cancer prevention trials.

Cancer patients and survivors are increasingly turning to CAM approaches for treatment and alleviating the side effects of treatment. In an early systematic review, Ernst and Cassileth (1998) estimated that one-third of all cancer patients in North America and the United Kingdom (UK) used CAM. The increasing and continued move toward CAM among cancer patients since that time (Oh et al. 2010) makes it even more important for researchers to test safety and effectiveness of these alternatives (Cassileth and Deng 2004). Over the past few years, the term "integrative oncology" has been increasingly used to describe clinical settings or research approaches that combine the best of conventional cancer care with evidence-based CAM practices. The Society for Integrative Oncology (SIO), their associated journal, and a growing body of researchers have progressed in building an evidence base for many aspects of integrative care (SIO 2007). This approach is largely based on the biomedical model, which allows some aspects of CAM to be more easily integrated into conventional care. Many of the modalities used focus on symptom relief during cancer care. However, some of them also focus on preventing cancer recurrence by strengthening the immune system or interventions having direct apoptotic effects (Gordon and Curtin 2000). It is of note that the more recent complementary and alternative cancer care books are increasingly evidence based and shifting toward integrating conventional and CAM approaches, emphasizing integrative care (Alschuler and Gazella 2007).

The use of CAM in cancer prevention has not been thoroughly evaluated despite growing evidence that the public is utilizing a wide range of practices and products with that intent. A report published in 2009 indicates that CAM accounted for approximately 1.5 percent of total health care expenditures ($ 2.2 trillion), including 11.2 percent of total out-of-pocket expenditures each year in the United States (Nahin et al. 2009). Specific to cancer prevention, 55 % of sampled men with a family member diagnosed with prostate cancer were using some form of CAM, and 30 % were using supplements specifically purported to be prostate-specific cancer prevention agents (Beebe-Dimmer et al. 2004).

8.2 Botanical Agents: Foods, Spices, and Herbs

CAM cancer prevention strategies that employ botanical agents are often directed toward specific physiological pathways. These strategies may include foods, spices, botanicals, or specific nutrients. Possible chemopreventive effects of these agents may be due to their antioxidant, immune-modulating, hormone-modulating,

anti-angiogenic, apoptotic, or antimetastatic properties. Many of these properties have been described in detail elsewhere (Boik 2001; Gullett et al. 2010; Park and Pezzuto 2002). Some of the most promising candidates for further exploration, according to the existing literature, are summarized here.

The definitive line between a food, a spice, and an herb is easily blurred depending on how substances are prepared or formulated. For example, garlic may be considered a food, a flavoring, or an extract. In general, a food is considered something that is eaten as a primary source of nutrition. Much of the food chemoprevention literature focuses on dietary approaches that encourage eating high amounts of fruits, vegetables, and whole foods (i.e., foods that have not been commercially processed ACS, 2009). Cruciferous vegetables, fiber, and soy continue to be investigated for activity in cancer prevention. Other dietary research efforts in cancer prevention have focused on the benefits of specific diets, such as a macrobiotic diet (Kushi et al. 2001). Micronutrient and dietary interventions for cancer prevention are addressed in more detail in Chap. 3 of this book.

Spices are the aromatic parts of plants that are used as seasonings, rather than for nutrition. Some spices, as well as many foods, contain concentrated amounts of phytochemicals (naturally occurring biochemicals that give plants their color, flavor, smell, and texture) that may have preventive properties (Nishino et al. 2000). Many of these properties have been demonstrated in vitro and in preclinical or animal studies, with only limited data in humans (Lampe 2003). Antioxidants, which help prevent free radical formation and damage, are found in cloves, cinnamon, oregano, pepper, ginger, garlic, curcumin, coriander, and cardamom (Wu et al. 2004). Biotransformation enzymes, which metabolize chemical carcinogens, are induced by coriander, curcumin, cinnamon, and *Wasabia japonica* (Japanese domestic horseradish). Garlic, cloves, cinnamon, chili, horseradish, cumin, tamarind, black cumin, pomegranate seeds, nutmeg, onion, and celery have all demonstrated antibacterial activity. Ginger and curcumin have anti-inflammatory properties.

Botanicals, more commonly known as herbs, may be fresh, dried, freeze-dried, juiced, or extracted. The whole or specific parts of the plant may be used, including the leaf, flower, stem, or root. Some of the cancer-related research on botanicals to date focuses on the role of botanicals to treat cancer (e.g., mistletoe extract) (Zarkovic et al. 2001). However, an increasing amount of research is focusing on botanical agents for their chemopreventive effects.

The specific agents reviewed below provide examples of the various mechanisms being investigated in botanical chemoprevention research: curcumin for its antioxidant and anti-inflammatory properties, flaxseed for its hormone-modulating effects, mushrooms for their immune-modulating properties, and ginseng for its immune-modulating and adaptogenic effects. It is important to note that these and other herbal agents have active substances that may interact with other herbs, supplements, or medicines and may have unexpected side effects. Herbal products that modulate certain enzymes or proteins may have adverse interactions with anticancer medications (e.g., ginkgo, echinacea, ginseng, St. John's wort, kava) (Sparreboom et al. 2004). All foods, spices, and herbs used for medicinal

purposes should only be taken under the care and supervision of a practitioner highly trained in the area of botanical medicine.

8.2.1 Curcumin

Curcumin, an extract of turmeric (*Curcuma longa*), has potent antioxidant and anti-inflammatory effects and has been studied as a chemopreventive agent for many cancer tumor sites. Preclinical studies of curcumin have demonstrated its ability to inhibit carcinogenesis in breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, and prostate cancer models (Agarwal et al. 2003; Aggarwal and Shishodia 2006). Multiple molecular targets have been identified, including, but not limited to, NF-κB (nuclear factor-kappa B), AP-1, STAT3, Akt, Bcl-2, Bcl-X_L, caspases, PARP [Poly (ADP-ribose) polymerase], IKK (Ikappa B kinase), EGFR (epidermal growth factor receptor), HER2 (human epidermal growth factor receptor 2), JNK (Jun N-terminal kinase), MAPK (mitogen-activated protein kinases), COX2 (cyclooxygenase 2), and 5-LOX (5-lipoxygenase). Curcumin's ability to preferentially kill tumor cells and not healthy cells makes it extremely valuable (Ravindran et al. 2009). In addition, curcumin has several mechanisms of action for killing cancerous cells making the cells less prone to resistance (Ravindran et al. 2009). Recent research has begun to explore the ability of curcumin to target stem cells that may become cancer cells, particularly in breast tissue (Li et al. 2011). Curcumin has also been shown to inhibit phase I enzymes and induce phase II enzymes, such as glutathione-S-transferase (Sharma et al. 2005). To date, some of the most promising effects have been demonstrated in colon cancer models. Phase I and II trials have shown the safety and tolerability of curcumin in colorectal cancer patients using doses of up to 8 g/day. Phase II trials are currently examining curcumin's effect in primary and secondary colon cancer prevention. Recent studies are beginning to focus on improving the delivery of curcumin because of its insolubility (Bansal et al. 2011).

8.2.2 Green Tea

The polyphenols contained in green tea (*Camellia sinensis*) are potent antioxidants that interfere with cancer initiation, development, and progression (Chen et al. 2011). Although the exact protective and treatment mechanisms remain unknown, green tea polyphenols modulate several of the cell cycle processes (Chen et al. 2011). One of the most abundant polyphenolic compounds, (-)-epigallocatechin-3-gallate (EGCG), is receiving a great deal of research attention for its chemopreventive effects, including antioxidant, anti-angiogenic, and apoptotic properties. To date, preclinical studies have identified specific effects of EGCG including regulating expression of VEGF (vascular endothelial growth factor), matrix metalloproteinases, uPA, IGF-1 (insulin-like growth factor 1), EGFR, and cell cycle regulatory proteins (Shankar et al. 2007). In addition, EGCG inhibits NF-κB, PI3-K/Akt, Ras/

Raf/MAPK, and AP-1 signalling pathways. Studies have shown that EGCG has the ability to inhibit carcinogenesis and prevent metastasis in established tumors (Kanwar et al. 2012). Animal and observational data suggest that green tea consumption may lower blood estrogen levels, thus lowering breast cancer risk, while limited data suggest that black tea may increase breast cancer risk (Butler and Wu 2011). Currently, phase I and phase II EGCG chemoprevention studies are investigating its effects on breast, skin, lung, prostate, cervical, and bladder cancers, as well as in chronic lymphocytic leukemia and in Barrett's esophagus.

Studies on the relationship between green tea and site-specific cancers have been inconclusive in quantifying the potential protective effects (Kanwar et al. 2012). The increasing clinical trials focusing on this relationship have been conducted mainly in breast, prostate, and lung cancers as well as chronic lymphocytic leukemia (Kanwar et al. 2012). Although several experimental studies have shown strong protective and treatment effects of green tea, epidemiological studies from the past three decades have been inconclusive (Yuan et al. 2011). Potential explanation for this inconsistency lies in the fact that green tea consumption in human populations is more variable than in experimental studies (Yuan et al. 2011).

8.2.3 Immune-Modulating Mushrooms

Several mushrooms have been identified as having immune-modulating effects (Pelley and Strickland 2000). Three mushrooms, *Coriolus versicolor*, *Ganoderma lucidum* (reishi or lingzhi), and *Grifola frondosa* (maitake), contain polysaccharides with particularly promising immune-modulating effects that may be effective in primary and secondary cancer prevention. *Coriolus versicolor* had historically been used in traditional Chinese medicine (TCM) and is frequently used in Japanese oncology settings. *Coriolus versicolor* is usually used in extract form, either as protein-bound polysaccharide-K (PSK) or polysaccharide-P (PSP). Some research has demonstrated the immune-stimulatory actions of these polysaccharides on T lymphocytes, B lymphocytes, monocytes/macrophages, bone marrow cells, natural killer (NK) cells, and lymphocyte-activated killer cells as well as promoting the proliferation and/or production of antibodies and various cytokines such as interleukin (IL)-2 and IL-6, interferons, and TNF (tumor necrotic factor) (Chu et al. 2002; Fisher and Yang 2002). Preclinical studies of *Ganoderma lucidum* have shown inhibitory effects on NF-κB, AP-1, uPA, and uPAR (Sliva 2003). Preliminary clinical trials have shown some beneficial effects on immune function in patients with colon cancer and lung cancer. Recent studies have also shown improved immunologic and hematologic function in breast cancer patients (Novaes et al. 2011). Maitake mushroom (*Grifola frondosa*) is an edible mushroom that is also under investigation for its anticancer properties. The most active ingredients in this mushroom appear to be polysaccharides 1,3 and 1,6 beta-glucan. These constituents are marketed in the form of proprietary D- or MD-fraction extracts. Maitake extracts have been shown to enhance bone marrow colony formation in vitro (Lin et al. 2004), induce apoptosis in prostate cancer

cells (Fullerton et al. 2000), decrease the effective dose of mitomycin-C in tumor-bearing mice, and activate NK cells in cancer patients (Kodama et al. 2003).

8.2.4 Ginseng

The concept of "adaptogen" was first proposed by Soviet scientists in the late 1950s, suggesting that an adaptogen is any substance that exerts effects on both sick and healthy individuals by "correcting" any dysfunction(s) without producing unwanted side effects (Davydov and Krikorian 2000). Several botanicals are purported to have adaptogenic effects that provide resistance to stress and fatigue, with various ginsengs meeting these criteria. The chemistry of the secondary compounds and pharmacological effects of *Eleutherococcus* (Siberian ginseng) isolated thus far support the hypothesis that the reported beneficial effects of such adaptogens derive from their capacity to exert protective or inhibitory action against free radicals. Of the compounds isolated from Siberian ginseng, six compounds show various levels of activity as antioxidants, four show anticancer action, three show hypocholesterolemic activity, two show immunostimulatory effects, one has choleretic activity, one has the ability to decrease/moderate insulin levels, one has activity as a radioprotectant, one shows anti-inflammatory and antipyretic activities, and yet another has shown activity as an antibacterial agent (Davydov and Krikorian 2000). Some of the compounds show more than one pharmacological effect, and some show similar effects although they belong to different chemical classes.

The most active components of another ginseng, Panax ginseng (also known as Asian or Korean ginseng), are ginsenoside saponins (Tyler 1993). There are approximately 30 different saponins that have been isolated from Panax ginseng; a number of these have been evaluated for their potential use in the field of cancer prevention (e.g., ginsenoside Rg_3, Rg_5, Rh_1, and Rh_2) (Yun et al. 2001b). The quantity of ginsenoside in roots varies by type and age of the plant. Ginsenosides have been shown to stimulate the immune system and inhibit cancer cell proliferation (Shin et al. 2000; Xiaoguang et al. 1998). They specifically inhibit tumor growth by affecting not only the proliferation of cancer cells but by affecting their blood supplies, too (Lu et al. 2009). Ginseng also affects key tumor suppressor proteins, adding to its chemopreventative qualities (Hofseth and Wargovich 2007). Clinically, ginseng has been shown to increase the effect of chemotherapeutic agents as well as to reduce the toxicity of chemotherapy and radiation (Qi et al. 2010). Preliminary in vitro and epidemiologic evidence show nonspecific preventive effects in multiple tumor sites including stomach, liver, pancreas, and colon tumors (Qi et al. 2010; Shin et al. 2000; Yun 2001, 2003; Yun et al. 2001a, b; Chang et al. 2003). Compound K, a ginseng metabolite, is responsible for some of the chemoprevention activity of ginseng (Qi et al. 2011). This compound has shown initiation of apoptosis as well as significant antiproliferative effects, specifically on colorectal cancer cells by inhibiting the progression of the G1 phase of the cell cycle (Qi et al. 2011). Ginseng has also demonstrated anti-inflammatory properties which target

many of the important pathways in the inflammation-to-cancer sequence (Hofseth and Wargovich 2007). Early clinical trials have shown some benefit in improving subjective quality of life reports in cancer patients. In 2013, an ongoing NIH study (clinicaltrials.gov study identifier NCT01375114) is investigating the effect of ginseng on cancer-related fatigue, which may have an effect on longer-term cancer outcomes. The most recent epidemiological studies report a 50 % lower risk of recurrent cancer in patients with ginseng intake as opposed to those without (Qi et al. 2010). Ginseng has very low toxic effects on non-cancer cells and has shown no host toxicity in animals (Lu et al. 2009).

8.2.5 Flaxseed

Flaxseed is rich in lignans (a type of phytoestrogen) and fiber and is associated with reducing the risk of a couple different types of cancers including cancers of the breast, colon, lung, and prostate (Adolphe 2010). Lignans may have chemoprotective properties in breast cancer due to their inhibition of estrogen production. A focus in the research in the recent past has been on serum enterolactone concentrations (Adolphe 2010). Enterolactone is a human lignan and is a convert of the plant lignans that are found in flaxseed. Because enterolactone is structurally similar to estradiol, the active form of estrogen, enterolactone binds to estrogenic receptors (Adolphe 2010). Lignans, such as enterolactone, have been shown to inhibit growth of human mammary tumor cells (Hirano et al. 1990); reduce mammary tumor initiation (Thompson et al. 1996); stimulate sex hormone-binding globulin, which binds estrogens that increase cancer risk (Adlercreutz et al. 1992); and inhibit aromatase activity, which then decreases endogenous estrogen level (Adlercreutz et al. 1992, 1994). More recent studies have focused on how flaxseed influences endogenous hormone concentration and urinary estrogen metabolites associated with increased cancer risk. Flaxseed in the diet has been shown to significantly reduce serum concentration of 17-beta-estradiol and estrone sulfate (Hutchins et al. 2001). Flaxseed supplementation significantly increased urinary 2-hydroxyestrone excretion and increased the 2:16 alpha-hydroxyestrone ratio in studies of premenopausal (Haggans et al. 2000) and postmenopausal women (Haggans et al. 1999). Flaxseed's influence on hormones (e.g., testosterone) and its high content of omega-3 fatty acids have led to initial research on its potential role in the prevention of prostate cancer (Demark-Wahnefried et al. 2001). Enterolactone has been shown to initiate apoptosis in prostate cancer cells as well as to suppress growth and migration of these cells (Adolphe 2010). Although serum enterolactone levels have been found to be inversely associated with cancer risk in several observational clinical studies, researchers have suggested that the amount of enterolactone that is produced from its plant lignan precursors may be influenced by other factors such as a person's amount of type of intestinal flora (Adolphe 2010).

Flax lignans' protection against colon cancer has been examined in mainly animal studies thus far (Adolphe 2010). Aberrant crypts and aberrant crypt foci are known as possible early markers of colon cancer (Adolphe 2010). In studies using

rat models, flaxseed reduced aberrant crypt multiplicity, which is suggestive of a protective effect of flaxseed against colon cancer (Adolphe 2010).

While these and other botanical agents show promise for a number of biological mechanisms related to cancer prevention, well-designed randomized controlled trials are needed in humans before they can be advocated as effective chemoprevention agents.

8.3 The Mind–Body Connection

Mind–body approaches to health are those practices that generate states of mental focus or clearing and physical relaxation, with or without movement (e.g., meditation, Tai Chi), or those that strive to improve attitudes and emotions regarding psychosocial experiences to reduce perceptions of stress (e.g., psychotherapy and support groups). Much of the CAM literature written for cancer patients provides thorough reviews of mind–body options to consider and suggests the potential use of mind–body techniques for prevention of recurrence of disease (ACS 2007; Alschuler and Gazella 2007; Lerner 1994; Gordon and Curtin 2000).

8.3.1 Physiological Responses to Stress in the Mind–Body Connection

A long history of research has explicated numerous ways in which psychology interacts with physiology to prevent or alleviate disease. Much of this work has been in the area of stress. The mechanisms of stress, and stress reduction through mind–body techniques, have been thoroughly described through more than five decades of research. Early work on stress and health focused on the correlates of risk and incidence of heart disease (Friedman and Rosenman 1974). In the 1980s, the emerging field of psychoneuroimmunology demonstrated the relationship between the hypothalamus, psychological states, and immune function. This work began to extend the paradigm of the stress response to incorporate much more sophisticated models of the interactions between mind and body (Ader et al. 1991; Pert 1997; Zorrilla et al. 2001).

Theories and research exploring the relationship between immune, nervous, and endocrine systems relate these factors directly to the development and progression of cancer. Current theories and ongoing research are contributing to an understanding of the effects of analogues of hypothalamic hormones on hormone-dependent cancer, the role of opioids and melatonin on cytokines, gene modulation, and the immune responses to behavioral therapy in cancer patients (Anderson et al. 2004, 2008; Temoshok 1987; Holland 1989; Schipper et al. 1995; Conti 2000; Elenkov and Chrousos 2002).

Stress has been defined as virtually any experience activating the sympathetic nervous system (SNS) with its concomitant release of epinephrine and norepinephrine, rise in blood pressure and heart rate, and outpouring of other mediators to fight,

flee, or freeze. More recent proposals have been made to eliminate the term stress as a mere reification and to speak about hypothalamic-pituitary-adrenal (HPA) activation and sympathetic nervous system arousal. What leads to this activation and arousal is highly individual and cultural, arising from participation in a social environment in which positive and negative experiences are defined and value is placed upon aspects of life. Certain judgments or valuations of one's own life or life experiences lead to activation of the HPA axis, exerting effects on peripheral target tissues through glucocorticoids. This activation helps the individual survive a challenge by mobilizing fuels for energy, inhibiting reproductive behavior and increasing arousal and vigilance. Excessively long or frequent HPA activation and SNS arousal prevent recovery or adaptation, which leads to an increased risk of disease (Raison and Miller 2001). Dysregulation of the SNS/HPA axis (due to increased exposure to cortisol) is hypothesized to contribute to the physiological decrements that accompany diseases associated with aging and suppressed immune function, factors implicated in cancer risk. These relationships have formed the basis of the models and growing body of knowledge in mind–body approaches to health and cancer prevention, with evidence accumulating for the complex ways in which some simple techniques and interventions may reverse the effects of stress-related declines.

8.3.2 Meditation and Meditative Movement

Excess activation of the HPA axis or excessive sympathetic arousal can be reduced by interventions that combine meditation, breathing, and movement. Mind–body methods that emphasize breathing along with progressive muscle relaxation, meditation, yoga postures, or autogenic training (a technique that uses a combination of attention and somatic suggestion to assist relaxation) have been shown to reduce blood pressure among people with hypertension (Astin et al. 2003), to increase phagocytic activity (Peavey et al. 1985) and to lower cortisol levels (Schmidt et al. 1997; Kamei et al. 2000; Gaab et al. 2003).

Mindfulness meditation has become one of the more standardized and popular methods of meditation taught in the West. Studies show direct improvements of immune function among other health indicators in response to mindfulness-based meditation, which focuses on breathing, relaxation, and a full consciousness of one's surroundings (Kabat-Zinn 1994; Williams et al. 2001; Davidson et al. 2003). Many mind–body approaches such as Mindfulness-Based Stress Reduction (MBSR) include a combination of practices. MBSR uses individual mindfulness-based meditation based on principles of nonjudgment and acceptance as the core but includes group sessions that teach breath awareness, sitting and walking meditation, and mindful yoga.

MBSR interventions with breast cancer survivors have shown positive outcomes on targets also considered important for prevention, including immune function, with specific benefits in increasing NK cell activity and reducing inflammatory cytokine activity (IL-4, IL-6, and IL-10) (Witek-Janusek et al., 2008). There is a wide variety of types of meditation for which evidence is slowly accruing for

various psychological and health benefits (Ospina et al. 2007). Popular among cancer patients since the late 1970s are the visualization techniques promoted by Carl Simonton et al. (1978). Preliminary studies of this technique have shown improvements in leukocyte and NK cell activity in response to imagery of healthy immune systems and retreating cancer cells (Achterberg and Lawlis 1984; Kiecolt-Glaser et al. 1985; Gruber et al. 1988).

Mindfulness practices that include body postures or movement, a focus on the breath, and meditative states have recently been defined as meditative movement (MM) (Larkey et al. 2009) and include such practices as Yoga, Qigong, and Tai Chi. Qigong and Tai Chi exercises, ancient TCM practices that include breathing and movement, are often seen as mind–body approaches to health (Kerr 2002). Tai Chi is one of the forms of Qigong exercise that has become increasingly popular in the USA; Qigong is gaining in use and popularity. The effects of Qigong and Tai Chi are clearly linked to the reduction of stress, including subjective assessment of anxiety and stress reduction, improvements in sleep quality, and more objective measures of reductions in blood pressure and sympathetic activity and increased parasympathetic activity (Audette et al. 2006; Channer et al. 1996; Cheung et al. 2005; Jahnke et al. 2010; Li et al. 2004; Skoglund and Jansson 2007). These practices hold potential for affecting the immune system; there are reports of increased phagocytic activity, lymphocyte transformation, normalized cortisol, reduced C-reactive protein, and improved cytokine profiles among those who practice Qigong (Oh et al. 2010, 2011; Jones 2001; Chen and Yeung 2002), and similar results have been shown for Tai Chi practice (Mustian et al. 2008; Wang et al. 2004) and yoga.

Beyond the known effects of MM practices on reducing the biological effects of stress, there is an additional benefit that is appearing in the literature that links these practices to another important risk factor for cancer—obesity. Weight loss has been shown to occur compared to controls in a number of yoga and Tai Chi intervention trials (Chen et al. 2010; Dechamps et al. 2007; Wolf et al. 2006). Each of the components of MM has demonstrated potential for creating a neurohormonal state that may impact weight. Meditation-based interventions may reduce anxiety, depression, and disordered eating through an emphasis on body awareness, emotional self-regulation, and attention to inner cues as well as decreased body mass index (Kristeller and Hallett 1999; Kristeller and Wolever 2011; Lillis et al. 2009) possibly facilitated by reductions in emotional eating and caloric intake. Slow deep breathing has been associated with reductions in blood pressure and oxidative stress and balance in the autonomic nervous system and may contribute to improved emotional state (Bhattacharya et al. 2002; Joseph et al. 2005). While breathing practices alone have not been directly tested/associated with weight loss, the calming of emotional states and self-regulation implies potential for changing *emotional eating patterns and dietary intake*. Tsang and Fung (2008) proposed a model of cascading effects for two MM practices, Qigong and Tai Chi, for patients with depression, shedding light on several routes through which weight loss may occur, including changes in serotonin levels, cortisol, and slowed release of glucocorticoids. Although very little has been done to test methods of normalizing cortisol levels and rhythms in cancer patients, interventions that reduce stress have been relatively

successful: cortisol levels were reduced in acute response to yoga (Kamei et al. 2000), and normal slopes were restored in a group of breast and prostate cancer patients who practiced mindfulness meditation (Carlson et al. 2003).

In summary, it is proposed that MM elements (meditative state, movement, breath focus) and specific forms such as Qigong and Tai Chi may serve to increase emotional self-regulation and body awareness, eating behaviors, and physical activity in favor of weight loss. Diurnal cortisol slope improvements, reduced insulin resistance, and decreased C-reactive protein levels (reducing leptin resistance) may be involved in the MM/weight loss relationship as mechanisms of change.

8.4 Psychosocial Factors and Stress

A meta-analysis among cancer patients revealed stress-related psychosocial factors to be associated with a higher cancer incidence in initially healthy people, poorer survival in patients diagnosed with cancer, and higher cancer mortality. When asked about the cause of their breast cancer, a Canadian sample of women cited "stress" above other possible causal factors such as genetics, diet, and environmental factors (Stewart et al. 2001). In the general case, the putative mechanism for stress/health effects has been stressor-induced activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis with their molecular cellular, organ level, and systemic effects. When stress is chronic, it negatively affects most systems because of prolonged exposure to catecholamines and glucocorticoids. Much of the prior research concerning stress and cancer has focused on suppressed immune responses (Dhabhar and McEwen 2007; Antoni et al. 2006; Miller et al. 2008).

Our social environments impact our bodies through relationships. For example, Kiecolt-Glaser and colleagues (2005) found that experimentally induced blister wounds healed slower after marital conflict than after supportive social interaction. Cytokine production in the area of the wound was also lower for interleukin-1-beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6. High-hostility couples healed at 60 % the rate of low-hostility couples. High-hostility couples also produced higher levels of IL-6 and TNF-α in the morning after a marital conflict than after a supportive social interaction when compared to low-hostility couples. More frequent and more intense production of pro-inflammatory cytokines could lead to increased susceptibility to a variety of disease states, including cancer.

Salant and Gehlert (2008) have proposed a model that links multiple levels of influence on disease, specifically addressing social conditions related to the development of breast cancer. Beginning with an epidemiological framework that examines population-level relationships, Gehlert and colleagues (2011) have linked breast cancer to social isolation and economic disparaties and the associated stress response through experimentation with animal models and community research. Similar progress has been made in developing models of how mind–body interventions targeting psychological, emotional, and a range of social mediators may impact inflammatory cytokines and immune function (Abrams and Weil 2009; Sagar and Lawenda 2009).

Although theories have been proposed to associate certain predispositions of personality or psychological factors with the development of cancer, the research has been inconsistent making it difficult to summarize conclusions (Garssen and Goodkin 1999). Prospective studies have implicated a number of possible psychological risk factors for developing cancer, with the most consistent finding being repression of emotion or depression (Dattore et al. 1980; Temoshok et al. 1985; Hislop et al. 1987; Temoshok 1987; Kaasa et al. 1989) yet even these have been disputed (Hahn and Petitti 1988; Kreitler et al. 1993). Mehl-Madrona (2007) has argued from a narrative perspective that traits are illusionary constructs and that cancer outcome is more predictable from the study of the plot of a life story rather than psychological constructs which can be arbitrary and socially constructed.

A preliminary understanding of these issues might best be gained in the context of survival, in that the factors influencing survival time may represent similar mechanisms that prevent recurrence. Work with animal models has clearly shown a relationship between psychological determinants and tumor growth (LaBarba 1970; Sklar and Anisman 1981; Visintainer et al. 1983), but in the human arena the relationship between psychology and the course of cancer initiation and progression is less clear. Factors shown to improve outcomes include social support (Ell et al. 1989; Waxler-Morrison et al. 1991), greater expression of distress, smaller numbers of severe or difficult life events (Ramirez et al. 1989), and "fighting spirit" (Pettingale et al. 1985). A discussion of the potential role of psychological variables moved to the forefront in 1989 with the publication of research that found a positive effect of a psychosocial intervention on breast cancer patients' survival time (a study that has since been called into question due to differences in baseline characteristics of patients and other study design issues) (Spiegel et al. 1989). This study kicked off a series of similar research projects, but all trials specifically designed to test the impact of a psychological intervention on survival have so far given inconclusive results, with some researchers concluding that the lack of significant findings demonstrates that such interventions simply do not impact survival time (Kissane 2007). Nevertheless, clinical experience points to the existence of a minority of cancer patients who make strong efforts to help themselves psychologically and appear to live longer than expected (Ikemi et al. 1975; Achterberg et al. 1977; Roud 1986; Berland 1995).

Cunningham and colleagues (Cunningham et al. 2000a, b, 2002) have conducted exploratory research with metastatic cancer patients enrolled in a year-long psychospiritual intervention. Standard psychometric instruments did not predict length of survival in this study, but a subsequent analysis of qualitative interview data from 22 participants suggested that there may be a survival benefit among those who (a) believed that the group activity would help them, (b) invested a greater level of effort in the group activities, (c) engaged to a greater degree in personal and spiritual change, and (d) had improved perceptions of quality of life as compared to those who did not. Cox regression analyses showed that a psychological composite score and five of six major themes were significantly related to survival duration. These themes were ability to act and change, willingness to initiate change, application to

self-help work, relationships with others, and quality of experience. In contrast, there was no relationship between survival and four standard psychometric measures taken at the onset of therapy. However, results on a 5-point scale measuring the subject's expectancy that psychological efforts would affect the disease showed a strong relationship to survival. To control for differences in severity of disease as a factor possibly influencing psychological work, the analyses were repeated, using the survival duration predicted for each patient by a panel of oncologists as a covariate. Closely similar results were obtained.

In another study, Cunningham et al. (2000a, b) reported the results of a prospective, longitudinal, correlative study of 22 patients with varying kinds of medically incurable metastatic cancer. The intervention was 1 year of weekly group psychological therapy. Extensive verbal data (patients' written homework and therapists' notes) were collected over the year. The extent of each patient's involvement with psychological work was estimated following a qualitative analysis of these data. Patients were classed as showing high, moderate, or low involvement on the basis of a quantitative rating of categories defined by the analysis. These three subgroups did not differ significantly in their expected median survival duration as estimated from independent quantitative predictions by a large panel of oncologists who analyzed the patients' medical charts at time of study entry.

A significant relationship was found between degree of involvement in psychological work and survival duration. Results were presented as Kaplan-Meier survival curves ($p = 0.006$, Logrank test). The main likely confounders (medical status, age, quality of life, and attendance at therapy) were similar across subgroups and did not change the relation between psychological work and survival duration. They concluded that the strong effects observed support clinical observations that dedicated involvement in psychological self-regulation may prolong the life of some patients with metastatic cancer.

A shorter-term study lends some support to these ideas. McGregora et al. (2004) examined the effect of a cognitive–behavioral stress management (CBSM) intervention on emotional well-being and immune function among women in the months following surgery for early-stage breast cancer. They randomly assigned 29 women to receive either a 10-week CBSM intervention ($n = 18$) or a comparison experience ($n = 11$). The primary immune function outcome measure was in vitro lymphocyte proliferative response to anti-CD3. Women in the CBSM intervention reported greater perceptions of benefit from having breast cancer compared to the women in the comparison group. At 3-month follow-up, women in the CBSM group also had improved lymphocyte proliferation. Finally, increases in benefit finding after the 10-week intervention predicted increases in lymphocyte proliferation at the 3-month follow-up. Thus, potential support exists for behavioral interventions having beneficial effects of immunity and, theoretically, survival.

Andersen et al. (2008) conducted a randomized clinical trial to test the hypothesis that cancer patients coping with their recent diagnosis but receiving a behavioral intervention would have improved survival compared with patients who were only assessed. A total of 227 patients who were surgically treated for regional breast cancer participated. Patients were randomized to the intervention plus assessment or

assessment-only study arms. The intervention was psychologist led, conducted in small groups, and included strategies to reduce stress, improve mood, alter health behaviors, and maintain adherence to cancer treatment and care. After a median of 11 years of follow-up, disease recurrence was reported to occur in 62 of 212 (29 %) women, and death was reported for 54 of 227 (24 %) women. Using Cox proportional hazards analysis, multivariate comparison of survival was conducted. Patients in the intervention arm had a reduced risk of breast cancer recurrence (hazard ratio [HR] of 0.55; $p = .034$) and death from breast cancer (HR of 0.44; $p = .016$) compared with patients in the assessment-only arm. Follow-up analyses also demonstrated that intervention patients had a reduced risk of death from all causes (HR of 0.51; $p = .028$).

The inconclusive results of previous randomized, controlled trials of psychological and spiritual interventions may be explained by patients who benefit, finding a way to get their needs met regardless of the randomization protocol. Mehl-Madrona and colleagues found this effect in a study of asthma and CAM. Motivated patients optimized their exposure to CAM modalities regardless of the group to which they were randomized, but they did not voluntarily disclose this information to researchers. Those predisposed to involve themselves in psychological work may find opportunities in the context of an intervention or may seek such opportunities on their own. Researchers are likely naïve in thinking they can control patient behaviors to the extent needed for this type of research. Furthermore, if only a proportion of patients in an intervention become strongly involved in trying to help themselves psychologically and theirs are the only lives substantially prolonged, this effect may be "diluted out" when group means are calculated. Another challenge to studies examining these effects includes the lack of inclusion criteria selecting patients for some degree of psychosocial distress. A randomized, controlled trial would thus need to be exceedingly large to produce a reliable treatment effect and would likely need to control for patients' expectations, level of involvement in the intervention or outside options, and level of distress or need prior to study initiation. Study designs could be improved by exploring unique selection criteria for baseline predisposition of seeking "growth" experiences, selection of baseline distress, and better choices of the factors assessed as potential mediators (Classen et al. 2008; Cunningham et al. 2002). Mehl-Madrona (2007) has argued that randomized, controlled trials of psychological interventions are not the best vehicle to demonstrate psychospiritual healing, given the many factors involved that cannot be controlled through randomization.

Given Cunningham's findings (Cunningham et al. 2002), there is reason to suspect that, although more challenging to design than originally thought, there is great potential for finding more robust relationships between the psychological, social, and even spiritual factors associated with patient involvement in their own healing. Preventing cancer, or preventing a recurrence of cancer, may similarly be dependent upon a set of psychoneuroimmunological factors more clearly demonstrated through studies that assess these relationships directly rather than through attempts at manipulating psychological and spiritual states indirectly through interventions. Although developing a sense of purpose in life, having a supportive community, and having faith for healing may not manifest in the same way with healthy individuals

as with those who have been challenged by a diagnosis of cancer, these factors are worth examining to reduce risk of disease as well as improving patient quality of life. Continuing to explore social, psychological, and spiritual factors related to the mind–body connection may prove fruitful, but there remains a need for evidence regarding the specific mechanisms of these mind–body approaches that affect cancer outcomes. Simpler demonstrations of the potential of interventions, however, such as a study testing a psychosocial intervention among prostate cancer patients (including guided imagery, relaxation training, and breathing techniques) that produced improvements in immune markers (Cohen et al. 2011), may initially be more useful for understanding these effects.

8.5 Wellness

Much of the interest in CAM from the public and practitioners has been guided by and intrinsically linked to emerging views based on the concept of "wellness." The wellness concept became popular in the early 1970s, and out of that original thrust, many wellness centers began to emerge. The term "wellness" has come to denote a way of thinking about health that goes beyond the simple absence of disease. In theory, wellness is not necessarily sought from a position of avoiding disease, but is holistic in the sense that it seeks to achieve greater balance and awareness in body, mind, and spirit, an evolution of one's whole being (Benson and Stuart 1993).

Several of the culturally based systems of health, such as traditional Chinese medicine, Ayurvedic medicine, and practices associated with Native American healing, match the holistic precepts of wellness. Although there may be practitioners and patients with a single-minded focus on a particular modality, most proponents of CAM view health as multifaceted, promoting balance and wellness of body, mind, and spirit. Because the systems promoting wellness tend to be broad in focus, prevention of a specific disease such as cancer is not an exclusive goal. Nevertheless, the expected outcomes of improved wellness include enhanced immune function, stamina, and overall well-being, factors that may reduce the risk of cancer as well as other diseases.

There is a particular challenge for drawing conclusions about the cancer-preventive potential of wellness-focused systems. Most are promoted as an entire wellness package, where a set of principles guide lifestyle, such as diet, form of exercise, meditation or other mindful practices, spiritual views, and even botanicals, each specifically chosen for balance based on the philosophy of that system. In the context of cancer treatment, several of these systems propose paradigms of etiology, disease progression, and healing that are very different from the Western medical model, which focuses on the treatment of a specific diagnosis or symptom.

CAM research in non-Western systems is problematic. The multiple modalities usually prescribed for treatment are based on individual readings of the various levels of involvement in body, mind, social, environmental, and spiritual factors. Research methods are not designed to test non-Western systems that treat every individual differently according to particular needs. Because of the lack of accepted

research methodology that is able to test this holistic approach to health, it is important that health-care practitioners become aware of, and researchers to begin to solve the puzzles of, scientifically understanding these integrated systems (Elder et al. 2006).

CAM practitioners promote balance for healing or for overall well-being, but the goals of achieving wellness are put into the hands of the individual taking responsibility for her or his own health (Wong and McKeen 2001). The movement toward self-responsibility in health and examining life as a whole are principles that sprouted in Western culture. This movement took place concurrently with a rekindled interest in more natural forms of healing that included mind–body approaches, spirituality, and non-Western medical practices and has been especially powerful among cancer patients (Tatsumura et al. 2003).

An exemplar of this philosophy is the Cancer Support Community (formerly, The Wellness Community), an international network of nonprofit centers "dedicated to providing free emotional support, education and hope for people with cancer and their loved ones" (www.cancersupportcommunity.org; Benjamin 1995; Penson et al. 2004). Using a whole-person (holistic) approach, patients are encouraged to actively support each other "to regain control, reduce feelings of isolation and restore hope-regardless of the stage of disease" (Penson et al. 2004). Varieties of meditation, Qigong, massage, yoga, Reiki, Healing Touch, and other such practices are commonly offered in these centers, making available to cancer patients a supportive community as well as opportunities for spiritual, emotional, and physical healing.

Popular writers such as Dr. Bernie Siegel (1990) and Dr. Andrew Weil (1995) have intrigued readers with stories of healing and profoundly changed lives. Many of these stories are recounted in books that catch the attention of the public, inspiring faith in the human ability to get well and stay well. For example, Dr. Caroline Myss, in her book about power and healing, suggests exploring symbolic meaning and balance, taking the reader through religious symbols, archetypal challenges, and stage-of-life passages to address life lessons and points of transition (Myss 1996). Moving through these lessons with conscious response is theorized to bring spiritual health cascading down through the psychological and physical systems. Even though Dr. Myss describes case histories of patients with cancer or precancerous conditions who get well, there is neither sufficient documentation of measurable physiological outcomes over time nor comparison to matched cases to draw conclusions.

Research on spontaneous remission was more prevalent in the early 1900s; numerous examples defy our current understanding of the disease process (O'Regan and Hirshberg 1993). A common ingredient in these healing testimonies is spirituality (Hammerschlag 1988; Struve 2002). It is important for the reader to understand that these are testimonies, not scientific research. The role of spirituality in wellness, although only emerging in Western societies over the past few decades, might be seen as a reclamation of ways of viewing health and life that have been prevalent in most cultures and societies worldwide.

Widespread interest exists in "exceptional survivors" and how they come to be so. The conventional oncological argument holds that they are merely the end of the

bell-shaped curve and are not different psychologically or spiritually from any other survivor. O'Regan and Hirshberg (1993) documented more than 1,000 cases in which cancer apparently went into spontaneous remission. Some of these fascinating cases and others were described in a best-selling book 2 years later (Hirshberg and Barash 1995).

Gotay et al. (2004) have defined exceptional survivors as people who have survived at least 5 years with less than 25 % actuarial probability of doing so, given their site and stage of cancer at diagnosis. They compared exceptional survivors of cancer to non-exceptional survivors with the same cancers and sites (but with greater than 25 % actuarial probability of living 5 or more years) and with normative data for the instruments used from the general population. They found that both types of survivors had high levels of well-being compared to the normative populations; cancer survivors exhibited higher levels of coherence and resiliency, but not optimism with few differences between the two types of survivors.

8.6 Indigenous Cultural Systems of Healing

Many cultures throughout the world have produced comprehensive, sophisticated systems of describing disease states and methods of healing that are very different from the Western medical model. What characterizes many of the systems, and distinguishes them from Western medicine, is the tendency to consider health to be a system of balance among body, mind, and spirit—often including social and environmental factors as part of the whole in some systems, rather than a constellation of biochemical and hormonal balances identified at a microbiological level (Villoldo and Krippner 1986; Achterberg 1987; Metzger 2004). Illness results from disrupting the natural order and disrupting harmonious relationships of all kinds. In these views, illness is not just something that happens to us or enters from without, but emerges from loss of personal power and balance that leaves us vulnerable to intrusion (Achterberg 1987). From African healing arts to Samoan fofō, from Native American ceremony to traditional Chinese medicine, it appears that nearly all of the indigenous cultural systems view human health and prevention of disease in the context of the natural world around us as well as the interaction of physical elements with mind and spirit (Kaptchuk 1983; Mehl-Madrona and Dossey 2003; Mishra et al. 2003). Understanding these other viewpoints or stories about the world is not just quaint anthropology; it gives us the possibility to take a fresh look at our own world views and stories from outside eyes through which we can see our blind spots and unchallenged assumptions.

Mehl-Madrona (2008) studied 47 people who sought traditional aboriginal healers for help with their cancer. All had 10 % or less chance of survival at 5 years given the site and stage of their cancer from actuarial table calculations. The subjects were compared to a similar group of people who were also working with aboriginal healers and who did not survive past 5 years. Narratives were obtained from the people before and after their work with the healer. These stories were enriched through interviews with family members, friends, health-care providers,

and the healers themselves, whenever possible. Panels of naïve medical students, graduate students, patients, and health-care providers evaluated the stories and picked themes that consistently emerged (dimension analysis). Once stable dimensions emerged, scenarios were developed to rate patients along these dimensions from "1" to "5." New panels did the ratings, with at least three panels of three people per narrative. Comparisons were made between these two groups of people, and differences emerged on the dimensions of present centeredness; forgiveness of others; release of blame, bitterness, and chronic anger; orientation to process versus outcome; sense of humor; refusal to accept death as immediate prognosis; plausible (to the patient, his or her family, and the healers) explanation for why he or she got well, including a story reflecting a belief about how he or she can stay well; supportive community who believes in the person's cure and protects the person from outsiders who think the person will die; people experience a quantum change, in which major improvements in self-esteem and quality of relationships occur; and spiritual transformation. The two groups of people reported equal increases on the dimensions of sense of meaning and purpose and faith and hope, which may be intrinsic to the style of healing of aboriginal elders. Review of the life stories of 50 patients with cancer who died did not reveal anywhere near the same degree of these qualities, lending possibility to the hypothesis that these may reflect "states of mind" that are compatible with longer-term survival. Cunningham et al. (2000a, b) hypothesized that the size of effects on survival would be proportional to the amount of effort and change patients made as opposed to particular traits that might be measurable. A subgroup making strong efforts of this kind might not be detectable in a comparison of means (as in a randomized trial) but might be demonstrated with a correlative design. They shifted the focus of investigation from the presence or absence of an intervention or a trait to what individual patients do with it, that is, on the relationships between individual behaviors or attitudes and outcome.

In a later study, Mainguy et al. (2013) looked at 45 nonindigenous cancer patients who sought traditional North American aboriginal healers in Canada, often after science-based medicine had "failed." In this mixed methods study, narratives produced through interviews and writings of the patients were used to assess the degree of spiritual transformation and to determine whether a relationship might exist between that transformation and subsequent changes in medical outcome. The healers used methods derived from their specific cultural traditions, though all commonly used storytelling. These methods included traditional aboriginal ceremonies and sweat lodge ceremonies, as well as other diagnosing ceremonies, such as the shaking tent among the Ojibway or the yuwipi ceremony of the Dakota, Nakota, and Lakota and sacred pipe-related practices. A combination of grounded theory modified from a critical constructivist point of view and narrative analysis was used to rate the degree of spiritual transformation experienced. Patients were followed for 5 years after their contact with the healer at intervals of every 6 months. Medical outcome was measured by a 5-point Likert scale and was confirmed with medical practitioners and other family members. The level of spiritual transformation achieved through interaction with healers was associated in a dose response relationship with subsequent improvement in cancer ($p < .0001$).

North American aboriginal healers emphasize the role of the spiritual dimensions in their work. Spirituality refers to those aspects of this striving that relate to God, the Divine, the Universe, the Largest Whole, Higher Beings, and/or those things that people believe to be sacred. Spirituality is a process: a verb and not a noun, active instead of passive, in motion rather than static. Pargament (1997) described three processes in the search for the sacred: (1) discovery (i.e., searching or pursuing), (2) conservation (i.e., sustaining oneself in times of crisis and preserving a sense of meaning through spiritual beliefs and practices), and (3) transformation (i.e., profound change or giving up some sources of meaning and discovering new sources of significance as changes take place in life). Stories abound regarding healing and curing that occurred in association with spiritual transformation, both in dominant religions and in indigenous spirituality. Pargament's descriptions were remarkably similar to what Mehl-Madrona (2008) and Mainguy et al. (2013) reported.

Questions about religious or spiritual healing—the extent to which it occurs and the degree to which it affects physiology—are important. Csordas conceived religious healing as a form of discourse embodying a cultural rhetoric and capable of performing three essential persuasive tasks; that is, it creates (1) a predisposition to be healed, (2) the experience of spiritual empowerment, and (3) a concrete perception of personal transformation. This threefold process activates and controls healing processes internal to the person seeking healing and either redirects his or her attention toward new aspects of his or her actions and experiences or alters the manner in which he or she attends to accustomed aspects of those actions and experiences. The result is the creation of both a new world view and a new sense of spiritual meaning for the person. Though Csordas was studying Catholic Pentecostals, the analysis is equally applicable to aboriginal healing and directs our attention to those aspects of the treatment's environment and the interaction with the healer that foster these three persuasive tasks.

For example, within spiritual and indigenous world views, the soul may be seen as deliberately choosing illness to develop specific qualities and contribute to the community (this must be distinguished from certain New Age stories in which the conscious individual is attributed causality for cancer). Hillman (1996) reflected upon traditional spiritual healing within multiple cultures, observing that value symptoms and illnesses differently from Western culture, seeing them as not necessarily negative, but potentially useful for revealing a person's unique calling or destiny. They may emerge from a combination of accidental happenings, neither good nor bad, that coalesce into something that wants to be seen or heard. Indigenous cultures also speak of the life force (ki or chi in Asia) not flowing naturally. Symptoms, then, may be seen as part of an initial shamanic calling or a developmental opportunity, whose refusal can result in increasingly worse physical condition and even death (Walsh 1991).

Three classic and common concepts across cultures are those of power loss, soul loss, and spiritual intrusions (Horrigan 2003). Spiritist healers around the world believe in the idea is that of spiritual intrusion in which a person has an opening or void in the body and something comes to fill it. One could readily relate this to the contemporary psychological construct of resiliency. Cancer can also be seen as

emerging from spirit possession, especially if one has already experienced significant soul loss (Horrigan 2003; Villoldo and Krippner 1986). Villoldo and Krippner's informants told them that the entering spirit may trigger in the host person similar symptoms to what the entering spirit suffered before or during death. In this view, entire families may be affected by these spirits, but frequently only the most sensitive person (translatable as the "least resilient"), often the youngest or the oldest, may be affected. Concepts such as intrusive spirits form a kind of plot line that can readily be translated into modern terms, like the unwanted intrusion of anger and hatred or bitterness into a person's life, who becomes unable to clear those emotions.

Each of these systems of healing typically has theories of how particular diseases develop and consequently suggest tactics for prevention. Health and disease is understood in the context of a particular person's experience of life, family, dietary and environmental factors, social conditions, and spiritual responses. Ayurvedic medicine and Native American healing are given as two examples of systems of healing that promote living in harmony with nature, with one's given constitution, and that promote connecting to spirit as ways to stay healthy.

8.7 Ayurveda

In Ayurvedic medicine, the buildup of toxic residues termed "ama" (more than physical substances in biomedical terms, but more subtle essences produced by imbalances in living, diet, and mental/emotional states) is believed to be one of the main causes of cancer. Recognizing one's primary "doshas," or essential natures, and living a lifestyle to manage and balance these elements alongside cleansing techniques designed to rid the body of ama are considered to be the best approach to avoiding cancer from the Ayurvedic point of view (Chopra 2000; Herron and Fagan 2002). Ayurvedic medicine uses the terms "mind" and "consciousness" to refer to the origin of physical conditions. "When you look at Ayurveda's anatomical charts, you don't see the familiar organs pictured in Gray's Anatomy, but a hidden diagram of where the mind is flowing as it creates the body. This flow is what Ayurveda treats" (Chopra 1989).

Although the combination of these many lifestyle and mind–body approaches are seen as central to treating cancer, research has focused primarily on Ayurvedic herbal formulas in more recent years. For example, *Maharishi Amrit Kalash*, an Ayurvedic food supplement, has been shown to regress mammary tumors and inhibit liver carcinogenesis in rats and has been evaluated for other anticancer effects due to its potent antioxidant properties (Arulkumaran et al. 2007; Fields et al. 1990; Sharma et al. 1990). Other Ayurvedic combination herbal preparations that have been tested include *Kalpaamruthaa*, demonstrating inhibition of carcinogenesis in animal models (Penza et al. 2007), and *Ashwaganda* (derived from the plant, Withania somnifera Dunal), found to have selective antitumor properties through activating growth arrest and apoptosis in mice and in vitro growth assays of normal and human transformed cells (Garodia et al. 2007; Widodo et al. 2007).

Given that these preparations are only one aspect of the many modalities used in Ayurvedic medicine and that more emphasis is placed on building balance through assessment and lifestyle changes to support essential constitutions, much work must be done to test the potential for this system to affect cancer risk. Singh (2002) provides a much needed framework for presenting various aspects of Ayurvedic practice in cancer treatment, linking theoretical constructs of that system to potential explanations of medical biomarkers that could be explored to begin explicating mechanisms of action for treatment and prevention. Such a framework would provide methodical guidance for testing this as whole system approach (Elder et al. 2006).

Deepak Chopra, M.D., has done much to promote the concept of mind–body healing and wellness through his center and in his book entitled *Perfect Health*: *The Complete Mind-Body Guide* (Chopra 2000). This book repackaged Ayurvedic principles of healing into an approach more palatable to Western tastes. The details of the Ayurvedic system are generalized to principles that are recognizable in modern wellness teaching. Such programs continue to represent the basic tenets of wellness—balance in life and responsiveness to life's lessons. These basic tenets are hypothesized to bring optimum health, and hence are also purported to prevent cancer.

8.8 Native American Healing Traditions

With so many tribes indigenous to the Americas, each with unique healing traditions, it becomes impossible to define a particular tradition as representative of Native American healing. There are, however, some themes that are common throughout the Americas. For example, Native American healers generally do not conceptualize a medicine–religion differentiation. Healing must acknowledge an Inner Healer. According to Dineh (Navajo) healer, Thomas Largewhiskers, this inner force explains why people get well or not or how they stay healthy in the first place (Largewhiskers T, 2004, personal communication). Many tribes and other indigenous cultures teach that spirit is indivisible from mind and body and that a healthy balance and connection with spirit is the path to prevention of disease.

An important source for connecting with spirit for healing and balance, for healthy and ill alike, is ceremony. Ceremony is not unique to Native American culture; it is often represented in one form or another in health systems that include a spiritual component (Hammerschlag and Silverman 1997). The importance of ceremony is consistent with the hypothesis that religiosity/spirituality may be associated with physiological processes, including cardiovascular, neuroendocrine, and immune function (Seeman et al. 2003). Immune function is important in cancer and its prevention. Although the evidence has not demonstrated that spirituality slows the progression of cancer, studies conducted to date have been small and limited (Powell et al. 2003). In cultural systems that involve ceremony, prevention should address mind, body, and spirit.

Native American healing practices hinge less upon the skills of the healer and are placed more in the hands of the spirits or the Creator who respond to the collective

requests of the community and "doctor" the patient. Success is seen as outside the realm of mere humans. Nor does the healer take credit for improvements or even cures, preferring to remember the spirit helpers and the Creator. Healers build their reputation based upon the power of the spirits who assist them. Healers and other participants in ceremonies "see" or listen to messages provided by spirits to help the patient, including how to change aspects of the person's individual spirit or energy body through sound, touch, or prayer. This is a traditional way of viewing what is now often called "energy medicine," a field that combines technology, physics, and ancient wisdom for healing.

8.9 Energy Medicine

Energy medicine is often used to refer to practices that involve subtle or very low intensity nonmaterial stimuli for purposes of healing (Rubik 1995). These stimuli may be (a) artificially generated fields, including measurable vibrations such as sound, visible light, laser beams, and electromagnetic fields [e.g., pulsed electromagnetic field (PEFM) therapy] or (b) healing energies generated by and purportedly transmitted to humans (e.g., Reiki, Healing Touch) or intentfully balanced from within through various meditative movement (Jahnke et al. 2010) practices (e.g., Qigong exercise, yoga, Sign Chi Do). These stimuli are theorized to work by causing a change in the human biomagnetic energy field and subsequently in biochemical responses.

Energy medicine includes a wide range of therapies. As noted above, many of the indigenous systems of healing acknowledge a life force such as Qi (the force that runs through meridians as defined in TCM), prana (in yoga practice and Ayurvedic medicine) or the fields of energy perceived and manipulated by those practicing any of the forms of energy healing. For purposes of this review, a broad definition will be used to encompass any modality designed to improve overall balance or improvement in some aspect of the human bioenergy field either through internal intent or external application. The mechanisms by which energy healing may work to prevent diseases such as cancer, and/or improve health are still being explicated. Without knowing yet whether there is one underlying principle or many ways in which nonmaterial stimuli might affect energy fields and, in turn, biological outcomes, these modalities will be considered as similar in this review.

The purpose for addressing the emerging field of energy medicine in the context of cancer prevention is twofold: (1) to explicate the non-Western theories underlying energy medicine approaches and (2) to discuss the theory inherent in energy medicine-based systems that early correction of stagnation or imbalances in energy patterns may lead to the prevention of cancer. Non-Western theories are based on the concept that there are flows of energy or essence patterns in the body that are dynamically balanced and must not be blocked; the blockages of energy will allow the development of disease, including preneoplastic lesions and eventually cancer. Energy-based medicine systems attempt to unblock these flows through various methods such as acupuncture treatments, specifically designed Qigong exercises, or externally applied biomagnetic emissions from the hands of a healer. Even more

remarkable is the hypothesis that detection of neoplastic changes may be possible with methods that assess Qi imbalance.

The term "biomagnetic field" refers to the various electromagnetic fields that run through and around the body (Oschmann and Pert 2000). Electrical impulses generated in the heart and brain (as measured conventionally via electroencephalograph, or EEG, and electrocardiogram) are known to generate biomagnetic fields. Such fields have been detected by trained energy medicine practitioners as emanating from the whole body as well as specific parts, notably the hands.

The most controversial aspect of energy medicine is the assumption that biomagnetic fields are more than artifacts of electrical activity in the body and that they not only provide indicators of health, but that they can be altered to produce improved states of health. For example, TCM is based on the concept that there are flows of energy that can be mapped representationally across the surface of the skin (although they are believed to flow through and beyond the limits of the physical body). These flows have names that link them to organs of the body (e.g., liver meridian or kidney flow), but their function is seen as much broader, including emotional and symbolic as well as physiological functions.

A more familiar and widely accepted version of energy medicine comes in the form of devices designed to deliver various stimuli. Applications of electromagnetic fields within certain frequency ranges have been shown to have a number of biological consequences with potential application in medicine. Pain control using transcutaneous electrical nerve stimulation (TENS) is one of the more well-known developments in energy medicine. Tissue regeneration, bone repair (Sharrard 1990), improvements in osteoarthritis (Trock et al. 1993), soft tissue wound healing (Becker 1990; O'Connor et al. 1990), neuroendocrine modulations, and immune system stimulation (Cadossi et al. 1988a, b; Cossarizza et al. 1989) have all been documented in response to various forms of electromagnetic stimuli. PEMF therapies used in many of these established applications have shown that certain body tissues are particularly responsive to specific frequency ranges (e.g., 7 Hz for bone growth, 15–20 Hz for capillary formation and fibroblast proliferation, and 2 Hz for nerve regeneration) (Sisken and Walker 1995). The usefulness for such externally, artificially applied therapies has not been demonstrated for cancer prevention directly; but studies show that selected frequencies of PEMF therapies inhibit tumor growth in animal models (Salvatore and Markov 2004) and can inhibit tumor angiogenesis (Markov et al. 2004). Even with the recent proliferation of research on PEMF therapies and potential health effects, there is still a limited understanding of how these effects occur and what specific dimensions of PEMF therapies (e.g., frequency, amplitude, waveform) are required to match targeted tissues and intended effects (Markov 2007).

There are numerous modalities of healing that are theorized to involve the interaction of biomagnetic fields between two humans, one "sending" healing and the other "receiving." These include practices such as Reiki therapy, Johrei, Healing Touch, Therapeutic Touch, and laying on of hands in the context of prayer (Anderson 2001). Although practitioners from these various fields of practice may argue for marked differences in their intent and work, studies examining the biomagnetic

fields emitted from the hands of healing practitioners across disciplines found similar emissions. Pulsing electromagnetic fields of extremely low frequency (ELF) emitted from the hands of healers have been detected, the majority falling between 7 and 10 Hz with a range of 0.03–30 Hz (Zimmerman 1990; Seto et al. 1992). Similarly, healing practitioners using a variety of modalities also demonstrate similar EEG signatures while in the healing mode, altered state, or in prayerful focus (Beck 1986). Although healing effects of emissions in these studies were not tested, the frequencies measured all fell into the same range as electromagnetic device therapies shown to have specific healing outcomes (e.g., 7–10 Hz) (Sisken and Walker 1995).

Other than the similarity of wave frequency between the PEMF therapies of targeted devices and the range of PEMF therapies from the hands of healers, there is little known about either measurable or putative energies or mechanisms of effects. Lutgendorf (2003) notes that research on energy healing has been confined mostly to studies of cancer cells in vitro, with positive findings generally providing evidence with well-characterized molecular endpoints, but that there have also been multiple studies with negative or equivocal findings. For example, studies of emissions from the hands of skilled healers have demonstrated cytotoxic effects, as tested on liver, breast, and pancreatic cancer and glioma cells (Ohnishi et al. 2005; Yan et al. 2006) and no effect on fibroblasts and human umbilical vein endothelial cells, while other studies have not demonstrated significant effects of human-delivered energy healing on cancer cells (Yount et al. 2004a, b; Zachariae et al. 2005).

One of the oldest documented forms of energy healing is the practice of Qigong, central to the system of TCM. Foreign to Western medicine and philosophy, Qigong is typically considered to be comprised of two forms, external and internal Qigong. The potential for Qigong exercises (i.e., internal Qigong) designed to balance the meridians to have an effect on health indicators such as cytokine profiles has already been discussed in the section on mind–body interventions. External Qigong or external Qi healing ("wai qi" or "wei qi") (Cohen 1997; Johnson 2000), an ancient Chinese method of healing touch, refers to the emission or conscious application of Qi. It is administered by transfer from the hands of experienced Qigong practitioners to other individuals for the purposes of healing or improving health. Emitted Qi also has been shown in numerous studies to have immune-modulating effects, mostly reported from research conducted in China with incomplete information on study design. Preliminary evidence is good for demonstrating potential of Qi emission to strengthen cellular immune function in animal models and humans.

More notable are the results that are beginning to be published in the USA on effects of Qi emission (external Qigong) on suppression of growth of induced lymphoma in mice. Although results were inconclusive relative to varying abilities of practitioners, one of the studies showed significant differences in tumor inhibition between intervention and control mice (Chen et al. 2002).

Beyond these claims, most of which focus either on healing for specific conditions or improvement in overall balance of endocrine function and immune status,

there is much to be learned from the theories and practice of Qigong. In this paradigm of health, the goal of balancing Qi is woven through the practices. From the Qi emission from the hands of a master practitioner who "sees" the blockages and areas of need in the biofield, to the exercises designed for movement of Qi through specific meridians, to the herbal remedies that stimulate, calm, or unblock meridian flow, each modality is intended to move one toward greater health. Validating through research a system so focused on prevention of disease, catching the imbalances in the energy field before illness manifests, seems unlikely.

Many people are familiar with the idea that TCM includes a range of modalities, such as acupuncture and herbal remedies. What is less well understood is that these treatments are all designed to influence the energy map of the body; in TCM, a network of energy lines called meridians represent various organs and functions, physical and emotional, and the balance of these are purported to maintain health. The theory behind a particular remedy is not necessarily direct action upon an organ or a biochemical reaction (as is the case with Western views of herbs), but rather its effects on promoting, inhibiting, or balancing the targeted energy meridians (Kaptchuk 2002).

Explanations for what structures in the body might account for relationships to energy phenomena have more recently been proposed, most notably in the context of acupuncture. The clinical efficacy of acupuncture has been demonstrated for a variety of outcomes, yet the theories of how it functions according to TCM principles are often not accepted even by physicians who practice this form of energy medicine (Kaptchuk 2002). Neurohumoral approaches in acupuncture research were instrumental in establishing the scientific validity of acupuncture. Recent advances in the morphogenetic singularity theory suggest that acupuncture points originate from the organizing centers in morphogenesis. Possible mechanisms of action are not necessarily dependent upon an association with nervous or lymphatic systems; acupuncture points and meridians have been shown to have high electric conductance that is related to high density of gap junctions in cellular structure (Shang 1993, 2001).

There is evidence that acupuncture has immunomodulatory effects (Petti et al. 1998; Kaptchuk 2002; Kim and Bae 2010). For example, T cells and activity of NK cells in cancer patients treated with acupuncture have been shown to remain stable over the course of chemotherapy (Ye et al. 2002). In a group of relatively healthy young volunteers, acupuncture normalized leukocytes (Mori et al. 2002).

Speculations about how healing interventions may work vary. One explanation is that "intent" may have an effect through the mind on the frequencies emitted and received. Recent developments in the science of mind and experiments of consciousness are beginning to reveal effects for "intent" on physical matter, such as reconfiguration of water molecules (Tiller 1997). Another theory suggests that physical resonance develops via "entrainment" (an accepted principle in physics whereby pulsing of waves or rhythms produced by pendulums in close proximity will entrain to the point of resonance) between the healer and target. Evidence of the potential for this explanation is provided in the work of Russek and Schwartz, who show that even without intent for healing, two people sitting quietly with eyes

closed in the same room will tend to attain coherence between both cardiac and brain wave rhythms (Russek and Schwartz 1994, 1996).

The nature of human biofield-based energy healing has not been fully explained, but the effects have been well documented in randomized, controlled clinical trials on healing interventions such as Healing Touch, Therapeutic Touch, and similar modalities. Despite continuing questions about exact modes of action, energy healing has been shown to significantly increase secretory immunoglobulin A (Wardell and Engebretson 2001; Wilkinson et al. 2002), enhance immune system response (Quinn and Strelkauskas 1993; Ryu et al. 1995; Kataoka et al. 1997), and produce relaxation or stress-reduction effects in general (Wirth et al. 1997). Other research has shown consistent results for improving quality of life and reducing stress-related symptoms in cancer patients undergoing treatment (Post-White et al. 2003; Cook et al. 2004). Although the application of the findings from these studies and the potential for cancer prevention have not yet been investigated, the results of these studies should attract enough attention to begin investigations of effects on biomarkers related to cancer risk or protection.

Large, randomized clinical trials that also allow for individualized treatment and practice plans, as is common in many forms of CAM, do not currently fit the research design standards in the USA. Until research is able to be designed to encompass such studies, only small parts of this puzzle may be examined to assess the potential of CAM. One such puzzle piece may be the research that is beginning to emerge in the field of energy medicine through instruments designed to assess meridian flow.

Although the use of diagnostic methods such as "seeing" imbalances in the human energy field (the mark of a Qigong master being the ability to see or detect Qi imbalances without the need of questioning, blood tests, or even hands-on pulse readings) may seem foreign to the Western medical mind, there are recent developments in measurement of biofield emissions that correlate with and validate these fields. For example, acupuncture meridians and stimulation/collection points are detectable via instruments, such as the MSA-21, that assess electrical impedance along the meridians (Roberts et al. 2002).

Instruments are available to assess purported flow of energy through meridians, such as the Gas Discharge Visualization device (GDV). The GDV captures the biofield emissions surrounding each of the ten fingers resulting in the measurement of biophotonic discharge that is in direct proportion to the amount of energy flowing through the 14 main meridians. The coronal discharges measured by the GDV are detected as a result of the human bioenergy field interacting with the electrical field pulsed through the device. At the time of measurement, the emitted light from the interaction is captured by a video camera, and then the images are analyzed with sophisticated software using a mathematical tool known as fractal dimensionality. The data can be integrated over the whole body resulting in a quantifiable analysis of the energy flow and balance throughout the meridian system (Korotkov 2002).

Experiments with the GDV in Russia have suggested potential for the detection of breast cancer. A study of 194 women, 140 with breast cancer, was conducted to assess the diagnostic potential of the GDV to see how it may be used to reflect the

patient's "energy state" in the process of chemotherapy, radiation therapy, and surgery. Statistically significant differences were found between the GDV parameters of the cancer patients when compared with a healthy control group. The patients with cancer had a wide range of stages and diagnoses (Korotkov 2002).

Despite growing evidence that biofields may be related to biological functions and may possibly precede material changes (Tiller et al. 2001), it will take more rigorous research to define ways that protecting from assaults or correcting imbalances in those fields may affect health. There are experiments going on everyday through exposures and behaviors that we cannot fully understand the role of biofields in health until they are evaluated in randomized controlled trials.

Nevertheless, energy medicine practices are common throughout the world. In China, the largest population on earth practices Tai Chi daily to balance energy fields. Although no correlation has yet been established, cancer rates in China are generally low (except for cancers directly attributable to tobacco) (Yuan et al. 1996). In fact, reviewing cancer rates worldwide, one might want to consider moving to Qidong, China, as a "best practice for preventing cancer." The role of culture, health practices and spirituality, and many more suspects in the theater of life exposures needs refined exploration. But until our understanding of mechanisms of energetic influences on the body and the biofield is understood in terms of the dominant microbiological paradigm, the research will neither be noticed nor applied to cancer prevention.

Conclusions

CAM is a continuously developing field, challenging researchers to find new epistemologies to match complex systems and competing evidence. As findings emerge from the cancer treatment realm, its potential application to cancer prevention may be better understood. Another potential source for exploring alternative prevention approaches is to observe population-level behaviors, not only where indigenous systems of healing are commonly practiced but also other factors that are not neatly tied to current medical models, nutrition, and conventional exercise. It may be important to find ways to investigate on a large scale what cultural lifestyles and accompanying methods of healing used in those cultures, may be associated with lower rates of cancer. In such explorations, it will be important to solve the problems of separating out cultural and genetic influences and ruling out spurious correlations from true effects. It may be necessary to develop an appropriate research paradigm to apply to trials on lifestyles before the potential for such systems is fully known.

In the meantime, smaller-scale studies may begin to uncover select mechanisms of action of the elements of CAM. One of the primary funding agencies for examining alternative approaches to cancer treatment, control, and prevention of recurrence, the US National Cancer Institute (NCI) Office of Cancer Complementary and Alternative Medicine (NCCAM), has shifted many modalities previously considered CAM to conventional status. In particular, NCCAM now suggests that many of the mind–body approaches for reducing stress and improving quality of life among patients with cancer or cancer survivors

(e.g., patient education, biofeedback, and cognitive–behavioral approaches) have become mainstream due to well-documented theoretical foundation and scientific evidence. These mind–body approaches are now assigned to funding within the main body of NCI divisions unless the focus of research is more clearly placed on novel mechanisms of action for cancer that have yet to be investigated. Currently, both in the current NCI research projects and in the statements of the modalities suggested for investigation (e.g., phase I/II trials of CAM mechanisms of action), it is evident that in the future there will be a broader research evidence base upon which to evaluate CAM approaches. This is good news; as the consumer continues to adjust lifestyle, seek wellness, and attempt to prevent disease through conventional as well as alternative systems, knowledge that comes from well-designed research may guide this search toward more effective prevention strategies.

The creative search for alternative modes of treatment and supportive care for cancer patients may serve as a useful starting point to identify potential candidate agents and practices for research in prevention. In this light, some of the therapies gaining popularity for supportive care may gain attention in the future as more than simply positive experiences. For example, music, art therapy, and guided imagery all have a long tradition of use with cancer patients, and many oncologists encourage their patients to integrate such extra-medical practices into their treatment program. Often these are not seen as modalities that could affect the course of cancer, only to help the patients cope psychologically with their disease. However, as more evidence accumulates that such activities, even for healthy patients, might affect overall health and immunity, potentially even at the cellular level (Chopra 2000), these may also be explored as ways to improve one's chances of avoiding cancer. Until that day, one should consider adding spices such as flaxseed and curcumin to a diet rich in fruits and vegetables; engage in some form of daily meditation; practice yoga, Tai Chi, or Qigong to the point of obtaining a balanced GDV reading; and watch the research unfold over the coming decades.

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Telemedicine, Telehealth, and e-Health Technologies in Cancer Prevention

9

Ana Maria Lopez

9.1 Telemedicine, Telehealth, and e-Health

Telemedicine utilizes telecommunications technology to facilitate access to health-care services to patients who are geographically separated from a physician or other health-care professional (Field 1996). Telemedicine is increasingly providing health-care delivery solutions worldwide. Telemedicine consults (teleconsultations) may be provided either in real time, that is, via direct interactive videoconferencing where "the doc is seen on TV" or in a modality known as store-forward, whereby clinical data are electronically "stored and forwarded" for clinical review by a medical team at a distance.

Real-time teleconsultations bring the patient and the teleconsultant face-to-face virtually. Although the referring clinician is often present during the teleconsultation to present the patient to the teleconsultant, she or he may designate a "patient presenter," often a midlevel or a nursing health professional. The referring clinician is the optimum patient presenter as she or he is acutely aware of the nuances of the clinical request and is best able to present the patient's condition. Under certain clinical conditions, these interactions have provided the referring clinician/presenter with continuing medical education credit as they provided real-time, interactive educational experiences. Real-time interaction also allows for direct communication between the teleconsultant and the patient and is rated highly with regard to patient satisfaction. Telepsychiatry is the most common application for real-time teleconsultation (Lopez et al. 2005).

Store-forward consultations are performed when the diagnostic question does not require direct audio and video interaction or a virtual physical examination. Teleradiology is the most common example of this type of teleconsultation. Patient information can be recorded as an image, either through video, photograph, or a diagnostic test, such as a radiograph, and can be transmitted after the initial

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consultation with the patient and referring physician has taken place. The teleconsultant reviews these data at a later time and provides a diagnostic assessment and therapeutic recommendation to the referring practitioner on his or her findings. Although the collection of patient data and the assessment of patient data by the teleconsultant are asynchronous and disconnected, accurate diagnostic assessments can be made based on the data transmitted and high levels of patient satisfaction have been reported (Lopez et al. 2005).

Telemedicine is generally considered to encompass direct health-care services, while telehealth is more expansive to include the use of telecommunications technology for the administrative, health promotion, and educational aspects of health care, such as patient and professional education. Telehealth encompasses the public health aspects of care (Lopez et al. 2005).

e-Health is a relatively new term defined by the World Health Organization as the "transfer of health resources and health care by electronic means." This broader vision for electronic communication for the benefit of health care is developing the use of the Internet for dissemination of health information and for facilitating interaction between health professionals and health-care institutions (World Health Organization 2012). Mobile technologies that are phone or Internet based are thought to have great potential to personalize interventions that could be delivered directly and in a timely manner to the individual or community in need.

9.2 Telemedicine, Telehealth, and e-Health in Cancer Care and Cancer Prevention

Telemedicine, telehealth, and e-health have the capacity to increase access to quality, timely, and cost-effective specialty health care. These technologies may not only revolutionize the way physicians care for patients but also change the way clinical care is structured with changes in workflow, quality management, and transmission of patient data. Since these are all factors which can influence the cost of care, telemedicine, telehealth, and e-health have the potential to introduce innovations in clinical and cost efficiencies (Ricke and Bartelink 2000). Multiple barriers exist to inhibit the development and implementation of telemedicine, telehealth, and e-health interventions. The *Telemedicine Action Report* of the Western Governors' Association, published in 1994, outlined potential barriers and recommended a variety of actions and solutions including the initiation of statewide telemedicine networks (Cooley 1996). Barriers detailed in the report include technological infrastructure, telecommunications regulation, reimbursement for telemedicine services, licensure and credentialing, medical malpractice liability, and patient confidentiality.

The care of cancer patients with the use of telemedicine, telehealth or e-health technologies, and teleoncology has begun to be assessed. In comparing a teleoncology clinic with a fly-in outreach clinic, both in rural areas with a traditional clinic in a city hospital, Doolittle et al demonstrated the cost and clinical efficacy of the teleoncology practice (Doolittle et al. 1997). The authors built on this work and initiated discussion on the importance of developing methodologies to evaluate cost efficacy for telemedicine practices (Doolittle et al. 1998). Critical to cost-efficacy

assessment is appropriate use of technology and defining the appropriate technology for the intended diagnostic question. Matching the appropriate telemedicine, telehealth, or e-health technology with the appropriate clinical question is critical to its success. The broader adoption of telemedicine, telehealth, and e-health technologies in oncology care has increased access to specialty cancer care; however, these interventions do not impact therapeutic costs which can remain a barrier to care (Kvedar et al. 2006).

As face-to-face medical care has begun to embrace prevention, so too have telemedicine, telehealth, and e-health technologies begun to embrace disease prevention, health promotion, and overall wellness. Patients' increased awareness of the prevalence of a cancer diagnosis leads more patients to identify as healthy patients at risk for cancer.

Although cancer prevention services may be provided by primary care health professionals, specialized genetic and high-risk follow-up and prevention is most often provided in cancer centers and by cancer prevention specialists. Onega et al. studied access to oncology care in the United States and found travel times to a National Cancer Institute (NCI)-designated cancer center to be an hour or more for the majority of citizens. Greater travel times have been noted for native and nonurban populations not only to NCI-designated cancer centers but to any cancer treatment center (Onega et al. 2008). It is estimated that fully 25 % of the population in the United States lives in remote or rural areas (Hightower 2003). Limited access to medical care can result in patients making health-care choices not based on best medical practice but simply in terms of availability. With the anticipated workforce shortages in health care, ways to extend and improve access to care via modalities such as via telemedicine will be significant assets that may ameliorate health outcomes (Onega et al. 2008).

Telemedicine applications in cancer care have been myriad. The technology has increased access to specialty consultation, to multidisciplinary care, to cancer clinical trials, and to supportive and adjunctive care, including home health care, home self-monitoring, patient education, professional education for midlevel providers and physicians in primary and specialty care, and interdisciplinary tumor boards (Doolittle and Allen 1997; Kunkler et al. 1998; Martino et al. 2003). Although generally, well accepted by both clinicians and patients, technology and business models are still evolving (Olver and Selva-Nayagam 2000).

Patient satisfaction with the clinical experience has not been reported to differ significantly between in-person oncology and teleoncology visits (Weinerman et al. 2005). Therefore, it is likely that the institution of teleoncology practices will result in cost savings, clinical efficiencies, as well as high levels of satisfaction and acceptance among both patients and clinicians (Allen et al. 1995).

9.3 Primary Cancer Prevention

Health promotion approaches lend themselves well to telemedicine, telehealth, and e-health interventions. From direct videoconferencing methodology to mobile interventions, these technologies bring the health-care team's support closer to the patient to support her or his cancer prevention behavior change.

9.3.1 Smoking Prevention

A randomized controlled smoking cessation telehealth study tested the efficacy of a lifestyle intervention in two populations. Each group needed either primary or secondary prevention efforts to reduce cardiovascular disease risk among midlife individuals. Results demonstrated clinical efficacy of the primary prevention intervention. Follow-up evaluation at 1 year also confirmed efficacy (Wister et al. 2007). A recent Cochrane review concluded that there was a demonstrable benefit to smoking cessation interventions that utilized mobile phone technology. Most studies effectively utilized a text messaging intervention to motivate and support smoking cessation behavior (Whittaker et al. 2012).

9.3.2 Nutrition Counseling

A baseline survey was conducted at Bassett Healthcare on outpatients who had follow-up appointments with subspecialty health professionals. The survey revealed that nutrition counseling has the highest no-show rate and largest percentage of patients who do not reschedule their appointments. This program's goal was to determine if appointments for nutrition counseling would increase once the barriers of distance, transportation, and time were removed through the use of telemedicine. To achieve this goal, the Clinical Nutrition Department utilized interactive videoconferencing equipment (e.g., PictureTel Group System) to provide outpatient nutrition counseling. This system enables the Registered Dietitian to observe and communicate with the patient at the outreach clinic despite the miles separating them. Six Bassett Healthcare outreach clinics are currently participating in this project. Primary care professionals at each clinic refer patients for telemedicine nutrition counseling. Pertinent medical history is sent to the Registered Dietitian for review prior to the patients' appointment. Support staff assists in patient scheduling, data collection, and equipment function. A phone survey and patient questionnaire assessed patient satisfaction and adherence. Positive outcomes include (1) increase in the number of initial and follow-up appointments and (2) decrease in the no-show and cancellation rates. Surveys indicate a high degree of satisfaction with telemedicine nutrition counseling. In addition, patients have realized a saving in time and travel expenses. This program has identified the need for interactive video teleconferencing in a rural population and has demonstrated the benefits of providing this service (Johnson et al. 2001).

9.3.3 Physical Activity

Although physical activity is increasingly recognized as a modifiable risk factor for cancer prevention, tele-exercise interventions have generally targeted cardiovascular health. These interventions have primarily targeted geographical barriers and have utilized the Internet as a medium for delivery of "virtual" exercise programs. Delivery of exercise education within our own program has utilized videophone technology to deliver qigong exercises to patients who are awaiting heart

transplantation. This experience was well accepted and appreciated since the patients were able to participate in the sessions even if they were unable to travel.

In a randomized controlled study on delivery of a cardiac rehabilitation program (CRP) to patients at a distance, the virtual CRP group significantly improved their HDL-C, triglycerides, total cholesterol/HDL-C ratio, and exercise capacity as assessed in metabolic equivalents, weekly physical activity, and exercise-specific self-efficacy. No significant improvements were noted in the control group. The virtual CRP results were similar to historical controls in a standard CRP. Participant responses from exit interviews of the virtual CRP were unanimously positive. This latter finding may be most significant for long-term behavioral change, since high user acceptance may have implications not only for generalizability to other patients who do not have access to traditional hospital-based CRP but also for long-term use of the intervention (Zutz et al. 2007).

In post-stroke management, telerehabilitation has been successfully piloted in a single-arm study with videoconferencing technology. The intervention consisted of education and exercise and psychosocial support conducted by a physiotherapist via videoconference. After the intervention, there were significant improvements in the Berg Balance Scale, State Self-Esteem Scale, and Medical Outcomes Study 36-item Short Form—all subscales and stroke knowledge. All subjects accepted videoconferencing well (Lai et al. 2004).

Recognizing the benefit of both physical activity and nutrition to promote a healthy body mass index to support cancer prevention and address other chronic disease risks, multitargeted mobile technology interventions have been developed. In a study by Spring et al., sedentary adult participants with a high saturated fat and low fruit and vegetable intake were randomized to one of four combinations of physical activity and nutritional intervention arms. The intervention included remote coaching and mobile self-monitoring. Addressing sedentary behavior and increases in fruits and vegetables proved to be the most effective approach (Spring et al. 2012).

Multiple dietary assessment tools exist. Access to these tools electronically through mobile devices has the potential to facilitate dietary modification recommendations and to record the process of behavior change more accurately. Defining these best practices is ripe for research as rapidly evolving novel mobile tools are entering the personal health market at an unprecedented rate and without well-delineated use guidelines and efficacy research (Hongu et al. 2011). Available commercial tools include digital images that clearly illustrate serving sizes and suggested food preparation and presentation, on-demand learning tools for patients, as well as online reference tools for dieticians, online dietary diaries with built-in nutritional reminders, and smartphone apps that can integrate nutritional and physical activity entries to track calorie intake and output. The appropriate use of these tools for the benefit of cancer prevention has not been defined.

9.3.4 Genetic Counseling

Clinical genetic consultations are not often available outside of a university or tertiary care center. Incidence of genetic problems in children is increasing and is of great public health concern. Current models for genetic health-care delivery largely

rely on a specialist's travel to communities in need. Unfortunately, this physical presence results in sporadic care that may leave the patient and family feeling unsupported for large periods of time. In an effort to provide a virtual presence in these communities, the Arizona Telemedicine Program has established a telegenetics outreach program. This program provides genetics services on an ongoing basis and thus supports continuity of care. This project built on existing relationships with rural communities and was enhanced by the mutual benefit achieved by this intervention. In an evaluation of the services, it was found that patients strongly agreed that they found telegenetics consultation to be beneficial; patients agreed that having the telemedicine visit now was preferable to waiting for a face-to-face appointment with the same doctor. In fact, overall, patients did not see a need to seek in-person genetic counseling services in the future as they were so satisfied with the telegenetics service (Cunniff et al. 2007).

Similarly, cancer genetics services are generally centered in urban settings and usually housed at an academic center. Exploring the feasibility and efficacy of using telemedicine in counseling patients and families with a history of cancer to increase access to cancer genetics services is ongoing. Anecdotal experience suggests that telegenetics consultations would lend themselves well to videoconferencing communication. Coelho and colleagues (Coelho et al. 2005) evaluated cancer genetic counseling when conducted via telemedicine and compared to face-to-face consultations. Participants were placed into a telemedicine group or a face-to-face group depending on their geographical location. Telemedicine consultations took place using real-time videoconferencing technology integrated services digital network (ISDN) digital telephone lines (specifically, ISDN6). Sixteen participants were evaluated in the telemedicine group compared to 21 in the face-to-face group, and all participants were asked to complete both a pre-counseling and post-counseling questionnaire, which assessed their understanding of cancer genetics, anxiety levels, and satisfaction levels, and allowed for personal comments. In both the telemedicine and face-to-face groups, a significant reduction in cancer-related anxiety levels and high satisfaction levels were reported. There was a trend towards increased cancer genetics knowledge post genetic counseling in both groups. The results show that telemedicine is a useful alternative by which to provide cancer genetics service (Coelho et al. 2005). Others have reported similar comparability of videoconferenced teleconsultations with face-to-face cancer genetic counseling consultations (Zilliacus et al. 2011; Gray et al. 2000; Iredale et al. 2002; d'Agincourt-Canning et al. 2008; Hilgart et al. 2012; Mitchell and Demiris 2005; Lea et al. 2005).

Kaiser Permanente has developed and implemented practice guidelines for genetic counseling referrals for persons at inherited susceptibility for breast and ovarian cancer. Implementation of these guidelines and protocols required dissemination of the "high-risk guidelines for breast and ovarian cancer, dissemination of patient and physician educational materials on the breast cancer guidelines, monthly classes, taped health phone messages for patients, interactive videoconferencing for physicians, training seminars for medical geneticists, publication of articles on breast cancer and genetic risk in health plan member- and physician-directed magazines, identification and training of clinical specialists and supporting clinicians to

care for patients before and after counseling, individual counseling and testing of patients and families, and development of a data registry" (Kutner 1999). The videoconferencing education is an extension of developing e-learning continuing education efforts throughout the country.

Direct marketing for patient-initiated global telegenetics services are emerging and raise concerns about the need for new approaches for remote comprehensive follow-up and support for patients who carry cancer genetic mutations.

9.3.5 Psychosocial Support

Patients with cancer in rural areas are more likely than their urban counterparts to exhaust their usual sources of psychosocial support while still facing challenges posed by their diagnosis. Rural cancer patients are unlikely to have access to professionally led support groups. In a community-based project, the feasibility and acceptability of providing support groups to women with breast cancer in a large rural area using videoconferencing and a workbook journal was assessed (Collie et al. 2007). Additionally, this study assessed the intervention's potential to reduce distress, to increase emotional expression, and to increase self-efficacy for coping with cancer. Twenty-seven women in the Intermountain Region of northeastern California participated in eight support group sessions led by an oncology social worker. All sessions were conducted via videoconferencing. The videoconference sessions were both feasible and acceptable to participants. Older as well as younger women were comfortable using videoconferencing. Participants reported that the groups were valuable because they promoted information sharing and emotional bonds with other women with breast cancer. The results emphasize the importance of a professional facilitator and note the advantages of using videoconferencing for support groups. Pretest and posttest comparisons showed significant decreases in depression and posttraumatic stress disorder symptoms. The results suggest that the intervention has the potential to provide a valuable service that is not readily available in rural communities (Collie et al. 2007). Structured phone support for breast cancer patients and their primary support person while undergoing adjuvant therapy in both urban and rural settings have also demonstrated clinical efficacy (Solberg et al. 2003) and cultural competency (Badger et al. 2004a, b, 2005, 2007; Dorros et al. 2006; Segrin et al. 2006). Studies have examined the effectiveness of telehealth as a means to provide cancer support in underserved populations. Doorenbos et al. (2010) demonstrated satisfaction with telehealth cancer support groups in rural American Indian and Alaska Native communities. Telehealth helped to bridge geographical sense of isolation in the cancer experience. With the dissemination of personal Internet-based technologies in the home, care coordination systems can incorporate home-based telehealth tools to facilitate cancer care. These efforts have demonstrated improvements in health-care coordination with decreased outpatient and inpatient service utilization (Chumbler et al. 2007).

Incentives to develop these tools are encountered in many health reform strategies.

Incorporation of videophones, mobile apps, and digital transmission of patient data create opportunities for the development of virtual support communities that engage patients, families, and health-care teams. Our understanding of the risks and benefits of these interactions is a subject of active study despite the commercial availability of many of these modalities. Although commercial tools are not generally incorporating encryption and other privacy elements, concern for patient privacy is critical once the health-care team is added to the "support team."

9.4 Secondary Prevention

9.4.1 Breast Cancer and Telehealth

Breast cancer is increasingly cited as the most common cancer diagnosis in women throughout the world. Women in the USA have a one in seven lifetime risk of developing the disease. As the prevalence of the disease increases, greater public health efforts must be instituted to improve early detection efforts. Telemedicine efforts in this area range from efforts to improve screening to efforts to enhance early detection.

Building on behavior modification interventions for medication compliance, diet, and exercise at Boston Medical Center, telehealth interventions are being used to enhance other reminders to obtain breast cancer screening. A telephone voice response system has been used to support mammography reminders among women 50–74 years of age. After the initial reminder letter, study participants receive an automated phone call with a recorded voice. The voice asks questions about barriers that the participant may have encountered in obtaining a mammogram. Women respond by using the telephone's touch tone keypad. Women may then be asked subsequent questions or may be offered encouragement and support about the value of annual mammography (Hightower 2003). Web sites to encourage breast cancer early detection have also been developed (Zdravkovic and StriberDevaja 2002). These web sites are popular in the USA and worldwide; however, assessments of efficacy and quality assurance measures are difficult to implement on a broad scale. Efforts to guide consumer use of these web sites are critical to ensure that the information that reaches the patient is accurate.

Mammography remains the gold standard for early detection of breast cancer. Increasing access to telemammography services has long been a public health concern. In remote communities, mammography services may be provided by a mobile van that brings the mammograms to the mammographer, by a traveling mammographer who periodically reads films on site, or by a mammographer who receives the mammograms by courier. These factors contribute to the women experiencing longer wait times to receive the final mammography results. When results are available, a patient may not easily be found to receive her results. Women may not have a phone or may have moved and therefore may not be reached to receive the results. If the patient is not receiving regular annual follow-up, abnormal test results may not be followed up until after the disease has advanced. This loss to follow-up can

be devastating. Telemammography services may help to ameliorate these problems. Mammograms can be performed at a "mobile" clinic and tele-transmitted for reads at a centralized mammography center, over a telecommunications network. The project, which was intended to enhance timeliness of service to the rural community, has far exceeded expectations and has had a major impact on women's health care in that community. By introducing an effective turnaround time of approximately 1 h, women willingly wait for their mammography results. This enhances cancer detection capacity by eradicating the need to track down patients who may have moved, who may not have a phone, or who do not have an address but who now have an abnormal mammogram result. Since the conception of this service in Arizona, nearly 20,000 mammograms have been performed from distant sites (Lopez et al. 2008). Additional measures adding rapid tissue assessments are ongoing (Grogan et al. 2000; Lopez et al. 2006). Although benefits of these interventions have generally targeted rural populations (Maserat 2008), urban needs and shortages are also being addressed. Telehealth and e-health tools and reminders can be integrated into the electronic medical record, can help the health-care team keep breast cancer prevention guidelines for survivors as well as the general population in mind, and can allow for tailored interventions (Hesse et al. 2010).

9.4.2 Cervical Cancer and Telecolposcopy

Telecolposcopy involves the use of telemedicine technology to assess the cervix from a distance. Studies have been conducted to compare the efficacy and accuracy of telecolposcopy versus traditional colposcopy. In one study in a tertiary care clinic, participants underwent a clinical exam, an in-person exam, and a store-forward telecolposcopy exam (Lopez et al. 2004a, b). Different examiners then assessed the store-forward images. Analysis included comparison of the clinical and telemedicine diagnosis alone, and with biopsy results, interobserver and intraobserver correlations, and time to assess and satisfaction with the image. Results indicate that the sensitivity of telecolposcopy was significantly better than chance ($p<0.001$). The positive predictive value of the colposcopic impression was highest for high-grade or invasive lesions and no cervical intraepithelial neoplasia. For the two physicians reviewing telecolposcopic images, the positive predictive value of the telecolposcopic impression was 81 and 82 %, respectively, while the positive predictive value of the in-person impression was 80 %. Patients accepted the technology well and expressed no discomfort that images would be transmitted. The conclusion of the study was that telecolposcopy diagnosis agreed well with in-person colposcopy diagnosis (Lopez et al. 2004a, b).

Subsequent work in a primary care clinic supports the feasibility for implementation and broader utilization (Lopez et al. 2004a, b; Lopez 2005). Work assessing and comparing synchronous real-time telecolposcopy with asynchronous computer evaluation demonstrate improved health-care access (Lopez et al. 2004a, b; Ferris et al. 2002a, b). Although computer, store-forward assessments are less costly and result in better images (Harper et al. 2000; Ferris et al. 2003), visualization of the

area in question and real-time clinical directions may be more effective with real-time telecolposcopy (Ferris et al. 2002a, b, 2004; Bishai et al. 2003). Assessment of the cervix via visual inspection after the application of 4 % acetic acid has demonstrated clinical efficacy and decreased costs (Quinley et al. 2011). Its effectiveness in HIV-positive women is a subject of active study (Gormley et al. 2010). Use of telemedicine technologies and interpretation of digital images to support quality assurance for nonphysician-based cervical assessments in the developing world are emerging (Mwanahamuntu et al. 2011; Parham et al. 2010).

9.4.3 Skin Cancer Prevention and Teledermatology

Teledermatology typically involves photos or videos of in-person dermatological consults that are assessed using store-forward teleconsultations. A study to compare the diagnostic accuracy of in-person versus store-forward teledermatologic consultations was undertaken (Krupinski et al. 1999). Three hundred and eight consecutive patients presenting to the University of Arizona's Dermatology Clinic participated in the study. Each patient was examined by one of three study dermatologists, each of whom examined approximately one third of the total number of patients. Digital photos were then obtained of the skin lesions from each of the patients. Each dermatologist rendered a teledermatology diagnosis, rated her or his level of confidence in the diagnosis, and rated her or his satisfaction with the image resolution and color. The viewing time for determining each diagnosis was also recorded. Eighty percent agreement existed between in-person and digital diagnoses. Intra-dermatologist agreement averaged 84 %, with slightly lower agreement when restricted to exact matches as opposed to matches with minor differences, which were not associated with different treatment. Confidence in diagnosis decisions was rated as definite or very definite across 70 % of cases. Agreement between diagnosis and biopsy results averaged approximately 75 %. Image resolution was rated as either good or excellent 83 % of the time, and color quality was rated the same as in-person assessments in 93 % of cases.

Oliveira and colleagues (2002) have described the development of a web site to enable nonmedical health professionals to screen skin for potentially malignant skin lesions. The nurse assistant photographed the lesions of 92 patients who presented some kind of dermatological condition. The images were then sent for evaluation by the dermatologist followed by in-person examination by the same physician. The diagnoses, which resulted from the examination in person and, in some cases, the biopsy results, were compared with the diagnostic impressions of the nurse assistant and with the diagnostic hypothesis of the dermatologist at a distance. The lesions were classified as either malignant or nonmalignant. Kappa statistics showed a high association between the suspected malignancy and nonmalignancy of the lesions between the dermatologist ($p = 6.01 \times 10^{-9}$) and the nurse assistant and between the diagnosis at distance and in person ($p < 1.0 \times 10^{-14}$). The web site allowed a nurse assistant to screen for potentially malignant skin lesions and, thus, proved to be appropriate for a large-scale test.

A study by Phillips and colleagues (1998) was conducted to determine the reliability of videoconferencing technology in evaluating skin tumors, the impact of the technology on the clinicians' degree of suspicion that a skin tumor is malignant, and the recommendation to do a biopsy. Four skin cancer screenings were conducted at rural health care facilities. A dermatologist saw the patients in person at the local facility, and the same patient was seen by a dermatologist using a high-speed digital (T-1) connection to Greenville, North Carolina. The two physicians were in absolute agreement for 59 % of the 107 skin tumors evaluated. There were five lesions identified by the on-site dermatologist as a probable or definite malignancy. The degree of concern about a lesion being malignant and the decision whether to do a biopsy were not significantly different, as shown by kappa analysis. The concern about the malignancy of a particular skin lesion and the recommendation whether to do a biopsy were not significantly affected by telemedicine technology.

The use of videoconferencing equipment for medical applications is undergoing evaluation in several centers in New Zealand. Patients with skin diseases who live in rural areas in New Zealand have no local access to specialist advice. The principal advantage of dermatology consultations using videoconferencing equipment is decreased travel time for the patient, although the costs of travel, time off work, and domestic help are also reduced. In a case report from this New Zealand teledermatology clinic, rapid assessment of a skin lesion and image storage allowed immediate referral to the appropriate surgical service so that the patient received rapid care for what was determined to be a melanoma (Oakley et al. 1996). Web-based tools facilitate access to expert dermatologic care and have demonstrated efficacy in skin cancer detection (Griffiths 2010).

e-Health tools have focused on both patient and professional education. Online e-health educational tools to promote and improve skin cancer detection in primary care physicians are being developed and assessed. Short- and long-term effectiveness as well as feasibility of incorporating the skin cancer physical exam evaluation into the visit is being assessed (Markova et al. 2011). With the ubiquity of cell phones, patient education has focused on the acceptability and feasibility of texting sun protection messages. Although feasibility and acceptability of text communication have been demonstrated in persons under the age of 40, message tailoring and timing of delivery are still being examined (Mair et al. 2012). Since skin cancer risk is associated with sun damage and with sun damage taking place under the age of 18, parental educational interventions as well as interventions for school-age children have been explored. Both have included interactive computer technologies with the latter engaging children in game formats (Suggs 2006).

9.4.4 Colorectal Cancer and Virtual Colonoscopy

Colonoscopy is the examination of choice to assess premalignant and malignant lesions in the colon. Virtual colonoscopy is a safe, minimally invasive, three-dimensional imaging method that may be an effective alternative especially in places where a colonoscopist may not be available. Pickhardt and colleagues

(Pickhardt et al. 2003) evaluated the performance characteristics of computed tomographic (CT) virtual colonoscopy for the detection of colorectal neoplasia in an average-risk screening population. A total of 1,233 asymptomatic adults (mean age, 57.8 years) underwent same-day virtual and optical colonoscopy. Radiologists used the three-dimensional endoluminal display for the initial detection of polyps on CT virtual colonoscopy. For the initial examination of each colonic segment, the colonoscopists were unaware of the findings on virtual colonoscopy, which were revealed to them before any subsequent reexamination. The sensitivity and specificity of virtual colonoscopy and the sensitivity of optical colonoscopy were calculated with the use of the findings of the final, unblinded optical colonoscopy as the reference standard. The sensitivity of virtual colonoscopy for adenomatous polyps was 93.8 % for polyps at least 10 mm in diameter, 93.9 % for polyps at least 8 mm in diameter, and 88.7 % for polyps at least 6 mm in diameter. The sensitivity of optical colonoscopy for adenomatous polyps was 87.5, 91.5, and 92.3 % for the three sizes of polyps, respectively. The specificity of virtual colonoscopy for adenomatous polyps was 96.0 % for polyps at least 10 mm in diameter, 92.2 % for polyps at least 8 mm in diameter, and 79.6 % for polyps at least 6 mm in diameter. Two polyps were malignant; both were detected on virtual colonoscopy, and one of them was missed on optical colonoscopy before the results on virtual colonoscopy were revealed. CT virtual colonoscopy with the use of a three-dimensional approach is an accurate screening method for the detection of colorectal neoplasia in asymptomatic average-risk adults and compares favorably with optical colonoscopy in terms of the detection of clinically relevant lesions (Pickhardt et al. 2003). Testing and evaluation of acceptability of this intervention is ongoing.

Baca and colleagues (2007) designed a study to determine the contributions of virtual colonoscopy to laparoscopic colorectal surgery. Virtual colonoscopy was performed in 40 consecutive patients who had undergone laparoscopic resection for colorectal neoplasm. Preoperative findings of optical colonoscopy and virtual colonoscopy, operative data, tumor localizations, and histopathologic findings were assessed. Accuracy rates for virtual colonoscopy and optical colonoscopy were 97.5 and 55 %, respectively ($p<0.05$). Polypectomy site was localized with virtual colonoscopy in five patients. There were nine partially obstructing tumors that did not allow optical endoscope passage. Four of six synchronous tumors (one tumor and three polyps) couldn't be shown with optical colonoscopy because of distal obstructing tumor. Histopathologic investigations revealed adenocarcinoma ($n=34$), adenoma demonstrating low-grade dysplasia ($n=3$) and high-grade dysplasia ($n=2$), and neuroendocrine carcinoma ($n=1$). Mean tumor size was 4 cm. Mean proximal and distal surgical margins were 15 and 7.3 cm, respectively. Overall patient preference was 87.5 % for virtual colonoscopy. Correct localization of colorectal neoplasm or polypectomy site is mandatory before laparoscopic colorectal surgery (Baca et al. 2007).

Integrated health-care systems are facilitating adherence to colorectal cancer screening guidelines by targeting both patients and health-care teams with reminders and education (Levin et al. 2011). Patient-focused telephone-based interventions have successfully increased uptake of fecal immunochemical test (FIT) screening

(Paskett et al. 2011). Large population-based Internet educational interventions have been developed and demonstrated increases in colorectal education utilization (Cooper et al. 2004). Following the impact of the educational intervention to colorectal screening behavior has not been accomplished.

9.4.5 Prostate Cancer and Telehealth

Specific uptake of telemedicine, telehealth, and e-health technologies has taken place in correctional facilities with demonstrated improvements in access to chronic, acute, and preventive services including cancer care and, specifically, prostate cancer care (Raimer and Stobo 2004; Kendig 2004). It has been shown that diagnostic teleconsultation and quantitative image analyses via the Internet are not only feasible, but practical, and allow a close collaboration between researchers widely separated by geographical distance and analytical resources. In this study, 1,168 histological images of normal prostate, high-grade prostatic intraepithelial neoplasia (PIN), and prostate cancer were recorded, archived in an image format developed at the Optical Sciences Center (OSC), University of Arizona, and transmitted to Ancona, Italy, as JPEG (joint photographic experts group) files (Montironi et al. 2002). Images were downloaded for review using the Internet application FTP (file transfer protocol). The images were then sent from Ancona, Italy, to other laboratories for additional histopathologic review and quantitative analyses. The three applications of the telecommunication system were remote histopathologic assessment, remote data acquisition, and selection of material. There were only negligible transmission errors and no problem in efficient communication, although real-time communication was an exception, because of the time zone differences. As far as the remote histopathologic assessment of the prostate was concerned, agreement between the pathologist's electronic diagnosis and the diagnostic label applied to the images by the recording scientist was present in 96.6 % of instances. When these images were forwarded to two pathologists, the level of concordance with the reviewing pathologist who originally downloaded the files was as high as 97.2 and 98.0 %. Initial results of these studies made by researchers belonging to this group but located in other laboratories showed the feasibility of making quantitative analysis on the same images (Montironi et al. 2002).

Since population approaches to prostate cancer prevention for men of average risk are in flux, development of prostate cancer prevention telemedicine, telehealth, and e-health programs have focused on high-risk populations. A computer-based educational intervention in African-American men demonstrated significant increases in prostate cancer knowledge and awareness. Long-term knowledge retention and impact on prostate cancer prevention behaviors remain to be elucidated (Weston et al. 2007).

A tailored telephone-based decision support intervention about prostate cancer testing in Black immigrant males improved prostate cancer knowledge, decision confidence, and likelihood of discussion of prostate cancer testing with the healthcare team without increasing anxiety. Increases in testing were not noted compared

to the control group (Lepore et al. 2012). With anticipated increases in global cancer burden, countries are developing national policies for cancer prevention that include increasing awareness and education through models that include telehealth and e-health strategies (Lingwood et al. 2008).

9.4.6 Telepathology

Pathology diagnosis remains the hallmark of cancer diagnosis. As we develop a greater understanding of the preneoplastic process and its histopathologic characteristics along with the molecular biology markers present before the frank diagnosis of cancer, a greater need for centralized pathology services will emerge. Telepathology may likely serve as the means by which this need can be met (Weinstein et al. 1997, 2001). Telepathology was initiated as a means to increase access to frozen section results (Liang et al. 2008; Winokur et al. 2000), second-opinion telepathology consultations, and quality control measures among remote or nonurban communities (Weinstein et al. 1987). Diagnostic accuracy for telepathology has been well established (Halliday et al. 1997).

As the field develops, a greater need for specialized pathology reviews for oncologic diagnosis has emerged. To allow for these services, technology facilitating the translation of the glass slide to the tissue slide was critical (Weinstein et al. 2009). The digital slide can be manipulated and viewed at a higher power, all while preserving the original digital transmission. In addition, with the development of rapid tissue processing technology, pathology diagnoses may be rendered within a 24-h period (Weinstein et al. 2004). Ultrarapid virtual slide processing and telepathology are being paired with cancer diagnostic measure to provide earlier diagnosis, decrease anxiety associated with the wait time, and facilitate earlier entry into the cancer treatment cycle (Grogan et al. 2000; Lopez et al. 2006).

9.5 Educating the Community Health Worker

Community health workers are valuable members of the health-care team who can deliver cancer prevention messages directly to community members in their homes or in community-based settings. Along the USA-Mexico border, *promotoras*, or lay community health outreach workers, deliver cancer information to underserved Latino populations. Uniform up-to-date education remains a challenge. In order to address this need, an educational telehealth intervention was developed to deliver and assess the effectiveness of a sustainable breast cancer tele-education curriculum for *promotoras* in Southern Arizona (Lopez et al. 2007). The program curriculum was transmitted to four communities along the border. Topics included risk assessment, treatment, nutrition, community resources, clinical trials, and survivorship. The videoconferencing equipment utilized included a Tandberg Healthcare Unit III, a Tandberg 880, and a Polycom set-top unit. Sites were bridged together by engineers using an Accord multipoint control unit. Program assessment included

satisfaction surveys, pre and post knowledge evaluation, 1-month interview, and 4-month focus group. Of the 20 *promotora* participants, 14 identified themselves as Latina, three identified themselves as White, and two identified themselves as African American. All participants had at least 1 year of experience as a community health outreach worker. Satisfaction surveys indicate an overall high level of satisfaction for all sessions. Findings of the pre/post evaluation revealed improved understanding and knowledge of breast cancer definitions. One-month follow-up data indicated that all participants had used the materials provided and that *promotoras* had developed an increased confidence in educating women about breast cancer. The 4-month follow-up focus group revealed that the participants experienced increased access to health information and expressed that they felt that program materials had been extremely useful in their work. They perceived that they were better able to serve their community. Outreach tele-education to *promotoras* improved their skills and confidence as health educators with reported improved benefits to the community that they serve (Lopez et al. 2007). Building on this experience, specific training in computer literacy and information technologies for *promotoras* was successfully implemented to develop e-promotoras (Lopez et al. 2012). Sustainability and engagement is accomplished with ongoing tele-education (Lopez 2011).

9.6 Future Directions

Cancer prevention is a rapidly evolving field; however, a major limitation in its efficacy is the limited access that persons have to cancer preventive care. Housed largely in academic centers, cancer preventive services are unreachable to many. Telemedicine, telehealth, and e-health technologies bring unprecedented opportunities to promote cancer prevention strategies directly to the "at-risk well." Multiple telemedicine, telehealth, and e-health approaches support successful cancer prevention applications for screenable cancers. Increased uptake of cancer preventive services via telemedicine, telehealth, and e-health technologies serve to bring state-of-the-art cancer preventive screening and interventions to persons in remote or underserved communities, thus enhancing the health care of the population.

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Global Cancer Prevention

10

Janet Okamoto and Scott J. Leischow

10.1 Introduction

Cancer is a leading cause of death worldwide (World Health Organization 2008a), and the burden of disease continues to increase in both economically developed and developing countries (WHO 2010). Cancer accounted for 7.6 million deaths, or about 13 % of all deaths, in 2008, and projections estimate that by 2030, death from cancer worldwide will reach 13.1 million people per year, and if cancer rates remain unchanged, new cases will increase to 21.4 million per year (Ferlay et al. 2008). This is a net increase of 60 % for cancer incidence, and the largest increases, proportionally, will occur in low- and middle-income countries (Bray et al. 2012). Globally, the leading causes of cancer mortality are from lung, stomach, liver, colorectal, breast, cervical, and prostate cancers (International Agency for Research on Cancer 2008). The most frequently occurring types of cancer differ between men and women, with regional differences as well as differences between high-income and low- and middle-income countries. The leading sites of new cases of cancer for men are lung, prostate, colorectum, stomach, liver, and esophagus. Those for women are breast, cervix, colorectum, lung, and stomach (International Agency for Research on Cancer 2008).

In 2008, the World Health Organization launched its Noncommunicable Diseases Action Plan (WHO 2010), which included cancer-specific interventions. This was followed by the Global Status Report on Noncommunicable Diseases in 2010 (WHO 2011b) and the United Nations high-level meeting on noncommunicable disease prevention and control in 2011 (WHO 2011c). This recent attention focused around noncommunicable diseases has brought about an understanding that the global burden of NCDs generally, and cancer more specifically, continues to increase largely because of the aging and growth of the world population and an increasing adoption of cancer-causing behaviors, particularly tobacco use, in economically

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developing countries (Jemal 2012). Risk factors for cancer often go hand-in-hand with economic growth, when one occurs so too does the other. Cancer risks commonly increase with increased globalization and urbanization. Unfortunately, for those seeking to address the cancer burden, cancer prevention efforts are often eclipsed by other issues in the global arena, such as economic and financial upheaval; water, food, and energy shortages; war and political conflict; infectious disease outbreaks; and natural disasters.

In terms of total and long-term impact, though, cancer and other noncommunicable diseases are at the forefront. For example, Stuckler (2008) found a 0.5 % reduction in yearly economic growth rates for every 10 % rise in the rates of noncommunicable diseases. The cost of treating NCDs, both direct and indirect, is already greater than the cost of treating communicable diseases in most low- and middle-income countries (LMICs). The burden of disease and the resulting costs are so significant that the World Economic Forum has ranked NCDs as a top threat to global economic development (World Economic Forum 2011).

10.2 The Double Burden: Cancer in Low- and Middle-Income Countries

While cancer is a growing cause of death worldwide, the burden is disproportionately escalating in low- and middle-income countries where 70 % of all deaths from cancers and 60 % of new cases are now occurring (Braithwaite et al. 2012). NCDs, including cancer, are now a major cause of disability and loss of productive years. Many LMICs, particularly the low-income countries, have a "double burden" of both communicable and noncommunicable diseases affecting the health and well-being of the population. Almost all major cancer types are occurring more in LMICs than high-income countries, accounting for over half of the global cancer burden for lung (64 %), colorectal (52 %) , breast (56 %), stomach (82 %), and cervical (over 90 %) cancers (Alwan and MacLean 2009).

Significant differences exist in the patterns of cancer incidence and mortality in high-income countries and LMICs (see Tables 10.1 and 10.2). In high-income countries, the major cancer types are lung, breast, colorectal, and prostate cancers. These cancers combine to make up about half of the total disease incidence (Bray et al. 2012). In low- and middle-income countries, lung cancer is still commonly diagnosed, but stomach and liver cancer comprise a significant burden in these countries and are more common than breast and colorectal cancers (Bray et al. 2012). Cervical and esophageal cancers also have high incidences in LMICs, with cervical cancer the most commonly diagnosed in the lowest income countries. Lung, stomach, liver, breast, colorectal, cervical, and esophageal cancer account for about two-thirds of the cancer burden in LMICs (Bray et al. 2012).

This rapidly developing cancer burden in LMICs is due, in large part, to population aging and increasing urbanization/globalization. Cancer is often considered a "disease of aging," with the chances of developing cancer increasing as a person ages. Population aging in LMICs results from an increased life expectancy due to

Table 10.1 Comparison of incidence of top cancer types by income groups

High-income countries	Middle income	Low income
Breast	Breast	Cervix
Prostate	Lung	Breast
Lung	Cervix	Prostate
Colorectum	Stomach	Liver
Cervix	Liver	Kaposi sarcoma
Stomach	Colorectum	Stomach

Source of Data: International Agency for Research on Cancer (2008)

Table 10.2 Comparison of mortality of top cancer types by income groups

High-income countries	Middle income	Low income
Lung	Lung	Cervix
Breast	Liver	Prostate
Prostate	Stomach	Breast
Colorectum	Breast	Liver
Stomach	Cervix	Stomach
Cervix	Esophagus	Esophagus

Source of Data: International Agency for Research on Cancer (2008)

many factors, such as less exposure to and better treatment of communicable diseases, better nutrition, and decreased infant and child mortality. Rapid urbanization and increased globalization, while good for economic growth and development, can also produce many negative effects as well. This type of growth and development can result in changes, sometimes major and dramatic shifts, in social, environmental, and political conditions that result in increased exposure to risk factors for cancer. For example, urbanization can often lead to increasingly sedentary lifestyles, and economic growth can result in more disposable income to spend on things like tobacco.

The majority of the world population resides in low- and middle-income countries, which highlights the importance of addressing the rising global cancer burden in these countries. LMICs also have comparatively younger populations than high-income countries, meaning the burden has the potential to be even greater because productive members of the population are being lost. More than half of all disability-adjusted life years (DALYs) occur in low-income countries, and 38 % occur in middle-income countries (WHO 2009), representing a disproportionate burden for LMICs that are already poorly equipped at the health system and population level to handle the long-term impact of NCDs.

Although the incidence and mortality rates for cancer in low- and middle-income countries are high and growing each year, awareness at the general population level is low. The Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries estimated that while the majority of the cancer burden occurs in LMICs, only about 5 % of the resources devoted to fighting the disease are expended in these countries (Braithwaite et al. 2012). Therefore, there is a critical, largely unrecognized, and unmet need for action to address the cancer burden in LMICs that also present a significant opportunity for prevention.

Cancer is a complicated mix of diseases that are heterogeneous in nature, with different causes and patterns that in some cases are understood and in others are not. The complex nature of cancer is a seemingly insurmountable obstacle; however, more than a third of cancer deaths are caused by potentially modifiable risk factors (Danaei et al. 2005). Cancer, and the resulting disease burden, can be prevented by addressing known, modifiable risk factors for which there already exists a significant amount of information and evidence for effective policy and intervention.

10.3 Modifiable Cancer Risk Factors

Modifiable risk factors are the greatest, and also the most efficient and effective, opportunities to address the global cancer burden. Key risk factors contribute to over 30 % of all cancers (Danaei et al. 2005). The major modifiable risk factors are tobacco use, poor diet, physical inactivity, alcohol use, infections, occupational exposures, and environmental factors such as pollution (Ott et al. 2010). Danaei and colleagues (2005) identified nine behavioral and environmental risks, along with seven infectious causes, that are responsible for almost half of the global cancer deaths. For some cancers, the modifiable risks make weightier contributions; for example, tobacco smoking alone accounts for over 70 % of lung cancer deaths. Other major risk factors in high-income countries include alcohol consumption, poor diet, and physical inactivity. Middle-income countries have these same risks, but risks also include unprotected sexual contact and unsafe water and sanitation in these countries. Low-income countries again have the same risks as both the high- and middle-income countries, but infection is also a major cancer risk (Bray et al. 2012). Lung, cervical, liver, and esophageal cancers have the largest number of deaths attributable to modifiable risk factors in low- and middle-income countries (Danaei et al. 2005). Tobacco use, alcohol use, unhealthy diet, and physical inactivity are the main behavioral cancer risk factors worldwide, while chronic infections are leading risk factors for cancer in LMICs. Understanding these risk factors and how to effectively prevent them is critical to developing a clear and effective strategy for global cancer control and prevention.

10.3.1 Global Burden of Tobacco

Tobacco is a common denominator for all countries and regions in terms of cancer risk; it is one of the leading risk factors for both high-income and LMICs. It accounts for 11 % of the cancer incidence and about 18 % of cancer deaths in high-income countries (WHO 2009). Tobacco use alone accounts for one in six of all deaths resulting from NCDs (American Cancer Society 2011). Tobacco use is currently responsible for a higher proportion of deaths from cancer in high-income countries than in LMICs, but the overall number of deaths from cancer is larger in the LMICs because of the larger total number of deaths from cancer (WHO 2009).

Tobacco use substantially increases the risk of death from lung and other cancers, as well as contributing to other NCDs, such as heart disease, stroke, and

chronic respiratory disease. Tobacco is a multiorgan carcinogen, contributing to oral, liver, bladder, pancreatic cancers, and leukemia; it has also been linked to breast cancer, though the mechanisms and evidence are not yet as clear for this cancer type as the others (Terry et al. 2011).

One billion people worldwide smoke cigarettes and half of cigarette users will die because they smoke. Tobacco not only affects those who use it but also about 600,000 nonsmokers exposed to secondhand smoke (American Cancer Society 2011). If tobacco prevalence and incidence continue on their current trajectories, it is projected that tobacco will cause eight million deaths annually by 2030. Over 80 % of these deaths will be in low- and middle-income countries (American Cancer Society 2011). More specifically, tobacco-attributable deaths are expected to double from 3.4 to 6.8 million in LMICs by 2030 (Mathers and Loncar 2006). Demonstrating the shift away from the global infectious disease burden, particularly in LMICs, it has also been estimated that by 2015, tobacco use will contribute to 50 % more deaths than HIV/AIDS and will be responsible for 10 % of deaths worldwide (Mathers and Loncar 2006). Tobacco use also accounts for half of the health inequalities, as assessed by education, in male mortality (Jha et al. 2006).

Tobacco use is actually declining in many high-income countries among men and leveling out for women. However, it is still rising in LMICs, among men in particular, though the prevalence of use among women in some of these countries is also increasing as traditional norms are changing with increasing globalization. Young people are also increasing their use of tobacco, with prevalence rates of more than 25 % in some countries (Beaglehole et al. 2011b). Use among younger age groups will continue to drive tobacco-attributable cancer rates for years to come and is due, along with rising rates among other groups, in large part to tobacco industry activities and efforts to influence tobacco control policies (Beaglehole et al. 2011b).

10.3.2 Global Diet and Physical Activity Patterns

The specific contribution of diet and nutritional factors to the cancer burden remains unclear and the evidence continues to develop; however, it is becoming increasingly clear that a link exists, and poor diet should be a focus of prevention efforts now in order to address the future burden of cancer. Poor diet is loosely defined, in this instance, and includes diets with excess energy intake that lead to overweight and obesity, such as is most common in higher-income countries. It also includes low fruit and vegetable intake, either due to lack of availability, cultural norms, or diets too full of high-fat, high-sugar foods.

Despite the lack of full and clear enumeration of the mechanisms involved in the diet/physical activity and cancer link, obesity and physical inactivity have been associated with increased risk of endometrial, colorectal, postmenopausal breast, kidney, pancreas, and esophageal cancers (World Cancer Research Fund/American Institute for Cancer Research 2007). Insufficient fruit and vegetable intake also contributes to stomach and lung cancer mortality worldwide, and more than 5 % of cancers worldwide have been attributed to this risk factor (Danaei et al. 2005).

Cancers attributed to poor diet are higher in LMICs than in high-income countries (Wagner and Brath 2012), likely due more to insufficient nutrition than to diets leading to obesity and overweight. Cancers linked to excess energy intake, rather than insufficient intake of fruits and vegetables and other poor diet factors, are more common in high- and middle-income countries. Body fatness, in particular, appears to be associated with increased cancer risk, likely through influences on hormone levels and inflammation (Beaglehole et al. 2011b).

Physical activity, in addition to its contribution to overweight and obesity, is considered a risk factor for female breast cancer, contributing to 26 % of breast cancer mortality in high-income countries and 25 % of breast cancer mortality in low-income countries (Ott et al. 2010). About 20 % of colorectal cancers have also been attributed to physical inactivity (Ott et al. 2010). Increasing physical activity has also been studied in relation to *reducing* cancer risk. For example, a report from the World Cancer Research Fund/American Institute for Cancer Research (2007) stated that "there is convincing evidence that physical activity reduces the risk of colorectal cancer and probable evidence of its role in reducing the risk of postmenopausal breast and colon cancer."

10.3.3 Global Alcohol Consumption

Alcohol contributes to injury and death in many forms, including alcohol addiction, motor vehicle accidents, and cirrhosis of the liver. The total impact of alcohol consumption on health is significant, with an estimated 3.8 % of all deaths and 4.6 % of disability-adjusted life years attributable to alcohol globally (Rehm et al. 2009). Alcohol is a notable but often overlooked cause of cancer mortality. It is responsible for approximately 400,000 deaths from cancer annually worldwide (Boffetta et al. 2006). The main cancers to which alcohol consumption is a significant contributor are esophageal, pharyngeal, oral, postmenopausal breast, and liver cancer (Danaei et al. 2005).

Worldwide, there is wide variation in alcohol consumption across regions, with consumption levels in some Eastern European countries around 2.5 times higher than the global average (Rehm et al. 2009). The lowest alcohol consumption levels, with a few exceptions, are seen in Africa and the Eastern Mediterranean (Rehm et al. 2009). Alcohol use is a cancer risk factor that is considered particularly amenable, using tobacco control as a model, to intervention (Beaglehole et al. 2011b). In particular, cost-effective, population-level interventions for alcohol consumption include policies, taxes, and bans/restrictions.

10.3.4 Global Risks of Infection

Chronic infections are a major contributor to the global cancer burden. This risk factor is particularly relevant in lower-income countries, with 18 % of the cancer burden attributable to infection worldwide (World Health Organization 2011b).

Infectious agents cause some of the most commonly diagnosed cancers in LMICs, such as cervix, liver, and stomach cancers, and Kaposi's sarcoma. The most common infectious agents contributing to cancer are blood and liver flukes, human papillomavirus, hepatitis B and C, herpes virus, and H. pylori (World Health Organization 2009). Globally, 73 % of liver cancer deaths are caused by infection with viral hepatitis or liver flukes, 63 % of stomach cancer deaths are caused by infection with Helicobacter pylori, and almost 100 % of cervical cancer deaths are caused by infection with human papillomavirus (World Health Organization 2009).

Worldwide, an estimated 530,000 new cases and over a quarter of a million deaths in 2008 were caused by cervical cancer in women, with over 85 % of these cases and deaths occurring in LMICs (World Health Organization 2009). This burden can be particularly high to families in lower-income countries when it affects the primary caregiver. The future cost of cervical cancer in LMIC's could potentially be reduced substantially through an increase in the availability and implementation of HPV vaccines to adolescent girls in these countries.

About half of all liver cancer cases in the world are attributed to chronic hepatitis B (HBV) and a little over a third are attributed to hepatitis C (HCV), emphasizing the impact that prevention efforts could have (World Health Organization 2009). Since 1992, the World Health Organization has recommended HBV vaccines as part of routine infant immunization programs to reduce the burden of liver cancer. Since that time, over 90 % of WHO member states have included HBV vaccines in their immunization programs. Despite this, coverage is far less than ideal. For example, in sub-Saharan Africa, where levels of HBV infection are among the highest in the world, less than 80 % of infants receive the third dose of the vaccine (World Health Organization 2011a), and a significant proportion did not receive the first dose in time to prevent potential mother-to-child transmission (MMWR 2008). Vaccinations for common cancer-causing infectious agents are one of the simpler methods of prevention with long-term and far-reaching impact. There are fewer behaviors to target for change in the short term in order to implement the prevention program, and the public health impact can be felt for generations.

10.4 Global Opportunities for Prevention

Among the main modifiable causes of cancer, tobacco has the largest impact worldwide, across all levels of development. The trend is decreasing in high-income countries and is on the rise in LMICs. Diet and physical activity have a greater impact in high-income countries but are increasing in both high-income and LMICs. Alcohol use has a fairly moderate impact overall on cancer, compared to some of the other risk factors, but is increasing in LMICs. Finally, infection has a large impact in LMICs and a minor impact in high-income countries, but is declining across all levels of development (Braithwaite et al. 2012). Primary prevention, the purpose of which is to reduce or eliminate cancer-causing risk factors, should serve as the foundation for global cancer control efforts. We have

considerable and solid evidence upon which to base these efforts for most, if not all, of the risk factors described in this chapter. The need for costly care and treatment, which low- and middle-income countries worldwide can ill afford, could be significantly diminished through implementation of evidence-based strategies for cancer prevention, such as immunization against cancer-causing infectious agents and effective tobacco control. Efficient and effective cancer prevention efforts would also have the added benefit of preventing other NCDs, such as cardiovascular disease, chronic respiratory diseases, and diabetes that share common risk factors. Therefore, global cancer prevention is a true, wide-ranging public, and population health endeavor.

10.4.1 Framework for Prevention

As mentioned previously, tremendous opportunities exist for reducing the risk of cancer through prevention. Although there is always a certain amount of cancer that naturally occurs as a result of random genetic mutations or genetic predispositions that are not influenced by outside factors, multiple opportunities exist for reducing cancer incidence and prevalence through prevention of modifiable risk factors. Indeed, it has been estimated that as much as 80–90 % of cancers can be avoided or significantly delayed if exposure to negative health behaviors (e.g., tobacco and alcohol use, poor diet, and unsafe sexual contact) and environmental risks is modified and optimal preventive care is available (Alberts et al. 2002). Others have contended that the numbers of preventable cancer deaths are closer to about half (Colditz and Wei 2012). No matter if 50 or 80 %, it is clear that the global community can do far more to reduce the cancer burden. For example, multiple avoidable viruses, like variants of the human papillomavirus and HBV, are directly or indirectly causally associated with cancer. These viral exposures could be significantly reduced or eliminated through behavior and policy changes, thus reducing the need for expensive immunization development efforts or for radically more expensive medical treatment if nothing is done.

Similarly, if tobacco use and exposure continues as it has, WHO projections indicate the as many as one billion people will die prematurely by the end of this century, many from one of several tobacco-caused forms of cancer (Eriksen et al. 2002). Further, as Peto and Lopez (1990) have demonstrated, between now and 2050, helping more people to *quit* tobacco use will have a greater impact on reducing the global lung cancer burden than efforts to increase primary prevention of tobacco use. This is due to the dramatically reduced risk of tobacco-caused lung cancer and other diseases for those who quit smoking, even as late as middle age, and because the benefit of preventing tobacco use takes many years to demonstrate a benefit as tobacco-caused cancer usually occurs 20 or more years after tobacco use and addiction has begun (Jha 2009). This illustrates that helping more people to quit

smoking now will have both an immediate impact on health as well as preventing future cancer deaths.

10.4.2 The Complexity of Cancer Prevention

The global cancer burden is dramatic, and likely to become increasingly deadly as populations age, so it is essential that the cancer community considers and evaluates frameworks for characterizing the complexity of intersecting causal factors so that priorities for cancer prevention can be determined and eventually implemented. This is particularly important because most cancer causal factors are not simple, like a gene turning on or off, but in fact typically involve multiple variables – biological, behavioral, and social – that together increase or decrease the probability that an individual will be exposed to a cancer risk factor or have the potential for a particular cancer risk to be prevented.

Moreover, the burden of preventable cancer is far greater in low- and middle-income countries because they often do not have the budget for basic prevention services, do not have the scientific infrastructure in place to guide such efforts in a way that are tailored to their needs, and often have so many other problems that the creation of prevention policies is not a priority. This added burden in LMIC's is exacerbated by the fact that prevention of cancer and other diseases involves a concerted and coordinated effort involving many moving parts and intersecting causal factors. When there is not an adequate infrastructure to meet the basic needs of a population, it is difficult for policy makers in a LMIC to marshal the expertise and resources needed to address the complexities involved.

One framework that has been developed to characterize the factors that impact tobacco use and disease, yet is relevant for understanding cancer prevention in general, is sometimes called the public health model of tobacco control (Giovino 2006). The public health model is comprised of four components: agent, host, vector, and environment (see Fig. 10.1). Agent refers to the proximal factor(s) that triggers

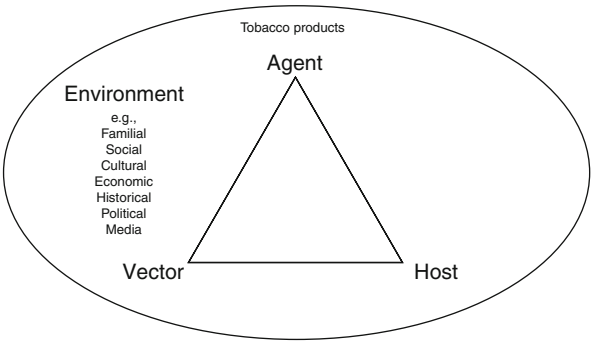

Fig. 10.1 Public health model of tobacco control

biological changes that in turn causes cancer, such as tobacco, food, virus, and chemicals in the environment. In the case of tobacco as an agent, it takes many forms around the world (e.g., very different forms of smokeless tobacco in India and Sweden) and changes frequently as a marketed commodity (e.g., the many varieties of cigarettes sold in the United States).

Indeed, there is interplay between agent and the host, i.e., the person who is exposed to, uses, or is otherwise impacted by the agent. In the case of tobacco, for example, different forms of tobacco have varied potentials for addiction potential in humans, and in fact there are genetic differences in how some individuals metabolize nicotine (the primary addicting agent in tobacco). Similarly, some individuals are less educated about the risks of unprotected sex because they live in a low-income country that has no resources for such education, or in a high-income country where sex education is a low priority, thus resulting in an agent like the human papillomavirus (HPV) causing biological changes in women and men that increase their risk for a variety of cancers.

The agent and host do not come into contact with each other, however, unless there is a vector to facilitate that interaction. For example, few humans would become exposed to tobacco products if not for the tobacco industry as a vector. Similarly, the food and beverage industry has become very effective in their promotion and marketing of foods that lead to obesity, which has direct and indirect effects on cancer risk. At the same time, a large variety of environmental factors impact agent, host, and vector in ways that increase or decrease the chances that cancer will occur or be prevented. For example, peer and family influences in a child's environment decrease the likelihood that tobacco as a vector will influence tobacco use behavior (Mahabee-Gittens et al. 2012), immunization policies have the potential to prevent the spread of HPV that can lead to cervical and other cancers, and policies that assure clean water and food can effectively prevent exposure to the Helicobacter pylori (H. pylori) agent that can increase the chances of stomach and other cancers in a human host (National Cancer Institute 2013).

As the public health model suggests (Fig. 10.1), the four components of the public health model are interrelated and together determine both the likelihood that a particular risk factor (e.g., tobacco, diet, genetic predisposition) will exist and also provides a broad framework for intervening – when intervention is possible – in order to reduce risk. This model is particularly important for cancer prevention since many of the preventable causes of cancer would, if altered, impact the incidence and prevalence of other diseases as well. For example, the leading preventable cause of cancer, tobacco use and exposure, is also a leading cause of other noncommunicable diseases such as cardiovascular disease and pulmonary disease. Similarly, diet and lack of physical activity impact not just cancer but also cardiovascular disease and diabetes. Increased attention to how multiple preventable risk factors impact multiple diseases has become identified as a higher priority by NIH and other organizations, because doing so is both cost-effective and has the greatest potential to lead to the fastest reduction in disease than any known approach.

While the public health model was developed primarily for the public health community, this model has great relevance to the clinical community as well. For

example, most primary care physicians do not and will not have the time, education, or inclination to provide the most effective tobacco treatment, dietary interventions, or sex education, so models that blend clinical practice with public health interventions have increased as a priority globally. Fortunately, considerable evidence indicates that lay educators – in particular those who have close and active ties to their local community – can have a significant impact on facilitating low-income and ethnic minority patients to obtain preventive care from a health-care provider (e.g., screening, tobacco treatment, sex education) that can have the potential to reduce cancer risk later in life (Byers 2012). Similarly, in countries where smoking cessation quitlines have been established with well-trained treatment interventionists, physicians and other clinicians can and do refer patients to this public health-oriented treatment modality because evidence shows that it can increase quit rates. Treatment models that blend clinical care and public health interventions have been implemented effectively for improving the assessment and care of alcoholism (Babor et al. 2007) and tobacco (McRobbie et al. 2008), where both approaches emphasize effective clinical screening and intervention followed by referral to relevant experts that are often found in the community (e.g., smoking cessation quitlines).

The public health model represents a nonlinear interplay of agent, host, vector, and environment that provides a useful framework for investigating and intervening to prevent cancer, but the interrelationships between these four variables also highlight the complexity of effectively improving cancer prevention even when a great deal of evidence exists on what could be achieved. For example, humans (the host) are often entrenched in behavior patterns (e.g., eating, smoking) that are exceedingly difficult to change, though increased research has shown that human behavior on a macroscale can be modified in the direction of cancer prevention by manipulating factors that would otherwise increase risk (e.g., "agents" such as tobacco and food) (Chaloupka et al. 2012). Moreover, multiple "vector" factors, including media by companies that market tobacco and high-fat foods, push back when efforts to curtail their marketing in the interest of public health are considered. For example, tobacco companies in the United States sued to prevent the implementation of graphic warning labels on cigarettes that were approved by law on the grounds that it is a violation of their right to free speech – even though evidence is strong that implementation of those labels would increase the number of smokers who make a quit attempt (Crosbie and Glantz 2012). Thus, not only is there a challenge in cancer prevention to increase research on what can prevent cancer but also how that knowledge can be most effectively implemented. Colditz and Wei (2012) identified several conceptual and environmental factors that they consider significant obstacles to implementation of what we know can prevent cancer, including:

1. Skepticism that cancer can be prevented.
2. The short-term focus of cancer research,
3. Interventions deployed too late in life..
4. Research focus on treatment, not prevention.
5. Debates among scientists (e.g. on priorities).
6. Societal factors that affect health outcomes (e.g., poverty).

7. Lack of transdisciplinary approaches (e.g., addressing components of the public health model at the same time).
8. The complexity of successful implementation.

Each of these factors is as relevant globally as it is in the United States, though we believe that some additional factors are particularly relevant globally. For example, in LMIC countries, there is greater incentive for large corporations to have greater impact because economic diversity is less than in high-income countries. Thus, companies that market alcohol, high-calorie fast foods, and tobacco have the potential to change traditional behaviors in those countries in ways that increase cancer risk. This has already occurred in low-income and transitional countries because they represent 84 % of the 1.3 billion smokers in the world (WHO 2012). Fortunately, the public health community has begun to mobilize in support of efforts that have great potential to prevent cancer. Two examples are the Framework Convention for Tobacco Control (FCTC) and the United Nations Non-Communicable Disease (NCD) initiative – both of which implicitly reflect the complex interactions between agent, host, vector, and environment as they pertain to both causing and addressing their respective (and overlapping) complex problems.

10.5 Action Steps to Cancer Prevention: FCTC and NCD

10.5.1 Framework Convention for Tobacco Control (FCTC)

The leading edge of cancer prevention is tobacco control, largely because the risks due to tobacco use and exposure have been known for decades and that has given the tobacco control community time to mobilize and take action globally. The most far-reaching and significant process for tobacco control, and as a consequence cancer prevention and control, is the first World Health Organization public health treaty ever: the FCTC.

The FCTC began as a proposal by Dr. Ruth Roemer in 1993 to the WHO to develop an international treaty to address the increasing tobacco epidemic that was causing dramatic increases in cancer and other diseases around the world (WHO and UNAIDS 2009). What made this proposal so unique is the fact that such a treaty had never been done before. After several years of wrangling, negotiations, and meetings, the newly elected WHO Director-General, Dr. Gro Harlem Bruntdland, identified tobacco control as one of her highest priorities by creating the Tobacco Free Initiative (TFI) in 1998 (WHO and UNAIDS 2009). Around this same time, there was a landmark lawsuit against the tobacco industry that was settled and that produced hundreds of millions of pages of internal tobacco industry documents that showed unequivocally that the tobacco industry was active in promoting tobacco use globally and that they were actively involved in striving to undermine tobacco control efforts. As a result, movement to create language for this landmark treaty led to resolutions, extensive meetings and negotiations on language, and eventually a

Table 10.3 Framework convention for tobacco control core provisions overview

The core provisions for demand reduction are contained in Articles 6–14, which address both price and tax measures and non-price measures to reduce the demand for tobacco. The latter include:
Protection from exposure to tobacco smoke
Regulation of the contents of tobacco products
Regulation of tobacco product disclosures
Packaging and labeling of tobacco products
Education, communication, training, and public awareness
Tobacco advertising, promotion, and sponsorship
Tobacco tax revenue (but not debit) seen by governments
Measures to reduce tobacco dependencies and to assist cessation
The core provisions for reducing supply are contained in Articles 15–17 and cover:
Illicit trade in tobacco products
Sales to and by minors
Support for economically viable alternative activities

The Framework Convention also covers other important areas, such as liability; protection of public health policies with respect to tobacco control from interests of the tobacco industry; protection of the environment; national coordinating mechanism; and international cooperation, reporting, and exchange of information and institutional arrangements (Articles 5 and 18–20)
Source: WHO (2003)

vote in 2003 by the World Health Assembly resulting in approval of the WHO Framework Convention for Tobacco Control.

This approval, however, was not the end of the story. As a global treaty, the FCTC, just like any other global treaty (e.g., Kyoto Protocol to the United Nations Framework Convention on Climate Change) could not become a law for any country (i.e., enter into force) until at least 40 countries had ratified the FCTC. In November 2004, Peru became the 40th nation to ratify the FCTC, which meant that the FCTC became a viable international treaty and the law in those 40 countries (WHO 2012). As of now, 176 nations have ratified the FCTC, so they are bound by law to enforce its provisions. The United States is among a small group of countries that has signed but not ratified the FCTC.

The provisions of the FCTC are broad and if effectively implemented will dramatically decrease tobacco use and exposure globally – particularly because the vast majority of countries around the world have ratified it. The provisions, called Articles, center primarily around ways to reduce tobacco supply and reduce tobacco demand and assure that appropriate research continues to provide data needed for effective policy and practice. Table 10.3 summarizes the provisions of the FCTC, and they include policy requirements that impact both public health practice (e.g., protection from exposure to tobacco smoke) and clinical care (e.g., measures to reduce tobacco dependence and to assist cessation) (WHO 2003). The WHO (2008b) simplified the recommendations by creating an acronym (MPOWER) to make implementation more straightforward, as follows:

M Monitor tobacco use and prevention policies
P Protect people from tobacco smoke

Table 10.4 Obstacles to implementing tobacco control policies

Lack of awareness of the risk or of the magnitude of risk
Preoccupation with diseases that may have much less serious consequences
Preoccupation with non-health events such as war and natural disaster
Tobacco may not yet cause many deaths in some places where life expectancy is low
The global focus in the medical profession on curative medicine, not on prevention
Smoking may be seen as personal behavior
Tobacco industry: promotion, distortion of health and economic evidence, financial might, challenge/threats to governments and to tobacco control policy and action, use of neolibertarian front groups, tobacco industry-funded research and buying undue influence
Tobacco tax revenue (but not debit) seen by governments
Misperceived concern about economic loss to farmers and manufacturers if tobacco use is reduced
Misperceived concern about the economic consequences of interventions, e.g., smoke-free restaurants, yet data suggest no loss of revenue to restaurants
Disproportionate lack of funds for research and intervention
Difficulty for some governments to work equally with civil society, NGOs, and academia
Uninformed or hostile media or even the perception of offering "equal time" to the industry
No understanding of environmental consequences—fires, cutting down wood to cure tobacco, billions of cigarette ends, matches, lighters discarded daily
No targets
War or military spending (sometimes one third of government funds) making less funds available for health

Source: Mackay (2012)

O Offer help to quit tobacco use
W Warn about the dangers of tobacco
E Enforce bans on tobacco advertising, promotion and sponsorship
R Raise taxes on tobacco

Hundreds of organizations have come together to support implementation of the FCTC in countries that ratified, including a global coalition called the Framework Convention Alliance and regular Conference of the Party (CoP) meetings of countries that ratified. However, multiple obstacles to implementation exist. Mackay (2012) summarized many of those obstacles presented in Table 10.4 and, not surprisingly, some of the barriers are consistent with those identified by Colditz and Wei (2012). For example, setting prevention as a higher priority continues to be a challenge, particularly in an environment of scarce resources, even though prevention of tobacco-caused diseases like cancer is highly cost-effective (Bloom et al. 2012). However, the FCTC has become the "gold standard" for mobilizing the global clinical and public health community toward action to reduce the leading global preventable cause of death.

It is important to note that initiatives to address other preventable causes of death have been implemented (Mamudu et al. 2008), though none to the same breadth and scope as the FCTC. Examples of these initiatives include the Global Strategy on Diet, Physical Activity, and Health in 2004 (Puska et al. 2003) and the Global Alliance against Chronic Respiratory Diseases (GARD) (Bousquet et al. 2007).

10.5.2 United Nations and Noncommunicable Disease (NCD)

As the incidence and prevalence of cancer and other noncommunicable diseases have continued to increase – largely due to preventable factors like tobacco use, unprotected sex, alcohol use, and unhealthy eating patterns – efforts to estimate the cost of NCDs are likewise expected to increase unless prevention efforts are implemented. In one estimate, the cost of global cancer treatment will increase from $290billion in 2010 to $458billion in 2030 (Bloom et al. 2012). Similar increases are projected for other noncommunicable diseases. These daunting projections prompted the global public health community, led by the WHO, to embark on a high-visibility effort to elevate NCDs as a global priority. More specifically, global efforts to address communicable diseases like HIV have made great strides in reducing disease and premature death, so the idea was to educate the public and policy makers on the need to increase focus on NCDs and to increase action on global NCDs through intergovernmental initiatives.

The focus on NCDs began in earnest in 1991 when the World Bank conducted and published a study called the Global Burden of Disease Project (GBDP) (Mamudu et al. 2011). This study, which has been updated, showed very clearly that 60 % of global mortality in both high-income countries and LMIC's are preventable NCDs such as cancer (particularly lung), cardiovascular diseases, COPD, and diabetes (Mamudu et al. 2011). This high prevalence mobilized governmental and nongovernmental organizations to develop recommendations for reducing global rates of NCD and that led to the 2008 Action Plan on the Global Strategy for the Prevention of Chronic Disease (APGSPCD) (WHO 2010). This action plan made the following three recommendations:

1. To map the emerging epidemics of noncommunicable diseases and to analyze their social, economic, behavioral, and political determinants with particular reference to poor and disadvantaged populations, in order to provide guidance for policy, legislative, and financial measures related to the development of an environment supportive of control
2. To reduce the level of exposure of individuals and populations to the common risk factors for noncommunicable diseases, namely, tobacco consumption, unhealthy diet and physical inactivity, and their determinants
3. To strengthen health care for people with noncommunicable diseases by developing norms and guidelines for cost-effective interventions, with priority given to cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes

As these recommendations demonstrate, there is again an inherent recognition of the role that agent, host, vector, and environment play as both causal factors and as a focus for intervention. In addition, they reflect the interplay between clinical practice and public health action, thus demonstrating the need for additional research on how to more effectively bridge clinical and public health efforts – particularly to address the needs of underserved populations.

The 2008 Action Plan provides very specific recommendations for addressing NCDs, and in fact its approach was heavily influenced by the very effective work done to ratify the FCTC. However, despite the strong evidence-based

approaches recommended within the Action Plan, there has been inadequate focus on reducing NCDs relative to their threat to humanity – particularly those with minimal resources. In order to increase global pressure to address the four leading noncommunicable causes of death in the world (i.e., heart disease, cancer, respiratory disease, and diabetes), world leaders met at the United Nations in September 2011 for a Summit to address the threats posed by NCDs. This historic meeting strongly emphasized that the threat and cost of NCDs are growing and will become far worse unless action is taken. In particular, evidence was presented showing that much of the NCD risk is preventable through changes in human behavior (individual, corporate, government) and environment. As a conclusion to the Summit, a set of recommendations were developed that are built on the many efforts that led to the Summit (e.g., FCTC and APGSPCD). Those recommendations are not binding in the same way as the Articles of the FCTC, but they are highly consistent with the FCTC, and implementation of the FCTC will have significant impact on multiple NCDs even if the UN recommendations are not followed. Those recommendations are summarized in Box 10.1 (Probst-Hensch et al. 2011).

In summary, cancer rates will continue to increase globally, but whether that happens is not a function of uncontrollable genetic factors but is largely a function of clinical and public efforts to reduce the factors that will prevent over 50 % of the cancers that might otherwise occur. Our fate is in our own hands, and the global public health community has challenged heads of state to intervene. Fortunately, many existing evidence-based approaches exist that, if implemented, can dramatically reduce the risk of cancer around the world.

Box 10.1

Recommendations from the 2011 UN NCS Summit for the Prevention and Control of NCDs

It is recommended that Member States:

- Include prevention and control of noncommunicable diseases among priorities in national health strategies and plans
- Implement cost-effective population-wide interventions, including through regulatory and legislative actions, for the noncommunicable disease-related risk factors of tobacco use, unhealthy diet, lack of physical activity, and harmful alcohol use
- Strengthen national information systems by implementing a surveillance framework that monitors key risk factors and determinants, morbidity and mortality, and health system capacity. Set standardized national targets and indicators to assess the progress made in addressing noncommunicable diseases
- Promote multisectoral and "health in all policies" approaches to address the social determinants and risk factors of noncommunicable diseases
- Engage non-health sectors and key stakeholders, including the private sector and civil society, in collaborative partnerships to promote health and reduce noncommunicable disease-related risk factors

Box 10.1 (continued)

- Implement international agreements and strategies to reduce risk factors, including the 2003 WHO Framework Convention on Tobacco Control, the Global Strategy on Diet, Physical Activity and Health, and the Global Strategy to Reduce the Harmful Use of Alcohol
- Revitalize primary health care and promote access to cost-effective interventions for noncommunicable diseases, including access to essential medicines and technologies
- Mobilize additional resources and support innovative approaches to financing essential noncommunicable disease health-care interventions within primary health care

It is recommended that the private sector:

- Promote healthy behavior among workers, including occupational safety through good corporate practices, workplace wellness programs and insurance plans
- Contribute to improved access and affordability for the essential medicines and technologies for noncommunicable diseases
- Ensure responsible and accountable marketing and advertising, especially with regard to children
- Ensure that foods needed for a healthy diet are accessible, including reformulating products to provide healthier options

It is recommended that civil society:

- Mobilize political and community awareness in support of noncommunicable disease prevention and control
- Address shortcomings in noncommunicable disease prevention and treatment services for marginalized populations and crisis situations and build community capacity in promoting healthy diets and lifestyles
- Mobilize additional resources and support innovative approaches to financing the prevention and control of noncommunicable disease

It is recommended that United Nations agencies and international organizations:

- Acknowledge the threat of the noncommunicable disease epidemics to sustainable development and integrate cost-effective preventive interventions into the development agenda and related investment programs, including poverty reduction initiatives, in low- and middle-income countries
- Develop, in collaboration with member states, a global set of indicators to monitor noncommunicable disease trends and assess the progress countries are making to reduce the burden of such diseases
- Ensure the effective engagement of all non-health sectors in health and noncommunicable disease policies
- Ensure the active engagement of United Nations agencies, funds, and programs in global and regional initiatives to address the health and socioeconomic impacts of noncommunicable diseases

Report of the Secretary-General, *UN General Assembly*, *May 19*, *2011*, *A/66/83*.
Source: Probst-Hensch et al. (2011)

Conclusion

Inequality and Cancer

Disparity in cancer remains one of the most fundamental health issues worldwide, including both higher-income countries and LMICs. It is an issue that the global community continues to struggle to address and is part of the larger health inequality problem. There are no longer differentiations between diseases of the rich and the poor. Poorer countries are often faced, as mentioned before, with the "double burden" of treating infectious diseases alongside chronic disease. The suffering from chronic illness is only magnified during times of infectious disease outbreak, system upheaval, armed conflict, natural disaster, and other crises that tend to be more common, or at least devastating and long-term, in LMICs than in more developed regions. As demonstrated previously, the chronic disease burden, in which cancer plays a major role, is increasing in LMICs, which contributes to poverty and is becoming another significant barrier to development.

Chronic disease disproportionately affects individuals who are poor, which only increases the inequalities. This is due to many factors, including living in settings where policies and regulations addressing chronic disease prevention and treatment are either inadequate or nonexistent. Health systems in these areas are also usually weak or underdeveloped and underequipped and economic and financial resources may not be available to cover comprehensive prevention and treatment services. Chronic disease can also lead to poverty, due to the continued care required for someone suffering from disease as well as a potential reduction or loss of income. This significant and continuous expenditure and lost productivity can lead to cycles of debt and illness that perpetuate health and economic inequality (Beaglehole et al. 2011b). There are also direct links between tobacco use and poverty. Smoking rates are higher amongst the poor, whose spending on tobacco has more impact on limited family resources as it not only diverts income away from critical expenditures on food but also from spending on medical care and education.

Future Directions and Prevention Strategies

Global cancer control and prevention will require addressing and preventing underlying causes and risk factors for cancer. This will require new approaches and collaborative efforts. To achieve successful global cancer prevention, capacity building around cancer will be needed. This, along with other concurrent NCD efforts, should help to strengthen health systems worldwide. However, in order to get to that point, cost-effective interventions and prevention strategies need to be applied. Applying existing cancer control knowledge is the first place to start, which includes implementing tobacco control, vaccination, alcohol control, and public health campaigns and policy efforts promoting healthy diets and physical activity. Additionally, more research on cancer risks and prevention is needed in LMICs, in order to begin developing tailored prevention activities in these countries.

Law and policy are important tools for cancer prevention due to the capacity to influence behavior at the population level. Advocacy for public health law and reform will naturally need to be varied between countries, due to governmental structure, the extent of current public health laws, and cultural factors. However, regardless of these necessary personalized elements, proposals for law reform need to be evidence informed and based on comprehensive understanding of the cancer burden. The real challenge working on prevention through policy and law reform is the ability to influence behavior and lifestyle factors while recognizing civil liberties and human rights. The international community is recognizing the need for cooperation and combined efforts to solve major public health and address chronic disease problems. Efforts such as the WHO FCTC can be used as models to inform future collaborative efforts and policy making.

There is also still a great need for accurate population-level morbidity and mortality data for cancer. Many countries, most of which are in Africa, still do not have reliable enough data to estimate accurate cause of death or epidemiological models (Jemal et al. 2012). In 2006, there were 449 cancer registries in the world producing cancer incidence data covering approximately 22 % of the world's population, which still leaves much work to be done in order to get a clear and detailed picture of the global cancer burden. There are inherent biases in the current cancer epidemiologic data which are often heightened in LMICs where health system infrastructure and resources are often lacking (Beaglehole et al. 2011b). Beaglehole and colleagues (2011b) pointed to the example of high-mortality cancers, such as liver and pancreatic cancer, in LMICs, to illustrate these biases. Those with high-mortality cancers in LMICs most often do not go to hospitals, where cancer data is collected, to get treated. Therefore, they are not counted and mortality numbers are more likely to be in accurate.

New research, including research on how to implement evidence-based practices in LMICs, will be required to steer the global cancer efforts in the right direction. However, while the approaches will need to be tailored and specific to each country, region, and culture, much of the knowledge and evidence needed to guide global cancer prevention already exists. Collaborations among researchers and health officials, community members, and public health workers will be key to the success of this global endeavor. Concerted effort and collective knowledge focused toward understanding and addressing modifiable risk factors are what will ultimately embody successful global cancer prevention and control.

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Sunscreen-Based Skin Protection Against Solar Insult: Molecular Mechanisms and Opportunities

11

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11.1 Sunscreens as Skin Photoprotectants and Cancer Chemopreventive Agents

The importance of efficient skin UVB (290–320 nm) photoprotection that attenuates photomutagenic events originating from direct absorption of UVB photons by DNA bases is firmly established as reviewed recently (Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Bens 2008; Marrot and Meunier 2008). In addition, cumulative evidence for the involvement of chronic UVA exposure in the causation of solar skin damage including photocarcinogenesis and photoaging now dictates the necessity for additional broad-spectrum skin photoprotection that includes the UVA spectral region of sunlight (Gasparro 2000; Fourtanier et al. 2012). Indeed, solar photons in the deeply penetrating UVA region (320–400 nm) account for more than 95 % of total solar UV energy incident on human skin, contributing to cutaneous photooxidative stress and redox dysregulation, photoallergic dermatoses including polymorphous light eruption, photoimmunosuppression, tumorigenic initiation and progression of nonmelanoma and melanoma skin cancer, and photoaging (Tyrrell 1995; Kvam and Tyrrell 1997; Scharffetter-Kochanek et al. 1997; de Gruijl 2000; Agar et al. 2004; Bowden 2004; Wondrak et al. 2006; Gonzaga 2009; Fourtanier et al. 2012).

Based on the emerging consensus that daily, year-round, broad-spectrum photoprotection is an effective key component of a sun-safe strategy to reduce cumulative lifetime exposure to UV light, much effort has been directed towards the identification, development, and optimization of topical photoprotectants that prevent and attenuate solar skin damage (Kullavanijaya and Lim 2005; Lautenschlager et al.

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2007; Bens 2008; Bissonnette 2008; Svobodova and Vostalova 2010; Fourtanier et al. 2012). Specifically, sunscreen development has aimed at (1) increased absorbance with broadened spectral coverage over the whole UVA/B spectrum, (2) optimized photostability of UV-active chromophores, and (3) prolonged skin residence time with minimal skin penetration and lack of systemic availability upon topical application. In addition, other aspects of drug safety including (4) lack of phototoxic reactivity as well as (5) absence of dark toxicities, originating, for example, from unwanted ligand activity towards the estrogen (ER) receptor, have been addressed by recent sunscreen development.

The SPF (sun protection factor) value is an important quality parameter that specifies potency of protection from UVB-induced erythema following a single exposure to solar-simulated radiation as determined according to EC (European Commission) and United States FDA (Food and Drug Administration) regulations (Bens 2008; Fourtanier et al. 2012). The FDA defines the SPF as follows: 'The UV energy required to produce an MED on protected skin divided by the UV energy required to produce an MED on unprotected skin, which may also be defined by the following ratio: SPF value = MED [protected skin (PS)]/MED [unprotected skin (US)], where MED (PS) is the minimal erythema dose for protected skin after application of 2 mg/cm^2 of the final formulation of the sunscreen product, and MED (US) is the minimal erythema dose for unprotected skin, i.e., skin to which no sunscreen product has been applied' (FDA Code of Regulations, Title 21, volume 5 (21CFR 352); revised as of April 1, 2012).

Importantly, the level of UV filtration achieved by cutaneous sunscreen application is not directly proportional to the SPF of the sunscreen product. This results from the fact that the amount of UV transmission observed upon sunscreen application equals 1/SPF. For example, an SPF of 2 allows 50 % UVB photon transmission (1/2 transmitted). An SPF of 4, will block out 75 % of UVB light (1/4 transmitted). An SPF of 8, will block out 87.5 % of UVB light (1/8 transmitted), and an SPF of 30 will block out 97 % of UVB light (1/30 transmitted). Consequently, the difference in photon transmission between high SPFs (>30) becomes marginal. Apart from the numeric SPF, anti-erythemal activity of a specific sunscreen product will depend on additional factors including the user's skin type, interval between prior topical application and subsequent sun exposure, amount and frequency of application, and cutaneous exposure to physical factors that influence skin residence time of the topical sunscreen including wash off during swimming or sweating.

For quantification of UVA protection suppression of persistent pigment darkening (PPD), a visual cutaneous response to UVA observed between 2 and 24 h after exposure thought to originate from photooxidation of preformed melanin and its precursors is now the standard methodology (Sklar et al. 2013). PPD-based quantification of UVA protection conferred by topical agents assessed in vivo has now been adapted to UVA testing in vitro as specified by the European Cosmetic Industry Association (COLIPA). In analogy to SPF interpretation, a PPD rating of 5 would indicate that the applied sunscreen allows a fivefold increase in UVA exposure before darkening occurs that equals that observed in unprotected skin (Bens 2008; Fourtanier et al. 2012). In addition, UVA photoprotection is also established by

spectrophotometric determination of the "critical wavelength," a physical parameter that indicates the quality of broad spectrum protection by specifying the wavelength below which 90 % of a photoprotectant's spectral coverage (absorbance between 290 and 400 nm) occurs.

It is important to note that photoprotection products designed for broad-spectrum (UVA-I/UVA-II/UVB) protection can achieve different levels of UVA protection even though they display the same SPF. Moreover, even though erythema is considered to be primarily UVB-induced, it has been demonstrated that a broad-spectrum combination sunscreen containing both UVA and UVB filters achieves superior anti-erythemogenic photoprotection as compared to a UVB only filter displaying the same SPF as the combination sunscreen (Young et al. 2010). According to recent European Commission requirements, all sunscreen products should display photoprotection against UVB and UVA with a ratio of protection levels (SPF/UVA protection factor) less or equal to 3.

Given the causative involvement of UV-induced photooxidative stress in solar skin photodamage, a free radical protection index has been proposed as an additional quality parameter that specifies the ability of sunscreen agents to suppress photooxidative stress as assessed by electron paramagnetic resonance-based detection of free radicals (Zastrow et al. 2004; Haywood et al. 2012).

11.2 US Food and Drug Administration (FDA)-Approved Sunscreen Drugs

Among the member states of the European Union where UV photoprotectants are listed as cosmetics, regulations are harmonized by the European Cosmetic Toiletry and Perfumery Association (COLIPA). However, in contrast to other countries where sunscreen agents are typically commercialized as cosmetic products, the United States FDA regulates sunscreen products as over-the-counter (OTC) drugs, and approval and marketing of novel sunscreen agents in the US is a rare event. In the US, 17 agents approved for OTC drug use are available as of early 2013, 15 organic filters and 2 inorganic metal oxides (zinc oxide and titanium dioxide; Table 11.1) (FDA Code of Regulations, Title 21, volume 5 (21CFR 352: § 352.10, § 352.20); revised as of April 1, 2012). The organic filters belong to eight chemical groups, subdivided into either UVB-directed (aminobenzoic acid, salicylate, cinnamate, benzimidazole derivatives) or UVA-directed (anthranilate, benzophenone, dibenzoylmethane, benzylidene camphor derivatives) molecules (Fig. 11.1).

It is remarkable that among organic UVA filters, only avobenzone and ecamsule are able to cover parts of the important spectral UVA-I (340–400 nm) region, whereas all other UVA-active agents only filter in the shorter UVA-II (320–340 nm) range, incapable of providing broad-spectrum protection if combined with UVB absorbers. Due to possible unfavorable photochemical interactions between some of these agents, the FDA restricts the choice of suitable combinations of UVB/UVA chemical filters. Importantly, some of these agents (e.g., PABA) are now considered obsolete due to known insufficiencies regarding spectral coverage, photostability,

Table 11.1 Organic and inorganic UV filters currently FDA-approved for OTC drug use

Active Ingredient/UV filter	Maximum allowed concentration (%)	Spectral coverage (UV)
Organic		
Aminobenzoic acid (para-aminobenzoic acid; PABA)	15	*UVB*
Avobenzone (4-tert.-butyl-4′- methoxy-dibenzoylmethane)	3	*UVA-I*
Cinoxate (2-ethoxyethyl p-methoxycinnamate)	3	*UVB*
Dioxybenzone (2,2′-dihydroxy-4-methoxybenzophenone; benzophenone-8)	3	*UVB*, *UVA-II*
Ecamsule[a] (terephthalylidene dicamphor sulfonic acid)	3	*UVA-II*
Ensulizole (phenylbenzimidazole sulfonic acid)	4	*UVB*
Homosalate (3,3,5-trimethylcyclohexyl 2-hydroxybenzoate)	15	*UVB*
Meradimate (menthyl anthranilate)	5	*UVA-II*
Octinoxate (octyl 4-methoxycinnamate)	7.5	*UVB*
Octisalate (octyl salicylate)	5	*UVB*
Octocrylene (2-ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate)	10	*UVB*
Oxybenzone (2-hydroxy-4-methoxybenzophenone; benzophenone-3)	6	*UVB*, *UVA-II*
Padimate O (2-ethylhexyl 4-(dimethylamino)-benzoate)	8	*UVB*
Sulisobenzone (benzophenone-4)	10	*UVB*, *UVA-II*
Trolamine salicylate [tris-(2-hydroxyethyl) ammonium 2-hydroxybenzoate]	12	*UVB*
Inorganic		
Titanium dioxide	25	(*UVB*, *UVA-II*)
Zinc oxide	25	(*UVB*, *UVA-II*, *UVA-I*)

[a]Limited FDA approval for specific sunscreen formulations marketed by a single manufacture

phototoxicity, systemic availability, and suspected estrogenicity, fueling an ongoing controversy that questions safety and efficacy of photoprotection that is solely based on topical application of synthetic sunscreens (Wolf et al. 2001; Serpone et al. 2002; Haywood et al. 2003; Hanson et al. 2006; Bens 2008; Burnett and Wang 2011; Fourtanier et al. 2012; Krause et al. 2012).

Worldwide, much research has focused on the development of more efficacious and safer sunscreen agents, their combinatorial synergistic use, and their incorporation into advanced formulations as detailed below. Out of four advanced organic filter ingredients approved by the European Commission (ecamsule, drometrizole trisiloxane, bisoctrizole, bemotrizinol), only ecamsule has become available in the USA since 2006, based on a limited FDA approval for specific ecamsule containing sunscreen formulations marketed by a single manufacturer (L'Oreal) (Fourtanier et al. 2012).

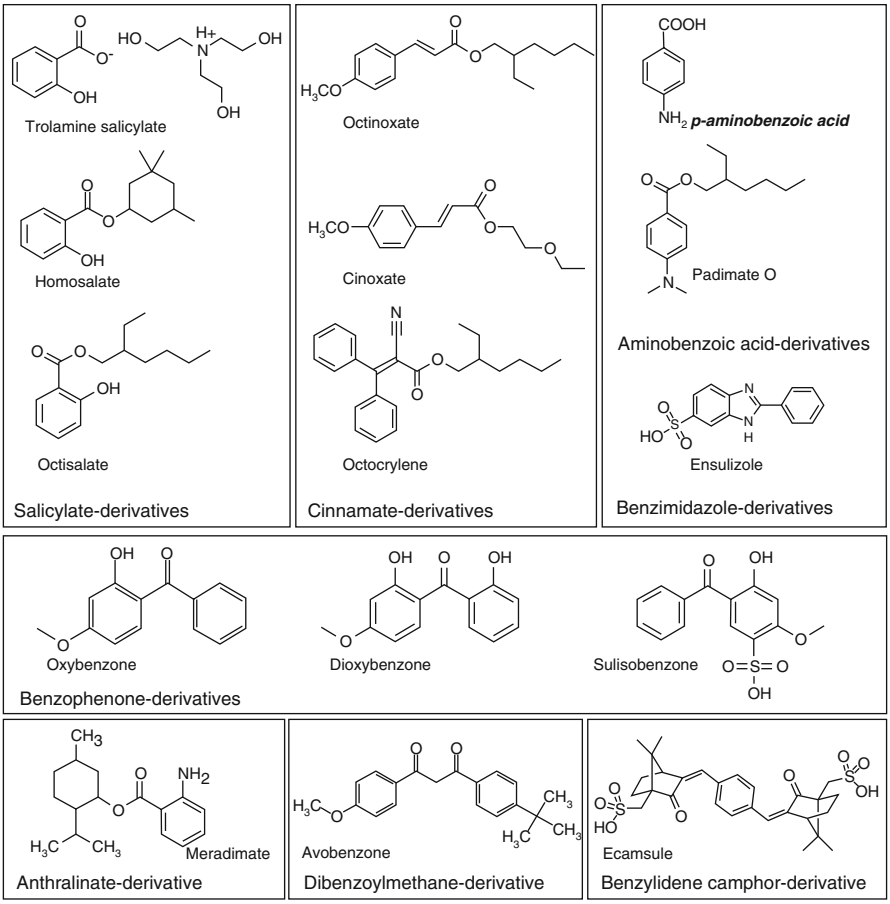

Fig. 11.1 Chemical classes of FDA-approved organic sunscreen agents

11.3 US FDA Regulations Concerning Sunscreens

In contrast to the stagnation experienced in the area of approval of new sunscreen agents, in June 2011 the FDA finalized several regulations that establish revised standards for testing the effectiveness of sunscreen products and require product labeling that accurately reflects test results. According to the regulations that became effective in 2012, the "drug facts" section of the product must indicate that sunscreens labeled as both "broad spectrum" and "SPF 15" (or higher) not only protect against sunburn, but "if used as directed with other sun protection measures can reduce the risk of skin cancer and early skin aging" (Fig. 11.2a), a specific drug use not approved by the FDA in the past when sunscreen use was limited to "prevention of sunburn."

Fig. 11.2 Sunscreen labeling according to 2011 FDA final rule (21CFR, parts 201 and 310, June 17, 2011). (**a**) Labeling of products that provide broad-spectrum and SPF15 protection. (**b**) Labeling of products that do not provide broad-spectrum and/or SPF15 protection (According to FDA guidelines: http://www.fda.gov/forconsumers/consumerupdates/ucm258416.htm); for explanations see text

According to the revised regulations, sunscreen products that are not broad spectrum and/or display an SPF lower than 15 are confined to the use indication "helps prevent sunburn" and must display the following "Skin Cancer/Skin Aging alert: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to prevent sunburn, not skin cancer or early skin aging" (Fig. 11.2b). Only products with combined broad-spectrum SPF15 and above performance display the following additional information that specifies the nature of other essential sun protection measures as follows: "Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a broad spectrum SPF of 15 or higher and other sun protection measures including: limiting time in the sun, especially from 10 a.m. to 2 p.m. and wearing long-sleeve shirts, pants, hats, and sunglasses" (Fig. 11.2a). Product labels such as "waterproof" or "sweatproof" specifying unsubstantiated water resistance are now banned by the FDA. Instead, labeling must indicate "water resistant (40 min)" or "water resistant (80 min)." In addition, due to insufficient evidence of clinical benefit for products displaying very high SPFs (>50), labels may now claim a maximum SPF value of "50+."

It is hoped that the revised FDA regulations revising sunscreen product labeling will contribute to more appropriate and informed sunscreen selection and use among consumers, stressing the importance of frequent and ample application of sunscreens and their obligatory combinatorial use in conjunction with behavioral sun protection measures (e.g., sun avoidance, protective clothing) as promoted widely by many initiatives including the SunWise Program of the US Environmental Protection Agency [http://www.epa.gov/sunwise/]. However, concerns remain regarding the unspecific and broad nature of the general skin cancer protection claim now permissible according to the revised FDA regulations for broad-spectrum SPF15+ OTC products. It can be argued that the FDA-approved drug claim implies a general cancer chemopreventive benefit resulting from sunscreen use that does not account for differences in the solar and nonsolar etiology of specific types of nonmelanoma and melanoma skin cancer and their respective precursor lesions. Indeed, an indiscriminate reduction of skin cancer risk by sunscreen application is not substantiated by the published scientific literature that mostly supports efficacy of topical sunscreen use for the suppression of acute UV skin damage and prevention of actinic keratosis and squamous cell carcinoma (Thompson et al. 1993; Naylor et al. 1995; Green et al. 1999, 2011; Gallagher et al. 2000; Kullavanijaya and Lim 2005; Lee et al. 2005; van der Pols et al. 2006; Lautenschlager et al. 2007; Gonzaga 2009; Ulrich et al. 2009; Autier et al. 2011).

11.4 Rational Molecular Design of Optimized Sunscreen Ingredients

11.4.1 General Considerations

Optimization of sunscreen compounds can be achieved by rational molecular design determining efficient photon absorption at specific wavelengths that should be followed by harmless dissipation of photon excitation energy (Fig. 11.3a) (Kullavanijaya

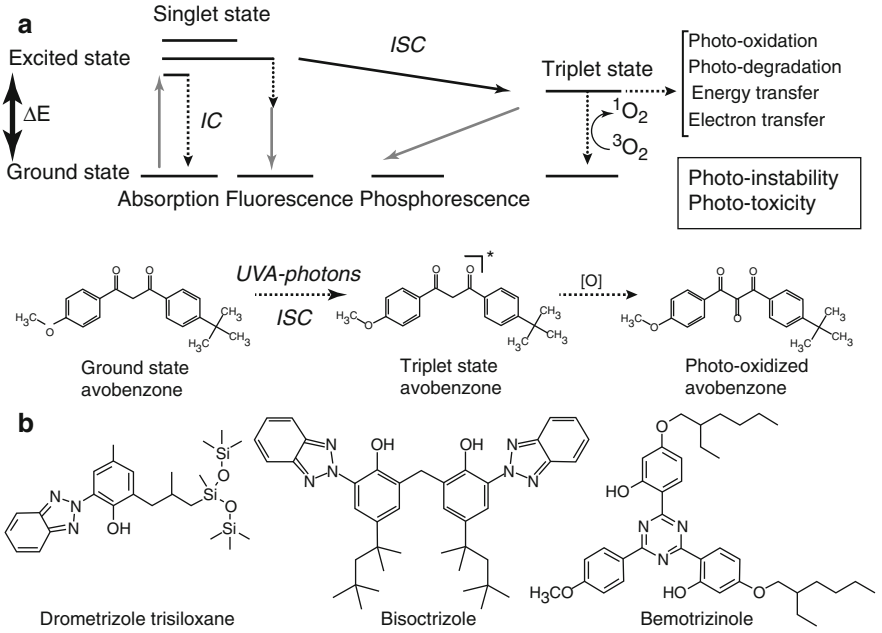

Fig. 11.3 Sunscreen excitation by solar photons followed by excited triplet-state formation. (**a**) *Upper section*: Photochemical reactions may occur downstream of absorption of solar photons by the sunscreen chromophore. *Lower section*: Photooxidation of avobenzone (chemical structure, *left*) results from excited triplet-state formation (chemical structure featuring an excited triplet carbonyl group, *center*) followed by formation of oxidation products such as the triketo-derivative shown (chemical structure, *right*). (**b**) Photostable broad-spectrum sunscreen agents of the hydroxybenzotriazole and hydroxytriazine classes. For explanations see text

and Lim 2005; Lautenschlager et al. 2007; Bens 2008; Bissonnette 2008; Forestier 2008; Svobodova and Vostalova 2010; Fourtanier et al. 2012). An organic filter substance will first absorb photons (excitation energy, ΔE) leading to excitation of electrons situated in π- and nonbinding orbitals of the molecule that undergo a transition to higher antibonding orbitals (excited singlet state formation), followed by return to the electronic ground state by thermal energy dissipation, a process referred to as internal conversion (IC). In specific cases, the excited singlet state can undergo further electronic rearrangements [referred to as intersystem crossing (ISC)] with formation of excited triplet states and biradical species (featuring unpaired electrons), highly reactive intermediates that cause photodegradation of the absorbing molecule itself, and can also damage molecules in its close vicinity through energy and electron transfer reactions. In addition, singlet oxygen ($^1O_2$), a highly reactive electronically excited form of molecular oxygen, can be generated by energy transfer that occurs between the triplet state of the initial absorber and ground state triplet oxygen ($^3O_2$). Numerous sunscreen compounds including the UVA filter avobenzone have been associated with undesirable photochemical reactivities involving photooxidaton, photodegradation, and phototoxicity [Fig. 11.3a, depicting the

reaction sequence for avobenzone photooxidation (tricarbonyl-formation) via UVA-driven triplet-state formation] (Tarras-Wahlberg et al. 1999).

Rational molecular design of sunscreen chromophores has therefore aimed at the generation of improved photostable molecules capable of efficient photon absorption at specific wavelengths with minimized excited state lifetimes and absence of intersystem crossing (triplet-state formation) avoiding singlet oxygen formation that would occur via energy transfer. Moreover, optimized sunscreens bear molecular moieties that facilitate harmless dissipation of photon excitation energy through reversible intramolecular reactions, such as excited state intramolecular proton transfer (ESIPT), keto-enol tautomerism, and cis-trans isomerization (Bens 2008; Forestier 2008).

11.4.2 Sunscreen Optimization by Coformulation

Avobenzone [1-(4-Methoxyphenyl)-3-(4-tert-butylphenyl)propane-1,3-dione] displays extended spectral coverage that extends far into the UVA-I region (340–400 nm; $\lambda_{max} = 357$ nm) making it an important constituent of broad-spectrum formulations that filter UVA-I. However, it has been observed that UVA excitation causes generation of triplet excited states that cause either avobenzone photodegradation or initiate the formation of singlet oxygen or other reactive species (Fig. 11.3a) (Tarras-Wahlberg et al. 1999; Cantrell and McGarvey 2001; Wolf et al. 2001; Serpone et al. 2002; Bens 2008; Fourtanier et al. 2012). Avobenzone photostabilization has been achieved in OTC-marketed sunscreen products by combining it with other more photostable UV filters such as octocrylene, a hydrophobic UVB absorber that photostabilizes and potentiates other UV absorbers (Forestier 2008). Similarly, diethylhexyl 2,6-naphthalate (DEHN), an organic non-UV-screen energy transfer acceptor has shown efficacy in stabilizing avobenzone against UVA-induced degradation and is therefore an established photostabilizer additive employed in numerous formulations.

11.4.3 Sunscreen Optimization Using Nanoparticle and Encapsulation Technology

Significant advances in materials science, specifically in the areas of nanoparticle and encapsulation technology, have impacted the design of improved sunscreen ingredients. Titanium dioxide (TiO_2) and zinc oxide (ZnO) are metal oxide-based inorganic UV filters that exert photoprotection by reflecting, scattering, and absorbing photons. Due to the large particle size of microsized metal oxide-based powders, photon reflection may also occur in the visible range of the solar spectrum potentially causing white cast and grainy skin feel that both limit cosmetic acceptance, problems that have been addressed by the development of nanosized TiO_2 and ZnO preparations (<100 nm), a particle size that allows transmission of visible light causing a transparent appearance while maintaining UV-blocking properties

(Smijs and Pavel 2011). UV and visible photon-directed blocking properties of metal oxide-based nanoparticles are a function of particle size that inversely correlates with the wavelength of incident photons, and among metal oxides zinc oxide displays superior absorption in the long UVA. For spherical TiO_2, a particle size of 20 nm blocks UVB only, a particle size of 50 nm allows UVB and some UVA-II coverage, and a particle size of 100 nm extends coverage over the entire UVA region. Thus, the cosmetically desirable size reduction of nanosized TiO_2 (and ZnO) increases UVB absorption of both particles at the expense of UVA absorption causing unbalanced UV protection. ZnO dispersions should therefore contain both small (nanosized) and large (microsized) particles to maintain a favorable balance between UVA and UVB protection.

The potential for percutaneous penetration of nanomaterials has fueled safety concerns associated with nanosized TiO_2- and ZnO-based sunscreens. However, a large number of studies suggests that nanosized TiO_2 and ZnO do not penetrate the intact stratum corneum of healthy human skin as reviewed extensively (Smijs and Pavel 2011). A consensus exists that further studies should examine the potential for nanoparticle sunscreen penetration through sunburned skin and under conditions of ultraviolet exposure (Newman et al. 2009). Indeed, in a recent study, UVB-damaged pigskin displayed slightly enhanced TiO_2 or ZnO nanoparticle penetration from sunscreen formulations but no transdermal absorption was detected (Monteiro-Riviere et al. 2011). It has also been reported that TiO_2 nanoparticles are efficient photocatalysts potentially enhancing UVA-induced skin photooxidative stress (Jaeger et al. 2012). Remarkably, the International Agency for Research on Cancer (IARC) classifies TiO_2 as an IARC group 2B carcinogen ("possibly carcinogenic to humans") based on the finding that high concentrations of ultrafine TiO_2 dust causes respiratory tract cancer in rats (Baan et al. 2006). However, a recent study has reported that TiO_2 nanoparticles do not promote UVB-initiated skin carcinogenesis in rats, a lack of carcinogenicity attributed to the test particles' inability to penetrate the epidermis (Xu et al. 2011).

Advanced encapsulation and coating strategies can potentially overcome limitations associated with insufficient photostability, unwanted photoreactivity, and skin penetration of inorganic and organic sunscreen agents. For inorganic filters, commonly used nanoparticle coatings that display minimal interference with photoprotective properties and quench light-driven free radical reactivity comprise inert polymeric materials such as silicon and polymethylacrylic acid (Jaeger et al. 2012). For stabilization of organic filters, macromolecular complexation by inclusion of hydroxypropyl-beta-cyclodextrin in sunscreen formulations may enhance photoprotection reducing both skin penetration and photodecomposition of UV absorbers such as avobenzone (Yang et al. 2008).

In an attempt to further block skin permeation and systemic availability of topical photoprotectants, surface immobilization of topical sunscreens has led to the concept of "non-permeating sunscreens" achieved either by covalent macromolecular polymerization of sunscreen chromophores (e.g., polyacrylamidomethyl benzylidene camphor) or through linkage to a macromolecular non-permeating backbone (Touitou and Godin 2008). Additionally, a nondelivery encapsulation

system has been developed based on entrapping organic UV filters in silica-based microparticles. Glass microencapsulation prevents direct physical contact between the active ingredients and skin, blocking skin permeation and enhancing sunscreen photostability, an innovative concept that has been referred to as "sunglasses for the skin."

11.4.4 Sunscreen Optimization by Designing Improved Chromophores

Apart from photostabilization by coformulation, a more UV-stable avobenzone derivative [1-(4-tert-butylphenyl)-2-decanyl-3-(4′-methoxyphenyl)-propane 1,3-dione] has been described carrying a ten-carbon aliphatic substituent at the alpha-carbonyl position of avobenzone, a modification thought to stabilize the enole form of the molecule in apolar water-in-oil emulsions attenuating photodegradation by limiting the occurrence of the keto-form of the molecule from which triplet-state formation and photodegradation can occur (Fig. 11.3a); however, these molecules have not reached the stage of efficacy testing on human skin (Wetz et al. 2005).

Benzylidene camphor and its derivatives [including 4-methylbenzylidene camphor] are potent UVB chromophores contained in a number of established UVB sunscreens approved in Europe but not the US. Benzylidene camphor is photostable and releases absorbed photon energy by internal conversion through cis-trans photoisomerization, a process characteristic of all benzylidene camphor derivatives (Beck et al. 1981). Further photochemical development aimed at shifting absorption towards longer wavelengths (allowing UVA-II coverage) and blocking skin permeation upon topical application (Forestier 2008). A blue-shifted absorption spectrum can be obtained through aromatic extension of the benzylidene camphor-based chromophore, and skin penetration is antagonized by addition of charged substituents (such as anionic sulfonic acid residues). Based on these considerations, a superior photostable UVA-II sunscreen ($\lambda_{max} = 345$ nm) has been generated (ecamsule, terephthalylidene dicamphor sulfonic acid), marketed in other parts of the world since 1993 and available to US customers since 2006 (Fig. 11.1, bottom right) (Seite et al. 1998; Fourtanier et al. 2012).

In contrast, the following three advanced sunscreen agents, used throughout Europe, Australia, and other parts of the world, remain unavailable to US consumers as of early 2013 (Fig. 11.3b). Bisoctrizole (methylene bis-benzotriazolyl tetramethylbutylphenol), a broad-spectrum photoprotectant featuring a photostable hydroxy-benzotriazole chromophore ($\lambda_{max} = 359$ nm), is a hybrid UV absorber (Osterwalder and Herzog 2010). Produced as microfine organic particles (<200 nm) combining characteristics of an organic filter and particle-based photoprotectant, bisoctrizole exerts photoprotection through both absorption and scattering. UVA-I photoprotection is superior among available organic filters as indicated by a "critical wavelength" of 388 nm (as defined in Sect. 11.1). Bisoctrizole also fulfills stringent requirements of advanced photoprotectants (such as lack of skin penetration and absence of estrogenicity) (Ashby et al. 2001).

Drometrizole trisiloxane is another hydroxy-benzotriazole-based broad-spectrum photoprotectant with excellent UVA coverage and photostability. A lipophilic trisiloxane substituent allows formulation optimized for increased water resistance upon topical application (Bens 2008). Combinatorial use between drometrizole trisiloxane and ecamsule potentiates UVA photoprotection (Moyal 2004). Bemotrizinol (bis-ethylhexyloxyphenol methoxyphenyltriazine), available in the European community and Australia since 2000, is a triazine-based lipophilic broad-spectrum UV screen with exceptional photostability, attributed in part to the molecule's ability to dissipate excitation energy by internal conversion though reversible intramolecular proton transfer that occurs between the phenolic substituents and the nitrogens of the core triazine (Osterwalder and Herzog 2010). Importantly, bemotrizinol also confers photostability to other coformulated sunscreen agents known to be intrinsically photoreactive due to triplet-state formation (such as avobenzone), a photostabilization effect attributed to excited state quenching representing an innovative mechanism of photoprotection (Chatelain and Gabard 2001).

11.4.5 Sunscreen Optimization Through Synergism with "Non-sunscreen" Molecular Approaches

Recent research has focused on the identification of molecular interventions and agents that are expected to provide synergistic photoprotective benefit if used together with sunscreen application (referred to as "non-sunscreen photoprotection") as reviewed extensively (Afaq and Mukhtar 2006; Baliga and Katiyar 2006; Wondrak 2007; Dinkova-Kostova 2008; Matsui et al. 2009; Nichols and Katiyar 2010).

11.4.5.1 Quenchers of Photoexcited States (QPES)

Compounds capable of inactivating photoexcited states by direct chemical and/or physical interaction are called quenchers of photoexcited states (Wondrak et al. 2005, 2006). As combinatorial agents used in conjunction with sunscreen compounds, they limit photoreactivity and instability associated with extended photoexcitation of numerous sunscreen agents as mentioned for diethylhexyl 2,6-naphthalate (DEHN) (Chatelain and Gabard 2001). In addition, photoexcited states of endogenous skin chromophores and singlet oxygen (photoexcited oxygen formed by photosensitization) are novel molecular targets for photoprotection by quencher substances, including the xanthone-derivative gentiacaulein, the amino acid L-proline, and the marine photoprotectant mycosporine glycine as reviewed previously (Wondrak 2007). Recent research indicates that light-driven redox cycling of non-DNA skin chromophores [including porphyrins, riboflavin (vitamin B_2), pyridoxine (vitamin B_6), collagen cross-links, melanin precursors, AGE pigments (protein epitopes that form during chronological aging and actinic skin damage)] acting as endogenous photosensitizers is a major source of reactive oxygen species (ROS) in UVA-exposed human skin (Scharffetter-Kochanek et al. 1997; Wondrak et al. 2004, 2006). The causative role of photoexcited states that occur downstream of photon

absorption but upstream of ROS formation in skin photodamage suggests that direct molecular antagonism of photosensitization reactions using physical and chemical quenchers represents a novel chemopreventive opportunity for skin photoprotection to be substantiated in the future (Wondrak et al. 2006).

11.4.5.2 Photoprotective Phytochemicals

Molecular photochemoprevention beyond sunscreen use aims at the identification and development of topical or systemic agents capable of ameliorating the adverse effects of solar radiation on skin. Among numerous experimental and investigational agents that have been tested for photochemopreventive activity, phytochemicals of dietary and non-dietary origin have attracted much research interest (Afaq and Mukhtar 2006; Baliga and Katiyar 2006; Dinkova-Kostova 2008; Nichols and Katiyar 2010). Impressive results documenting chemopreventive potential in mouse models of photocarcinogenesis with topical and systemic administration of phytochemicals have been obtained, including phenolic compounds (e.g., curcumin, resveratrol, tyrosol, caffeic and ferulic acid), flavonoids [e.g., (−) epigallocatechin-3-gallate, apigenin, silibinin], anthocyanidins [e.g., delphinidin] and anthocyanins (e.g., cyanidin-3-*O*-glucoside), and various carotinoids and xanthophylls (e.g., lutein, zeaxanthin) (Gensler et al. 1996; Singh and Agarwal 2005; Tarozzi et al. 2005). Beyond activity as antioxidants and redox modulators, efficacy of these photochemicals is related to modulation of multiple molecular pathways and targets involved in skin solar damage [including Nrf2-dependent activation of the cellular antioxidant response, inhibition of inflammatory signaling (e.g., through modulation of NFκB, AP-1, and COX2), and attenuation of UV-induced photoimmunosuppression] as expertly reviewed elsewhere (Afaq and Mukhtar 2006; Baliga and Katiyar 2006; Nichols and Katiyar 2010).

11.4.5.3 Nrf2 Activators

Recent research strongly suggests that the redox-sensitive transcription factor Nrf2 (nuclear factor-E2-related factor 2) is a promising molecular target for skin photoprotection and cancer chemoprevention that works through pathways that do not involve photon screening (Dinkova-Kostova et al. 2006; Kawachi et al. 2008; Saw et al. 2011). Nrf2 transcriptional activity orchestrates major cellular antioxidant, phase-II detoxification, and anti-inflammatory pathways that protect tissue against electrophilic insult (Zhang 2006). It is well established that numerous dietary chemopreventive factors activate Nrf2 through covalent adduction and/or oxidation of redox-sensitive thiol residues in Keap1 (Kelch-like ECH-associated protein 1), the negative regulator of Nrf2 (Zhang et al. 2004). Inhibition of Keap1-dependent ubiquitination and subsequent suppression of proteasomal degradation of Nrf2 allows Nrf2 nuclear translocation, a process followed by Nrf2-dependent transcriptional activation of cytoprotective target genes underlying Nrf2-dependent suppression of environmental toxicity and carcinogenesis (Hayes et al. 2010). The key role of Nrf2 in the coordination of anti-inflammatory and cytoprotective pathways is supported by extensive studies using Nrf2 knockout (Nrf2 KO) versus wild-type mice demonstrating that Nrf2 KO mice are more susceptible to environmental electrophilic

stress and inflammatory stimuli (including solar ultraviolet radiation, arsenic, benzo[a]pyrene, hyperoxia, cigarette smoke, and diesel exhaust) as reviewed recently (Surh et al. 2005; Osburn and Kensler 2008; Kensler and Wakabayashi 2010; Kundu and Surh 2010).

Pharmacological intervention using dietary factors that activate Nrf2 represents a promising strategy for chemoprevention of various types of cancer (Surh et al. 2005; Hayes et al. 2010; Kundu and Surh 2010). Recent studies strongly suggest a role of Nrf2-mediated gene expression in the prevention of epidermal chemical (TPA/DMBA-induced) and UV-induced carcinogenesis (auf dem Keller and Huber 2006). In cultured human skin cells, the small molecule Nrf2 activator cinnamaldehyde displayed strong cytoprotective activity by suppressing reactive oxygen species (ROS)-dependent photooxidative stress, and Nrf2-dependent protection against UVA-induced keratinocyte damage has been observed (Wondrak et al. 2008; Tian et al. 2011). Protection against UVB-induced skin carcinogenesis by topical application of an Nrf2 activator (sulforaphane-enriched broccoli sprout extract) has been demonstrated in SKH-1 mice (Dinkova-Kostova et al. 2006; Talalay et al. 2007), but the photochemopreventive activity of topical sulforaphane application has also been attributed to potent inhibition of AP-1 (Dickinson et al. 2009). Sulforaphane-based Nrf2 activation confers a protective effect against UVB-induced acute inflammation and sunburn reaction, and Nrf2-dependent attenuation of UVB-induced sunburn reaction and oxidative DNA damage can be observed in Nrf2 wild-type versus KO mice (Kawachi et al. 2008; Saw et al. 2011). However, no increased susceptibility towards UVB-induced skin carcinogenesis was detected in Nrf2 KO mice. In contrast, UVB-induced photoaging is accelerated in Nrf2 KO mice based on increased wrinkle formation, epidermal thickening, dermal deposition of extracellular matrix, lipid peroxidation, and loss of cutaneous glutathione (Hirota et al. 2011). In addition, topical Nrf2 activation using a synthetic tricyclic bis(cyanoenone)-based Nrf2 inducer has shown efficacy protecting against UVA-induced cutaneous photooxidative stress in a murine model of systemic immunomodulatory thiopurine therapy (Kalra et al. 2012).

Taken together, cumulative evidence suggests feasibility of using topical Nrf2 activators as novel photoprotectants and photochemopreventive agents. However, performance of these agents must be tested more rigorously as a function of solar spectral range in acute and chronic models of human skin photodamage in order to better define their efficacy as single or combinatorial photoprotective ingredients optimized for targeted topical delivery, photostability, long-term safety, and mechanistic synergism with other photoprotective agents.

11.4.5.4 Nutritional Photoprotection

The dietary origin of numerous photochemopreventive factors suggests the possibility of achieving efficient skin delivery through oral systemic administration, an emerging concept referred to as “nutritional photoprotection.” Indeed, clinical studies document feasibility of human skin photoprotection by dietary intake of lycopene from processed tomato and flavonoid-rich cocoa (Sies and Stahl 2004; Heinrich et al. 2006; Williams et al. 2009). In addition, oral administration of non-dietary

photoprotectants including aqueous extracts of Polypodium leucotomos has given impressive clinical results, particularly in the context of attenuation of skin photohypersensitivity reactions (e.g., polymorphic light eruption) in human patients (Middelkamp-Hup et al. 2004; Gonzalez et al. 2010). Photoprotective efficacy of nutritional intervention has been attributed to direct UV absorption by chromophores contained in phytochemicals such as conjugated polyenes in carotinoids or 2-phenylchromen-4-one in flavonoids (Astner et al. 2007). Additionally, other molecular mechanisms beyond UV screening including excited state quenching, Nrf2 activation of the cellular antioxidant response, inhibition of inflammatory signaling (NFκB, AP-1), and attenuation of photoimmunosuppression may determine the photochemopreventive activity of specific dietary biofactors that have shown efficacy in animal models (Afaq and Mukhtar 2006; Baliga and Katiyar 2006; Nichols and Katiyar 2010). It should be mentioned that the degree of protection against acute solar insult achievable by nutritional intervention (as assessed by suppression of solar erythema) is generally moderate and does not reach the level of protection achieved by synthetic sunscreen agents. Moreover, safety concerns related to chronic administration of specific phytochemicals such as carotinoids at elevated oral doses have been raised. More research is needed in order to substantiate feasibility and preventive benefits of dietary photoprotection aiming at an optimal cutaneous supply of specific phytochemicals that increase constitutive skin defense against the deleterious consequences of acute and chronic UV exposure.

11.5 Outlook

Many opportunities for improved solar photoprotection and cancer chemoprevention involving the use of sunscreen agents remain to be explored. Areas of current interest include (1) optimization of cancer chemopreventive activity of sunscreens used in conjunction with other measures of photoprotection, (2) potential inhibition of UV-dependent skin vitamin D photosynthesis, a matter of ongoing debate based on accumulating evidence for the chemopreventive action of this solar vitamin against major types of cancer (Giovannucci 2005; Reichrath and Nurnberg 2009; Diehl and Chiu 2010; Gordon-Thomson et al. 2012), (3) insufficient protection against solar photooxidative stress together with inadequate spectral coverage, particularly in the regions of near-visible UVA, visible (blue), and infrared light, known to contribute to skin photoaging and photo-genotoxicity (Moseley et al. 2001; Wondrak et al. 2006; Mahmoud et al. 2008; Darvin et al. 2010; Kolbe 2012), (4) photoinstability and phototoxicity due to light-induced harmful excited state chemistry of many ingredients used in current formulations (Maier et al. 2001; Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Bens 2008; Bissonnette 2008; Svobodova and Vostalova 2010), and (5) insufficient consumer compliance (Bech-Thomsen and Wulf 1992; Autier et al. 2007; Boniol et al. 2008). Undoubtedly, current sunscreen use is inadequate and does not comply with the recommendations of the American Academy of Dermatology [http://www.aad.org/media-resources/stats-and-facts/prevention-and-care/sunscreens]. Concerns have specifically been

raised regarding insufficient frequency and quantity of sunscreen application (Diffey 2001). Research suggests that sunscreen application is the single most frequently used method of sun protection across all age groups, contrary to guidelines that it should be employed in conjunction with other solar protection measures (Stanton et al. 2004). Moreover, it has been argued that, guided by the perceivable benefit of suppression of UV-induced sunburn, consumers might use sunscreens in order to massively overextend skin solar exposure time, thereby receiving high cumulative doses of solar radiation in spectral regions where photon screening by currently available photoprotectants is insufficient or completely absent (Autier et al. 2007; Bens 2008; Boniol et al. 2008). This might be of particular relevance in the regions of deeply penetrating near-visible UVA, blue visible, and infrared light, all suggested to be significant contributors to skin photooxidative and potentially genotoxic solar insult (Kvam and Tyrrell 1997; Haywood et al. 2003; Wondrak et al. 2006; Bissonnette et al. 2008; Schroeder et al. 2010; Liebel et al. 2012).

An informed use of modern sunscreen products remains a key component of the chemopreventive armamentarium for contemporary skin protection against carcinogenic solar insult. A concerted effort that better integrates, expands, and develops the current portfolio of regulatory, educational, behavioral, and pharmacological interventions will ensure that informed consumers can benefit from improved options for effective sun protection that reflects the current state of research.

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Skin Cancer Prevention

12

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12.1 Epidemiology of Skin Cancer

Australia has the highest rates of NMSC in the world with 1,000 per 100,000. In Australia, NMSC accounts for 75 % of all cancers and is 30 times more prevalent than lung cancer among men and 10 times more prevalent than breast cancer among women (Burton 2000). Incidence data for NMSC are sparse because traditional cancer registries do not track NMSC; however, it has been estimated that the incidence of NMSC is 18–20 times greater than that of melanoma. Incidence rates of NMSC increase proportionally with the proximity to the equator, with high cumulative ultraviolet radiation (UVR) light exposure and with age (Diepgen and Mahler 2002). The incidence of NMSC has until most recently affected the older population – especially men who have worked outdoors; however, the age of onset has steadily decreased. While the incidence rates for NMSC continue to rise, the mortality rate has decreased in recent years; however, there continues to be a substantial impact on morbidity, health, and health-care costs. In 2001, approximately 2,000 deaths were reported due to NMSC mostly due to metastasis of squamous cell carcinoma (SCC) to the lymph nodes and other sites. Early diagnosis and appropriate therapy result in a 95 % cure rate. Prevention is the key management tool for NMSC.

Melanoma is the skin cancer with the most fatal potential. The number of melanoma cases is increasing faster than any other cancer in the USA (Linos et al. 2009). In 2012, an estimated 76,250 persons were expected to be diagnosed with melanoma, and 9,180 deaths will occur due to melanoma (Siegal et al. 2012). Data from the U.S. Surveillance, Epidemiology, and End Results (SEER) registry

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demonstrated that melanoma was the most rapidly increasing malignancy in both sexes in the USA from 1973 to 1997 (Lens and Dawes 2004). In the last few decades, the incidence rate of melanoma has substantially increased especially among the Caucasian population. During the 1970s, the incidence rate of melanoma was approximately 6 % a year. However, the rate of increase has slowed to less than 3 % per year. Statistics obtained between 1990 and 2003 demonstrated that the death rates for melanoma were one of four major cancers which were still increasing in males with only a 4.4 % decrease in females (Jemal 2007). The rate of melanoma incidence is ten times higher in whites than in African Americans (Jemal et al. 2004). In Australia, melanoma is the fourth most common cancer among males and the third most common among females. Statistical data suggests that the lifetime risk for melanoma in Australia is now 1 in 25 for men and 1 in 34 for women (Burton 2000). In the USA, the lifetime risk of developing melanoma was 1 in 1,500 individuals in the year 1935; however, currently it is 1 in 59 overall, 1 in 39 for white men, and 1 in 58 in white women (Rigel 2010). It has been estimated that melanoma is the sixth most common cancer among females and the fifth most common cancer among females in the USA in the year 2012 (Siegal et al. 2012).

NMSC arises from keratinocytes and originates in the epidermis. Basal cell carcinoma (BCC) originates from the basal cells of the epidermis and occasionally those of the infundibular and outer root sheath of the hair follicles (Lang and Maize 1991). BCCs are rarely fatal and seldom metastasize; however, they can be locally invasive and destructive (Randle 1996). SCC originates from keratinizing cells of the epidermis. These tumors are more aggressive than BCC and more likely to metastasize. While death rates remain low for NMSC, the incidence is very high and therefore treatment is very costly. The U.S. Medicare system cost of treating NMSC between 1992 and 1995 was nearly $500 million consuming (Housman et al. 2003). Of additional concern, individuals who develop NMSC are at increased risk for the development of new skin cancers within the next few years following diagnosis (Diepgen and Mahler 2002). A follow-up study found that 52 % of individuals diagnosed with SCC developed subsequent NMSC within 5 years of initial therapy (Frankel et al. 1992). Prevention of NMSC is a sensible strategy to lowering these costs.

Melanoma arises from melanocytes, the pigment-producing cells, which reside in the dermal and epidermal junction of the skin. Survival is strongly associated with the thickness of the lesion. If caught early, melanoma can be cured by surgical excision of thinner lesions (0.75 mm or less) and has a 5-year survival rate of 99 % (Koh 1991). Patients with thicker melanoma (more than 3.5 mm) have a steep decrease in survival rates (Lens and Dawes 2004). Tumors greater than 4 mm in depth are associated with a 5-year survival rate of less than 50 %. If the disease spreads, the survival of 5 years after diagnosis is only about 30–40 %. Estimated annual cost for the treatment of melanoma in 1997 was estimated to be $563 million in the USA (Tsao et al. 1998). Stage I and II disease comprised 5 % of the total cost, while stage II and stage IV disease consumed 34 and 55 % of the total cost, respectively. Aggressive primary prevention could substantially reduce this economic burden.

12.2 Risk Factors

12.2.1 Ultraviolet Radiation Exposure

Skin cancer is perhaps one of the most preventable cancers because more the 50–90 % of melanoma or basal cell skin cancer and 50–70 % of SCC worldwide are caused by ultraviolet (UV) radiation (Lucas et al. 2008). Therefore, effective protection from UV irradiation would prevent the greater majority of cases of skin cancer. Aside from genetics, the major risk factors for all skin cancers are exposure to ultraviolet radiation (UVR) and skin color or the inability to tan. All skin cancers have been associated with exposure to sunlight; however, the pattern of sun exposure may vary between skin cancers types.

UVR is comprised of wavelengths from 200 to 400 nm. The ozone of the earth's atmosphere absorbs most light wavelengths below 290 nm. Therefore, UVB (290–320 nm) and UVA (320–400 nm) are the only portions reaching the earth's surface. UVR light reaching the earth's surface is comprised of 90–99 % UVA and 1–10 % UVB. UVR causes many biological reactions in the skin, including inflammatory response in a sunburn, hindrance of immune activity, premature aging, and damage to DNA resulting in potential development of skin cancer (Dissanayake et al. 1993).

UVR exposure causes an increase in reactive oxygen species (ROS) which can overwhelm the natural antioxidant defense mechanisms in the skin. This oxidative stress can result in ROS that interact with proteins, lipids, and DNA (Berton et al. 1997; Li et al. 1996). UVR can result in mutations in genes that regulate cell proliferation and repair. UVR-induced linkage between two adjacent pyrimidines (cytosine or thymine) on the same DNA strand is usually repaired by nucleotide excision repair enzymes before replication. However, if the repair fails or is delayed, fixed DNA mutations can occur when DNA polymerase inserts adenine dinucleotide (AA) opposite the unrepaired dimer. The erroneous pairing of AA with CC or CT linked photoproducts mutations are observed as CC→TT and C→T, respectively. These are characteristically induced by only UVR and as such are designated UVR signature mutations (Wikonkal and Brash 1999).

In the past, UVB was thought to be more important than UVA in the generation of sun damage and skin cancer. However, UVA has become increasingly suspect in the development of skin cancer (Runger 1999). The photocarcinogenesis of UVA differs from UVB in that UVA is not readily absorbed by DNA, but is absorbed by other molecules within the cell, giving rise to reactive oxygen species, which in turn damage DNA, membranes, and other cellular constituents (de Gruijl 2000). UVA has been shown to induce mutations in DNA including p53, which is discussed later in this chapter as an important genetic marker for NMSC (Burren et al. 1998). UVA has been found to be an important factor in the development of melanoma. Several investigators have argued that UVA is more relevant in melanoma causation than the UVB range (Setlow et al. 1993). Much of the evidence of UVA exposure as a risk factor for melanoma has come from epidemiological studies of users of sunbeds or tanning equipment with spectral output that is in the UVA range (Swerdlow and Weinstock 1998; Wang et al. 2001). A study of women from Norway and Sweden

found that women who visited a tanning parlor at least once a month were 55 % more likely to later develop melanoma than women who did not artificially suntan. Those who used sunlamps during their 20s had the greatest risk, approximately 150 % higher than similarly aged women who did not use tanning beds (Veierod et al. 2003). Meta-analysis of 19 studies of indoor tanning and melanoma risk suggests that the use of indoor tanning was associated with a relative risk of 1.15 for developing melanoma, and if the use occurred before the age of 35 years, the relative risk increased to 1.75 (International Agency for Research on Cancer 2007). More recent publications continue to demonstrate the association of indoor tanning and melanoma risk including an epidemic of melanoma in Iceland possible due to increase use of sunbeds (Lazovich et al. 2010; Hery et al. 2010). Further contributing to the controversy, a preclinical study showed that UVB, and not UVA, exposure promoted melanoma growth in a mouse model (De Fabo et al. 2004).

Chronic exposure to UVR is the predominant cause of NMSC. Over 80 % of these cancers develop on parts of the body exposed to the sun including the face, neck, and arms (Diepgen and Mahler 2002). Incidence rates for NMSC correspond well with increased UVR exposure as demonstrated by the increased incidence among individuals with occupational or recreational outdoor exposure or who reside at latitudes closer to the equator (Diepgen and Mahler 2002). Many studies have shown an inverse relationship between latitude and NMSC incidence (Almahroos and Kurban 2004). A report from southeastern Arizona suggests that the incidence rates of NMSC in Arizona are three to six times higher than those in subjects with similar skin type and living in regions of higher latitude (Harris et al. 2001a, b). A compilation of these and several other studies demonstrates a more than 50-fold difference in rates of NMSC incidence between Australia and Arizona (low latitude) and Finland (high latitude), with the higher incidence occurring in the lower latitudes (Almahroos and Kurban 2004). Several Australian studies have demonstrated that people in countries with high ambient solar radiation have a higher incidence of NMSC than migrants with the same genetic background from countries with lower ambient solar radiation (Almahroos and Kurban 2004). People who move during childhood to the countries of high ambient solar radiation from countries with low ambient solar radiation have equal incidence of NMSC as natives (English et al. 1998). However, individuals who make this same move later in life have a lower incidence. This data supports the idea that NMSC develops from a chronic exposure of UVR. The risk factor of skin color for the development of NMSC is demonstrated by the lower risk of ethnically darker skinned migrants.

Melanoma incidence is also associated with exposure to UVR. Childhood sunburns and intense intermittent sun exposure are major risk factors for melanoma (Gilchrest et al. 1999). Anatomic locations of melanoma development support the basis for intermittent UVR exposure as a risk factor. Melanoma is most commonly found on the trunk of men and the trunk and lower extremities of women. These sites are not normally acclimated to the sun by chronic exposure, but rather tend to be exposed during outdoor recreational activities. The effects of the sun on the development of melanoma are modulated by skin type. Light pigmentation increases the risk of the development of melanoma.

In a study conducted at the University of Arizona, risk factors for SCC were evaluated among 918 Arizona residents with sun-damaged skin (at least ten clinically assessable AK lesions) who had been randomized to the placebo arm of a skin cancer chemoprevention trial (Foote et al. 2001). Risk factors for BCC included older age, male gender, red hair color, and at least 10 years' residence in the state of Arizona, which is located in a lower-latitude region of the USA with documented rates of SCC and BCC that are among the highest in the world (Harris et al. 2001a, b).

12.2.2 Other Risk Factors

The presence of precancerous lesions increases the risk of developing skin cancer. For SCC, the precancerous lesion is actinic keratosis (AK), and for melanoma, the precancerous lesion is thought to be dysplastic nevus (DN). BCC does not appear to have a precancerous lesion; however, the presence of AK can often be an indicator of risk. Additional risk for skin cancer includes genetics, immune suppressive disease, past history of skin cancer, and occupational exposure to coal tar, pitch, creosote, arsenic compounds, or radium. Age, male gender, and DNA repair disorders such as xeroderma pigmentosum are also risk factors for skin cancer. For melanoma, additional risk factors include one or more family members who had melanoma and a large number of moles (risk increases with number of moles) or the presence of DN. Approximately 5–12 % of patients with melanoma have a family history of melanoma in one or more first-degree relatives (Goldstein and Tucker 2001). Mutations in two melanoma susceptibility genes, CDKN2A (p16) located on chromosome 9 (9p21) and CDK4 located on chromosome 12 (12q13), have been identified. Mutations in p16 have been identified in 20 % of tested melanoma families (Bishop et al. 2002).

12.2.3 Genetic Alterations in NMSC

Genetic studies of AK and SCC have found alterations on possible tumor suppressor genes of chromosomes 9p, 13q, 17p, 17q, and 3p (Quinn et al. 1994; Hunter 1997). The targets for most of these mutations have not been identified except for p53, which lies on chromosome 17p. p53 is a tumor suppressor gene that plays a role in protecting cells from DNA damage. Recognized genetic targets in NMSC include p53 mutations demonstrated in a progression of normal skin to sun-damaged skin to AK to SCC (Einspahr et al. 1999). p53 mutations have also been identified in BCC (Matsumura et al. 1996). Many of these mutations are CC→TT or C→T changes at dipyrimidine sites suggestive of UVR damage (Tsao 2001). Recent studies indicate that UVA may be also contribute to "signature" dipyrimidine mutations instead of only UVB (Runger et al. 2008), suggesting that UVA may be a complete carcinogen. Runger et al. (2008) postulate that UVA DNA damage may be more mutagenic than UVB, due to a lack of stimulation of the robust DNA repair response noted with UVB exposure.

Results from an analysis of genetic changes in 36 AKs and 23 invasive SCCs (Rehman et al. 1996) suggest that the relationship between the accumulation of

genetic change and behavior for NMSC is complex. However, the overall pattern of autosome loss in AKs was similar to that seen for SCCs. Loss of chromosome 17p was the most frequent target of loss of heterozygosity (LOH), which is consistent with data showing a high rate of UVR-induced mutations in p53 (Brash et al. 1991), detection of p53 mutations in irradiated skin and cultured keratinocytes (Nakazawa et al. 1994), and evidence showing p53 mutations in preinvasive lesions (Einspahr et al. 1999). However, the number of SCCs with chromosome 17p loss far exceeded the number in which mutations were detected in p53 exons 5–8, consistent with the presence of other targets of inactivation on chromosome 17 (Wales et al. 1995). Increased $p21^{WAF1/CIP1}$ immunostaining and p53 immunostaining were observed in 97 and 83 % of AKs, respectively, and were observed in lesions without any detectable LOH or p53 mutation, suggesting that changes in proliferation, $p21^{WAF1/CIP1}$ expression, and p53 expression may precede allelic loss or p53 mutation. Pacifico et al. (2008) noted that NMSC also harbors high rates (up to 82 %) of deletion of exon 1 or 2 of the CDKN2A locus, which encodes proteins p16INK4a and p14ARF. These tumor suppressors are also linked to the p53 and retinoblastoma pathways. A large number of AKs showing multiple areas of LOH and p53 mutation may not have acquired the relevant genetic change to allow invasion of the underlying dermis (Wales et al. 1995).

Genetic alterations in NMSC also include mutations in the ras gene. The frequency of ras mutations in SCC ranges up to almost 50 % and up to 30 % in BCC (Pierceall et al. 1991). Mutations in ras have also been identified in AKs (Spencer et al. 1995). Different rates reported for SCC and BCC ras mutations may reflect different techniques, different study populations, and/or the differing molecular epidemiology of low and high sun exposure. Additional studies have also implicated viral infection with NMSC progression. Zaravinos et al. (2010) noted that HPV and CMV infection was detectable in ~30 % of AK, SCC, and BCC specimens. Although normal skin did not harbor CMV, this virus was detected in ~20 % of skin lesions. These samples were collected from immunocompetent subjects and did not seem to be dependent upon H-ras mutation.

Although more commonly reported in melanoma, recent studies suggest that alterations in p16 can be found in up to 24 % of SCC and 3.5 % of BCC (Soufir et al. 1999). Several of the detected mutations were UVR signature mutations. These mutations may account for alterations observed on chromosome 9p21 in SCC (Tsao 2001).

Genetic alterations in BCC are found in both hereditary and sporadic cases. The PTCH gene is found in patients with nevoid BCC syndrome, characterized by the rapid development of numerous BCCs early in life (Tsao 2001). Recent studies have demonstrated that 15–39 % of these patients harbor mutations in the PTCH gene (Aszterbaum et al. 1998). Genes involved in chemical detoxification and abnormal inflammatory responses are also linked to increased risk of BCC (Madan et al. 2006).

12.3 Genetic Alterations in Melanoma

The most prevalent signaling pathway identified in the development of melanoma is the mitogen activation protein kinase (MAPK) pathway. Genotyping of melanoma tumors demonstrates a range of activating mutations in the BRAF kinase of up to

70 %, with a specific point mutation, V600E, in up to 90 % (Chin et al. 2006; Dutton-Regester and Hayward 2012; Agarwala et al. 2010). Developments from the Cancer Genome Project revealed that 66 % of melanomas tested had a mutation in BRAF with the same single substitution occurring in 80 % of melanomas (Davies et al. 2002). This mutation was observed in 68 % of melanoma metastases and 80 % of primary melanoma. Investigators observed this same BRAF mutation in 63 of 77 (82 %) histologically diverse nevi including 4 of 5 (80 %) dysplastic nevi (Pollock et al. 2003). This suggests an early role for BRAF in the development of melanoma. BRAF mutations do not appear to be inherited; instead the mutations are common (59 %) in melanomas arising in skin which has received intermittent sun exposure, such as the trunks and arms (Chin et al. 2006). However, the transversion that occurs with this mutation is not classically associated with UV-induced damage. BRAF is known to play a role in cell growth and division. By introducing an activated mutation of BRAF into cultured melanocytes, investigators showed that BRAF can act as an oncogene in early stages of melanoma. This activation resulted in a constitutive activation of MEK and ERK and ultimately tumorigenicity in nude mice (Wellbrock et al. 2004). Dr. Arbiser of Emory University School of Medicine identified the activation of mitogen-activated protein kinase (MAPK) as an early event in melanoma progression (Cohen et al. 2002). One hundred and thirty-one melanocytic lesions, ranging from atypical nevi to metastatic melanoma, were studied for the expression of phosphorylated (active) MAPK and two target genes known to be induced by MAPK signaling, tissue factor, and vascular endothelial growth factor. While MAPK activation was positive in only 21.5 % of benign nevi (with mild atypia), MAPK activation was seen in both radial and vertical growth phase melanomas. These findings suggest MAPK signaling as a potential target of chemoprevention in early melanoma. These findings demonstrate that the mutation of BRAF and activation of the RAS-RAF-MEK-ERK-MAP kinase pathway, which mediates cellular responses to growth signals, are crucial and early steps in the progression of melanoma.

Also part of the MAPK pathway, NRAS is found mutated in 10–20 % of melanomas. In one study, 5–35 % of various graded melanomas or nevi had some type of RAS mutation (Yasuda et al. 1989). Within the ras family, N-ras has the most significant association with melanoma progression. Herlyn and colleagues found a role for ras in approximately 15–20 % of melanomas with a positive association with sun exposure (Herlyn and Satyamoorthy 1996). Mutations in NRAS can also activate the PI3-kinase pathway that can lead to increase cell proliferation, apoptosis, and tumor cell chemoresistance. Mutations in melanoma occur at low frequencies in other components of this pathway including AKT and PIK3CA (Davies et al. 2008; Omholt and Krockel 2006).

The phosphatases PTEN/MMAC1, located at 10q23,3, have been found deleted in more than 40 % of melanoma cell lines (Ortonne 2002). In a study of melanoma progression from normal skin, acquired melanocytic nevi and cutaneous melanoma, nuclear PTEN expression was lost in both benign and malignant melanocytic lesions. However, the benign tumor retained cytoplasmic expression while the cutaneous melanoma demonstrated a complete lack in PTEN expression (Tsao et al. 2003). Bcl-2 has been demonstrated to be overexpressed in melanoma cells (Jansen et al. 2000). In addition, approximately a 20 or 40 % increase of Bcl-X_L mRNA

levels was detected in primary or metastasized melanoma tissue, respectively. The metastasized melanomas expressed higher Bcl-X_L than their matched primary tumors. These studies also showed that the expression of Bcl-X_L resulted in UVB resistance in both primary and metastatic melanoma cells (Zhang and Rosdahl 2006). The transcription factor AP-2 and three of its downstream targets, c-kit, E-cadherin, and p21, were found to be involved in later phases of melanoma progression (Baldi et al. 2001).

Another frequently altered chromosome region, 9p21, contains a group of genes involved in cell cycle regulation. Among several potential tumor suppressor genes located on 9p21, p16 (CDKN2A/$p16^{ink4a}$) is the most important melanoma susceptibility gene identified to date with germ line mutations present in 9p-linked melanoma families (Hussussian et al. 1994; Kamb et al. 1994) and in 30–50 % of members of melanoma kindreds (Halachmi and Gilchrest 2001). p16 inhibits the ability of cyclin-dependent kinases, CDK-4 and CDK-6, to activate substrates needed for progression past G1 of the cell cycle and therefore acts as a cell cycle check point protein (Liggett and Sidransky 1998). Germ line mutations in the gene encoding CDK4 have also been described in a small number of melanoma-prone cases (Zou et al. 1996; Soufir et al. 1998). In sporadic tumors, loss of p16 protein expression has been shown to occur only in invasive and metastatic stages of melanoma and to be infrequent in primary thick nodular melanoma (Reed et al. 1995; Straume and Akslen 1997). The loss of p16 also seems to be associated with recurrent disease and has been the most useful marker for progressive disease. Alterations in p16 include CpG island methylation and translation repression mutations in the five prime untranslated regions (Haluska and Hodi 1998). Transcriptional upregulation of p16 has been shown in melanoma cells following UVB irradiation (Piepkorn 2000). UV-induced mutations of p16 have been reported in epithelial skin tumors from sporadic patients and from xeroderma pigmentosum patients, who suffer from hypersensitivity to UVR (Soufir et al. 2000).

Linkage studies of families with multiple cases of melanoma have been important in pursuing genetic analysis; however, the genetic relationship between melanoma and the dysplastic nevus syndrome is complex. Karyotype studies of both familial and sporadic melanomas frequently showed large deletions of band region 1p36, del(1)(p36.1–p36.3) (Dracopoli et al. 1994), suggesting that multiple tumor suppressor genes in this region were deleted. The PITSLRE protein kinase gene locus maps to band region 1p36. Several of its products may affect apoptotic signaling (Lahti et al. 1995). Studies have demonstrated alterations in the PITSLRE protein kinase gene complex in melanomas (Nelson et al. 1999).

12.4 Screening and Early Detection

Early screening of SCC is often done by the diagnosis of AK. Self-exams are strongly recommended. Warning signs include a skin growth that increases in size or changes color or thickness or a sore that continues to crust, bleed, or itch. Identification of these changes warrants a more extensive checkup from a dermatologist. A precursor

lesion to SCC, AK often requires treatment. AKs can be difficult to treat and require frequent visits to a dermatologist, since patients usually have multiple AKs that present at different times. The treatment for AK is usually cryosurgery with liquid nitrogen, excision, or topical 5-FU cream (International Medical News Group 2002). Cryosurgery is the most common treatment but is associated with blistering, scabbing, hypopigmentation, inflammation, and occasionally pain. Treatment with 5-FU often results in severe blistering. Other options for AK treatment include dermabrasion or chemical peeling (Dinehart 2000). Topical diclofenac (Del Rosso 2003), imiquimod (Berman et al. 2004), and aminolevulinic acid (in photodynamic therapy) have also been approved by the U.S. Food and Drug Administration (FDA) for the treatment of AK. While these drugs can be effective, they also cause painful and irritating local skin toxicities. Appropriate chemoprevention strategies of AK or pre-AK treatment would not only reduce incidence of SCC but also eradicate the need for these disagreeable treatments mentioned above.

Screening for early melanoma includes a dermatological assessment; however, self-examinations are strongly recommended as well. This assessment includes a review of one's moles carefully looking for what the Skin Cancer Foundation calls the ABCDs of melanoma: asymmetry, borders, color, and diameter. Most early melanomas are asymmetrical where the common mole is round and symmetrical. Early melanomas often have irregular borders with scalloped or notched edges. Normal moles have smooth borders. The color of early melanoma tends to have several shades of brown, tan, or black, and as the melanoma progresses, the colors red, white, and blue may appear. Normal moles tend to be a single shade of color. Early melanomas tend to grow larger than normal moles with diameters of at least 6 mm. The discovery of any of these characteristics should be promptly reported to a physician, preferably one that specializes in skin cancer and is trained to identify early signs of melanoma.

It is apparent that with the increase of skin cancer incidence, incomplete resolution by early detection, and the current treatments, there is an urgent need to develop well-tolerated and effective prevention strategies for NMSC and melanoma.

12.5 Prevention of Skin Cancer

12.5.1 Primary Prevention

Since exposure to UVR is a major risk factor in the development of skin cancer, the focus of primary prevention has been to limit exposure to UVR. The recommendations from the American Academy of Dermatology, the American College of Preventive Medicine, and the American Cancer Society are (1) to reduce sun exposure during peak hours of intense ultraviolet exposure (usually 10 a.m. to 4 p.m.); (2) to wear protective clothing to cover as much of the skin as possible, including long sleeved shirts and hats with wide brims; and (3) to seek shade (Manson et al. 2000). Public health campaigns have been underway since the 1980s for the prevention of skin cancers. These campaigns recommend limited exposure to sun, the use of

sunscreen, and early detection through screening. In Australia, where skin cancer is of epidemic proportions (two out of three people born in Australia will likely require treatment for at least one skin cancer in their lifetime) (Giles et al. 1988), major campaigns have taken place such as the "Slip! Slop! Slap!" ("slip" on a shirt, "slop" on sunscreen, "slap" on a hat), "Sunsmart," and "Me No Fry." While 90 % of Australians now recognize the dangers of skin cancer and the associated risks (Borland et al. 1992; Hill et al. 1993), the relationship between education and incidence reduction is still unclear. In an article by a leading Australian academic dermatologist, several cohort studies are reviewed and indicate some leveling or reduction in skin cancer incidence in younger populations of Australia, potentially associated with the success of the skin cancer awareness public campaigns (Marks 1999).

The Cancer Progress Report from the U.S. Department of Health and Human Services and related departments reports limited success in the US population's attitudes toward sun exposure (2001). This report contains data gathered by the Centers for Disease Control and Prevention/National Center for Health Statistics. In the year 2000, 60 % of adults said they were likely to seek some sort of sun protection, 31 % were likely to use sunscreen, 26 % were likely to use sunscreen with a sun protection factor (SPF) of 15 or higher, 32 % were very likely to wear protective clothing, and 28 % were very likely to seek shade. This data shows an increase from 1998 where there was an actual decline in the sun protection from previous years. In the June 3, 2002, issue of the Philadelphia Inquirer, the author remarks: "Most adolescents avoid sunscreen like a summer reading list" (Uhlman 2002). The desire for a golden tan and the messy inconvenience of sunscreen outweigh the distant threat of skin cancer in the minds of these adolescents. In a study of sun protection practices in adolescents, only one third of the respondents reported routine sunscreen use during the past summer (Geller et al. 2002). Eighty-three percent reported sun burning at least once and 36 % reported three or more burns during the previous summer. Nearly 10 % of all respondents used tanning beds during the previous year, with 24.6 % of girl's age 15–18 reporting tanning bed use. Many girls who used tanning beds reported a belief that it was worth getting burned. These findings are very alarming considering that tanning in the teen years is a key factor for lifetime cumulative sun exposure and increased risk for skin cancer, particularly melanoma, which is clearly related to early age sunburns. An extensive review of the molecular design, effectiveness, and regulations of sunscreens are discussed in Chap. 11 by Dr. Georg Wondrak.

12.5.2 Secondary Prevention

The current primary methods for skin cancer prevention, including behavioral modification and the use of sunscreens, have not proven sufficient to protect against rise in skin cancer incidence. Therefore, other strategies of prevention need to be coupled with primary prevention. The most promising of these strategies is the development of chemopreventive agents, which target early-stage or precancerous lesions. Sporn and Suh (2000) describes chemoprevention as a "pharmacological approach to intervention in order to arrest or reverse the process of carcinogenesis."

He emphasizes the importance of an increased cancer research effort to control carcinogenesis "rather than attempting to cure end-stage disease." Control of carcinogenesis should be targeted at early stages because "it is easier to fix anything when the smallest numbers of its components are broken." The control of carcinogenesis through chemoprevention has gained credibility due to the FDA approval of tamoxifen for reducing breast cancer (Fisher et al. 1998; Lippman and Brown 1999) and from FDA approvals of agents for treating intraepithelial neoplasias (IENs) such as diclofenac for AK (O'Shaughnessy et al. 2002) and celecoxib for familial adenomatous polyposis (Steinbach et al. 2000). Agents for chemoprevention are ultimately applied to the general healthy population at high risk for particular cancers. Safety and efficacy must be established in large-scale prospective randomized clinical trials. Furthermore, agents need to be nontoxic, inexpensive, and available in oral or topical form (for skin). Clinical trials in patients with premalignant lesions are initially performed to investigate the modulation of biomarkers as surrogate endpoints. Lippman and Hong equate the current cancer chemoprevention studies to a delay in cancer development where the measures include a reduction in the rate of tumor development and overall decrease in the incidence of number of tumors (Lippman and Hong 2002). Meyskens described chemoprevention as an interaction between sciences of carcinogenesis, cellular biology, and cancer screening/early detection and cancer prevention/treatment (Meyskens 1988). Clearly, all of these scientific disciplines are required to develop highly efficacious chemopreventive strategies for skin cancer. Several reviews have been written which describe the current development of chemoprevention of skin cancer (Bowden 2004; Stratton et al. 2000, 2005; Wright et al. 2006).

For skin cancer, the eradication of AK and DN would most likely reduce the incidence of NMSC and melanoma, respectively. The approaches employed in the development of chemopreventive agents include the following: (1) availability of precancerous lesions (AK or DN) to evaluate the potential reduction in risk of progression; (2) identifying target molecules that are often modified and subsequently contribute to skin carcinogenesis; (3) developing animal model systems to test potential chemopreventive agents in skin; (4) delivery of highly potent agents directly into the epidermis, even more specifically through the development of novel formulations; and (5) availability of intermediate molecular or histological markers of the carcinogenic process to be used as endpoints.

12.5.3 Targeting Precursor Lesions for Chemoprevention

Current chemoprevention trials evaluate the efficacy of chemoprevention agents by the eradication or reduction of intraepithelial neoplasias (IENs). In skin, the IENs include AK for SCC and dysplastic nevi (DN) for melanoma. Individuals with AK are at increased risk for developing NMSC, and the presence of DN is the single most important risk factor for developing melanoma.

In general, IENs near-obligate cancer precursor lesions that have genetic abnormalities, loss of cellular control function, similar phenotypic

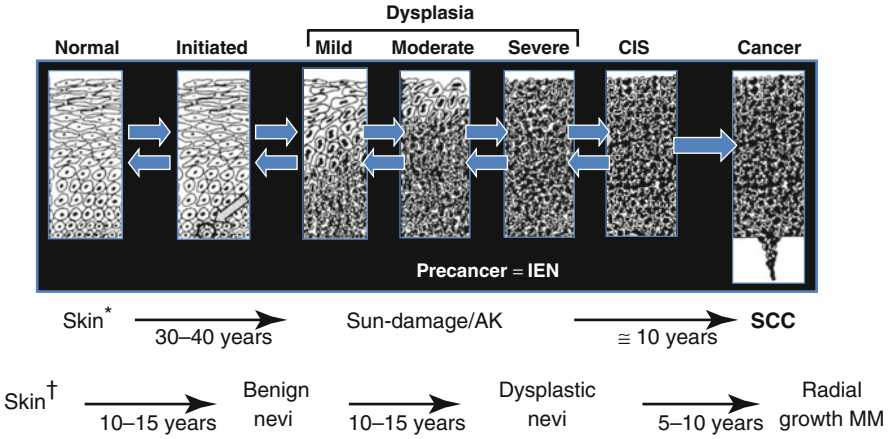

Fig. 12.1 Intraepithelial neoplasia in skin cancer. The strategy for evaluating the efficacy of chemoprevention agents is targeting precursor lesions in the development of skin cancers. These intraepithelial neoplasias in the skin include AK for SCC and dysplastic nevi for melanoma. These lesions are also important risk factors for the development of skin cancer (*Adapted from O'Shaughnessy et al. (2002); †Adapted from Li and Herlyn (2000))

characteristics of invasive cancer and are risk markers for cancer. The presence of IENs in an individual is indicative of an increased likelihood of developing invasive cancer as compared to unaffected individuals (O'Shaughnessy et al. 2002). The American Association for Cancer Research (AACR) Task Force on the Treatment and Prevention of Intraepithelial Neoplasia recommends targeting individuals with or at risk for IENs for new agent development because of the potential preventive consequence on developing invasive cancer (O'Shaughnessy et al. 2002). IENs have been described for many types of cancers including colorectal adenomas for colorectal cancer, dysplastic oral leukoplakia for head and neck cancers, Barrett's esophagus for esophageal cancer, cervical intraepithelial neoplasia for cervical cancer, prostatic intraepithelial neoplasia for prostate cancer, transitional cell carcinoma in situ for bladder cancer, and AK for NMSC (Fig. 12.1).

Targeting precancerous lesions for chemoprevention is a rational strategy for the reduction of SCC incidence. Evidence for this rational includes (1) the FDA approval of diclofenac for treating AK as a preventive measure against SCC (O'Shaughnessy et al. 2002) and (2) a report from the Southeastern Arizona Skin Cancer Registry that suggests the leveling of SCC incidence in southeastern Arizona could be due to the removal of the precursor lesion, AK, while BCC incidence appears to continue to rise because there is no known precursor lesion for BCC to be removed or treated (Harris et al. 2001a, b). Both surgical and FDA-approved topical drug treatments available for the management of AK are listed in Table 12.1. Of these, only diclofenac is molecularly targeted (i.e., against cyclooxygenase I and 2 enzymes).

Table 12.1 Management of actinic keratosis is done both surgically and by FDA-approved topical drug treatments. Of those listed below, the only molecularly targeted treatment is diclofenac (Lober and Fenske 2004; Spencer et al. 2005; Martin and Swanson 2013)

Surgical therapy
Cryotherapy
Curettage
Current FDA-approved topical drugs
5-Fluorouracil (e.g., Efudex®, Carac®)
Diclofenac (e.g., Solaraze®)
Aminolevulinic acid HCl (+UV light) (i.e., photodynamic therapy)
Imiquimod (e.g., Aldara®)
Ingenol mebutate gel (e.g., Picato®)

AKs, also known as solar or senile keratoses, are cutaneous lesions with chromosomal abnormalities that occur primarily on sun-exposed skin surfaces (Callen 2000). AK is a proliferating mass of transformed neoplastic keratinocytes confined to the epidermis. AKs develop on the surface of the skin as thickened, cornified, scaly lesions (O'Shaughnessy et al. 2002). Papules and plaques are often found on a background of sun-damaged skin with telangiectasias, hyper- or blotchy pigmentation, and a yellowish hue. The lesions range in size from 1 to 2 mm papules to large plaques (Callen 2000). AKs are most often diagnosed by histopathologic examination, since diagnosis by appearance can often be unclear as to whether the lesion is an AK or SCC. Typical histological characteristics of AKs include irregular arrangement of cells with atypical, pleomorphic keratinocytes at the basal cell layer demonstrating nuclear pleomorphism, loss of polarity, crowding of nuclei, and disordered maturation (Callen 2000).

The lack of significant cytological differences between AK and SCC gives rise to the premise that AKs represent early SCCs (Dinehart et al. 1997). Several investigators consider AKs to be precursors or early forms of SCC (Glogau 2000; Salasche 2000). Inasmuch as AK is well accepted as a precursor to SCC, the U.S. Centers for Medicare and Medicaid Services have added a national coverage policy to include the treatment of AK (2002). As shown in Fig. 12.2, the percent at which AK progresses to SCC has been demonstrated in the range of 0.1–16 %(Glogau 2000; Stratton 2001) (Fig.12.2). Approximately 60 % of SCCs have been demonstrated to arise from preexisting AKs or the contiguous skin surface (Sober and Burstein 1995). Therefore, AK can be defined as a potential risk factor for the development of SCC.

Based on histological features, melanoma development has been described by Li and Herlyn as follows: (1) common acquired and congenital nevi with normal melanocytes that have a finite lifespan and no cytogenetic abnormalities, (2) DN that displays both cellular and architectural atypia, (3) radial growth of a melanoma, (4) vertical growth phase of the primary melanoma, and (5) metastatic melanoma (Li and Herlyn 2000).

While there remains controversy over whether DNs progress to melanoma, it is very evident that DNs confer a major risk for melanoma (Farber et al. 2012; Elder 2010). DNs are found at a much higher frequency in patients with a history of melanoma. Prevalence rates range from 34 to 59 % (Farber et al. 2012). One study demonstrated that on average, 34 % of patients with melanoma had DN, in comparison

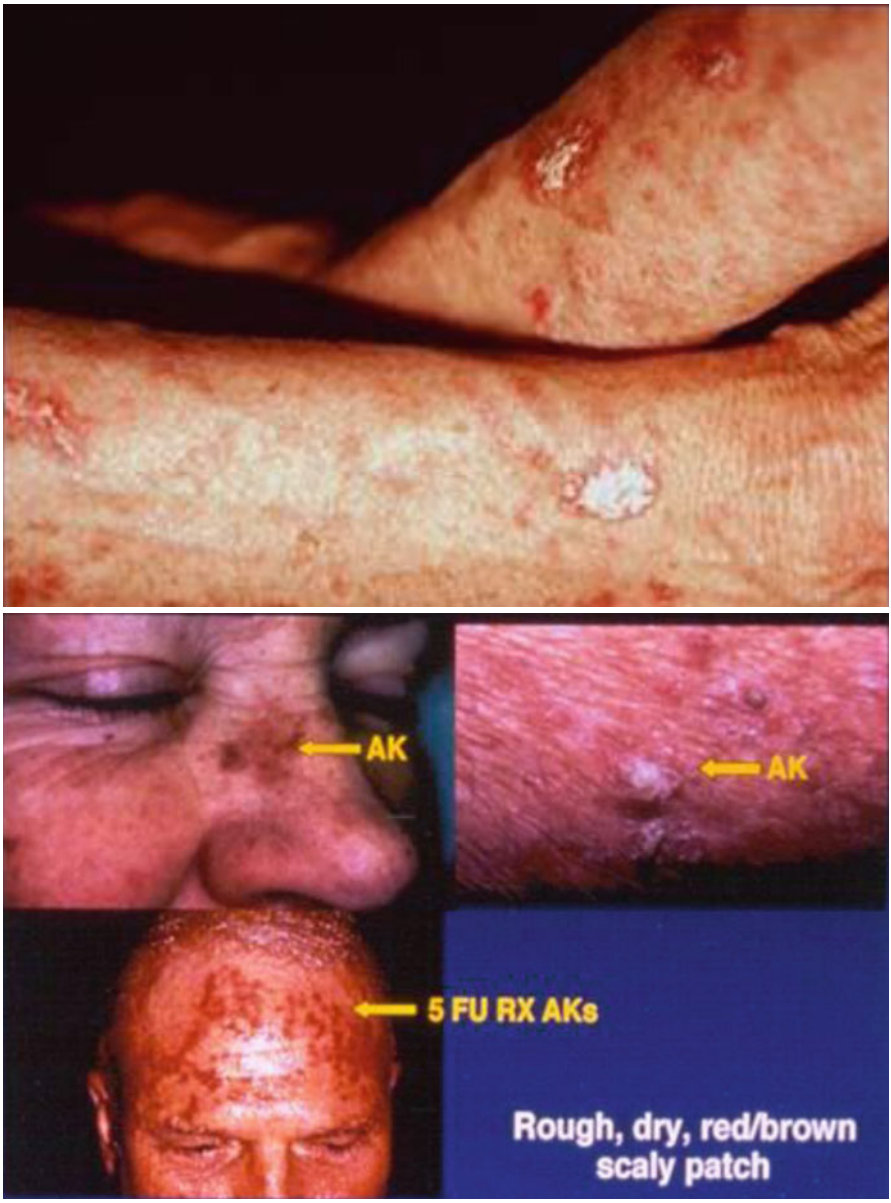

Fig. 12.2 SCC precursor: actinic keratosis. Most AKs spontaneously regress. However, 0.1–16 % may convert to SCC. AKs are risk markers for SCC

with 11 % of control subjects. Relative risk ranged from 1.0 to 16.7 for melanoma in the presence of DN. Several studies also reported an increased risk for melanoma with an increase in the number of DN. Cohort studies of patients with familial DN have also provided evidence for presence of DN as a risk factor for the development

of new melanomas (Greene 1997). In a retrospective study drawn from 820 patients diagnosed with a first primary cutaneous melanoma, 82 % of 50 examined patients with multiple melanomas were clinically diagnosed with DN (Stam-Posthuma et al. 2001). Histological confirmation was demonstrated in 78.0 % of these patients, and 16 of 37 patients had more than 30 clinically diagnosed DNs, 8 patients had 11–20 DNs, 4 patients had 21–30 DNs, and 9 patients had 1 DN. Finally, prospective studies have concluded that patients with DN and no family history also have an increased risk of melanoma (Greene 1997).

Other studies have investigated the idea that melanoma actually arises from DN (Marras et al. 1999). One such report performed cytogenetic analyses of DN in a young patient with a family history of melanoma (Marras et al. 1999). A t(6;15)(q13;q21) translocation found in one of the DN was similar to a translocation, with a breakpoint at 6q13 reported in a benign, nondysplastic nevi (Richmond et al. 1986) and in a cutaneous metastatic melanoma (Thompson et al. 1995). The repeated occurrence of this rearrangement provides initial support for the hypothesis that melanoma progresses from normal melanocytes to benign nevus, to DN, to early melanoma, to late melanoma, and then to metastatic melanoma.

In a study by investigators at the National Cancer Institute (NCI) and the University of Pennsylvania, almost all members of a family cohort with melanoma also had DN. New melanomas were only diagnosed in family members with DN (Greene et al. 1985a, b). These data suggest that not only are DNs risk factors for melanoma, but they may also be the precursor lesions from which new melanomas evolve.

The use of dysplastic nevi, as a precancerous lesion and an indication of chemoprevention efficacy, has been used in previous research and is proposed in upcoming trials. To date, four chemoprevention trials with topical tretinoin have been performed on individuals with DN (Stam-Posthuma 1998). In these trials, DNs were targeted as surrogate markers for chemoprevention of melanoma.

12.5.4 Molecular Targets for Chemoprevention Identified in UVR Signaling Pathways

Skin carcinogenesis caused by UVR is a multistep process of initiation, promotion, and progression (Fig. 12.3). The best phases to intervene are the tumor promotion and progression phases, which are slow, rate-limiting stages. The initiation phase occurs rapidly. The targeting of AK and DN is at the promotion phase where several specific genetic alterations can occur. In order to produce specific chemopreventive agents, it is necessary to first identify important molecular targets, which are modified in the carcinogenesis process. Bode and colleagues (2004) describe three major criteria for "valid" targets for cancer prevention: (1) The target molecule is deregulated in tumor development. The target molecule is affected by a tumor promoter resulting in a cascade of activation or inhibition of signal transduction pathways implicated in carcinogenesis. (2) The outcome of the deregulation of the target molecule results in malignant transformation, cell proliferation, and cell cycle arrest

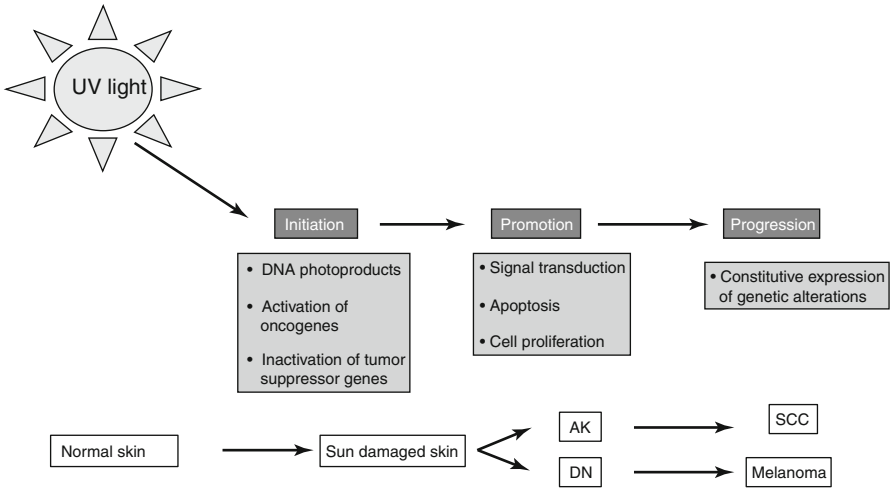

Fig. 12.3 Multistep UV-induced carcinogenesis. This multistep process involves sun exposure of normal skin or benign nevi to develop into AK or DN and progress to SCC or melanoma, respectively. The process involves initiation, promotion, and progression via the formation of photoproducts, activation of oncogenes, or inactivation of tumor suppressor genes to signal transduction, cell proliferation, or apoptosis and finally to constitutive activation of genetic alterations

and/or apoptosis. (3) The deregulation of the target molecule significantly impacts carcinogenesis in vivo. For both NMSC and melanoma, many of these targets can be identified by understanding the UVR signaling pathways and identifying the points where alterations occur due to UVR signaling. This chapter briefly discusses select targets which are discussed in more detail in two extensive reviews of chemoprevention of photocarcinogenesis by targeting UVR signaling (Afaq et al. 2005; Bowden 2004). Bachelor and Bowden have reviewed UVA-mediated signaling which may be involved in skin tumor promotion and progression and eventually provide additional targets for chemoprevention (Bachelor and Bowden 2004). The identification of these targets has been revealed by in vitro and in vivo model systems in the laboratory. The initiating events in skin cancer appear to involve gene mutations in proto-oncogenes or tumor suppressor genes. In the case of UVR-induced skin carcinogenesis, these initiating mutations have been identified in the TP53 tumor suppressor gene as UVR signature mutations (Ziegler et al. 1993). These mutations have been identified in AK and SCC (Nelson et al. 1994). The initiated cell undergoes a clonal expansion during the promotion phase at which point it is most likely that AK and DN in human skin arise. UVR tumor promotion is carried out by signaling molecules that give rise to altered gene expression. For SCC development, the UVR-induced clonal expansion signaling has been demonstrated to lead to the activation of activator protein-1 (AP-1) transcription factor or to cyclooxygenase-2 (COX2) expression (Bowden 2004). Three signaling molecules identified in the UVR signaling cascade (Fig. 12.4) during the promotion stage of SCC include mitogen-activated protein kinases (MAPKs) (Chen et al. 2001a),

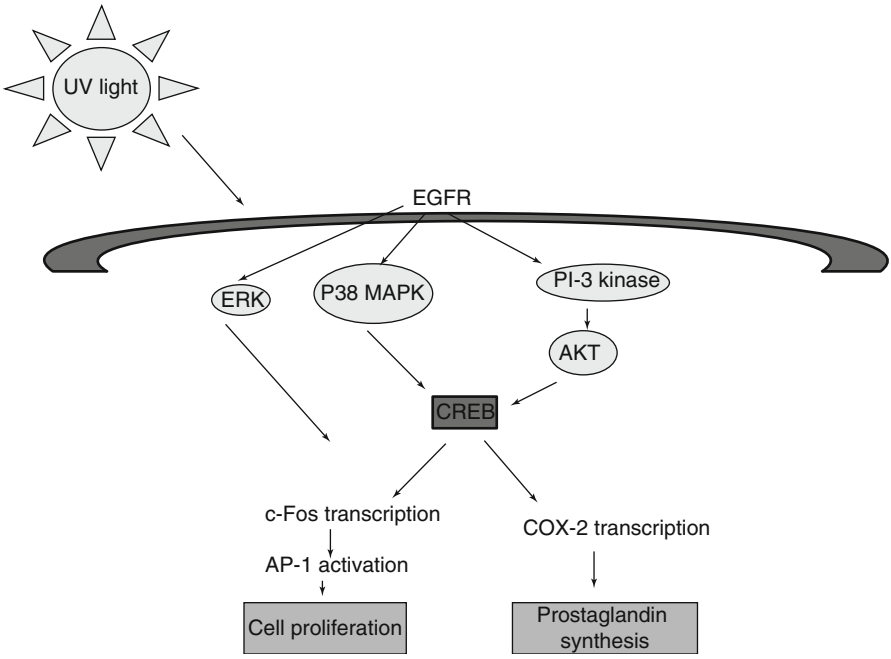

Fig. 12.4 UV signaling pathway via the EGFR involves ERK, MAPK, and PI-3 kinase activation that leads to the activation of AP-1 and/or COX-2. These markers have been identified as potential targets for chemoprevention in NMSC. Current ongoing investigations are exploring a UV signaling cascade including PI-3 kinase, AKT, MAPK, and Raf as potential chemoprevention targets for melanoma

phosphatidylinositol 3-kinase (PI3K) (Kabayama et al. 1998), and epidermal growth factor (EGF) receptors (Wan et al. 2001a, b). These three molecules serve as excellent targets for the development of chemoprevention.

AP-1 is upregulated in response to UVR-induced MAPK signaling in human keratinocytes in vitro (Chen and Bowden 2000). The transcription factor, AP-1, mediates the transcription of genes containing a 12-O-tetradecanoylphorbol-13-acetate (TPA) response element (TRE) (Lee et al. 1987). AP-1 is made up of homo- and heterodimers of proteins from the Jun and Fos families (Curran and Franza 1988). These genes are considered early response genes because of their rapid response to environmental changes, such as growth factors, stress, or DNA damage (Angel et al. 1988; Ryseck et al. 1988). Induction of Jun and Fos results from post-translational modification (Stein et al. 1992). In contrast, UVR activation of AP-1-dependent genes, such as the metalloproteinase genes and c-Fos, appears to require new protein synthesis of Jun and Fos (Konig et al. 1992).

c-Fos is constitutively expressed in both rodent and human epidermis (Basset-Seguin et al. 1990; Fisher et al. 1991) as demonstrated by immunohistochemical localization, suggesting that c-Fos has a role in growth and cell proliferation (Basset-Seguin et al. 1990). Additionally, UVB (Chen et al. 1998) and UVA irradiation

(Silvers and Bowden 2002) has been shown to induce c-Fos expression in human keratinocytes. Similarly, in rat epidermis, single doses of UVB produced a rapid and sustained increase in c-Fos and c-Jun mRNA and protein throughout the epidermis at early time points, but were restricted to the basal layer at later time points. This suggests their possible role in the induction of both apoptosis and cell proliferation (Gillardon et al. 1994).

Investigators have demonstrated the important role of AP-1 in UVR carcinogenesis in human and mouse keratinocytes as well as transgenic mice. UVB (Chen et al. 1998) and UVA (Silvers and Bowden 2002) were shown to activate AP-1 in HaCaT cells (human keratinocyte cell line) with a correlative increase in c-Fos expression. The blocking of AP-1 transactivation in malignant mouse SCC cell lines inhibits the formation of tumors in athymic nude mice (Domann et al. 1994). c-Fos and junD were identified as the main components of the AP-1 complex induced by UVB. The upregulation of AP-1 by UVB has been demonstrated in mouse skin (Barthelman et al. 1998b) and human skin (Fisher and Voorhees 1998). In studies with mouse epidermal JB6 cells, it has been demonstrated that blocking tumor promoter-induced AP-1 activity inhibited neoplastic transformation by an AP-1-inhibiting dominant-negative Jun (Dong et al. 1994). UVB irradiation studies have demonstrated an induction of AP-1 through the MAPK signaling cascade in human keratinocytes (Chen and Bowden 1999). A critical role for MAPK signaling (p38 and JNK) in AP-1 transactivation has also been demonstrated by UVA irradiation (Silvers et al. 2003). A mouse model that was used for testing the hypothesis that AP-1 activation has a functional role in the promotion of UVB-induced skin tumors is a TAM67 mouse crossed with a mouse expressing an AP-1 luciferase reporter gene. The TAM67 transgenic mouse contains a dominant-negative c-Jun mutant transgene (TAM67) under the control of the human keratin 14 promoter expressed in the epidermis of SKH-1 hairless mice. These mice show a decrease in UVB light-induced AP-1 activation with a signal UVB exposure. The expression of the TAM67 delayed the appearance of tumors, reduced the number of tumors per mouse, and reduced the size of the tumors subsequent to chronic UVB exposure. The data demonstrated that the expression of the TAM67 inhibited UVB-induced AP-1 activation in the epidermis and inhibited UVB-induced skin tumor development. Information gathered from these studies has enabled the formulation of a UVB signaling pathway that leads to AP-1 activation and provides a good molecular target for the development of new chemoprevention strategies to prevent UVR-induced skin cancers (Bowden 2004).

More, recently Einspahr et al. (2012) demonstrated protein pathway activations in the progression of normal skin (upper inner arm), AK, and SCC using reverse-phase protein microarray analysis. Two sets of samples looking at 51 signaling proteins in the first set and 102 key signaling proteins in the second set demonstrated that the MEK-ERK pathway was activated in SCC compared with the AK and normal skin. The EGFR and mTOR pathways were aberrantly activated in SCC. In AK, an increase in Bax and Bak expression was demonstrated compared to normal skin. Several of these connected pathways provide targets for potential chemoprevention agents.

The MAPKs are part of signaling cascades that involve the regulation of cell proliferation and differentiation in human epidermis (Geilen et al. 1996). Mitogen-activated protein (MAP) kinases are a family of serine/threonine protein kinases. These kinases have been found to be important in cellular response to growth stimuli (Peyssonnaux and Eychene 2001). MAP kinases are activated by translocation to the nucleus, where kinases phosphorylate their targets substrates such as transcription factors (Coso et al. 1995). The MAP kinase family includes c-Jun-NH_2 terminal kinases (JNKs/SAPKs), extracellular signal-regulated protein kinases (ERKs), and p38 MAP kinases. JNKs/SAPKs and p38 kinases are activated by stress, including UVR irradiation (Kallunki et al. 1994). Investigators have demonstrated that UVA and UVB irradiation causes activation of ERKs, JNKs, and p38 kinases in cell culture (Huang et al. 1997a, b, c; Dong et al. 1998).

p38 MAP kinase plays an important role in UVB-induced c-Fos expression in human keratinocytes (Chen and Bowden 1999). Both p38 and ERK were significantly activated by UVB irradiation in human keratinocytes. Treatment of these cells with a p38 inhibitor, SB202190, inhibited UVB-induced p38 activation but did not induce ERK activation. In addition, the treatment of the cells with MEK1 inhibitor, PD98059, inhibited UVB-induced ERK activation but not UVB-induced p38 activation (Chen and Bowden 1999). The blocking of p38 almost completely abrogates UVB-induced c-Fos gene transcription and c-Fos protein synthesis. Inhibition of ERK partially abrogates UVB-induced c-Fos transcriptional and protein levels. Inhibiting both p38 and ERK completely blocked UVB-induced c-Fos expression but also decreased c-Fos basal gene expression. The p38 inhibitor, SB202190, strongly inhibited UVB-induced AP-1 transactivation as well as AP-1 DNA binding (Chen and Bowden 2000). Studies with UVA demonstrated that UVA-induced p38 MAP kinase activity also plays an important role in the survival of keratinocytes (Bachelor and Bowden 2004). The UVA-induced activation of p38 and JNK plays a role in AP-1 activation, COX-2, and Bcl-X_L (Zhang and Bowden 2012). The inhibition of p38 MAP kinase by SB202190 decreases expression of Bcl-X_L and results increased apoptosis. Consequently, it was shown that UVA induces p38 MAPK activity and the subsequent increase in Bcl-X_L resulted in a resistance to UVA-induced apoptosis. These data together suggest that the upstream molecules of c-Fos and AP-1 signaling, p38, and ERK are potential targets for chemoprevention in NMSC.

Another target gene in UVB signaling is COX-2. COX-2 is a key enzyme involved in the synthesis of prostaglandins. Prostaglandins have been linked to several important events of the carcinogenesis process. Studies of malignant melanoma progression have demonstrated that no COX-2 expression was observed in dysplastic nevi, primary skin melanoma cells, and vertical and radial growth phase cases, but COX-2 was strongly detected in the metastatic cancer cells (Goulet et al. 2004). In addition, five out of seven melanoma cell lines overexpressed COX-2 compared to normal melanocytes. An increase in COX-2 expression occurs after UVB exposure in both human skin (Buckman et al. 1998) and cultured human keratinocytes (An et al. 2002). There is also an increased expression of COX-2 protein in human squamous cell carcinoma biopsies and when compared to normal non-sun-exposed

control skin. Selective inhibition of COX-2 in hairless mice has resulted in a significant reduction of UVR-induced skin tumors in hairless mice (Pentland et al. 1999). Of particular interest is another study which demonstrated that p38 is required for UVB-induced COX-2 gene expression in human keratinocytes (Chen et al. 2001a, b). Inhibition of p38 with SB202190 markedly inhibited UVB-induced COX-2 mRNA. There was no effect when the Mek inhibitor PD98059 was used. UVA has also been shown to induce COX-2 in keratinocytes (Bachelor et al. 2002). The expression of a dominant-negative p38α in the epidermis of SKH-1 hairless mice led to a significant decrease in UVB-induced tumor growth and number compared to wild-type littermates in a UVB skin carcinogenesis model (Dickinson et al. 2011). The expression of this transgene inhibited UVB-induced apoptosis of keratinocytes. The reduction of skin carcinogenesis in this model appears to be due to the inhibition of COX-2 expression and proliferation of UVB-irradiated cells. Since p38 MAPK appears to be an important step in two UV-induced signaling pathways (ending in the transcription factors AP-1 and COX-2), it is an excellent candidate as a target for chemoprevention.

JNK phosphorylates c-Jun (Derijard et al. 1994; Kallunki et al. 1994), a component of the AP-1 transcription factor. There are three JNK genes (JNK-1, JNK-2, and JNK-3) that have been identified in humans. It has been demonstrated that JNK2 knockout ($JNK2^{-/-}$) mice, in a two-stage tumor promotion skin carcinogenesis model with DMBA and TPA, exhibited significant reduction in papilloma burden compared with wild-type controls (Chen et al. 2001a, b). Further studies to look at the UVR signaling pathway for skin carcinogenesis may point toward JNK as another potential target for chemoprevention of skin cancer.

The phosphatidylinositol-3 kinase (PI-3 kinase) pathway regulates cellular proliferation, growth, apoptosis, and cytoskeletal rearrangement. PI-3 kinases are heterodimeric lipid kinases composed of regulatory and catalytic domains (Vivanco and Sawyers 2002). PI-3 kinase is an important enzyme associated with a variety of receptors or protein-tyrosine kinases and acts as a direct biochemical link between a novel phosphatidylinositol pathway and a number of receptor proteins, including the receptors for insulin or platelet-derived growth factor (Downes and Carter 1991). This enzyme is a heterodimer of a 110-kDa unit (Auger et al. 1989). It can phosphorylate phosphatidylinositol (Ptdins), Ptdins (4) phosphate [Ptdins (4) P], or Ptdins(4,5) bisphosphate [Ptdins(4,5)P2] to produce Ptdins(3)P, Ptdins(3,4)P2, or Ptdins(3,4,5) trisphosphate [Ptdins(3,4,5)P3], respectively (Whitman et al. 1988; Cohen et al. 1990; Nomura et al. 2001b). Insulin or growth factor stimulation of the associated tyrosine kinase results in phosphorylation of the p85 subunit of PI-3 kinase. This phosphorylation is important for activation of PI-3 kinase (Huang et al. 1997a, b). Akt works downstream in the PI-3 kinase pathway to regulate proliferation, apoptosis, and growth (Vivanco and Sawyers 2002). Akt, a serine/threonine kinase, is activated by recruitment to the plasma membrane. Clinical evidence of PI-3 kinase activation has been reported in various cancers, and the identification of downstream kinases provides a potential target for mediating tumorigenesis (Vivanco and Sawyers 2002). Investigators have shown that UVB irradiation activates Akt in JB6, mouse epidermal cells. This activation was attenuated by

inhibitors for MAP kinase/ERK kinase-1 and p38 (Nomura et al. 2001b). It has been reported that PI-3 kinase plays an important role in UVB-induced AP-1 and Akt activation (Huang et al. 1997a, b; Nomura et al. 2001a, b). Inhibition of PI-3 kinase was found to block UVB-induced activation of p90 ribosomal protein S6 kinase (P70S6K), known to be associated with AP-1 in tumor promoter-induced cell transformation (Zhang et al. 2001b).

Wan and colleagues demonstrated that solar UVR irradiation of human skin activated epidermal growth factor receptor (EGFR) as well as other downstream signals including MAP kinases ERK, JNK, and p38 (Wan et al. 2001a, b). Their investigations revealed activation of the PI3-kinase/AKT survival pathway via EGFR. They also found that EGF crosstalks with cytokine receptors such as IL-1 receptor leading to the activation of c-Jun kinase in response to UVR irradiation of human keratinocytes. Additional investigators have shown that UVA-induced EGFR signaling is required for activation of p90RSK/p70S6K, PI-3 kinase, and ERK (Zhang et al. 2001a).

Signaling cascades due to UVR stimulation that leads to skin carcinogenesis of melanoma are not defined as extensively as for NMSC. Investigators have outline UVR signaling pathways for melanogenesis (Tada et al. 2002). However, there is a thus far only a few identified molecules that could potentially serve as molecular targets (Raf and MAPK) for chemoprevention of melanoma. The Raf kinases were the first Ras effectors identified and have been the most extensively studied (Hunter 1997). Ras associates with and activates Raf-1, which in turn phosphorylates and activates MEK kinase, which in turn phosphorylates the MAP kinases ERK1 and ERK2 (Liaw et al. 1993; Samuels et al. 1993; Warne et al. 1993; Ghosh et al. 1994). Activated MAP kinases translocate to the nucleus where they can modulate gene expression (Hill and Treisman 1995; Marshall 1995). Raf-1 has also been shown to interact with PKC, a key regulatory protein associated with a second signal transduction pathway (Kolch et al. 1993). Two well-established biological events that are associated with activation of the Raf/MEK/ERK pathway are cell proliferation and cell cycle progression. Halaban and colleagues have observed that several of the mitogenic factors for melanocytes, bFGF, MCGF, and HGF/SF, stimulate ERK1/ERK2 phosphorylation (Halaban et al. 1992a, b; Funasaka et al. 1992). Others have demonstrated that Raf plays an important role in progression of melanoma (Pollock et al. 2003). The data from these studies identified a particular mutation that was found in 68 % of metastatic melanoma, 80 % of primary melanoma, and 82 % of a diverse set of nevi. These findings implicate Raf as a potential target for chemoprevention of melanoma, since Raf mutations are evident at the early stage of primary melanoma and nevi. The identification of MAPK as an early event in melanoma progression (Cohen et al. 2002) provides another potential target for the chemoprevention of melanoma.

A recent review by Zhang and Bowden (2007) describes the targeting of Bcl-X_L for both the prevention and therapy of skin cancer. Bcl-X_L is localized on the mitochondrial outer membrane and plays a critical role in the homeostasis of both the intrinsic and extrinsic apoptotic pathways. Several studies have shown an antiapoptotic role of Bcl-X_L in skin. In immortalized keratinocytes, Bcl-X_L has been shown

to be protective against UVA-induced apoptosis (Bachelor and Bowden 2004). Zhang and Bowden describe the plausibility of targeting Bcl-X_L for NMSC and melanoma (Zhang and Bowden 2007). Melanoma cell lines have shown higher expression of Bcl-X_L than melanocytes (Bush and Li 2003), and both primary and metastatic melanomas have demonstrated increased expression (Zhang and Rosdahl 2006). Bcl-X_L has been shown to render primary and metastatic melanoma cells resistant to UVB irradiation. In a chemically induced skin carcinogenesis mouse model, expression of Bcl-X_L in a transgenic mouse resulted in a twofold increase in the number of papillomas formed compared to the wild-type mouse (Pena et al. 1998). In addition, more than half the transgenic mice developed SCC within 7 months of treatment, while none of the wild-type mice had SCC in the same time. The critical role in several stages of skin carcinogenesis, including initiation and promotion, make Bcl-X_L a very plausible target for prevention of skin cancer through the development of chemopreventive agents.

12.5.5 Animal Models for Studying Chemoprevention Agents

In order to understand the mechanism of carcinogenesis and investigate efficacy of chemoprevention agents prior to clinical application, animal models that closely resemble human disease must be developed. The SKH-1 hairless mouse is a model for the studies of skin cancer pathogenesis and the evaluation of chemoprevention of UVB-induced skin cancer (Bowden 2004). The most obvious advantage of these mice is that they are hairless and therefore do not require any removal of hair that may actually protect the skin from UVR light. With increasing dose level, three times a week for 25 weeks nearly 100 % of the mice develop at least one skin tumor with an average of seven to nine tumors per mouse. Most of these tumors are SCC, which arise from benign papillomas. UVB irradiation is used as a complete carcinogen in these mice. Another protocol used with these mice is UVB exposure twice a week for 20 weeks. This results in epidermal hyperplasia; no immediate tumors occur but a high risk of developing skin tumors during the next several months in the absence of any further UVR. This latter model system resembles humans who are heavily exposed to UVR early in life with reduced exposure later in life. Chemoprevention agents can be tested in these models.

A mouse strain with abnormalities in the hedgehog signaling pathway develops neoplasms which closely resembles human BCC. These mice contain a heterozygous allele in the PTCH gene (Ptc+/−). Chemoprevention studies with green and black tea have been studied in this mouse model (Herbert et al. 2001).

Multiple animal models of melanoma have been reported; however, difficulties with these models for studies of chemoprevention are that tumors develop at a low incidence rate and the latency period is often very long. There are two prominent models for melanoma, which are useful for the studies of chemoprevention agents. Powell and colleagues (1999) report the development of a transgenic mouse for which when chemically induced develops melanoma. The mouse line expresses a mutated human Ha-ras (TPras) gene driven by a mouse tyrosinase promoter. This transgene is

therefore expressed in pigment-producing cells of the mice. The protocol for inducing melanoma in these mice is topical application of 50 μg 7,12-dimethylbenz-[a]anthracene (DMBA) once a week for 5 weeks. Development of melanoma occurs around 15 weeks. Tumors only occur in the mice expressing the transgene, and no tumors develop in the negative littermates. Tumors develop in more than 80 % of the treated mice. No spontaneous cutaneous melanoma or other skin cancers develop in these mice. Metastatic lesions have been observed in the skin, lungs, and lymph nodes of the DMBA-treated transgenic mice (Powell et al.1999). Melanomas isolated from TPras transgenic mice display alterations and/or losses of p16 (Gause et al. 1997) much like human melanoma. Early experiments with these TPras mice did not result in UVR-induced melanoma perhaps because of the highly pigmented skin of the adult TPras mouse. Further investigations using this model have found ways to indeed produce UVR-induced melanoma in this model system. The first was a single neonatal exposure (2–3-day-old mice) of UVR light which resulted in a penetrance of 57 % by 12 months (Hacker et al. 2005). Another development of this model has been to cross it with an activated Cdk4 mouse. This resulted in spontaneous melanomas with an increase of penetrance of 83 % when treated with UVR (Hacker et al. 2006). Another model is a transgenic model, which utilizes a metallothionein-gene promoter driving a hepatocyte growth factor/scatter factor (c-Met receptor tyrosine kinase ligand) gene based on the albino FVB background (Noonan et al. 2001). Development of melanoma occurs in this model system after a single acute exposure of an erythemal dose of UVR irradiation. Development of invasive melanoma occurs in 80 % of the animals. These melanomas closely resemble human melanoma in terms of the development between the dermis and epidermis.

One concern with UVR studies is the ability of the experimental UVR exposure to imitate the true solar spectral output. Many studies with UVR use light sources which produce primarily UVB output with minimal UVA output. One recent debate has been brought forward in study by Ibuki and colleagues (2007) which produced data that suggested that UVA produces a protective role against UVB by inhibiting UVB-induced apoptosis. However, a published commentary (Runger 2007) to this publication noted that since the UVA radiation inhibits UVB-induced apoptosis, this may only increase the mutation burden that would normally be eliminated by UVB-induced apoptosis and therefore increase skin cancer formation. With these questions still left to be answered, it is best to choose animal models that use UVR sources which combine both UVA and UVB spectral output which best mimics the solar output for any studies of chemoprevention agent which will be proposed for future human, clinical trials.

12.5.6 Endpoints for Evaluating Efficacy of Chemoprevention Agents

Because the process of carcinogenesis can take many years, assessment of clinical chemoprevention trials using cancer incidence as an endpoint requires a long follow-up period and large sample sizes. In addition to evaluating the modulation of

targets for a specific chemopreventive agent such as those involved in the UV signaling pathway discussed above (p38 MAPK, PI-3 kinase, etc.), biomarkers are useful for evaluating the efficacy of a chemopreventive agent. The rationale for the use of intermediate biomarkers is to circumvent these issues in chemoprevention trials (Einspahr et al. 1997), since biomarkers occur at steps preceding the occurrence of malignancy. As discussed by Lippman and colleagues (1990), biomarkers of intermediate endpoints can be defined as measurable markers of cellular or molecular events associated with specific stages of the multistep progression of carcinogenesis. Thus, the risk of carcinogenic transformation, whether in the skin or other sites, can be correlated with the quantitative degree and pattern of biomarker expression. Criteria for identifying and evaluating the potential efficacy of biomarkers are as follows:

- Variability of expression between phases of the carcinogenesis process (i.e., normal, premalignant, malignant)
- Ability for early detection in the carcinogenesis pathway
- Association with risk of developing cancer or recurrence of the precancer
- Potential for modification by a chemopreventive agent
- Presence in tissues that are easily accessible for multiple biopsies
- Capability to develop adequate assay quality control procedures

Markers of cellular proliferation can be used as intermediate biomarker to evaluate the efficacy of chemoprevention agents in clinical trials and animal model systems. Enhanced cellular proliferation has been closely associated with the process of tumorigenesis in numerous tissues including the skin (Einspahr et al. 1996). Proliferating cellular nuclear antigen (PCNA) functions as an auxiliary protein to DNA polymerase d and e in DNA replication and repair (Hall et al. 1990). Expression of PCNA increases late in G1, is maximally expressed in S, and decreases in the G2/M phases of the cell cycle. Therefore, PCNA can be used to evaluate cell proliferation and possibly chemoprevention efficacy. Studies have indeed found a significant difference in PCNA expression in AK compared to sun-damaged skin (Einspahr et al. 1996, 2006) but not sun-damaged forearms compared to forearms from subjects with AK (Einspahr et al. 2006). PCNA was not useful in detecting an effect of the chemoprevention agent difluoromethylornithine (DFMO) (Einspahr et al. 2002). These investigators suggest that PCNA may be useful in combination with the number of apoptotic cells as an endpoint for clinical trials with chemoprevention agents. Another extensively used marker for proliferation is Ki67 which is present in all active phases of the cell cycle (G1, S, G2, and mitosis) but is absent from resting cells. MIB-1 is a commonly used monoclonal antibody that detects the Ki-67 antigen. Bordbar and colleagues (2007) evaluated the MIB-1 antibody in its usefulness in differentiating benign, premalignant, and malignant skin lesions.

Apoptosis also serves as biomarker for the efficacy of chemoprevention agents in clinical trials and animal model systems. Apoptosis is a unique mode of cell death, characterized by ultrastructural changes distinct from necrosis (Kerr et al. 1972). In the developing animal, programmed cell death removes cells during remodeling of a number of organs (Haake and Polakowska 1993). Apoptosis is also involved in tissue regression following hormone stimulation or deprivation in hormone-sensitive

tissues, such as the prostate, and functions in development of the immune system (Haake and Polakowska 1993). In continually renewing tissues such as the epidermis, homeostasis is maintained through a balance between cellular proliferation and cell death. Apoptosis may also play an important role in regression of neoplasms (Haake and Polakowska 1993). Alterations in either cell proliferation or cell death can lead to loss of growth control, thereby playing major roles in the process of tumorigenesis. Apoptosis is characterized by cell shrinkage, plasma membrane blebbing, nuclear fragmentation, and chromatin condensation. Apoptotic cells are rapidly phagocytosed by neighboring cells in order to prevent the release of cell contents. In contrast to necrosis, apoptosis is an organized and controlled process of cell death (Kerr et al. 1972). Measurements for apoptosis may include morphology, in situ TUNEL, and caspase-3 detection.

Investigators have shown that p53 mutations increase through the progression of normal skin, sun-damaged skin, AK, and SCC. While the frequency of p53 mutations was 14 % in normal skin, this percentage rose to 38.5 % in sun-damaged skin, 63 % in AK, and 54 % in SCC. Proliferation was also increased through this same progression. SCC samples demonstrated an increased presence of BAX compared to AK (Einspahr et al. 1999). An additional study confirmed the use of p53 expression as a valid biomarker in the progression of sun damage skin to AK to SCC (Einspahr et al. 2006). This latter study demonstrated that p53 expression as well as expression of selected polyamines is effective in differentiating early stages of skin cancer progression and was not affected by sunscreen use. This data supports the use of p53 as a biomarker for disease progression when evaluating the efficacy of chemoprevention agents. A recently presented study demonstrated that vascular endothelial growth factor (VEGF) may serve as a biomarker for detection and chemopreventive modulation for melanoma studies. Investigators found that there was a higher VEGF expression in dysplastic nevi compared to benign nevi (Thomas et al. 2006). Biomarkers that measure micronutrient and biochemical levels in tissue and blood may also be useful biomarkers in studies that evaluate chemopreventive agents' ability to slow or inhibit progression from a benign to premalignant to malignant stage.

Karyometric evaluation of the epidermis has been used as a developmental secondary endpoint in clinical studies (Bozzo et al. 2001). Ranger-Moore and colleagues have published a complete review of karyometric measures in intraepithelial lesions, discussing the usefulness of karyometry as an integrating biomarker for evaluating progression and effectiveness of chemopreventive agents (Ranger-Moore et al. 2005; Bartels et al. 2006). The advantage to this type of biomarker is that it can detect activity of a chemopreventive agent even when the mechanism for a given progression pathway is unknown or when multiple pathways exist. Nuclear chromatin patterns can be used diagnostically to assess changes in the development of cells, particularly the development into a cancerous cell, which could then be correlated with the prognosis of individual patients. Image analysis of nuclear chromatin patterns provides a quantitative approach (Weyn et al. 2000). With image analysis, karyometric features are described by the arrangement of a combination of pixels. These features are then combined by means of multivariate analysis of

criteria used for prognosis. Digital microscopic studies of epithelia from the ectocervix (Wied et al. 1980), lung mucosa (MacAulay et al. 1995), colonic mucosa (Bibbo et al. 1990), glandular epithelium of the thyroid (Bibbo et al. 1986), breast (Susnik et al. 1995), bladder (Sherman and Koss 1983), and prostate (Irinopoulou et al. 1993) have detected very subtle, possibly preneoplastic changes in the organization of nuclear chromatin in biopsies from individuals with premalignant and malignant lesions of these organ sites. When these same tissue sections were examined with standard histopathological techniques, no abnormalities were detected. Thus, digital microscopy can provide highly sensitive detection of early change and may provide novel diagnostic clues. Digital imagery can reliably detect very early subtle changes in the organization of nuclear chromatin in epithelial cells that appear to be entirely normal during histopathologic examination. This technology, which uses high-resolution imagery of cell nuclei to assign values to karyometric features, may enable the quantitative assessment of progressive change from normal-appearing to severely sun-damaged skin to AK to SCC as well as from DN to melanoma. Nuclear karyometric measurements have been performed on both benign and malignant melanocytic lesions (Bjornhagen et al. 1994; Stolz et al. 1994). Using imprint specimens, Stolz and colleagues (1994) found five features (mean value and standard deviation of nuclear area and the 80th, 90th, and 95th percentiles of the DNA distribution) to be significantly different between benign melanocytic lesions and melanoma. A second report (Stolz et al. 1994) found significant differences between benign melanocytic tumors and malignant melanoma for the following features: mean nuclear area, coefficient of variation (cv) of nuclear area, cv of nuclear shape, nuclear contour index, mean and cv of nuclear area, and DNA distribution rates. Investigators have conducted feasibility studies for the karyometric assessment of skin shave biopsies of AKs and for the assessment of the effects of chemopreventive intervention, using quantitative characterization by digital microscopy (Bozzo et al. 1998). Sections of shave skin biopsies were digitized and a minimum of 100 nuclei from each was recorded per case. After image segmentation, feature extraction software produced 93 karyometric features per nucleus that were stored for analysis. Discriminant functions were derived according to differences between normal nuclei and those with sun damage. Profiles commonly found in malignant cells were seen in the AK lesions. Using these features, a grading score was developed based on a plot of degree of solar damage versus the mean discriminant function. While upper inner arm (minimally sun-exposed) skin biopsies demonstrated as few as 3 % of nuclei affected by sun damage, the AK lesions included approximately 50 % affected nuclei. Discriminant functions derived from values obtained from samples ranging from normal to sun-damaged to premalignant (AK or DN) to malignant (SCC or melanoma) phenotypes establish a progression curve that can be used to determine the efficacy of applied chemopreventive agents (Bozzo et al. 2001) (Fig. 12.5). They have also applied this novel technology to demonstrate the efficacy of two chemoprevention agents, α-DFMO and vitamin A, in patients with moderately severe sun-damaged skin (Bozzo et al. 2001; Alberts et al. 2004). More evidence that this technology is useful in predicting prognosis and risk of skin cancer patients was recently published (Glazer et al. 2011). In these

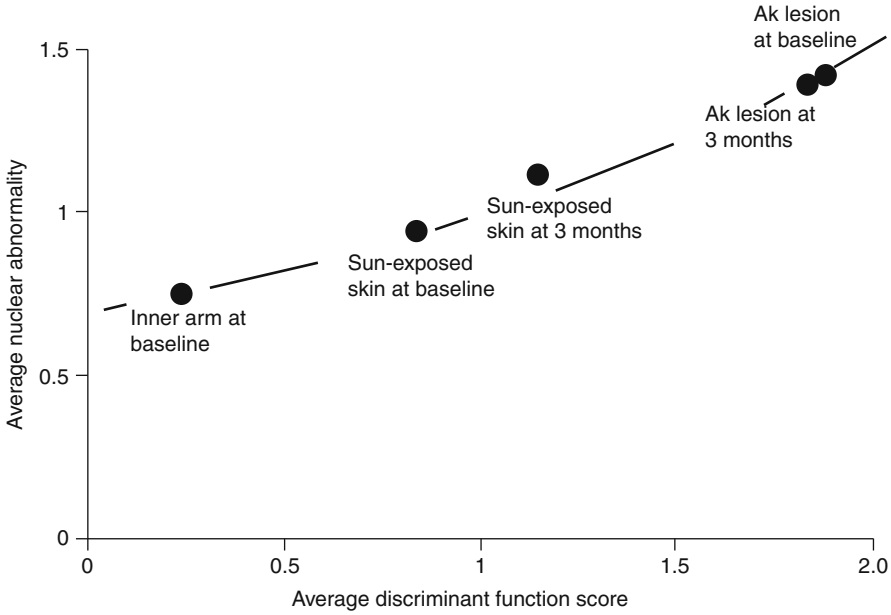

Fig. 12.5 Average nuclear abnormality versus average discriminant function scores for the 10 % worst nuclei from the upper inner arm at baseline, sun-exposed skin at baseline and 3 months, and AK lesions at baseline and 3 months (Bartes et al. 2002)

studies, the investigators demonstrated that aggressive cutaneous SCCs have a unique karyometric pattern distinct from nonaggressive cutaneous SCC lesions in low-risk patients. The classification accurately categorized 80 % of the patients in this study as either aggressive cutaneous SCC or nonaggressive SCC.

Optical coherence tomography (OCT) is a potentially new technique for identifying and characterizing AKs and monitoring their response to chemoprevention agents (Barton et al. 2003). Based on Michelson interferometry, this technique was first introduced for investigations of the human eye (Fercher et al. 1988). This noninvasive technique uses coherent light operating in the near-infrared region of 1,300 nm to produce two-dimensional images of the skin (Welzel 2001). The resulting photons have a typical penetrating depth of 1.0–1.5 mm allowing for multiple layers and structures to be distinguished. The resolution afforded by this technique makes it possible to distinguish features such as stratum cornea, epidermal layer, hair follicles, sebaceous glands, and blood vessels. In addition, it is possible to evaluate the efficacy of topical application of ointments and similar treatments, as these compounds tend to increase the detection/penetrating depth of the coherent light (Welzel 2001). In OCT, images of epithelial skin tumors and cell aggregation from the epidermis are visible. In some cases, lateral borders of the tumor adjacent to healthy skin are detectable and BCC can be distinguished from fibrous stroma. It is also possible to diagnose various inflammatory skin diseases such as psoriasis and eczema. The OCT measurement is an unobtrusive and safe technique with no side effects for the patient.

In a pilot study on 20 subjects to investigate the OCT appearance of upper inner arm, sun-damaged skin, and mild AKs (Barton et al. 2003) and to determine if features or quantitative measures in OCT images could be used to reliably differentiate between these categories, OCT images of upper inner arm showed skin layers and features (stratum corneum, epidermis, dermis, blood vessels) seen in previous studies; additionally in this subject base, the subcutaneous fat layer was usually seen. Sun-damaged skin was characterized by increased signal in the epidermis and rapid attenuation of light. AKs were diverse in appearance but frequently characterized by high surface reflection, the presence of a low-signal band in the stratum corneum, and heterogeneous appearance in the epidermis/dermis. Significant differences were found between skin categories using measures of stratum corneum and epidermal/dermal depths and intensities. The presence of a dark band in the stratum corneum was 79 % sensitive and 100 specific for AK. This study suggests that OCT may be a useful noninvasive technique for monitoring AK during the clinical studies to evaluate the efficacy of chemoprevention agents.

12.6 Potential Chemoprevention Agents for Skin Cancer

The previous chapter (Chap. 11) describes a novel way to deliver chemoprevention compounds to the skin by the development of topical prodrug formulations. Therefore, this chapter focuses primarily on agents that have not yet been discussed in the previous chapter nor the technology used for prodrug formulation for skin chemoprevention agents. However, many of these compounds could also be considered for prodrug formulation. Figure 12.6 depicts potential UVR-induced targets and chemoprevention agents which may act on these targets for the prevention of skin cancer progression. The investigators at the Arizona Cancer Center use a decision tree which results in leads for chemoprevention agents that will potentially result in a clinical trial (Einspahr et al. 2003). The agents are selected based on epidemiological literature and activity in in vitro and in vivo models of UV skin carcinogenesis. Agents with novel mechanisms of action that are active against identified molecular targets are tested for their ability to modify the target and inhibit tumorigenesis in the animal models. Subsequent to toxicological evaluation and proper formulation, promising agents then progress to human phase I and then to phase II trials in subjects with AKs, DNs, or sun-damaged skin. Intermediate endpoints are evaluated to identify efficacy of the select agent. The following discussion provides an overview of chemoprevention agents for skin cancer which have been or are currently in clinical trials as well as future agents which may result in clinical trials due to their activity toward modulation of molecular targets previously discussed for NMSC and melanoma in in vitro or in vivo models systems.

Several potential chemopreventive agents have been taken through phase III clinical trials in people at high risk for NMSC (Stratton 2001; Bowden 2004). The agents include beta-carotene (Greenberg et al. 1990), selenium (Clark et al. 1996), retinol (Moon et al. 1997), and 13-cis-retinoic acid (Tangrea et al. 1992). Of these trials, the only one with positive results involved oral administration of 25,000 U/day

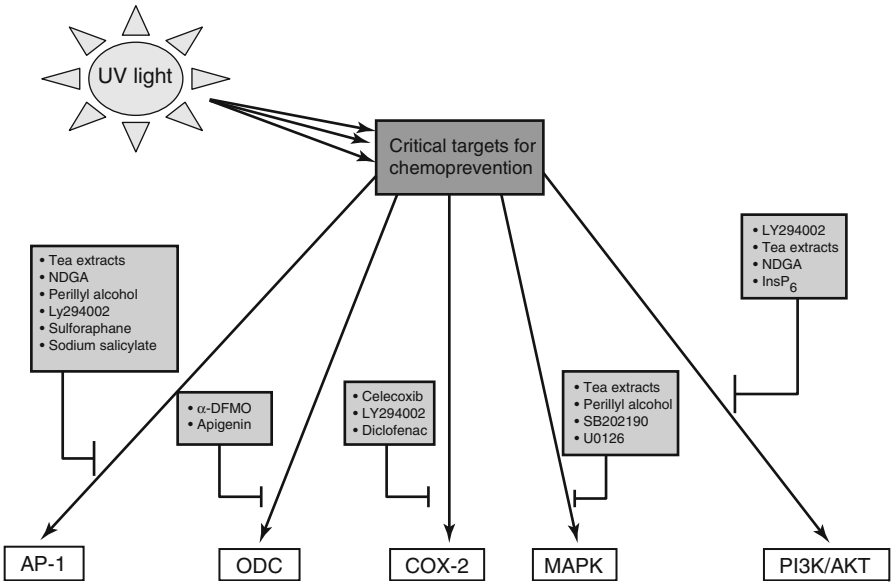

Fig. 12.6 UVR-induced targets can be modulated by specific potential chemoprevention agents

of retinol in 2,297 subjects with moderate to severe AK (Moon et al. 1997). This trial resulted in a reduction in SCC but not in BCC. The hazard ratio for first new SCC was 0.74 when comparing subjects from the retinol-supplemented group to placebo. Vitamin A (retinol) has been demonstrated to be necessary for cell growth and differentiation of human epithelial tissues, reproduction, and visual function (Gudas 1994). Retinoids have been shown to be involved in cell growth, cell differentiation, and carcinogenesis, all mediated in part by nuclear retinoic acid receptors and retinoid X receptors (Mangelsdorf et al. 1994; Xu et al. 1994).

There have been several smaller phase II trials in subjects at risk for NMSC that have resulted in positive outcomes. Recently, a phase IIa/IIb safety, dose-finding, and efficacy study of orally administered vitamin A in participants with sun-damaged skin resulted in a positive outcome (Alberts et al. 2004). The results were evaluated using karyometric analysis (described previously). One hundred twenty randomized participants were given daily oral placebo, 25 K, 50 K, or 75 K units of vitamin A (retinyl palmitate) for 12 months. The primary endpoints included quantitative, karyometric image analysis and assessment of retinoid receptors in sun-damaged skin. This analysis suggests that orally administered vitamin A is effective as a skin cancer chemopreventive agent by reducing levels of actinic nuclear damage as measured by average nuclear abnormality levels and discriminant function scores derived from appropriate karyometric features (Fig. 12.7). The dose effects of vitamin A correlated with increases in retinoid receptors, RAR-α, RAR-β, and RXR-α, at the 50,000 IU/day vitamin A dose.

Another clinical trial performed by Alberts and colleagues demonstrated that topical 2-(difluoromethyl)-dl-ornithine (α-DFMO) can reduce spermidine

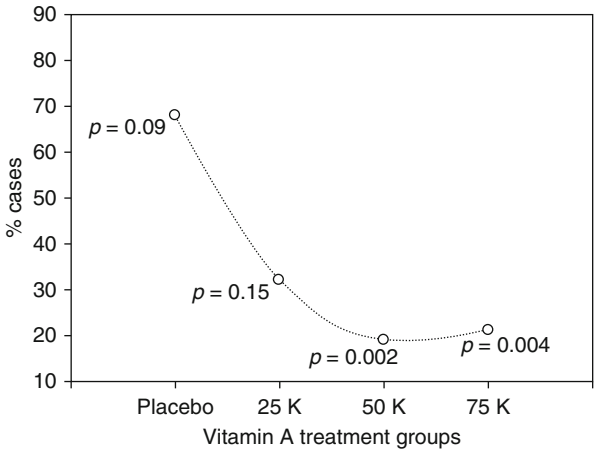

Fig. 12.7 Dose response to vitamin A treatment as demonstrated by percent of cases with increased actinic damage decreases based on karyometric analysis (Adapted from Bartels et al. (2002))

concentrations and the number of AK lesions in patients at high risk of skin cancer (Alberts et al. 2000). Forty-eight participants with moderately severe AKs on their forearms were assigned randomly to topical α-DFMO treatment. A reduction of 23.5 % in the number of AK lesions was seen from baseline to the 6-month follow-up. Spermidine concentration was reduced by 26 % in skin biopsies from α-DFMO-treated arms. No systemic toxicities were detected; however, 7 of the 48 (14.6 %) participants experienced severe (4.2 %) or moderate (10.4 %) inflammatory reaction on their α-DFMO-treated arms. In skin biopsies from this study, investigators were able to demonstrate a significant reduction of 22 % in p53-positive cells (Einspahr et al. 2002). However, there were no significant changes in proliferation cell nuclear antigen (PCNA) index, apoptotic indices, or p53 mutation frequencies. With karyometric analysis, α-DFMO treatment markedly decreased the discriminant function score indicating effectiveness in reducing nuclear abnormalities. α-DFMO is an irreversible inhibitor of ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis, and may exert its chemoprevention effects by inhibiting growth and/or inducing apoptosis. α-DFMO inhibits polyamine biosynthesis by covalently binding to ODC, thus inhibiting proliferation and inducing apoptosis. Leads for the use of α-DFMO came from previous studies where α-DFMO had been demonstrated as an antitumor agent in several animal models for carcinogenesis including a report that oral α-DFMO inhibited cutaneous carcinogenesis and immunosuppression in a mouse model (Gensler 1991). In Xpa knockout mice, α-DFMO, given in drinking water, reduced UVR-induced skin tumors in mice (Takigawa et al. 1990). Tumor-suppressive activity was demonstrated for α-DFMO in melanoma (in vitro and in metastatic melanoma in a clinical trial) (Bregman and Meyskens 1986; Meyskens et al. 1986).

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) often used alone for degenerative arthritis management or with opioids in the treatment of pain associated with cancer. Investigations have shown that diclofenac has activity in the treatment of AK, thereby potentially preventing progression to SCC. An early study of 29

subjects assessed the efficacy and safety of topical diclofenac (Solaraze). Three percent diclofenac in 2.5 % hyaluronic acid gel was generally well tolerated with the exception of seven (24 %) patients who experienced irritant-type contact dermatitis (Rivers and McLean 1997). Additional clinical trials have further explored the potential therapeutic effect of this gel formulation. One randomized double-blind controlled trial of 130 patients, which did not include a follow-up period, did not find a significant difference between the use of diclofenac/hyaluronan and placebo in the eradication of AKs (McEwan and Smith 1997). However, two other randomized, double-blind, placebo-controlled studies found treatment with 3.0 % diclofenac to be effective in the treatment of AK. A study of 195 patients with at least five AKs investigated the duration of treatment for 30 or 60 days with two daily applications of the gel (Rivers et al. 2002). While no significant difference was seen after 30 days, the 60-day treatment group showed a statistically significant difference in the number of patients (33–10 %) with complete resolution of all target lesions in treated areas when compared to placebo group. The 60-day treatment group was also significantly different than placebo in the number of patients with resolution of target and new lesions in treated area, visible but no longer palpable lesions, and investigator and patient global improvement indices. Another study of 96 subjects also demonstrated a statistically significant difference in a 60-day treatment regimen when comparing the above criteria (Wolf et al. 2001). In both these studies, the gel was well tolerated with only a few subjects reporting skin reactions. The mechanism of action of the 3.0 % diclofenac, with regard to tumor resolution, is unknown. As an NSAID, diclofenac inhibits cyclooxygenase enzymes (COX-1 and COX-2). A case control study in women found an inverse association of NSAIDS intake and malignant melanoma (Harris et al. 2001b). One group demonstrated that 26–28 primary melanoma cell lines expressed COX-2 (Denkert et al. 2001).

The COX-2 inhibitor, celecoxib, has been shown to suppress the formation of UV-induced skin cancers when given orally to mice (Pentland et al. 1999; Fischer et al. 1999). Topical application of celecoxib reduced cutaneous inflammation (Wilgus et al. 2000). Reduction of the inflammatory response could prove protective against long-term UV exposure and the development of skin cancer and the conversion of benign AK to cancerous ones. An UVR-induced tumor mouse model demonstrated a lengthening in tumor latency period and reduced tumor multiplicity when mice were treated with a COX-2 inhibitor, celecoxib (Orengo et al. 2002). An increase in arachidonic acid metabolism in keratinocytes due to exposure to UVB (Buckman et al. 1998) may be a target for this type of chemoprevention. A study of a topical combination of celecoxib and 5-FU, a common treatment for AK, found that the combination was 70 % more effective in reducing the number of UVB-induced skin tumors than with 5-FU alone (Wilgus et al. 2004). A randomized, double-blind, placebo-controlled trial demonstrated that individuals with extensive actinic damage(number of AK at screening was approximately 24) given twice daily oral administration of 200 mg of celecoxib for 9 months demonstrated fewer nonmelanoma skin cancers, both BCC and SCC, in the celecoxib arm compared to the placebo arm (Elmets et al. 2010). These results were seen 11 months after randomization. These studies indicate a genuine possibility of celecoxib being a

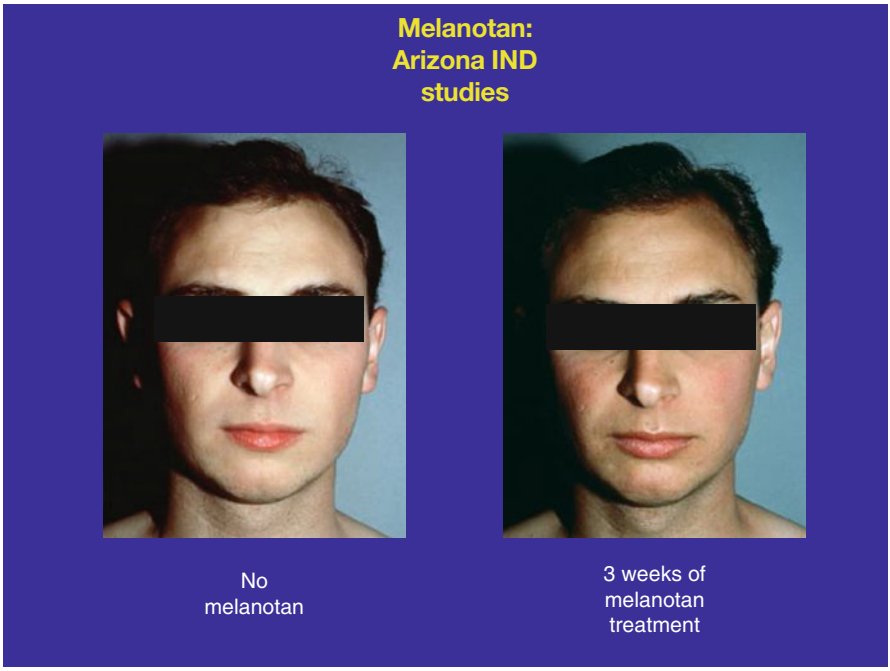

Fig. 12.8 Early clinical trials (Levine 1991) demonstrated skin tanning. *Left*: pretreatment state. *Right*: tanning of the face and neck after start of therapy

chemopreventive agent for skin cancer at least for those with extensive actinic damage who are then at high risk for the development of nonmelanoma skin cancers.

An agent developed at the University of Arizona, Melanotan-1 (MT-1) could potentially be used as a chemopreventive agent against melanoma and NMSC. This agent is a superpotent melanotropic peptide that results in darkening of the skin (Fig. 12.8). In clinical studies with MT-1, there was no improvement of tanning in doses greater than 0.16 mg/kg/day for 10 days by subcutaneous (SC) injection. No moderate toxicities occurred at this dose as in the higher doses (Levine et al. 1999); a single exposure of three minimal erythema doses (MED) of UVB did not enhance eumelanin content of the skin either before or after MT-1 administration (Dorr et al. 2000). While treatment showed darkening of the skin on days 14 and 21, there was no significant difference from baseline to 3 weeks after dosing. Investigators found that the most effective delivery was by SC administration, which resulted in an increase in eumelanin and measured tanning by reflectance in the forearm and forehead. For the purpose of prolonging skin darkening by the use of MT-1, investigators formulated a controlled release MT-1 implant formulation based on a PLGA polymer. In studies with an in vitro frog skin bioassay, they found that the implants (1 mg of peptide) showed that the melanophores migrated to the dendritic processes of the pigment cells, which resulted in skin darkening. In in vivo studies using pigmented haired and hairless guinea pigs with the MT-1 implants (4 mg peptide),

increase of skin darkening was observed for up to 3 months and eumelanin content demonstrated a 2.5-fold increase 1 month and persisted for 3 months. This prolonged increase in pigment, specifically eumelanin, can be favorable to the prevention against photodamage induced by UVR radiation.

Three phase I clinical trials performed at the Arizona Health Sciences Center in Tucson demonstrated that MT-1 can be safely combined with UVB light or sunlight and appears to act synergistically in the tanning response to light (Dorr et al. 2004). In these studies enhanced tanning was achieved in the groups receiving MT-1 as well as 47 % fewer sunburn cells at the irradiated site. Subcutaneous doses of 0.16 mg/kg/day for 10 days provided an increased darkening and a maintained tanning for at least 3 weeks longer than those exposed to sunlight exposure alone. The sun exposure time for equivalent tanning in the sunlight-only controls required 50 % more time for an equivalent tanning. Currently, MT-1 is under development in Australia, licensed by Clinuvel Pharmaceuticals, Ltd. (formerly Epitan, Ltd.) under the proprietary name CUV1647. Two objectives for the Australian studies have been (1) to determine the efficacy of MT-1 in at-risk skin-damage-prone populations and (2) the development of an improved formulation/schedule for delivery, namely, a slow release depot formulation designed to release drug from a single subcutaneous injection over several months (Hadley and Dorr 2006). In phase I/II trials, Australia found that the 0.16 mg/kg/day injection dose caused increased eumelanin deposition in the skin, similar to results reported in the Arizona studies (Fitzgerald et al. 2006). No dose-limiting side effects were noted. Of additional interest, patients with variant MC1R genotypes were evaluated for their response to MT-1 to evaluate if it is useful for individuals most in need of photoprotection (Fitzgerald et al. 2006). These variants such as Arg151Cys, Arg160Trp, and Asp294His are associated with fair skin color and red hair (Box et al. 1997; John and Ramsay 2002; Valverde et al. 1996). Individuals with one or more of these variants have been shown to be less able to tan naturally with UV light (Healy et al. 2000), and the variants have been associated with an increased risk of skin cancer (Bastiaens et al. 2001; Kennedy et al. 2001; Palmer et al. 2000). The study on the effect of MT-1 on humans with MC1R variant alleles demonstrated that the agent effectively increased the melanin content in the skin of individuals with variant alleles and therefore those most in need of photoprotection (Fitzgerald et al. 2006). A human depot formulation of MT1 (20 mg) successfully produced pigmentation in a pilot phase I study (Hadley and Dorr 2006). Following pharmacokinetic studies in healthy volunteers, the "controlled release" implants contain 16 mg of MT-1. The increased pigmentation of the skin appears approximately 4–5 days after implantation and may last for several months (www.clinuvel.com). In 2007, this agent, afamelanotide formulation, CUV1647, began phase III clinical trials for polymorphic light eruption (sun poisoning) and erythropoietic protoporphyria (absolute sun intolerance). In November of 2007, Clinuvel Pharmaceuticals, Ltd. initiated a phase II trial in Australia and Europe for CUV1647 as a preventive for sun damage and AK in fair-skinned, immune-compromised organ transplant recipients (FDA News 2007). The trial evaluates the ability of the agent to reduce the number of AK on the head, back of hand, and forearms during a 24-month test period. A secondary

endpoint will determine the effect of this agent on the number of SCC on the head, back of hand, and forearms during the 24-month test period. In 2009, Clinuvel began a study to determine whether afamelanotide (CUV1647) is effective in reducing the number of actinic keratoses and squamous cell carcinomas developing in immune-compromised organ transplant recipients, who are at particularly high risk, over a 24-month test period. Most recently, a 3-times-weekly narrowband UVB exposure along with a 4-monthly implant containing a 16 mg afamelanotide demonstrated potential efficacy in the treatment for vitiligo (Grimes et al. 2013). The afamelanotide induced repigmentation within 2 days to 4 weeks of the initial implant.

Dellavalle and colleagues (2003) review the role of statins or fibrates in melanoma chemoprevention. Results from two large clinical trials demonstrated a decrease in melanoma incidence in subjects given lipid-lowering medications for coronary artery disease. In another study 27 melanomas were newly diagnosed in 3,301 placebo-treated patients, whereas only 14 melanomas were diagnosed in 3,304 lovastatin-treated patients (Buchwald 1992). The incidence of all other cancers was not statistically different. In another study with gemfibrozil, a hypolipidemic medication, nine melanomas were diagnosed in 1,267 patients treated with placebo and only one melanoma was diagnosed in a 5-year period in 1,264 gemfibrozil-treated patients (Rubins et al. 1999). Again, all other cancers were not significantly different. Statins are known to inhibit the isoprenoid protein modification and therefore may be inhibiting ras farnesylation and cause a downregulation of ras oncogenic potential in melanoma.

Other phase II trials have focused on the potential chemoprevention activity of topical green tea extracts (e.g., Polyphenon E) in patients with AK on their arm (Stratton 2001). Animal studies have demonstrated a chemopreventive effect of epigallocatechin gallate (EGCG). Investigators have reported a reduction in tumor incidence with topical application of EGCG in UVB-irradiated mice. Mice were irradiated at a total dose of 2.1×10^6 J/m^2. Skin cancer developed in 96 % of control mice and 62 % of mice given 10 mg of EGCG and 39 % of mice given 50 mg of EGCG. EGCG did not affect immunosuppression and oral administration did not decrease UVR-induced skin tumor incidence. In the investigation of a mechanism of action for EGCG, it was demonstrated that EGCG can inhibit UVB-induced AP-1 activity in a dose range of 5.45 nM to 54.5 μM in human keratinocytes when applied before, after, or both before and after UVB irradiation (Barthelman et al. 1998a). Inhibition of AP-1 by topical EGCG application was also evident in a transgenic mouse model. EGCG inhibited UVB-induced steady-state message and transcriptional activation of the c-Fos gene as well as the accumulation of the c-Fos protein. Upstream of c-Fos, EGCG significantly inhibited activation of p38 MAPK yet did not affect JNK or ERK activation. AP-1 inhibition potentially, through the reduction of c-Fos by EGCG, may be the mechanism by which EGCG inhibits UVB-induced tumor formation in mice (Chen et al. 1999). Theaflavins from black tea demonstrated a stronger inhibition of AP-1 than EGCG and inhibition of the activation of ERK and JNK was also significant with theaflavin treatment (Nomura et al. 2000). In addition, Nomura and colleagues demonstrated in mouse epidermal

cells that EGCG and theaflavins inhibited the activation of UV-induced PI3K and attenuated UV-induced Akt and p70 S6-K, both downstream effectors of PI3K (Nomura et al. 2001a). Studies with oral administration of green tea or caffeine to mice reported chemopreventive effects on UV-induced carcinogenesis mediated through stimulation of UV-induced increases in the number of p53-positive cells, $p21^{Waf1/cip1}$-positive cells, and apoptotic sunburn cells (Lu et al. 2001).

Investigators have developed a 10 % (w/w) EGCG formulation in hydrophilic ointment USP for topical application. An intradermal uptake of 19 and 0.9 % of the applied dose was evident in the mouse and human skin, respectively, while transdermal penetration was observed only in the mouse skin (Dvorakova et al. 1999). The 10 % EGCG formulation was used in a phase I clinical trial to assess safety and the sun protection factor (SPF). An SPF of 3.6 was recorded for this ointment, applied to buttock skin. No systemic toxicities with topical application to the arms were seen in 19 participants that completed the study. However, 42 % of the participants reported moderately severe skin reaction, and histological evaluation corroborated the clinical findings.

The chemopreventive activity of aspirin and sodium salicylate was investigated in a UVB-induced NMSC hairless SKH-1 mouse model (Bair et al. 2002). While sodium salicylate significantly inhibited UVB-induced tumor formation, aspirin had only a moderate effect. The protection supplied by sodium salicylate appears to be in part due to its sunscreen effect, which was demonstrated by the reduction of thymine dimers in the epidermis of mice treated with sodium salicylate. Aspirin was unable to prevent dimer formation (Bair et al. 2002).

In vitro studies revealed that a derivative of nordihydroguaiaretic acid (NDGA), tetra-*O*-methylnordihydroguaiaretic acid, inhibited growth of several tumor cell lines, including a melanoma line where there was morphologic evidence of apoptosis. This compound also inhibited the synthesis of DNA and caused cell cycle arrest in G_0/G_1 and G_2/M phases of the cell cycle. Growth inhibitory effects of this compound were also exhibited in vivo (Lambert et al. 2001). Bowden and colleagues have also identified NDGA as an inhibitor of UVB-induced c-Fos and AP-1 transactivation by inhibiting the PI-3 kinase signal transduction pathway (Gonzales and Bowden 2002).

A potential chemopreventive agent for melanoma, Apomine, has been studied in a clinical and preclinical setting. Apomine is a bisphosphonate ester that has been reported to activate the farnesoid X receptor, increase the rate of degradation of HMG-CoA reductase, and induce apoptosis (Niesor et al. 1999). Apomine has been shown to inhibit the growth of many tumor cell lines, including those derived from leukemia, colon, liver, ovary, and breast (Falch et al. 2000). Growth inhibition and apoptotic activity were compared to those of simvastatin, farnesol, and 25-hydroxycholesterol, which all affect HMG-CoA reductase. Apomine was most like farnesol, a non-sterol regulator of cholesterol synthesis. In a phase I trial at the Arizona Cancer Center, it was demonstrated by plasma pharmacokinetics that a daily dose of 125 mg/m^2 of Apomine was sufficiently bioavailable to levels used in in vitro studies that demonstrated activity against fresh human solid cancers. In preliminary studies in a TPras transgenic melanoma mouse model (Powell et al. 2002), Apomine caused a 55 % reduction in melanoma development induced by

DMBA. In vitro studies with melanoma cell lines derived from the transgenic TPras mouse model and treated with Apomine demonstrated a significant reduction in Ras detected in the membrane fraction (activated Ras). Apomine was also able to reduce UVR-induced Akt phosphorylation but had no effect on phosphorylation of ERK1/2 (Powell et al. 2002). A study in human melanoma cells found that Apomine cytotoxicity to the cells was mediated primarily through a non-apoptotic pathway (Pourpak et al. 2005). In a phase I clinical trial at the Arizona Cancer Center, Apomine expressed prolonged cancer stabilization in patients with metastatic melanoma and recurrent ovarian cancer with minimal or no toxicity (Powell et al. 2002). A topical formulation with Apomine is in preparation for clinical trials in skin cancer. Investigators at the University of Arizona Cancer Center have developed the high performance liquid chromatography method to analyze Apomine in topical cream formulations (Kuehl et al. 2006).

Another agent with potential chemopreventive activity in both melanoma and NMSC is perillyl alcohol (POH). POH is a cyclic monoterpene that reduces the amount of Ras and Ras-related proteins and has been reported to induce apoptosis. POH is found in the essential oils of numerous plants including citrus fruit, cherries, and mint. Limonene (a precursor of POH) has been demonstrated to reduce the incidence of spontaneous lymphomas in $p53^{-/-}$ mice and to inhibit the development of chemically induced rodent mammary, liver, lung, and forestomach tumors (Crowell 1999). Ras oncogene-induced mammary carcinoma development has also been inhibited by limonene (Gould et al. 1994). POH has demonstrated chemopreventive properties in several types of cancers, including liver cancer in rats (Mills et al. 1995), pancreatic cancer in hamsters (Stratton et al. 2000), and mammary tumors in rats (Haag and Gould 1994). POH and limonene as oral agents have also been used in clinical trials (Gould et al. 1994; Crowell 1999). Chemopreventive properties of topical POH have been demonstrated in a nonmelanoma and a melanoma mouse model (Barthelman et al. 1998b; Lluria-Prevatt et al. 2002). In both models, topically applied POH significantly reduced the incidence of tumors. Investigators also reported that POH reduced detectable levels of Ras, inhibited the activation of Akt and MAPK, and reduced UVR-induced reactive oxygen species in melanoma cells (Lluria-Prevatt et al. 2002). POH inhibited UVB-induced AP-1 transactivation in vitro and in vivo (Barthelman et al. 1998a). The mechanisms of action for POH identified thus far include inhibition of cell proliferation, induced tumor cell differentiation (Morse and Stoner 1993), and increased apoptosis (Mills et al. 1995). POH has been shown to inhibit protein isoprenylation in Ras (Hohl and Lewis 1995; Stayrook et al. 1998). Evidence of chemopreventive activity in mouse models and the suspected molecular targets for POH makes it an ideal compound for potential chemoprevention studies in melanoma and NMSC. For clinical studies, POH has been formulated into a topical cream (Gupta and Myrdal 2004). The formulation was found to be physically and chemically stable over a period of 1 year at 4° and 25 ° C. A phase IIa randomized, placebo-controlled, double-blind trial of topical POH in sun-damaged skin was initiated at the University of Arizona Cancer Center in Tucson, Arizona, to evaluate its chemopreventive activity in humans (Stratton et al. 2010). Karyometric evaluation demonstrated a slight reduction in the

histopathologic score in those treated with a topical 20 mmol/L formulation compared to the placebo group. A statistically, significant reduction in the proportion of nuclei deviating from normal was observed by karyometric analysis in the group treated with 50 mmol/L formulation. However, there was no change observed in p53 expression, cellular proliferation, or apoptosis in either treatment group. The study suggests that an improved delivery into the epidermis may be necessary to deliver the appropriate dose to see an effect other than by karyometric analysis.

Future agents will most likely be identified by their mechanism of action. The selected agents will have specific targets such as those described earlier as important in the UV signaling pathways and carcinogenesis process of skin cancer development (Fig. 12.4). For p38 MAPK, there are inhibitors which are a group of polycyclic pyridinylimidazole compounds. SFK86002, a bicyclic pyridinylimidazole, first reported to inhibit LPS-stimulated cytokine production (Lee et al. 2000). Early reports indicated a role of cytokine inhibition as a potential mechanism for the potent anti-inflammatory activity of these compounds (Lee et al. 1988). Subsequently, SB203580 and other 2,4,5-triaryl imidazoles were prepared as a tool for finding the molecular target involved in cytokine regulation (Lee et al. 1993). Later discoveries indicated p38/CSBP as the molecular target of these compounds (Gallagher et al. 1997). One such compound, SB202190, inhibits p38 phosphorylation of myelin basic protein (MBP) while not effecting ERK or JNK MAP kinases. The compound also inhibits p38 phosphorylation of activating transcription factor 2 and blocks LPS-induced TNF and interleukin biosynthesis as well as inducing LDL receptors in vitro. Investigators have used SB202190 to understand the mechanisms of UVB- and UVA-mediated p38 MAPK (Bachelor et al. 2005; Bachelor and Bowden 2004). Topical treatment to mouse epidermis with SB202190 resulted in a 84 % decrease in UVB-induced AP-1 activation as well as COX-2 expression (Bachelor et al. 2005).

It has been demonstrated that topical application of the compound resveratrol demonstrates chemopreventive effects against multiple short-term UVB exposures to the skin of hairless mice by decreasing the UVB-mediated upregulation of MAPKK and the 42 kDa isotope of MAPK (Reagan-Shaw et al. 2004). Resveratrol is a naturally occurring antioxidant phytoalexin produced by some plants subsequent to injury or fungal infection and is found in red wine and grapes (Aziz et al. 2003, 2005). This agent has shown cancer chemopreventive effects in a variety of tumor bioassays (Aziz et al. 2003; Jang et al. 1997; Kapadia et al. 2002) and has been attributed to the "French Paradox" (Aziz et al. 2003; Kopp 1998; Sun et al. 2002). Early studies demonstrated that resveratrol inhibited chemically induced skin tumorigenesis in a mouse model (Jang et al. 1997). Most recently, Aziz and colleagues demonstrated that topical resveratrol was a chemopreventive agent in long-term UVB exposure of a mouse skin carcinogenesis model (Aziz et al. 2005). The untreated group resulted in SCC, Bowen's disease, invasive carcinomas in situ, and AK. The resveratrol-treated group (pre- and post-treated) had a significant reduction in tumor incidence and the majority of the lesions were AKs, suggesting that the agent was inhibiting the malignant conversion of AKs. The chemopreventive effects of resveratrol appear to be against modulation of cki-cyclin-cdk network

and MAPK pathway (Reagan-Shaw et al. 2004). The activity of the agent appears to be through signaling pathways rather than a sunscreen effect (the treatment was also effective post UV irradiation) (Aziz et al. 2005). These studies suggest that the target for resveratrol is the modulation of the expression and function of survivin. Survivin is a critical regulator of cell survival/death (Altieri 2001; Altieri and Marchisio 1999). Deregulation of survivin has been shown to inhibit melanoma tumor growth (Grossman et al. 2001) and found to prevent papilloma regression and promote conversion to SCC (Altieri 2003).

SP600125, an anthrapyrazole, is an inhibitor of JNK catalytic activity (Bennett et al. 2001). This inhibitor was identified in a high-throughput biochemical screen by using purified recombinant JNK2 and c-Jun. SP600125 demonstrated inhibitory activity consistent with the role of JNK in CD4+ cell activation and differentiation, in CD14+ cell gene expression, and in thymocyte death. SP600125 inhibits c-Jun phosphorylation in cells and also COX-2, IL-2, IFN-c, TNF-α, IL-10, and MMP gene expression (Han et al. 2001). In vivo studies demonstrated that SP600125 inhibited LPS-induced TNF-α expression in mice (Bennett et al. 2001). SP600125 also prevented anti-CD3-mediated thymocyte apoptosis in a C57BL/6 mouse model (Bennett et al. 2001). In addition, this inhibitor of JNK blocked cell proliferation but did not kill CD4+ cells, resulting in a cytostatic effect on T cell proliferation. Although several anthrapyrazoles have been identified as chelators of DNA (i.e., doxorubicin), SP600125 did not exhibit characteristics of a strong interchelator of DNA in competitive binding assays. SP600125 also did not induce apoptosis (Bennett et al. 2001). Both compounds, the MAPK inhibitor, SB202190, and the JNK inhibitor, SP600125, were able to inhibit UVA-induced AP-1 and c-Fos transactivation as well as c-Fos expression in the HaCaT cell line transfected with a luciferase reporter (Silvers et al. 2003).

Inositol hexaphosphate ($InsP_6$) is a direct inhibitor of PI-3 kinase in vitro (Huang et al. 1997a, b). This agent has also demonstrated inhibition of EGF-induced AP-1 activation and cell transformation of JB6 epidermal cells (Huang et al. 1997c). $InsP_6$ also inhibits UVB-induced AP-1 and NF-jB transcriptional activity. This compound is similar in structure to a potent PI-3 kinase inhibitor, D-3-deoxy-3-fluoro-PtdIns (Powis et al. 1995).

LY294002 is a morpholino derivative of the broad-spectrum kinase inhibitor quercetin. This compound is also an inhibitor of PI-3 kinase. This agent has been shown to cause inhibition of UVB-induced COX-2 promoter activity and protein expression of COX-2 in human keratinocytes (Tang et al. 2001). Topical LY294002 treatment in SKH-1 mouse epidermis demonstrated a significant induction of UVB-induced AP-1 activation as well as COX-2 expression (Bachelor et al. 2005). Studies using TPras transgenic melanomas in SCID mice demonstrated a reduction in invasion, correlated with a reduction in MMP2, when treated with LY294002 (Bedogni et al. 2004). Using the TPras mouse model for melanoma development, discussed earlier in this chapter, topical application of LY294002 resulted in a delay in melanoma development by 8 weeks (Bedogni et al. 2006). In addition, treatment with LY294002 after tumors had developed in this model resulted in only a 17 % progression compared to 93 % progression in the control mice. There was a 67 %

partial regression and a 17 % regression in the mice treated with LY294002. Most interesting of these studies is that a combination of LY294002 and U0126, a specific inhibitor of MEK 1/2, increased the effectiveness. In the topical combination treatment, 70–75 % of the mice did not develop melanoma while the control group only contained 9 % of mice that were melanoma-free at the end of the study. The response to these agents corresponds to increased apoptosis and decreased proliferation both in vitro and in vivo as well as a reduction in tumor angiogenesis. These studies support the role of PI-3 kinase/Akt and Raf/MAPKK pathways as important in the development of melanoma. In addition, the studies point to a potential for using LY294002 or other PI-3 kinase inhibitors as a topical chemopreventive agents in both melanoma and nonmelanoma and a combination of LY294002 with U0126 in melanoma. Finally, treatments of these compounds in animal models demonstrated no systemic toxicities or skin irritations.

Three specific inhibitors of EGFR tyrosine kinase, PD153035, AG1478, and ZD1839, may be potentially useful as chemopreventive agents. PD153035 is a 4-anilinoquinazoline compound that acts via competitive binding at the ATP site with the RGF receptor (Fry et al. 1994). AG1478 is a member of a family of tyrosine phosphor kinase inhibitors called tyrophostins (Gazit et al. 1996), which were designed to mimic the tyrosine substrates. Investigators have shown that these inhibitors (Zhang et al. 2001a) can block UVA-induced EGFR signaling. ZD1839 (Iressa; AstraZeneca Pharmaceuticals) is another inhibitor of EGFR, which could be considered for topical formulation development as a chemoprevention agent. ZD1839 has been shown to inhibit activation in a variety of human skin cell types in vivo subsequent to oral therapy (Albanell et al. 2002). In association with the EGFR inhibition, MAP kinase activation and keratinocyte proliferative rates decreased and an increase in the apoptotic index also occurred during therapy. ZD1839 is a substituted anilinoquinazoline that selectively inhibits EGF-stimulated tumor cell growth and blocks EGF-stimulated autophosphorylation in tumor cells (Wakeling et al. 2002). Clinical trials with oral ZD1839 have shown this compound to provide well-tolerated antitumor activity in patients (Wakeling 2002; Lorusso 2003).

As discussed earlier, BRAF is a potential molecular target for the chemoprevention of melanoma. BAY 43–9006 is a potent inhibitor of Raf kinase (Lyons et al. 2001). Oral administration of this compound has shown significant activity in four different human tumor types including colon (Gianpaolo-Ostravage et al. 2001), pancreatic, lung, and ovarian tumors carried out in xenograft models. Clinical testing of this compound in cancer patients began in July 2000 (Strumberg et al. 2001). Preliminary clinical data reported the compound to be well tolerated. At least 37 % of patients in the initial study had stable disease lasting longer than 12 weeks. This compound could be a promising agent for chemoprevention specifically for melanoma.

One compound which has shown an induction of apoptosis via the activation of the Bcl-2 family in human keratinocytes is sanguinarine (Adhami et al. 2003). This agent is derived from the root of *Sanguinaria canadensis* and is also found in poppy and *Fumaria* species (Shamma and Guinaudeau 1986). The agent has been found to act as an antioxidant (Vavreckova et al. 1994) as well an antimicrobial (Mitscher et al. 1978) and anti-inflammatory compound (Mandel 1988). Sanguinarine has

demonstrated potential as a chemopreventive agent in UVB-irradiated human keratinocytes (Reagan-Shaw et al. 2006) and resulted in a decrease in UVB-mediated skin edema, skin hyperplasia, and infiltration of leukocytes in mice treated with topical sanguinarine (Ahsan et al. 2007).

A review by Juge and colleagues describes the chemopreventive effects of sulforaphane, a natural isothiocyanate found in broccoli seeds, sprouts, and plants (2007). The chemopreventive properties of sulforaphane include inhibition of phase 1 cytochrome P450 enzymes, induction of phase 2 metabolism enzymes, antioxidant functions through increased tissue GSH levels, apoptosis-inducing properties, induction of cell cycle arrest, anti-inflammatory properties, and inhibition of angiogenesis. Many of these effects are downstream of sulforaphane's ability to activate the Nf-E2-related factor-2 (Nrf2) transcription factor, which regulates many cytoprotective and antioxidant genes in the cell. Topical application of sulforaphane demonstrated an inhibition of skin tumorigenesis when applied to a mouse model system that uses DMBA as an initiator and TPA as the promoter of tumorigenesis (Gills et al. 2006). The topical application of sulforaphane was effective during the promotion phase where it caused a significant decrease in both the percent of mice with tumors and in tumor multiplicity. In addition, the agent inhibited TPA-induced ODC activity in the mouse skin which has also been demonstrated in mouse epidermal cells in culture (Lee et al. 1999). Further studies found that the effects of sulforaphane on DMBA-/TPA-induced tumorigenesis are dependent upon the presence of the Nrf2 transcription factor (Xu et al 2006).

As discussed previously in this chapter, UVB can induce the activation of AP-1, and it is suggested that AP-1 plays a critical role in UVB-induced skin tumor development (Barthelman et al. 1998a; Huang et al. 2000). Investigators have demonstrated that sulforaphane can inhibit UVB-induced AP-1 activation in human keratinocytes by inhibiting AP-1 DNA binding activity (Zhu and Bowden 2004; Dickinson et al. 2009). Other researchers have used a hairless mouse model to demonstrate that topical sulforaphane substantially inhibited skin carcinogenesis induced by UVR (Dinkova-Kostova et al. 2006; Dickinson et al. 2009). One study showed a 50 % reduction in tumor burden, incidence, and multiplicity in animals which received topical sulforaphane in the form of broccoli sprout extract, or BSE, after the completion of a 20-week regimen of UV irradiation. Another study showed that purified sulforaphane can also inhibit tumorigenesis in mice when used concurrently with UVB (Dickinson et al. 2009). A dose escalation safety study in healthy humans revealed no adverse reactions with cumulative doses up to 450 nmol of topical sulforaphane (in BSE) and showed an increase in NAD(P)H:quinine oxidoreductase 1 (NQO1), therefore demonstrating an induction of phase 2 response in humans (Dinkova-Kostova et al. 2006). Sulforaphane is also effective at reducing UV-induced inflammation: treatment with BSE significantly reduced UVB-induced erythema in a clinical study (Talalay et al. 2007), and mice fed 1 mg/day of sulforaphane by oral gavage demonstrated significantly reduced the skin thickening and Cox2 activation associated with UVB exposure (Shibata et al. 2010). The evidence presented here provides evidence that topical sulforaphane should be pursued as a potential chemoprevention for skin cancer.

Additional potential chemopreventive agents for skin cancer include curcumin, which induces apoptosis in human melanoma cells through a cell membrane-mediated mechanism independent of the p53 pathway by induction of the Fas receptor and activation of caspase-8 (Bush et al. 2001), and topical apigenin which has been shown to be effective in preventing UV-induced mouse skin tumorigenesis by inhibition ornithine decarboxylase (ODC) activity (Birt et al. 1997).

Meyskens et al. (2004) present a review of studies that suggest that ROS may be central to the pathogenesis of melanocyte transformation and melanoma progression. They suggest that a critical early pathogenic event is the change of antioxidant to pro-oxidant melanin, the pigment produced by melanocytes. Once the melanin is oxidized by ROS generated by UV, an accumulation of metals occurs, and the antioxidant response is depleted, the buildup of ROS occurs. This, in turn, leads to melanosomal damage, DNA mutations, transcription activation, and enhancement and activation of an antiapoptotic (drug-resistant) phenotype of melanocytes. Chemoprevention of melanoma within the context of this etiological hypothesis may involve the early use of antioxidants.

Other UVR-induced oxidative stress studies are emerging to understand the signaling pathways leading to antioxidant response elements (ARE) for its potential in developing skin cancer chemoprevention strategies. These investigations have found that UVB irradiation can interrupt the signaling of ARE through the JNK pathway in human keratinocytes (Zhu et al. 2006). Additional findings include UVB-induced glutathione depletion in cultured keratinocytes through the caspase cascade (Zhu and Bowden 2004). Therefore, targeting events in the JNK or caspase pathways may be suitable as a chemopreventive measure to allow the signaling of the ARE during UVR exposure that causes damage in skin cells that can develop into skin cancer.

Development of a group of novel agents for skin photoprotection called quencher of photoexcited states (QPES) (Wondrak et al. 2005) may also be included as strategies of chemoprevention. These compounds directly antagonize the potentially damaging excited state of skin chromophores and molecular oxygen which cause damage to cellular targets leading to skin photoaging or photocarcinogenesis. These compounds suppress skin photooxidative damage upstream of ROS formation. Investigators suggest that this compounds be used in combination with antioxidants and sunscreens for a complete form of photoprotection. With a thorough screening process in place for QPES agents, Wondrak and colleagues (2005) suggest proline ester derivatives to be optimized for topical application in the skin.

Conclusion

Skin cancer is a major health problem in the USA as well as in countries such as Australia. With high health-care costs, at 5 % of Medicare health-care expenses, increasing incidence, limited treatments, and a significant loss of life specifically for melanoma, prevention of this disease is imminent. Primary prevention strategies focus on an avoidance of sun exposure and the use of sunscreen compounds; however, new individualized prevention strategies will revolutionize these extremely important areas of dermatologic research. Significant advances in

molecular biology in combination with pharmaceutical developments have opened the door for research in the field of chemoprevention and personalized medicine. For skin cancer, the formulation of a UV-induced signal transduction pathway (Fig. 12.4) that identifies important molecules involved in the carcinogenesis process has provided molecular targets for the development of target-specific agents. This pathway has been developed by the use of animal and cellular model systems of skin carcinogenesis. These targets include AP-1 and COX-2, as well as upstream targets such as EGFR, PI-3 kinase, MAPK, JNK, RSK-2, and Raf. Ongoing and future clinical trials will evaluate agents that act specifically to block molecules that are altered early in the development of skin cancer. These agents will most likely be delivered in a topical formulation using technology (e.g., prodrug development) that allows for maximum epidermal delivery with minimal systemic toxicity. The combination of several chemoprevention agents working in a synergistic fashion in these topical formulations will provide a promising strategy for the prevention of skin cancer.

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Prevention of Colorectal Cancer

13

Peter Lance and Patricia Thompson

13.1 Molecular Etiology

In 5 % or fewer of cases, predisposition to CRC is inherited as an autosomal dominant genetic disorder, often with associated predisposition to benign or malignant tumors of other organs (Jasperson et al. 2010). Familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome account for most of the heritable forms of CRC. In FAP, the inherited abnormality (germline) is in the *adenomatous polyposis coli* (*APC*) gene, a potent tumor suppressor gene in the colorectum. In HNPCC patients, the germline mutation occurs in one of the mismatch repair (MMR) genes (*i.e.*, *MLH1*, *MSH2*, *MSH6*, *or PMS2*), whose protein products coordinate the repair of damaged DNA. In carriers of a germline FAP or MMR mutation, colorectal tumorigenesis occurs when an inactivating or silencing mutation (somatic event) occurs in the corresponding wild-type allele of a glandular epithelial cell. This loss of the corresponding wild-type allele follows the two-hit hypothesis of tumorigenesis proposed by Knudsen that in families is accelerated by the presence of one defective germline allele at birth.

Most cases of CRC arise outside the context of the inherited CRC syndromes and are termed sporadic. It is now clear that the molecular pathogenesis of most sporadic CRCs involves the complete loss of *APC* or MMR gene pathway members. In the sporadic setting, approximately 85 % of CRC is derived from the somatic loss of *APC* and 15 % from loss of the MMR pathway. In the sporadic cases, both "hits"

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to the *APC* or MMR alleles are somatic. As in the familial setting, the loss of *APC* or MMR function alone is necessary, but insufficient, to cause malignant transformation. Rather, an initiated cell must acquire sequential malfunction of multiple genes, usually four to six or more, before progression to invasive CRC takes place (Fearon 2011; Hanahan and Weinberg 2011).

Three forms of genetic instability, recognized to underlie the development of the majority of cancers (Lengauer et al. 1998), have been identified in CRC: chromosomal instability (CIN) (Bakhoum and Compton 2012), microsatellite instability (MSI) (Vilar and Gruber 2010), and the CpG island methylator phenotype (CIMP) (Jass 2007). CIN is the tumorigenic mechanism in inherited and sporadic *APC* pathway CRCs, whereas MSI arises as a consequence of loss of MMR. In addition to these mechanisms of genomic deregulation, clusters of cytosine-guanosine pairs—CpG islands—are found in the promoter regions of many genes. CpG islands are prone to age-related epigenetic gene-specific methylation ("hypermethylation") as well as global hypomethylation, which can lead to gene deregulation and is a hallmark of CIMP CRCs (Markowitz and Bertagnolli 2009). Hypermethylation of the *MLH1* MMR gene leading to gene silencing and consequent MSI is the tumorigenic mechanism in the CIMP CRCs that accounts for a major proportion of the sporadic MSI CRCs. The adenomas from which CIMP CRCs develop is characterized by a serrated morphology and known as sessile serrated adenomas (SSAs) (Noffsinger 2009). The histopathological features of SSAs are quite distinct from the much more common CRAs, which are considered the primary precursor for *APC* pathway CRCs.

13.2 Epidemiology

CRC is the second most common cause of death from cancer in the USA. It is estimated that in 2013 there will be 142,820 new cases and 50,830 deaths from the disease (Siegel et al. 2013). The lifetime probability of developing CRC in men and women, respectively, is 5.17 % (1 in 19) and 4.78 % (1 in 21). Although sporadic CRC is uncommon below the age of 50, there is evidence that incidence is increasing in this age group (Edwards et al. 2010). In men and women aged ≥50 years, incidence rates for left-sided CRCs (*i.e.*, splenic flexure, descending colon, sigmoid colon, and rectum) have been decreasing since 1992 (Siegel et al. 2012). Since 2000, incidence rates of right-sided CRCs (*i.e.*, cecum, ascending colon, hepatic flexure, and transverse colon) have been declining annually by 2.6 % in men and 2.3 % in women. CRC rates are highest in African Americans, with intermediate rates observed among Whites, Asians, Pacific Islanders, and Hispanics (Ward et al. 2004). Low incidence rates have traditionally been observed among American Indians and Alaska Natives, though recent evidence suggests this pattern may be changing.

Worldwide, CRC is the fourth most common cancer in men and the third most common cancer in women (Center et al. 2009a, b). From 1998 to 2002, the highest CRC rates were in North America, Oceania, and Europe (including Eastern European countries) according to national cancer registry data. The lowest incidence rates were from registries in Asia, Africa, and South America. From 1998 to

2002, CRC incidence rates per 100,000 ranged from 4.1 in India to 59.1 in the Czech Republic among men and from 3.6 in India to 39.5 among women.

The risk for developing CRC increases with migration from a low-risk to a high-risk area (Potter 1999). This was seen in the 1950s and 1960s for Japanese migrants to the USA and Hawaii (Haenszel and Kurihara 1968). Within one generation, CRC risk among migrants exceeded CRC risk among native Japanese living in Japan. Furthermore, offspring of Japanese migrants developed risks similar to those of US white populations.

Approximately 45 % of CRCs occur in the rectum and sigmoid colon, 15 % in the descending colon, 10 % in the transverse colon, and 30 % in the ascending colon, including the cecum. The proportion of right-sided (proximal) CRCs increases with age.

13.3 Risk Factors

13.3.1 Physical Activity and Obesity

The wide range of CRC incidence rates around the world (Center et al. 2009a, b) is attributed to differences in the prevalence of obesity, physical inactivity, diet, and other lifestyle factors associated with CRC (Popkin 1994; Peto 2001). The evidence that physical activity protects against colon cancer is convincing (Chan and Giovannucci 2010; Colditz and Wei 2012; Colditz et al. 2012), and while physical activity may also protect against rectal cancer, the findings across studies are less consistent. The role of physical inactivity or sedentary behavior in the overall causation of colon cancer has been estimated at 10–20 % (Lee et al. 2012). Current recommendations for adults to avoid the risk of CRC are similar to those recommended to prevent common chronic diseases of aging (*e.g.*, diabetes, cardiovascular) and include engaging in 150 min/week of moderately-intense or 75 min of intense physical activity (Kushi et al. 2012). Walking and leisurely cycling are examples of moderate-intensity activities. Jogging or running, fast cycling, and heavy manual labor are considered vigorous-intensity activities.

Excess body weight or body mass index (BMI) has consistently been associated with increased risk of colon but not rectal cancer (Chan and Giovannucci 2010; Renehan et al. 2012). The association is stronger in men than women, and weight gain in early to middle adulthood appears to have a greater effect on later risk for colon cancer (Renehan et al. 2012). Risk for CRAs is also associated with BMI (Jacobs et al. 2009), and this risk may be stronger for colon than rectal CRAs (Ben et al. 2012). There is great interest currently in the association of risk for both type 2 diabetes and CRC with obesity (Yuhara et al. 2011; Renehan et al. 2012), but the causal mechanisms linking obesity with risk for CRC and other cancers are poorly understood (Taubes 2012). Chronic inflammation, higher risk of mutation from elevated production of DNA damaging free radical generation with chronic positive energy, hyperinsulinemia, insulin-like growth factor, the Warburg effect—tumor cell anaerobic glycolysis—and chronic activation of phosphoinositol-3-kinase (PI3K), which regulates cell sensitivity to insulin, are plausible contributors.

13.3.2 Diet

Diets rich in foods from plant sources, low in saturated fat and red meat, and low in calories and alcohol are considered protective against CRC (Chan and Giovannucci 2010). Conversely, consumption of a Western diet high in calories, animal fat, and refined carbohydrates and a high BMI combine to increase CRC risk (Cross et al. 2010; Aune et al. 2011). Evidence for the hypothesis that consumption of a diet high in fruit- and vegetable-derived fiber lowers risk of CRC has been inconsistent (Chan and Giovannucci 2010). Weak or nonexistent evidence from large prospective cohort studies has been at odds with generally more positive case-control studies. However, in a recent meta-analysis of 25 prospective studies, a high intake of dietary fiber, in particular cereal fiber and whole grains, was associated with a reduced risk of CRC (Aune et al. 2011). Further, individuals who reported consuming legumes (e.g., beans, alfalfa, peas, lentils, soy, and peanuts) as a primary source of dietary fiber had a 38 % reduction in relative risk of CRC. Based on these findings, in 2011 the World Cancer Research Fund/American Institute for Cancer Research (AICR/WCRF) elevated the evidence for the protective action of dietary fiber for CRC to "convincing."

The AICR/WCRF World Cancer Research Fund/American Institute for Cancer Research considers "convincing" the evidence that a high intake of red and processed meat increases the risk of CRC (Anonymous 2007). In a recent meta-analysis, risk of CRC was increased approximately 20 % in the group with the highest consumption of red and processed meats compared to the lowest (Chan et al. 2011). Heterocyclic amines are among putative carcinogens formed during cooking and processing that have been suggested to cause the association between meat consumption and CRC risk (Wang et al. 2012); polymorphisms in the genes encoding certain carcinogen metabolizing enzymes may modify individual risk from this association (Wang et al. 2012).

Evidence from observational studies has long associated a Western, high-fat diet with high levels of fecal secondary bile acids and increased risk of CRC (Hill 1975; Reddy et al. 1980; Degirolamo et al. 2011). Secondary bile acids have multiple carcinogenic effects on human colorectal cells in vitro and in preclinical rodent studies that are of potential significance for the etiology of CRC (Venturi et al. 1997; Pearson et al. 2009; Degirolamo et al. 2011).

A modest inverse association has been consistently demonstrated between dietary intake of calcium and risk of CRC (Martinez and Willett 1998; Cho et al. 2004b; Chan and Giovannucci 2010), and calcium supplementation at a daily dose of 1,200 mg of elemental calcium in a randomized controlled trial modestly, but significantly, reduced CRA development compared to placebo (Baron et al. 1999). In meta-analyses of large cohorts, low levels of vitamin D have been associated with increased risk for CRAs (Wei et al. 2008; Gandini et al. 2011) and CRC (Yin et al. 2009; Gandini et al. 2011).

13.3.3 Lifestyle

An association between high alcohol intake and increased risk of CRC, particularly for men, has been a consistent observation (Giovannucci 2004; Chan and

Giovannucci 2010). An analysis of ~500,000 individuals pooled from eight prospective studies conducted in five countries reported increased risk of CRC of 4 % for women and 13 % for men who consumed ≥30 g/day alcohol (≥2 drinks/day) (Cho et al. 2004a). For those consuming ≥45 g/day, CRC risk was 1.41 (95 % CI, 1.16–1.72) when compared to nondrinkers.

Cigarette smoking was not linked to CRC risk in earlier studies of cancer risk from smoking, most likely because of the lengthy exposure required in colorectal neoplasia (Chan and Giovannucci 2010). However, in more recent meta-analyses, a clear association has emerged. The estimated risk of CRAs was 2.14 (95 % CI, 1.86–2.46) greater in current smokers compared to never-smokers in a pooled analysis of 42 independent studies (Botteri et al. 2008). In an analysis of 106 observational studies, a statistically significant association between cigarette smoking and risk of CRC was found only after 30 years of smoking (Botteri et al. 2008). CRC risk in this group of ever-smokers was 1.25 (95 % CI, 1.14–1.37) compared to never-smokers. In a separate pooled analysis of eight unrelated studies, the odds ratio of CRC in current smokers was 1.26 (95 % CI, 1.11–1.43) compared to never-smokers (Gong et al. 2012). Importantly, in this study, former smokers remained at higher CRC risk, relative to never-smokers, for as long as 25 years after quitting. The excess risk of CRC attributable to smoking was sustained longer for cancers of the distal colon than for cancers located in the proximal colon or rectum after quitting. There was also suggestive evidence for additive interactions of increased CRC risk from cigarette smoking with BMI and low fruit intake.

13.3.4 Family History of Colorectal Adenoma or Cancer

As discussed above, a genetic predisposition to CRC as an autosomal dominant syndrome occurs in certain kindreds with FAP or HNPCC (also known as Lynch Syndrome). In FAP, CRAs numbered in the hundreds or thousands usually develop during the second decade of life. Without prophylactic panproctocolectomy, the likelihood of malignant transformation in carriers approaches 100 %. An attenuated form of FAP (AFAP) has been described (Spirio et al. 1998). AFAP is characterized by lifetime accumulation of 10–20 CRAs, rather than hundreds or thousands, and a later age of onset than with unmodified FAP. Gene penetrance in AFAP carriers is 75–80 %. Diagnosis of CRC in these patients is rare before the age of 25 years, occurs on average at age 45, and has occurred in 70–80 % of those affected by age 70.

In HNPCC patients, the majority of CRCs occur in the proximal colon (75 %) with the average carrier developing no more than tens of CRAs, very rarely more than 100 (Jasperson et al. 2010). The mean age of diagnosis for carriers who meet syndrome criteria is 44 years. Female family members have an 80 % lifetime risk of endometrial cancer with an average age at diagnosis of 46 years. Other common cancers that occur in HNPCC carriers include gastric cancer (average age of diagnosis 56 years), HNPCC-associated ovarian cancer (average age of diagnosis 42.5 years old), and more rarely urinary tract cancers, small bowel cancers, breast cancers, and glioblastoma.

FAP and HNPCC account for less than 5 % of CRC cases, but clustering of CRC in families is common (Jasperson et al. 2010). A heritable component is thought to account for as much as 20–30 % of "sporadic" cases with risk increasing significantly with the number of affected first-degree relatives (parents, siblings, or children). The magnitude of risk depends on the age at diagnosis of the index case (the younger the index case at diagnosis, the greater the risk of CRC in first-degree relatives) and the number of affected relatives.

13.3.5 Inflammatory Bowel Disease

Patients with chronic idiopathic inflammatory intestinal conditions (inflammatory bowel disease or IBD) including ulcerative colitis (UC) and Crohn's disease (Abraham and Cho 2009; Danese and Fiocchi 2011) are at increased risk for CRC. The evidence is stronger for UC than Crohn's colitis (Xie and Itzkowitz 2008; Feagins et al. 2009; Farraye et al. 2010; Raja Ali et al. 2011). The major determinants of CRC risk in patients with UC are the duration and extent of the disease. Risk is not elevated for the first 8–10 years after diagnosis but increases thereafter by 0.5–1.0 % yearly (Munkholm 2003). Patients with pancolitis (total colitis as judged by appearances at colonoscopy) are at greatest risk. This association is corroborated by evidence that the severity of inflammation due to UC is an important component of risk for CRC (Rutter et al. 2004). Primary sclerosing cholangitis complicating UC compounds the risk for CRC.

CRC-related mortality rates in UC patients have been lower in recent reports than in older studies. Several factors likely contribute to the reduction in risk of cancer. The more recent reports are derived from large population-based studies in contrast to the earlier studies that reported selected series of patients with mostly severe disease from specialist referral centers. Some of the lowest reported rates are from countries, such as Denmark, or regions where prophylactic colectomy rates are high. It has also been claimed that prolonged therapy with 5-aminosalicylic acid (5-ASA), used to suppress disease activity, might have chemopreventive benefit against progression to CRC. However, a recent meta-analysis did not support a role for 5-ASA in lower CRC risk in IBD patients (Nguyen et al. 2012). Population-based studies suggest an overall normal life expectancy in patients with UC and a modest reduction of life expectancy in younger patients with Crohn's disease that is not attributable to CRC.

13.4 Screening and Early Detection

The initial rationale for CRC screening was based on the evidence that disease-free survival for CRCs detected at an earlier stage was significantly greater compared to patients diagnosed after symptoms had developed (Niv et al. 2002;

Whynes et al. 2003). This directly reflects greater cure rates in early-stage, localized disease (Stage I and II) compared to more advanced disease with regional or distant metastases. Detection and removal of CRAs decreases the incidence of CRC by as much as 90 % compared to the predicted incidence (Winawer et al. 1993a, b; Zauber et al. 2012). As a likely result of widespread implementation of CRC screening, there has been a steady decline in CRC incidence in the USA for left-sided cancers beginning as early as 1992 and since 2000, a steady decline in right-sided. Thus, the evidence favoring population-wide CRC screening as an effective strategy for the prevention of CRC-associated morbidity and mortality is compelling. A number of modalities are now in clinical practice for CRC screening.

13.4.1 Population for Screening

Individual risk for CRC is commonly categorized as being of "average risk" or "increased risk." Groups considered to be at increased risk include the following: (1) known genetic carriers of FAP or HNPCC genes or a member of a CRC syndrome kindred; (2) individuals with one or more first-degree relatives who have had CRAs or CRCs, especially occurring under the age of 50 years; (3) patients with a history of CRC; and (4) patients with IBD. Future risk of CRC is considered "increased" for: patients having CRAs with "advanced" features, which include large diameter (≥1 cm), villous histology, or the presence of high-grade dysplasia; and patients having ≥3 CRAs of any description. Patients having ≤2 non-advanced CRAs are considered at "average" risk for future CRC.

Population-wide screening programs are primarily aimed at detecting "sporadic" colorectal neoplasia at the earliest stage (asymptomatic CRAs and CRCs) in average-risk individuals without a known familial predisposition to the disease. Three expert bodies, the United States Preventive Services Task Force (USPSTF) (USPSTF 2008), the American Cancer Society (ACS) (Smith et al. 2013), and the English Bowel Cancer Screening Program (BCSP) (Logan et al. 2012), have developed recommendations to guide screening practices. These are outlined in Table 13.1. The relative merits and performance of the screening recommendations and their differences are discussed later in the chapter after a review of the individual screening modalities.

13.4.2 Screening Test Modalities

As noted, there are multiple modalities now in routine clinical use for CRC screening. Three primary categories of test are currently in use (Table 13.1):

- *Stool-Based Tests Include Fecal Occult Blood Tests (FOBT) and Fecal DNA Tests*. FOBTs detect tumor-derived blood that is present in quantities insuffi-

Table 13.1 Recommendations for colorectal cancer screening in average-risk individuals

	United States Preventive Services Task Force (USPSTF)	American Cancer Society (ACS)	UK Bowel Cancer Screening Program (BCSP)
Population	Men and women age 50–75 years	Men and women age ≥50 years	Men and women age 60–69 years
Screening tests	High-sensitivity FOBT Sigmoidoscopy Colonoscopy	FOBT with ≥50 % sensitivity for CRC FIT Stool DNA test Sigmoidoscopy DCBE Colonoscopy CT colonography	gFOBT
Screening test intervals	Annual FOBT Sigmoidoscopy every 5 years + FOBT every 3 years Colonoscopy every 10 years	Annual FOBT or FIT Stool DNA test, interval uncertain Sigmoidoscopy every 5 years alone or combined with FOBT/FIT every 5 years DCBE every 5 years Colonoscopy every 10 years CT colonography every 5 years	Invitation to undergo gFOBT mailed every 2 years followed by FOBT sent 1 week later. Samples returned by individual to central laboratory for developing Individuals age ≥70 years can call toll-free to request a screening kit

cient to change stool color. Traditional guaiac-based tests (gFOBT) detect peroxidase activity of intact hemoglobin or free heme from blood that is produced at the site of the tumor and shed into the stool. The gFOBTs are nonspecific for colorectal neoplasia; oral iron supplements, ingested meat or vitamin C, and peroxidase-containing fruit and vegetables can cause (false) positive results. Fecal immunochemical tests (FIT, also often abbreviated as iFOBT) are newer fecal tests that use antibodies highly specific to human hemoglobin for the detection of tumor-derived blood. The pretest restrictions of diet and medications that are necessary with gFOBTs are not required with FITs. Diagnostic colonoscopy is indicated for all individuals with a positive FOBT.

- *Endoscopic Procedures*. Sigmoidoscopy and colonoscopy are endoscopic procedures that allow direct visual inspection of the rectum and colon. The rectum and

the entire colon to the cecum are accessible with colonoscopy. The rectum and the distal colon are accessible with sigmoidoscopy. Endoscopy of the colon or rectum allows biopsy and polyp resection (polypectomy) as an integral part of endoscopic practice for diagnosis and treatment. Extensive bowel cleansing (or bowel preparation) by oral solution is necessary before performance of colonoscopy for adequate visualization of the bowel. For sigmoidoscopy, administration of an enema immediately prior to the exam is sufficient for bowel preparation. Colonoscopy is usually performed under intravenous conscious or deep sedation (see below), which is not required for sigmoidoscopy. Most CRAs and other polyps can be removed when detected during a screening colonoscopy so that a second procedure is unnecessary. Likewise, many polyps found at screening sigmoidoscopy can be removed as part of that procedure. However, given the higher rate of a polyp in the right colon of patients with distal polyps, a colonoscopy is usually indicated when CRAs are found during sigmoidoscopy.

- *Imaging Procedures*. A number of noninvasive imaging approaches are available to assess the bowel. The majority of these are older methods developed to detect masses on the bowel wall that encroach into the colorectal lumen. For example, in the double contrast barium enema (DCBE), barium is introduced into the rectum in sufficient quantity to coat the surface of the colorectum thinly, which is delineated radiographically by air insufflated into the bowel. Although still approved by the ACS for CRC screening (Smith et al. 2013), inadequate sensitivity of the test for early CRC led the USPSTF and most other authorities to no longer recommend DCBE. Thus, the test is effectively obsolete as a CRC screening tool.
- A more recent development includes thin-section, helical computed tomography (CT) followed by off-line processing. This technique, termed CT colonography (CTC) or virtual colonoscopy, can yield high-resolution, two- and three-dimensional images of the colon. Polyps and cancers are visualized as masses projecting from the bowel wall into the bowel lumen (Fig. 13.1). Intravenous sedation is not required but bowel preparation with laxatives is usually administered before CTC (Friedman et al. 2010). Protocols for performing "prepless" CTC without prior bowel preparation are evolving (Stoop et al. 2012). A common approach is to administer barium orally before CTC to coat fecal material, which is then "subtracted" electronically to reveal underlying masses that project from the bowel wall. Magnetic resonance (MR) could potentially be used instead of CT for noninvasive colonography (Graser et al. 2013) but is not yet in clinical use. MR colonography has the advantage of not subjecting patients to the low doses of radiation, with potential associated cancer risk, that is administered for CT scanning (Brenner et al. 2003; Brenner and Georgsson 2005). With caveats concerning poor sensitivity for smaller polyps (i.e., <1.0 cm) apart (see below), a positive imaging study (DCBE, CTC or MR colonography) serves as the clinical indication for colonoscopy to confirm the presence of a lesion for its removal or to obtain biopsies.

The US Multi-Society Task Force (MSTF) on Colorectal Cancer has proposed classifying CRC screening methods into tests that "mainly detect cancers" and

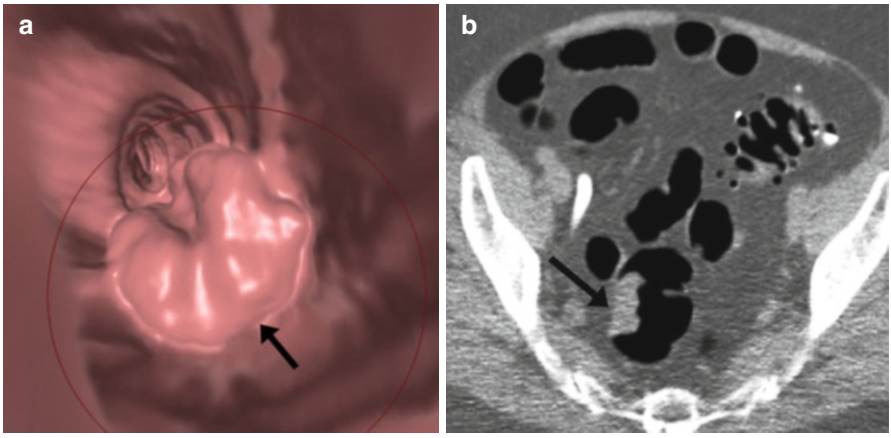

Fig. 13.1 Adenocarcinoma discovered in the sigmoid colon of 64-year-old woman. (**a**) Mass (*arrow*) seen on supine endoluminal fly-through. (**b**) 2D axial supine view shows mass (*arrow*)

those that "detect both early cancer and cancer precursors" (Levin et al. 2008; Lieberman 2013). In this scheme, FOBTs and stool DNA tests mainly detect cancers, even though advocates emphasize detection of a proportion of advanced adenoma cancer precursors by these tests. Endoscopic (sigmoidoscopy and colonoscopy) and noninvasive imaging (CTC and MR colonography) detect both early cancer and cancer precursors (CRAs).

13.4.3 Individual Screening Tests

13.4.3.1 Stool Tests

The gFOBTs have been in clinical use for over 40 years, and in published studies of FOBT, the Beckman Hemoccult (Beckman Coulter, Brea, CA) has been the most widely used product. A few studies have compared gFOBT performance with findings at a contemporaneous colonoscopy or DCBE in the same subjects. Under these circumstances, gFOBT sensitivity for invasive CRC is approximately 30 % (Ahlquist et al. 1993). Thus, gFOBT is negative in two-thirds or more of asymptomatic subjects who undergo a structural evaluation of the rectum and colon shortly after a positive gFOBT. Nonetheless, gFOBT has been shown in randomized controlled trials, with colonoscopy and appropriate treatment for individuals testing positive, to reduce CRC mortality; gFOBT administered at 1- or 2-year intervals, respectively, to 46,551 participants over 18 years of follow-up reduced CRC mortality by 33 and 21 % (Mandel et al. 1999). CRC incidence in the same cohort was reduced by 20 and 17 %, respectively, in the groups tested at 1- and 2-year intervals (Mandel et al. 2000).

Although there have been incremental improvements in sensitivity with modified gFOBTs, such as Hemoccult II and HemoccultSENSA (St John et al. 1993;

Kershenbaum et al. 2013), evidence that FITs (often abbreviated as iFOBT), as a class, are superior to gFOBTs for CRC screening has been accumulating since the 1990s (Allison et al. 2007; Allison 2010). Adoption of FIT has taken longer in the USA than in parts of Europe and Australia because of the strong advocacy for colonoscopy as the "gold standard" tool for CRC screening. In the past few years, however, FIT has steadily gained broader acceptance in many US healthcare delivery systems as the primary tool for CRC screening. Accordingly, the major current targets for CRC screening are advanced CRAs and CRCs, together termed advanced colorectal neoplasms (ACRN). Detection rates for ACRN are increasingly used to compare the efficacies of diffent CRC screening tools.

The evidence that FIT has superior sensitivity and specificity to gFOBT for detection of ACRN, and greater patient acceptability, is clear. For example, in recent studies, FIT sensitivity for CRC and ACRN is estimated at 84–88 % and 38–43 %, respectively (Allison et al. 2007; Park et al. 2010; de Wijkerslooth et al. 2012). However, a number of FITs with varying performance characteristics are available commercially and the optimal methodology FIT remains to be settled (Levin 2011; Allison et al. 2012). For example, the specific antibody to human hemoglobin (Hb) varies between FIT products with some tests qualitative in nature (positive or negative) and others quantitative (absolute Hb concentration). At present only qualitative FITs are approved for clinical use in the USA. In addition, commercially available tests differ in the number of stook to be sampled ranging from one to three separately passed stools. The OC FIT-CHEK® (Polymedco, Cortlandt Manor, NY) and MagStream HT (Fujirebio, Inc, Tokyo, Japan) are approved for use with one stool sample but two separate consecutive stools have often been sampled and tested in the protocols of studies reporting results with these tests. Two- and three-day kits are available for Hemoccult ITC (Beckman Coulter, Brea, CA). Qualitative FITs use a defined hemoglobin (Hb) concentration cutoff for positive (above the cutoff) and negative (below the cutoff) test results. Different FITs cover varying cutoff concentrations (Allison et al. 2012), characteristically in the range of 50–100 ng Hb/mL buffer (de Wijkerslooth et al. 2012). Other aspects in which FITs standardization is needed include an Hb calibrant that can be related to an international reference standard, and the amount of feces collected and volume of buffer in collection devices (Allison et al. 2012). Even with progressive refinement and standardization, FIT will remain a nonspecific test for colorectal neoplasms.

Fecal DNA testing to detect shed tumor DNA is an emerging, stool-based strategy intended to enhance the sensitivity and specificity of stool-based screening. The observation that cellular material from colorectal neoplasms is shed into the fecal stream has promoted considerable effort toward detecting tumor DNA in the feces of asymptomatic individuals. It is argued that fecal DNA detection could be developed as a specific CRC screening test with the proof of concept established (Ahlquist et al. 2000; Osborn and Ahlquist 2005). However, initial promise of fecal tumor DNA detection has not yet translated into a routine screening test that can approach the sensitivity and specificity or compete with the cost effectiveness of FITs (Ahlquist et al. 2008, 2012). Although approved in principle by MSTF (Levin et al.

2008) and ACS (Smith et al. 2013), but not USPSTF (USPSTF 2008), no fecal DNA test is currently available commercially.

13.4.3.2 Endoscopic Screening

Sigmoidoscopy: Case-control studies indicate that mortality from CRCs within reach of the sigmoidoscope may be reduced by 60–80 % as a result of therapy implemented for findings at sigmoidoscopy (Newcomb et al. 1992; Selby et al. 1992). The disadvantage of screening sigmoidoscopy is failure to identify right-sided (or proximal) CRAs and CRCs, which are accessible only with the colonoscope. A proportion of right-sided lesions are subsequently identified at colonoscopies performed because of sigmoidoscopy of left-sided (distal) CRAs and CRCs found at flexible sigmoidoscopy. The effect of once-only screening sigmoidoscopy was investigated in a UK randomized controlled trial (RCT) conducted in 170,432 men and women between the ages of 55 and 64 years (Atkin et al. 2010). After a median follow-up of 11.2 years, CRC incidence was reduced by 33 % (hazard ratio (HR) = 0.67, 95 % CI 0.60–0.76) and mortality by 43 % (HR = 0.57, 95 % CI 0.45–0.72) in individuals randomized to sigmoidoscopy vs. control (usual care). Incidence of distal CRC was reduced by 50 % (HR = 0.50, 95 % CI 0.42–0.59).

Benefits of screening sigmoidoscopy were also reported in the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Trial (Schoen et al. 2012), in which 154,900 men and women between the ages of 55 and 74 years were randomized to sigmoidoscopy or to usual care. After a median follow-up of 11.9 years, CRC incidence was reduced by 21 % (relative risk (RR) = 0.79, 95 % CI 0.72–0.85) and mortality by 26 % (RR = 0.74, 95 % CI 0.63–0.87). Mortality from distal CRC was reduced by 50 % (RR = 0.50, 95 % CI 0.38–0.64). A meta-analysis of five RCTs, including the UK trial described above, found 18 and 28 % reductions, respectively, in the incidence and mortality of CRC (Elmunzer et al. 2012). The efficacy estimate—the amount of benefit for those who actually adhered to the recommended treatment—suggested that sigmoidoscopy reduced overall CRC-related mortality by 50 %.

Colonoscopy: In contrast to robust RCT evidence to support the benefits of sigmoidoscopy, no prospective RCTs investigating the effect of screening colonoscopy on CRC incidence and mortality have been reported. But indirect evidence has traditionally been advanced suggesting substantial benefit from colonoscopy. Original estimates from the National Polyp Study (NPS) were that up to 90 % of CRCs could be prevented by colonoscopic polypectomy (Winawer et al. 1993a, b); after long-term follow-up of the NPS cohort for a median of 15.8 years, mortality from CRC had been reduced by an estimated 53 % compared to expected CRC mortality in the general population (Zauber et al. 2012). In a study of cost-effectiveness using models based on multiple assumptions, it was estimated that colonoscopic screening every 10 years would reduce CRC incidence and mortality, respectively, by 58 and 61 % (Frazier et al. 2000). However, evidence from two lines of investigation has been used to challenge earlier assumptions about the efficacy of screening colonoscopy: (1) interval CRCs developing in patients enrolled in colonoscopy surveillance protocols and (2) the lack of protection in some studies from proximal CRC among individuals who previously underwent colonoscopy.

Clinical trials in patients with CRAs who undergo clearing colonoscopy report CRC rates of between 3 and 9 per 1,000 persons within 3–6 years after a colonoscopy (Pohl and Robertson 2010). And observational studies using administrative data have found that between 5 and 9 % of patients diagnosed with CRC underwent colonoscopy within the previous 6–36 months (Pohl and Robertson 2010). Several studies have shown that colonoscopy is less effective for preventing proximal than distal neoplasms (Brenner et al. 2010; Singh et al. 2010). In a population-based case-control study from Ontario, Canada, in 10,292 cases and 51,460 controls, complete colonoscopy was strongly associated with fewer deaths from distal CRC (odds ratio 0.33, 95 % CI 0.28–0.39) but not from proximal CRC (0.99, 0.86–1.14) (Baxter et al. 2009). It should be noted, however, that in some studies screening colonoscopy has been equally effective for preventing proximal and distal CRCs (Doubeni et al. 2013).

Proposed explanations for the inadequacies of colonoscopy in CRC prevention, i.e., interval CRCs after a clearing colonoscopy and poor protection from proximal CRC after total colonoscopy in some studies, are in two broad categories: technical and biology-related factors (Pohl and Robertson 2010; Sanduleanu et al. 2012). In the technical category, lesions, particularly ACRNs, may simply have been missed or incompletely removed at a preceding colonoscopy only to present later as an interval CRC; lesions may be missed through being covered by fecal material, obscured by bowel folds, or because intubation of the entire colon to the cecum was not achieved.

Assessment of the accuracy of optical colonoscopy is problematic, because it is considered the criterion ("gold") standard for other CRC screening modalities. To tackle this problem, the miss rate of colonoscopy can be determined from findings at same-day, back-to-back, "tandem" colonoscopies performed by different endoscopists (Rex et al. 1997). In a pooled analysis of six tandem colonoscopy studies with a total of 465 patients, the miss rate for polyps of any size was 22 % (van Rijn et al. 2006). Miss rates for CRAs ≥10, 5–10 and <5 mm in size, respectively, were 2, 13, and 26 %.

In the biology-related category of factors that might be responsible for colonoscopic inadequacies morphologic and molecular classification has led to recognition of discrete colorectal tumor subtypes discussed above in Sect. 13.1. This includes CRCs developing through defects in MMR that are located predominantly in the proximal colon and that are thought to undergo a more rapid transition from premalignant neoplasia to cancer (a few years) compared to the more classic adenoma-carcinoma (APC loss) sequence (a few decades). The non-polypoid (flat) CRNs (Soetikno et al. 2008) that include the serrated adenomas and the rare, depressed lesions (Noffsinger 2009; Rex et al. 2012) are in this category.

The multiple reports challenging the effectiveness of colonoscopy for preventing subsequent CRC have elicited a concerted effort to improve the quality of colonoscopy (Rex 2011). Standardization of endoscopy reporting is advocated (Korman 2012). Adenoma detection rate (ADR), the proportion of patients undergoing first-time screening colonoscopy in whom a CRA or CRC is found (Corley et al. 2011), is an independent predictor of the risk of interval CRC after screening colonoscopy

(Kaminski et al. 2010). It is recommended that individuals performing colonoscopy should achieve ADR rates in men and women respectively aged 50 years or more undergoing screening colonoscopy of at least 25 and 15 % women, (Rex et al. 2006). Colonoscopists should achieve cecal intubation in at least 90 % of their cases.

In addition to issues of sensitivity and specificity, cost-effectiveness and complications are important considerations when comparing colonoscopy to other CRC screening tools. In the USA cost-effectiveness of colonoscopy is under increasing and not always favorable scrutiny (Austin et al. 2012). The overall cost of the procedure in the USA. is increased by widespread routine use of deep sedation, usually in the form of propofol administered by anesthesiology personnel (Cooper et al. 2013). The most serious complications of colonoscopy arise from sedation administered for the procedure, hemorrhage (usually following polypectomy), and bowel perforation, which necessitates emergency abdominal surgery and can very rarely be fatal. Perforation rates due to colonoscopy vary quite widely. In the Veterans Administration Cooperative Study of 3,196 patients undergoing screening colonoscopy, there were no perforations (Nelson et al. 2002). In a 5 % sample of Medicare beneficiaries from regions of the USA covered by the Surveillance, Epidemiology, and End Results (SEER) Program, there were 77 reported perforations after 39,286 colonoscopies for a rate of 1.96 in every 1,000 procedures (Gatto et al. 2003). In a prospective study of 9,223 colonoscopies performed over a 4-month period in three regions of the UK National Health Service, the perforation rate was 1.30 in every 1,000 procedures (Bowles et al. 2004). In a recent population-based German study, the incidence of perforation was 0.8 per 1,000 screening colonoscopies (Stock et al. 2013).

13.4.3.3 Computed Tomographic Colonography

Conflicting results were reported in early studies that compared optical colonoscopy and computed tomographic colonography (CTC). For example, Pickhardt et al. reported almost identical sensitivities of around 90 % for detection of CRAs ≥6 mm in diameter by CTC and optical colonoscopy (Pickhardt et al. 2003). In contract, Cotton et al. reported a sensitivity of only 39 % for detection of CRAs ≥6 mm in diameter by CTC compared to 99 % sensitivity for the same lesions by optical colonoscopy (Cotton et al. 2004).

Various explanations have been proposed for these discrepant results. Patients in the Pickhardt study received double the usual volume of sodium phosphate for bowel preparation. This group used superior computer software for a virtual "fly-through" of the colon that was not available to most other groups at the time. The sensitivity of optical colonoscopy achieved by the Cotton group was superior to most published reports and almost certainly not matched in routine daily practice. Acknowledged disadvantages of virtual colonoscopy are the bowel preparation that is required, insufflation of the colon, which is uncomfortable, and the need for a second procedure, optical colonoscopy, to biopsy or remove lesions identified at a positive virtual procedure. Cancer risks associated with the radiation exposure from CTC mentioned above (Brenner et al. 2003; Brenner and Georgsson 2005; Smith-Bindman 2010) are small.

Since the earlier studies, performance characteristics of CTC and optical colonoscopy have generally been similar in more recent comparative studies. For example, in a series of patients at increased risk for CRC, CTC compared with optical colonoscopy resulted in a negative predictive value of 96.3 % overall (Regge et al. 2009). When limited to FOBT-positive individuals, the negative predictive value was 84.9 %. An RCT of CTC and optical colonoscopy was conducted in almost 9,000 individuals in the Netherlands (Pickhardt 2012; Stoop et al. 2012). Of note, there was a significant 55 % improvement in screening participation with CTC over optical colonoscopy. The diagnostic yield for ACRNs per 100 persons invited to participate was similar for both tests. CTC could be a cost-effective option for CRC screening if the rate of reimbursement per CTC scan is substantially less than that for colonoscopy or if a large proportion of colonoscopy-screened persons (majority are negative) were to undergo CTC screening (Knudsen et al. 2010). An advantage of CTC over optical colonoscopy is that the scans can be performed locally, for instance in medically underserved communities that lack capability for screening colonoscopy, and the images can be transferred for expert interpretation at a remote site (Friedman et al. 2010). At present, it is agreed that patients with lesions ≥6 mm in diameter on CTC should be referred for optical colonoscopy (Pickhardt et al. 2003; Johnson et al. 2008; Stoop et al. 2012). Simulation modeling is being used to explore whether the referral threshold for optical colonoscopy could be raised to patients with polyps of ≥10 mm size, combined with a "watchful waiting" protocol for those with 6–9 mm polyps (Hassan and Pickhardt 2013).

13.4.4 Screening Recommendations in Individuals at Average Risk

Given the multiple screening modalities in widespread use, it is not surprising that multiple protocols for screening in the "average-risk" setting are recommended by different organizations (Table 13.1). There are striking differences between the recommended protocols, including the age range for the target population and other guidelines. An important example is the use of gFOBT as the only modality recommended by the UK BCSP even though the strongest RCT evidence for sigmoidoscopy screening comes from the UK. High-sensitivity gFOBTs are still included among acceptable modalities by USPSTF and ACS, despite the clear superiority of FIT. ACS still lists stool DNA, although no such test is commercially available at present. DCBE is also included in the ACS recommendations although this modality is obsolete as a screening tool. The Council of the European Union recommends only FOBT (von Karsa et al. 2012) but "calls for introduction of new cancer screening tests in routine healthcare only after they have been evaluated in RCTs." The recommendation for using only FOBT is unclear in light of the RCT evidence for sigmoidoscopy screening and the fact that colonoscopy screening is widely performed at the population level in Germany (Brenner et al. 2009). Against this background of discord among authorities issuing CRC

screening guidelines, the ACS has recently recommended adoption of much greater stringency in the processes for the development of screening guidelines (Brawley et al. 2011).

Because of the overwhelming evidence supporting the efficacy of CRC screening, USPSTF gives its Grade A highest level of recommendation (USPSTF) for implementation of population-wide CRC screening (USPSTF 2008). Prevalence of CRC screening by any modality in the USA for all adults combined, African Americans, Hispanics, and uninsured individuals, respectively, was reported recently as 53.2, 48.9, 37.2, and 19.5 % (Smith et al. 2011). The percentage of US adults aged 50–64 years who never had a screening colonoscopy among those with private insurance, public-only insurance, or no insurance, respectively, was 54.1, 60.6, and 77.1 % (Mitka 2008). Regrettably, poor uptake of CRC screening overall in the USA and in traditionally underserved populations is in sharp contrast to the clearly established benefit that compliance with guidelines would produce for reducing morbidity and mortality due to CRC. To remedy this situation in which multiple guidelines are available the American College of Physicians believes that "it is more valuable to provide clinicians with a rigorous review of the available guidelines rather than develop a new guideline on the same topic."(Qaseem et al. 2012) The greater acceptability of CTC over optical colonoscopy mentioned above (Stoop et al. 2012) may offer a solution to enhance uptake in otherwise hard to reach populations. Further, there is compelling evidence that a centralized, electronic health record-linked, mailed CRC screening program can as much as double the number of persons being current for screening (Green et al. 2013).

13.4.5 Screening and Surveillance Recommendations in Individuals at High Risk

13.4.5.1 History of CRA or CRC

Management of patients who have had one or more CRAs removed at colonoscopy is based on long-term follow-up studies of post-polypectomy populations (Lieberman et al. 2012). Patients who present with three or more CRAs or an advanced CRA (size ≥1.0 cm, villous histology, or high-grade dysplasia) are recommended to undergo a surveillance colonoscopy at 3 years (Martinez et al. 2009). Patients with one or two, small tubular, or "non-advanced" CRAs are recommended to have a follow-up colonoscopy at 5 years. If total colonoscopy was not performed prior to resection of a cancer, patients should have the procedure 6 months after their surgical resection of a CRC. The presence of synchronous CRAs in patients with CRC is high and in the absence of removal increases the risk for a second primary CRC. For those who had a preoperative colonoscopy, a surveillance colonoscopy should be performed 3 years after surgery. Depending on the number and size of serrated or flat lesions, the recommended surveillance interval is 1–5 years (Lieberman et al. 2012).

13.5 Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)

As noted above, patients with a history of Crohn's disease (CD) or ulcerative colitis (UC) are at increased risk for CRC. Detailed guidelines, summarized here, are available for the management of colorectal neoplasia in patients with inflammatory bowel disease (IBD) (Farraye et al. 2010; Mowat et al. 2011). Risk of CRC is determined by the extent (how much of the rectum and colon) and duration of CD or UC. Depending on disease extent, patients have up to a 20 % risk of developing CRC after 30 years of disease. However, because UC and CD are relatively uncommon in the general population, antecedent CD or UC are responsible for less than 1 % of all cases of CRC. For similar extent and duration of disease, CRC risk is equivalent in CD and UC. Patients with IBD confined to the rectum and distal colon (ulcerative proctitis and ulcerative proctosigmoiditis) are not considered to be at increased risk for IBD-related CRC.

All patients with UC or CD colitis, regardless of the extent of their disease at initial diagnosis, should undergo colonoscopy no later than 8–10 years after initial diagnosis. Objectives are to remove polyps, sample elevated lesions (the dysplasia-associated lesion or mass, DALM), and obtain multiple biopsies over the full length of the colon. Biopsies should be read by pathologists with specialist expertise in gastroenterology for the presence and degree of dysplasia, which is used as an index of risk for future invasive cancer. The purpose of surveillance is to offer and perform prophylactic surgery before frank malignancy, which is often multifocal, develops. There is reasonable, though not conclusive, evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis. Optimal care for these patients can best be provided by a multidisciplinary team of experts. High-grade dysplasia is usually an indication for panproctocolectomy, which may also be indicated for low-grade dysplasia and for patients with UC or CD under other circumstances. Colonoscopic surveillance intervals are determined by the presence of DALMs and degree of any dysplasia, but even if there is no dysplasia, repeat colonoscopy for patients with extensive colitis is indicated in 1–2 years.

13.6 Family History of Colorectal Cancer

Estimates from family and twin studies are that heredity contributes to approximately 30 % of all CRC cases (Lichtenstein et al. 2000; Grady 2003; Jasperson et al. 2010). Approximately 5 % of cases arise from high-penetrance inherited mutations and have well characterized clinical features; FAP and Lynch syndrome (HNPCC) account for most of these cases. The genetic etiology of the remaining 20–30 % of CRCs with a heritable component is less well understood and likely manifest as a consequence of gene × environment interactions. However, consideration of family history is an important factor in when to initiate screening and how often to screen.

13.6.1 FAP and APC Families and Mutation Carriers

Clinical testing for *APC* germline mutations is widely available but should only be offered in conjunction with genetic counseling by qualified individuals. When a family's *APC* mutation has been identified, children born to the family can be tested for that mutation. If negative, they will not develop FAP and need not undergo surveillance sigmoidoscopy. Annual sigmoidoscopy starting at age 10–12 years to look for the first signs of polyps is recommended for any child of a parent with FAP unless genetically tested as negative (Grady 2003; Jasperson et al. 2010).

Genetic testing is also available for HNPCC families for which the MMR gene mutation has been identified. If positive, the critical importance of surveillance for gastrointestinal cancers is emphasized to the patient and family; the risk and recommended surveillance for endometrial, ovarian, and other extraintestinal cancers associated with HNPCC patients is also emphasized. Colonoscopy is recommended every 1–2 years beginning at age 25 years for HNPCC family members. For HNPCC family members testing negative for the mutation, screening should follow those of the average-risk population. Please refer to Chap. 5 for a complete discussion of genetic testing and the hereditary risk of cancer.

13.6.2 First-Degree Relatives of People with CRAs or CRCs

First-degree relatives of CRC patients are at increased risk for ACRNs (Johns and Houlston 2001; Butterworth et al. 2006; Ng et al. 2013), and risk for CRC may be increased in individuals who have first-degree relatives with CRAs (Imperiale and Ransohoff 2012). Persons with a first-degree relative with CRC or CRAs diagnosed before age 60 years or two first-degree relatives diagnosed with CRC at any age should have screening colonoscopy starting at age 40 years or 10 years younger than the earliest diagnosis in their family, whichever comes first (Winawer et al. 2003). Colonoscopy should be repeated every 5 years. People with a first-degree relative with CRC or CRAs diagnosed at the age of 60 years or older or two second-degree relatives with CRC should be screened as average-risk individuals, but from the age of 40 rather than 50 years.

13.7 Chemoprevention

Chemoprevention, which is defined as the use of natural agents or synthetic drugs to halt or reverse the carcinogenesis process before the emergence of invasive cancer (Sporn et al. 1976), has been advocated as a potential adjunct to screening for reducing CRC morbidity and mortality. However, despite significant effort over the past three decades, no chemopreventive intervention for CRC has entered routine clinical practice (Lance 2008). Agents considered for potential chemopreventive activity against CRC fall into three categories: macronutrients, micronutrients, and drugs.

Up to 50 % of individuals from whom CRAs have been removed will develop ≥1 new (metachronous) CRAs within 3–5 years (Winawer et al. 1993a, b; Alberts et al. 2000; Schatzkin et al. 2000). On this basis, the prevention of the metachronous (recurrent) CRA in this patient population has been used as a surrogate to assess the efficacy of agents to prevent CRC in RCT. RCTs that have reported a statistically significant reduction in CRA recurrence are summarized in Table 13.2. Findings across the three categories of intervention types are described below.

13.7.1 Macronutrients

Randomized controlled trials were conducted of wheat bran fiber supplements (13.5 g vs. 2 g/day) (Alberts et al. 2000) and consumption of a diet low in animal fat and high in fiber, fruit, and vegetables (Schatzkin et al. 2000) for 3–5 years for CRA prevention. Adherence to the interventions in both trials was high and the outcome in both interventions was negative.

13.7.2 Micronutrients

13.7.2.1 Calcium and Vitamin D

Calcium is an important micronutrient that controls a large number of intracellular processes with antineoplastic potential. Dietary calcium also binds to bile and fatty acids with the effect of curbing intestinal cell proliferation. Calcium supplements (Calcium carbonate 3 g daily, equivalent to 1,200 mg of elemental Ca^{2+}) reduced CRA recurrence in an RCT by 19 % compared to placebo (Table 13.2, Baron et al. 1999). It was shown in the same trial that among participants with baseline 25-(OH) vitamin D levels at or below the median, calcium supplementation was not associated with CRA recurrence, whereas among those with levels above the median, calcium supplementation was associated with a reduced risk ratio (RR = 0.71, 95 % CI 0.57–0.89) (Grau et al. 2003). Thus, calcium supplementation and vitamin D status appear to act together. An ongoing Phase III trial of vitamin D and calcium is expected to report in the next year and will help establish the requirement for both agents to reduce the risk of CRA recurrence.

13.7.2.2 Folate

In its chemically reduced form of tetrahydrofolate, folate is essential for genomic integrity. Folate plays important antineoplastic roles in the control of DNA methylation and DNA synthesis and maintenance. Folate consumption by participants in the Nurses' Health Study cohort was associated with a significant reduction in risk of CRC. For those with consumption in the highest quintile (more than 400 μg/day), the relative risk for developing CRC was 0.25 compared to those in the lowest quintile of intake (200 μg/day or less) after 15 years of use (Giovannucci et al. 1998). Further, the greatest protection of high folate consumption against developing CRC was in participants with a family history of the CRC (Fuchs et al. 2002).

Table 13.2 Randomized CRA recurrence trials with positive outcomes

Agent	Group	Reduction in CRA recurrence vs. placebo (%)
Calcium carbonate 3 g daily (1,200 mg elemental Ca^{2+})	Baron et al. (1999)	15
Aspirin 81 mg daily	Baron et al. (2003)	19 (any CRA) 41 (advanced CRA)
Aspirin 325 mg daily	Sandler et al. (2003)	35
Soluble aspirin 160 or 300 mg daily	Benamouzig et al. (2003)	27
Celecoxib 400 mg daily	Arber et al. (2006)	36 (any CRA) 51 (advanced CRA)
Celecoxib 200 mg twice daily or 400 mg twice daily	Bertagnolli et al. (2006)	33 (200 mg twice daily) 45 (400 mg twice daily)
Rofecoxib 25 mg daily	Baron et al. (2006)	24
Aspirin 300 mg daily + folic acid 0.5 mg daily	Logan et al. (2008)	21 (any adenoma) 37 (advanced CRA) No effect from folic acid
Difluoromethylornithine 500 mg daily + sulindac 150 mg once daily	Meyskens et al. (2008)	70 (any CRA) 90 (advanced CRA)

Based on the epidemiologic evidence that folate may have antineoplastic effects in the colorectum, an RCT of folic acid (1 mg daily) for CRA prevention was conducted (Cole et al. 2007). The folic acid intervention did not reduce development of CRA. In contrast, there was evidence for an increased risk of developing advanced CRAs. A possible explanation for the apparently paradoxical findings from observational and CTC studies is that folate might prevent the initiation of colorectal neoplasia but enhance progression of already initiated CRAs; such CRAs might have escaped detection at trial-qualifying clearing colonoscopies because of their small, even microscopic size. Concern has been raised that mandatory dietary folic acid supplementation, introduced in the USA to prevent fetal neural tube defects by elevating maternal peri-conceptional folate levels, might enhance the progression of already existing, undiagnosed premalignant (e.g., CRAs) and malignant lesions (Kim 2006).

In the ukCAP trial (Table 13.2, Logan et al.), participants were randomized to daily doses of aspirin 300 mg and folic acid 0.5 mg (a lower dose than the 1 mg dose in the trial described above) (Lance 2008; Logan et al. 2008). CRA recurrence was significantly reduced by aspirin but folic acid supplementation had no effect on CRA recurrence. The authors suggest that folic acid supplementation in the ukCAP trial, conducted in a country that does not have dietary fortification, might be equivalent to dietary fortification of folic acid in the USA. Although confirmatory evidence is required, it is reassuring that folic acid supplementation at a dose of 0.5 mg, in contrast to a dose at the 1 mg level (Cole et al. 2007), did not increase risk for advanced CRA.

13.7.2.3 Selenium

Selenium is an essential micronutrient, which is incorporated into at least 30 selenoproteins (Kryukov et al. 2003) after absorption. On the basis of epidemiologic data suggesting that high selenium levels protect against nonmelanoma skin cancer, a randomized trial of selenium supplementation in the form of brewer's yeast was conducted in patients at high risk for this cancer (Clark et al. 1996). The incidence of nonmelanoma skin cancer, the primary endpoint of the trial, was not reduced, but significant results were observed for several secondary cancer endpoints (Duffield-Lillico et al. 2002). These included reduction in total cancer mortality of 41 % and colon cancer incidence of 54 %. A Phase III trial of selenium supplementation, as selenized yeast, with CRA recurrence as the primary endpoint is now in progress at the University Arizona Cancer Center and will be unblinded in early 2014 (Thompson et al. 2012).

13.7.3 Synthetic Drugs

13.7.3.1 Aspirin and Other Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

There is extensive epidemiological, clinical, and experimental evidence that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) reduce CRC risk and may reduce mortality from the disease by as much as 40–50 % (Chan et al. 2012; Thun et al. 2012). Older studies suggest that high doses of aspirin, with associated substantial gastrointestinal and bleeding toxicities (Cryer and Kimmey 1998; Derry and Loke 2000; Cryer 2002), were required for chemopreventive benefit. In the Nurses' Health Study, the greatest effect was evident at a weekly total dosage of at least 14 standard-dose tablets (Chan et al. 2004), which is much higher than is recommended for cardiovascular prophylaxis. Similar dose–response relationships were found among regular short-term users (5 years of less) and long-term users (more than 5 years). However, in a recent meta-analysis of cardiovascular prevention trials, low-dose aspirin reduced CRC risk and mortality, respectively, by 24 and 35 % (Rothwell et al. 2010). The chemopreventive benefits were seen at a daily dose of 75 mg and incremental benefits were not seen with higher doses. Further studies are required for definitive determination of the aspirin dose and duration of administration required for worthwhile prevention of CRC with an acceptable level of toxicity.

Although most of what is known about the colorectal chemopreventive benefits of NSAIDs concerns aspirin, nonaspirin NSAIDs also have antineoplastic effects. For example, the nonselective NSAID sulindac reduced CRA burden in patients with FAP (Cruz-Correa et al. 2002) as did the selective cyclooxygenase (COX)-2 inhibitor celecoxib (Steinbach et al. 2000).

RCTs of aspirin for CRA prevention with positive outcomes are summarized in Table 13.2 (Baron et al. 2003; Benamouzig et al. 2003; Sandler et al. 2003; Logan et al. 2008). In a meta-analysis, the pooled risk ratio of any CRA for any dose of

aspirin vs. placebo was 0.83 (95 % CI, 0.72–0.96) (Cole et al. 2009). For any advanced CRA, the pooled risk ratio was 0.72 (95 % CI, 0.57–0.90). The selective COX-2 inhibitors (coxibs) celecoxib (Arber et al. 2006; Bertagnolli et al. 2006) and rofecoxib (Baron et al. 2006) reduced CRA risk by 24–45 %, but an associated increased risk of serious cardiovascular events with both agents has prohibited the subsequent clinical use of coxibs for chemoprevention (Bresalier et al. 2005; Solomon et al. 2005, 2008; Bertagnolli et al. 2006).

The first positive RCT of an NSAID with a CRC rather than a CRA endpoint was published recently (CAPP2) (Burn et al. 2011). A total of 861 HNPCC patients were randomized to aspirin 600 mg daily or placebo. For participants completing 2 years of intervention, the hazard ratio for developing CRC was 0.41 (CI, 0.19–0.86) compared to placebo. Further studies are needed to develop the optimum dose and duration of aspirin treatment for HNPCC patients.

13.7.3.2 Difluoromethylornithine (DFMO)

An evolving approach to chemoprevention is to combine modest doses of agents targeting different carcinogenesis pathways to optimize efficacy and minimize toxicity. DFMO and sulindac interact additively to prevent the growth and viability of human colon cancer cells in vitro (Lawson et al. 2000). The combination of DFMO 500 mg and sulindac 150 mg daily reduced recurrence of any CRA and advanced CRAs, respectively, by 70 and 90 % (Meyskens et al. 1998). Only the combination of DFMO and sulindac was compared to placebo in this trial and so it is not known whether either agent alone would have had a comparable effect. An actively accruing trial conducted by the Southwest Oncology Group in patients at increased risk (Stage 0–III CRC patients) is ongoing to compare the two agents given alone to the combination in a placebo-controlled, randomized trial. Results from this trial may be available in the next 5–8 years depending on the rate of accrual.

13.7.3.3 Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used in the primary and secondary prevention of cardiovascular disease, and there is some evidence that they might also have chemopreventive effects against CRC and other cancers (Demierre et al. 2005) though largely negative associations has dampened enthusiasm for a role for statins in the chemoprevention of CRC (Lochhead and Chan 2013) with more recent interest in metformin, a commonly prescribed glucose-lowering drug with potent antitumor activity entering a number of cancer treatment and prevention trials (Emami Riedmaier et al. 2013).

13.7.3.4 Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a minor natural component of the human bile acid pool. In synthetic form it is widely used for the treatment of primary bile duct disorders (Beuers 2006). Patients with UC are at risk for a bile duct disorder, primary sclerosing cholangitis (PSC), for which UDCA is often administered. There is some evidence that UDCA protects against the development of colorectal dysplasia and

CRC in patients with PSC (Tung et al. 2001; Pardi et al. 2003). With this background, an RCT of UDCA for CRA prevention was conducted (Alberts et al. 2005). The primary trial outcome, CRA recurrence, was negative, but in a planned secondary analysis, there was a significant reduction in recurrence of CRAs with high-grade dysplasia, a category of CRA at high risk for progression to CRC. In a further secondary analysis of the effect of sex, there was a significant 38 % reduction in recurrence of advanced CRAs in men but not women (Thompson et al. 2009).

13.7.3.5 Current Status of Chemoprevention for CRC

As noted, despite much effort over almost three decades, no chemopreventive intervention for CRC has yet entered routine clinical practice. Aspirin is the best validated agent for primary or secondary prevention of colorectal neoplasia, yet the USPSTF withheld approval of using aspirin for primary prevention of CRC (Dube et al. 2007). Funding agencies are unlikely to continue supporting chemoprevention studies indefinitely, unless safe, cost-effective agents and strategies can be identified. A framework for future chemoprevention studies and their implementation is depicted in Fig. 13.2. This framework assumes that CRC screening has been implemented according to current guidelines and that only a minority of individuals will be at sufficiently increased risk for CRC to merit long-term chemoprevention. The goal is to develop new chemopreventive strategies for these high-risk individuals that will be sufficiently effective for the frequency of colonoscopic surveillance to be relaxed.

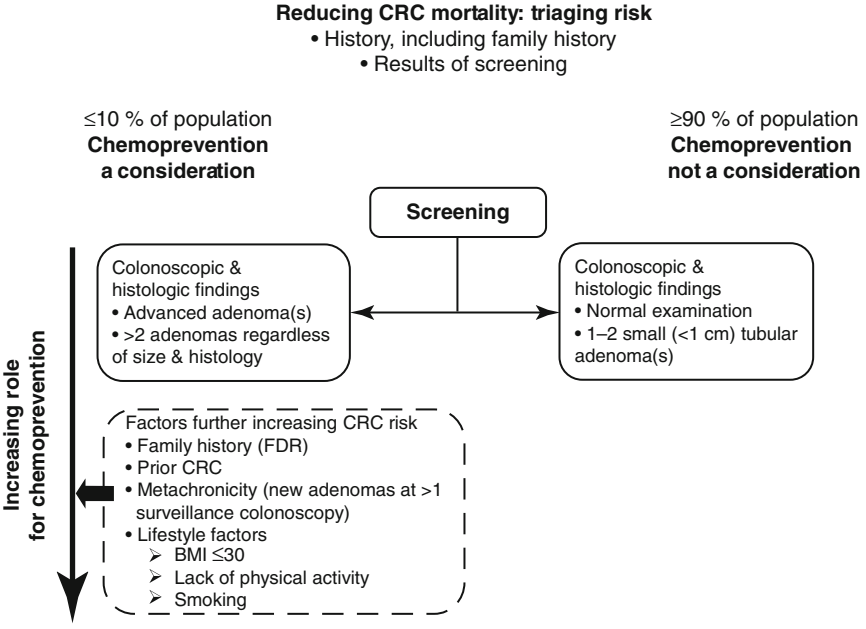

Fig. 13.2 Framework for selection of candidates for CRC chemoprevention

13.8 Future Perspective

Screening and early detection for CRA and CRC has resulted in substantial reductions in morbidity and mortality due to CRC. This success is tempered by some disappointment in lower-than-expected uptake of screening and increasing concerns over the cost/benefit ratio of screening average-risk individuals with colonoscopy. Recent support for lower cost fecal-based screening, particularly with FIT, and greater acceptability and performance of CTC are expected to influence screening practices in the USA and other countries in the next decade. For risk, an immediate concern is the association between obesity, diabetes, and CRC, risk factors that are increasing in their prevalence worldwide and at younger and younger ages. It is likely that these factors may result in an increasing need for screening and early detection to reduce CRC morbidity and mortality in the USA in coming decades. Screening is an area where we anticipate the substantial changes over the next 5–10 years. Evaluation of the comparative effectiveness of the multiple screening modalities and their respective costs is likely to change clinical practice. Given the observation that as much as half of the population does not undergo screening, we expect interest in safe, low-cost chemopreventive strategies to prevent or delay CRC to remain an important priority area of research. Findings from active trials including the selenium RCT and vitamin D/calcium RCT may provide new evidence for micronutrient recommendations to decrease population burden. In addition, extensive efforts to control the underlying factors that link obesity and diabetes to a number of chronic diseases, including CRC, such as therapeutic management with metformin, statins, and low-dose aspirin, we predict, will emerge through secular trends as CRC prevention agents at the population level.

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Lung Cancer Prevention

14

Iman Hakim and Linda Garland

14.1 Epidemiology of Lung Cancer

14.1.1 Trends in Tobacco Use in the USA

The lung cancer epidemic that has now manifested in the USA had its roots in the tremendous increase in smoking prevalence through the 1900s. In the early 1900s, smoking, especially among women, was relatively rare (USDHHS 1980). Over the past 50 years, smoking prevalence increased dramatically, influenced by expanding tobacco marketing initiatives by the tobacco industry. Both male and female smokers were cultivated; in fact, as early as the 1920s, the tobacco industry first began its targeting of women utilizing the concept of "image advertising," offering lipstick-colored cigarette tips for the woman smoker and developing advertising campaigns illustrated by the slogan "Reach for a Lucky instead of a sweet" to create the association between cigarette use with staying slim, a theme particularly appealing to women (Wallace 1929). There was a significant increase in the numbers of men and women who took up the habit of smoking cigarettes during World War II, with cigarettes being included in government issue ration kits, and image advertising capitalizing on the war effort to promote smoking in women.

14.1.2 The Narrowing of the Gender Gap in Smoking Prevalence

While early in the century, a large gender gap in smoking prevalence existed; the gap narrowed significantly over the middle and latter parts of the century as a

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consequence of several trends. First, women's use of cigarettes virtually soared over the mid-1900s in the face of aggressive niche marketing that linked women's smoking to their burgeoning social and political independence, a marketing effort best typified by the Virginia Slims advertising slogan "You've Come a Long Way, Baby." Second, in the 1950s, the first epidemiologic studies were conducted that definitively linked tobacco exposure and lung cancer (Levin et al. 1950; Doll and Hill 1952). In 1964, the influential report of the Advisory Committee to the Surgeon General cited evidence of the adverse health effects of tobacco use (USDEW 1964). At that time, 51.9 % of men and 33.9 % of women were smoking (Giovino et al. 1994).

In 1964, the Surgeon General's Report on Smoking and Health became the first national declaration of the association between cigarette smoking as a cause of cancer and other diseases. The publication of this report was followed in 1965 by a congressional act requiring a general health warning on all cigarette packaging regarding the dangers of cigarette smoking. The landmark 1964 Surgeon General's Report on Smoking and Health (USDHHS 1964) provided official evidence that cigarette smoking is a cause of cancer and other serious diseases. The following year, Congress passed the Federal Cigarette Labeling and Advertising Act, requiring health warnings on all cigarette packages: "Caution: Cigarette Smoking May be Hazardous to Your Health."

A wave of aggressive private, state and federal-based tobacco control initiatives followed, promoting smoking cessation and placing restrictions on some venues for tobacco advertisements such as broadcast advertising on televisions, bans on billboard advertising, and restrictions on sales and advertising to children and adolescents. For men, the latter part of the century saw a decline in smoking prevalence; for women, smoking prevalence continued to increase. Thus, at the very end of the twentieth century, the gender gap had narrowed to only around 5 %, with 22% of women aged 18 or older in the USA smoking cigarettes, compared to 26.4 % of US men. Figure 14.1 illustrates the trend in all adult cigarette smoking over the twentieth century in relation to public health milestones.

While the decline in overall cigarette use in the USA over the latter part of the twentieth century is considered to have been one of great public health achievements of that century, there were in 2010 an estimated 45.3 million persons, or 19.3 % of adults 18 years or older, in the USA who smoked cigarettes (Centers for Disease Control and Prevention 2011). Economically, the burden of tobacco use continues to exact a staggering $50 billion in medical expenditures and another $50 billion in indirect costs such as lost wages (Tobacco use—United States 1999). (close to $96 billion a year in medical costs and another $97 billion a year from lost productivity) (Centers for Disease Control and Prevention 2008).

14.1.3 Demographic Variables and Tobacco Use

Tobacco use varies by a number of variables apart from gender; these include age, education, socioeconomic status, and ethnicity/race. A Centers for Disease Control

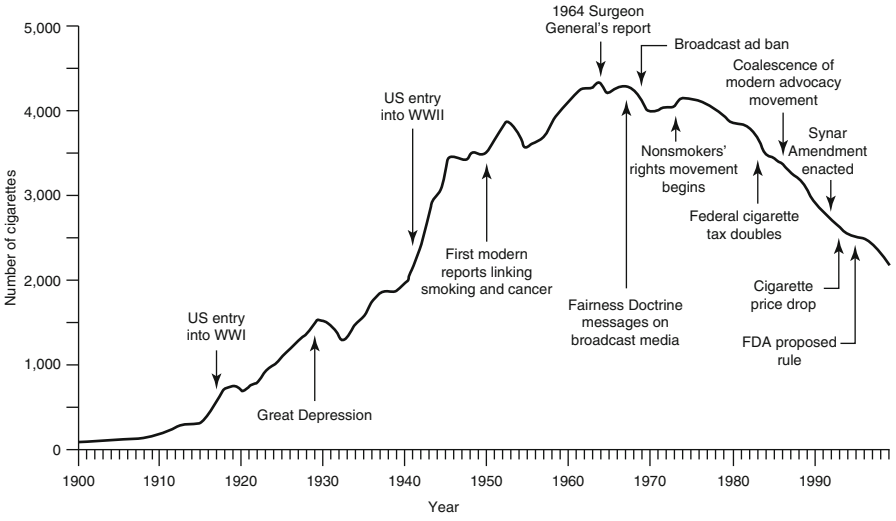

Fig. 14.1 Annual adult per capita cigarette consumption and major smoking and health events – United State, 1900–1990 (*Sources of data*: US Department of Agriculture, 1986 Surgeon General's Report)

analysis of self-reported data from the 2000 National Health Interview Survey (NHIS) sample showed smoking prevalence was highest among adults 18–44 years of age and lowest among adults aged greater than 65 years of age. Cigarette use varied inversely with level of education, with a prevalence of 47.2 % in adults with a general education degree as compared to a prevalence of 8.4 % among adults with a master's, professional, or doctoral degree. Persons living below the poverty level had higher prevalence of smoking than persons at or above the poverty level (31.7 % versus 22.9 %, respectively) (CDC 2002).

Cigarette use varies widely by ethnic/racial groups. Factors that have been implicated in the complex interactions that influence tobacco use by ethnic group include socioeconomic status, cultural factors and norms, acculturation, biologic factors, impact of advertising targeted by ethnicity, price of tobacco products, and variation in the ability of communities to implement effective tobacco-control initiatives (2004). Smoking prevalence among five defined ethnic/racial groups varies widely (Table 14.1), with Asians (14.4 %) and Hispanics (18.6 %) having the lowest prevalence of cigarette use while American Indians/Alaska Natives having the highest prevalence (36.0 %) (2002). The need to tailor tobacco control interventions by cultural demographics is underscored by a further analysis of the NHIS data showing that, even within each of the four primary racial/ethnic minority populations (non-Hispanic blacks, American Indians/Alaska Natives, Asians/Pacific Islanders, and Hispanics), cigarette use by youth and adults varies widely (2004).

Table 14.1 Percentage of persons aged ≥18 years who were current smokers[a], by selected characteristics

Characteristic	Men ($n=13{,}986$)		Women ($n=18{,}388$)		Total ($n=32{,}374$)	
	%	(95 % CI[b])	%	(95 % CI)	%	(95 % CI)
Race/ethnicity[c]						
White, non-Hispanic	25.9	(±1.0)	22.4	(±0.8)	24.1	(±0.7)
Black, non-Hispanic	26.1	(±2.5)	20.9	(±1.7)	23.2	(±1.5)
Hispanic	24.0	(±2.1)	13.3	(±1.6)	18.6	(±1.3)
American Indian/ Alaska Native[d]	29.1	(±11.0)	42.5	(±11.0)	36.0	(±8.0)
Asian[e]	21.0	(±4.6)	7.6	(±2.8)	14.4	(±2.8)
Education[f]						
0–12 (no diploma)	33.2	(±2.2)	23.6	(±1.7)	28.2	(±1.4)
≤8	26.1	(±3.1)	14.2	(±2.2)	20.0	(±1.9)
9–11	37.6	(±3.5)	30.8	(±2.7)	33.9	(±2.2)
12	40.1	(±6.8)	25.3	(±5.1)	32.7	(±4.4)
GED[g] diploma	50.1	(±6.2)	44.3	(±5.7)	47.2	(±4.3)
12 (diploma)	31.7	(±1.9)	23.5	(±1.4)	27.2	(±1.2)
Associate degree	21.9	(±2.8)	20.4	(±2.4)	21.1	(±1.8)
Some college	25.8	(±2.1)	21.6	(±1.7)	23.5	(±1.3)
Undergraduate degree	14.2	(±1.7)	12.4	(±1.5)	13.2	(±1.1)
Graduate degree	9.1	(±1.8)	7.5	(±1.6)	8.4	(±1.2)
Age group (years)						
18–24	28.5	(±2.7)	25.1	(±2.4)	26.8	(±1.8)
25–44	29.7	(±1.4)	24.5	(±1.1)	27.0	(±0.9)
45–64	26.4	(±1.5)	21.6	(±1.3)	24.0	(±1.0)
≥65	10.2	(±1.3)	9.3	(±1.0)	9.7	(±0.8)
Poverty status[h]						
At or above	25.4	(±1.0)	20.4	(±0.9)	22.9	(±0.7)
Below	35.3	(±3.2)	29.1	(±2.3)	31.7	(±1.9)
Unknown	23.6	(±1.8)	19.5	(±1.4)	21.4	(±1.1)
Total	**25.7**	(±**0.8**)	**21.0**	(±**0.7**)	**23.3**	(±**0.5**)

National Health Interview Survey, USA, 2000, reprinted with permission from Morbidity and Mortality Weekly Report (2002)

[a]Smoked ≥100 cigarettes during their lifetime and reported at the time of interview smoking every-day or some days. Excludes 301 respondents for whom smoking status was unknown

[b]Confidence interval

[c]Excludes 287 respondents of unknown, multiple, and other racial/ethnic categories

[d]Wide variances among estimates reflect limited sample sizes

[e]Does not include Native Hawaiians and Other Pacific Islanders

[f]Persons aged ≥25 years. Excludes 305 persons with unknown years of education

[g]General Education Development

[h]The 1999 poverty thresholds from the Bureau of the Census were used in these calculations

14.2 Risk Factors for Lung Cancer

14.2.1 Tobacco Products

Cigarette smoking, the primary risk factor for lung cancer, accounts for approximately 90 % of cases in men and 70 % of cases in women (Shopland 1995). A dose–response relationship between daily tobacco smoking and risk of death

from lung cancer has been established in prospective analyses, with the relative risk of lung cancer mortality ranging from 4.6 to 7.8 in users of less than 10 cigarettes per day, compared to never smokers. This relative risk increases to more than 20 in individuals who smoke 25–40 or more cigarettes per day (Hammond 1966; Rogot and Murray 1980).

Cigarette smoking may result in chronic bronchitis, chronic obstructive pulmonary disease, and/or lung cancer. In the early 1960s, Passey (1962) hypothesized that it was the irritating properties of tobacco smoke, resulting in chronic bronchitis and inflammatory destruction of lung tissue, that was of pathogenic significance in the causal pathway of lung cancer rather than any direct action by volatile and particulate carcinogens in tobacco smoke. The experiments of Kuschner (1968), however, suggested an alternative explanation, namely, that bronchial and bronchiolar inflammation, accompanied by reactive proliferation, squamous metaplasia, and dysplasia in basal epithelial cells, provided a cocarcinogenic mechanism for neoplastic cell transformation upon exposure to polycyclic aromatic hydrocarbons.

At least 40–50 million Americans are former smokers (Resnicow et al. 1991). The risk of former smokers developing lung cancer actually increases during the first 3–5 years after smoking cessation; many smokers stop because they are symptomatic and may already have the disease (Hammond 1966). Eventually and gradually, over at least a decade or more, the risk of lung cancer for these individuals will come to approach that of never smokers (Halpern et al. 1993). In several studies, the risk of lung cancer in former smokers had not reached that of lifetime never smokers, even after 20 years since cessation (Burns 2000; Ebbert et al. 2003).

Current and former smokers older than 40 years with a smoking history of 20 pack-years or more and airflow obstruction, defined as a forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) of 70 % or less and a FEV1 lower than 70 %, are at high risk of developing lung cancer (Kennedy et al. 1996). Patients with chronic obstructive pulmonary disease (COPD) have a four- to sixfold increased risk of lung cancer independent of their smoking history. The chronic inflammation associated with COPD appears to enhance lung cancer risk. At least ten cohort studies have reported that COPD is an independent predictor of lung cancer risk (Tenkanen et al. 1987; Tockman et al. 1987).

Reactive oxygen species (ROS) play an important role in toxicity of environmental chemicals. During passive smoking, the body is attacked by an excess of free radicals inducing oxidative stress. In nonsmokers, even a short period of passive smoking breaks down serum antioxidant defense and accelerates lipid peroxidation (Zhang et al. 2001). Tobacco smoke contains many carcinogens that exert their biological effects through interaction of reactive intermediates with DNA to form DNA adducts. The same electrophilic species also react with cellular proteins. The effects of smoking are evident by the detection of elevated levels of carcinogen-DNA adducts in many human tissues and of carcinogen-protein adducts in blood. Components of tobacco smoke also induce oxidative DNA damage (Phillips 2002). Exposure to environmental tobacco smoke resulted in a statistically significant increase of 63 % of the oxidative DNA mutagen, 8-OHdG, in the blood of exposed subjects. This oxidative DNA damage has been linked to an increased risk of developing several degenerative chronic diseases, including coronary heart disease and cancer (Howard et al. 1998). Significant effects on oxygen free radical production

were found for gender and ethnicity, with men having greater values than women ($p<0.001$) and white subjects having greater values than black subjects ($p=0.025$).

Environmental tobacco smoke (ETS) constitutes both a residential and an occupational exposure. Animal data show that ROS introduced by passive smoking may contribute to KRAS activation as an initiator of a tumor model, possibly through the oxygen-induced DNA damage, and may also contribute to an initial activation and the subsequent downregulation of protein kinase as a promoter (Maehira et al. 2000). Rats exposed to sidestream cigarette smoke, the major component of ETS, showed significant increases in the accumulation of 8-OHdG in lung DNA (Maehira et al. 2000; Izzotti et al. 2001). Similarly, exposure to sidestream cigarette smoke significantly increased oxidative stress in mouse heart, liver, and lung tissues. In all three tissues, ETS increased the presence of 8-OHdG above the control levels (Howard et al. 1998). The assessment of pathological effects produced by ETS in humans is controversial in epidemiological studies. However, based on a collection of studies, there is an association between exposure to ETS and lung cancer, with a relative risk around 1.2 (Boffetta and Nyberg 2003).

14.2.2 Environmental Exposures

Occupational exposures have been estimated to account for up to 20 % of all lung cancer diagnoses. Many studies that comprise the body of literature on occupational exposure and lung cancer risk have been based on exposures in male smokers, thus introducing confounders in the analysis of pure exposure risk. Little data is available on the effect of occupational exposures in women and nonsmokers. Strong evidence exists for asbestos, ETS, radon prodigy, and arsenic as occupational carcinogens in nonsmokers (Neuberger and Field 2003). Nonetheless, the International Agency for Research on Cancer (IARC) maintains a much longer list of workplace-related carcinogens, including both chemical and physical agents, implicated in the risk of lung cancer.

Because women have relatively recently been assimilated into many occupational environments formerly reserved for men, the role of occupational exposures is estimated to be lower than that for men, around 5 %. A more current analysis of occupational risk of lung cancer for women is needed so that a more accurate risk assessment for women in the workplace can be generated.

Worldwide, an increased risk of lung cancer independent of tobacco exposure has been documented for exposure to environmental carcinogens, a term that includes both outdoor and indoor air pollutants as well as contaminants of soil and drinking water. Persons are exposed to environmental carcinogens from both natural and man-made exposures, and exposures occur in both residential and occupational settings. While there appear overall to be relatively small relative risks of cancer following environmental exposure, the impact on worldwide health is great, given a high prevalence of exposures to these carcinogens.

The naturally occurring radioactive gas radon and its radioactive progeny are sources of exposure to inhaled radioactive substances. Radon exposure occurs in

occupational settings, such as uranium and tin mines, and in homes built on radon-containing soil. Studies have consistently shown an excess of lung cancer risk in radon-exposed populations. Studies of radon-exposed underground miners have predicted that residential radon would be an important cause of nontobacco-related lung cancer; in fact, residential exposure to radioactive radon and its decay products is estimated to account for 10–12 % of all lung cancer deaths in the USA (Lubin and Steindorf 1995). Radon mitigation programs for homes and improved workplace measures to mitigate exposure to radon and other radioactive elements will likely impact favorably on lung cancer risk.

A high incidence of lung cancer has been reported in some Asian women who have a traditionally low prevalence of cigarette smoking. This elevated risk of lung cancer has been related to indoor pollution from cooking and heating sources with chronic exposure to non-vented, potentially mutagenic cooking oil fumes and the carcinogenic metabolic products of heterocyclic amines aerosolized during the cooking of meat at high temperatures (He et al. 1991; Seow et al. 2001).

Outdoor air pollution is composed of complex mixtures of chemical compounds, radionuclides, gas and particulate combustion products, and fibers, a number of which are known carcinogens. Major sources of air pollution include industrial- and automobile-related fossil fuel combustion, diesel exhaust, power plants, and residential sources of emissions. Air pollution as a contributor to the risk of lung cancer has been supported by occupational studies of workers exposed to fossil fuel combustion products. After adjusting for smoking history, exposed workers had a twofold risk of lung cancer relative to nonexposed workers (Doll et al. 1972). Other studies have measured tissue biomarkers of exposure to respiratory carcinogens such as levels of benzo(a)pyrene, carcinogenic DNA adducts, chromosomal abnormalities, and other measures of genetic damage in relation to exposure to air pollutants. Epidemiologic studies of lung cancer risk related to air pollution must account for a number of variables that are often difficult to quantify, such as concentration of pollutant carcinogens, length of exposure, geographic variables, genetic variables, and individual tobacco smoke-related exposure within the study population. Nevertheless, there is a large body of data that supports a role for air pollution contributing independently to the risk of lung cancer, although estimates of lung cancer attributed to air pollutants range from less than 1 % (Doll 1978) to 12 % (Karch and Schneiderman 1981). The causal relationship between air pollution and lung cancer risk remains of great public health import, given the migration of populations from rural into more urban settings, and the increasing expanding populations worldwide residing in highly polluted cities in many developing parts of the world (Cohen 2000).

14.2.3 Family History

There appears to be a small contribution to an individual's risk of developing lung cancer from family history, suggesting a role for genetic susceptibility that is independent of tobacco exposure. A number of studies have shown an increased risk of

cancers in relatives of persons with lung cancer. A landmark study reported in 1963 showed suggestive evidence of familial aggregation of lung cancer specifically, with an excess of lung cancer mortality reported in relatives of 270 lung cancer probands (Tokuhata and Lilienfeld 1963). A number of more recent studies have also found an increase in both lung cancer and total cancers in the first-degree relatives of persons with lung cancer; these familial aggregations of cancer risk have been seen in both smoking *and nonsmoking* persons with lung cancer. In an investigation of family cancer history as a risk factor for lung cancer in nonsmoking men and women, a population-based case–control study showed an excess of certain cancers, especially lung, aerodigestive tract, and female breast cancer in first-degree relatives of nonsmoking cases (Mayne et al. 1999).

Lung cancer risk in families is influenced by familial aggregation of smoking habits; this variable is an important potential confounder of studies investigating pure genetic risk related to lung cancer. A recently reported large case–control study of persons with lung cancer and their first-degree relatives investigated tobacco exposure-specific familial risk of lung and other smoking-related cancers. Eight hundred and six persons with lung cancer and 663 controls matched to the cases on age (within 5 years), sex, ethnicity, and smoking history addressed whether there was an excess of cancer in relatives of persons with lung cancer (Etzel et al. 2003). Cancer family history data were available for 6,430 first-degree relatives of the cases and 4,936 first-degree relatives of the controls. Adjustment was made for smoking history and age of lung cancer cases and their relatives. In first-degree relatives of lung cancer cases, there was a significantly increased risk of smoking-related cancers (defined as cancers of the lung, bladder, head and neck, kidney, and pancreas) and lung cancer specifically. Relative risks were 1.28 for smoking-related cancer and 1.33 for lung cancer. Additionally, there was a sevenfold increased risk of breast cancer among daughters of lung cancer cases (Etzel et al. 2003). These data suggest that genetic factors modulate lung cancer risk independent of tobacco exposure and that a better understanding of these factors may influence the way in which the health of families of lung cancer patients are monitored.

14.2.4 Genetic Susceptibility

Although smoking is the major risk factor for lung cancer, other factors, such as nutrition or genetic predisposition, may be involved. Genetic susceptibility to environmental carcinogens is thought to be attributable to genetic polymorphisms in metabolism enzymes, which have been found to substantially alter the activation and elimination of carcinogens (Smith et al. 1994).

Glutathione S-transferases (GSTs) constitute a complex multigene family that, in most instances, deactivates carcinogens, environmental pollutants, drugs, and a broad spectrum of other xenobiotics through conjugation with glutathione (Hayes and Pulford 1995). Therefore, GST induction may improve detoxification and excretion of potentially harmful compounds. Polymorphic variants in GSTs, l (GSTM1), h (GSTT1), and p (GSTP), have been studied extensively in relation to

cancer etiology. Complete gene deletions in GSTM1 and GSTT1 and single nucleotide polymorphism in GSTP may result in a significant change in the function of the enzymes.

Both GSTM1 and GSTT1 are polymorphic, and the null alleles of these genes have deletions of the entire protein-coding region (Seidegard et al. 1988; Pemble et al. 1994). The GSTM1-null and GSTT1-null alleles are transmitted as autosomal recessive, with the phenotypic absence of the isozymes resulting from inheritance of a null allele from both parents. The prevalence of GSTM1-null and GSTT1-null genotypes differs markedly across ethnic and racial groups (GSTM1, 30–60 %; GSTT1, 9–64 %) (Bell et al. 1993; Katoh et al. 1996). GSTM1-null and GSTT1-null genotypes have been associated with increased risk of cancer in a number of studies, and it is hypothesized that individuals with putative high-risk genotypes suffer higher levels of carcinogen-induced genotoxic damage (Bell et al. 1993; Rebbeck 1997).

Among the several classes of GSTs, GSTl enzyme activity has been found to vary substantially between individuals because of an inherited deletion of the GSTM1 gene. GSTM1 is involved in the detoxification of tobacco smoke carcinogens including the polyaromatic hydrocarbons (PAHs) such as benzo(a)pyrene (Ketterer et al. 1992). Up to 50 % of Whites have no GSTM1 enzyme because of the homozygous deletion of the gene (Seidegard et al. 1988), referred to as the GSTM1-null genotype. Individuals with the null genotype are unable to detoxify PAHs through this particular glutathione pathway. Although several epidemiological studies have found the null genotype to be associated with increased risk for the development of lung and other tobacco-related cancers (Hirvonen et al. 1993; Kihara and Noda 1994; Saarikoski et al. 1998), the findings in other studies are conflicting, and this association remains controversial (Zhong et al. 1991; Brockmoller et al. 1993).

14.3 Biology of Lung Carcinogenesis

14.3.1 Oxidative Damage

Oxidative damage is implicated in several chronic diseases including cancer and chronic inflammation. Oxidative reactions have been implicated as important modulators of human health and can play a role in both disease prevention and disease development. Small-cell carcinoma of the lung (SCLC) is a highly malignant systemic disease characterized by rapid and widespread dissemination of tumor cells at the time of diagnosis (Erhola et al. 1997). Decreased plasma peroxyl radical-trapping capacity was reported in SCLC patients (Erhola et al. 1997). The most enhanced lipid peroxidation in tumor tissue was noted in specimens of adenocarcinoma and SCLC tissue, in case of which “early” dissemination and fast growth are common features (Zieba et al. 2000). Thus it appears that lung cancer of these histologic types is associated with an increased oxidative stress that is most likely due to the systemic nature of the disease (Erhola et al. 1997). Oxidative damage to the DNA of key cellular genes is a fundamental event leading to malignancy (Ames et al. 1995), whereas

cellular generation of oxidants is important in the control of infectious agents (Peterhans 1997; Akaike et al. 1998) and eliminating newly developed tumors (Farias-Eisner et al. 1994; Filep et al. 1996; Yamashita et al. 1997). Cellular-generated small molecules, such as nitrogen oxides and oxygen radicals, have the potential to cause significant genetic and cellular damage (Ames and Shigenaga 1992; Keefer and Wink 1996), yet they are also key cellular signaling molecules (Lane and Gross 1999), which may either protect against or enhance the development of malignancy.

The sources of increased oxidative stress derive from the increased burden of oxidants present in cigarette smoke or from the increased amounts of reactive oxygen species released from leukocytes into the airspaces and blood (MacNee 2001). Oxidative processes have fundamental roles in inflammation through redox-sensitive transcription factors, such as NF-κB and AP-1, that regulate the genes for proinflammatory mediators and through protective mechanisms, such as antioxidant gene expression. In addition to the oxidative stress produced by cigarette smoking, dietary deficiency in antioxidants is shown to be related to the development of airflow limitation (MacNee 2001). Hence dietary supplementation may be a beneficial therapeutic intervention in this condition.

A common oxidative damage to DNA is the highly mutagenic 7,8-dihydro-8-oxoguanine adduct, which can be repaired by 8-oxoguanine glycosylase I (OGG1). The human homologue of the yeast OGG1 gene, hOGG1, has been cloned, and its genetic structure has been determined. Several polymorphisms in the hOGG1 gene were detected in humans. The distributions of this polymorphism vary for different populations, and among the different polymorphisms, the Ser-Cys polymorphism at codon 326 has been suggested to reduce the activity of the enzyme. Because many environmental carcinogens produce 8-hydroxyguanine residue and mismatching to this modified base potentially causes oncogenic mutations, the capacity to repair these lesions can be involved in cancer susceptibility in human beings. Published data suggest that the presence of two hOGG1 326Cys alleles confers a twofold increased risk of lung cancer (Le Marchand et al. 2002).

Although the specific mechanisms by which oxidative stress contributes to the development of carcinogenesis are largely unknown, oxidative DNA damage is thought to play a role in the development of carcinogenesis via at least two different mechanisms. In the first mechanism, genetic alterations induced by oxidants, such as mutations and chromosomal rearrangements, can play a role in the initiation and malignant conversion stages of carcinogenesis (Guyton and Kensler 1993). Most oxidative DNA damage results in a wide range of chromosomal abnormalities, causing a blockage of DNA replication and wide cytotoxicity (Bohr et al. 1995). Mutations can occur through misrepair or due to incorrect replication past a damaged site, while chromosomal rearrangements can result from strand breakage misrepair (Halliwell and Aruoma 1991; Bohr et al. 1995). These genetic alterations can result in permanent DNA damage and a population of initiated cells that must escape repair processes, overcoming cytotoxicity in order to be carried on to the progeny. The initiation potential of oxidants may be due to their ability to induce DNA base changes in certain oncogenes and tumor suppressor genes, contributing to carcinogenesis (Jackson 1994). Hydroxy

radicals have been demonstrated to activate certain oncogenes, such as KRAS and C-Raf-1, respectively, through the induction of DNA point mutations in GC base pairs and N-terminal deletions in these genes (Jackson 1994). Base point mutations in CpG dinucleotides are also frequently found in certain tumor suppressor genes, such as p53 and retinoblastoma, leading to their inactivation (Nigro et al. 1989; Yandell et al. 1989). Furthermore, hydroxy radical exposure of cells that contain mutant or absent p53 resulted in a failure to arrest in G1, reducing their capacity to repair damaged DNA (Jackson 1994). This increase in replication errors can compromise DNA fidelity, predisposing initiated cells to undergo additional oncogene activation and tumor suppressor gene inactivation, ultimately contributing to malignancy (Jackson 1994). Oxidant-induced cytotoxicity may also contribute to the initiation of carcinogenesis by depleting the normal cell population, promoting the clonal expansion of more resistant initiated cells, thus increasing the probability of mutation.

Among various markers of DNA damage, 8-hydroxydeoxyguanosine (8-OHdG), an oxidative adduct form of deoxyguanosine, is considered to be one of the most sensitive (Floyd et al. 1986). 8-OHdG is induced by several carcinogens and tumor promoters (Floyd 1990; Takeuchi et al. 1994; Shen et al. 1995) and causes mutation both in vitro and in vivo (Wood et al. 1990; Cheng et al. 1992). 8-OHdG occurs specifically in DNA and appears to be a reasonable marker for oxidative DNA damage (assuming a steady state), because the rate of output of 8-OHdG by repair should balance the rate of input of damage. Toyokuni and co-workers (Toyokuni et al. 1995) reported that human carcinoma cells (breast, lung, liver, kidney, brain, stomach, ovary) have a higher content of 8-OHdG than adjacent non-tumorous tissues. Moreover, investigators have reported a high concentration of 8-OHdG in lung cancer tissues (Inoue et al. 1998). They hypothesized that the tumor cells themselves produce ROS spontaneously, which results in an increase of 8-OHdG in DNA. 8-OHdG levels in DNA of leukocytes and the central part of the lung were significantly associated with the number of cigarette smoked (Kasai 1998). An increased level of 8-OHdG was found in peripheral part of the lung from lung cancer patients when compared to non-cancer controls (Inoue et al. 1998). Lung cancer patients showed higher levels of urinary 8-OHdG/creatinine than the controls. Furthermore, patients with complete or partial response to chemotherapy showed a significant decrease in urinary 8-OHdG/creatinine, while patients with no change or progressive disease showed an increase. Nevertheless, 8-OHDG in blood DNA rather than urinary 8-OHdG might be a better marker of oxidative damage because the latter might reflect the repair process.

A group of prostaglandin (PG)-like compounds, known as isoprostanes, has been discovered in the late twentieth century. 8-F2 isoprostanes (8-epi-PGF2) have been measured as indices of lipid peroxidation in body fluids such as urine, blood, bile (Leo et al. 1997; Pratico et al. 1998a), pericardial (Mallat et al. 1998) and cerebrospinal fluid (Pratico et al. 1998b; Montine et al. 1999), and lung condensate (Montuschi et al. 1998). Isoprostanes are formed from arachidonic acid in vivo, not by involvement of oxidizing enzymes, such as cyclooxygenase, but by free radical-catalyzed peroxidation. Free F2-isoprostanes are released from the esterified stores

on the cell surface by the action of phospholipases (Ohashi and Yoshikawa 2000). Therefore, the amount of isoprostanes should reflect the levels of oxidant stress and free radicals in vivo (Morrow et al. 1994; Awad et al. 1996).

14.3.2 Cellular Proliferation and Lung Carcinogenesis

Lung cancer, like many other epithelial malignancies, is thought to be the outcome of genetic and epigenetic changes that result in a constellation of phenotypic abnormalities in bronchial epithelium. These include morphologic epithelial dysplasia, angiogenesis, increased proliferative rate, and changes in expression of cell surface proteins, particularly overexpression of epidermal growth factor receptor (EGFR) family proteins. EGFR overexpression is pronounced in virtually all squamous cell lung cancers and is also found in 65 % of large cell and adenocarcinomas of the lung. Overexpression of EGFR is one of the earliest and most consistent abnormalities in bronchial epithelium of high-risk smokers. It is present at the stage of basal cell hyperplasia and persists through squamous metaplasia, dysplasia, and carcinoma in situ (Khuri et al. 2001). The PI3K pathway is a signaling pathway that is frequently activated in lung cancer and results in proliferation, inhibition of programmed cell death, angiogenesis, and metastasis. This pathway has been shown through gene expression profiling to be activated in normal-appearing proximal airways in persons with lung cancer as well as persons without lung cancer but with dysplastic airway lesions (Gustafson et al. 2010).

The expression level of the proliferating cell nuclear antigen (PCNA) has been associated with the histological grade of the bronchial biopsy site. Intervention with 13-cic-retinoic acid augmented the decreased proliferation status and decreased metaplasia index associated with discontinuation of smoking but had little impact on the proliferation status of the bronchial epithelium in those who continued to smoke (Khuri et al. 2001). The level of PCNA expression in the bronchial epithelium correlated with the degree of EGFR expression, which is also found to be increased in metaplastic lesions (Hommura et al. 2000). Another proliferation marker, Ki-67, has been shown to be increased in lung tumors and to provide some prognostic information (Nguyen et al. 2000; Hittleman 2002). In patients who had stopped smoking, the Ki-67 labeling index dropped significantly within a year and continued to drop thereafter. However, abnormal levels of Ki-67 labeling are detectable for more than 20 years after smoking cessation (Lee et al. 2001).

14.3.3 Apoptosis and Lung Carcinogenesis

Use of biomarkers to predict induction of apoptosis allows identification of biological signs that may indicate increased risk for disease. In cells undergoing apoptosis, the release of cytochrome c from the mitochondria to the cytoplasm and the activation of caspase-3, a key enzyme in the execution stage of apoptotic pathway, have been studied as biomarkers of apoptosis (Koomagi and Volm 2000). A significant

correlation was observed between the expression of caspase-3 and survival and metastasis in 135 non-small cell lung carcinomas. Caspase-3 expression correlated with a lower incidence of lymph node involvement ($p = 0.0007$). The median survival was longer for patients with caspase-3-positive carcinomas than for those with caspase-3-negative tumors (Chen et al. 1999).

Apoptosis is a highly programmed process regulated by many genes, including Bcl-2 family genes (Wang et al. 2000). The Bcl-2 proto-oncogene, an indirect measure of apoptosis, is known to promote cell survival and to act as a negative regulator of the biological cascade that leads to apoptosis and to provide a growth advantage eventually leading to neoplastic transformation. The mRNA expressions of the Bcl-2 gene were studied in a series of 137 pulmonary tissues collected at various sites and with different properties. According to the observations on benign lesions, non-cancer tissues distant from tumor, para-tumor tissues, and cancer tissues, there was a trend toward increased Bcl-2 mRNA expression. Among them, Bcl-2 mRNA expression in lung cancer tissues was significantly increased as compared to benign lesions and tissues distant from tumor ($p < 0.01$) (Yang et al. 1998). Expression of the Bcl-2 protein has been reported for a variety of tumors, including the lung. The overexpression of Bcl-2 is thought to be early event in carcinogenesis, allowing cells with DNA damage to escape the normal mechanisms of apoptotic cell death. Conversely, the loss of Bcl-2 expression may be relatively late in the pathogenesis of lung cancer (Wang et al. 2000).

14.3.4 Genetic Factors in Carcinogen Metabolism

Cigarette smoke contains numerous compounds that generate reactive oxygen species (ROS) that can damage DNA directly or indirectly via inflammatory processes (Frenkel et al. 1988; Wei et al. 1993; Hecht 1999). Oxidants, either present in cigarette smoke and/or formed in the lungs of smokers, may trigger oxidative damage to DNA and cellular components, contributing to carcinogenesis. Free radical attack upon DNA generates a multiplicity of DNA damage, including modified bases. Some of these modifications have considerable potential to damage the integrity of the genome.

DNA damage was proposed as a useful parameter for assessing the genotoxic properties of environmental pollutants. The correlation between exposure to carcinogenic substance and the level of DNA damage is essential. ROS are highly biologically active chemicals. They may interact with DNA and damage its structure. Because the human population is biologically diverse and genetically heterogeneous, it is not surprising that differences in susceptibility to disease among individuals with or without exposure to environmental agents exist. Individuals vary greatly in their susceptibility to disease. This is true of adults and children. The etiologies of many diseases of childhood are due to a combination of factors, including genetic susceptibility and environmental exposures during vulnerable periods of development. Genes regulate cellular growth and development, DNA replication and repair, the metabolism of endogenous agents in the body, and the metabolism

and excretion of exogenous agents that the body comes in contact with in the environment. This regulation varies over the life span, contributing to the cellular consequences of the environmental exposures.

14.3.5 DNA Hypermethylation and Lung Carcinogenesis

Methylation is the main epigenetic modification in humans; changes in methylation patterns play an important role in tumorigenesis. Aberrant promoter methylation has been described for several genes in various malignant diseases including lung cancer (Esteller et al. 1998, 1999a, 2000). In a large study of primary resected non-small cell lung cancer (NSCLC), a high frequency of methylation was observed, demonstrating that methylation may be the most common mechanism to inactivate cancer-related protection genes in NSCLC (Zochbauer-Muller et al. 2001).

The tumor suppressor gene (p16), DNA repair gene (MGMT), and genes related to metastasis and invasion (DAP-K and TIMP3) are well characterized. Each possesses a CpG island in the 5′ region which is unmethylated in normal tissues, as expected for a typical CpG island (Esteller et al. 2001). Methylation of p16, MGMT, DAP-K, and TIMP3 has been described in lung cancer cell lines and a small number of primary lung tumors (Esteller et al. 1999a). Furthermore, when these CpG islands were hypermethylated in cancer cells, expression of the corresponding gene was silenced. The silencing was partially reversed by demethylation of the promoter region (Esteller et al. 1999a). Thus, chemopreventive agents that have the ability to demethylate these genes may be able to restore their function and help slow or prevent carcinogenesis.

Belinsky and co-workers (Belinsky et al. 1998) were the first to demonstrate that inactivation of the p16 tumor suppressor gene by aberrant methylation is an early and likely critical event in the development of NSCLC. Palmisano et al. (2000) corroborated Belinsky's work, reporting that p16 hypermethylation was detected in 60–80 % of squamous cell carcinoma (SCC) and 30–45 % of adenocarcinomas. Several other studies have shown that inactivation of the p16 tumor gene is common in lung cancer (Belinsky et al. 1998; Kersting et al. 2000) and that methylation of the p16 gene is clearly associated with loss of gene transcription in lung tumors (Belinsky et al. 1998). p16 methylation has also been observed in the precursor lesions of SCC, including basal cell hyperplasia, squamous metaplasia, and carcinoma in situ of the lung. The frequency of p16 methylation increased from the lowest to highest-grade precursor lesions to SCC (Kersting et al. 2000). The high frequency of p16 methylation in alveolar hyperplasias and adenomas – precursor lesions with an extremely high conversion rate to adenocarcinomas in NNK-treated rats – indicates that p16 hypermethylation is an early molecular event in lung carcinogenesis and thus a sound candidate biomarker for lung chemoprevention trials (Belinsky et al. 1998).

The DNA repair protein, O^6-methylguanine DNA methyltransferase (MGMT), is a major determinant of susceptibility to methylating carcinogens and of tumor resistance to chloroethylating drugs (Danam et al. 1999). MGMT protein expression is decreased in some human tumors, including lung, with respect to their normal tissue counterparts. Loss of expression is rarely due to deletion, mutation, or

rearrangement of the MGMT gene. However, the methylation of discrete regions of the CpG island of MGMT is associated with the silencing of the gene in cell lines (Esteller et al. 1999a). Aberrant methylation of MGMT was detected in 21–29 % of NSCLCs (Esteller et al. 1999a, 2001). Palmisano et al. (2000) detected MGMT methylation in epithelial cells shed from the airways in persons at risk for lung cancer and reported a frequency of 16 % in samples investigated. In contrast, methylation of MGMT has not been observed in normal lung tissue (Esteller et al. 1999a).

Death-associated protein (DAP) kinase, also known as DAP-2, is a novel serine/threonine kinase required for interferon gamma-induced apoptotic cell death (Tang et al. 2000) that may function as a metastasis suppressor. Expression of DAP kinase was repressed in human cancers by hypermethylation in the promoter CpG region (Esteller et al. 1999b; Tang et al. 2000). Esteller et al. (1999b) studied primary NSCLC samples from 22 patients and found that DAP kinase was hypermethylated in five (23 %) of the 22 tumors. In 135 lung tumors, 44 % of the tumors were hypermethylated at the CpG sites of the DAP kinase gene; DAP kinase methylation was negatively associated with the expression of DAP kinase in lung cancer cell lines and demethylation restored DAP kinase gene expression (Tang et al. 2000).

DNA repair plays a critical role in protecting the genome of the cell from insults of cancer-causing agents, such as those found in tobacco smoke. Reduced DNA repair capacity, therefore, can increase the susceptibility to smoking-related cancers. Recently, three coding polymorphisms in x-ray cross-complementing group 1 (XRCC1) DNA repair gene have been identified, and it is possible that these polymorphisms may affect DNA repair capacity and thus modulate cancer susceptibility. Polymorphisms of XRCC1 appear to influence risk of lung cancer and may modify risk attributable to environmental exposures. A recent published study suggests that XRCC1 codon 399 polymorphism may be an important genetic determinant of SCC of the lung in persons with lower amounts of cigarette use (Park et al. 2002).

14.3.6 Preneoplasia and Intraepithelial Neoplasia

Increased risk of developing lung cancer among long-term heavy smokers continues for many decades after stopping smoking; one study of a prospective cohort of women from the Iowa Women's Health Study found the risk for lung cancer increased for both current smokers and former smokers compared with never smokers (relative risk 6.6; 95 % C.I. 5.0–8.7), and notably, for former smokers the risk was increased for up to 30 years after smoking cessation (Ebbert et al. 2003). Lung cancer is not the result of a sudden transforming event in the bronchial epithelium but a multistep process in which gradually accruing sequential genetic and cellular changes result in the formation of an invasive (i.e., malignant) tumor. Mucosal changes in the large airways that may precede or accompany invasive squamous carcinoma include hyperplasia, metaplasia, dysplasia, and carcinoma in situ (CIS) (Franklin 2000). Hyperplasia of the bronchial epithelium and squamous metaplasia are generally considered reversible and are believed to be reactive changes in the bronchial epithelium, as opposed to true preneoplastic changes (Wistuba et al. 1999).

In contrast, moderate to severe dysplasia and CIS lesions seldom regress after smoking cessation (Lam et al. 1999) and frequently precede squamous cell carcinoma of the lung (Colby 1999). Advances in the understanding of lung cancer biology have led to observations that specific genetic changes occur in premalignant dysplasia (Kennedy et al. 1996).

14.3.7 The "Field of Cancerization" Concept

The concept of "field cancerization" was originally coined by Slaughter et al. more than 60 years ago to describe molecular abnormalities noted in histologically normal epithelium adjacent to tumors in the head and neck region (Slaughter et al. 1953). This concept has been shown to apply to epithelial cancers in general and is particularly relevant to lung carcinogenesis in that in smokers the entire aerodigestive epithelium encompassing the oral and nasopharynx, hypopharynx, larynx, tracheobronchial tree, and upper GI epithelium is exposed chronically to tobacco smoke. Molecular/genetic and epigenetic changes have been found not only in histologically normal respiratory epithelium of patients with lung cancer but also in that of current and former smokers without lung cancer. For example, KRAS mutations, which act as drivers of the malignant process in lung and many cancers, have been found in histologically normal epithelium adjacent to lung cancers (Nelson et al. 1996). EGFR gene mutations have been noted in normal adjacent epithelium in patients with lung cancers harboring EGFR gene mutations that drive development of the lung cancer (Tang et al. 2005). More recently, gene expression profiling of the aerodigestive tract has yielded "signatures" of aberrant gene expression (see below) in tobacco-exposed individuals as well as individuals with lung cancer across the tobacco-exposed epithelium (Gustafson et al. 2010; Spira et al. 2004).

14.4 Chemoprevention of Lung Cancer

It is recognized that the optimal means to prevent lung cancer are through the prevention of tobacco use and through smoking cessation programs. However, former smokers remain at elevated risk of lung cancer. Thus, strategies designed to prevent cancers in high-risk populations are a critical element in reducing the burden of lung cancer. A central concept of chemoprevention is that intervention is likely to be most effective during identifiable premalignant steps of carcinogenesis.

14.4.1 Biomarkers in Lung Cancer Chemoprevention Studies

Because the multistep process of carcinogenesis can take many years, assessment of clinical chemoprevention trials using cancer incidence as an endpoint requires lengthy follow-up period and large sample sizes. The use of surrogate endpoint biomarkers (SEBs) potentially circumvents these issues by evaluating a biologic event that takes place between a carcinogen or external exposure and the subsequent

development of cancer. Because of the field of cancerization and the fact that the multipath process of carcinogenesis is not regarded as a series of linear steps but rather as overlapping networks, multiple surrogate endpoint markers (SEBs) are preferable to identify potential epigenetic or genetic alterations leading to cancer. In order to be valid, the quantitative degree and pattern of the SEBs should correlate with carcinogenic transformation, should respond to the intervention in a timely manner, and should reflect reversible events.

SEBs of lung carcinogenesis include tissue-associated biomarkers such as histologic lesions of preneoplasia and intraepithelial neoplasia as described above; measures of cellular proliferation such as Ki-67 and PCNA; mutated genes such as KRAS, EGFR, and p53; and markers of aberrant signaling pathways such as overexpression of AKT/MAPK, angiogenesis.

Abnormal gene expression profiles have been identified in the aerodigestive epithelium of smokers and in lung cancer patients through global mRNA and microRNA profiling. A robust smoking-related signature has been identified in the bronchial epithelium of smokers in which genes involved in the regulation of oxidant stress, xenobiotic metabolism, and oncogenesis are induced and genes involved in regulation of inflammation and tumor suppression are suppressed (Spira et al. 2004). Of great interest is that this smoking-related gene expression signature has been identified in the nasal and buccal epithelia, which appear to be a valid surrogate tissue for bronchial epithelium that can be sampled in a relatively noninvasive fashion compared to invasive techniques to sample the bronchial epithelium (Sridhar et al. 2008). Epigenetic changes that affect gene expression have been shown to play a role in lung carcinogenesis. One type of epigenetic mechanism shown to be dysregulated with chronic smoke exposure involves microRNAs, which regulate the translation of expressed genes into proteins. The dysregulation of microRNAs that can activate carcinogenetic mechanisms, such as oncogene and tumor suppressor gene dysregulation, carcinogen detoxification, DNA repair mechanisms, apoptotic pathway regulation, angiogenesis, and inflammation, has been noted in chronic smoke-exposed respiratory epithelium and can serve as a biomarker for lung chemoprevention studies (De Flora et al. 2012). Gene promoter hypomethylation, an epigenetic mechanism by which gene expression is silenced and a good candidate biomarker for early lung carcinogenesis, can be assessed in bronchial epithelium but also in the more noninvasively sampled-induced sputum (Belinsky et al. 2002).

Circulating SEBs are of interest in that they are collected in relatively noninvasive ways. Circulating levels of biomarkers of inflammation such as measures of oxidative stress may be measured in urine and have been used in lung cancer chemoprevention trials. Protein profiling (proteomics) in blood and urine has been introduced as a biomarker for lung carcinogenesis.

14.4.2 Chemopreventive Agents Under Investigation

The explosive growth in the understanding of the molecular and genetic mechanisms underlying lung carcinogenesis has allowed for identification of critical genes that may be mutated, silenced epigenetically, or overexpressed in preneoplastic and

neoplastic tissue; additionally, key proteins, growth receptors, and cellular pathways have been identified that may be aberrantly expressed in the carcinogenic pathway and/or invasive cancer. Consequently, it has become possible to select natural products that have modulatory effects on one or several of these molecular/genetic targets and to rationally design synthetic agents that efficiently target these critical elements in the carcinogenic process in relatively selective or nonselective fashion. Given that molecular targets relevant to the carcinogenic process are often not highly nor aberrantly expressed in normal tissue, targeted agents often have good safety profiles for normal tissues. Optimal chemoprevention agents are those that have minimal normal tissue toxicity, that have good bioavailability, and that have excellent safety profiles over the long term. Below is a non-exhaustive list of natural products and derivatives as well as synthetic agents that have been studied or are currently under study in lung cancer chemoprevention.

14.4.3 Dietary Supplements, Foods, and Phytonutrients

In today's society, human activities and lifestyles generate numerous forms of environmental oxidative stress. Oxidative stress is defined as a process in which the balance between oxidants and antioxidants is shifted toward the oxidant side. This shift can lead to antioxidant depletion and potentially to biological damage if the body has an insufficient reserve to compensate for consumed antioxidants. The "antioxidant hypothesis" proposes that vitamin C, vitamin E, carotenoids, and other antioxidants in fruit and vegetables afford protection against heart disease and cancer by preventing oxidative damage to lipids and to DNA, respectively. Therefore, an increased oxidative stress accompanied by reduced endogenous antioxidant defenses may have a role in the pathogenesis of cancer.

The ability to evaluate any reduction in the primary endpoint of lung cancer requires large studies with large samples and lengthy follow-up. Several phase III trials completed, including the Alpha-Tocopherol Beta Carotene Cancer Prevention Study (ATBC Study) (1994) and the Beta-Carotene and Retinol Efficacy Trial (CARET) (Omenn et al. 1996), designed to prevent the occurrence of lung cancer in male current smokers, yielded negative results. The CARET study evaluated beta-carotene and retinol in two populations at risk for lung cancer, including male asbestos workers and female and male cigarette smokers with 20 pack-years or greater history (either current or former smoker within 6 years of cessation). This was a randomized trial utilizing a 2 by 2 factorial design. An increase in lung cancer in the cohort receiving study vitamins was noted, although it did not reach statistical significance. With further analysis, it appeared that the beta-carotene supplemented cohort of current smokers had a 28 % increase in rate of lung cancer (Omenn et al. 1996).

The surprising detrimental effect of beta-carotene in the CARET trial was in accordance with findings of another large 2 by 2 factorial design study in Finnish male smokers utilizing beta-carotene and vitamin E (ATBC Study). This study reported that the group taking beta-carotene supplements had an 18 % increase in lung cancer as well as an 8 % increase in total mortality (1994). There did not

appear to be a benefit, in terms of lowering lung cancer risk, for α-tocopherol. It has been since hypothesized that oxidation products of beta-carotene formed in the presence of smoke may have procarcinogenic effects, with some in vitro and in vivo data supportive of this hypothesis (Wang and Russell 1999). These studies illustrate the importance of testing hypotheses derived from epidemiologic and laboratory data in the setting of large, randomized controlled trials, with careful consideration of potential and possibly unexpected interaction in the populations to be studied.

Despite the unexpected results from the CARET and similar supplementation trials showing that supplementation with certain micronutrients may *increase* rather than decrease lung cancer incidence in certain at risk populations, considerable interest remains in investigating how other compounds in fruits and vegetables may affect lung cancer risk.

Gene promoter hypermethylation causing silencing of genes implicated in lung cancer but also silenced earlier in the carcinogenic process is a candidate biomarker for lung cancer risk. The role of diet and multivitamin use in modulating gene promoter methylation in sputum was studied in a large cohort of current smokers. There was significant protection against gene promoter methylation by ingestion of leafy green vegetables and folate as well as current use of multivitamins (Stidley et al. 2010). This study supports further study of these dietary components as chemopreventive strategies in smokers.

Interest in cruciferous vegetables and their active derivatives is supported by results of a case–control study that showed an inverse association between cruciferous vegetable intake and lung cancer risk (Lam et al. 2010). Clinical studies have been recently completed or are underway that investigate a cruciferous vegetable derivative (broccoli sprout extract) and a naturally occurring class of agent found in cruciferous vegetables shown to inhibit carcinogenesis in laboratory studies (isothiocyanates) for the ability to modulate biomarkers of lung carcinogenesis (http://Clinicaltrials.gov).

A naturally occurring product of great interest in lung cancer chemoprevention is *myo*inositol, a naturally occurring isomer of glucose that is found in many foods including whole grains, seeds, and fruits. It has been shown to inhibit lung tumorigenesis in tobacco-induced mouse models (Estensen and Wattenberg 1993; Hecht et al. 2001). In a small study of nine smokers who took *myo*inositol, six had regression of bronchial dysplasia; interestingly, dysplastic tissue from the airways of these with lesion regression showed alterations in gene expression associated with a reduction of proximal airway P13K pathway activation, a signaling pathway whose activation is an early, reversible event in the development of lung cancer (Gustafson et al. 2010).

14.4.4 Beverage Tea and Tea Catechins

Tea is a beverage made from the leaves of *Camellia sinensis* species of the Theaceae family. This beverage is one of the most ancient and, next to water, the most widely consumed liquid in the world. Tea leaves are primarily manufactured as green or black or oolong, with black tea representing approximately 80 % of the tea products

consumed. Green tea is the nonoxidized, non-fermented product of the leaves and contains several polyphenolic components, such as epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG). EGCG is the major green tea polyphenol (more than 40 % dry weight). The lowest effective dose of 0.016 mmol EGCG/kg/day in rodent cancer models is comparable to the consumption of four cups of green tea or 17.7 mmol/kg/day of EGCG by a 70 kg man (1996).

Tea polyphenols are the major polyphenolic compounds of tea. They scavenge active oxygen radicals (Cheng 1989) and inhibit DNA biosynthesis of the tumor cells (Katiyar et al. 1992) and chemocarcinogen-induced carcinogenesis (Xu et al. 1993). They also block the inhibitory effect of carcinogens on normal intercellular communication (Siegler and Ruch 1993) and induce apoptosis (Zhao et al. 1997). Tea-derived polyphenols exhibit antimutagenic and genotoxic activities that may be associated with anticarcinogenic activity (Okai and Higashi-Okai 1997). Stich et al. (Stich et al. 1982) showed that water-soluble extracts of green and black teas inhibited the mutagenicity in a nitrosation model system.

Because cigarette smoking and tea drinking are very common in many diverse populations, several studies have explored the possible inhibitory effects of tea on lung cancer formation induced by cigarette smoking. Several studies have reported that green tea and black tea inhibit the formation of lung tumors in A/J mice induced by the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), the most potent carcinogen found in cigarette smoke (Wang et al. 1992; Xu et al. 1992). The effect of tea may be related to the significant inhibitory effects on NNK-induced oncogene expression in mouse lung (Hu et al. 1995).

Tea is a promising agent for the potential chemoprevention of cancer (Yang and Wang 1993; Stoner and Mukhtar 1995). Polyphenolic compounds present in tea afford protection against chemical carcinogen-induced tumor initiation and tumor promotion in lung and forestomach of A/J mice (Wang et al. 1992; Xu et al. 1992). An investigation of the effects of oral administration of decaffeinated green tea or black tea on NNK-induced lung tumorigenesis (Yang et al. 1998) reported significant protection against lung tumor formation when tea was given either during or after NNK treatment. A study on the bioavailability of radioactive EGCG revealed that radioactivity was widely distributed into various organs of mouse and that 0.16 % of total administered radioactivity was observed in lung tissue 24 h after oral administration (Suganuma et al. 2001).

Ohno et al. (1995) showed that daily tea consumption significantly decreased the risk of lung squamous cell carcinoma in males and females; the odds ratios were 0.50 and 0.8, respectively. Mendilaharsu et al. (1998) investigated the effect of drinking tea on the lung cancer risk of male cigarette smokers in a case–control study in Uruguay. They found that high intake (two or more cups per day) was associated with a reduced risk of lung cancer in smokers (0.34; 95 % confidence interval [CI]: 0.14–0.84). Flavonoids, including catechins, have been reported to protect against chronic lung disease. Total antioxidant capacity of plasma was significantly increased after taking green tea in amounts of 300 and 450 ml, and a positive increment according to green tea dosage was also observed (Sung et al. 2000). A Japanese prospective cohort study revealed that the consumption of ten cups (120 ml each) of

green tea per day delayed cancer onset of both never smokers and current smokers. Green tea showed the strongest protective effects on lung cancer (relative risk = 0.33) (Fujiki et al. 2001). However, results have not been consistent; Tewes and colleagues (Tewes et al. 1990) reported a tentative increase in lung cancer risk among green tea drinkers. Results were stated as tentative since only 23 cases (11.5 %) and 13 controls (6.5 %) reported regular tea drinking and the authors did not have data to perform a dose–response analysis.

Investigations into the anticarcinogenic properties of tea (studies of green tea and green tea extracts) have shown growth inhibitory effects in a number cancer cell lines (Ahmad et al. 1997; Suganuma et al. 1999). Investigation into the mechanism of EGCG-induced apoptosis revealed that treatment with EGCG resulted in DNA fragmentation, induction of caspase-3/CPP32 activity, and cleavage of the death substrate poly(ADP-ribose)polymerase (Islam et al. 2000). Masuda and co-workers (Masuda et al. 2001) examined the molecular effects of EGCG on two human head and neck SCC cell lines, YCU-N861 and YCU-H891, focusing on the EGFR signaling pathway. Treatment with EGCG induced apoptosis and caused a decrease in the Bcl-2 and Bcl-X(L) proteins, an increase in the Bax protein, and activation of caspase 9, suggesting that EGCG induces apoptosis via a mitochondrial pathway. Treatment with EGCG also inhibited phosphorylation of the EGFR and also inhibited basal and transforming growth factor-alpha-stimulated c-fos and cyclin D1 promoter activity. EGCG at 0.1 mcg/ml (a concentration found in serum after oral administration) enhanced the growth-inhibitory effects of 5-fluorouracil. Taken together, these findings provide insights into molecular mechanisms of growth inhibition by EGCG.

The effect of high consumption of decaffeinated green or black tea on oxidative DNA damage in current smokers was investigated in a phase II randomized, controlled intervention trial. After 4 months of four cups of tea ingestion daily, smokers in the green tea group had a significant decrease in urinary 8OHdG (−31 %), while there was no change noted in smokers in the black tea group (Hakim et al. 2003). These results, taken together other epidemiologic and preclinical data supporting a preventive role for tea and its derivatives, provided a rationale for several large, randomized placebo-controlled phase III trials of green and black beverage tea and tea catechins in cohorts of former and current smokers which have been completed and are being analyzed (Hakim et al. 2012). The primary biomarkers for these studies are measures of oxidative stress. Emerging data from these studies will help define the role of tea and tea catechins in lung cancer chemoprevention.

14.4.5 Nonsteroidal Antiinflammatory Drugs (NSAIDs)

The cyclooxygenase (COX) enzymes, which catalyze the production of prostaglandins from arachidonic acid, play an important role in inflammation and cancer (Subbaramaiah and Dannenberg 2003; Krysan et al. 2006). Two isoforms of COX enzymes, COX-1 (constitutively expressed) and COX-2 (inducible early response gene product) are targets of the traditional (nonselective) NSAIDs, whereas coxibs selectively inhibit COX-2. Epidemiologic studies of long-term NSAID use

collectively support a chemopreventive role for NSAIDs in epithelial cancer chemoprevention, including chemoprevention of lung cancer (Harris and Beebe-Donk 2005). The chemopreventive effect of NSAIDs increases with increasing duration of use. In animal models of lung carcinogenesis, treatment with nonselective NSAIDs and coxibs has chemopreventive activity. In the DMBA-induced model of lung carcinogenesis, treatment with aspirin, an irreversible COX-1 and COX-2 inhibitor, and the selective COX-2 inhibitors celecoxib and etoricoxib decreased the incidence of pulmonary tumors, dysplastic changes, and inflammation (Saini and Sanyal 2009). In the DMBA-induced model of lung carcinogenesis, treatment with the traditional NSAID indomethacin and etoricoxib restored apoptosis (programmed cell death), with a greater effect seen with etoricoxib (Setia et al. 2012).

A set of unique challenges is posed with each of the two main classes of COX inhibitors in their long-term use as chemoprevention agents. Chronic treatment with NSAIDs has a cardioprotective effect while causing an increase in gastrointestinal toxicity, including peptic ulcers and gastrointestinal bleeding events. The more recently developed coxibs as a class have been associated with a lower risk of gastrointestinal side effects but with increased cardiovascular side effects, including myocardial infarction and clotting events (Dajani and Islam 2008). The coxib safety profile thus presents challenges to their long-term use in chemoprevention strategies, especially in persons with underlying cardiovascular disease.

These data have provided a rationale to test COX inhibitors in chemoprevention studies in cohorts at risk for lung cancer. A randomized, placebo-controlled phase II trial of sulindac, a nonselective Cox-2 inhibitor, was conducted in current or former smokers. Eligible participants had at least one bronchial dysplastic lesion identified by fluorescence bronchoscopy (a method that is more sensitive for detecting high-grade dysplastic bronchial lesions and carcinoma in situ than white light bronchoscopy (Lam et al. 2000); trial endpoints included changes in histologic grade of dysplasia, number of dysplastic lesions per participant, and Ki67 labeling index (a measure of cellular proliferation). No statistically significant differences in these endpoints were noted for the sulindac arm (Limburg et al. 2013). Celecoxib, a selective COX-2 inhibitor, was administered for 6 months to a small number of active heavy smokers. Bronchial biopsies obtained before and after intervention showed that celecoxib reduced Ki-67 labeling index, a measure of cellular proliferation, and favorably modulated surviving expression, which plays a role in programmed cell death (Mao et al. 2006). A randomized, double-blind placebo-controlled trial of celecoxib in former smokers showed that celecoxib modulated bronchial Ki-67 labeling index. Additionally, decreases in Ki-67 labeling index correlated with a reduction and/or resolution of lung nodules on computed tomographic imaging. Celecoxib remains of interest as a lung chemopreventive agent in persons with a low cardiovascular risk profile (Mao et al. 2011).

Aspirin (ASA) is a nonselective NSAID whose use has been associated with a reduced risk of a number of precancerous conditions and cancers; a meta-analysis of observational studies through 2011 reported the strongest favorable effect on risk of colorectal cancer (RR of 0.73) and other GI cancers (RR of 0.61), with greater support for risk reduction reported in case–control than in cohort studies. More modest risk reductions were reported for breast cancer (RR of 0.90) and prostate

cancer (RR 0.90), while there was significant reduction in risk of lung cancer noted in case–control studies (RR 0.73) but not in cohort studies (RR 0.98) (Mills et al. 2012; Algra and Rothwell 2012; Bosetti et al. 2012). A second recent meta-analysis reported a nonsignificant trend toward reduction in risk of lung cancer in a analysis of randomized trials utilizing ASA intervention (RR of 0.84, CI 0.69–1.03) (Algra and Rothwell 2012). In an analysis of a large cohort study (VITamin And Lifestyle study), total NSAID use (greater than 10 years) was associated with a borderline significant reduction in risk of lung cancer (HR 0.82; 95 % C.I. 0.64–1.04), with the strongest association noted for adenocarcinoma (HR 0.59); this trend was limited to men (HR 0.66) and to long-term (≥10 years) former smokers (HR0.65). These trends did not differ for ASA (excluding low-dose ASA) versus total NSAID use (Slatore et al. 2009). This analysis, as well as an analysis of the Iowa Women's Health Study cohort which reported no significant trend for reduced lung cancer risk with ASA or non-ASA NSAID use (P_{trend}=0.53, with no difference when analyzed by histologic subtype and smoking status), suggests a possible gender effect in the chemoprotective effect of ASA for lung cancer (Hayes et al. 2006).

Proposed cellular/molecular mechanisms of action for the chemopreventive activity of ASA, which is an irreversible, nonselective COX-1 and COX-2 inhibitor, include inhibition of COX-2 and possibly COX-1, induction of tumor suppressor NAG-1, and other non-COX related induction of apoptosis and anti-angiogenic actions (Thun et al. 2002; Schror 2011; Baek and Eling 2006).

Interest in ASA for lung cancer prevention also derives from the study of ASA in preclinical models of tobacco- and chemical-induced lung carcinogenesis. In a 4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanone (NNK)-induced murine model of lung tumorigenesis, ASA inhibited tumorigenesis by 60 % and lowered PGE2 levels to basal levels (Castonguay et al. 1998). In a 9,10-dimethylbenz(a)anthracene (DMBA)-exposed murine model of lung carcinogenesis, ASA intervention decreased the incidence of lung tumors (Saini and Sanyal 2009). In contrast, ASA did not reduce incidence or multiplicity of lung tumors in tobacco smoke-exposed A/J mice (Witschi 2000).

Collectively, these data support further studies of ASA in the chemoprevention of lung carcinogenesis in high-risk individuals. However, the optimal ASA dose and, importantly, dosing schedule remain to be determined. One limitation of chronic daily ASA use is its side effect profile. The safety profile of ASA for chemoprevention has been well established in the setting of prevention of cardiovascular disease. The most frequently reported adverse events for regular ASA are gastrointestinal bleeding. There is interest in evaluating alternative ASA dosing schedules that utilize intermittent as compared to continuous dosing, which may prove to be safer with chronic use.

14.4.6 Steroids

Interest in steroids as a lung chemopreventive class is based in part on an epidemiologic study of patients with chronic obstructive pulmonary disease treated with inhaled steroids that showed a dose dependent decrease in risk of lung cancer (Parimon et al. 2007).

The aerosolized administration of the glucocorticoid budesonide, which is a widely used in the treatment of asthma, inhibited progression of bronchial hyperplasia to lung cancer in a chemical carcinogen-induced mouse model of lung carcinogenesis (Estensen et al. 2004). A randomized study of inhaled budesonide in smokers with central bronchial dysplastic lesions did not cause regression of lesions nor prevent new lesions, compared to placebo. However, a small but statistically significant decrease in computed tomography (CT) scan-detected pulmonary nodules of indeterminate etiology in the inhaled budesonide treatment group was noted (Lam et al. 2004). This intriguing finding suggested that inhaled steroids might impact on more peripheral lung carcinogenesis, which is mainly attributable to precursors of adenocarcinoma. Thus, a randomized, placebo-controlled phase II trial of a year-long intervention of inhaled budesonide in current and former smokers with preexisting CT-detected lung nodules was undertaken. The effect of budesonide on lung nodule size was the primary endpoint. While budesonide intervention did not impact existing lung nodules overall, a subgroup analysis showed a trend toward decreased size of nonsolid and partially solid nodules which are more likely precursors of adenocarcinoma. These data support the further investigation of inhaled steroids to reverse the premalignant process that underlies the development of adenocarcinomas of the lung.

14.4.7 Prostacyclins

Prostacyclin is a naturally occurring eicosanoid that is derived through the COX pathway. Prostacyclin is expressed in normal lung and also in lung cancers; decreased expression has been reported in lung adenocarcinomas (Stearman et al. 2006). In multiple preclinical models of lung cancer including smoke exposure-induced models, prostacyclin supplementation via genetic overexpression or supplementation of an oral analogue of prostacyclin prevents the development of lung cancer (Keith et al. 2002, 2004). A preclinical study showed that iloprost, a prostacyclin analogue, can activate the peroxisome proliferator-activated receptor γ (PPARγ), a ligand-activated family of nuclear receptors whose expression is increased in NSCLC and that appears to be target for lung chemoprevention (Theocharis et al. 2002; Nemenoff et al. 2008). A double-blind, randomized, phase II placebo-controlled trial of oral iloprost was studied in current and former smokers harboring sputum cytologic or endobronchial atypia. Compared to placebo, a 6-month intervention of oral iloprost in former smokers resulted in improved endobronchial histology; this was not, however, noted in current smokers (Keith et al. 2011). This study provides a rationale for further studies of iloprost in high-risk former smoker cohorts with interest in exploring other routes of delivery (i.e., inhalation delivered agent).

14.4.8 Antidiabetic Agents

The thioglitazones (TZDs) are drugs which are used commonly to control blood glucose in the setting of type II diabetes. TZDs act as agonists of PPARγ, a relevant target for lung chemoprevention, and also have what are likely "off-target" effects

which include decreasing PGE_2, whose high expression in lung cancer is thought to drive carcinogenesis, and enhancement of apoptosis (programmed cell death) (Nemenoff 2007). Retrospective studies of large cohorts of persons using TZDs for diabetes control have shown a decrease in lung cancer risk in these populations, suggesting that the TZDs may prove useful as chemopreventive agents in high-risk groups (Nemenoff 2007). The TZDs pioglitazone and troglitazone have inhibitory activity in mouse models of lung cancer (Keshamouni et al. 2004; Satoh et al. 2002; Wang et al. 2010). There is currently a randomized, placebo-controlled trial underway testing pioglitazone in current and former smokers to see how it may retard progression of preneoplastic endobronchial lesions and also to assess the activity of pioglitazone in modulating the PPARγ signaling pathway in endobronchial tissue (http://Clinicaltrials.gov).

Metformin represents another class of antidiabetic drug that activates AMPK, a regulator of cellular metabolism whose activation is linked to carcinogenesis via the mTOR pathway, an important pathway in lung cancer development. Metformin inhibits the development of lung tumors in a mouse tobacco carcinogen model of lung cancer (Memmot et al. 2010). A randomized, placebo-controlled study of metformin is underway that evaluates its role after surgical resection of lung cancer in decreasing the frequency of bronchial dysplasia after surgery (http://Clinicaltrials.gov).

14.5 Screening for Early Detection of Lung Cancer

The ideal method for decreasing the burden of lung cancer in the near and distant future is through primary prevention (i.e., decreasing the initiation of cigarette use), especially in children and adolescents. Nevertheless, there are more than 40 million current smokers who are at risk for the development of lung cancer, only some of whom will successfully stop smoking. Additionally, there are 40–50 million former smokers in the USA who remain at an increased risk for the development of lung cancer even decades after quitting smoking (Hammond 1966; Doll and Peto 1976; Rogot and Murray 1980). Therefore, the development of effective lung cancer screening programs has been the focus of much interest in scientific research and public health domains. Early strategies for screening for lung cancer included the use of chest x-rays with or without cytologic analysis of sputum. More recent strategies have looked at the use of more sophisticated chest imaging and the incorporation of molecular biomarkers of lung carcinogenesis.

14.5.1 Standard Chest X-Rays and Sputum Cytology

Lung cancer screening programs were first initiated in the early 1950s, around the time that the link between tobacco exposure and lung cancer was reported in the scientific literature. Since then, ten prospective trials have been designed and implemented that have utilized chest x-rays or sputum cytology in high-risk populations. Of note, nine of these trials did not include women. Three studies sponsored by the National Cancer Institute in the 1970s utilized a randomized trial design. Two of

these studies, the Memorial-Sloan Kettering Study and the Johns Hopkins Lung Project, looked at the addition of cytology to chest x-ray screening (Melamed et al. 1984; Tockman 1986). While no benefit in terms of reduction of lung cancer mortality (considered the optimal endpoint due to absence of bias of screening efficacy) was gained with the addition of cytology, there were improvements in resectability and 5-year survival in the study population as compared to the Surveillance, Epidemiology, and End Results database. The Mayo Lung Project (Fontana et al. 1984) evaluated chest x-ray plus cytology on an intensive schedule as compared to a control group, a portion of whom did receive chest x-rays on an annual or less frequent schedule outside of the study setting. There was no significant reduction in lung cancer mortality in the screened arm, and therefore the trial was originally deemed a negative screening trial. However, more recent analysis has shown that survival as an endpoint, which was improved in the screened arm, was not subject to biases (length, lead time, and overdiagnosis); as such, the reanalysis argues for a positive effect for this screening intervention (Strauss et al. 1997).

14.5.2 Low-Dose Helical Computed Tomography

A step forward in the development of lung cancer screening technologies was the design of low-dose helical or spiral computed tomography scan (LDCT). Developed in the 1990s, this scan allows for x-ray scanning of the entire chest in approximately 15–25 s. Images approximating a three-dimensional model of the lungs are generated via a computer program. Additionally, this technology employs a low dose of radiation and eliminates use of an intravenous contrast material, thus making it safer than the traditional high-resolution contrasted CT scan. Limitations of this technology include a decreased sensitivity for detecting imaging abnormalities in the central regions of the lung, where more squamous cell lung cancers are located, and in the soft tissues of the middle of the thorax, where lymph nodes that may be involved by metastatic lung cancer are detected. Another potential limitation in the utilization of CT imaging in populations at risk for lung cancer is the detection of benign abnormalities, which may provoke unwarranted invasive and costly diagnostic procedures, such as biopsy.

A landmark study of the use of helical CT imaging in the screening of persons at risk for lung cancer yielded important new data in lung cancer screening and early detection. The New York Early Lung Cancer Project (ELCAP) evaluated the usefulness of LDCT screening in finding early-stage lung cancers (Henschke et al. 1999). The ELCAP study evaluated a nonrandomized cohort of 1,000 smokers over the age of 60 and with a history of significant cigarette use with both annual chest x-ray (CXR) and LDCT. The main outcome measure was the frequency of detection of noncalcified lung nodules by imaging technique. This study showed the superiority of LDCT screening over CXR screening in the detection of non-calcified lung nodules (found in 233 persons by LDCT compared with 68 persons by CXR). By an algorithm that included the use of an additional high resolution CT scan to better assess the nodules and by assigning either a close follow-up program with reimaging of the nodules versus proceeding directly to biopsy, LDCT screening detected

close to six times more malignant nodules than did CXR (2.3 versus 0.4 %). Of 28 nodules biopsied, 27 were malignant; thus only one biopsy was performed for a benign nodule. Eighty percent of those lung cancers found by LDCT were Stage I cancers (less than 3 cm in greatest dimension, without lymph node involvement or distant metastases), which have the highest potential for cure via surgical resection or radiation therapy. In general, CXR detected the larger tumors. Of the 27 nodules detected by LDCT, 26 were surgically resectable. Importantly, the cost-effectiveness of this strategy thus far has been impressive. The cost of a screening program consisting of a single baseline LDCT screening study in a fit person at least 60 years of age with at least 10 pack-years of smoking was only $2,500 per year of life saved (Wisnivesky et al. 2003). The cost of treating an early-stage lung cancer is at least half the cost of treating an advanced-stage lung cancer.

14.5.3 The National Lung Screening Trial

The provocative findings of the ELCAP study, in concert with reanalyses of earlier chest x-ray-based screening studies, prompted a large screening initiative sponsored by the National Cancer Institute and the American Cancer Society. Initiated in 2002, the National Lung Screening Trial (NLST) reached its accrual goal of 50,000 current or former smokers aged 55–74 at high risk for lung cancer (at least a 30 pack-year history of smoking, and those who had quit had to have quit smoking within the past 15 years). The participants were randomized to receive annual screening with either LDCT or CXR imaging for 3 years, followed by annual monitoring of participant health status through 2009. Collection of relevant biologic samples (blood, urine, and sputum) for use with diagnostic markers of lung cancer, as well as biomarkers of the carcinogenic pathway, were also collected (NCI 2004). In October 2011 the National Cancer Institute announced that the primary analysis of NLST showed a statistically significant reduction in lung cancer mortality of 20 % (95 % CI, 6.8–26.7) with LDCT screening compared to CXR screening. Overall mortality was reduced by 6.7 % (95 % CI, 1.2–13.6). The number needed to screen with low-dose CT to prevent one death from lung cancer was 320. Furthermore, the LDCT arm had not experienced unforeseen adverse screening effects that would lead to uncertainty about the benefit/harm ratio for LDCT screening (Aberle et al. 2011). Other randomized trials evaluating LDCT in lung cancer screening are underway in other countries, and data from NLST are in further analysis to answer important questions regarding cost-effectiveness, quality of life, and in defining other risk groups (i.e., younger persons with significant smoking histories, persons with a family history of lung cancer).

While there remain important questions regarding potential benefits and harms that may be associated with LDCT screening, these data clearly suggest that the implementation of LDCT screening in large populations of persons at high risk of lung cancer may impact lung cancer mortality in the USA and global in a significant way. A number of organizations including the American Cancer Society have provided interim guidances on lung cancer screening (ACS 2013).

Conclusion

In the New Millennium, lung cancer continues to exact an extremely large toll in terms of cancer-related morbidity and mortality as well as its effect on health care systems and economies worldwide. This is in spite of public health efforts initiated in the 1960s to educate the public about the dangers of tobacco use and the implementation of smoking cessation programs. While up to 50–60 % of adults in some countries continue to smoke, formers smokers form a growing population who remain at elevated risk for developing lung cancer for many decades after stopping tobacco use

A growing understanding of lung carcinogenesis from the molecular/genetic standpoint has complemented epidemiologic studies that have identified high-risk populations that are most likely to benefit from intervention strategies. Chemoprevention strategies currently employ a wide range of selective chemopreventive approaches that include dietary modification and supplementation using natural products and their derivatives, as well as a range of synthetic agents that target relevant pathways in lung carcinogenesis. Complementing chemoprevention efforts is a growing body of research that suggests that state-of-the-art screening techniques for early detection will impact on the morbidity and mortality associated with lung cancer.

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Breast Cancer Prevention

15

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In this chapter, we update information on breast cancer etiology and changing patterns of disease incidence in the U.S.A. considering race, ethnicity, and age with a focus on female breast cancers. Male breast cancer is rare and distinct from breast cancers that occur among women and are discussed elsewhere (Dimitrov et al. 2007; Tai et al. 2007; Ravi et al. 2012). This chapter details current information on breast cancer risk factors emphasizing their contribution in risk assessment tools used in patient counseling. We include information on differences by race and ethnicity with a focus on what the physician needs to know about screening and risk assessment in specific populations. For example, the status on the efficacy of available genetic testing for familial forms of the disease and risk assessment tools is described when available as they apply to African American, Asian, Hispanic, as well as White women. With the recent debates regarding screening, we present a discussion of the evidence surrounding the controversial issues along with providing a summary of current screening guidelines and resources for the reader on this topic. This chapter concludes with a discussion of current and future thinking on the role of prevention strategies for women of average, moderate, and high risk of developing breast cancer, with special focus on recommendations for the use of the selective estrogen receptor (ER) modulators or SERMs (e.g., tamoxifen, raloxifene) and aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane), for the primary prevention of breast cancer in high-risk patients.

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15.1 Etiology of Breast Cancer

Tumors of the mammary gland arise through a series of complex molecular alterations that result in deregulated cellular processes ending in the outgrowth and spread of transformed breast epithelial cells with immortal features, uncontrolled growth, and the ability to spread to distant organs (Hanahan and Weinberg 2000; Lacroix et al. 2004; Hanahan and Weinberg 2011). Perhaps the most significant recent advance in our understanding of breast tumorigenesis has come from the extensive genomic efforts that have concluded that "breast cancer" is a more than one disease (Prat and Perou 2011; Network 2012). Breast cancer in humans is comprised of molecularly reproducible tumor subtypes with distinct and increasingly more predictable clinical behavior (Perou et al. 2000; Sorlie 2004, 2009; Sotiriou and Pusztai 2009). While the nomenclature for the molecular subgroups remains debated, clinically the subtypes are identified by the expression levels of the hormone receptors for estrogen (ER) and progesterone (PR) and the human epidermal growth factor receptor 2 (HER2). These include four clinical groupings of the disease.

The view that breast cancer is not a set of stochastic molecular events but a limited set of "separable" diseases of distinct origins has altered thinking about breast cancer etiology. This has resulted in recent efforts to gain a better understanding of risk factors for the disease subtypes. Figure 15.1 summarizes our current understanding of these breast tumor subtypes, prevalence, nature of presentation, and risk factors. Given the significance of the tumor subtypes in terms of clinical appearance and behavior, we have attempted to include available data that integrates information on prevention and risk assessment by subtype when relevant and where possible.

15.1.1 Breast Cancer Incidence in the United States and Subtypes

In the USA, the lifetime risk of breast cancer is estimated from the SEER Registry at 12.4 % for all women (approximately 1 in 8), 13.14 % for non-Hispanic White, 9.83 % for Hispanic, and 10.87 % for Black women (http://seer.cancer.gov). Using data from the California Cancer Registry and defining the subtypes of breast cancers as HR+/HER2−, HER2+, or triple-negative, Kurian et al. (2010) found that for all racial/ethnic groups the lifetime risk of developing HR+ breast cancer was significantly higher than for HER2+ or triple-negative breast tumors. In addition, the authors found that the lifetime risk of the different subtypes differed significantly by race/ethnicity. For example, the risk of developing HR+ disease differed by nearly twofold across the four study groups (White, Black, Hispanic, and Asian) with Hispanics having the lowest absolute lifetime risk of 4.79 % compared to the highest rates in Whites of 8.0 %. The differences for absolute risk of HER2+ tumors by race/ethnicity were small with the absolute risk estimated for HER2+ at 1.70 % (95 % CI 1.66–1.75) disease in all women. In contrast, significant differences were observed for triple-negative breast cancer confirming the recognized high-risk rates for triple-negative disease in Black women at 1.91 % compared to that of Asian 0.72 %, Hispanic 0.98 %, and Whites 1.19 %.

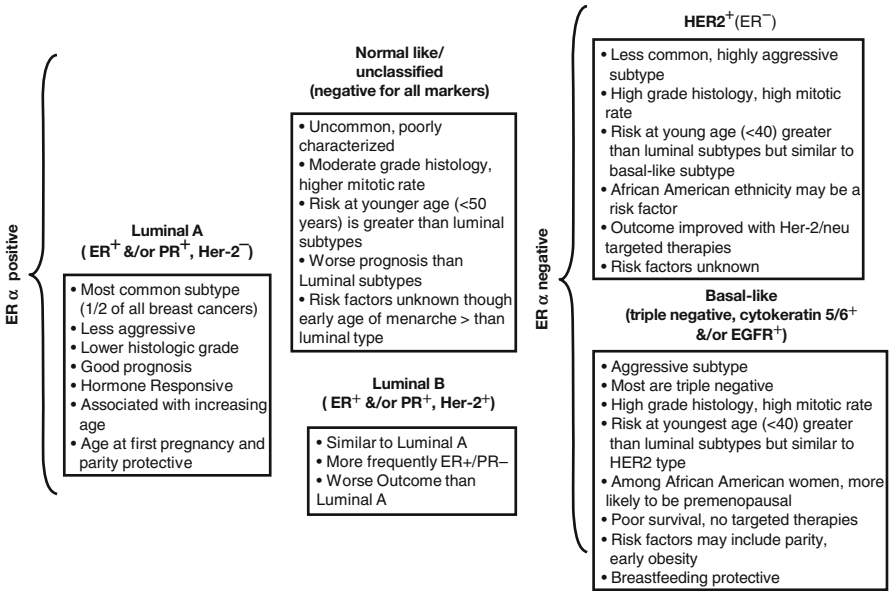

Fig. 15.1 Intrinsic subtypes of breast cancer. *Note*: this figure represents an important emergent area in breast cancer biology, risk assessment and prevention. These descriptions represent a limited number of studies completed to date and are not to be considered established. This figure is included as a glimpse of what future stratification of risk factors and tumor characteristics are likely to develop in the next 5 years and to engage the reader to carefully follow the rapidly evolving understanding of breast cancer etiology and risk factors (This information was compiled from Millikan et al. (2008), Carey et al. (2006), Mullan and Millikan (2007))

15.1.2 Breast Cancer Incidence, Mammography, and Hormone Replacement Therapy

With the introduction of mammography-based screening in the 1970s, a dramatic increase in the incidence of breast cancer was observed and peaked in the 1980s, particularly among women between the ages of 50 and 69. This increased incidence coincided with a doubling of the number of small tumors (<2 cm) with a modest reduction in the rates for advanced disease as early as 1987 (Garfinkel et al. 1994).

After 1987, overall rates of invasive breast cancers continued to rise but at a much slower rate, specifically among White women age 50 or older (increase of 0.5 % per year). For specific histological types, rates varied dramatically. Common ductal carcinomas showed a modest 3 % increase from 1987 to 1999, while invasive lobular carcinomas and mixed ductal–lobular increased 52 and 96 %, respectively, during this time period (Li and Daling 2007). Overall, the annual incidence rates in African American (119.4 out of every 100,000) and Hispanic/Latina (89.9 out of every 100,000) women have remained stable since the early 1990s and remain lower than rates in White women (141.1 out of every 100,000). Incidence rates for women <50 have remained stable since the mid-to-late 1980s, with rates declining in African

American women under 50 in the early 1990s. A similar decline has also been observed in breast cancer rates among American Indians and Alaska Natives (decreasing by approximately 3.7 % per year) (Smigal et al. 2006). This is in contrast to rates among Asians and Pacific Islanders, which have continued to increase at 1.5 % per year. In spite of lower overall rates compared to Whites, African American women remain more likely than White women to be diagnosed with large, advanced stage tumors (>5 cm) and disproportionately with triple-negative breast cancer.

Between 2001 and 2004, breast cancer rates in the Surveillance, Epidemiology, and End Results (SEER) Program data show a dramatic 8.6 % decrease in invasive disease across all age groups, an 11.8 % annual decline for all breast cancer types, and a 14.7 % decline for ER-positive cancers among women 50–69 years of age (Ravdin et al. 2007). During this same time period, no significant change was observed in the incidence of ER-negative cancers or cancers in women <50. This decrease in new cases leveled off in 2005 with ~230,000 new invasive breast cancers estimated for 2012 with an additional 63,000 new incidence of in situ carcinoma of the breast (Siegel et al. 2012).

Within the timeframe of 2001–2004, the decline in rates among older women was greatest between 2002 and 2003 and was limited to non-Hispanic Whites (Glass et al. 2007; Jemal et al. 2007; Ravdin et al. 2007; Katalinic and Rawal 2008). This significant and dramatic decline in incidence sparked considerable debate as to the underlying cause or causes of the change. Given the sharp and near-immediate decline in breast cancer rates coincident with the July 2002 publication of the Women's Health Initiative (Beral 2003) on the risks associated with combined use of estrogen and progestin (E+P) hormone replacement therapy (HRT), significant attention was directed to the decreased use in E plus P combination HRT therapy on breast cancer incidence rates (Ravdin et al. 2007).

To examine the reasons for declining rates of breast cancer in the USA, Jemal and colleagues evaluated data from the nine oldest SEER cancer registries dating back to 1975 (Jemal et al. 2007). Two trends in incidence patterns were observed. First, age-specific incidence rates declined in all women 45 and older beginning as early as 1999. This was subsequently supported by a study on rates, ethnicity, and histologic subtypes using 13 of the SEER population-based cancer registries with rates for both ductal and lobular types of invasive breast cancer (Li and Daling 2007). Both Jemal and Li argue that the declining rates are in part explained by a "saturation" in use of screening mammography of the target population giving rise to an expected plateau in incidence at or near the late 1990s when the adoption of mammogram-based screening stabilized at 70 % use. This saturation in uptake has resulted in a reduction in the pool of previously undiagnosed prevalent cases and therefore declines in new diagnoses. In particular, this appears to be the case for women older than 69 years of age, whose rates of breast cancer began to show evidence of decline as early as 1998 when screening rates had first reached a plateau. This observation is also consistent with the prediction that with widespread screening and earlier detection, breast cancer rates are likely to peak among women during the sixth and seventh decades of life and then decline, exactly the incidence pattern that is now reported for screened populations (Anderson et al. 2007).

Jemal and colleagues further describe how the plateau effect alone could not explain the observed age differences in the magnitude and years of observed declines in rates. Breast cancer rates among women between the ages of 55 and 59 years decreased by 11.3 %, rates decreased by 10.6 % among women 60–64 years of age, and decreased by 14.3 % among women 65–69 years of age (Glass et al. 2007; Kerlikowske et al. 2007b; Ravdin et al. 2007; Katalinic and Rawal 2008). It is important to note that a significant decline was only observed among HR+ tumors. Women 65–69 years of age experienced a 20 % reduction in HR+ tumors compared to a 2 % increase in HR- tumors. These findings supported the hypothesis that exogenous hormones (e.g., HRT) as E in combination with synthetic P may promote the growth of undetected tumors where withdrawal results in regression or a slowing of tumor growth, possibly leading to a delay in detection.

While overall rates from 2005 to 2009, for which recent data are currently available from SEER, suggest that overall new breast cancer case rates have been fairly stable with a +0.9 % annual percentage change (APC) from 2005 to 2009, the observed statistically significant APC of +2.7 % for women 65–74 years during this period parallels the incidence rates of 2001 for this age group (http://seer.cancer.gov accessed 12/27/2012). This rise is occurring in spite of low population use of HRT (Burger et al. 2012) and suggest that the drop in E+P in post 2002 did not result in a sustained decrease in new breast cancer cases.

15.2 Established Breast Cancer Risk Factors

There are several risk factors clinically useful for assessing a patient's risk for breast cancer (Table 15.1). Many of these factors form the basis of breast cancer risk assessment tools that are currently available in the practice setting.

15.2.1 Age, Gender, and Breast Cancer Risk

Increasing age and female sex are established risk factors for breast cancer. Sporadic breast cancer is relatively uncommon among women younger than 40 years of age but increases significantly thereafter. Among screened populations, incidence rates appear to be highest between 50 and 69 years of age, followed by a leveling off or even decline with age after 70 (Anderson et al. 2007). The significant shift in incidence rates during the years surrounding menopause is the basis for initiating annual mammography screening for all women at age 40. Screening the general population under age 40 is not recommended due to low rates of breast cancer and reduced sensitivity of current screening methods in younger women (Smith 2000; Buist et al. 2004). The effect of age on risk is illustrated in the SEER data where the incidence rate of invasive breast cancer for women under the age of 50 years is 44.0 per 100,000 as compared to 345 per 100,000 for women 50 years of age or older (updated http://seer.cancer.gov accessed 12/27/2012). The total and age-specific incidence for breast cancer is bimodal (Jatoi et al. 2008), with the first peak

Table 15.1 Established breast cancer risk factors and estimate relative risk

Risk factor	Relative risk
Advanced age	>4
Family history	>5
Two or more relatives (mother, sister)	>2
One 1st-degree relative (mother, sister)	>2
Family history of ovarian cancer <50	
Personal history	
Breast cancer	3–4
Positive for BRCA1/BRCA2 mutation	>4
Breast biopsy with atypical hyperplasia	4–5
Breast biopsy with LCIS or DCIS	8–10
Reproductive history	
Early age at menarche (<12 years)	2
Late age of menopause	1.5–2
Late age of 1st term pregnancy (>30 years) or nulliparity	2
Use of combined estrogen/progesterone HRT	1.1–1.3
Current or recent use of oral contraceptives	1.5
Lifestyle factors	
Adult weight gain	1.5–2
Sedentary lifestyle	1.3–1.5
Alcohol consumption	1.5
Other	
Breast density	3–5

occurring at about 50 years of age and the second occurring at about 70 years of age. This bimodal pattern may reflect the influence of age within the different tumor subtypes with prevalence of poorly differentiated, high-grade disease occurring earlier compared to hormone-sensitive, slower-growing tumors that occur with advancing age. These results, however, remain controversial with incidence data between 1985–1989 and 1998–2002 from the National Cancer Institute and the North American Association of Central Cancer Registries suggesting that postmenopausal breast cancer rates peak between 75 and 79 years and decline thereafter, secondary to lower screening rates in the advanced elderly (Smigal et al. 2006). These data support the use of screening mammography as women age taking into consideration individual health status and estimated life expectancy (see more extensive discussion on screening guidelines in Screening and Detection, Sect. 15.3).

15.2.2 Family History of Breast Cancer

A positive family history of breast cancer is the most widely recognized risk factor for breast cancer. Risk is approximately five times greater in women with two or more first-degree relatives with breast cancer and is also greater among women with a single first-degree relative, particularly if diagnosed at an early age (age 50 or younger). A family history of ovarian cancer in a first-degree relative, especially if

the disease occurred at an early age (younger than age 50), has been associated with a doubling of risk of breast cancer. In 5–10 % of familial cancer cases, risk is inherited as an autosomal dominant disorder. These hereditary cancers represent a distinct subset of familial breast cancers, which exhibit high penetrance and clustering with ovarian cancers (Antoniou et al. 2003). Mutations in the *BRCA1* and *BRCA2* gene, on chromosome 17 and 13, respectively, are the most commonly identified mutations in families with autosomal dominant inherited breast cancers (Narod and Foulkes 2004; Walsh and King 2007). Mutation rates and type vary by ethnic and racial groups (John et al. 2007; Kwong et al. 2012; Rodríguez et al. 2012). For *BRCA1* mutations, the highest rates occur among Ashkenazi Jewish women (8.3 %) followed by Hispanics (3.5 %), non-Hispanic Whites (2.2 %), African Americans (1.3 %), and Asian Americans (0.5 %). Women who inherit a mutation in the *BRCA1* or *BRCA2* gene suffer an estimated 50–80 % lifetime risk of developing breast cancer (Antoniou et al. 2003).

To aid the clinician in the identification of mutation carriers of *BRCA1/2*, a number of family history-based risk assessment tools have been developed. These include BRCAPRO, Couch, Myriad I and II, Ontario Family History Assessment Tool (FHAT), and the Manchester models. All of these assessment tools are highly predictive of carrier status and aid in reducing testing costs for the majority of mutation negative families (Parmigiani et al. 2007). The most commonly used BRCAPRO model identifies approximately 50 % of mutation negative families, avoiding unnecessary genetic testing, and only fails to screen approximately 10 % of mutation carriers. It is important to note that these clinical genetic risk assessment tools have been developed from mutation rates in Ashkenazi Jewish families and families of European descent. However, these models have been evaluated for their applicability to other populations and have proven to be robust for African American and for Hispanic women. Age of onset and the number of affected family members with breast or ovarian cancer are the most powerful predictors of mutation carrier status (Nanda et al. 2005; Vogel et al. 2007). Thus, these tools are applicable for use in screening all women with strong family histories for possible *BRCA* mutations and should be offered with appropriate counseling. Physicians should be mindful of published findings of disparities in BRCA testing among eligible and insured patients (Olaya et al. 2009) that suggest patient understanding of risks and benefits in relation to their educational level should be optimized to insure equal patient outcomes.

For health care providers, it is notable that a significant portion of ovarian cancers, not previously considered familial, can be attributed to *BRCA1* or *BRCA2* mutations (Pal et al. 2005). In one study of 209 women with invasive ovarian carcinoma not previously identified as familial, 15.3 % had mutations in *BRCA1* or *BRCA2* (20) BRCA1 and 12 BRCA2 mutations. None of the ovarian cancers positive for *BRCA1* or *BRCA2* mutations were of the lower-risk borderline or mucinous histologies. In another study conducted on Colombian women with ovarian cancer, 15.6 % of patients with ovarian cancer with modest or no family history of breast cancer were carriers of a *BRCA1* or *2* mutation (Rodríguez et al. 2012). After excluding cases referred for genetic risk, an American study of 360 women

undergoing surgery for primary ovarian, peritoneal, or fallopian tube carcinoma revealed that 17.5 % carried mutations in *BRCA1* or *2* and another 6.1 % had another identifiable gene mutation (Walsh et al. 2010). These data have led to the suggestion that women with non-mucinous, invasive ovarian cancers may benefit from genetic testing to determine mutation status independent of a family history of a strong history or no history of breast cancer.

Inherited mutations in *BRCA1* and *BRCA2* genes account for only small percentage of all breast cancers but are the primary genes implicated in familial breast cancers. Among patients with strong family histories who initially test negative for *BRCA1* and *BRCA2*, an additional 12 % of cases may carry more complex genomic deletions or duplications in either *BRCA1* or *BRCA2* with nearly 5 % carrying mutations in a third cell-cycle checkpoint kinase gene (CHEK2) or mutations in the tumor suppressor gene TP53 (Walsh et al. 2006). Three additional genetic conditions have been associated with a high risk of early onset breast cancer (Hodgson et al. 2004). These include Li–Fraumeni syndrome, Cowden syndrome, and Peutz–Jeghers syndrome, rare syndromes caused by mutations in TP53, PTEN, and LKB1, respectively.

Even in families without documented high-penetrance mutations, breast cancer in a single first-degree relative or second-degree relative confers a two- to threefold or moderate increase in risk (Culver et al. 2006). Thus, genetic susceptibility is suspected in 25 % of all breast cancer cases and may contribute to a portion of apparent sporadic disease through a mode of inheritance thought to be more complex than a single dominant-acting gene (Peto and Mack 2000; Stratton and Rahman 2008). For example, a specific variant in the CHEK2 gene designated 1100delC that occurs in the heterozygous state in about 0.5–1 % of the population has been associated with between a three- to fivefold increased risk for breast cancer in the general population and a risk approximating that of *BRCA1* mutation carriers for women at age 70 years or more (Weischer et al. 2008). Currently, a genetic test for the CHEK2 gene deletion is available through the City of Hope Clinical Molecular Diagnostic Laboratory. In addition to CHEK2, in recent years a handful of rare variants ($\leq$1.5 % in the population) in genes involved in DNA damage repair response, much like *BRCA1* and *2*, have been identified (Hollestelle et al. 2010). These genes, which include *ATM*, *BRIP1*, *PALB2*, and *NBS*, are currently under investigation as moderate-risk genes, conferring two to four-fold increase in risk. Altogether, mutations in highly (*BRCA1*, *BRCA2*, *TP53*, *PTEN*, *LKB1*, *CHEK2*) and moderately (*ATM*, *BRIP1*, *PALB2*, and *NBS*) penetrant genes are found in about half of families with familial breast cancer (Walsh and King 2007; Walsh et al. 2010).

In contrast to the CHEK2 and the emerging moderate-acting risk genes, a number of similar direct-to-consumer tests are rapidly emerging for newly identified modifier genes of undetermined significance (e.g., variants on chromosomes 2 and 8, FGFR2, the TNRC9/TOX3, the LSP1, the MAP3K1, and the CASP8 genes). While variants in these newly identified genes may occur in 28–46 % of breast cancer patients, they confer only very weak to modest effects on risk (Easton et al. 2007; Hunter et al. 2007). Inclusion of these common, but weak-acting genetic variants into risk assessment models showed that they add little discrimination for

individual patient breast cancer risk (Wacholder et al. 2010) and thus have not been widely embraced for use in the clinical setting.

Physicians should be aware of the growing availability of gene-based tests (Hudson et al. 2007). Patients suspected to be at risk for hereditary forms of breast cancer should be advised to seek expert genetic counseling. It is anticipated that a number of genetic tests and information are likely to emerge in the near future, especially as large-scale genomic studies are in progress to identify important risk modifier genes akin to the CHEK2 1100delC. While it is anticipated that genetic information will ultimately improve individual risk assessment, premature delivery of unconfirmed gene-risk associations to the public carries potential to negatively impact the medical and patient community. To identify a genetic counseling center in your area, the National Institutes of Health (NIH) provides a partial listing of services at the Cancer Genetics Services Directory (http://www.cancer.gov/search/geneticsservices/).

15.2.3 Reproductive Risk Factors

Late age at first pregnancy, nulliparity, early onset of menses, and late age of menopause have all been consistently associated with an increased risk of breast cancer (Kelsey and Bernstein 1996; Colditz and Rosner 2000; Deligeoroglou et al. 2003; Colditz et al. 2004; Pike et al. 2004). Among the reproductive risk factors, women who experience natural menopause after 55 years of age have about twice the risk of breast cancer compared to women who experience natural menopause before age 45 (Trichopoulos et al. 1972). The observed increased risk among women with early menarche (<12 years of age) appears to be strongest in the premenopausal period, whereas risk of later onset breast cancer appears to be greater among women who experience a late first full-term pregnancy. Women who bear their first child after the age of 30 have twice the risk of developing breast cancer as compared to those who experience first full-term pregnancy before 20 years of age. Meta-analysis results suggest that each birth is associated with an 11 % decrease in risk of developing HR+ cancer with no effect observed for HR- cancers (Ma et al. 2006a, b). In contrast, breastfeeding and late age at menarche decreased the risk of both subtypes of breast cancer with late age of menarche more strongly protective for ER^+PR^+ cancers. At present, the effect of reproductive factors among *BRCA* mutation carriers and women with a strong family history of breast cancer is unclear. There may be differing effects of reproductive factors among *BRCA1* as compared with *BRCA2* mutation carriers. Among *BRCA1* carriers, breastfeeding for 1 year and late first pregnancy are associated with a reduced risk of breast cancer (Jernstrom et al. 2004). This contrasts with *BRCA2* mutation carriers where late age at first pregnancy is associated with higher risk of breast cancer (Andrieu et al. 2006). These data are consistent with emerging evidence that support differential effects of reproductive risk factors on tumor subtypes and differences among tumor histologies that arise in *BRCA1* mutation carriers, who are at risk of breast cancers that are more likely to be high-grade, triple-negative, or basal-like tumors (Lakhani et al. 2005). *BRCA2* mutation carriers are at risk of breast cancers that are more likely to be intermediate or high-grade, HR+/HER2− (also known as luminal type) (Bane et al. 2007).

15.2.4 Endogenous Hormone Exposures

Prolonged exposure to elevated levels of sex hormones has long been postulated as a risk factor for developing breast cancer, explaining the association between breast cancer and reproductive behaviors (Eliassen et al. 2006b; Hankinson and Eliassen 2010). The results of numerous clinical trials demonstrate the protective effect of selective estrogen receptor modulators (SERMs) and aromatase inhibitors on recurrence and the development of contralateral breast cancers (Cuzick et al. 2011). Use of SERMs in individuals at increased risk of breast cancer has been demonstrated to prevent invasive ER+ cancers (Fisher et al. 1998, 2005; Vogel et al. 2006). These data support estradiol and its receptor as a primary target in risk reduction strategies, but do not provide evidence that circulating hormone levels predict susceptibility. The National Surgical Adjuvant Breast and Bowel Project Cancer Prevention (NSABP) P-1 trial did not find any association between the efficacy of tamoxifen and the levels of circulating estradiol, testosterone, or sex hormone-binding globulin (Beattie et al. 2006). While it has been argued that participants in the NSABP P-1 trial were enriched for risk and not representative of the general population (Beattie et al. 2006), it has been difficult to reconcile the lack of association between hormone levels and risk if indeed circulating hormone levels accurately inform on tissue exposures and tissue susceptibility. A number of issues have plagued assessment and interpretation of serum hormone levels in women including sampling issues, poor lab-to-lab and assay-to-assay correlation, and general methodological issues of inadequate sensitivity and reliability. A number of recent epidemiologic and pooled studies (Key et al. 2002; Santen et al. 2007) support an elevated risk among women with high estradiol levels. For example, the Endogenous Hormones and Breast Cancer Collaborative Group (EHBCG) reported a relative risk of 2.58 (95 % confidence interval, CI: 1.76–3.78) among women in the top quintile of estradiol levels. Upon thorough review of the collective data, the Breast Cancer Prevention Collaborative Group (BCPCG), which included authors of the study of serum hormones in the P-1 trial, favors prioritizing measures of plasma hormone levels (particularly free plasma estradiol levels) as an additional component of existing tools to improve risk assessment for the individual woman (Santen et al. 2007). At present, the routine measurement of plasma hormone levels is not recommended in the assessment of breast cancer risk.

15.2.5 Exogenous Hormone Exposures

15.2.5.1 Oral Contraceptive Hormone Therapy

One of the most widely studied factors in breast cancer etiology is the use of exogenous hormones in the form of oral contraceptives (OCs) and HRT (1996; Bonn 1996; Garbe et al. 2004). Current use of OCs has been inconsistently associated with a slight increased risk of breast cancer (Cibula et al. 2010). The overall evidence suggests an approximately 25 % greater risk of breast cancer among current users of OCs. The risk appears to decrease with age and time since OC discontinuation.

Risk returns to that of the average population risk approximately 10 years after cessation. Among families at increased risk of breast cancer, OC use reduces the risk of ovarian cancer by 40–50 % (Cibula et al. 2011). Unlike the strong and consistent protective effect of OC for ovarian cancer risk, the results of studies of OC use and risk of breast cancer in *BRCA1/2* mutation carriers are inconsistent and do not support either a protective or adverse effect; limited sample size, however, do not rule out small effects (Cibula et al. 2011). At present, women at increased genetic risk should be evaluated on an individual basis, taking into consideration the prevalence of ovarian cancer in the family history with potential risks (slight elevation in risk of breast cancer) and benefits (significant protection for ovarian cancer) of OC use.

15.2.5.2 Postmenopausal Hormone Replacement Therapy (HR) and Breast Cancer

Data obtained from the case–control and prospective cohort settings (1997) support an increased risk of breast cancer incidence and mortality with the use of postmenopausal HRT (Speroff 2003). Increased risk of breast cancer has been positively associated with length of exposure with greatest risk observed for the development of hormonally responsive lobular, mixed ductal–lobular, and tubular cancers (Reeves et al. 2006). Risk is greater among women taking combination E plus P formulations than E-only formulations (1997; Schairer et al. 2000). Findings from the Women's Health Initiative (WHI) placebo controlled, randomized trial (RCT) of E-only and E plus P-HRT for the prevention of chronic disease has generated more questions than answers on the role of HRT therapy and breast cancer that challenges the conclusions of observational studies that suffer issues of confounding and reporting bias. Considering that the study was conducted to assess the beneficial effects of HRT on cardiovascular health, for which there was no evidence of a protective effect observed in the WHI, the conclusion that the adverse outcomes associated with long-term use outweigh the potential disease prevention benefits for "most women," particularly for women >65 years is perhaps the most constructive conclusion of the study (Anderson et al. 2004). In women randomized to combination HRT, the incidence of invasive breast cancer increased by 26 % in women randomly assigned to combination HRT compared to placebo. In contrast, E-only (conjugated equine estrogen) use in women with hysterectomy in the WHI RCT was associated with a 23 %, but not significant, decrease in breast cancer risk compared to placebo at initial reporting. A more recent report (Anderson et al. 2012) from extended follow-up (median follow-up 11.8 years) of the E-only cohort found that E-only therapy for 5–9 years in women with hysterectomy was associated with a significant 23 % lower incidence of invasive breast cancer (0.27 % per year) compared with placebo (0.35 % per year) (HR 0.77, 95 % CI 0.62–0.95; $p = 0.02$). Additionally, the authors report a stronger risk reduction in women without a history of benign breast disease or a family history of breast cancer. Most importantly, fewer women died from breast cancer in the E-only arm compared with controls. These findings from the WHI for E-only use are in stark contrast to those reported from large observational case–control and prospective cohort studies where E only has been associated with an increased risk, though at a consistently lower magnitude than that associated

with combined HRT use (Speroff 2003). Estimated absolute increases in breast cancer cases for E only in the Million Woman (Prospective Cohort) Study reflect an effect on risk with exposure time with 1.5–2 additional cases per 1,000 women with 5-year use, as compared to five to six per 1,000 with 10-year use (1997; Beral 2003). For users of combination HRT, results from the WHI (Rossouw et al. 2002) and the Million Woman Study (Beral 2003) suggest an excess of six cases per 1,000 with 5 years E+P use and 18–19 cases per 1,000 with 7–10 years use.

Following publication of the WHI findings, the relevance of the findings has been challenged. The WHI RCTs were conducted in older, postmenopausal women with the intention of evaluating effects of HRT for the prevention of heart disease. Thus, it is less clear what effect HRT has on breast cancer or cardiovascular risk when used in the management of menopausal symptoms in women entering the menopause. In the absence of RCT data for this target population, the current recommendations are based on a conservative interpretation of the evidence indicating a slight increased risk of breast cancer for E only in women with 10 or more years of use and a modest increased risk for E+P with use >5 years with risk increasing as duration of use increases. Current recommendations for the use of combined and single-agent HRT to prevent chronic disease other than bone fracture are not recommended (Nelson et al. 2012). For the management of moderate to severe menopausal symptoms, HRT use is recommended to be delivered on the basis of individual benefit and risk with treatment duration limited to the shortest time at the lowest effective dose. Risks and benefits associated with alternative hormonal agents, doses, and time of exposure are currently unknown, although a summary of knowledge to date is provided at the conclusion of Chap. 18.

To aid the medical community in HRT use, a number of agencies and groups have published recommendations for HRT use for the treatment of menopause and associated bone loss. HRT is not recommended at present for the prevention of cardiovascular disease, dementia, or generally for long-term use for disease prevention. Recommendations differ slightly by agency and by country; for US and non-US evidence-based treatment recommendations, we direct the reader to the National Guidelines Clearinghouse website (http://www.guideline.gov/). When prescribing HRT, a discussion of the most current evidence and an assessment of the potential benefit and harm should be provided to the individual patient. Because of the known risk of endometrial cancer for estrogen-only formulations, the U.S. Food and Drug Administration (FDA) currently advises the use of combined (estrogen plus progesterone) HRT for the management of menopausal symptoms in women with an intact uterus tailored to the individual patient at the lowest effective dose for the shortest time needed to abate symptoms.

There are currently no formal guidelines for the use of HRT in women at high risk of breast cancer (i.e., women with a family history of breast cancer, personal history of breast cancer, or benign breast disease). Only a few studies have evaluated the effect of HRT after a diagnosis of breast cancer. The largest of these, the HABITS (hormonal replacement therapy after breast cancer—is it safe?) study was stopped early due to unacceptable breast cancer recurrence and contralateral disease with 2-year HRT use (hazard ratio of 3.5, 95 % CI: 1.5–8.1) (Holmberg and Anderson 2004).

In another randomized clinical trial (Loprinzi et al. 1994), no increase in risk of breast cancer recurrences were observed in women with a median follow-up of 4.1 years. Use of progesterone-containing HRT was limited by intermittent use with continuous exposure avoided. Though argued to be biased towards more adverse outcomes with a high prevalence of cases with estrogen responsive tumors and greater use of formulations including progesterone, the HABITS study cautions against the use of hormonal agents in women with a history of breast cancer and others at increased risk.

E+P in combination formulations are contraindicated in women with a prior history of invasive disease, history of ductal or lobular carcinoma in situ, or strong family history of breast cancer. This recommendation poses a significant challenge when confronted with a patient suffering severe menopausal symptoms. Thus, the reader is referred to Chap. 18 of this text for a more in-depth discussion of nonhormonal alternatives to treat the symptoms of menopause. In women at increased risk, including women with a history of breast cancer and those where estrogen exposure is actively suppressed with oophorectomy, aromatase inhibitors, or SERMs, treating physicians may wish to rely on nonhormonal treatment strategies for the management of hot flashes, night sweats, and vaginal dryness (Mom et al. 2006; Cheema et al. 2007). There are no randomized clinical trials among women at increased risk of breast cancer or among women with a history of breast cancer that have assessed the overall efficacy or risks associated with many new treatments (e.g., clonidine, venlafaxine, gabapentin, and combination venlafaxine plus gabapentin) (Bordeleau et al. 2007). Use of these agents is controversial and should target severity of menopausal symptoms. Other hormone-based approaches, such as the use of low-dose vaginal estrogen for vaginal and urinary symptoms including dyspareunia, are felt to be safer, particularly in patients on SERMs. However, these may also carry a slight increased risk as they can raise estradiol levels, at least transiently, depending on the dose and frequency administered. There is little evidence to support the benefit of commonly used dietary isoflavones, black cohosh, or vitamin E. Nonhormonal alternatives to treat the symptoms of menopause are summarized in more detail in Chap. 18.

15.2.6 Prior Breast Health History

A history of breast cancer is associated with a three- to fourfold increased risk of a second primary cancer in the contralateral breast (Page and Jensen 1994; Kollias et al. 1999; Page et al. 2003). Presence of any premalignant ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) confers an eight- to tenfold increase in risk of developing breast cancer in women who harbor untreated preinvasive lesions (Page 2004; Ashbeck et al. 2007). The introduction of widespread screening has resulted in a nearly fivefold increase in the detection of in situ or locally contained disease (i.e., cancerous-type lesions of the ducts and terminal lobular units that have not breached the basement membrane). The majority of these early-stage lesions are diagnosed as DCIS, which are often not clinically appreciated and only detectable by imaging methods (Ernster et al. 1996). Nearly 55,000 women are diagnosed

annually in the U.S.A with DCIS. The increase incidence rates of DCIS have occurred in all age groups but especially among women over age 50. Because of the high risk of invasive disease in women with DCIS, surgical excision followed by radiation therapy and long-term use of tamoxifen or aromatase inhibitor for HR+ lesions has been widely adopted as treatment to prevent invasive disease. Among women in whom tamoxifen use is contraindicated, aromatase inhibitors are now being extensively used despite absence of strong clinical trial data. The current NSABP B-35 trial comparing tamoxifen to aromatase inhibitors in women with DCIS completed accrual with results expected on the primary outcome of invasive breast cancer due for publication in 2016 (http://clinicaltrials.gov).

A second, less common type of in situ disease, LCIS, accounts for approximately 10–15 % of in situ lesions. The incidence rate of LCIS has increased at about two times the rate of invasive cancers, particularly among postmenopausal women (Li et al. 2002). In LCIS, atypical cells occur throughout the breast lobules with both breasts involved in approximately one-third of patients. LCIS often involves the entire breast parenchyma and is characterized by multifocality and a high rate of bilaterality (30–50 % of cases). Mammograms of women with LCIS show sheetlike areas of breast density with higher percentages of fibroglandular density compared to age-matched controls. LCIS confers an increased risk of invasive breast cancer in either breast with cancer arising in either ducts or lobules. Though controversial and difficult to diagnose given the multifocal and bilateral nature of the lesions, LCIS confers between a six- and 12-fold increase in risk for the development of invasive carcinoma (Simpson et al. 2003). Crisi and colleagues concluded that LCIS on core biopsy is a significant marker for concurrent and near-term breast pathology requiring increased clinical follow-up with specific individualization of patient care (Crisi et al. 2003). Current recommendations support more active surveillance in women with these lesions. Adjuvant use of tamoxifen in women diagnosed with these high-risk premalignant lesions has proven efficacious in both LCIS and DCIS patients for the prevention of invasive cancers. Tamoxifen for 5 years has been shown to cut the risk of HR+ invasive cancers by half in women with a history of LCIS or DCIS, an effect that appears to be sustained for at least 10 years (Fisher et al. 1998; Cuzick et al. 2007). At present, patients should understand that there are no data that support a survival advantage for women who choose tamoxifen to prevent the development of invasive disease and that use in women 70 years and older is not routinely recommended. Longer follow-up studies are needed to determine the long-term benefit of tamoxifen in terms of survival. At present, there are limited options for women with ER- DCIS other than surgical excision and radiation therapy. It should be noted that approximately 25 % of high-grade DCIS (i.e., high-risk lesions) lack ER expression and share features with associated invasive disease in the same individual (Steinman et al. 2007). With advances in molecular profiling and improved detection of small lesions that harbor aggressive features, clinical treatment of such lesions may soon mirror the differential treatment of early-stage tumors where molecular subtype characterization overrides the importance of tumor size and other previously used prognostic indicators.

A history of breast biopsy that is positive for hyperplasia, fibroadenoma with complex features, sclerosing adenosis, and solitary papilloma have been associated with a modest 1.5- to two-fold increase in risk of breast cancer (Page 2004; Ashbeck et al. 2007). In contrast, any diagnosis of atypical hyperplasia that is ductal or lobular in nature, especially if diagnosed under the age of 45 years, carries a four- to fivefold increased risk of breast cancer with risk rising to eight- to ten-fold risk among women with multiple foci of atypia or calcifications in the breast (Degnim et al. 2007). Benign pathologies of the breast, including fibrocystic disease such as fibrocystic change without proliferative breast disease or fibroadenoma, have not been associated with increased risk (Dupont et al. 1994).

15.2.7 Lifestyle Risk Factors

The wide range of breast cancer incidence rates around the world (e.g., nearly fivefold differences between Eastern Africa and Western Europe) has long been attributed to differences in dietary intake and reproductive patterns (Henderson and Bernstein 1991; Kaaks 1996; Stoll 1998a, b; Holmes et al. 2004). In general, rates differ by the level of industrial development with >80 cases per 100,000 in developed countries compared to <40 per 100,000 in less developed countries. As with cancers of the colon and prostate, diets that are rich in grains, fruits and vegetables, low in saturated fats, and low in energy (calories) and low in alcohol, the more common pattern in less industrialized countries, are thought to be protective against breast cancer (Holmes and Willett 2004). And as discussed above in the section on reproductive risk factors, reproductive patterns that include early first pregnancy, multiparity, and high rates of breastfeeding are all associated with a reduced risk of the more common HR-positive breast cancers that arise in older, postmenopausal woman. As such, breast cancers presenting in areas of the world with more traditional reproductive patterns tend to have lower rates of HR+, postmenopausal disease. In contrast, the less developed countries have disproportionately higher rates of premenopausal disease with more aggressive features, a pattern associated with worse survival if diagnosed late. These differences might explain why the range in mortality rates of 6–19/100,000 worldwide is much narrower despite dramatically different incidence rates.

In addition to the clear effect of reproductive differences between populations, postmenopausal breast cancer has been consistently associated with adult weight gain of 20–25 kg from body weight at age 18 (Eliassen et al. 2006a; Han et al. 2006), a Western dietary pattern (high energy content in the form of animal fats and refined carbohydrates), a sedentary lifestyle, and regular, moderate consumption of alcohol (3–5 alcoholic beverages per week). The Western lifestyle (i.e., chronic excess energy intake from meat, fat, and carbohydrates and lack of exercise) strongly correlates with the development of obesity, particularly abdominal obesity, and chronic states of hyperinsulinemia and higher production and availability of insulin-like growth factor (IGF)-1 and endogenous sex hormones through suppression of sex hormone-binding globulin (Kaaks 2004; Lukanova et al. 2004). Studies of

dietary fat, total energy, and meat intake levels have largely been inconsistent in population studies of adult women with regard to risk of breast cancer. In contrast, epidemiological studies have more consistently found a positive relationship between early life exposures of unknown mechanism that includes early life diet, obesity, body size including height, and breast cancer risk (Baer et al. 2005; Ruder et al. 2008; Fuemmeler et al. 2009). This is an area that we expect to receive considerable attention in the next few years given current trends in childhood obesity and therefore merits a brief discussion here.

In the last few decades, increasing rates of childhood obesity associated with body fat, exacerbated by high energy diets, have been implicated in shifts towards earlier onset of puberty and menarche in young girls (Freedman et al. 2002; Kaplowitz 2006); early menarche is an established breast cancer risk factor (Berkey et al. 1999). While it is too soon to assess if these secular trends in age of puberty will manifest in elevated breast cancer rates (Euling et al. 2008), recent findings in animal models are concerning. It has been accepted for decades that mammary gland development was exclusively an ovarian-driven process dependent on estrogen, progesterone, and growth hormone initiating at puberty (Flux 1954). In a recent study, Berryhill et al. (2012) showed that the dietary fat trans-10, cis-12 isomer of conjugated linoleic acid (10,12 CLA) induced disturbances in insulin sensitivity and insulin-like growth factor (IGF-1) promoting mammary gland growth in ovarectomized mice (i.e., in the absence of estrogen). Further, in an experimental model prone to mammary tumorigenesis, the exposure to 10, 12 CLA significantly increased the degree of epithelial hyperplasia in the mammary gland; a risk factor for tumor development. These highly novel findings raise concerns about the effects of the increasing rate of childhood obesity, insulin resistance, and diet-induced metabolic disturbances on breast tumor development and disease progression. These findings are made more alarming considering the observed increased risk for the development of triple-negative breast cancer in women reporting being obese prior to the onset of puberty (see next section (Millikan et al. 2008)). As stated, it is too soon to causally link childhood obesity, early mammary gland development, and breast cancer. However, the general adverse effects of early-age weight gain on future all-cause morbidity and mortality, the rising rates of childhood obesity, and the potential impact on breast cancer certainly justify proactive interventions targeting parents and their young children. Importantly, this should include socially and culturally tailored education on age-appropriate growth and body weight as well as information on healthy foods, energy needs, and the important role of being physically active. Similarly, focus on reducing sugar intake should also follow as sugar overconsumption is among the most strongly linked factors for disturbances in insulin and IGF-1 hormones. The importance of the role of insulin and IGF-1 in breast tumorigenesis can be further appreciated by review of the section on chemoprevention in the latter part of this chapter that highlights ongoing efforts in the prevention setting with the insulin-sensitizing drug metformin.

In addition to our efforts here in raising awareness about the important role of diet, physical activity, alcohol consumption, and body composition in breast cancer prevention, Chap. 3 of this book focuses specifically on this topic for all cancers.

While we refer the reader to this chapter and also highly recommend the comprehensive Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective published jointly by the World Cancer Research Fund and the American Institute for Cancer Research (AICR 2007), we also recommend the following references for the reader interested in breast cancer risk and early life exposures (Forman et al. 2005).

15.2.8 Risk Factors and Tumor Subtypes

In 1995, Potter and colleagues reported an inverse association between parity and ER+/PR+ tumors that was not present for ER⁻/PR⁻ tumors (Potter et al. 1995). A number of smaller studies have investigated the relationship between established breast cancer risk factors and hormone receptor status. This body of work concluded that there were no major differences in risk factors by hormone receptor status or in tumor etiology by receptor status (Stanford et al. 1986; Cooper et al. 1989; Habel and Stanford 1993). More recently, the Nurses' Health Study found that parity and early age of first birth were inversely associated with ER+/PR+ tumors but not with ER⁻/PR⁻ tumors (Colditz et al. 2004). These data were replicated in a meta-analysis (Ma et al. 2006a). While the number of studies that have evaluated risk factors separately for tumor subtypes remains limited, an overall picture supporting the hypothesis that breast cancers are not homogeneous but rather a group of separate diseases with distinct origins is emerging (Summary of findings illustrated in Fig. 15.1). The work by Millikan and colleagues (Millikan et al. 2008) found that luminal A tumors (strongly ER+) showed the expected association with reproductive risk factors including increase in risk with late age of first pregnancy and nulliparity. However, the triple-negative or "basal-like" tumors were positively associated with high parity (particularly among women with short or failed breastfeeding), young age at first full-term pregnancy, elevated early waist-to-hip ratio (or abdominal obesity), and weight gain (obesity) in childhood, as well as with earlier age at menarche and a family history of breast or ovarian cancer (Yang et al. 2007a; Millikan et al. 2008). These findings were largely replicated by Yang and colleagues (2007b). It is notable that the reproductive risk factors (i.e., high parity, early age of menarche) are more common in African American women and likely explain the nearly threefold higher risk of triple-negative disease in African American women (Boyle 2012). When the reproductive risk factors are evaluated among women living in poverty, a similar increase in triple-negative breast cancer is observed, independent of race/ethnicity as well as menopausal status. In contrast to HR-positive and HR-negative studies, few groups have looked at factors that increase the risk of HER2+ tumors. Recent findings suggest a role for more recent time since last pregnancy (<10 years) in HER2+ disease independent of HR status as well as potential overrepresentation of HER2+/HR⁻ tumors in highly parous Hispanic women (Cruz et al. 2013). Additional work, particularly on the HER2+ subset is needed given the lack of known risk factors for this subgroup. While the majority of work to date has focused on the relationship between reproductive risk factors and tumor subtypes, similar distinct associations have now

been observed between the subtypes and common genetic risk variants, with the BRCA1 and triple-negative association being the prototype of this effect as well as studies showing distinct relationships between tumor subtypes and nutrient intakes including emerging hypotheses about the role of vitamin D and triple-negative breast cancer risk (Yao and Ambrosone 2013; Yao et al. 2012).

Looking forward, these findings strongly suggest that risk assessment tools will need to consider different risk factor patterns separately for the breast cancer subtypes and include characteristics not currently integrated into the clinical models. These will rely heavily on obtaining information from tumor type-specific epidemiological studies to clarify the importance of living in poverty, genetic background, oral contraceptive use, HRT use, obesity and timing of obesity, diet, skin type, and other environmental factors such as sun exposure on individual risk of specific tumor types. Ongoing consideration of these factors in risk assessment is discussed later in this chapter.

15.2.9 Emerging Breast Cancer Risk Factors for Patient Management

A panel of experts on breast cancer risk factors comprising the Breast Cancer Prevention Collaborative (BCPC) has cited the quantitative measure of breast density as a high priority risk factor for validation with the specific intent to more efficaciously deliver prevention agents. There is convincing evidence that extensive areas of radiographically dense tissue in the breast are an independent risk factor for the development of breast cancer (Saftlas et al. 1989; Oza and Boyd 1993; Byrne et al. 1995; Boyd et al. 2007; Santen et al. 2007; Assi et al. 2012). The presence of dense tissue that occupies more than 50 % of the area of a mammographic image, which occurs in up to 30 % of postmenopausal women, is associated with a three- to five-fold elevated risk of breast cancer. The implementation of BI-RADS measurement would be largely straightforward from a clinical perspective. In the Kerlikowske study (Kerlikowske et al. 2007a), women who experienced an increase in their BI-RADS breast density category over an average of 3 years had a higher risk of developing breast cancer. For example, among those women whose BI-RADS category increased from one to two, or from one to three, over a 3-year time period had a double or triple increase in risk, respectively, compared to women who remained unchanged from the initial BI-RADS category one. This increase in risk with each rise in category was evident only for women initially categorized with BI-RADS categories one through three. Women with an initial classification of BI-RADS category four suffered the highest adjusted rates of breast cancer and demonstrated no reduction in risk if their BI-RADS score decreased at follow-up. This observation is consistent with work by Boyd and colleagues that suggests that the elevated breast cancer risk associated with highly dense breasts persists up to 8–10 years following initial evaluation (Boyd et al. 2007). Over the past few years, computer-aided systems to accurately quantify mammographic density have become more widely available for the routine assessment of a woman's mammographic density in the clinic.

This has spurred interest and action from the public to have access to their density scores. However, mammographic density remains a phenomenon associated with, but not causally linked, to breast cancer. There are currently no evidence-based medical recommendations for women with dense breast. More importantly, the recent findings from Gierach et al. (2012) raise questions about the utility of mammographic density for predicting the risk of clinically significant breast cancer reporting that women with high mammographic density did not have a higher risk of dying from breast cancer. Further, they found that risk of death related to breast density was present for women with *low* not high density who were obese or who presented with tumors <2.0 cm; the opposite of what might have been expected. These findings raise serious questions about the value of providing women a measure of their breast density when the scientific community does not yet understand the relationship that underlies higher breast density and increased risk of breast cancer.

15.2.10 Environmental Risk Factors

A number of environmental exposures, including tobacco smoke (both active and passive exposure), dietary (e.g., charred and processed meats), alcohol consumption, and environmental carcinogens, such as exposure to pesticides, irradiation, and environmental and dietary estrogens, have been investigated in relation to breast cancer risk in humans (Laden and Hunter 1998; Coyle 2004; Gammon et al. 2004; Smith-Bindman 2012). Of these environmental exposures, only high doses of ionizing irradiation to the chest area, particularly during puberty, has been unequivocally linked with an increased risk of breast cancer in adulthood (Carmichael et al. 2003; Smith-Bindman 2012). Because of the strong association between ionizing irradiation and breast cancer risk, care is given in medical diagnostics procedures to minimize exposure to the chest area, particularly during adolescence. Women with a prior history of irradiation exposure to the chest area should be examined and counseled on their risk of breast cancer based upon timing and dose of prior exposure. A patient treated for Hodgkin's lymphoma with Mantel radiation that includes the breasts in the radiation field has a fivefold increased risk of developing breast cancer. This risk increases markedly for women who were treated during their adolescence (Clemons et al. 2000) with evidence that cumulative risk increases with age as a function of age of exposure and type of therapy (Travis et al. 2005). Current evidence does not support a significant and reproducible link between other environmental exposures and breast cancer risk. Thus, a number of factors remain suspect but unproven.

15.3 Mammographic Screening and Early Breast Cancer Detection

While early detection has been advocated as a primary defense against the development of life-threatening breast cancer, the age at which to initiate, the modality to use (self or clinical breast exam with or without mammography or other advanced imaging),

the interval between screenings, whether to screen older women and even the impact on breast cancer-related deaths, have a history of being contentious topics. It has widely been believed that the detection of breast tumors that are smaller or non-palpable and that present with a favorable tumor marker profile are more treatable when detected early and thus have a more favorable prognosis. A survival benefit of early detection with mammography screening has been demonstrated (Berry et al. 2005; Elmore et al. 2005). Therefore, early detection has been widely endorsed for the past 30 years by organizations that issue clinical recommendations for breast cancer care. The most widely accepted recommendations in the U.S.A. come from the ACS, which recommends annual screening mammography beginning at age 40 years for all women. For women younger than 40 years of age, monthly breast self-exam practices and clinical breast exams every 3 years are recommended, beginning at 20 years of age (Smith et al. 2003).

Mammography is currently the best available population-based method to detect breast cancer at an early stage when treatment is believed to be the most effective (Nystrom et al. 2002; Tabar et al. 2003; Elmore et al. 2005). Mammography often detects a lesion before it is palpable by CBE and, on average, 1–2 years before noted by BSE. Recent advances in mammography include the development of digital mammography and the increased use of computer-aided diagnosis (CAD) systems (Noble et al. 2009). CAD systems have been developed to help the radiologist identify mammographic abnormalities. Digital mammography allows the image to be recorded and stored. Using computer technology, digital mammogram images can be magnified and the image modified to improve evaluation of specific areas in question. Digital images can be transmitted electronically, decreasing the time to second opinion without the risk of losing the film. The U.S. Preventive Services Task Force estimates the benefit of mammography in women between 50 and 74 years of age to be a 30 % reduction in risk of death from breast cancer. For women age 40–49, the risk of death is decreased by 17 % (Humphrey et al. 2002). In 2005, Berry and colleagues concluded that screening and treatment both contribute equally to the recent declines in deaths from breast cancer (Berry et al. 2005). Although mammography guidelines have been in place for over 30 years, between 20 and 30 % of women still do not undergo screening as indicated. The two most significant factors for a woman to undergo mammography are physician recommendation and access to health insurance. Non-White women and those of lower socioeconomic status remain less likely to obtain mammography services and more likely to present with life-threatening, advanced stage disease (Ward et al. 2005).

More recently, two important issues have emerged that have challenged the benefit of the routine use of mammography for breast cancer screening for the average risk woman. First, in 2009 the U.S. Preventive Services Task Force (USPSTF) published an update to their 2002 recommendations for breast cancer screening with mammography (USPSTF 2009), which concluded by providing a B recommendation [i.e., recommends the service]. However, the Task Force recommended "against routine screening mammography in women aged 40–49 years" based on a systematic review of the RCT evidence that concluded that nearly 1,904 women ages 40–49 had to be screened to extend one woman's life compared to 1,339 for women

Table 15.2 Breast cancer early detection guidelines by risk category and age

Age	Average and moderate risk	High risk
20–40 years	Monthly breast self-exam (BSE) following instruction Clinical breast exam (CBE) as part of regular health exams, minimum every 3 years Awareness to report any change in breast health	BSE and CBE as recommended in average-risk women Consideration of earlier initiation of screening methods with shorter screening intervals Consideration of other screening modalities to include ultrasound and magnetic resonance imaging (MRI) methods Heighten awareness to report any change in breast health
40–70 years	Continuance of BSE, CBE and introduction of mammography screening Heighten patient awareness to report any change in breast health	Vigilance in patient surveillance and consideration of shorter intervals for screening
>70 years	Consideration of overall health benefit with mammography in context of health status and expected longevity	Continuance of surveillance vigilance in context of expected patient longevity

Modified from Smith et al. (2003)

50–59 years. Based on the rates of false-negative findings and perceived harm of unnecessary biopsy and concern for the harm associated with overdiagnosis and overtreatment (discussed below), the Task Force scored routine screening, or screening of the average risk woman between the age of 40 and 49, a C [i.e., recommending that clinicians may provide this service to select patients in this age range depending on individual circumstances]. The Task Force further concluded that for most individuals without signs or symptoms, there is likely to be only a small benefit from screening.

This recommendation was met with a negative response from the public and the professional community that was in part due to poor communication on the part of the USPSTF as to the nuanced meaning of the word "routine" and media implication that the Task Force was recommending against any screening in this age group. As a result of the controversial nature of the conclusions of the USPSTF (Hendrick and Helvie 2011; Shen et al. 2011), the ACS and other groups continue to recommend routine mammography in the U.S.A. for women beginning at age 40 years (see 2012 recommendations below and in Table 15.2).

The second issue that was raised by the USPSTF (Shen et al. 2011) is the evidence that a sizable fraction (~25 % (2012)) of breast tumors (including invasive and noninvasive) detected by mammography, particularly among older women, have low malignancy potential and thus are not likely to ever be life-threatening. This has raised concerns similar to that observed in the prostate cancer setting of overdiagnosis (Ciatto 2009; Jorgensen et al. 2009) that increases the risk of overtreatment and unnecessary harm to patients. This is best illustrated in findings from a recent study reported in the New England Journal of Medicine by Bleyer and

Welch (2012) on the effect of three decades of screening on breast cancer incidence in the U.S.A. In this study, the authors concluded that from 1976 to 2008, approximately 1.3 million women were overdiagnosed with breast cancer with the authors estimating that in 2008, ~70,000 of the ~230,000 new cases detected, or 30 %, were overdiagnosed that likely resulted in significant overtreatment. These findings are controversial (de Gelder et al. 2011; Puliti et al. 2012) but are notable for their similarity to those reported from a number of other countries with screening programs (Jørgensen and Gøtzsche 2009; Veronesi and Serraino 2009; Morrell et al. 2010; Bleyer 2011; Kalager et al. 2012).

In the Bleyer study, the conclusions are largely based on the observation that while screening doubled the number of breast cancer cases, there has only been an 8 % decline in the rate at which advanced stage disease has been detected. This led the authors to conclude that introduction of screening mammography has not had any sizable impact on reducing the prevalence of advanced stage disease in the population and that gains observed in breast cancer survival are largely the result of advances in treatment that were occurring in parallel with introduction of screening. Further, the authors conclude that the benefit of mammography screening is much smaller than previously recognized and that the harms are much larger than appreciated. To put this issue into a digestible context and to appreciate the intent of screening at the population level, one can look to the impact of low-cost screening tests for colorectal cancer. In the United Kingdom, for example, a comparison of individuals who opted for a flexible sigmoidoscopy to no screening at all over an 11-year period found uptake of 71 %, slightly less than mammography, with a 23 % reduction in colorectal cancer (opportunity to remove the precursor polyp) and a 33 % reduction in colorectal cancer-specific deaths (Mansouri et al. 2013). This result is in line with the goal of an effective screening strategy, which is to detect disease at an early stage where it is hypothetically more treatable to prevent death.

Given the questions about the benefits in certain age groups and discrepancy between studies on the magnitude of harm due to overdiagnosis (estimates range from 0 to as high as 50 %), the ACS has not amended its breast cancer screening recommendations as of this writing. The 2012 review of the ACS's cancer screening guidelines (Table 15.2) follows the 2003 guideline (Smith et al. 2003) with the recommendation for MRI addressed in the 2007 update covered in women at high risk (Table 15.3). The ACS recommends that physicians continue to use mammography as a primary tool to detect breast cancer among women who would be candidates for cancer treatment, regardless of their age (Smith et al. 2012). The breast cancer screening recommendation updates from the ACS has not been published as of this writing but is expected in 2013.

15.3.1 Breast Self-Exam (BSE) and Clinical Breast Exam (CBE)

Both BSE and CBE involve inexpensive and noninvasive procedures for the regular examination of breasts (i.e., monthly for BSE and annually for CBE). Evidence supporting the effectiveness of BSE and CBE are controversial and largely inferred.

Table 15.3 Patient management options for women at high risk for breast cancer: benefits and risks

	Imaging-based surveillance	Bilateral oophorectomy	Risk reduction mastectomy	Tamoxifen/aromatase inhibitor
Benefits	Noninvasive	Significant lowering of risk among premenopausal women	Significant risk reduction (>90 %) in all high-risk women including BRCA1/2 carriers	Approximate 50–65 % reduction in ER (+) tumors
	Promise of new methods with improved sensitivity (e.g., MRI)	Risk reduction observed in both BRCA1/2 carriers, greatest among BRCA2 carriers undergoing surgery before 40 years		Greatest benefit for women with history of premalignant disease or family history ('high-risk' women)
				Effective against ER (+) disease
				Limited data suggest efficacy in BRCA carriers
Risks	Lack of sensitivity in young women	Premature menopause	Cosmetic	Increased risk of thrombotic and endometrial cancer events (TAM only)
	Concerns over low-dose irradiation exposure	Irreversible	Psychological	Bone loss and risk of osteoporosis (AI only)
	Lack of strong evidence that early detection reduces mortality for all women, particularly in *BRCA1/2* carriers	Psychological/quality of life	Irreversible	AI effective only in postmenopausal women
	Lack of specificity with MRI and higher rates of false-negative biopsy			No efficacy for ER (−) tumors
				Efficacy in BRCA carriers not established
				Age of initiation and duration for optimum health benefit unknown
				Overall health benefit not demonstrated

Even with appropriate training, BSE has not been found to reduce breast cancer mortality (Thomas et al. 1997). However, with increasing improvements in treatment regimens for early, localized disease, BSE and CBE, particularly among women younger than 40 who otherwise have no screening options, are still considered promising and safe methods of intervening early and continue to be recommended (Vahabi 2003). Most recently, randomized clinical trial results support combining CBE with mammography to enhance screening sensitivity, particularly in younger women where mammography may be less effective and in women receiving mammograms every other year as opposed to annually (Shen and Parmigiani 2005).

15.3.2 Alternative Screening Modalities and Future Directions

While mammography remains the most cost-effective approach for breast cancer screening, the sensitivity (67.8 %) and specificity (75 %) are not ideal (Berg et al. 2004). As reported (Vahabi 2003), mammography combined with CBE slightly improves sensitivity (77.4 %) with a modest reduction in specificity (72 %) (Berg et al. 2004). Comparisons between recently introduced digital mammography and screen-film mammography suggest that the sensitivity of full-field digital mammography is superior to screen-film mammography in certain subsets of women (Brem et al. 2003; Del Turco et al. 2007). For example, digital mammography demonstrates improved detection rates for younger women and for women with more dense breasts. Improved imaging modalities with greater sensitivity are of particular benefit for women at the highest risk and for women whose breast images are difficult to interpret. Ultrasound has become a widely available and useful adjunct to mammography in the clinical setting. Ultrasound is generally used to assist the clinical exam of a suspicious lesion detected by mammogram or physical examination. As a screening device, the ultrasound is limited by a number of factors but most notably by the failure to detect microcalcifications and poor specificity (34 %) (Smith et al. 2003; Berg et al. 2004).

In an effort to overcome the limitations of mammography and ultrasound, magnetic resonance imaging (MRI) has been explored as a modality for detecting breast cancer in women at high risk and in younger women. A combination of T-1, T-2, and 3-D contrast-enhanced MRI techniques has been found to be highly sensitive (approximating 99 % when combined with mammogram and clinical breast exam) to malignant changes in the breast (Morris et al. 2003; Liberman 2004; Lord et al. 2007). MRI has been demonstrated to be an important adjunct screening tool for women with *BRCA1* or *BRCA2* mutations (Kriege et al. 2004a, b), identifying cancers at earlier stages (Kuhl et al. 2010). However, breast MRI has limited utility as a general screening tool with a tenfold higher cost than mammography and poor specificity (26 %) resulting in significantly more false-positive reads that generate significant additional diagnostic costs and procedures (Berg et al. 2004; Kriege et al. 2004a, b). In the 2007 specific update to the American Cancer Society (ACS) Guidelines for Breast Cancer Screening (Saslow et al. 2007) and in the recent

general cancer screening update (Smith et al. 2003), MRI as an adjunct to mammography is recommended for women at highest risk (e.g., those with an approximately 20–25 % or greater lifetime risk of breast cancer), such as *BRCA1/2* mutation carriers, women with a strong family history of breast or ovarian cancer, and women who received irradiation for the treatment of Hodgkin's disease. Specific recommendations include breast MRI with annual mammogram as active surveillance for early cancer detection starting at age 30 years (Saslow et al. 2007). In either update, the ACS does not recommend the use of MRI in women at average risk of breast cancer. Among those at average risk, a combination of CBE and yearly mammograms remains the recommendation. There is not sufficient evidence to support the use of MRI in women with a personal history of breast cancer or for women with a prior history of LCIS or atypical hyperplasia. The ACS conclusion that the use of MRI "should be decided on a case-by-case basis, based on factors such as age, family history, characteristics of the biopsy sample, breast density, and patient preference (Saslow et al. 2007)," however, has created a field of use posing a challenge to practitioners. As noted previously, updates to the 2003 ACS "Comprehensive" Guidelines for Breast Cancer Screening are due and will potentially provide more refined guidelines for the use of MRI in breast cancer screening and surveillance to optimize the benefit while containing costs and harm from overuse and unnecessary biopsy procedures.

15.4 Primary Prevention of Breast Cancer

Pharmacologic and surgical strategies have demonstrated efficacy in lowering the incidence of breast cancer in women at high risk (Smith et al. 2003; Newman and Vogel 2007; Euhus 2012). However, most breast cancer cases do not arise in a readily identifiable group of women of known risk but occur sporadically in the population. At present, there are no practice guidelines for the prevention of breast cancer for women with average to moderate breast cancer risk. It is recommended that women maintain a healthy body weight throughout their adult life, engage in regular physical activity; breastfeed; eat diets rich in grains, fruits, and vegetables; minimize exposure to exogenous hormones; and consume alcoholic beverages in moderation (Kushi et al. 2012). Although the amount of physical activity needed to reduce risk remains unclear, women who engage in some modest physical activity, walking two to four times per week, are afforded a 10–20 % percent reduction in risk of breast cancer with risk reduction greater in younger women with lower body mass index (<25 kg/m^2 or normal body weight); the effect is also higher for ER-negative than ER-positive disease (Wu et al. 2012). Additionally, any intentional weight loss of more than 20 lb at any time during adult life has been associated with a modest reduction in breast cancer risk (Parker and Folsom 2003; Radimer et al. 2004). The ACS provides a set of risk-lowering recommendations on their website that can be accessed at www.cancer.gov/cancertopics/pdq/prevention/breast. Along with the risk factors in Table 15.3, we summarize these recommendations for the reviewer.

Future recommendations for the general population are likely to include a greater emphasis on the reduction of simple sugars in the diet and decreasing abdominal obesity (Umar et al. 2012). Further research on the influence of diet on reproductive risk factors and mammary gland development including the influence of diet on age of onset of menarche is needed. These findings will likely guide future recommendations that shift the delivery of prevention counseling related to lifestyle factors from adults to children and their parents. It is likely that earlier lifestyle modification will have a greater effect on lifetime risk reduction and ultimately prove to be the most beneficial for the individual and for society in terms of maximum benefit, minimum harm, and minimum cost.

There are several options for the primary prevention of breast cancer in women at significantly increased risk (e.g., *BRCA1/2* mutation carriers, women with multiple affected relative with breast or ovarian cancer presenting at early age, and women with a personal history of breast cancer or history of premalignant disease such as DCIS or LCIS). Available options are aimed at removing tissue before it can become cancerous and/or decreasing endogenous hormone exposure. Current prevention strategies include intervention with bilateral mastectomy, salpingo-oophorectomy, or the use of selective ER modulators (e.g., SERMs or aromatase inhibitors) (Newman and Vogel 2007).

Bilateral prophylactic mastectomy and bilateral salpingo-oophorectomy are considered highly effective options for risk reduction in women at very high risk. Bilateral prophylactic mastectomy (BPM) has been associated with as much as an 85 % reduction in breast cancer risk among *BRCA1* and *BRCA2* mutation carriers (reviewed in Euhus (2012)). While BPM is most effective in lowering breast cancer risk, bilateral salpingo-oophorectomy (BSO) is currently the most common choice for *BRCA* mutation carriers in the U.S.A. and Canada. BSO alone followed by short exposure to HRT is associated with a 90 % reduction in ovarian cancer risk and a 50 % or more lowering of breast cancer risk. Risk reduction is greatest when BSO is performed during the premenopausal years. The current recommendation is that *BRCA1/2* mutation carriers should consider undergoing BSO by age 35–40 years or at the time that childbearing is completed. Materials are available to aid with patient decision making to undergo BPM or BSO. One valuable resource is a text entitled "Ovarian Cancer: Risk-Reducing Surgery," which may be requested from surgerybook@fccc.edu or by calling the Margaret Dyson Family Risk Assessment Program at 1-800-325-4145. It is very important that patients take the time to give appropriate thought and consideration to this major decision (Bresser et al. 2006; Geiger et al. 2007; Isern et al. 2008). Patients should be aware of the risks and benefits associated with these and other options to reduce risk before deciding to undergo BPM or BSO, including realistic expectation of breast reconstructive outcomes and side effects.

It is important to recognize that only a portion of women at very high risk and, even fewer women at moderate risk, will ultimately develop breast cancers. Thus, a great benefit to the individual patient will be gained with improvements in the accuracy of risk assessment. For example, as we gain more information on the types and effects of specific mutations in the *BRCA* genes, identify and validate new gene

determinants, and understand the role of modifying genes and the effects of the environment, we will see improved stratification of women into risk categories and targeted chemoprevention therapies. We envision that this will delay and possibly prevent the use of aggressive surgical procedures in risk mitigation.

15.4.1 Chemoprevention

The use of natural or synthetic chemical agents to prevent, reverse, or suppress carcinogenic events in the breast defines the practice of breast cancer chemoprevention. This definition of chemoprevention excludes the use of dietary (e.g., whole foods), lifestyle, or behavioral interventions. The goal of chemoprevention is to reduce the incidence of breast cancer by inhibiting or delaying the progression of premalignant mammary epithelial cells. Thus, well-designed randomized clinical trials that demonstrate agent efficacy and define an appropriate risk-to-benefit ratio are prerequisite to improving the clinical practice of breast cancer prevention. Several key chemoprevention agents for the reduction of breast cancer risk are discussed in more detail below.

15.4.1.1 Selective Estrogen Receptor Modulators (SERMs)

Having identified estrogen exposure as a risk factor for breast cancer, it was not surprising that adjuvant treatment trials with the selective ER modulator, tamoxifen, showed not only reduced recurrence of breast cancer among women with breast cancers but also a reduction in the number of second primary breast cancers (Nayfield et al. 1991). Based on these data, a large randomized clinical trial with tamoxifen was initiated by the National Surgical Adjuvant Breast and Bowel Project (NSABP) to test its efficacy as a chemoprevention agent among women at increased risk of breast cancer. There was a 49 % reduction in the incidence of invasive breast cancer and a 50 % reduction in DCIS among patients randomized to tamoxifen compared to those receiving placebo. The benefit was exclusive for lowering the risk of ER-positive disease, consistent with the known mechanism of action. The greatest benefit was achieved among women with a prior history of LCIS (56 %) or atypical hyperplasia (86 %). In addition, it was noted that fewer fractures occurred among those treated with tamoxifen, suggesting an added protective effect on the bone. However, a greater number of endometrial cancers, pulmonary embolism, strokes, and deep vein thromboses were observed among women taking tamoxifen (Fisher et al. 1998). Subsequent analyses demonstrated that the overall health benefit for the patient depended on individual risk of breast cancer, endometrial cancer, and thrombosis (Gail et al. 1999). To further improve efficacy, additional SERMs with lower toxicity, such as raloxifene, have been developed. Within the context of a secondary analysis of the Multiple Outcome of Raloxifene Evaluation study (MORE Study), postmenopausal women randomized to raloxifene had a 72 % reduction in breast cancer incidence compared to women randomized to placebo (Cauley et al. 2001). Greatly encouraged by these data, NSABP investigators conducted a study to compare the effectiveness of raloxifene to tamoxifen in a

Table 15.4 Recommendations to lower the lifetime risk of breast cancer

Breastfeeding[a] is encouraged with each child
Maintain healthy body weight appropriate to height throughout adulthood
Assuming normal body weight at age 18, maintain adult body weight within 10–20 % (increased risk of breast cancer is associated with a 10–20 kg change in body weight between 18 and 50 years of age)
Engage in regular physical activity throughout life (such as 10,000 steps of walking at a vigorous pace 4–5 times per week)
Eat a diet rich in fruits, vegetables, and grains
Eat a diet low in total fats and refined sugars
Substitute saturated fats in diet with unsaturated healthy fats
Drink alcoholic beverages in moderation
Weigh risk and benefits of hormone replacement therapy
Use HRT for shortest interval to manage menopausal symptoms
Follow recommended screening guidelines
Practice monthly self-breast exam
Schedule and attend regular health checkups

[a]While the protective effect of breastfeeding is better established, there are currently no established guidelines on the necessary length to achieve benefit

randomized, double-blind study of postmenopausal women at high-risk of breast cancer (The STAR Trial). However, prior to completion of the STAR Trial, an analysis of the current evidence by the U.S. Preventive Services Task Force (USPSTF) in 2002 resulted in the recommendation for the routine use of tamoxifen or raloxifene for the primary prevention of breast cancer only for women at high risk for breast cancer. The USPSTF cautioned about the greater incidence of adverse events in older women, suggesting an improved risk-to-benefit ratio profile for younger women (Kinsinger and Harris 2002; Kinsinger et al. 2002). The summary evaluation of the Task Force resulted in recommendations to clinicians to discuss the benefits and risks of these interventions with patients at high risk of breast cancer. In 2006, the STAR Trial reported near equal incidence of invasive breast cancers between tamoxifen and raloxifene, but fewer thromboses, endometrial cancers, vaginal side effects, and cataracts in women on raloxifene compared to tamoxifen (Vogel et al. 2006). The incidence of strokes, fractures, and cardiovascular disease did not differ between groups. Consistent with a previous study (Martino et al. 2004), the incidence of DCIS and LCIS was statistically higher among those receiving raloxifene compared to the tamoxifen, suggesting no or little activity for raloxifene in these premalignant lesions. A summary of management options for patients at high risk of breast cancer is presented in Table 15.3, and a summary of general recommendations for all women is presented in Table 15.4.

15.4.1.2 Aromatase Inhibitors

Aromatase inhibitors represent a newer class of agents targeting estrogen production at the tissue level by specifically inhibiting the last step in estrogen biosynthesis. There are two general classes of aromatase inhibitors: irreversible steroidal activators and reversible nonsteroidal imidazole-based inhibitors. Aromatase

inhibitors act to suppress the low levels of estrogen production in postmenopausal women but are ineffective in women whose estrogen production is primarily from their ovaries (e.g., premenopausal women) (Rugo 2008).

Clinical trials of aromatase inhibitors suggest that aromatase inhibitors may be effective in the primary prevention of breast cancer in the postmenopausal setting. Results from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and Breast International Group (BIG) 1–98 trial found that aromatase inhibitors are better at reducing recurrence and contralateral breast cancers as well as not having the toxicity profile that is associated with tamoxifen use (i.e., vaginal dryness, endometrial cancer, venous thromboembolism) (Ingle 2011).

Superior reductions in contralateral breast cancers and improved disease-free survival in early-stage breast cancer patients along with fewer serious adverse events led to widespread interest in evaluating the efficacy of aromatase inhibitors for the primary prevention of invasive breast cancer for postmenopausal women at high risk of breast cancer. The National Cancer Institute of Canada Clinical Trials Group conducted the Mammary Prevention 3 or MAP3 study, which compared exemestane to placebo in postmenopausal women at high risk of breast cancer (Goss et al. 2007). Results of the study, reported in 2011, showed that among the 2,285 women on study for an average of 35 months, those receiving exemestane experienced 11 invasive breast cancers compared to 32 in the control group for an overall 65 % reduction in the annual incidence of any invasive breast cancer. Analysis for ER-positive invasive cancer showed a 72 % relative reduction with little efficacy for the prevention of DCIS. The benefits appear to be greater in women who are older than 60 and who had no history of premalignant DCIS, LCIS, or atypical hyperplasia (Goss et al. 2011). Further while adverse effects on bone density, bone fractures, and other musculoskeletal side effects were expected from experience with exemestane and other AIs in the adjuvant setting, similar adverse event rates were reported between the study arms. Limitations in the MAP3 study design for adverse outcomes have been raised (Decensi et al. 2012) including the short duration of follow-up and a failure of the investigators to prospectively collect information on bone, muscle, and joints health. Thus, at this time, aromatase inhibitors have not been approved by the Food and Drug Administration for use in the prevention setting. The field is awaiting the reporting of results from the British IBIS-II study. The International Breast Cancer Intervention Study II (IBIS II) began enrollment in 2003. IBIS II is designed to compare 5 years of daily anastrozole to daily tamoxifen (Cuzick 2008) in 6,000 postmenopausal women with a history of DCIS. Accrual is complete and awaiting final outcomes for expected reporting in 2013.

The actual acceptance of AIs for use in primary prevention will face similar challenges as tamoxifen and raloxifene and will depend significantly on our ability to improve risk discrimination. It will also become a challenge to defend the use of hormone therapies in primary prevention if these drugs only prevent tumors that would have been cured by early detection and subsequent endocrine therapy. Analysis of MAP3 study results show that 26 women must receive a 5-year course of exemestane to prevent a single case of cancer. Alternatively, if we cannot do a better job at identifying the woman at risk, then it becomes more effective to treat the one

early-stage invasive breast cancer with AI to achieve cure. Such a strategy would spare thousands the toxicities and costs associated with SERM or AI chemoprevention. This will remain a major challenge to the field of primary prevention when effective adjuvant therapies for the disease are applied in the prevention setting.

15.4.1.3 Retinoids

Vitamin A analogs or retinoids have been shown to inhibit the in vitro and in vivo growth of breast tumor cells (Serrano et al. 2004). Two types of nuclear retinoid receptors, the retinoid X receptor (RXR) and the retinoic acid receptor, bind to the retinoids to mediate their transcriptional effects on genes involved in controlling cell proliferation, differentiation, and apoptosis. The retinoids or vitamin A analogs have shown promise as agents for primary breast cancer prevention; however, issues related to their toxicity pose a challenge for dosing and patient acceptance. There is promise in the development of less toxic synthetic retinoids, such as N-4-hydroxyphenyl retinamide (4-HPR, fenretinide) and specific modulators of RXR that prevent tumor development in chemically induced animal models of mammary tumorigenesis, including ER-negative tumors in mouse models. Results from an early randomized breast cancer trial (Decensi et al. 2003) evaluating the efficacy of fenretinide to prevent a second breast malignancy in women with cancer were disappointing, with no overall reduction in risk observed (Decensi et al. 2009). Secondary analyses have raised questions about the interaction of retinoids on the IGF system and potential effects of age and menopausal status. Animal studies have suggested a potential benefit of the retinoids for the less common, but more aggressive, ER-negative tumors. Ongoing studies to identify intermediate response biomarkers for these agents and to diminish their potential toxicity may prove informative for the design of future retinoid-based prevention trials (Zanardi et al. 2006). Fenretinide is currently being tested in combination with tamoxifen in premenopausal women at increased risk of breast cancer with other retinoids and dietary components on early phase study (Cuzick et al. 2011).

15.4.1.4 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Several large epidemiological studies provide strong and compelling evidence for a protective role of NSAIDs to reduce the risk of breast cancer (Cuzick et al. 2011). In a study of 80,741 postmenopausal women participating in the prospective Women's Health Initiative (WHI) Observational Study, regular NSAID use (largely restricted to ibuprofen or aspirin) of two or more tablets per week was associated with a 21 % lower incidence with 5–9 years of use and a 28 % reduced incidence with 10 years of use (Harris et al. 2003). There was a statistically significant inverse linear trend of breast cancer incidence with the duration of use. More recent studies report a 20–30 % reduced risk in breast cancer incidence with NSAID use (Gill et al. 2007). The most recent evidence suggests the risk reduction is limited to ER-positive disease (Terry et al. 2004; Gill et al. 2007). These studies highlight the need for clinical trials to determine the efficacy of NSAIDs as cancer prevention agents and, ultimately, to determine their specificity for disease subtypes (e.g., ER positive versus ER negative).

The use of NSAIDs is not a novel concept for chemoprevention research. However, prevention trials evaluating the cyclooxygenase type 2 (COX-2)-specific NSAIDs (e.g., celecoxib, rofecoxib, and valdecoxib) are more recent developments in chemoprevention research. Interest in COX-2-specific NSAIDs has been spurred by their improved toxicity profile as compared to other NSAIDs (e.g., reduced gastrointestinal toxicity) and proven efficacy in preventing colon cancer with support for use in the breast and prostate (Harris 2009). Worrisome cardiotoxicity associated with the twice-daily dosing of COX-2 inhibitors has led to the closure of many trials and reevaluation of risk and application of COX-2 inhibitors in the prevention setting for breast cancer despite the strongly positive risk reductions seen in clinical trials and epidemiologic studies. COX-2 inhibitors remain under investigation for the chemoprevention of other cancers (e.g., cervical cancer chemoprevention trials are underway using celecoxib). Additional effort is needed to evaluate the effect of aspirin and NSAIDs with lower toxicity for the prevention of breast cancer and early phase trials are ongoing in combination with aromatase inhibitors for the modulation of intermediate biomarkers (ClinicalTrials.gov).

15.4.1.5 Metformin

One of the agents that the field is most excited about is metformin, a glucose-lowering drug that shows antitumor activity in vitro on breast cancer cell lines by acting on AMPK (its target in the liver for glucose-lowering activity) and indirectly through effects on IRS-1 that inhibit the AKT and the mTOR pathways resulting in both inhibition of cell proliferation and in some cases apoptosis (Zakikhani et al. 2010). It is this effect that is thought to explain observational data that shows a lower risk of breast cancer among diabetic women taking metformin for glucose control (Col et al. 2012). Metformin is currently undergoing investigation in the adjuvant setting for the prevention of breast cancer relapse in the phase III NCIC MA.32 (Goodwin et al. 2011). This trial has recently closed to accrual (January 2013), which will facilitate more rapid reporting of results. Information on contralateral breast cancer events in this study as well as positive findings for benefit in the prevention of recurrence would add a new and relatively well-tolerated prevention drug to the growing number of potential drug candidates for the prevention setting.

15.4.1.6 Other Agents

There are a number of additional compounds that do not act through the modulation of estrogen or the estrogen receptor that have demonstrated activity in animal models of breast and other solid tumors. Interest in these agents is strong because of the potential for the broader, ER-independent action of these agents. In addition to agents that target the retinoid receptor or the use of NSAIDs, tyrosine kinase inhibitors, antibodies that target the epidermal growth factor receptor (EGFR) signaling pathway, specific inhibitors of downstream targets of the COX-2 enzyme, inducers of apoptosis, modulators of the IGF signaling pathways, and inhibitors of angiogenesis are under investigation as chemoprevention agents for breast cancer (Cuzick et al. 2011; Howe and Brown 2011).

15.5 Risk Assessment and Clinical Applications

One of the primary challenges to successful prevention in the breast is the need for accurate assessment and communication of risk to the individual patient for prevention trials (refer to Chap. 5 for a more thorough discussion of the role of genetic counseling in the hereditary risk of cancer). The development of clinical practice guidelines that allow for informed decision making regarding surveillance and the weighing of benefits and risks of available prevention options remains hindered by the lack of accuracy in determining risk at the level of the individual patient. Risk assessment practice guidelines are likely to continue to improve as more information on risk factors, molecular biology of premalignancies, and their predictive potential are incorporated into existing models.

15.5.1 Elevated Risk

Elevated risk of breast cancer has been defined across groups as the presence of any factor that is reliably identifiable (i.e., family history, prior history of atypia) and when present has been consistently associated with an increase in risk that nears twice that or greater of the general population. In general, a low elevation in risk has been associated with factors that confer 1.5- to twofold increase over the general population of women at average risk. Moderate risk is associated with a three- to fivefold increase in risk, and high risk is associated with factors that confer a greater than fivefold elevated risk. Patients with moderate or high risk of breast cancer should be counseled on the importance of early detection and surveillance methods and should be informed on the benefits and risks of primary prevention and chemoprevention.

15.5.2 Risk Assessment Models

There has been a concerted effort by several groups to develop multivariate methods to derive a breast cancer risk assessment tools based on sets of risk factors (genetic and other) that are informative for estimating the risk of breast cancer. Two types of risk models have been developed that are clinically relevant—those that estimate a woman's absolute risk of developing breast cancer over time and those that determine the likelihood that an individual is a carrier of a *BRCA1* or *BRCA2* or unknown gene mutation (i.e., *BRCA1/2* Probability Models) (Nelson et al. 2005; Culver et al. 2007). The models that predict mutation carrier status and their clinical use have been discussed briefly above under genetic risk factors. A review of these models and their performance relative to each other is available elsewhere (Nelson et al. 2005; Culver et al. 2006; Amir et al. 2010). The U.S. Preventive Services Task Force (USPSTF) has assigned a B recommendation, indicating that there is fair evidence that women with sufficient family history suggestive of deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation

Table 15.5 Comparison of risk factors used in risk assessment models

BCRT	Claus/Ford[a]	IBIS
Age	Age	Age
Reproductive Age menarche Age first live birth	Reproductive None	Reproductive Age menarche Age menopause Age first live birth
Personal history Biopsy ADH[b]	Personal history None	Personal history Biopsy Atypical hyperplasia LCIS
Family history 1st-degree relative	Family history 1st-degree relative 2nd-degree relative Age of onset Ovarian cancer (Ford) Male breast cancer	Family history 1st-degree relative 2nd-degree relative Age of onset Ovarian cancer Male breast cancer
Lifestyle None	Lifestyle None	Lifestyle BMI[c] (IBIS)

Models do not apply to women with personal history of in situ or invasive disease
[a]BRCAPro package software
[b]Atypical ductal hyperplasia
[c]Body mass index as surrogate for adult weight

for BRCA testing (Nelson et al. 2005). Several risk tools have been developed to aid the physician and patient in the decision to seek further genetic testing for hereditary breast cancer (Culver et al. 2007; Amir et al. 2010; Gail and Mai 2010). These include a model developed by Myriad Genetic Laboratories, the Couch model, BRCAPRO (most widely used), the International Breast Cancer Intervention Study model (IBIS) also known as the Tyrer–Cuzick Model, and the more recently developed Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (Culver et al. 2007). The USPSTF does not specifically endorse any of these genetic risk assessment models because of insufficient data to evaluate their applicability to asymptomatic, cancer-free women. The USPSTF does support the use of a greater than 10 % risk probability for recommending further evaluation with an experienced genetics counselor for decisions regarding genetic testing (USPSTF 2005).

In contrast to BRCA probability tools, risk prediction models are also designed to derive individual risk estimates for the development of breast cancer over time for application in women without a family history suggestive of a known genetic mutation. These models are presented in Table 15.5 and include the Claus (or CASH) Model, the IBIS, and the Breast Cancer Risk Assessment Tool or BRCAT based on the modified Gail model or Gail model 2. The Gail model is the most widely used model (Amir et al. 2010) originally developed in 1989 from data derived from the Breast Cancer Detection and Demonstration Project (BCDDP) (Gail et al. 1989). It was developed to estimate the probability of developing breast cancer over a defined

age interval and was originally intended to improve screening guidelines. The model was subsequently revised (Gail model 2) and validated to predict risk of invasive breast cancer including information on history on first-degree affected family members (Gail et al. 1999; Rockhill et al. 2001). The Gail model 2 has been used extensively in clinical practice and has served as the basis of eligibility for a number of the breast cancer prevention trials (Fisher et al. 1998). At present, the U.S. FDA guidelines utilize the NSABP's modified Gail model as the basis for eligibility for the prophylactic use of tamoxifen. Tamoxifen is approved for women 35 years and older who have a 5-year Gail risk of breast cancer of 1.67 or greater (Freedman et al. 2003). As stated the Gail model 2 forms the basis of the US National Cancer Institute's BCRAT, accessible at http://www.cancer.gov/bcrisktool/. The BCRAT is most accurate for non-Hispanic White women who receive annual mammograms but tends to overestimate risk in younger women who do not receive annual mammograms. The model demonstrates reduced accuracy in populations with demographics (age, race, screening habits) that differ from the population on which it was built. At the individual level, the model lacks adequate discrimination in predicting risk and has been challenged on its generalizability across populations (Rockhill et al. 2001). For example, among women participating in the Nurses' Health Study, only 3.3 % of 1,354 cases of breast cancer that arose in women within the age-risk strata were defined by the Gail model (Rockhill et al. 2001). Low discrimination, particularly across populations, has spurred numerous efforts to overcome some of the limitations of the previous models (Bondy and Newman 2006). To address concerns regarding applicability of the Gail model to African American women (Bondy and Newman 2003) (Adams-Campbell et al. 2007), Gail and colleagues have derived a CARE Model using data from a large case–control study of African American women participating in the Women's Contraceptive and Reproductive Experiences (CARE) Study. The CARE Model has improved predictive accuracy over the Breast Cancer Risk Assessment Tool, which significantly underestimated risk for African American women. The CARE Model demonstrated high concordance between the numbers of cancer predicted and the number of cancers observed among African American women when validated in the WHI cohort (Gail et al. 2007). Improvements in risk prediction and clinical tools are likely to emerge in the next few years with the addition of such factors as breast density (Barlow et al. 2006), mammographic density change across exams (Kerlikowske et al. 2007a), use of HRT (Santen et al. 2007), and a variety of other factors such as weight, age at birth of first live child, and number of first-degree relatives (Barlow et al. 2006; Chen et al. 2006) and extended relatives with breast cancer as in the IBIS (Quante et al. 2012). The importance of a more comprehensive risk assessment tool that integrates more comprehensive family history with nongenetic factors is illustrated in the recent findings of Quante et al. (2012). By comparing the IBIS tool, which includes an extensive family history assessment with nongenetic factors, to the BRCAT, which does not include extended family history information, Quante et al. found that while both tools underestimated the actual 10-year cumulative probability of breast cancer in a prospective cohort of 1,857 women followed for an average of 8.5 years, the IBIS tool showed better agreement between the assigned and

observed outcomes as well as better risk discrimination with an area under the receiver operator curve or AUC of 69.5 % (95 % confidence interval 63.8–75.2 %) compared to that observed for the BRCAT (AUC = 63.2 %, CI = 57.6–68.9 %).

Going forward, it is likely that there will be models specifically for risks of premenopausal versus postmenopausal cancers and for specific cancer subtypes (luminal versus basal) (Colditz et al. 2004; Ma et al. 2006b; Chlebowski et al. 2007; Gail et al. 2007; Yang et al. 2007b; Millikan et al. 2008). For example, Chlebowski and colleagues, using data from the WHI cohort, found that the component risk factors of the Gail model and the Gail model itself were more predictive for ER-positive than ER-negative tumors in postmenopausal women where age, family history (first-degree relative), and previous biopsy were sufficient to capture the observed elevation in initial risk (Chlebowski et al. 2007). Additional integration of risk factors and validation considering differential etiology for disease subtypes will likely further improve the performance of these tools; an advance that will enhance screening and surveillance as well as efforts to prevent disease in higher risk individuals where the risk/benefit ratio is more favorable to the individual.

Conclusion

The ultimate goal of breast cancer risk factor studies is to identify factors that contribute to the disease. The purpose of these studies is to gain insights on how to reduce or prevent disease as a primary strategy to eradicate morbidity and mortality from breast cancer. The impact of the work is both to help guide the research community as well as to inform the public for health policy recommendations. As our chapter highlights, numerous advances have been made in all of these aspects (e.g., genetic screening for high-risk families, effective prevention in at-risk women, early detection and advances in targeted therapies). However, our chapter also highlights remaining critical gaps (i.e., uptake and impact of screening, role and challenges of obesity in breast cancer etiology, difficulty of balancing risks and benefits of chemoprevention, and the presence of disease heterogeneity). It is important to appreciate that sometimes the goals of individualizing or tailoring patient management, which seeks to prevent, eradicate, or cure, are not always compatible with public health goals of achieving cost-effective decreases in incidence, morbidity, and mortality.

At present, scientific evidence supports the integration of prevention counseling and consideration of prevention options (i.e., routine screening with MRI, prophylactic surgery or pharmaceutical interventions) for women with strong family histories of breast cancer, BRCA1/2 cancers, and for those with personal histories of breast biopsy with proliferative changes (i.e., women at moderate to high risk). Unfortunately, this approach only captures a minority of the women who will be affected by a breast cancer diagnosis. Despite the demonstrated prevention efficacy of tamoxifen, and now aromatase inhibitors, side effects and adverse outcomes (stroke and endometrial cancers with tamoxifen and bone loss and musculoskeletal effects with aromatase inhibitors), our inability to discriminate between average- and moderate-risk women challenges the clinical implementation of these approaches. The demonstration of solid evidence that we can

prevent or delay the development of breast cancer should be applauded as a major advance on which to guide future efforts. Although the mortality rates due to breast cancer are declining with advances in treatment, breast cancer remains a major health concern for women. The next major breakthrough for breast cancer in terms of reducing morbidity and mortality will come from the application of the knowledge discussed here to effective, tolerable, and beneficial prevention strategies.

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Prevention of Prostate Cancer

16

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16.1 Introduction

The American Cancer Society estimated 241,740 new diagnoses and 28,170 deaths due to prostate cancer in the USA in 2012, making it the most commonly diagnosed non-skin cancer (28 %) and the second most common cause (11 %) of cancer-related mortality among US men (ACS 2012). Figure 16.1a, b depicts time trends in prostate cancer incidence and mortality from 1975 to 2009. If the current trends continue, incidence is expected to reach 300,000 per year by 2015 (Crawford 2009).

In 2011, there were approximately 2.4 million prostate cancer survivors in the United States. Given current screening trends, it is estimated that 16.2 % (1 in 6) of American men alive today will be diagnosed with the disease and approximately 3 % (1 in 33) will die of the disease (Brawley 2012). Incidence and mortality trends for White and Black men in the USA indicate a steady increase in the incidence of prostate cancer in both these racial groups since 1975, with a prominent peak between 1991 and 1995, attributable to increased screening based on prostate-specific antigen (PSA) testing (SEER 2012). Mortality trends demonstrate steady increase until 1992, followed by a steady decrease. Dissociation between the incidence and mortality

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curves has prompted experts to conclude that PSA-based screening may lead to increased incidence of prostate cancer diagnosis, but many of the cancers identified may be clinically insignificant disease with no impact on mortality.

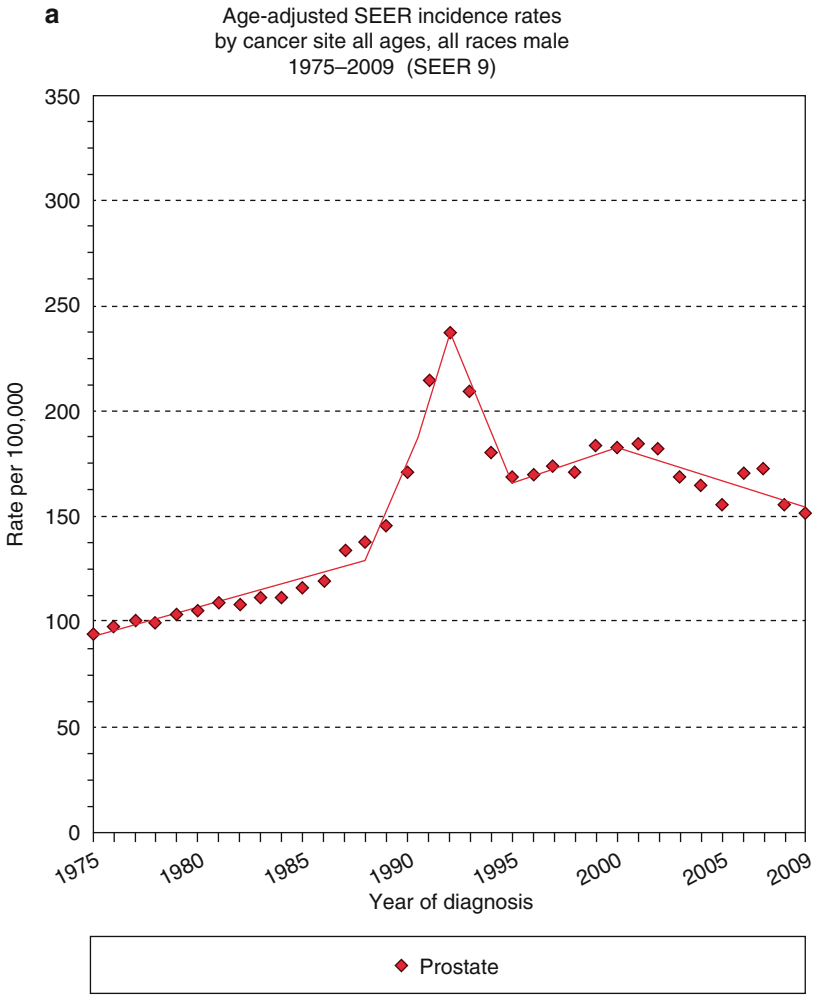

Fig. 16.1 (**a**) Age-adjusted SEER incidence rates by cancer site; all ages, all races, male 1975–2009 (SEER 9). Cancer sites include invasive cases only unless otherwise noted. Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 US Std population (19 age groups – census P25–1130). Regression lines are calculated using the Joinpoint Regression Program version 3.5, April 2011, National Cancer Institute. (**b**) Age-adjusted US mortality rates by cancer site; all ages, all races, male 1975–2009. Cancer sites include invasive cases only unless otherwise noted. Mortality source: US mortality files, National Center for Health Statistics, CDC. Rates are per 100,000 and are age-adjusted to the 2000 US Std population (19 age groups – census P25–1130). Regression lines are calculated using the Joinpoint Regression Program version 3.5, April 2011, National Cancer Institute

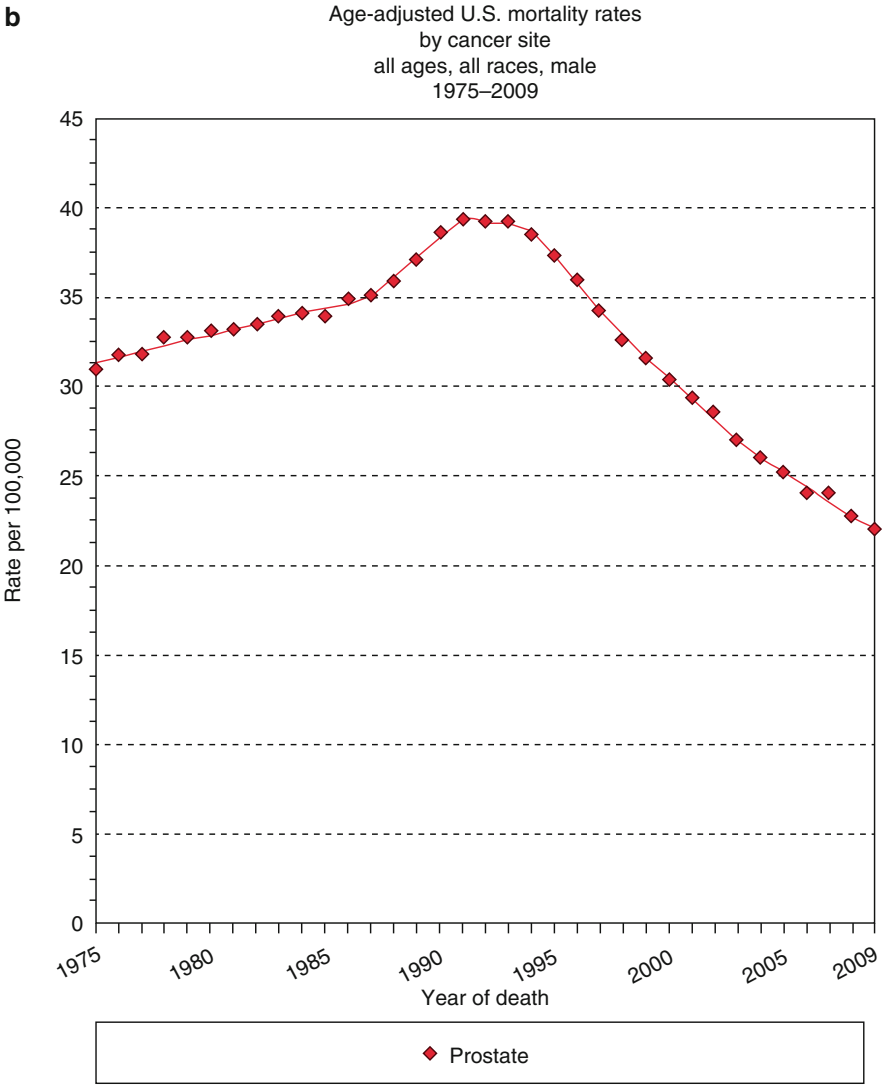

Fig. 16.1 (continued)

Internationally, prostate cancer is the second most common cancer diagnosed among men (behind lung cancer) and is the sixth most common cause of cancer death among men (Baade et al. 2009). Prostate cancer is particularly prevalent in developed countries, although the increasing impact of PSA testing complicates the interpretation of these trends in incidence as well as survival. However, it seems clear that prostate cancer incidence rates in less-developed countries tend to increase as Western influences become more pronounced.

16.2 Etiology of Prostate Cancer

With an emphasis on etiologic aspects, the following section explores the unique aspects of prostate cancer that set it apart from other cancers and offers relevant research on the role of prevention.

16.2.1 Established Risk Factors

The only well-established risk factors for prostate cancer are age, family history of the disease, and race (Brawley 2012). Prostate cancer is primarily a disease of older men and its incidence increases with age (Haas et al. 2008). Prior to the PSA screening era, the median age at diagnosis was 70 years. The median age at diagnosis between 2001 and 2010 was 67 years. The incidence of prostate cancer increases steadily after the fifth decade of life peaking in the seventh and eighth decade before again declining (Brawley 2012). Mortality, on the other hand, keeps rising with age. After the sixth decade, the prevalence is very close to a man's age. For example, in an individual who is 60 years old, there is a 60 % chance that he harbors at least one focus of prostate cancer (Thompson and Ankerst 2012). Genetics also plays a role in prostate cancer. Having a first degree male relative who has prostate cancer doubles the risk of a subject developing this disease. Genetic studies suggest that strong familial predisposition may be responsible for 5–10 % of prostate cancers (Brawley 2012). Genes that are associated with it are hereditary prostate cancer gene 1 (HPCG), BRCA1, or BRCA2.

Race is also an important risk factor for prostate cancer. Among US men, Black men have the highest incidence rates of prostate cancer, at 226 cases per 100,000 person-years. White men have an incidence of 145 per 100,000, Hispanic men have an incidence of 122 per 100,000, and Asian/Pacific Islander and Native American men have incidence rates of 78 and 72 per 100,000, respectively (Chou et al. 2011).

Risk of diagnosis for African-American is 1.6 times and the risk of death is 2.5 times the risk the White male population (Brawley 2012). Men of Asian descent living in the United States have a lower prostate cancer risk compared to White Americans, but their risk is higher than that of men of similar backgrounds living in Asia (Brawley 2012). There are studies suggesting that the prostate cancer risk of minority groups increases as their members acculturate into the Western society (Whittemore et al. 1995). In order to understand these racial differences, researchers have explored avenues such as diet, genetics, and environmental exposure, although with little success.

16.2.2 Screening and Mortality

The increasing use of PSA screening has led to an increasing number of men diagnosed with localized disease (Brawley 2012). Among men diagnosed between 1999 and 2006, 80 % had localized disease, 12 % had regional disease, and only 4 % had

distant disease. Approximately 30–40 % of men diagnosed with "apparently" localized disease and treated with radical prostatectomy eventually relapsed as determined by serum PSA testing (Lu-Yao et al. 1996; Wright et al. 2009).

The 5-year relative survival rates have increased with the shift toward a greater proportion of men diagnosed with localized disease (Altekruse et al. 2010). Among men diagnosed in the mid-1970s, 69 % were still living after 5 years. By the mid-1980s, the survival rate had increased to 76 %, and today, 5-year relative survival rate for men with local and regional disease is 100 %. The 10-year survival for this cohort is 95 %, and 15-year survival is 82 %. However, fewer than one-third of men diagnosed with metastatic disease survive 5 years (Altekruse et al. 2010). Unlike in the 1980s and early 1990s, today there is minimal racial difference in stage distribution at diagnosis and in 5-year survival statistics (Brawley 2012).

With respect to advanced prostate cancer (stage IV), a review of data from the Surveillance, Epidemiology, and End Results Program (SEER) from 1988 to 2005 indicated that age-adjusted incidence has significantly declined by 6.4 % each year (Cetin et al. 2010). Five-year relative survival improved across the study period (from 41.6 to 62.3 %), particularly in those diagnosed at younger ages or with moderately to well-differentiated tumors. Later years of diagnosis were independently associated with a decreased risk of death (from all causes and from prostate cancer specifically) after controlling for important patient, tumor, and treatment characteristics (Cetin et al. 2010). Risk factors such as age at diagnosis, high baseline PSA, and high nadir PSA have been associated with poor overall survival in patients with metastatic prostate cancer (Nayyar et al. 2010).

As compared to other major cancers, prostate cancer has some unique features. Although 1 in 6 men receives a prostate cancer diagnosis, only 1 in 33 men will die from the disease. Despite this, prostate cancer is the most commonly diagnosed non-skin cancer (at 29 %) and the second most common cause of cancer-related death (at 9 %) among US men (ACS 2012). This indicates that this disease has a highly heterogeneous course. Despite this, evidence suggests that 28,421 will die from prostate cancer in USA in 2012 (ACS 2012). Many men receive a diagnosis and seek treatment for it. For a certain percent, treatment cures them, but they risk exposure to the morbidity associated with treatment options. The rates are as high as 47–94 % for morbidities such as urinary incontinence and impotence associated with radiation and surgical treatment respectively (Fowler et al. 1993).

PSA screening is widely used in prostate cancer detection, helping to identify prostate cancer in thousands of men, as well as diagnosing tumors in men for whom the cancer may not have yet reached clinical significance. Treatment of clinically silent cancers is termed "overtreatment" (Klotz 2012). Estimates place the cost of this phenomenon in excess of $31 and $55 million respectively (Heijnsdijk et al. 2009).

After extensive review of literature, the United States Preventive Services Task Force (USPTF) has issued a grade D recommendation ("discourage the use of this service") for screening with PSA (Force 2012). This means that the USPTF believes there is moderate or high certainty that screening with PSA has no net benefit or that the harm outweighs the benefit. This grade D recommendation applies to healthy

men of all ages, regardless of race or family history. Although urologists and oncologist specializing in prostate cancer applaud the review methods of the task force, they disagree with their conclusions. They recommend that although PSA is not the perfect screening tool, discouraging its use in all men, as proposed by the task force, is not appropriate. They recommend judicious use of PSA screening in asymptomatic men after a thorough discussion regarding its risks and benefits and allowing patients to make an informed decision about their health (Schroder 2011). These recommendations are in agreement with those proposed by the American Cancer Society (Wolf et al. 2010). As evidenced by the controversy over PSA screening, there is currently no consensus with respect to primary screening protocols for prostate cancer. This situation is very different from the widely accepted primary screening protocols that exist for other major cancers such as colon and breast (Smith et al. 2001).

16.2.3 Treatment

Prostate cancer is also different from other cancers with respect to the treatment options available. Active surveillance is a viable treatment option for prostate cancer, which is not the case with most other major cancers such as bowel, breast, or lung cancers. Patients who choose active surveillance receive close monitoring for signs of disease progression, but do not receive active treatment. If the cancer becomes more aggressive, patients then may choose to receive active treatment. Economic analysis indicates active surveillance appears to reduce prostate cancer healthcare expenditures by reducing overtreatment and its associated costs (Corcoran et al. 2010).

Additionally, due to its high incidence but low mortality, heterogeneous disease course, long latency period, high treatment-related morbidity, and associated overdiagnosis and overtreatment, secondary prevention (diagnosis and treatment of early-stage disease before it reaches clinical significance) plays a greater role in prostate cancer than in other cancers.

16.3 Prevention

Every man faces a high risk of receiving a prostate cancer diagnosis within his lifetime. Therefore, an efficacious preventive agent could profoundly affect men's healthcare and healthcare economics. In the past few decades, numerous strategies for prostate cancer prevention have been evaluated including nutritional supplements (Reid et al. 2004; Lippman et al. 2009; Algotar et al. 2012), lifestyle modifications (Moore et al. 2009), and pharmaceutical agents (Hamilton and Freedland 2011). Currently, interest in curcumin and specific curcuminoids has grown following promising rat studies (Ravindran et al. 2009). Likewise, interest in vitamin D analogs showed promise in observational studies, but the results are inconclusive and positive observational data have led to dead ends (Ahn et al. 2008), although

other researchers have found a preventive effect for men with the FokI *ff* genotype who present with low serum vitamin D levels (Li et al. 2007). Trials initiated to test the chemopreventive properties of the nonsteroidal anti-inflammatory drug, rofecoxib, ended with the drug's withdrawal from the market due to safety concerns (van Adelsberg et al. 2007). Statins also hold some promise, although the data is conflicting and adverse effects could be substantial (Beltowski et al. 2009). In summary, it seems unlikely that an FDA-approved agent for prostate cancer prevention will be available in the near future. The disappointing results suggest the need for a better strategy.

16.3.1 5-Alpha-Reductase Inhibitors

5-Alpha-reductase inhibitors (5ARIs) show the most promise as a class of compounds with potential use in prostate cancer prevention. However, use of these drugs generates significant controversy. Two large, randomized trials—the Prostate Cancer Prevention Trial (PCPT) (Grover et al. 2006; Kaplan et al. 2009) and the REduction by DUtasteride of Prostate Cancer Events (REDUCE) trial (Wilt et al. 2010)—tested finasteride and dutasteride as prostate cancer chemoprevention agents, respectively. Both agents are FDA approved for treatment of benign prostatic hyperplasia. While primary end point analyses were originally promising, the complexities of using hormones to prevent carcinogenesis of the prostate are multifaceted. As a result, the US Food and Drug Administration (FDA) ruled against the proposed labeling change for the agents that would have allowed providers to prescribe them for chemoprevention.

Unlike some of the nutritional supplements that have been of interest in prostate cancer prevention, the physiologic and biological rationale for 5ARIs is clear. The enzyme, 5-α reductase (5-AR), catalyzes conversion of testosterone into dihydrotestosterone (DHT) (Nacusi and Tindall 2011; Parekh 2011), a potent androgen that mediates embryonic development of the prostate, growth of the prostate, and prostate cancer. Finasteride is a potent inhibitor of 5AR type 2, and dutasteride inhibits 5AR types 1 and 2.

The first study mentioned above, PCPT, was a randomized, controlled study that aimed to randomize 18,000 US men ≥55 years of age (Thompson et al. 2003) according to eligibility requirements—a normal digital rectal exam (DRE) and a PSA no greater than 3 ng/mL. After 7 years, the treatment arm showed a 25 % reduction in the incidence of prostate cancer compared to the placebo arm (18.4 % vs. 24.4 %; $P<0.001$). The REDUCE study, designed similarly to PCPT, studied the hypothesis that dutasteride had greater inhibitory action due to this agent's ability to inhibit 5AR types 1 and 2. This randomized, controlled trial enrolled 6,729 men aged 50–75 with a history of a negative prostate biopsy, which would put this population of men in a higher risk category than those enrolled onto PCPT. The dutasteride arm showed a 23 % reduction in prostate cancer incidence after 4 years of follow-up (19.9 % vs. 25.1 %; $P<0.001$). Therefore, on the surface, the trial was highly positive. However, that is not the end of the story.

Several criticisms arose including a lack of generalizability because end-of-study time points triggered biopsies rather than clinical indications such as abnormal DRE and/or rise in PSA. Subgroup biopsy analyses triggered by clinical events suggested the 5ARIs risk reduction was much more modest (PCPT: 9 % RRR; REDUCE: 1 % RRR) (Thompson et al. 2003; Andriole et al. 2010). However, some data strongly suggested that both finasteride and dutasteride were effective in preventing low-grade cancers. In both trials, the reduction in Gleason ≥6 tumors determined the end point of "overall cancer risk reduction." Low-grade cancers generally do not develop into clinically significant disease that would result in mortality, so risky chemopreventive efforts are unwarranted in these men (Albertsen et al. 2005; Eggener et al. 2011). In PCPT, central pathologic review revealed that 40 % of the cases diagnosed with Gleason ≤6 met the established criteria for insignificant disease (Epstein et al. 1994; Lucia et al. 2008).

Although full analyses remain unpublished for the REDUCE trial as of 2012, a pathologic review commissioned by the US FDA showed that 80 % of the cases diagnosed with a Gleason ≤6 fit the category of insignificant disease. Many men diagnosed with a Gleason ≤6, however, still receive either surgery or radiation. Thus, additional findings may influence healthcare and healthcare economics in this demographic. Current research suggests overtreatment occurs with low Gleason score cancers, which highlights the most enigmatic issue in prostate cancer prevention—identifying aggressive disease versus clinically indolent disease.

Significantly, both 5ARI studies demonstrated a marked increase in high-grade disease. The PCPT showed a 27 % higher incidence of Gleason score ≥7 tumors in the finasteride arm (280 (6.4 %) vs. 237 (5.1 %); $P=0.005$); and in the REDUCE trial, the dutasteride arm showed greater incidence of Gleason ≥8 tumors overall (220 (6.7 %) vs. 233 (6.8 %); $P=0.81$) with the effect most pronounced in years 3 and 4 (12 (0.5 %) vs. 1 (<0.1 %); $P=0.003$). Some researchers hypothesize that 5ARIs shrink prostate volume, thereby increasing likelihood of detecting high-grade disease when present (Kulkarni et al. 2006). Second, because the 5ARIs are effective in treating benign prostate hypertrophy (BPH), reduced BPH is a confounding factor potentiating the sensitivity of normal screening (PSA and DRE) to detect high-grade disease (Thompson 2006; Thompson and Ankerst 2007). After subsequent analyses taking these theories into account, investigators determined that while there was a 25 % increase in risk of Gleason ≤6 tumors, there was actually a 27 % reduction in tumors with Gleason ≥7 or greater (Redman et al. 2008). The REDUCE investigators concluded that the increased risk of tumors with Gleason ≥8 resulted from the diagnosis of more cancers in the placebo group in the first 2 years after randomization. Thus, the inclusion of these cases with the analyses of years 3 and 4 would have balanced out those diagnosed in the treatment arm with high-grade disease. Other investigators criticize both of these findings.

Lastly, while the 5ARIs have shown some promise in the prevention of prostate cancer, albeit with controversial data, the side effects of these agents include dizziness, fatigue, and nausea, as well as toxic effects that are more problematic, including gynecomastia, sexual side effects, weight gain, and bone loss (Evans and Goa 2003; Grover et al. 2006). These are important considerations and must be taken

into account, especially in treating asymptomatic patients. The two large trials testing 5ARIs for prostate cancer chemoprevention generated controversy, and the FDA denied approval of 5ARIs for chemoprevention.

16.3.2 Nutritional Supplements

Over the past three decades, numerous supplements and "nutraceuticals" piqued the interest of investigators in the field of prostate cancer prevention research. They based their interest on epidemiologic and preclinical data references for various substances (Kelloff et al. 1999, 2000). However, to date, the epidemiologic findings did not translate into successful chemopreventive agents. Selenium is clearly the most widely studied agent for prostate cancer chemoprevention, followed by vitamin E, which was a component of the SELenium and vitamin E Clinical Trial (SELECT), the largest chemoprevention study funded by the US National Institutes of Health (NIH). Other natural agents showing potential in prostate cancer chemoprevention include vitamin D (Vijayakumar et al. 2005; Krishnan and Feldman 2011), retinoids (Chen et al. 2012; Kelsey et al. 2012), and green tea (Bettuzzi et al. 2006; Khan et al. 2009). However, all clinical trials thus far have been negative.

16.3.2.1 The Nutritional Prevention of Cancer Study

Selenium was in the spotlight of prostate cancer chemoprevention after showing promise as a prostate cancer chemopreventive agent in secondary analyses of the Nutritional Prevention of Cancer (NPC) study. The NPC study was a randomized, controlled trial designed to test selenium's ability to decrease recurrence of two nonmelanoma skin cancers—squamous cell carcinoma and basal cell carcinoma. While the primary end point was not satisfied, the secondary analyses published in 1993 examining prostate cancer incidence showed a decrease in incidence of prostate cancer (Clark et al. 1996). Interestingly, men that fell within the highest level of baseline selenium showed the most pronounced effect, suggesting that the chemopreventive benefit could be associated directly with selenium deficiency. The preventive effect decreased over the last 3 years of the analyses. However, the decrease of prostate cancer incidence in the treatment arm remained statistically significant (Duffield-Lillico et al. 2003). This trial showed the largest effect size of any chemoprevention trial of its kind.

In the wake of the exciting positive data yielded by the NPC study, the NIH initiated funding for three clinical trials. In each of the trials, analyses of the adverse effect profile for selenium suggested it was well tolerated, and there was no increase in squamous cell carcinoma as observed in the NPS trial. However, primary end point analyses of all three studies showed selenium's lack of effect in prostate cancer incidence or in retardation of PSA velocity. Many researchers performed subsequent ad hoc analyses to identify a subgroup for which the treatment arms were effective, with no effect in any group identified to date. Furthermore, many theories exist as to why the studies did not reflect the data observed in the NPC study, but

none is definitive. Perhaps we can learn from these results to design more strategic and effective approaches to prostate cancer chemoprevention.

16.3.2.2 SELECT

SELECT received funding from the US NIH based on a broad body of well-accepted epidemiologic and preclinical data on both selenium and vitamin E, which also showed promise for prostate cancer chemoprevention based on epidemiologic and preclinical data. SELECT, the largest cancer chemoprevention trial funded by the NIH, was a placebo-controlled study with a 2×2 factorial design randomizing 35,533 men to one of four treatment groups: selenium with matching placebo, vitamin E with matching placebo, both agents, or placebo. Accrual began on 2001, and in 2008, the independent Data Safety and Monitoring Committee (DSMC) performed a planned interim analysis. Results from a futility analysis showed no possibility of benefit according the study design, prompting recommendations for early discontinuation (Lippman et al. 2009). In summary, with median follow-up of 5.5 years, the numbers of prostate cancers detected were 473 for vitamin E (hazard ratio [HR], 1.13; 99 %CI, 0.95–1.35), 432 for selenium (HR, 1.04; 99 % CI, 0.87–1.24), 437 for selenium plus vitamin E (HR, 1.05; 99 % CI, 0.88–1.25), and 416 for placebo (HR, 1.0). The DSMC also expressed concern about nonsignificant increases in prostate cancer incidence of the vitamin E arm ($P = .06$) and type 2 diabetes mellitus in the selenium plus placebo group ($P = .16$). Based on a review of follow-up data in 2011, the DSMC recommended reporting the increase in prostate cancer in the vitamin E arm (Klein et al. 2011).

16.3.2.3 The University of Arizona Cancer Center Prostate Cancer Prevention Program

Based primarily on the results from the NPC study, also conducted from the University of Arizona, investigators at the University of Arizona Cancer Center (AZCC), with NIH support, initiated two randomized, controlled clinical trials testing selenium as a primary and secondary chemopreventive agent for prostate cancer. The Negative Biopsy Trial (NBT) was a randomized, double-blind, placebo-controlled, multicenter, phase three clinical trial designed to investigate the effects of two doses of high-selenium yeast (200 or 400 mg/day) versus placebo on the incidence of prostate cancer. Follow-ups on subjects occurred every 6 months for up to 5 years (Algotar et al. 2012). The Watchful Waiting (WW) study was a phase two randomized, double-blind, placebo-controlled clinical trial conducted in men with localized nonmetastatic prostate cancer who elected to forgo active treatment and adopt active surveillance. For this study, 140 subjects were randomized to placebo ($n = 46$), 200 μg/day ($n = 47$), or 800 μg/day ($n = 47$) of oral selenium (as selenized yeast) and followed every 3 months for up to 5 years (Algotar et al. 2012).

Analyses of NBT showed 26 (11.3 %), 24 (10.3 %), and 23 (10 %) subjects developed biopsy-proven prostate cancer in the placebo cohort, 200 mcg/day selenium, and 400 mcg/day treatment cohorts, respectively ($P = 0.88$). Mean and standard deviation of Gleason sum score was 6.7 (0.9), 6.6 (1.2), and 6.3 (1.2),

respectively ($P=0.53$). In addition, the time to development of prostate cancer was not statistically significantly different in the two selenium groups versus placebo after adjusting for confounders. Further analyses demonstrated that none of the baseline variables had any effect on the NBT primary end point.

In the WW study primary end point analysis, the median PSA doubling times for the three treatment cohorts were 6.24, 6.98, and 8.45 years, respectively. Point estimates and 95 % confidence intervals for differences in PSA trajectories of the 200 mcg/day selenium and 800 mcg/day selenium treatment groups as compared with placebo were −0.03 (−0.09 to 0.03) and −0.02 (−0.08 to 0.04), respectively. Thus, after adjusting for confounders including baseline levels of plasma selenium and PSA, age, race, BMI, baseline PSA, type of assay used to estimate PSA, and Gleason score, the PSA velocities for the 200 mcg/day selenium and 800 mcg/day selenium treatment groups did not differ significantly from placebo or from each other. Analyses stratified by quartiles of baseline selenium assessed if selenium supplementation had a differential effect on PSA velocity. In the lower three, quartiles were not significantly different from placebo. In the fourth quartile, the trajectory of PSA for the 200 mcg/day selenium treatment group was not statistically significantly different than that shown by subjects on placebo ($P=0.243$); however, it was of interest that the trajectory of PSA for men in the 800 mcg/day selenium treatment group was statistically significantly higher than that for men on placebo ($P=0.018$). This suggests that supplementation with a relatively high dose of selenium may have deleterious effects on PSA velocity in men already at modestly high levels of plasma selenium.

16.3.3 Discussion

Because of its high incidence in US men, prostate cancer remains an important health concern in the USA. As with all cancers, in the arena of chemoprevention, a favorable side effect profile is always vital since you are giving an intervention to a relatively healthy group of people. But in prostate cancer, an additional factor comes into play. While there are high-grade prostatic tumors that require immediate, frontline treatment, numerous prostate cancers are slow growing or indolent with no resulting clinically significant disease, morbidity, or mortality within the man's lifetime. Therefore, a preventive prostate cancer intervention is not necessary for a large number of men. In the healthy population of men considered to be at average risk of prostate cancer, agents with even mildly unfavorable adverse effect profiles may not be acceptable.

16.4 Alternative Approaches to Prostate Cancer Prevention

The natural health industry has a reputation for making unsubstantiated health claims for various herbs, foods, and spices. However, clinical research offers an avenue to evaluate these claims, offering the hope of finding the next aspirin in

terms of health benefits versus risks. A few of these supplements show potential in cancer treatment and prevention, most notably curcumin, and resveratrol, and manipulation of lifestyle factors should also be considered as an alternative approach.

16.4.1 Curcumin

Curcumin is one of the rising stars in the alternative health market and has been touted as a treatment for arthritis via regulation of 5-LOX and COX-2 pathways (Rao 2007), as a cancer prevention agent (Rao 2007; Khan et al. 2008), to support liver health (Vitaglione et al. 2005; Reuter et al. 2008), for life extension (Naik et al. 2004), and for a host of other health issues. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hepatadiene-3,5-dione] is the primary constituent of turmeric (*Curcuma longa*), a spice used in cooking and folk medicine throughout Southeast Asia, a region evidencing low incidence for most cancer types (Salvioli et al. 2007). Over the last 20 years, researchers have been assembling a considerable body of evidence that curcumin may be a powerful tool in the fight against cancer—via apoptosis (Vitaglione et al. 2005; Khan et al. 2008) and due to its antitumor and anti-inflammatory properties (Piper et al. 1998; Ravindran et al. 2009)—and in slowing the progression of cancer (Plummer et al. 2001; Aggarwal et al. 2006; Bae et al. 2006). Curcumin induces apoptosis in both androgen-dependent and metastatic hormone refractory prostate cancer cells (Yoysungnoen et al. 2006), as well as demonstrating antimetastatic activity (Dorai et al. 2000; Kuttan et al. 2007).

In addition to its own antioxidant activity (Killian et al. 2012), curcumin increases glutathione S-transferase, which upregulates the creation of glutathione (Rao 2007; Basnet and Skalko-Basnet 2011), the body's master antioxidant [accordingly, researchers are studying curcumin as a liver detoxification supplement (Naik et al. 2004; Vitaglione et al. 2005). Curcumin affects several cell-signaling pathways identified as tumor growth and survival mechanisms for several types of cancer, including prostate cancer (Sharma et al. 2001, 2005). Furthermore, curcumin demonstrates androgen receptor-binding capabilities, downregulating the expression of AR (Dorai et al. 2000; Aggarwal 2008). Finally, curcumin promotes PSA inhibition, while one of its constituent curcuminoids also serves as an AR antagonist (Nakamura et al. 2002; Tsui et al. 2008).

Despite these demonstrated chemopreventive benefits of curcumin, researchers remain unclear about the specific mechanisms of action (Shi et al. 2009). Turmeric contains, in addition to curcumin, several minor fractions such as demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and cyclocurcumin (Shen and Ji 2012b). Most commercially available products contain three major curcuminoids: 77 % curcumin, 17 % demethoxycurcumin, and 3 % bisdemethoxycurcumin (Kiuchi et al. 1993). Ravindran et al. propose that the presence of these methoxy groups accounts for curcumin's anti-inflammatory and antiproliferative activity (Ravindran et al. 2009), while the hydroxyl groups provide the antioxidant activity. One of the ongoing issues with curcumin pharmacology is its minimal in

vivo bioavailability, resulting in low serum levels and miniscule presence in tissues (Karunagaran et al. 2005; Anand et al. 2007; Aggarwal and Sung 2009). The low absorption and bioavailability of curcumin led some researchers to propose the mechanism of action is not only in the curcuminoids but also in the metabolites and degradation products (Anand et al. 2007; Aggarwal and Sung 2009; Shen and Ji 2012a). Nonetheless, several labs are seeking to isolate specific curcumin compounds according to which pathways they affect. The goal is to develop alternative delivery systems, leading to better absorption, which includes nanoparticle conjugation (Shen and Ji 2012a), β-cyclodextrin, fibrinogen, liposome, and hydrogel (Shankar and Srivastava 2012).

16.4.2 Resveratrol

The headline proclaims, "Daily dose of red wine compound backed for cancer fight" (Gray 2012), but does the research support these claims? Resveratrol (3, 5, 4′ trihydroxy-trans-stilbene) is a natural phytochemical with cardioprotective, anti-inflammatory, and anticancer properties (Jang et al. 1997). There is no definitive research confirming resveratrol as a first-line chemopreventive strategy, but there is growing evidence to support continued research.

Pezzuto's review of the literature, as well as his own research, suggests that resveratrol shows potential as a carcinogenesis inhibitor (Pezzuto 2008). Kraft et al. suggest resveratrol is a promising chemopreventive agent due to its ability to decrease metabolism of phase-I enzyme genes (CYP2E1 and CYP1A1), which are pro-carcinogenic, and/or by increasing the metabolism of phase-II detoxifying enzymes (Kraft et al. 2009) [glutathione S-transferases, uridine diphosphate-glucuronosyltransferases, and quinone reductase enzymes (Hebbar et al. 2005)]. Kai, Samuel, and Levenson examined the ability of resveratrol to enhance p53 acetylation and apoptosis in prostate cancer by inhibiting the MTA1/NuRD complex, which then allows the activation of proapoptotic genes (Kai et al. 2010). The expression of MTA1 protein is higher in androgen-independent metastatic tumors in relation to early-stage localized disease and benign prostatic tissues (Hofer et al. 2004). These authors suggest their research identifies MTA1 as a new target in prostate cancer treatment and prevention.

16.4.3 Lifestyle Factors

Based on the research presented for curcumin and resveratrol, there are a few generalizations that can act as guiding principles for prostate cancer prevention. What follows might be considered an ecological approach in that it takes into account the whole ecology of tumorigenesis in the human body [see also (Pienta et al. 2008) for an ecological approach focused on the environment of the tumor itself], where the body is the ecosystem we seek to manipulate. It seems possible now to create an inhospitable environment for the survival of cancer cells in the body.

Estimations from the World Health Organization (WHO) are that 300 million adults are obese and more than a billion adults are overweight (Faloia et al. 2012). This has implications for prostate cancer. Gong et al. identified a 29 % increased risk for high-grade prostate cancer (Gleason ≥7) and an 18 % decreased risk of low-grade tumors in men with a body mass index ≥30 in comparison to men with body mass index <25 [$n = 10{,}258$, 1,936 prostate cancers] (Gong et al. 2006). The consensus in meta-analyses of the connection between obesity and high-grade prostate cancer supports the findings of Gong and colleagues (Gong et al. 2006; Rodriguez et al. 2007; Wright et al. 2007). Burton et al. have correlated obesity with unusually high levels of adipocyte-derived peptides (adipokines), sex hormones [including estrogen, which may be the initiating driver of prostate adenocarcinoma progression (Singha et al. 2008)], and inflammatory cytokines, with both in vitro and epidemiological studies showing that adipokines influence prostate carcinogenesis (Burton et al. 2010). As suggested by Gong et al., Burton et al. found that testosterone levels are lower in obesity, which may select for more aggressive, androgen-independent tumors. However, there is no connection between moderate and high-normal levels of testosterone and prostate cancer (Stattin et al. 2004).

One of the comorbidities of obesity is low-grade or "smoldering" inflammation (Balkwill et al. 2005), which contributes to various forms of disease, including prostate cancer. COX-2 expression, a pro-inflammatory enzyme and the primary target of nonsteroidal anti-inflammatory drugs (NSAIDs), is highly increased in several cancers, including prostate cancer (Gupta et al. 1999). There is some evidence that aspirin use may offer COX-2-mediated protection against esophageal, lung, stomach, and ovarian cancers (Fosslien 2000). In a follow-up for patients in a vascular event prevention study, with randomized trials of daily aspirin versus control, those in the aspirin group had a 40 % reduction in cancer deaths from the 5-year mark forward and consistent death-rate reductions for certain cancers at the 20-year follow-up (Rothwell et al. 2011). Through a review of the records from the United Kingdom's five large randomized trials of daily aspirin versus no aspirin (cardiovascular event prevention), all participants who showed incident cancers had a 30–40 % risk reduction for distant metastasis and nearly a 50 % risk reduction for metastatic adenocarcinoma (Rothwell et al. 2012).

The major recommendation for lifestyle factors in prostate cancer prevention is that men need to be more physically active (Orsini et al. 2009), which helps prevent obesity, another risk factor for prostate cancer (Rodriguez et al. 2007; Burton et al. 2010). In addition, men must reduce their reliance on the current Western diet, which is high in processed foods, low in fresh fruit and vegetables (sources of phytonutrients), and nearly void of omega-3 fats (anti-inflammatory) while containing abundant omega-6 fats, including arachidonic acid, a powerful driver of the inflammatory process (Matsuyama and Yoshimura 2008). The research has not revealed the definitive diet, and each person processes food a little differently. Consuming more fresh fruits and vegetables [especially cruciferous vegetables, which offer chemoprevention for the prostate (Beaver et al. 2012)], lean meats (chicken, fish, turkey), and nuts and seeds (walnuts, almonds, pumpkin seeds, hemp seed), as part of a diet also rich in curry, would offer a solid foundation for general health.

16.5 Promising Avenues for the Future of Prostate Cancer Prevention

Having laid out the etiology and the various efforts toward prevention of prostate cancer, this section discusses promising and novel avenues in the areas of molecular genetics, metastasis, imaging, and diagnosis. Following a brief overview, discussion will focus on the potential role of these topics in prostate cancer prevention.

16.5.1 Diagnostics

Prostate-specific antigen (PSA) is the most important biomarker with respect to diagnosis and prognosis of prostate cancer. PSA is highly sensitive but lacks specificity (Harvey et al. 2009). High PSA levels are not exclusive to prostate cancer but occur also in other prostatic pathologies, such as benign prostatic hypertrophy or prostatitis (Stephan et al. 2009). It is important to distinguish between these conditions since the treatment and prognosis for each of these is significantly different. Using the kinetic properties of PSA (rate of PSA change over time, also known as PSA velocity) has been instrumental in improving the specificity of PSA toward diagnosing prostate cancer (Thanigasalam et al. 2009); however, it is still short of ideal since there continues to be significant morbidity and mortality due to prostate cancer (ACS 2012). Therefore, the quest for improving diagnostic specificity for prostate cancer continues.

Several studies indicate that use of individual PSA isoforms in developing diagnostic algorithms may improve specificity of PSA as a diagnostic marker of prostate cancer (Lilja et al. 1991; Stenman et al. 1991; Stephan et al. 2007; Thompson and Ankerst 2007; Makarov et al. 2009). A prospective multicenter study by the Early Detection Research Network investigated the utility of -[proPSA], an isoform of PSA, for early detection of prostate cancer (Sokoll et al. 2010). In this study, serum PSA, free PSA, and [−2]proPSA were measured in 566 subjects. At 70 % specificity, the sensitivity of %[−2]proPSA ([−2]proPSA/fPSA) was 54 %. Including %[−2]proPSA in a multivariate prediction model incorporating PSA and %fPSA improved the diagnostic performance ($P<0.01$). In the 2–4 ng/mL PSA range, %[−2]proPSA outperformed %fPSA (receiver operator characteristic areas under the curve, 0.73 vs. 0.61; $P=0.01$). At 80 % sensitivity, the specificity of %[−2]proPSA (44.9 %; 95 % CI, 38.4–51.5 %) was significantly higher than PSA (30.8 %; 95 % CI, 24.9–37.1 %) and relatively higher than %fPSA (34.6 %; 95 % CI, 28.5–41.4 %). %[−2]proPSA increased with increasing Gleason score ($P<0.001$) and was higher in aggressive cancers ($P=0.03$).

Several other authors have also noted the utility of PSA isoforms toward improving diagnostic specificity for prostate tumors (Lilja et al. 1991; Stephan et al. 2007; Thompson and Ankerst 2007; Makarov et al. 2009). These studies have investigated various isoforms, their various combinations and ratios, as well as techniques (univariate models, multivariate models, and artificial neural networks) to analyze the data. Although we need definitive studies before PSA isoform measurement

becomes part of routine clinical practice, this seems to be a promising area with great potential.

Another prominent area for improving the diagnostic specificity of prostate cancer relates to the technique used in conducting a prostate biopsy. For the last 15 years, techniques used for conducting the prostate biopsy underwent a gradual change. In the late 1990s, ultrasound-guided transrectal sextant biopsy was the standard technique for a prostate biopsy (Jones 2007). This technique takes three cores from each side of the prostate. Around 2000, papers examining improved efficacy with increased numbers of cores and different techniques (laterally directed biopsies) indicated promising results (Norberg et al. 1997; Chang et al. 1998; Presti et al. 2000; Epstein et al. 2001; Stewart et al. 2001). This led to changes in biopsy techniques, moving from a 6-core standard to a standard 12-core biopsy. Others propose saturation biopsies, having as many as 23–31 cores, for men with repeated negative biopsies but high PSA (Borboroglu et al. 2000; Stewart et al. 2001). False-negative rates for the sextant biopsy technique ranged from 20 to 23 % (Rabbani et al. 1998; Presti et al. 2000). As the number of biopsy cores increased, the false-negative rate dropped to approximately 11 %.

16.5.2 Imaging

Imaging is the key to diagnosis and staging of various malignancies. However, despite the availability of a multitude of imaging options, prostate cancer is the only major malignancy without a clear and accepted role for imaging. The following section summarizes the imaging modalities currently available in prostate cancer and their potential role in prostate cancer prevention.

16.5.2.1 Transrectal Ultrasound (TRUS) and Computed Tomography (CT)

TRUS is the most widely used imaging modality for prostate cancer, used mainly to guide prostate biopsies (Pinto et al. 2012). It only can be used in local staging if there is gross extension outside the capsule or seminal vesicles due to its minimal ability to visualize small foci (Turkbey et al. 2009a). Incorporation of color power Doppler ultrasound, as well as contrast-enhanced TRUS with microbubbles, demonstrates an ability to improve detection rates (Ellegala et al. 2003; Sauvain et al. 2003; Ravizzini et al. 2009; Turkbey et al. 2009a); however these have not been investigated for local staging or on a multi-institutional level. CT has a very limited role in diagnosing prostate cancer because its resolution is insufficient to differentiate the prostate gland from surrounding tissue. Similar to TRUS, CT's low differentiation confines its utility to grossly advanced, locally spread disease (Pinto et al. 2012).

16.5.2.2 Magnetic Resonance Imaging (MRI)

Conventional anatomical MRI techniques use T1- and T2-weighted sequences captured using endorectal and phased-array body coil on a magnet with a field strength of 1.5T to image the prostate (Pinto et al. 2012). This allows for high spatial

resolution of the prostate. The sensitivity and specificity for MRI vary widely for local staging of prostate cancer, 14–100 and 67–100 % (Turkbey et al. 2009a) respectively. Sensitivity and specificity numbers for extracapsular extension and seminal vesicles are 13–95 % and 49–97 % and 23–80 % and 81–99 %, respectively (Bartolozzi et al. 1996; Perrotti et al. 1996; Presti et al. 1996; Ikonen et al. 1998; Rorvik et al. 1999; Ikonen et al. 2001; Cornud et al. 2002; Sala et al. 2006). Individual radiologist expertise, especially those specializing in genitourinary MRI, is an important determinant of staging accuracy (Schiebler et al. 1992).

Use of functional MRI (fMRI) techniques—such as magnetic spectroscopic imaging (MRSI), dynamic contrast-enhanced MRI (DCE-MRI), and diffusion-weighted MRI (DW-MRI)—provides detailed prostate imaging. MRSI is a technique that creates images based on differences in characteristic resonant frequencies of cellular metabolites like citrate, polyamines, creatine, and choline within the prostate gland (Pinto et al. 2012). Normal prostate tissue contains low levels of choline and high levels of citrate, whereas prostate cancer shows high levels of choline and decreased levels of citrate. The ratio of choline to citrate relates to the Gleason score, suggesting that MRSI may provide information about cancer aggressiveness. Integration of MRSI into routine prostate MRI practice has improved tumor detection rates in several studies (Ravizzini et al. 2009; Turkbey et al. 2009a; Pinto et al. 2011, 2012). Using metabolic mapping of prostate tumors in the near future may allow better selection of the appropriate surgical plan (Sciarra et al. 2011).

DCE-MRI evaluates the vascularity of tumors over time. Fast MR scanning sequences, combined with rapid injections of a low molecular weight contrast agent, allow noninvasive imaging of tumor angiogenesis (Pinto et al. 2012). Prostate cancers show early, rapid enhancement and early washout on DCE-MRI. This pattern is highly predictive of prostate cancer but is not pathognomonic. Several benign conditions, such as prostatitis and post-biopsy hemorrhage, can mimic the appearance of tumors on DCE-MRI (Engelbrecht et al. 2003; Pinto et al. 2011). This method still lacks standardization and testing in multi-institutional large trials and requires testing in small case series only, whereas the combination of high-spatial-resolution DCE-MRI and T2 MRI improved prostate cancer staging when compared to either technique alone (Bloch et al. 2007). Prostate cancer lesions can be detected with DW-MRI as regions of restricted diffusion and high signal intensity foci, but they are low in signal intensity on the apparent diffusion coefficient map (Ravizzini et al. 2009; Seitz et al. 2009; Turkbey et al. 2009a). DW-MRI studies have reported an improvement in SVI prediction for 3T DWI-MRI in conjunction with T2 W imaging compared with T2 W imaging alone, independent of the experience of the reader (Kim et al. 2008). DW-MRI is still not in routine clinical use for prostate cancer staging even though recent technical advances in DW-MRI appear promising (Pinto et al. 2012).

16.5.2.3 Positron Emission Tomography/ Computed Tomography (PET/CT)

PET/CT combines the molecular functional element with a computed tomography tool. Integrated PET/CT improves diagnosis and staging through its creation of

fused images, enabling the physician to associate increased metabolism with anatomical location. The most commonly available PET tracer is fluoro-2-deoxy-2-d-glucose (FDG), an indicator of glycolytic activity in cells. Cancer cells have increased metabolism and utilize the glycolytic pathway, which leads to increased glucose analog uptake (Weber 1977). Although useful in other cancers, FDG is not recommended for diagnosis and staging of localized prostate cancer because of the low metabolic glucose activity of prostate cancer. A further drawback is that the normal urinary FDG excretion results in high bladder activity that can mask prostate tumors (Effert et al. 1996; Liu et al. 2001; Bouchelouche and Oehr 2008; Ravizzini et al. 2009; Turkbey et al. 2009b). Studies comparing choline PET/CT with MRI for extra-prostatic extension showed a very low sensitivity (22 vs. 63 %, $P = 0.001$) (Martorana et al. 2006). Rinnab et al., in a small cohort of patients, compared C-choline PET/CT to TRUS showing how, even if superior to TRUS, PET/CT tended to under-stage prostate cancer in terms of local extension of the disease (Rinnab et al. 2007). Further studies in large populations of patients are still necessary to establish the clinical role of PET/CT in the local staging of prostate cancer.

16.5.2.4 Imaging in Metastatic Prostate Cancer

Nodal metastases are often small or microscopic, and nodal enlargement due to metastases occurs relatively late in the progression of prostate cancer; hence CT and MRI give poor yield for this purpose. In a meta-analysis by Hovels et al., CT and MRI demonstrated sensitivity and specificity of 40 and 80 % in detecting lymph node metastases (Hovels et al. 2008). Using ultra-small particles of iron oxide (USPIO) as a contrast agent for MRI has increased the sensitivity to 90.5 %. Macrophages consume these particles in normal lymph nodes resulting in a signal decrease on MRI sequences. Despite the increase in sensitivity, node-by-node comparison between the pre- and post-USPIO images still consumes considerable time (Harisinghani et al. 2003; Pouliot et al. 2009; Zaheer et al. 2009).

The advantage of PET over CT and MRI is its ability to detect metabolic changes of tumor cells in a structurally normal lymph node before tumor cells enlarge the lymph node. Since 2003, different authors have investigated the role of choline PET/CT in prostate cancer staging, reporting a wide variability in sensitivity (0–100 %) and high specificity (95–100 %) (de Jong et al. 2003; Schiavina et al. 2008; Beheshti et al. 2010; Poulsen et al. 2010; Steuber et al. 2010; Budiharto et al. 2011). Variability in results could be due to small subject numbers or poor population selection. At present, routine clinical use of choline PET/CT cannot be recommended. Performance of large, prospective, cost-effectiveness studies is necessary in order to assess its usefulness.

Metastatic prostate cancer most commonly spreads via the hematogenous route to well-vascularized areas of the skeleton, preferentially as osteoblastic lesions (Thurairaja et al. 2004). Trauma and other noncancerous processes can mimic the characteristic osteoblastic lesions seen with prostate cancer, which leads to false-positives. Due to this, improving diagnostic accuracy requires modalities such as plain radiography, CT, MRI, and PET. MRI is the technique of choice in detecting

prostatic bone metastases because of its high spatial resolution and its excellent soft tissue contrast. One prospective study has shown that MRI has a sensitivity of 100 % and a specificity of 88 % to detect bone metastases (Lecouvet et al. 2007). DCE-MRI and DW-MRI have shown potential in detecting metastatic bone disease and monitoring response to therapy in several tumor types, but their use in metastatic bone disease from prostate cancer is in its infancy (Aigner et al. 2010; Gutzeit et al. 2010; Reischauer et al. 2010).

Single photon emission computed tomography (SPECT) is more sensitive in the detection of metastatic disease than planar images alone and is usually performed when symptoms or clinical suspicion of disease are present, particularly bone pain (Pinto et al. 2012). SPECT images offer higher accuracy than bone scintigraphy for vertebral lesions but are not yet widely used (Even-Sapir et al. 1993; Delpassand et al. 1995; Nozaki et al. 2008). Sensitivity of FDG-PET for detecting prostate cancer metastatic to the bone varied between 18 and 75 % (Aigner et al. 2010) and is considered to be inferior to bone scintigraphy for prostate cancer (Schoder and Larson 2004; Akin and Hricak 2007). However, an advantage of FDG-PET over bone scintigraphy is its ability also to identify non-skeletal metastatic disease, local recurrence, and distant spread after treatment failure (Schoder and Larson 2004; Gutzeit et al. 2010). Moreover, in patients with metastatic disease receiving chemotherapy, an important role of PET imaging may lie in its ability to evaluate early treatment response (Aigner et al. 2010). Future applications of PET involving new tracers are currently under investigation. Using PET with multiple radiotracers simultaneously is likely to become an important innovation in the future of metabolic prostate cancer imaging (Nunez et al. 2002; Jadvar 2011). Investigators are currently researching antibodies that target important prostate-specific molecules such as prostate-specific membrane antigen, glutamate carboxypeptidase II, found in the central nervous system (Foss et al. 2012).

16.5.2.5 Concluding Thoughts on Imaging

The avenues mentioned above hold promise for radically improving clinical care for prostate cancer. This could not only have an impact on the secondary prevention of prostate cancer but also possibly impact early detection and treatment of organ-confined disease. Imaging has a bright future in prostate cancer detection but, currently, prostate cancer is the only major cancer that does not have a prominent role for imaging in diagnosing primary disease. The lack of reliable imaging creates difficulty in performing prostate biopsy, which is currently the only definitive modality for diagnosing prostate cancer. On average, a prostate biopsy sample is less than 1 % of the total prostate area. Although the highest incidence of prostate cancer is in the peripheral zones, foci can be located anywhere in the prostate. Due to this, prostate biopsies are associated with a high degree of sampling bias. Until imaging techniques allow visualization of cancerous tissue, this sampling bias will affect diagnosis and secondary prevention of prostate cancer. Hence, until the development of specific imaging techniques or the development of blood- or urine-based tests for the diagnosis of prostate cancer, biopsy-associated sampling bias limits diagnostic techniques.

The two current urgent unmet needs in prostate cancer are improving diagnostic specificity and the reliable ability to differentiate between indolent and aggressive disease. An ideal test to do this could be one that has high accuracy and high sensitivity and specificity and can be carried out in a noninvasive manner, either through imaging, through serum or urine, or through a combination of the above. Developing such an ideal test could significantly affect the morbidity and mortality caused by this disease. In addition, we could also greatly reduce the financial costs and the morbidity associated with overdiagnosis and overtreatment associated with this disease, which is currently estimated to range in excess of 31 and 55 million dollars (US), respectively (Heijnsdijk et al. 2009).

16.6 Bone Metastasis

At the time of diagnosis, approximately 30 % of prostate cancer patients will have clinically significant bone metastases and another 30 % will carry occult metastases. Further, the relapse rate in most patients with early-stage solid tumors (such as breast cancer and prostate cancer) is approximately 20 % in those having 1 cm tumors or smaller, which suggests these cancers metastasize early in their development (Coleman 2006). Bone metastases are almost always multiple, usually involving vertebral bodies (Jacobs 1983). Distribution of bone metastases is essentially the same as active marrow in adults. Taken together, these facts suggest that early bone metastases are indolent and resident in multiple active bone marrow locations. Since prostate cancer is fundamentally an indolent tumor (Haustermans et al. 1997), prevention or eradication of early bone metastases would arrest progression or cure the disease. The indolent nature of metastasis has been described as tumor dormancy (Chambers et al. 2002) and is consistent with the known chemotherapeutic resistance of metastatic disease (Steeg and Theodorescu 2008). New approaches to eradication will need to consider noncytotoxic approaches since conventional cytotoxic therapies target actively growing tumors rather than indolent disease.

16.6.1 Indolence of Prostate Cancer

The majority of prostate cancer is indolent and localized disease, with around 1 in 6 men diagnosed with prostatic tumors, but only 1 in 33 dying from the disease (Brawley 2012). As discussed earlier in this chapter, screening for PSA generates a considerable percentage of early diagnoses—resulting in overdiagnosis—of cancers that are not clinically significant, although early diagnosis and treatment has led to the substantial drop in prostate cancer mortality. Despite the development of more sensitive PSA measures (e.g., complex PSA, free PSA, ratio of free PSA to total PSA) and monitoring PSA levels over time, this diagnostic issue persists (Bastian et al. 2009).

In addition to the need for new therapy options to eradicate indolent disease, there is a pressing need for continuing research efforts to identify aggressive tumor

forms arising in the gland and those tumors that escape dormancy in the bone. Both groups would require aggressive treatment and new biomarker discovery would reduce the treatment of otherwise indolent cancers. One of the more promising research avenues involves utilizing genetic information from the tumor to identify significant prognostic signatures. For example, single-nucleotide polymorphisms (SNPs) particularly the TT genotype of SNP (rs4054823 at 17p12) and a series of five genotypes [LEPR, RNASEL, IL4, CRY1, and ARVCF] (Lin et al. 2011) are promising candidates. In the first study, differences in TT genotype frequency were greatest between subjects with the least indolent disease (29 %, Gleason score =6 and organ-confined stage, pT2, $n = 3{,}080$) and those with the most aggressive tumors (46 %, Gleason score =8 and non-organ-confined stage, =pT3b, $n = 136$). This research led to the second study, where it was found that subjects with 4 or 5 of the high-risk genotypes (compared to those with 0–2) had a 50 % greater risk of prostate cancer-specific mortality (PCSM). The future of screening will likely involve a combination of genetic testing of the individual, somatic mutation analysis of the tumor (referred to as genomic grading) (Sklar et al. 2002), molecular imaging of progression (Sloane et al. 2006), and the development of robust diagnostic and prognostic nomograms (Scher and Pantel 2009).

16.6.2 Indolent Skeletal Metastasis and Disease Recurrence

Aggressive prostate cancer is lethal due to bone metastasis—often referred to as skeletal-related events (SREs)—and not from the consequences of disrupted physiology at the primary site. Human breast and prostate cancer metastasizes predominantly to the bone and is an early event in tumor progression (Coleman 2006). Approximately 85 % of patients with advanced disease have bone metastases (Coleman 2001). Cytokeratin-positive cells are present in the bone marrow of prostate cancer patients at a stable frequency of 20 % for several years (Weckermann et al. 2009). Widespread recurrence occurs as aggressive skeletal metastatic disease, which can appear 5 or even 10 years after primary therapy (Allen et al. 2007).

An alternative strategy to aggressive treatment—which is both expensive and generates high morbidity (Heijnsdijk et al. 2009)—is early blockage of SREs and their complications as secondary prevention steps, including (a) preventing early tumor cell seeding (bone tropism), (b) preventing successful colonization of the bone, (c) preventing the escape from tumor dormancy in the bone (Chambers et al. 2002), (d) stimulating the host response to convert active lesions into sclerotic bone lesions, and (e) bone health as a preemptive determinant of secondary prevention (Lattouf and Saad 2007).

One relevant molecular determinant of bone tropism and colonization in prostate cancer progression is the axis of hepatocyte growth factor (HGF) and the receptor (c-Met) [see (Hurle et al. 2005)]. The c-Met/HGF axis is one of the most frequently dysregulated pathways in human cancers. The c-Met/HGF axis is associated with the switch to aggressive disease and current clinical trials are ongoing to uncover

ways to interrupt the axis. In experimental model systems, the c-Met/HGF axis is selected for during bone tropism and colonization (Sroka et al. 2009), and specific targeting agents are being tested in clinical trials (Smith et al. 2013). While other growth factors such as FGF and TGF-b are implicated in the stimulation of tumor cell invasion (Lee et al. 2006; Marchesi et al. 2010), the lack of a dominant EMT response in human prostate cancer (Nagle and Cress 2011) suggests that growth factors associated with tubulogenesis, such as the c-Met/HGF axis, would be dominant molecular factors to target.

16.6.3 Targeting Tumor Residency in the Bone

In addition to specific growth factors, the microenvironment during human tumor invasion contains abundant laminin 511(Aguirre Ghiso et al. 1999; Bello-DeOcampo and Tindall 2003) and within the bone metastatic site. Laminin 511 is a specific extracellular matrix molecule now associated with morphogenesis of stem cell niches in a variety of tissues, including the bone. The α6 integrin (ITGA6, CD49f) is an essential laminin adhesion receptor (Sonnenberg et al. 1991; Georges-Labouesse et al. 1996) and is a marker for human hematopoietic stem cells and is essential for maintenance of several different stem cell niches (Tumbar et al. 2004; Stingl et al. 2006; Belvindrah et al. 2007; Qian et al. 2007; Taddei et al. 2008; Kloepper et al. 2008; Notta et al. 2011). Human prostate tumor cells in human bone express ITGA6 coincident with abundant laminin 511 in normal human bone (Nagle and Cress 2011). Positive staining of tumor cells for laminin-binding integrin (A6B1, CD49f) was present at variable frequency in >70 % of metastases. Taken together, the ITGA6/laminin 511 axis is a target candidate for preventing bone metastasis.

ITGA6 is expressed on human tumor cell surfaces and is associated with poor patient prognosis, reduced survival, and increased metastasis in a variety of tumors (Bonkhoff et al. 1993; Danen et al. 1993; Friedrichs et al. 1995; Hangan et al. 1997; Lee et al. 2009). A novel tumor-specific form of α6 integrin, called α6p, is generated by cleavage of the laminin-binding domain from the tumor cell surface by urokinase-type plasminogen activator (uPA), a pro-metastatic factor (Chauhan et al. 2004). Expression levels of both uPA and its cognate receptor correlate negatively with prostate cancer patient survival (Sheng 2001; Shariat et al. 2007). The uPA-dependent cleavage of α6 integrin increased cellular migration in vitro and was proposed as a mechanism for tumor cell release from adhesion to laminin (Pawar et al. 2007). Deployment of tumor cells from the bone via A6pB1 may explain the clinical reality of widespread skeletal recurrence as aggressive metastatic disease 5–10 years after primary therapy (Husemann et al. 2008; Scher and Pantel 2009a, b). Blocking the tumor-specific ITGA6 function will block tumor migration toward a vascular-rich region within the living bone and results in lower bone pain scores in animals and significant delay in the onset of bone metastases without normal tissue toxicity (Affolter and Caussinus 2008; Ports et al. 2009). Preventing the

tumor-specific utilization of the ITGA6/laminin 511 axis and blocking progression within the bone using a systemic approach using humanized antibodies or small peptides holds promise as a secondary nontoxic prevention strategy for humans.

An alternative strategy for secondary prevention is interrupting or systemically redirecting the vicious cycle of signaling by paracrine and autocrine factors within the microenvironment of the distinct cell types that interact within the bone (Kang et al. 2003; Gupta and Massague 2006). While bone colonization provides a sanctuary or protective adhesion site for early metastatic tumors to resist elimination by the immune system (Becker et al. 2006; Wels et al. 2008; Mastro and Vogler 2009; David et al. 2011), dynamic interactions of tumor cells with the normal cellular components, including osteoblasts and osteoclasts, would be a key intervention step.

It is worth noting that sclerotic lesions comprise approximately 50 % of human breast and prostate tumors residing in the bone (Conti et al. 2008). Clinically, the development of sclerotic lesions often signals curative results (Scher et al. 2011). Sclerotic lesions, a benign-type lesion, progress slowly and stimulate a host reaction for entombment of the tumor. In addition, sclerotic metastases are less painful than lytic-type lesions (Conti et al. 2008). Understanding how normal bone health contributes to promote increased host reaction may also lead to systemic prevention strategies.

In summary, the widespread distribution and indolent nature of bone metastasis in prostate cancer is compelling rationale for investigating alternatives to cytotoxic therapy for the eradication of the disease. In addition, the lack of cytotoxic selection may eliminate emergence of recurrent aggressive disease. Candidate pathways for noncytotoxic therapy include mechanisms of tumor cell adhesion within the bone, key paracrine and autocrine factors in the bone microenvironment, and the stimulation of bone healing and health by the host. Future advances will likely require identification of genetic and phenotypic partners within the tumor and its cellular and structural microenvironment to prevent prostate cancer progression to the bone.

16.7 Molecular Genetics

Despite extensive research on the pathophysiology of prostate cancer and its risk factors, there is surprisingly scant information regarding the molecular mechanisms involved in prostate cancer. Research in this area not only would correct major deficiencies in the current literature but also could point toward potential strategies for primary as well as secondary prevention of prostate cancer.

16.7.1 Tumor Suppressors and Oncogenes

Androgen receptor (AR)-mediated signaling drives the development and differentiation of normal prostate epithelium as well as promotes early tumorigenesis by

stimulating the growth of prostate cancer cells (Hallstrom and Laiho 2008). Androgen ablation can be used successfully as a short-term treatment for prostate cancer; however, prostate cancer inevitably progresses to an androgen-independent state (Hallstrom and Laiho 2008). In tumors, several mechanisms have evolved to bypass ligand-dependent regulation of AR. Techniques to prevent or delay this could contribute a great deal toward the secondary prevention of prostate cancer and thereby revolutionize the treatment of prostate cancer.

A recurrent fusion between the androgen-regulated gene TMPRSS2 (21q22.3) and the ETS transcription factor family member ERG (21q22.2) has been shown to be a common occurrence in prostate cancer (Tomlins et al. 2005; Mehra et al. 2008). Fusion rates of 15–80 % have been reported by various groups, making it the most common rearrangement identified in human cancer to date (Cerveira et al. 2006; Perner et al. 2006; Lapointe et al. 2007; Rajput et al. 2007; Mehra et al. 2008; Wang et al. 2008). The fusion can be the result of a small deletion on chromosome 21 or can occur through a translocation (Perner et al. 2007). In either type of rearrangement, an androgen-regulated promoter controls ERG and overexpression of the protein ensues. Studies addressing the clinical significance of TMPRSS2/ERG fusion have demonstrated associations with aggressive disease outcome (Demichelis et al. 2007; Nam et al. 2007; Attard et al. 2008). Using data from 445 men on conservative management, Attard et al. demonstrated that duplication of the TMPRSS2/ERG fusion product and concurrent interstitial deletion of sequences 5′ to ERG were associated with 25 % prostate cancer-specific survival at eight (Attard et al. 2008). In another cohort of patients on conservative management ($N = 252$), TMPRSS2/ERG fusion was associated with statistically significant increased risk of death due to prostate cancer (Demichelis et al. 2007).

Similar to TMPRSS2/ERG, PTEN (a phosphatase and tensin homolog located on chromosome 10) inactivation has also been associated with aggressive prostate cancer. Both animal and human studies demonstrate a role for PTEN in prostate carcinogenesis. PTEN is an important negative regulator of the PI3/AKT signal transduction pathway and remains inactivated in 30–60 % of prostate cancer cases (Downes et al. 2001; Yoshimoto et al. 2012). In studies conducted by Yoshimoto et al., PTEN loss, combined with TMPRSS2/ERG fusion, was associated with earlier biochemical recurrence of tumors (Yoshimoto et al. 2006). Other authors have also noted the joint effect of TMPRSS2/ERG fusion and PTEN loss on prostate cancer. Studies by Carver et al. show that PTEN protein expression was reduced or absent in two-thirds of the tumors, whereas TMPRSS2/ERG fusions detected by fluorescence in situ hybridization (FISH) analysis were present in ~40 % of tumors, but significantly, most ERG-positive samples had reduced or absent PTEN expression (Carver et al. 2009). This led Han to conclude that PTEN deletion may be a late genetic event in human prostate cancer, presumably a “second hit” after ERG rearrangement (Han et al. 2009). These data indicate that PTEN deletion and ERG rearrangement may cooperate, but contribute at different stages, in prostate cancer progression (Squire 2009).

16.7.2 Somatic Mutations

A recent study by Grasso et al. described the mutational landscape of metastatic prostate cancer. For this study, the researchers sequenced exomes of 50 lethal, heavily pretreated metastatic castrate-resistant prostate cancers (CRPCs) and 11 treatment-naive, high-grade localized prostate cancers to investigate the role of mutation in prostate cancer (Grasso et al. 2012). They identified low overall mutation rates, confirmed the monoclonal origin of lethal CRPC, and discovered that ETS2 deregulates through mutation and not just through deletion, as previously thought. Novel recurrent mutations in multiple chromatin- and histone-modifying genes MLL2 (8.6 %) and AR collaborating factor FOXA1 (3.4 %) were identified. FOXA1 represses androgen signaling and increases tumor growth.

Barbeiri et al., in a separate study, sequenced the exomes of 112 prostate tumor and normal tissue pairs (Barbieri et al. 2012). In addition to confirming mutations in FOXA1, this study identified recurrent mutations in *MED12* as well. They observed that prostate cancers with mutant *SPOP* lacked ETS family gene rearrangements and showed a distinct pattern of genomic alterations. Thus, *SPOP* mutations may define a new molecular subtype of prostate cancer. These could serve as future targets for secondary prevention of prostate cancer.

16.7.3 Copy Number Variation

Copy number variants (CNVs) are a recently recognized class of human germline polymorphisms associated with a variety of human diseases such as Alzheimer's, schizophrenia, and cancer syndromes such as neuroblastoma and Li-Fraumeni (Oesterling et al. 1993; Oberaigner et al. 2006; Bartsch et al. 2008). Dr. Demichelis and her group investigated its utility in prostate cancer screening by studying CNVs from 1,903 men enrolled in the Tyrol Prostate-Specific Antigen Screening Cohort (Demichelis et al. 2012). They discovered two CNVs strongly associated with prostate cancer risk. The first risk locus maps to 15q21.3 and overlaps a noncoding enhancer element that contains multiple activator protein-1 (AP-1) transcription factor binding sites. The second risk locus maps to the α-1,3-mannosyl-glycoprotein 4-β-N-acetylglucosaminyltransferase C (MGAT4C) gene on 12q21.31, which has demonstrated an association with cell proliferation and migration in both benign and cancerous prostate cells. As might be expected with this finding, MGAT4C was significantly overexpressed in metastatic versus localized prostate cancer.

The later study establishes noncoding and coding germline CNVs as significant risk factors for prostate cancer susceptibility and suggests their role in disease development and progression. Functional characterization of these risk CNVs shows that gene coding and noncoding "gene desert" germline CNVs may directly or indirectly modulate the transcriptome machinery of known oncogenic pathways in prostate cancer, thereby enabling carcinogenesis. The genes and loci identified in this study are candidates for further functional investigation—and for replication in

independent cohorts—and provide alternative information in the assessment of prostate cancer risk.

Other groups also have noted the role of CNVs in prostate cancer. Jin et al. hypothesized that CNVs may be associated with prostate cancer aggressiveness, and to test this hypothesis, they conducted a genome-wide CNV analysis in 448 aggressive and 500 nonaggressive prostate cancer cases (Jin et al. 2011). They found that CNP2454, a 32.3 kb deletion polymorphism at 20p13, was significantly associated with aggressive forms of prostate cancer.

Norskov et al. aimed to determine the ability of glutathione S-transferase T1 (GSTT1) and GSTM1 copy number variation (CNV) to predict the risk of cancer in the general population. The study measured exact CNVs of GSTT1 and GSTM1 by real-time PCR in 10,247 individuals, 2090 of whom had cancer. In men, the cumulative incidence of prostate cancer increased and the cumulative 5-year survival decreased with decreasing GSTT1 copy numbers (trends = 0.02). The hazard ratios (HRs) (95 % CIs) for prostate cancer and for death after prostate cancer diagnosis were, respectively, 1.2 (0.8–1.8) and 1.2 (0.6–2.1) for GSTT1*1/0 and 1.8 (1.1–3.0) and 2.2 (1.1–4.4) for GSTT1*0/0 versus GSTT1*1/1(Norskov et al. 2011).

In another study conducted in Sweden, researchers compared the germline genome among 498 aggressive prostate cancer cases and 494 controls. A germline deletion at 2p24.3 was observed to be significantly more common in prostate cancer (12.63 %) than in controls (8.28 %); $P = 0.028$. A cohort study from Johns Hopkins Hospital confirmed these findings. Overall, among 4,314 cases and 2,176 controls examined, the CNV was significantly associated with prostate cancer risk [odds ratio (OR), 1.25; 95 % confidence interval (95 % CI), 1.06–1.48; $P = 0.009$]. More importantly, the association was stronger for aggressive prostate cancer (OR, 1.31; 95 % CI, 1.08–1.58; $P = 0.006$) than for nonaggressive prostate cancer (OR, 1.19; 95 % CI, 0.98–1.45; $P = 0.08$) (Liu et al. 2009). Variation in copy number helps to stratify men according to risk categories, but CNV can also improve the diagnostic specificity in men who may be at high risk for prostate cancer.

16.7.4 Role of DNA Damage in Prostate Cancer

One of the key features of prostate cancer is its high incidence and its multifocality, both of which may be due to defects in DNA damage repair and cell cycle checkpoint pathways (Hallstrom and Laiho 2008). Human prostate epithelial cells (HPECs) have been shown to be deficient in G1/S, intra-S, and G2/M checkpoints and are also resistant to ionizing radiation-induced apoptosis (Girinsky et al. 1995; Kiviharju-af Hallstrom et al. 2007). A major indicator of this resistance is the delay in clearance of γH2AX foci in irradiated HPECs (Kiviharju-af Hallstrom et al. 2007). Phosphorylation of histone H2AX (γH2AX) is a marker of DNA damage, and its delayed clearance indicates sustained DNA damage in the presence of continuous replication. In contrast to cells with intact DNA damage responses, p53 is not stabilized in HPECs, leading to a lack of induction of

transcriptional targets of p53 and the failure of HPECs to undergo cell cycle arrest or apoptosis (Girinsky et al. 1995; Kiviharju-af Hallstrom et al. 2007).

The lack of DNA damage-induced Cdk2Tyr15 inhibitory phosphorylation results from fast turnover and thwarted activity of Wee1A tyrosine kinase in HPECs (Hallstrom and Laiho 2008). These defects render cyclin E(A)/Cdk2 kinase active, leading to uninterrupted cell cycle progression after genotoxic stress. It is plausible that the apparent lack of DNA damage checkpoints after natural stress signals correlates to the high incidence of cancers in the prostate. It seems that p53 is inactivated or under negative feedback control in prostate epithelial cells. Experts have speculated that as a consequence of the indolent nature of the prostate gland, p53 activity is diminished at the expense of accumulating of DNA lesions. Accumulating nonspecific DNA lesions may explain the known heterogeneity of the malignancy (Hallstrom and Laiho 2008).

In summary, understanding the molecular mechanisms involved in prostate cancer may rewrite the future of prostate cancer diagnosis and treatment. The more information gathered in this realm, from tumor suppressors and oncogenes, defects in DNA damage repair and cell cycle checkpoint pathways, and how CNVs may directly or indirectly modulate the transcriptome, the better the chances of differentiating between indolent and aggressive disease.

Conclusion

As mentioned, the American Cancer Society estimated 241,740 new diagnoses and 28,170 deaths due to prostate cancer in 2012, making it the second most common cause (11 %) of cancer-related mortality for US men (ACS 2012). The avenues mentioned above hold promise for radically improving clinical care for prostate cancer. Improved chemoprevention, diagnosis (especially the ability to distinguish between indolent and aggressive cancers), imaging techniques, and techniques to prevent or sequester bone metastases could not only affect the secondary prevention of prostate cancer but also increase early detection and treatment.

The most obvious risk for men is age, with the highest incidence of cancer in seventh and eighth decades. However, race is also a risk factor. The risk of diagnosis for African-American men is 1.6 times, and the risk of death is 2.5 times, the risk for the Caucasian male population (Brawley 2012). In addition, lifestyle factors contribute to risk, with higher levels of physical activity showing a preventive effect (Orsini et al. 2009). Further, obesity increases the risk of cancers, and especially more aggressive cancers (Rodriguez et al. 2007; Burton et al. 2010), so diet plays a role in determining risk. Over the coming decade, there is likely to be considerable research in the ways lifestyle relates to prostate cancer risk.

One of the largest issues in treatment is the overdiagnosis and overtreatment associated with this disease, which is currently estimated to range in excess of 31 and 55 million dollars (US), respectively (Heijnsdijk et al. 2009). In light of this, the United States Preventive Services Task Force (USPTF) issued a grade D recommendation (“discourage the use of this service”) for PSA screening

(Force 2012), meaning that the USPTF believes with moderate or high certainty that PSA screening has no net benefit or may harm more than help. Improved secondary prevention requires the development of better imaging techniques and diagnostic tools, including better and more sensitive nomograms.

Finally, since prostate cancer is fundamentally an indolent tumor (Haustermans et al. 1997), prevention or eradication of early bone metastases would arrest progression or cure the disease. The indolent nature of metastasis has been described as tumor dormancy (Chambers et al. 2002) and is consistent with the known chemotherapeutic resistance of metastatic disease (Steeg and Theodorescu 2008). New approaches to eradication will need to consider noncytotoxic approaches since conventional cytotoxic therapies target actively growing tumors rather than indolent disease.

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Cervical Cancer Prevention

17

Tomas Nuño, Jessamyn Bowling, and Francisco Garcia

17.1 Epidemiology of Cervical Cancer

Cervical cancer is the most common gynecologic malignancy worldwide, accounting for about 530,000 new cases each year (Ferlay et al. 2010). Most of these cases (90 %) occur in the developing world where it is the second most common malignancy in women after breast cancer (WHO Report 2006). By contrast, in the United States of America (USA) cervical cancer has decreased dramatically since the introduction of cytologic screening (Pap smear), and is now a relatively infrequent neoplasm, especially among well-screened majority populations with access to health-care services. In the USA, an individual woman's lifetime risk of developing cervical cancer is estimated to be 1 in 147. In 2012, it is estimated that there were approximately 12,170 new cases of cervical cancer and 4,220 deaths in the USA (American Cancer Society 2012a).

In the developed world, cervical cancer disproportionately affects poor and minority women without adequate access to cervical cancer screening. It is estimated that nearly 50 % of US cervical cancer cases occur in women who have never been screened and an additional 10 % in women who have not been screened within 5 years of their diagnosis (Sawaya and Washington 1999; Leyden et al. 2005; Schwartz et al. 1996). Significant racial and ethnic disparities exist with regard to cervical cancer incidence, mortality in the USA (Fig. 17.1) (2012). Notably, the gap in incidence and mortality between White women and other racial/ethnic groups significantly increases with age. Although disparities in overall incidence and mortality have decreased in recent years, cervical cancer incidence remains higher among African American women (9.8 out of every 100,000) and Hispanic women (11.8 out of every 100,000) compared to White women (8.0 out of every 100,000) (Howlader et al. 2012) and cervical cancer mortality among

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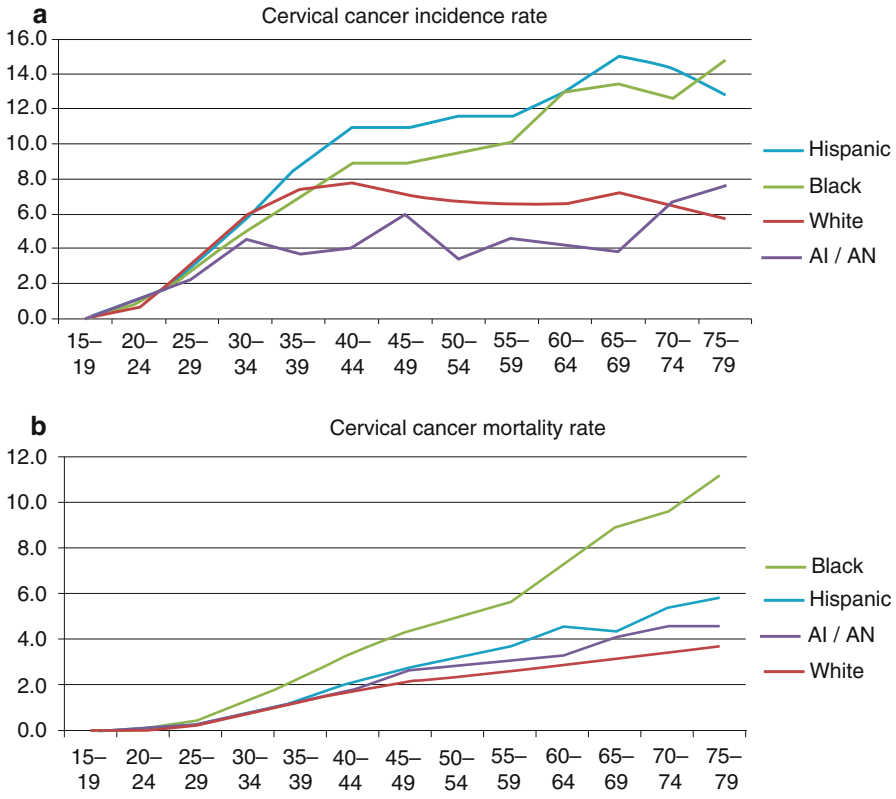

Fig. 17.1 (**a**) Racial and ethnic disparities in United States cervical cancer incidence. (**b**) Racial and ethnic disparities in United States cervical cancer mortality (*Source*: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub, Vintage 2009 Pops (2000–2009) <Katrina/Rita Population Adjustment> – Linked To County Attributes – Total U.S., 1969–2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission)

African American women which is the highest (4.3 out of every 100,000) of any racial or ethnic group (Howlader et al. 2012). African American women are less likely to present with localized disease (40 % compared to 49 % of White women) and are more than three times as likely to die of their disease (Fast Stats 2013; Howlader et al. 2012). Additionally, African American women are more likely than White women to report therapeutic delays to cervical cancer treatment (Ashing-Giwa et al. 2010), less likely to receive surgery (33.5 % compared to 48.2 % in White women), and more likely to receive radiation (35.3 % compared to 25.2 %) (Howell et al. 1999).

Surveillance, epidemiology, and end result (SEER) data for 2005–2009 continue to demonstrate a disproportionately higher incidence (11.8 out of every 100,000)

and mortality (3.0 out of every 100,000) for Hispanic compared to non-Hispanic Whites (7.2 and 2.1 out of every 100,000 for incidence and mortality rates, respectively) (American Cancer Society 2012b). Hispanics are also more likely to present with advanced stages of invasive disease (Napoles-Springer et al. 1996; Mitchell and McCormack 1997; Howe et al. 1998; Scarinci et al. 2010; Watson et al. 2008). Cervical cancer incidence and mortality rates for the US-Mexico border region exceed those of the rest of the nation, with Hispanic women largely accounting for this differential (American Cancer Society 2012b; Coughlin et al. 2008). Age-adjusted cervical cancer rates for Hispanic women living in border counties are twice those of their non-Hispanic peers in the same communities (13.9 of 100,000 vs. 7.0 of 100,000) and are significantly higher than for other Hispanics residing in the USA (13.2 of 100,000) (Coughlin et al. 2008).

17.2 Etiology of Cervical Cancer

Prior to the definitive identification of human papillomavirus (HPV) infection as a necessary agent in cervical carcinogenesis, observational studies had already suggested that a sexually transmitted agent was involved in the disease and that male sexual behavior could affect the risk of cancer in the female partners. Specifically, research demonstrated geographic clustering of cervical and penile cancers, the low prevalence of disease among nonsexually active women, and increased risk in partners of men whose first wives had died of cervical cancer. More sophisticated molecular epidemiology work has further clarified this relationship (Buckley et al. 1981; Zunzunegui et al. 1986; Agarwal et al. 1993; Thomas et al. 1996) and has highlighted the role of a potential "male factor" (Castellsague et al. 2002).

In the mid-1970s, zur Hausen first suggested a relationship between HPV infection and cervical cancer (zur Hausen 1977); by the early 1980s, electron micrography work had identified the presence of the virus in cervical intraepithelial neoplasia (CIN) (Meisels et al. 1983). Since that time, cervical carcinoma and its precursor lesion, CIN, have been consistently causally linked to the sexual transmission of HPV infection (Schiffman et al. 1993; Palefsky and Holly 1995; Morris et al. 1996).

HPV infection is ubiquitous and widespread across many species; more than 100 different types can infect humans. Transmission of this small icosahedral double-stranded DNA virus occurs through direct contact with epithelial surfaces. Lower genital tract HPV infection is common during the second and third decade of life and is a marker of human sexual activity (Fig. 17.2). The vast majority of immunocompetent women appear to clear the infection without sequelae. By comparison, cervical cancer is a relatively rare event that peaks in the fourth and fifth decade. Infections with HPV are classified as high-risk (oncogenic) or low-risk (nononcogenic) genotypes, based on the association with cervical cancer. High-risk HPV infection with types 16 and 18 has the highest prevalence and is associated with approximately three quarters of all cancer and high-grade precursor lesions. Additional high-risk types include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82,

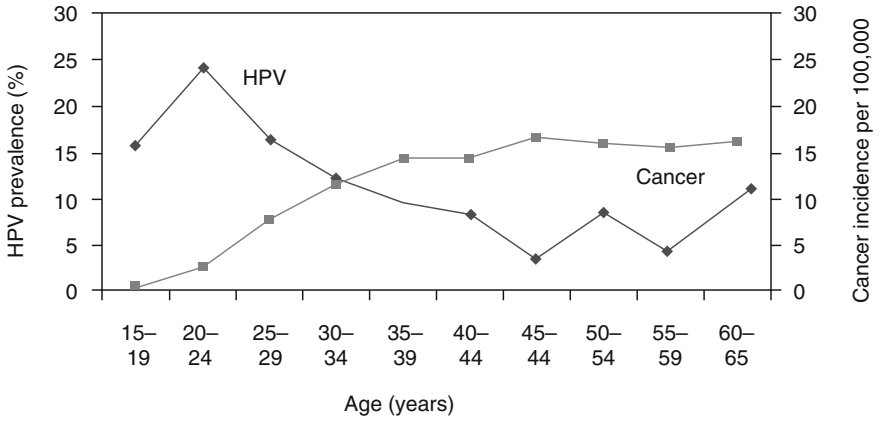

Fig. 17.2 HPV point prevalence and cervical cancer incidence by age (Sellors et al. 2000, 2002; Ries et al. 2000)

and possibly 26, 53, and 66. By contrast, HPV 6 and 11, the etiologic agents of genital warts, and types 42, 43, 44, 54, 61, 70, 72, and 81 are infrequently associated with advanced cervical lesions and are considered low risk (Palefsky and Holly 1995; Franco 1996; Munoz et al. 2003). Beyond viral type differences, there are significant differences in genetic variation, viral load (van Duin et al. 2002), and persistence which may confer increased risk for cervical neoplasia. In total, the strength of the association between high-risk HPV infection and cervical cancer is such that all squamous cell cervical malignancies are now thought to be related to HPV infection. It is clear that HPV infection is a necessary prerequisite, but by itself an insufficient cause for cervical cancer. Cervical cancer alone represents 53 % of the total number of HPV-associated cancers (Jemal et al. 2013).

17.3 Natural History of Cervical Cancer

HPV enters the basal layer of the genital tract through micro-tears that occur in the squamous epithelium during the course of sexual activity. The mitotically active transformation zone is particularly vulnerable, especially early in adolescence when it covers a relatively broad surface area of the cervix. The viral DNA enters the cellular nucleus where it exists as a circular episome composed of three distinct regions. In general, the long control region (LCR) regulates early viral transcription, while the late (L) region encodes structural proteins involved in the assembly and production of the viral capsid. The early (E) region encodes proteins necessary for viral replication. The E6 and E7 gene products bind p53 and retinoblastoma proteins, respectively, and interfere with their tumor suppressor function leading ultimately to cellular transformation (Shirodkar et al. 1992; Scheffner et al. 1993; Jones et al. 1997; Denk et al. 2001). Precursor lesions and cervical carcinoma

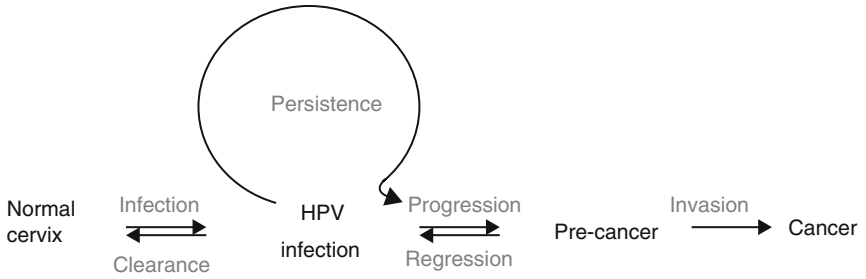

Fig. 17.3 Natural history of HPV and cervical cancer (Adapted Alberts et al. (2004), Schiffman and Kjaer (2003))

require the nonrandom integration of extra chromosomal viral DNA into the host genome (Thorland et al. 2000). This integration of viral DNA into the host genome results in disruption of the E2 region of the viral episome (Choo et al. 1987), which is responsible for downregulation of E6 and E7, and ultimately to cellular transformation.

As the cells of the basal layer of the squamous epithelium mature, they are pushed out to the epithelial surface where replication of the viral genome takes place. Eventually the viral DNA copies are packaged in the protein capsid. These viral particles are released through the normal process of epithelial desquamation and cell death and, upon shedding, are available for transmission of the infection.

Generally, HPV infection is transient, asymptomatic, clinically insignificant, and occasionally associated with temporary cytologic and/or histologic abnormalities (Fig. 17.3). The median duration of infection has been estimated to be about 8 months for young sexually active women (Ho et al. 1998). This time period may be longer for women infected with oncogenic viral types (Richardson et al. 2003). Although older individuals may be less likely to clear the virus, in general, about 90 % of infected women will have undetectable evidence of infection at 24 months (Moscicki et al. 1998).

In some cases, infection leads to characteristic cellular abnormalities beginning at the basal layer and involving increasingly more layers of cervical epithelium. These are described histologically as CIN (Wright 1994). CIN is generally divided into low-grade (CIN 1) and high-grade (CIN 2 and CIN 3) disease. This grading generally reflects the underlying risk for progression to malignancy (highest for CIN 3) and decreasing likelihood of spontaneous regression (highest for CIN 1) (Ostor 1993; Barker et al. 2001). Low-grade CIN occurs most frequently in younger women (Jones and Novis 2000) and is more likely to spontaneously regress in that age group. Viral persistence is required for progression from high-grade CIN and invasive carcinoma, and is related not only to viral type, but also to viral load and increasing age (Koutsky et al. 1992; Londesborough et al. 1996; Ho et al. 1998). The protracted process of progression (estimated at more than 10 years) from CIN 3 to invasive disease provides an ideal time frame that permits screening, identification, and treatment of these precursor lesions.

Table 17.1 Theoretical framework for cervical cancer prevention

Primary prevention – HPV infection prevention	Secondary prevention – CIN detection and treatment	Tertiary prevention – cervical cancer treatment and control
Behavioral modification Sexual Tobacco cessation	Behavioral modification Sexual Tobacco cessation	Behavioral modification Tobacco cessation
Prophylactic vaccine	Screening programs	Medical therapeutics
Nutrition	Medical therapeutics Excisional therapy Therapeutic vaccines Chemopreventive agents Retinoids Indole carbinol Immune response modulators	Radical surgery Radiation therapy Chemotherapy Therapeutic vaccines Surveillance

17.4 Cofactors for Cervical Cancer

The largely endemic nature of HPV infection and the relative rarity of cervical cancer argue for an important role of cofactors that may affect progression or regression of cervical cancer precursors (Table 17.1). Historically, parity has been identified consistently as an important risk factor in cervical cancer (Brinton et al. 1989; Parkin et al. 1994; Yoo et al. 1997; Munoz et al. 2002). It is unlikely that the effect of parity is simply related to childbirth itself; instead parity may be a surrogate for a spectrum of high-risk sexual behavior including total lifetime number of male sexual partners, early age at sexual intercourse, comorbid sexually transmitted infections (STI), and potentially even smoking and hormonal contraceptive use with regard to smoking, nicotine metabolites can be recovered in the cervical and vaginal secretions of women who smoke or those exposed passively (McCann et al. 1992; Prokopczyk et al. 1997). In particular, the use of tobacco products may be associated with a two- to fourfold increased risk for cervical cancer and its precursors (McCann et al. 1992; de Vet et al. 1994; Prokopczyk et al. 1997; Deacon et al. 2000). Likewise, there may be a role for other STIs that infect the female lower genital tract and may potentiate the oncogenicity of high-risk HPV. This may be mediated through the cellular-mediated immune mechanism (Konya and Dillner 2001) or a localized inflammatory effect on the cervicovaginal epithelium (van Duin et al. 2002; Garcia et al. 2003). Long-term use of combined oral contraceptive pills (OCPs) is also associated with cervical cancer risk in the presence of HPV infection (Moreno et al. 2002). These findings are particularly difficult to interpret given the complex nature of sexual behavior and the adverse effect of multiparity on the risk for cervical cancer. It is possible that the effects of tobacco and OCP use are mediated by promoting persistence of the viral infection.

17.4.1 Viral Persistence

Numerous studies consistently demonstrate that persistent, as compared to transient, high-risk HPV infection is required for the development of cervical cancer precursor lesions (Koutsky et al. 1992; Ho et al. 1995; Coker and Bond 1999; Hernandez and Goodman 1999; ter Harmsel et al. 1999). It has also been shown that persistent high-risk HPV infection is a prerequisite for development and maintenance of CIN 3 (Meijer et al. 1999), while low-risk type infections have very high rates of regression (Moscicki et al. 1998).

Clearance of HPV from the genital tract requires an active cell-mediated immune response. Cellular immune response is characterized by an interaction between antigen-presenting cells (APCs), T-helper cells, and cytotoxic T cells. Activated natural killer (NK) cells may also play a role. Cell-mediated viral clearance and control of tumor growth were identified in studies of CIN in human immunodeficiency virus (HIV)-positive women. The observation that CIN occurs with disproportionate frequency among immunocompromised women (e.g., acquired immunodeficiency syndrome [AIDS], transplantion) suggests that CD4 lymphocytes (T-helper cells) are involved in prevention or limitation of HPV-associated lesions (Maiman 1998). Studies of immunocyte counts in HPV lesions have confirmed the role of the cellular immune system in controlling viral infection. Significantly, greater numbers of T lymphocytes and macrophages are found within the stroma and epithelium of HPV lesions that regress as compared to non-regressing lesions (Coleman et al. 1994).

Cytotoxic responses against HPV are mediated by T-helper cells (CD4 cells) and antigen-presenting cells such as Langerhans cells (LCs), whose interactions result in the stimulation of cytotoxic T cells (CD8 cells). Immune response is generated and maintained through the release of cytokines, intracellular chemical signals, from these different cell types. Cytokines secreted by CD4 cells include type 1 cytokines such as interleukin 2 (IL-2) and interferon gamma (IFN) and type 2 cytokines, including IL-4, IL-6, and IL-10. Type 1 cytokines are immunostimulatory for cell-mediated immune response; they promote CD8 responses, activate NK cell functions, and have been shown to be capable of limiting tumor growth. Interleukin 12 (IL-12) is a type 1 cytokine which is secreted by dendritic cells, including Langerhans cells (LCs), and which has been demonstrated to induce differentiation of naïve T cells, to upregulate IFN gamma production in T cells and NK cells, and to have antitumor activity (Nastala et al. 1994; Zola et al. 1995; Clerici et al. 1998; Giannini et al. 1998).

Cytokine expression in cervical tissue has been variously associated with cervical intraepithelial neoplasia. Investigators have found a significant increase in the density of IL-4 positive cells in low-grade and high-grade squamous intraepithelial lesions (LSILs and HSILs), compared with histologically normal tissues from adjacent ectocervical regions (al-Saleh et al. 1995). Another study showed that expression of IL-10 increased continuously from a relatively low level in normal ectocervix to a high level in HSIL, and that IL-12 expression was higher in LSIL than in HSIL (Giannini et al. 1998). In women with CIN 3, in vitro production of IL-2 by

peripheral mononuclear blood cells (PMBCs) was found to be decreased, and production of type 2 cytokines IL-4 and IL-10 increased, in women with more extensive HPV infection (Clerici et al. 1997).

17.5 Screening and Early Detection of Cervical Cancer

Exfoliative cytology has been the mainstay of cervical cancer prevention since its description by Papanicolaou in the 1940s, and its large-scale adoption is frequently credited for the drop in cervical cancer incidence and mortality in North America and Western Europe (Anttila et al. 1999). This technique takes advantage of the prolonged preinvasive nature of CIN and samples the transformation zone of the uterine cervix where the process of metaplasia turns the columnar epithelium of the endocervical canal into the more robust mature squamous epithelium of the ectocervix and vagina. It is these metaplastic cells that are the most vulnerable to oncogenic HPV infection; the most invasive and precursor lesions arise from this area. Although in widespread use there have never been, nor would it now be ethical to conduct, large randomized control trials of cervical cytology. Nonetheless, prolonged clinical experience with this technique has permitted the characterization of the test performance qualities. The sensitivity of cytologic screening is estimated to range between 50 and 70 %, with specificity in the 70 % range (Fahey et al. 1995).

Detailed evidence-based screening recommendations (Table 17.2) and triage algorithms for the management of abnormal cervical cytology are published elsewhere (Saslow et al. 2012).

17.5.1 HPV Testing

The etiologic role of HPV in cervical cancer has led to incorporation of HPV testing into a variety of screening and management algorithms for cervical disease.

Table 17.2 Summary of American Cancer Society (ACS) recommendations for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors

Women <21	No screening
Women ages 21–29	Cytology alone every 3 years (liquid or conventional) Recommend against annual cytology
Women ages 30–65	HPV+ cytology "cotesting" every 5 years (preferred) or every 3 years with cytology alone (acceptable) Recommend against more frequent screening
Women ages >65	Discontinue after age 65 if 3 negative cytology tests or 2 negative HPV tests in the last 10 years with the most recent test in last 5 years
Post hysterectomy	Discontinue if for benign reason
Screening after HPV vaccination	Follow age-appropriate recommendations (same as unvaccinated women)

Reprinted with permission from Saslow et al. (2007)

Oncogenic HPV testing has been proposed as a primary screening modality for screening for cervical cancer and its precursors (Cuzick et al. 2003). While in some settings HPV testing is more sensitive than cervical cytology; the endemic nature of high-risk oncogenic HPV infection, especially among young reproductive age populations, would lead to low specificity of screening with predictably high false-positive rates (Cuzick et al. 2000).

More recent guidelines have opened the door to the use of HPV testing as an adjunct to cytology, in an effort to safely extend screening intervals (Table 17.2) (Saslow et al. 2012). In general, the test performance characteristics of combined HPV and cytology screening (sensitivity of about 92–100 % and specificity of 70–96 %) exceed that of cytology alone (Wright et al. 2004). Current evidence suggests that co-testing with HPV and cytology should be limited to women between 30 and 65 years of age and should be performed no more frequently than every 5 years (Saslow et al. 2012).

High-risk HPV testing has come into clinical use as one of three evidence-based management strategies for the triage of atypical squamous cells of undetermined significance (ASCUS) cytology (along with repeat cytology and colposcopy). The sensitivity of HPV DNA hybrid capture testing for the detection of CIN 2 and CIN 3 is estimated to be between 80 and 100 % (Wright et al. 1998; Sherman et al. 2002); women with negative testing in this setting have an extremely low likelihood of having clinically significant disease. When testing is available from liquid-based cytology specimen or when viral specimens are co-collected at the time of screening cytology, this is the preferred triage for the ASCUS pap (Wright et al. 2002).

17.6 Therapeutic Approach to Precursor Lesions of Cervical Cancer

The foundation of cervical cancer precursor therapy involves access to definitive colposcopic evaluation and histologic diagnosis. Treatment has been divided into ablative and excisional modalities. Excisional therapy has generally been reserved for high-grade lesions (CIN 2 and 3) with true malignant potential. Loop electrosurgical excision procedure (LEEP) requires an experienced operator but may be performed in the office setting. It is the most common approach to treatment of high-grade lesions in the USA, is well tolerated by patients, and results in a histologic specimen that are evaluable for evidence of invasion. Bleeding and infection are potential complications of LEEP procedures and may occur in about 2 % of cases (compared to 10 % for cold knife conizations) (Montz 2000). While cervical stenosis and impaired fertility are rare complications, women who undergo LEEP may be at increased risk for preterm delivery and low birth weight infants in subsequent pregnancies (Samson et al. 2005).

Cryotherapy, by comparison, is used most commonly for low-grade lesions (CIN 1), which should be treated only when they are persistent (24 months or more) (Wright et al. 2003), because 90 % of these lesions will regress spontaneously within 2 years (Ostor 1993). The regression rate is generally lower for women after

their midthirties and among those who smoke. Cryotherapy is safe, effective, and economical, typically requiring less operator experience than excisional modalities. It does not, however, produce a histologic specimen and should never be used when there is any question of potential microinvasive disease. In general the resolution rates for both these therapies are in the 90 % range (Martin-Hirsch et al. 2000), and a recent randomized trial of cryotherapy, laser vaporization, and LEEP found comparable cure rates for CIN 2/3 (Mitchell et al. 1998a). This trial also found that failure rates were highest for women with large lesion (3 or 4 quadrants). Previously treated patients, those over 30 years of age, and women with oncogenic HPV infection were also at significantly higher risk for treatment failure. Outpatient therapeutic modalities may lend themselves well for single-visit and "see-and-treat" therapy that obviate the need for biopsy and even colposcopic examination and may promote compliance among poor or underserved women.

17.7 Novel Agents for Cervical Cancer Prevention

17.7.1 Chemopreventive Agents

The search for chemopreventive agents for use in cervical cancer prevention is logical given the well-characterized, protracted, preinvasive character of CIN, encouraging preclinical laboratory data and epidemiologic findings that suggest a protective role for a variety of nutritional agents. These chemoprevention studies, however, have been largely disappointing and plagued by a variety of methodological challenges. Problems include a lack of consensus as to the appropriate grade of disease to be studied (CIN 1, 2, or 3), the appropriate definition of response (e.g., histologic regression, viral clearance) given significant rates of spontaneous regression, the selection of appropriate endpoint biomarkers, as well as ethical and safety considerations (withholding treatment for potentially preinvasive disease). Despite these challenges, a significant number of trials have been conducted in this area (Table 17.3). A thorough review of cervical chemoprevention trials was published by Mitchell and colleagues (Follen et al. 2003).

Topical and oral retinoids are a group of agents that have been well characterized and that have significant promise in this tissue type. These agents may decrease the expression of E6/E7, tumor growth factors, and telomerase activity associated with carcinogenesis (Sizemore et al. 1998; Ding et al. 2002). They have generally good toxicity and tolerability profiles, and early phase I data suggest significant chemopreventive activity (Surwit et al. 1982; Meyskens et al. 1983; Weiner et al. 1986). One clinical trial of cervical all-trans retinoic (0.327 %) acid application demonstrated significant activity for CIN 2 (43 % compared to 27 % in the placebo group), but not for CIN 3 (Meyskens et al. 1994). Likewise, trials of an oral synthetic retinoid (4-HPR) and cis retinoic acid have been negative (Follen et al. 2001; Alvarez et al. 2003). Indole-3-carbinol is another promising agent that may in part explain the cancer protective effect of cruciferous vegetable intake in some epidemiologic studies. This compound has been demonstrated to induce the protective effective

Table 17.3 Published chemopreventive clinical trials for cervical intraepithelial neoplasia (CIN)

Agent	Author/year	Inclusion criteria point
Live vector-based vaccine		
Recombinant vaccinia virus (MVA E2)	Corona Gutierrez et al. (2004)	CIN 1, CIN 2, CIN 3
Recombinant vaccinia virus (MVA E2)	García-Hernández et al. (2006)	CIN 2, CIN 3
Recombinant vaccinia virus (TG4001)	Brun et al. (2011)	CIN 2, CIN 3
Antioxidants		
Diferuloylmethane (curcumin)	Cheng et al. (2001)	CIN 1, CIN 2
Green tea	Ahn et al. (2003)	CIN 1, CIN 2, CIN 3
Polyherbal tablet (Praneem) *Azadirachta indica* (Neem), 80 mg; saponins from *Sapindus mukorossi*, 40 mg; *Mentha citrata* oil, 20 mg; quinine hydrochloride, 30 mg	Shukla et al. (2009)	HPV positive (with or without CIN 1)
Peptide based		
HPV 16 E7 12–20/ 86–93	Muderspach et al. (2000)	CIN 2, CIN 3
CIGB-228 (HLA-restricted HPV16 E7 epitope adjuvated with very small size proteoliposomes (VSSP))	Solares et al. (2011)	CIN 2, CIN 3
Protein based		
Heat shock protein fusion (SGN 00101)	Einstein et al. (2007)	CIN 3
Heat shock protein fusion (SGN 00101)	Roman et al. (2007)	CIN 2, CIN 3
HPV 16 immunotherapeutic (E6E7 fusion protein and ISCOMATRIX adjuvant)	Frazer et al. (2004)	CIN1, CIN 2, CIN 3
Fusion protein (PD-E7)	Hallez et al. (2004)	CIN 1, CIN 3
Prot D HPV16/E7 in SB adjuvant ASO2B	Simon et al. (2003)	CIN 3
DNA based		
Cidofovir, an acyclic phosphonate nucleoside	Van Pachterbeke et al. (2009)	CIN 2, CIN 3
pNGVL4a-Sig/E7(detox)/HSP70	Trimble et al. (2009)	CIN 2, CIN 3
ZYC101	Sheets et al. (2003)	CIN 2, CIN 3
ZYC101a	Garcia et al. (2004)	CIN 2, CIN 3
Suicide inhibitor of ornithine decarboxylase		
Alpha-difluoromethylornithine (DFMO)	Mitchell et al. (1998a, b)	CIN 3
Alpha-difluoromethylornithine (DFMO)	Vlastos et al. (2005)	CIN 2, CIN 3

(continued)

Table 17.3 (continued)

Agent	Author/year	Inclusion criteria point
Retinoids		
Retinyl acetate topical gel	Romney et al. (1985)	CIN 1, CIN 2
Trans-retinoic acid (tretinoin)	Meyskens et al. (1983)	CIN 2, CIN 3
Trans-retinoic acid (tretinoin)	Graham et al. (1986)	CIN 1, CIN 2, CIN 3
Trans-retinoic acid (tretinoin)	Meyskens et al. (1994)	CIN 2, CIN 3
4-Hydroxyphenylretinamide	Follen et al. (2001)	CIN 2, CIN 3
Pan-retinoid receptor agonist (alitretinoin)	Alvarez et al. (2003)	CIN 2, CIN 3
All-trans retinoic acid (Ruffin et al. 2004)	Ruffin et al. (2004)	CIN 2, CIN 3
Dendrimer		
Topical microbicide (VivaGel)	Cohen et al. (2011)	No CIN (with or without HPV)
COX-2 Inhibitor		
Celecoxib	Farley et al. (2006)	CIN 2, CIN 3
Rofecoxib	Hefler et al. (2006)	CIN 2, CIN 3
Hormone		
Vaginal progesterone	Hefler et al. (2010)	CIN 1
Micronutrients		
Folic acid	Butterworth et al. (1992)	CIN 1, CIN 2
Folic acid	Childers et al. (1995)	CIN 1, CIN 2
Beta-carotene	Manetta et al. (1996)	CIN 1, CIN 2
Beta-carotene	Romney et al. (1997)	CIN 1, CIN 2, CIN 3
Beta-carotene	Keefe et al. (2001)	CIN 2, CIN 3
Beta-carotene and vitamin C	Mackerras et al. (1999)	CIN 1
Indole-3-carbinol	Bell et al. (2000)	CIN 2, CIN 3
Diindolylmethane (DIM)	Castanon et al. (2012)	CIN 2, CIN 3
Diindolylmethane (DIM)	Del Priore et al. (2010)	CIN 2, CIN 3
Zinc-citrate compound (CIZAR)	Kim et al. (2011)	HR-HPV positive, no CIN

cytochrome P-450 (Wattenberg and Loub 1978; Grubbs et al. 1995). A phase II study, of two different doses of this agent for 90 days in subjects with CIN 2/3, reported a consistent response rate of 44–50 % (compared to no responders in the control group) (Bell et al. 2000). Randomized trials of imiquimod, a topical cellular immune response modulator, used for HPV-related genital condyloma, have been performed although not yet reported for cervical disease end points. Clinical trials are ongoing at the Arizona Cancer Center for selective cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib) and green tea-related compounds (e.g., polyphenon E) and are planned for diindylomethane (e.g., DIM).

17.7.2 Therapeutic Vaccines

An alternative therapeutic approach has targeted the elimination of high-grade precursor and even invasive lesions in individuals with established HPV infection.

Such a strategy is dependent on cellular immune response, rather than antibody development. In general, this involves the stimulation of a cytotoxic T-lymphocyte response to the E6 and E7 oncoproteins. HPV peptide trials that have used this approach have shown modest promise. A small trial of a preparation using E7 epitope peptides in subjects with cervical and vulvar squamous intraepithelial lesions demonstrated T-lymphocyte response in 10 of 18 subjects, with three demonstrating a complete response (Muderspach et al. 2000). Another trial using a longer E7 peptide with a palmitic acid adjuvant in 12 cervical cancer patients resulted in a 25 % T-lymphocyte response rate and a single complete response (Zwaveling et al. 2002). An alternate promising approach involves the use of a non-integrating, non-replicating, plasmid-encoding multiple HPV 16 and 18 E6 and E7 epitopes, formulated in small biodegradable polymer microparticles with a good profile of safety and tolerability (ZYC101) (Klencke et al. 2002; Sheets et al. 2003). A recent large, multicenter, randomized, placebo-controlled trial tested the safety and efficacy of this agent in subjects with histologically confirmed CIN 2 or 3 (Garcia et al. 2004). Of 127 randomized participants for whom cervical conization specimens were available, there was a trend toward higher rates of regression in the active drug group, 43 % compared to 27 %. More significantly 70 % of subjects less than 25 years of age demonstrated histologically-confirmed regression (compared to 23 % in the placebo group). Additional encouraging data from an early phase E7 heat shock protein vaccine has been published (Einstein et al. 2007; Van Doorslaer et al. 2010).

The search for therapeutic medical modalities to address cervical and endometrial intraepithelial neoplasias is particularly important within the larger framework for cervical cancer prevention. Chemopreventive and immune therapies open the door for potentially nonsurgical, fertility-sparing, minimally morbid interventions especially for young women who are increasingly burdened by these diseases. These efforts also provide a vehicle for an even more profound understanding of HPV infection, which will serve future generations of women.

17.7.3 HPV Prophylactic Vaccines

The development of prophylactic vaccines together presents the first realistic opportunity for primary prevention. Two prophylactic HPV vaccines have been developed based on the recombinant expression of the L1 major capsid protein and subsequent self-assembly into virus-like particles (VLPs) that resemble the outer shell of the virus. VLPs are synthetic and contain no DNA and are not live/attenuated viruses. Injection of the HPV VLPs elicits a strong and sustained type-specific response (Future II Study Group 2007a, b). One of the vaccines, Gardasil® (Merck & Co., Inc.), protects against HPV types 6, 11, 16, and 18 (quadrivalent vaccine), and the other, Cervarix (GlaxoSmithKline), protects against types 16 and 18 (bivalent vaccine). The goal of prophylactic vaccination is to reduce the incidence of HPV-related cervical, as well as vulvar, vaginal, and anal premalignant and invasive disease and the diagnostic and therapeutic interventions associated with these disease entities.

The quadrivalent product is also expected to protect against genital warts, which potentially should be associated with a reduction in vertical transmission associated with laryngeal papillomatosis.

A series of well-designed industry-sponsored trials have demonstrated the prophylactic vaccines for HPV types 16 (Koutsky et al. 2002); 16 and 18 (Harper et al. 2004, 2006; Dubin 2005); and 6, 11, 16, and 18 (Barr 2005, 2006; Villa et al. 2005) to be effective for the prevention of persistent HPV 16 and 18 infections and HPV 16- and 18-related CIN 2/3 (Mao et al. 2006). The populations studied in these trials restricted the age, lifetime number of sex partners, past history of cervical abnormality, and prevalent HPV 16 or 18 infections. In this population however, at more than 5 years of follow up, clinical studies consistently demonstrate near 100 % efficacy in the prevention of persistent type-specific HPV infections and CIN 2/3 among subjects adherent to the study protocol (per protocol analysis group) and who did not have evidence of the specific viral type found in the vaccine formulation prior to prophylactic vaccination. The quadrivalent product also protected against HPV 6-, 11-, 16-, and 18-related external genital lesions including genital warts and vulvar and vaginal neoplasia. While for women with normal cytology at baseline and no carcinogenic HPV types within 90 days of study enrollment, the bivalent vaccine reduced the rate of HPV 16/18-associated abnormal cytologic results by 93 %. Although the ultimate goal of these products is to prevent malignancy, persistent HPV infection and infection-related CIN 2/3 were used as valid and appropriate intermediate clinical end points due to ethical and practical considerations which preclude the use of invasive disease as an end point.

The Females United to Unilaterally Reduce Endo/Ectocervical Disease II (FUTURE II) trial focused solely on high-grade cervical disease (i.e., CIN 2 or 3, adenocarcinoma in situ [AIS], cancer) end points (Future II Study Group 2007b). After 3 years of follow-up, 12,167 women (age 15–26 years) who completed the vaccination regimen per protocol and were negative for the respective HPV vaccine type at entry through 1 month following the third vaccine dose, vaccine efficacy was 98 % (95 % confidence interval [CI]: 86–100) for preventing HPV 16- or HPV 18-related CIN 2/3 and AIS, with only one case of CIN 3 in the vaccine group compared to 41 cases of CIN plus an additional AIS case in the control group.

By contrast, FUTURE I (Garland et al. 2007) considered both cervical and vulvovaginal disease end points. In 3 years of follow-up of 5,455 subjects (age 16–23 years) who completed the quadrivalent vaccine regimen did not violate the protocol and who had no virological evidence of infection with the specific HPV vaccine type at study entry through 1 month following the third vaccine dose, the vaccine prevented 100 % (95 % CI: 94–100) of HPV 6-, 11-, 16-, and 18-related cervical lesions of any grade.

An intent to treat (ITT) analyses was conducted to evaluate the impact of the quadrivalent vaccine with respect to HPV 6-, 11-, 16-, and 18-related cervical in all women randomized in both trials and received at least one dose of vaccine. The goal was to estimate the overall vaccine impact on prevalent disease regardless of baseline HPV status (i.e., prevalent infection at study entry) and serostatus (i.e., prior infection). This included events arising from HPV infections and disease related to

the vaccine-specific HPV present at time of vaccination as well as those arising from infections that were acquired after vaccination. Impact was measured starting 1 month post-dose one, with 3 year follow up.

The majority of CIN and detected in the group that received quadrivalent vaccine occurred as a consequence of HPV infection present at enrollment. In FUTURE II (Future II Study Group 2007b), efficacy for HPV 16- or 18-related CIN 2/3 or AIS was estimated at 44 % (95 % CI: 26–58 %), with 83 cases of high-grade disease in the vaccine arm compared to 148 among the placebo arm. For FUTURE I (Garland et al. 2007) the efficacy for HPV 6-, 11-, 16-, or 18-related CIN or AIS was 55% (95 % CI: 40–66 %), with 71 and 155 events in the vaccine and control arms, respectively. An interim analysis of combined phase II and III quadrivalent vaccine studies (median follow-up of 1.9 years) demonstrated a 12.2 % (95 % CI: −3.2–25.3 %) reduction for CIN 2/3 (compared with placebo) regardless of HPV type (Miller 2007). As would be expected, when subjects entered these studies with evidence of current or past HPV infection, by PCR or serology positive for HPV-related vaccine types, there was no protection from subsequent disease with prophylactic quadrivalent vaccination (Hildesheim et al. 2007).

The phase II bivalent vaccine trial provides information regarding vaccine efficacy and durability of the immune response. Approximately 776 women (age 15–25 years) who completed the three-dose vaccination regimen were followed for 25–53 months (mean follow-up was 48 months). Vaccine efficacy was 100 % (95 % CI: 42.4–100 %) for preventing HPV 16- or HPV 18-related CIN 2 or 3; this included no cases in the vaccine group and five cases in the placebo group. Additionally there was a single case of persistent HPV 16 or 18 among vaccinated women compared to 23 cases among controls receiving placebo (96 % efficacy) (Harper, et al. 2006).

An interim analysis of the placebo-controlled trial of the bivalent product involving 18,644 young women (aged 15–24) who completed the 3-dose vaccination regimen (per protocol group) and participated in an extended follow-up study demonstrated efficacy of 93 and 83 % for preventing HPV 16- or HPV 18-related CIN 2 or greater, with a total of two cases in the vaccine group and 21 in the placebo group (Paavonen et al. 2007). The results failed to reach significance for HPV 18 due to the low number of events. The efficacy for preventing persistent (12 months) HPV 16- or 18-related CIN 2, the obligate precursor of high-grade cervical disease and cancer, was estimated to be 80 % for HPV 16, and there was a trend toward significance for HPV 18 and the related viral types 33, 45, and 52.

There are limited data on the long-term duration of HPV vaccine-induced immunity, and no practical immune correlates of vaccine or naturally induced immunity that might be useful in estimating this.

Based on these clinical trial data, the greatest cervical cancer prevention benefit of this primary prevention intervention will likely be for young women (median age of 16 years) reporting on average two (and no more than four) lifetime sexual partners at vaccination. In an ideal setting vaccination prior to sexual intercourse would be implemented to achieve optimal effectiveness with regard to the public health end point of cervical cancer prevention. However, identifying this population in clinical settings is problematic for many reasons, and public health policy strategy

should target individuals based on age thresholds at which exposure is likely to occur. One challenge is that about a quarter of girls report being sexually active by age 15, 40 % by age 16, and 70 % by age 18 (Abma, et al. 2004). Additionally, 6 % of high school students report initiation of intercourse before age 13 and 34 % of students had had sexual intercourse with at least one person during the 3 months before being surveyed (CDC 2011). Current population-based estimates suggest that women between the age of 20 and 49 years have a median number of six lifetime partners (Nagelkerke et al. 2006).

The risk of exposure to carcinogenic and noncarcinogenic HPV types increases with number of lifetime sex partners (Vaccarella et al. 2006). Given that HPV acquisition is a marker of the onset of sexual activity, it is not surprising that among 13–21-year-old women, 70 % had evidence of HPV infection within 5–7 years of onset of sexual intercourse (Moscicki et al. 2001). For college-age women, 39 % will acquire HPV within 24 months of onset of sexual activity (Winer et al. 2003).

Unlike vaccine performance in younger populations which will likely mirror clinical trial findings, the efficacy and potential cervical cancer prevention benefit of HPV vaccines after the age of 19 years is less compelling at this time. Certainly women older than 19 years of age who have not commenced sexual activity will derive the full cervical cancer prevention benefit from HPV vaccination. For women 19–26 years of age who have not been exposed to all four HPV types in the vaccine, there will likely be a cancer benefit. However, many currently and/or previously sexually active women in this age group who have been exposed to HPV 16 or 18 and will have less cervical cancer prevention benefit from prophylactic vaccination. This population is not easily identified given the current lack of a clinically available HPV typing assay. The public health benefit for HPV 6- and 11-related condylomatous vaginal and vulvar disease derived from quadrivalent vaccination is not in dispute for this population segment.

Based on such information the American Cancer Society guidelines support the vaccination of girls and women up to 18 years of age. They also advise available evidence that is insufficient to recommend for or against vaccination of women age 19–26 years of age and no evidence for women over 26 years of age (Saslow et al. 2007). The ACS prophylactic vaccination recommendations are summarized in Table 17.2.

Conclusion

Cervical cancer is a potentially devastating disease with major emotional and economic implications for women and their families. Cervical cancer is perhaps the best understood of any malignancy, and its etiologic agent, although ubiquitous, is well characterized and typically innocuous. Moreover, a cost-effective screening intervention is generally available for the detection of preinvasive disease. At least theoretically, cervical cancer is entirely preventable given the tools available to practitioners today. Efforts should therefore be aimed at bringing the significant numbers of under and unscreened women into the screening pool and providing clinical services that facilitate their accurate diagnosis and adequate treatment prior to the point of developing invasive disease. Such women are in

general medically underserved and uninsured, and bringing them into the health-care system presents challenges that are at least as formidable as vaccine development.

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Ovarian Cancer Prevention

18

Setsuko K. Chambers and Lisa M. Hess

18.1 Introduction

Despite advances in surgical care and in pharmaceutical treatments for ovarian cancer, the mortality rate from this disease remains high. There have been improvements in the therapeutics that are able to keep people alive longer with their disease, but both strategies to improve cure rates and effective approaches for screening and early detection remain elusive (Huang et al. 2008; Buys et al. 2011). Unfortunately, most patients still have advanced disease at the time of diagnosis (Maringe et al. 2012; O'Malley et al. 2012).

Approximately 80 % of all cancers occur in the absence of familial or genetic risk factors. Ovarian cancer is frequently associated with symptoms that are consistent with those of menstruation (e.g., pelvic, back or abdominal pain, constipation, indigestion, frequent urination), but are more severe and persist longer than would be expected (Goff et al. 2004). The Gynecologic Cancer Foundation (GCF), Society of Gynecologic Oncologists (SGO), and American Cancer Society (ACS) issued a consensus statement in 2007 (CGF 2007), identifying the following most common symptoms (persisting several weeks):

- Bloating
- Pelvic or abdominal pain
- Difficulty eating or feeling full quickly
- Urinary symptoms (urgency or frequency)

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Since the majority of patients with these common symptoms do not have ovarian cancer, attention to symptomology has neither translated to earlier detection nor to improved survival outcomes from ovarian cancer (Lim et al. 2012; Nagle et al. 2011). There remains a need to identify strategies to detect ovarian cancer. The Cancer Genome Atlas Project has been completed with analysis pertaining to epithelial ovarian cancer and to breast cancer recently published (Cancer Genome Atlas Research Network 2011). What is clear is that there is significant genomic complexity with high copy number variations, many different mutations, and driver genes found in both epithelial ovarian cancer and the basal or triple-negative form of breast cancer. Neither epithelial ovarian nor breast cancer is one disease at the molecular level. Such complexity, in addition to the findings of predominance of tumor suppressor losses, rather than presence of activating oncogenes, leads to challenges in the therapeutic application of these findings to patients.

The National Institutes of Health (NIH) Consensus Panel issued a statement in 1995, which states that all patients suspected to have ovarian cancer be offered preoperative consultation with a gynecologic oncologist (NIH 1995). This recommendation is also supported by the American College of Obstetricians and Gynecologists (SGO 2005). Since the vast majority of patients with early-stage disease (more than 90 %) and many patients with advanced disease (approximately 30 %) do not receive appropriate care, as they would from a gynecologic oncologist, patients experience unnecessary loss in fertility, increased risk of complications, the need for additional surgery, and increased morbidity and mortality (SGO 2005). The recommendation for care from a gynecologic oncologist is also supported by evidence that suggests that gynecologic oncologists are more efficient, in terms of both time and health-care resources utilized, at reaching an accurate diagnosis in the setting of a suspected ovarian cancer (Hess et al. 2012).

Appropriate care from the time a malignancy is first suspected provides patients with the best outcome possible if they are diagnosed with this disease and reduces unnecessary surgical and medical procedures. Appropriate and comprehensive care, which includes appropriate surgical staging and optimal cytoreduction, followed by appropriate chemotherapy, must be performed by board-certified physicians trained in the management of ovarian cancer to ensure the management is both comprehensive and accurate. In the USA, only gynecologic oncologists have this certification. Gynecologic oncologists have been shown to stage the patient more accurately (McGowan et al. 1985). As experts, they also are much more likely to perform surgery that results in optimal debulking, an independent predictor of overall survival. Optimal debulking is associated with a 25 % reduction in mortality among women with advanced ovarian cancer (Bristow et al. 2002; Junor et al. 2005).

While a number of prognostic factors influence ovarian cancer survival (e.g., appropriate surgical care, stage of disease at diagnosis, age at diagnosis, appropriate chemotherapy treatment), early-stage ovarian cancer is curable in a high percentage of patients (Table 18.1) (McGuire et al. 2002). However, the biology of ovarian cancer (discussed later in this chapter) may impede efforts that seek to diagnose patients before their disease has progressed to an advanced stage (Fig. 18.1).

Table 18.1 1-, 5-, and 10-year survival rates by stage in the USA (Kosary 2007)

AJCC stage	Percent of all cases	1-year survival (%)	5-year survival (%)	10-year survival (%)
I	22.1	96.8	89.3	84.1
IA	13.2	98.9	94.0	88.9
IB	1.4	98.0	91.1	78.7
IC	6.5	92.4	79.8	76.0
I NOS[a]	0.9	94.8	84.7	73.7
II	7.8	87.1	65.5	55.7
IIA	2.1	96.4	76.4	66.8
IIB	2.5	88.3	66.9	57.4
IIC	3.0	80.4	57.0	45.9
II NOS[a]	0.3	78.0	58.9	38.8
III	35.3	78.8	33.5	22.2
IIIA	2.0	86.4	45.3	31.4
IIIB	2.8	81.5	38.6	26.1
IIIC	19.4	82.2	35.2	22.6
III NOS[a]	11.1	70.5	26.9	17.9
IV	31.7	61.7	17.9	10.4
Unknown	3.1	61.8	29.5	20.2

[a]*NOS* not otherwise specified

18.2 Histopathology of Ovarian Cancer

Ovarian cancer is not a single disease, neither at a morphologic nor molecular level; there are more than 30 types and subtypes of ovarian malignancies, each with its own histopathologic appearance, biologic behavior, and etiology (Hildreth et al. 1981). The histologic and molecular variability of ovarian cancer is challenging for researchers for both the early detection and treatment of these malignancies. Unlike many other cancers that follow a multistep progression to reach metastatic disease (e.g., beginning with a precancerous lesion and progressing from stage by stage as the cancer is undetected), ovarian cancers (particularly high-grade serous epithelial ovarian cancers as described below) do not appear to follow this stepwise progression model, which is a significant barrier for early detection strategies.

Ovarian malignancies are categorized into three major groups: epithelial, germ cell, and sex cord-stromal tumors. Epithelial ovarian carcinoma is the most common type; more than 85 % of ovarian cancers are epithelial cancers, which are also the most likely to be malignant and to cause premature death (Jelovac and Armstrong 2011). Adenocarcinomas of low malignant potential are a subtype of epithelial ovarian cancer and are now grouped with the low-grade epithelial ovarian cancers. Carcinosarcoma of the ovary, a particularly aggressive subtype of epithelial ovarian cancer, defined by the presence of malignant epithelial and mesenchymal elements, accounts for fewer than 1 % of ovarian malignancies. Malignant germ cell tumors and sex cord-stromal tumors are less common. Germ cell cancers are more common among younger women, are often diagnosed in early stages (75 % of cases), and are

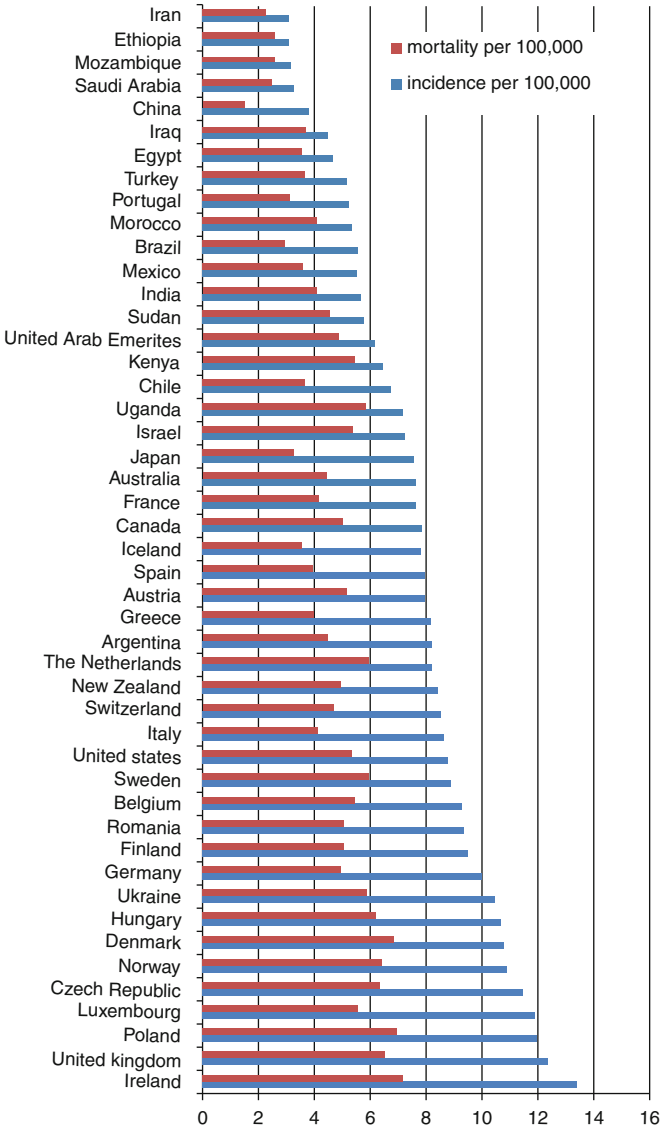

Fig. 18.1 Age-adjusted incidence and mortality rates from ovarian cancer, selected countries (Data from GLOBOCAN 2008)

associated with a more than 90 % 10-year survival rate (Kosary 2007). Granulosa cell tumors are the most common subtype of sex cord-stromal tumors and generally have a good prognosis. We will primarily focus on the epithelial ovarian cancers in this chapter.

Within the broad category of epithelial cancers, there are various subtypes of serous, endometrioid, mucinous clear cell, transitional cell, and undifferentiated cancers. Serous cancers are the most common (approximately 75 % of all epithelial cancers). A subset of high-grade serous carcinomas likely originates from the

fallopian tube (Salvador et al. 2009), in particular among women at increased genetic risk for breast and ovarian cancers. The anatomical location of the cell of origin is important as this finding impacts research on early detection, identification of novel biomarkers, as well as the type of risk-reducing surgery.

Due to the challenges with early detection and prognosis and similarity in treatment strategies, particularly within epithelial ovarian cancers, they are increasingly referred to as either low grade (type I) or high grade (type II) (Landen et al. 2008). Type I tumors tend to have low-grade features (e.g., little cellular differentiation, suggesting they are less likely to spread) and are associated with slow growth. Type I tumors include most low-grade endometrioid, low-grade serous, mucinous, transitional, and possibly clear cell carcinomas (Kurman and Shih 2011). Ultrasound-detected masses are more likely to be type I tumors. In addition to histologic subtypes, type I cancers are likely to have cell signaling mutations, such as *KRAS*, *BRAF*, *ERBB2*, *CTNNB1*, *PTEN PIK3CA*, *ARID1A*, and *PPPR1A* (Kurman and Shih 2011). These tumors tend to express estrogen receptor (ER) and progesterone receptor (PR) and to be more genetically stable. Type II tumors are genetically unstable with frequent rapid spread even with small volume primary adnexal disease. These tumors develop along a different molecular pathway than type I tumors and are high-grade, often serous cell tumors. Type II tumors include high-grade serous, high-grade endometrioid, undifferentiated cancers, and carcinosarcomas.

18.3 Origins of Ovarian Cancer

At this time, serous carcinomas stemming from the ovary, fallopian tube, and primary peritoneum are grouped together as "pelvic serous carcinomas." This grouping is a result of the similar genomic complexity, clinical behavior, response to treatment, and prognosis. Work is ongoing to more fully understand the extraovarian epithelial origin of these cancers (Jarboe et al. 2008). The ovarian surface epithelium and fimbriae may encompass a region of transition, where there is no clear or distinct line of differentiation from one epithelium to the other despite clear morphologic differences between the fallopian fimbriae and the ovary (Auersperg 2011). Some of the serous malignancies previously attributed to the ovary or peritoneum are now believed to originate from fimbria or ampulla of the fallopian tube. In a study of *BRCA*-positive patients with cancers found at the time of prophylactic surgery, all identified cancers were found to originate in the fallopian tube (Callahan et al. 2007). These lesions were frequently associated with an intraepithelial component of the tube (STIC or serous tubal intraepithelial carcinoma) as shown in Fig. 18.2. Among fallopian tubes containing STICs, there is evidence of a p53 signature consistent with a serous carcinoma precursor that has been detected in the distal fallopian tube, specifically among women with *BRCA* mutations (Lee et al. 2007). Identical p53 somatic mutations are found in STIC and the concurrent high-grade serous carcinomas, supporting a clonal relationship (Kuhn et al. 2012). There is also a suggestion of a tubal origin of low-grade pelvic serous carcinomas (Li et al. 2011). Although this work needs further confirmation, there remains the possibility

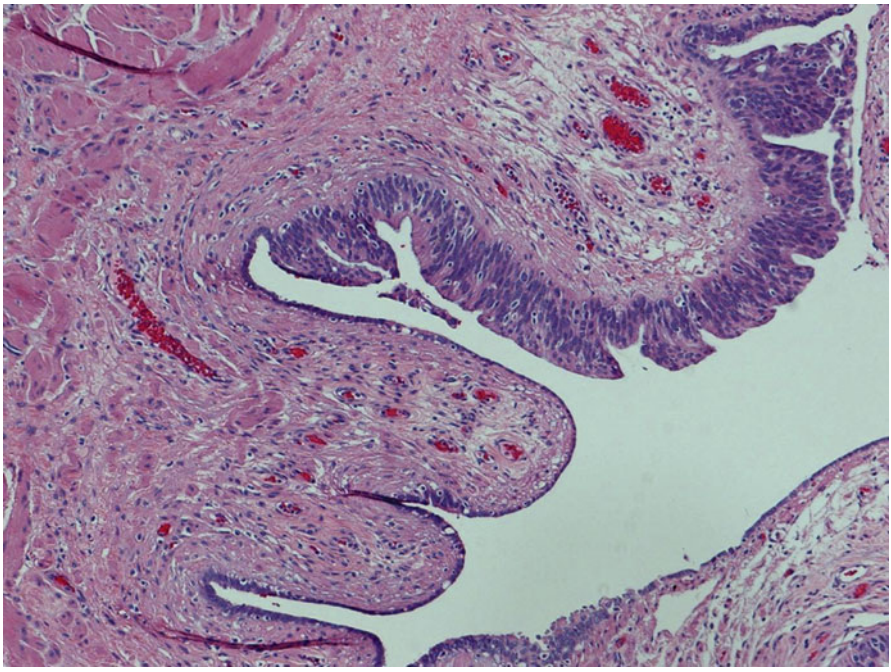

Fig. 18.2 Fallopian tube with serous tubal intraepithelial carcinoma (STIC)

of a molecular lesion in the fallopian tube that is a precursor to serous ovarian, peritoneal, or tubal carcinoma that may be useful in future efforts to develop screening tools for this disease. There is also increasing evidence of the multifocal nature of serous carcinomas, adding to the complexity for early detection strategies (Tang et al. 2012). Although the exact location of origin differs, ovarian, peritoneal, and tubal cancers act similarly and in many ways are indistinguishable in terms of their clinical or pathologic presentation, and as a result, patients with these diagnoses receive similar treatment regimens. It is generally impossible to make a clear distinction between an ovarian, tubal, or peritoneal carcinoma, and hence, they are considered pelvic serous carcinomas (Barda et al. 2004).

The original hypothesis for ovarian cancer initiation is the incessant ovulation hypothesis, which proposes that repeated ovulation causes trauma to the ovarian surface epithelium that must constantly be repaired. Repeated trauma to the ovarian surface epithelium was suggested to lead to malignant transformation (Fathalla 1971). This theory arose from the knowledge of an increased risk of ovarian cancer among nulliparous women and the protective effects of pregnancy, lactation, and oral contraceptive use that suppress ovulation. Endometriosis is a precursor (risk factor) specifically for endometrioid or clear cell ovarian cancers (Kurman and shih 2011). The biology, including inflammatory cytokines now known to be associated with signaling by endometriotic implants, may contribute to cellular susceptibility to neoplastic change (Keita et al. 2010). However, structural changes during ovulation-inflicted

malignant transformation are insufficient to explain the origins of the range of ovarian cancers (Risch 1998) and may perhaps only be relevant for the tumors that develop from the ovary (e.g., gonadal stromal, germ cell tumors, or ovarian surface epithelium) and not secondary to the fallopian tube as a subset of ovarian cancers are now believed to arise, or the peritoneal lining.

Other theories of ovarian cancer initiation include the Gonadotropin Theory, built on Fathalla's theory to suggest that fertility-enhancing hormones increased activation of the ovarian surface epithelium, leading to increased risk of epithelial ovarian cancers. This theory addressed gaps in the incessant ovulation theory, such as the increased risk associated with use of fertility medications and among women with polycystic ovarian syndrome, as well as the lack of reduction in risk among progestin-only oral contraceptive use. During ovulation, there is an increase in gonadotropins to regulate gametogenesis. The Gonadotropin Theory is in line with the protective effect of pregnancy and OC use and the increased risk of ovarian cancer during menopause, when gonadotropins rise. However, the mechanism by which gonadotropins may increase cancer risk is unknown (Choi et al. 2007). Hormone stimulation may play a role in carcinogenesis, as there has been an increased risk of ovarian cancer associated with estrogens and androgens and a decreased risk associated with progestin in the tumor microenvironment (Risch 1998; Landen et al. 2008; Ricciardelli and Oehler 2009). Despite the current lack of knowledge about the mechanism of action of the various hormones implicated in epidemiologic data to date, the hormonal milieu of the ovarian epithelium is currently thought to be an important factor associated with ovarian cancer risk.

Inflammation has been associated with ovulation (e.g., tissue reconstruction). This may play a role in carcinogenesis as suggested by epidemiologic evidence that may demonstrate a decreased risk of ovarian cancer among chronic anti-inflammatory medication users; inflammatory processes may also explain the protective role of tubal ligation (Ricciardelli and Oehler 2009). However, despite the increasing number of hypotheses with supporting biologic and epidemiologic evidence, there is no unifying model that can encompass the breadth of ovarian cancers.

18.4 Risk Factors for Epithelial Ovarian Cancer

In general, a woman is considered at high risk of ovarian, fallopian tube, or primary peritoneal cancer if she has a *BRCA1* or *BRCA2* mutation or has a family history of ovarian cancer (Holschneider and Berek 2000; King et al. 2003). However, a variety of other reproductive, menstrual, hormonal, dietary, and genetic factors contribute to a woman's lifetime risk of developing ovarian cancer. In general, protective factors include multiparity, increased time spent breast feeding, oral contraceptive use, and tubal ligation or hysterectomy (Holschneider and Berek 2000), while risk factors include increasing age; unexplained infertility; endometriosis; nulliparity; family history of ovarian cancer; premenopausal breast, bilateral breast, or male breast cancer; and certain inherited genetic mutations (e.g., *BRCA 1/2*, *STK11*).

Table 18.2 5-year survival rates by age at diagnosis (Ries et al. 2004, 2005)

Age at diagnosis	% of all ovarian cancers diagnosed	5-year survival (%)
<45	12.6	72.3
45–54	18.8	52.9
55–64	21.5	46.4
65–74	20.6	35.7
75+	26.5	20.3

18.4.1 Age

Similar to most other cancers, epithelial ovarian cancer is a disease associated with aging (Yancik 1993). Incidence begins to rise in the late teenage years and gradually increases with age (Table 18.2). After age 45, incidence and mortality rise sharply, and the highest incidence occurs among women from 80 to 84 years of age (61.8 per 100,000 women) (Edmondson and Monaghan 2001). Ovarian cancer is most frequently (at least 85 % of cases) diagnosed among peri- and postmenopausal women (Choi et al. 2007).

18.4.2 Endogenous and Exogenous Hormones

While certain reproductive factors, such as multiparity and breast-feeding, may offer protection against ovarian cancer, others, including early onset of menstruation, nulliparity, and having a first child after age 35, may increase risk. Thus, factors that reduce the total number of ovulations reduce ovarian cancer risk and those that increase the number of ovulations tend to increase risk. The risk of ovarian cancer is reduced with early childbirth (e.g., first pregnancy at age 25 or earlier) and is increased with late childbirth (e.g., first pregnancy after age 35) (Negri et al. 1991; Daly and Obrams 1998). Nulliparous women are also at significantly higher risk of ovarian cancer than parous women, regardless of the age of first childbirth (Vachon et al. 2002). In a prospective cohort study of 31,377 Iowa women, age 55–69 years, nulliparous women with a family history of first- and second-degree relatives with breast or ovarian cancer were at much higher risk than were their parous counterparts (relative risk, RR = 2.7, 95 % confidence interval, CI: 1.1–6.6) (Vachon et al. 2002). There was an increased risk for nulliparous women with family history of breast or ovarian cancer. Ovulation may also be interrupted by the use of oral contraceptives and breast-feeding, and therefore, similar to the number of full-term pregnancies, OCs have also demonstrated a protective effect against the development of ovarian cancer (Whittemore et al. 1992).

An analysis of pooled interview data on infertility and fertility drug use from eight case-control studies conducted in the USA, Denmark, Canada, and Australia found that nulligravid women who attempted to become pregnant for more than 5 years, compared with nulligravid women who attempted to become pregnant for less than 1 year, experienced a 2.7-fold increased risk of ovarian cancer (Ness et al. 2002). Significant controversy surrounds the relationships among infertility,

fertility drug use, and the risk of ovarian cancer (Sit et al. 2002). These pooled interview data on infertility and fertility drug use found that among nulliparous, subfertile women, neither use of any fertility drug nor use of fertility drug for more than 12 months was associated with ovarian cancer risk (Ness et al. 2002). These data suggest that specific biological causes of infertility (such as endometriosis), and not the use of fertility drugs, may play a role in overall risk for ovarian cancer.

Multiparity and interrupted ovulation appear to decrease the risk of ovarian cancer (Daly and Obrams 1998). The Nurses Cohort Study of 121,700 women found that parity reduced ovarian cancer risk (odds ratio, OR = 0.84; 95 % CI: 0.77–0.91 for each pregnancy) (Hankinson et al. 1995). A summary of seven case-control studies found that one full-term pregnancy had a significant reduction on ovarian cancer risk (OR = 0.47) (John et al. 1993). Risk decreased as the number of pregnancies increased; after six full-term pregnancies, the odds ratio was 0.29, with a 95 % confidence interval of 0.20–0.42. Risk declined by about 15 % for each additional full-term pregnancy (Risch et al. 1994).

The lifetime cumulative duration of ovulation may play a role in the risk of ovarian cancer, with early menarche being associated with increased risk of ovarian cancer in a number of studies conducted in the USA and elsewhere (Wu et al. 1988). Late menopause has also been associated with a higher risk of ovarian cancer (Hildreth et al. 1981; Malik 2002), but the data are inconsistent. However, a woman's age at menopause has not been associated with the risk of ovarian cancer in several ovarian cancer case-control studies (Hartge et al. 1988; Schildkraut et al. 2001).

The protective effects of ovulation inhibition, such as by hysterectomy or oral contraceptive (OC) use, may decrease the risk of ovarian cancer (Kjaerbye-Thygesen et al. 2006; Merrill 2006). In a case-control study, Rosenblatt and Thomas (1996) found that the possible protective effect of tubal ligation was greatest in women of parity less than four and that the protective effect was only for clear cell and endometrioid tumors. When Cramer and Xu (1995) combined data from two case-control studies, they found that both tubal ligation and prior hysterectomy were protective.

Oral contraceptives (OCs) suppress ovulation by a combined therapy of progestin plus estrogen and have demonstrated the ability to reduce ovarian cancer risk. In a follow-up analysis of the Norwegian women and Cancer Cohort Study, there were 171 cases of ovarian cancer diagnosed in the 96,355 woman cohort. The risk of ovarian cancer decreased with the use of OCs (p for trend <0.0001) (Kumle et al. 2003). In Australia, a case-control study examined the effects of OC use (Siskind et al. 2000). After controlling for estimated number of ovulatory cycles, the protective effect of OC use appeared to be multiplicative. There was a 7 % decrease in relative risk per year that persisted beyond 15 years of exposure (95 % CI: 4.0–9.0 %). Even short-term use, up to 1 year, may have an effect (OR = 0.57; 95 % CI: 0.40–0.82) (Siskind et al. 2000). Women with pathogenic mutations in the *BRCA1* and *BRCA2* genes may also experience a reduced risk of ovarian cancer with OC use (Narod et al. 1998). Any history of OC use was associated with a 0.5 odds ratio (95 % CI: 0.3–0.8). OC use was protective for both *BRCA1* (OR = 0.5; 95 % CI: 0.3–0.9) and *BRCA2* mutation carriers (OR = 0.4; 95 % CI: 0.2–1.1) (Narod et al.

1998). A population-based case-control study of 767 women also found that 4–8 years of OC use may reduce the risk of ovarian cancer by approximately 50 % in women with a family history of the disease (Walker et al. 2002). However, one must be cautious in continuing OCs in the mid-to-late reproductive years in the high-risk population because of concerns related to increasing the risk of breast cancer.

As discussed earlier (origin of ovarian cancer), estrogens and androgens are thought to increase ovarian cancer risk, while exposure to progesterone is protective. During menopause, androgen levels rise and, with binding to the surface epithelium, may promote carcinogenesis. Although the exact role of androgens in the ovarian epithelium is unclear, ovarian epithelium contains a high level of androgen receptors (Risch 1998). OCs act as mild antiandrogens, and it is hypothesized that this mechanism could contribute to their protective effect. Importantly, OCs are progesterone-dominant, which further enhances their protective role against ovarian cancer. The excess of progesterone during pregnancy, instead of the cessation of ovulation, may in fact be the protective factor. There is epidemiologic evidence supporting this, as progestin-only oral contraceptives confer a similar protective effect to combination oral contraceptives, yet do not inhibit ovulation (Risch 1998). This suggests that ovulation cessation is not the primary contributing factor to the reduced risk of ovarian cancer associated with long-term use of oral contraceptives.

There is an association between long-term use (e.g., 10 years or more) of estrogen replacement therapy (ERT) and increased ovarian cancer risk. Estrogens may act as promoters in the carcinogenic process, and occasionally their metabolites may act as antihormones or have other physiologic effects (Lipsett 1979). A study of 44,241 postmenopausal women found that those who used ERT, particularly use for 10 years or more, were at significantly increased risk of ovarian cancer (Lacey et al. 2002). However, combination hormone replacement therapy (HRT), which contains both estrogen and progesterone, has not demonstrated consistent findings related to ovarian cancer risk, suggesting that unopposed estrogen formulations are of greater concern, particularly among women who are already at risk of ovarian cancer.

There remains a great deal of controversy regarding the potential risk of ovarian cancer from hormone replacement therapy (HRT) or estrogen replacement therapy (ERT). The inconsistency in findings may be in part related to the fact that estrogen formulations in HRT vary in their effects on estrogen-sensitive target tissues, such as the ovary. Further, it is the balance between progestin and estrogen which is believed to be a key factor. A prospective study of 211,581 healthy postmenopausal women in the USA evaluated women who had taken oral HRT or ERT after age 35 to compare ovarian cancer mortality with the effect of HRT (Rodriguez et al. 2001). In 2007, data were published from the Million Woman Study (948,576 postmenopausal women in the UK), which demonstrated an increased risk of ovarian cancer among women who used HRT, and the rate increased with duration of use (Beral et al. 2007). A study of 655 histologically verified epithelial ovarian cancer cases and 3,899 randomly selected controls found that risk of ovarian cancer was elevated among ever users as compared with never users of both ERT and HRT (Riman et al. 2002). Ever users of ERT and HRT sequentially added progestins, but not HRT

continuously added progestins, may increase risk of ovarian cancer (Riman et al. 2002). The slight declines in ovarian cancer incidence in the USA (primarily among White women) have been attributed to the increased use of OCs in the 1980s and the reduced use of HRT in the early 2000s (Espey et al. 2007). A large study from Denmark showed that postmenopausal HRT (any kind of combination of estrogen and progestin) increased risk of ovarian cancer (*JAMA* 2009).

Risk of ovarian cancer mortality was reported to be higher in HRT users at baseline and slightly higher for previous users than never users. Risk doubled with 10 years or more duration of use; however, only 66 of the 944 women who died of ovarian cancer had used HRT for at least 10 years. Furthermore, most of these 66 women took unopposed estrogen (ERT) during the 1970s and early 1980s, when the use of higher doses of synthetic estrogen was common. Others have also found that long-term, high-dose unopposed ERT may increase the risk of ovarian cancer (Drew 2001). Women who used short-term ERT did not experience increased risk.

18.4.3 Genetic Risk Factors

At least 10 % of all ovarian cancers are associated with family history and inherited genetic factors, such as *BRCA1/2* mutations (Claus et al. 1996). Researchers have identified two primary syndromes by which ovarian cancer can be inherited. The syndromes include the hereditary breast/ovarian cancer syndromes (involving mutations in the *BRCA1* or *BRCA2* genes) and the Lynch syndrome II (involving mutations in DNA mismatch repair genes), which applies to women with female or male relatives who have had nonpolyposis-related colorectal (NHPCC) or early-age endometrial cancer (Murdoch and McDonnel 2002). Rare mutations at other loci, such as STK11 (Peutz-Jeghers syndrome), increase risk for the sex cord-stromal tumors of the ovary.

BRCA1 and *BRCA2* are DNA repair genes. When a mutated or altered form of *BRCA1* or *BRCA2* is inherited, this mutation interferes with the normal activity of the gene, making individuals more susceptible to both breast and ovarian cancer, as well as to other cancers. Individuals with one of these gene mutations have a higher risk of developing breast and ovarian cancers, and parents who are carriers have a 50 % chance of passing that gene mutation onto his or her children.

Genetic mutations in the *BRCA* genes (*BRCA1* and *BRCA2*) are inherited risk factors for ovarian cancer that do not fall into either the incessant ovulation or hormonal milieu theories. Women with *BRCA1* mutations have a 47–63 % risk of developing ovarian cancer over the course of life and a 71 % lifetime risk of developing breast cancer; women with *BRCA2* mutations have a 23–27 % and 84 % lifetime risk of developing ovarian or breast cancers, respectively (Couzin 2003; King et al. 2003; Levy-Lahad and Friedman 2007). These mutations substantially increase personal risk above that of the general female population, which has a lifetime risk of 1.5 % for ovarian cancer and 12.7 % for breast cancer (Ries et al. 2005). Only one out of every 500–1,000 women from the general population has a *BRCA*

mutation (less than 0.2 %), while the prevalence is estimated to be one out of every 50 women (at least 2 %) of Ashkenazi Jewish ethnicity (Saslow et al. 2007).

The *BRCA* genes seem to work differently in different environments; a number of factors (e.g., reproductive history, hormone therapy, diet, and the presence of other genes which, for example, control the metabolism of hormones) modify the effect of any gene in determining the final outcome. All cancers, including ovarian cancer, are ultimately determined by a combination of genetic and environmental factors.

18.4.4 Family History

A family history of ovarian cancer, especially if two or more first- or second-degree relatives have been affected, is associated with an increased risk of ovarian cancer. Ovarian cancers tend to occur at an early age among cancer family members (e.g., before age 50) and tend to be advanced high-grade serous epithelial cancers. However, family history of ovarian cancer without a known *BRCA* mutation is also a risk factor. Women with two or more first- or second-degree relatives who have been diagnosed with ovarian cancer are at significantly increased risk (risk ratio = 2.12; 95 % CI, 1.19–3.78) (Kerber and Slattery 1995).

18.4.5 Sociodemographic Factors

The incidence rates of ovarian cancer in US Latina, American Indian, and African American women are lower than those for White women. There are no differences in survival outcomes among African American, Hispanic, or any other racial/ethnic group when controlling for socioeconomic factors (e.g., health insurance, income, poverty status) and treatment (Du et al. 2011). There was also no difference in cancer care received between these groups, unlike what has been found for other cancers. Retrospective data analysis of SEER-Medicare claims also found that there were no differences in the rates of care received from a gynecologic oncologist among racial/ethnic or other sociodemographic groups, with the exception of women over the age of 70, who were less likely than their counterparts to receive care from a gynecologic oncologist (Austin et al. 2012).

Founder populations (e.g., those descending from a small group of ancestors) have a significantly greater risk of mutations in *BRCA1* or *BRCA2* as well as many other genetic mutations associated with cancer risk (Koifman and Koifman 2001; Weitzel et al. 2005; Anagnostopoulos et al. 2008; Fackenthal and Olopade 2007). In the USA, a greater proportion of women from Ashkenazi Jewish ancestry have *BRCA1* or *BRCA2* mutations (approximately 1 in every 50) (Hartge et al. 1999) than the general population (approximately 1 in every 400) (McClain et al. 2005). The vast majority of *BRCA* mutations are inherited; however, carriers of germ line *BRCA1* mutations more frequently will experience somatic mutations in *BRCA2* and vice versa (Welcsh and King 2001). In fact, most sporadic ovarian cancers also demonstrate somatic inactivation of the *BRCA* genes, but lack the point mutations

seen in those with *BRCA* hereditary syndromes (Welcsh and King 2001). In fact, among the high-grade serous carcinomas, the Cancer Genome Atlas Project found that 50 % of tumors show defective homologous recombination or BRCA pathway (Cancer Genome Atlas Research Project 2011). Although the majority of research among populations with *BRCA* mutations has focused on individuals of Ashkenazi Jewish ethnicity, the founder effect is common among a variety of populations internationally, such as Icelanders (*BRCA2* 999del5 mutation), founder populations from Belgium (*BRCA1* IVS5 +3A>G), African Americans (*BRCA1* 943ins10 and *BRCA1* M1775R), Russians (*BRCA1* 5382insC, *BRCA1* 4153delA), Germans (*BRCA1* 5382insC and *BRCA1* C61G), Hispanics (*BRCA1* 185delAG), and others, and is not limited to the Ashkenazim (*BRCA1* 5382insC, *BRCA1* 185delAG, and *BRCA2* 6174delT mutations) (Neuhausen 2000; Weitzel et al. 2005). Within the University of Arizona high-risk cancer genetics population, which is diverse in both Hispanic and Native Americans, we have found an unusual high incidence of the *BRCA2* 886delGT mutations among Hispanics and have identified six novel *BRCA2* mutations (Nelson-Moseke et al. 2013).

18.4.6 Lynch Syndrome

This is a relatively rare infected genetic disorder that is primarily associated with an increased risk of colorectal cancer (hereditary nonpolyposis colorectal cancer, NHPCC). There are a number of mismatch repair (MMR) genes that may be mutated in Lynch syndrome (e.g., *MSH2*, *MLH1*, *MSH6*, *PMS2*), with the majority of mutations found in the *MLH1* or *MSH2* genes. Lynch syndrome is associated with a significantly increased risk of colorectal, gastric, and endometrial cancers, as well as an increased 6–10 % lifetime risk of ovarian cancer (Engel et al. 2012). Important to the determination of Lynch syndrome is obtaining an appropriate family history and aligning this information with the Amsterdam criteria and Bethesda guidelines (Morrison et al. 2011). Additional details of this syndrome are included in the chapter on hereditary risk in this book (Chap. 5).

The known BRCA mutations along with those comprising the Lynch syndrome do not appear to account for all hereditary cases. A genome-wide association study of ovarian cancer cases versus controls has found new but more common ovarian cancer susceptibility alleles, with moderate to low penetrance (Song et al. 2009). Validation was performed of the most significant single-nucleotide polymorphism found on the susceptibility locus 9p22.2, found to have a strong association with risk for the serous subtype. It is estimated that these single-nucleotide polymorphisms may account for the remaining risk for ovarian cancer.

18.4.7 Diet

A number of studies have proposed that high dietary fat intake is associated with increased risk of epithelial ovarian cancer; this conclusion, however, remains speculative in part due to the fact that the mechanism by which dietary fat, or even stored

fat, increases risk is unknown. The effect of dietary fat may be independent or may act primarily though an influence on hormonal status. Dietary fat consumption appears to impact enteric reabsorption of steroid hormones mediated by the intestinal flora (Mansfield 1993). A meta-analysis of the association between high as compared to low dietary fat intake and risk of ovarian cancer found that high dietary fat intake appeared to represent a significant risk factor in the development of ovarian cancer (Huncharek and Kupelnick 2001). A case-control study in China investigated whether dietary factors had an etiological association with ovarian cancer (Zhang et al. 2002). Controlling for demographic, lifestyle, familial factors, hormonal status, family history, and total energy intake, ovarian cancer risk decreased with a high consumption of vegetables and fruits and increased with high intake of animal fat and salted vegetables. Risk appeared to increase among women who consumed high-fat, fried, cured, and smoked food (Zhang et al. 2002). Analyses of the Women's Health Initiative (WHI), a study of 48,835 women who were randomized to either a healthy diet (reduced fat and increased fruit and vegetable intake) or observation, found a statistically significant reduction in the risk of developing ovarian cancer among those randomized to the healthy diet ($p = 0.03$) (Prentice et al. 2007). Not all studies showed a positive association (Bertone and Rosner 2002b). The mechanisms for a benefit from a low-fat, more plant-based, eating pattern include reduction in immunomodulation and inflammation including prostaglandins, oxidative stress, levels of hormonal exposure, and insulin-adiposity interactions.

18.4.8 Obesity and Physical Activity

While obesity is more common in westernized than non-westernized societies, obesity rates vary by race and ethnicity. In the USA, 35.7 % of all adults were obese in 2009–2010, according to analyses of the National Health and Nutrition Examination Survey (Ogden et al. 2012). Obesity may be a risk factor for cancer incidence and mortality. This may in part be due to higher levels of circulating estrogens among those with a higher proportion of adipose tissue containing aromatase that contributes to an increased risk of hormone-dependent cancers (Key et al. 2003). However, the relationship is not consistent across all cancers. The risk of mortality due to ovarian cancer mortality has been shown to be higher among those with higher body mass index (a measure of body weight scaled to one's height) (Hoyo et al. 2005; Modesitt and van Nagell 2005; Zhang et al. 2005). Obesity and body fat distribution may increase risk for ovarian cancer, perhaps due to the effect of obesity on estrogen levels. Further, where the body fat is stored and the age at which obesity occurs may also be important in ovarian cancer risk. Women who have a high waist-to-hip ratio and a family history of ovarian cancer experience a 4.83-fold increased risk (95 % CI: 1.55–15.1) (Sellers et al. 1993). In another study, obesity was found to be associated with a slight decrease in survival of ovarian cancer patients; however, the findings were not definite (Protani et al. 2012). There remains conflicting evidence about the findings related to obesity, primarily because of the lack of control for potential confounding variables, such as surgical or treatment-related factors.

The role of physical activity and ovarian cancer risk is not understood. Physical activity has demonstrated a protective effect against ovarian cancer in studies, while had not demonstrated the same effect in others. A case-control study of women living in Pennsylvania, New Jersey, or Delaware (767 cases and 1,367 controls) found that leisure-time physical activity was associated with a reduction in the incidence of ovarian cancer ($p = 0.01$) (Cottreau et al. 2000). This association remained statistically significant even after controlling for tubal ligation, age, body mass index, family history, and OC use (OR = 0.73; 95 % CI: 0.56–0.94). After adjusting for age, parity, and other risk factors, a case-control study in Massachusetts and Wisconsin (327 cases and 3,129 controls) found no significant reduction in the incidence of ovarian cancer among women who participated in vigorous physical activity (RR = 0.85; 95 % CI: 0.39–1.86) (Bertone et al. 2002a).

18.5 Early Detection and Prevention of Ovarian Cancer

There are no population-based screening tests for ovarian cancer, and there are no known early detection strategies that are feasible to deliver to the general population. Screening for ovarian cancer is difficult because the disease is not highly prevalent in the general population (only 0.075 % of the US female population has been diagnosed with ovarian cancer) (Ries et al. 2004). An effective screening test for ovarian cancer would need to have a sensitivity of at least 80 % for early-stage, curable disease, a positive predictive value of at least 10 %, and, consequently, a specificity of over 99 % (Jacobs 1998). Prior to implementing a population-based ovarian cancer prevention program, the at-risk population needs to be defined. The focus is on screening the high-risk population due to the lack of effective population-based strategies. This can only be accomplished currently by questioning the patient about family history. Family history of ovarian cancer or early-age (e.g., premenopausal) breast cancer is associated with an increased risk of ovarian cancer. Since a small percentage of women with ovarian cancer have a positive family history for ovarian cancer (Schildkraut and Thompson 1988), genetic testing, while increasingly covered by health insurance providers, is still not universally available to patients. Furthermore, a mutation is only identified in approximately 10 % of patients referred for testing, additional methods must be developed to better identify women at increased risk of ovarian cancer.

A second major factor regarding the inability of the medical community to identify an effective early detection method is due to the lack of identification of a precursor lesion. Many other epithelial cancers (e.g., cervix, colon/rectum, endometrium) arise from precancerous lesions. For these cancers, progression is thought to occur in a stepwise, reversible pattern from a mildly dysplastic lesion (e.g., colorectal adenoma, hyperplasia without atypia, or mild dysplasia) to a highly dysplastic lesion (e.g., advanced colorectal adenoma with high-grade dysplasia, cervical intraepithelial neoplasia III, or complex hyperplasia with atypia) to carcinoma. Screening tests have been designed to identify and remove these precursor lesions (e.g., colonoscopy to remove an adenoma, colposcopy followed by loop electrosurgical

excision procedure, or LEEP, to remove cervical intraepithelial neoplasia) before they can become cancerous. There is increasing knowledge about the origin of ovarian cancers, but no such precancerous or intraepithelial lesion has yet been identified with clarity. Although research is moving forward to try to identify a molecular signature that may indicate the future development of cancerous cells (Jarboe et al. 2008), screening at this time can at best be developed to detect existing cancers.

Early detection tests have also not been successful due to the challenge of visualizing or palpating the ovary to detect growths. The ovary is located in the pelvis, closely surrounded by the bladder, uterus, and the rectum. It is not uncommon for an ovarian mass many centimeters in diameter to be completely undetectable to both patient and non-gynecologist physician without the utilization of advanced imaging technologies. Because of the nonspecificity of ovarian cancer symptoms, the work-up of patients later diagnosed with ovarian cancer is often left to the non-gynecologist. Pap smear, a test to detect cervical dysplasia, cannot detect ovarian cancer unless it has spread through the uterus down to the cervix (a very rare event) where it can be identified during cervical cancer screening.

Most imaging technologies currently available are also not well suited for the early detection of ovarian cancer. Those imaging approaches are still not optimal for detection of wide spread disease throughout the peritoneal cavity. Computed tomography (CT) (Anderson et al. 2004) scans and magnetic resonance imaging (MRI) are not sensitive enough for early detection of peritoneal disease (they generally cannot detect lesions less than one centimeter in diameter, especially in the pelvis), and as a result, they tend to have a high rate of false-negative results even among women undergoing evaluation for recurrence (van der Burg et al. 1993; De Rosa et al. 1995). CT scans are not sensitive enough for the detection of pelvic pathology, whether benign or malignant. Positron emission tomography (PET) scans are not standard of care in ovarian cancer, because of its cost and its high false-positive rate. The Risk of Malignancy Index (RMI) was first developed in 1990 to aid in the determination of malignancy from ultrasound imaging. RMI combines CA-125 and menopausal status with features from ultrasound evaluation to discriminate between a benign and malignant mass (Andersen et al. 2003; Geomini et al. 2009). Several versions of the RMI and adaptations have been used and evaluated and have shown to have moderate-high prognostic value (e.g., the RMI-III showed 79 % sensitivity and 81 % specificity with a cutoff score of 200). However, there remains no definitive way to rule out malignancy in the absence of pathologic evaluation.

Currently, the best imaging technology for patients with indications of ovarian cancer or other suspected pelvic diseases (e.g., fibroid tumor, pelvic inflammatory disease) is transvaginal ultrasound (TVUS), which can generally detect the presence of a mass in the correct hands (Fig. 18.3). TVUS has a calculated specificity and sensitivity of 98.7 and 85 %, respectively (van Nagell et al. 2007). This improvement over other imaging technologies is due to the fact that with transvaginal procedures the transducer is placed closer to the ovaries than is possible with abdominal ultrasound procedures (Takahashi et al. 1993). Unfortunately, the positive predictive value is low (22 %) even among those at high risk, as it is only able to detect

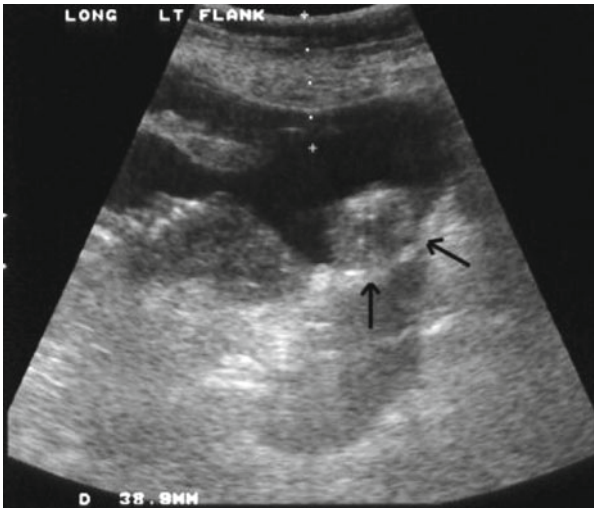

Fig. 18.3 Transvaginal ultrasound image of a complex ovarian mass (*arrow* indicates solid features)

structural abnormalities and is unable to differentiate benign from malignant conditions with accuracy. Furthermore, TVUS is unable to detect peritoneal cancers or cancers that do not affect ovary size or ovarian morphology.

18.5.1 CA-125

The CA-125 antigen is a reliable marker for initial disease progression or regression in approximately 80 % of advanced epithelial ovarian cancer cases (Gladstone 1994; Meyer and Rustin 2000). CA-125 levels are elevated in an estimated 40–60 % of patients with early-stage disease and are not elevated in patients with mucinous ovarian cancers and some high-grade cancers (Meyer and Rustin 2000; Kozak et al. 2003, 2005). For women diagnosed with ovarian cancer, CA-125 is measured each clinical visit to evaluate tumor response to therapy among patients who present with elevated CA-125 at the time of diagnosis (Verheijen et al. 1999). Despite its relative reliability in the established ovarian cancer patient, it is not a useful screening marker due to its lack of specificity. CA-125 levels fluctuate throughout menstrual cycle among premenopausal women (Bon et al. 1999) and are elevated in approximately 20 other benign conditions, some gynecologic and others non-gynecologic (Buamah 2000). CA-125 has only a 21–33 % positive detection rate when used as a screening tool in the general population (Jacobs et al. 1993; Hakama et al. 1996).

18.5.2 Screening Strategies in the Average Risk Population

Screening strategies have not been successful for use in the general population. Transvaginal ultrasound (TVUS) had been proposed because of its ability to

more closely visualize the ovaries than conventional abdominal ultrasound (DePriest et al. 1997), and CA-125 has been suggested as a potential early detection tool due to its value in monitoring disease status following diagnosis. However, these tests have demonstrated very high rates of false positives, leading to the conclusion that these screening strategies do more harm than good. The combination of TVUS and CA-125 in postmenopausal women improves the positive predictive value of screening to 26.8 % to up to 40 %, but still results in many false positives (Jacobs et al. 1993; Olivier et al. 2006). The addition of a pelvic exam (bimanual and rectovaginal examination) increases the likelihood of detecting advanced disease (Olivier et al. 2006). This combined screening strategy has not yet resulted in a reduction in mortality from ovarian cancer (USPSTF 2004). This screening strategy may include the use of imaging technologies when there is substantial risk of ovarian cancer and risk-reducing or exploratory surgery is not a reasonable or preferred option.

In 2011, the Prostate, Colorectal, Lung and Ovarian (PCLO) study investigated the effect of population-based CA-125 and TVUS screening on mortality outcomes from ovarian cancer (Buys et al 2011). In this study, 34,253 women were randomized to screening with TVUS and CA-125, and 34,403 were randomized to usual care. There were 3,497 abnormal findings from the TVUS/CA-125 screening which resulted in more than 1,000 surgical interventions that identified 212 cancers. This represents a positive predictive value of 23.5 % for the detection of invasive cancer. Additionally, there were no reduction in mortality with prospective screening as compared to those who did not receive annual screening (relative risk = 1.21, 95 % confidence interval 0.99–1.48), and there were no differences between groups with regard to stage at time of diagnosis (78 and 77 % of the cancers detected were stage III–IV in the screening and usual care groups, respectively).

Previous studies have found similar results with regard to population-based ovarian cancer screening strategies using CA-125 and TVUS. In 2005, Menon and colleagues tested the use of an algorithm (based on age and CA-125 values) as a screening strategy for early detection (Menon et al. 2005). In this study, 6,532 asymptomatic postmenopausal women were randomized to screening for ovarian cancer using this algorithm. Of these, 1,306 (20 %) were found to have abnormal results resulting in further follow-up testing, including TVUS evaluation. Of these, 65 women went on to surgery resulting in the identification of three invasive cancers. Therefore, the positive predictive value of screening according to this CA-125 algorithm was 19 % for the identification of invasive cancer and led to a CA-125 screening algorithm which was tested in a population of women at increased risk of ovarian cancer (Greene et al. 2008) (see Sect. 18.5.2).

In 2009, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study published its findings (Menon et al. 2009). In the UKCTOCS study, 202,638 postmenopausal asymptomatic women were randomly assigned to TVUS alone, TVUS plus CA-125, or no screening. Of the 50,078 randomized to the TVUS plus CA-125 screening strategy, 4,335 who were found to have abnormal results and went on for additional testing, 97 underwent surgical evaluation resulting in the detection of 42 cancers. An additional 48,230 women underwent annual TVUS. Of these, 5,889 were found to have abnormalities, resulting in 845 surgical

procedures to find 45 cancers. They found the positive predictive value of TVUS and TVUS plus CA-125 was determined to be 2.8 and 35.1 %, respectively.

Also in 2009, the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) published the results of their study which randomly assigned asymptomatic women to receive annual screening by TVUS plus CA-125 or usual care (Kobayashi et al. 2008). Only 27 cancer diagnoses resulted from annual screening of 41,668 women. There were no significant differences between the number of cancers detected, stage or grade at diagnosis, or histology between the screened and unscreened study groups.

These studies reaffirmed the 2004 US Preventive Task Force recommendation against the utilization of these screening strategies in a normal-risk, asymptomatic population (USPSTF 2012). The overall recommendation was that that the risk for unnecessary surgery was greater than the benefit from routine screening with CA-125 and TVUS. These studies further demonstrated that many health-care resources are consumed in the process of detecting ovarian cancer, including unnecessary surgical procedures. However, in the absence of any known effective ovarian cancer detection strategies, it is unclear how women in routine clinical care are diagnosed with this disease. The burden both in terms of time and health-care system resources remains unknown.

18.5.3 Screening Among Those at Increased Risk of Ovarian Cancer

Screening based on TVUS and CA-125 has been shown to be of more value in the postmenopausal, high-risk population (Skates et al 2011). Research is ongoing within the Gynecologic Oncology Group (protocol number GOG-0199) to compare cancer incidence between women at high risk of ovarian cancer who select screening with the ROCA (Risk of Ovarian Cancer Algorithm) as compared to those who choose RRSO (Greene et al. 2008), with final results pending data maturity in 2014. However, early analyses of data collected from the women on this study who selected surgery found that 3.2 % of women were found to harbor cancers (Mai et al. 2012). As these women were asymptomatic at the time of surgery, the findings suggest that symptoms may not be present early enough to aid in detection among women at increased risk of ovarian cancer. These findings also reinforce the current recommendations for prophylactic RRSO among women at increased risk of cancer after completion of childbearing and emphasizes the need for surgery to be performed by a gynecologic oncologist, as 12 of the 24 cancers detected were microscopic at the time of surgery (e.g., could not have been visualized or detected without thorough pathologic analysis). Currently, a combined strategy of TVUS, CA-125, and pelvic examination remains the recommended screening option for women at high risk of ovarian cancer who do not elect to undergo risk-reducing surgery. Unfortunately, despite progress with malignancy indices and biomarker research, at this time only surgery can determine with certainty if a woman has ovarian cancer or if an abnormality detected on imaging studies is benign or malignant.

18.5.4 Proteomics

Proteomics has been explored as potential screening tool for the detection of ovarian cancer. A variety of protein panels have progressed through various stages of development (e.g., Correlogic Systems, Ciphergen, Luminex, Mor, and Yale protein panels) (Kozak et al. 2003, 2005; Rapkiewicz et al. 2004; Mor et al. 2005; Cramer 2007; Fredriksson et al. 2008) with preliminary data, suggesting they may be at least 80 % accurate in the detection of ovarian cancer. However, these initial findings have not been realized in larger validation studies, with performance for early detection often falling short of CA-125 alone (Cramer et al. 2011). As the body of knowledge has expanded, there are now known to be more than 160 proteins that are shown to be more highly expressed in ovarian cancers compared to controls, reflecting the heterogeneity of this cancer (Nolen and Lokshin 2012). While initial results of these studies showed promise, none has yet demonstrated the necessary properties for validation trials, limiting the potential future commercialization of these protein-based screening assays.

18.5.5 Symptomatology

Although symptoms of ovarian cancer have been identified to occur in some patients later diagnosed with ovarian cancer, as discussed earlier, the identification of symptoms has not improved the early detection or survival of patients with ovarian cancer (Twombly 2007; Nagle et al. 2011). In most cases, women demonstrating these symptoms do not have ovarian cancer but have symptoms that result from other conditions. Because of the nonspecificity of the symptoms of ovarian cancer, women who are later diagnosed with ovarian cancer have often been misdiagnosed several times, told there was nothing wrong with them, or that the symptoms they have been feeling were normal throughout their experience until at some point an imaging or surgical procedure was performed leading to an accurate diagnosis (Hess et al. 2012). In addition to the lack of screening and early detection methods currently available, delays in diagnoses occur within the health-care system due to misinterpretation of symptoms. Only half of women later diagnosed with ovarian cancer in the Goff study (Goff et al. 2004) who went to their physicians complaining of symptoms received an accurate diagnosis within 3 months of their first health-care visit. Twenty-six percent (26 %) were diagnosed after 6 months, and 11 % were diagnosed after a full year. This and other studies suggest that improvements in the health-care delivery system may be needed to improve the outcomes of women who are diagnosed with ovarian cancer (Hess et al. 2012) and that additional work is needed to differentiate between patients with cancer and those with other disorders who have similar symptoms.

18.5.6 Risk Reducing Strategies

At this time, the only known way to significantly reduce the risk of ovarian cancer is by surgical approaches. Tubal ligation has been shown to decrease the risk of

primarily endometrioid carcinomas (Nagle et al. 2008). However, this approach would not be appropriate in women desiring future childbearing and does not appear to reduce the risk of the type II cancers, including the high-grade pelvic serous carcinomas. The primary surgical method offered to women at risk for "ovarian" cancer is prophylactic removal of the adnexa, including both ovaries and the fallopian tubes (salpingo-oophorectomy). Among women with *BRCA* mutations, prophylactic salpingo-oophorectomy reduces the risk of ovarian cancer by up to 95 % and, in premenopausal women, reduces the risk of breast cancer by up to 50 % (Kauff and Barakat 2007). During prophylactic salpingo-oophorectomy, the ovaries and as much of the fallopian tubes as possible are removed because of the risk of fallopian tube cancer, particularly in women at high risk, because the fallopian tube may function as a point of origin for ovarian cancer. The risk of fallopian tube malignancies is specifically elevated in women with *BRCA* mutations (Callahan et al. 2007). Surgery may also involve a hysterectomy (removal of the uterus). Women at high risk of ovarian cancer (e.g., *BRCA1/2* mutation, Lynch syndrome, family history) are the most likely to be offered the option of a prophylactic salpingo-oophorectomy plus hysterectomy (Rebbeck 2000; Chen et al. 2007). Removal of the uterus reduces the risk of type I endometrial cancer, which is elevated with hormone replacement therapy, which may be needed following oophorectomy (Kauff and Barakat 2007). Patients with *BRCA1/2* or Lynch type II mutations are already at increased risk of type I and II endometrial cancer (e.g., uterine papillary serous or clear cell cancers) (Lavie et al. 2004; Biron-Shental et al. 2006; Broaddus et al. 2006). The risk is exacerbated in tamoxifen users (Beiner et al. 2007). In addition to the enhanced risk of type I and II endometrial cancers, tamoxifen use also increases the risk of uterine-mixed mesodermal tumors (Kedar et al. 1994; Bergman et al. 2000). It is important to note that women who have had hysterectomies for other reasons generally do not have the ovaries removed, so hysterectomy alone cannot prevent the development of ovarian cancer. However, prior hysterectomy may reduce the risk of ovarian cancer by up to 40 % (Kjaerbye-Thygesen et al. 2006; Merrill 2006).

Although salpingo-oophorectomy can significantly reduce the risk of ovarian cancer, prophylactic surgery is unable to completely prevent the development of ovarian cancer. Cancer may still develop in the peritoneum at any time following surgical removal of normal-appearing ovaries, so it is not possible to assure that cancer has been prevented. Two to ten percent (2–10 %) of patients who undergo oophorectomy without any evidence of disease will still be diagnosed with ovarian or peritoneal cancer at some point following surgery (Tobacman et al. 1982; Piver et al. 1993). Furthermore, 9–17 % of patients at high risk have ovarian cancer detected incidentally during the risk-reducing surgical procedure (Morice et al. 1999; Leeper et al. 2002). Therefore, it is very important that prophylactic surgery be performed by a gynecologic oncologist to ensure that appropriate pathologic review of no larger than 2–3 mm sections of the ovary and fallopian tube is thoroughly completed to detect possible microscopic disease (SGO 2005). Despite its demonstrated effectiveness in early detection and reducing the risk of future cancers, surgery is not without risk. In addition to the general risks associated with pelvic surgery, removal of the reproductive organs in the premenopausal woman is associated with loss of fertility, induced menopause and its symptoms, and adverse effects (e.g., bone loss, hormonal changes).

18.6 Chemoprevention of Ovarian Cancer

The ability of OCs to prevent ovulation has resulted in their study as an ovarian cancer preventive agent. It is currently estimated that over 50 % of ovarian cancers could be prevented by long-term use (more than 5 years) of estrogen and progestin-containing OCs (Stanford 1991; Ness et al. 2000). An additional benefit of OC use may be an increased rate of progestin-induced apoptosis of aberrant epithelial cells as demonstrated in animal models (Rodriguez et al. 1998). However, OC use is contraindicated as women age (e.g., over age 40) due to the increased risk of venous thromboembolism and stroke, particularly among women who smoke. Additionally, OC use may be contraindicated in women at risk of breast cancer due to the slight but statistically significant increased risk of breast cancer among OC users (Narod et al. 2002). Therefore, it is of interest to assess the use of medications that target similar pathways at a lower risk of adverse effects to explore opportunities for the chemoprevention of ovarian cancer.

Due to the hormone receptors on the ovarian epithelium and based on the hormonal milieu theories of cancer initiation, a number of potential chemotherapeutic agents are under investigation for their role in ovarian cancer prevention. In animal models, progestins have been shown to induce apoptosis, to inhibit proliferation, and to upregulate TGF-β (Rodriguez et al. 1998). As compared to control and ethinyl estradiol-treated monkeys, a six-fold, statistically significant increase in apoptosis was noted in the ovarian epithelium of monkeys treated with levonorgestrel alone. The degree of apoptosis was not different between ethinyl estradiol-treated monkeys and controls. This demonstrated that exposure to the progestin component of oral contraceptives induced apoptosis in the ovarian epithelium (Rodriguez et al. 1998). The induction of apoptosis may also be the primary mechanism of action for a number of other proposed chemopreventive agents, such as the retinoids (Delia et al. 1993; Ponzoni et al. 1995; Toma et al. 1997), anti-inflammatory drugs (Thompson et al. 1997), and selenium (Thompson et al. 1994; el-Bayoumy et al. 1995).

In 2008, the Gynecologic Oncology Group (GOG) initiated a 60-participant study of the progestin levonorgestrel (GOG-214, "Phase II Double Blind Randomized Trial Evaluating the Biologic Effect of Levonorgestrel on the Ovarian Epithelium in Women at High Risk for Ovarian Cancer"). This study was designed to evaluate the ovarian and fallopian tube epithelium of women at increased risk of ovarian cancer who have decided to undergo prophylactic salpingo-oophorectomy. The ovarian and fallopian tube epithelia are obtained following 4–6 weeks of treatment with levonorgestrel or placebo at the time of surgery. Tissue will be evaluated to determine the relative frequency of apoptosis as well as proliferation and expression of TGF-β. Progestin is a risk factor for breast cancer; therefore, it is likely that this approach may not find universal acceptance among women with BRCA1/2 mutations, except at an early age.

Vitamin A and its derivatives (retinoids) have been evaluated as potential chemopreventive agents because of their ability to induce differentiation and inhibit cellular proliferation. Naturally occurring retinoids often require high doses and are associated with significant side effects; therefore, vitamin A analogs have been

developed. Fenretinide, *N*-(4-hydroxyphenyl)retinamide or 4-HPR, has been demonstrated to have antitumor activity in human ovarian cancer cell lines (Formelli and Cleris 1993). Further studies have demonstrated the antiproliferative and apoptotic effects of fenretinide (Supino et al. 1996). Clinical trial data from a chemopreventive study of women with early-stage breast cancer revealed a statistically significant decreased incidence of ovarian cancer in the fenretinide treatment group (De Palo et al. 1995). However, more recent trials (e.g., GOG-190, "An Exploratory Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Carcinoma") failed to accrue sufficient numbers of high-risk patients in part due to the fear of retinoid toxicity (e.g., night blindness), reducing the appeal of these agents as an acceptable strategy for the chemoprevention of ovarian cancer.

Nonsteroidal anti-inflammatory agents (NSAIDs), specifically cyclooxygenase-2 (COX-2) inhibitors due to the high COX-2 positivity in ovarian cancer tumors of patients who do not respond to chemotherapy (Ferrandina et al. 2002), may have a potential role in the chemoprevention of ovarian cancer. The biologic mechanisms may be related to immune enhancement, inhibition of COX, and inhibition of apoptosis associated with NSAID treatment (Rodriguez-Burford et al. 2002). An 18-patient cohort study failed to see significant reduction in serum VEGF following 3 months of celecoxib treatment, although the study was not randomized and was likely underpowered to detect statistical significance pre- and posttreatment (Barnes et al. 2005). Research to date has been inconclusive, with some preclinical studies demonstrating a possible protective effect, while case-control and cohort trials of NSAIDs and other analgesics (e.g., acetaminophen or paracetamol) have not consistently seen a protective effect (Cramer et al. 1998; Tavani et al. 2000; Fairfield et al. 2002; Friis et al. 2002). Other anti-inflammatory agents (e.g., omega-3 fatty acid) have been proposed as potential candidates for the chemoprevention of ovarian cancer; however, epidemiologic data have not provided evidence supporting their ability to protect against ovarian cancer (Bertone et al. 2002a, b; Larsson and Wolk 2005). A meta-analysis of NSAIDs and ovarian cancer risk did not find significant relationships with any medication other than aspirin, which demonstrated a reduced risk of ovarian cancer with a risk ratio of 0.88 (95 % CI: 0.79–0.98) (Baandrup et al. 2012). Prospective, adequately powered, randomized trials are needed to evaluate these agents for their potential use as chemopreventive agents in ovarian cancer.

Whether inherited or somatic, genetic mutations are necessary for cancer to develop. These mutations cause the turning on of oncogenes and/or turning off of tumor suppressor genes, which then cause a single cell to no longer follow the normal cellular cycle. Instead of normal apoptosis, a cancer cell will continue to split and divide, creating a population of genetically mutated cells. These cells can grow out of control until a tumor is visible. The hormonal, environmental, and inherited factors may simply be promoters or suppressors of a genetic mutation due to some other random or nonrandom factor or set of factors that have not yet been discovered. Therefore, current ovarian cancer chemoprevention strategies are based on identifying and impacting hormonal and molecular targets. Much work has yet to be done to understand the mechanisms by which these agents may act on the ovarian epithelium and to identify appropriate biomarkers for clinical chemoprevention research trials.

18.7 Quality of Life

Premenopausal women at risk of ovarian cancer who elect prophylactic oophorectomy will reduce their risk of ovarian and breast cancer. Surgery should be planned at least a decade prior to the time when ovarian cancer would be expected to develop yet must be postponed until the patient is no longer interested in childbearing. Early removal of the ovaries will cause premature menopause due to the sudden loss of estrogen. Women who undergo premature menopause as a result of surgery that results in the removal of both ovaries are usually younger than women who undergo natural menopause; these younger women may experience hot flashes or night sweats that are more bothersome than those that occur at the time of natural menopause. The symptoms of menopause can be mild to severe and can include a variety of symptoms that can affect quality of life and sexual functioning. For most women, these symptoms will resolve over a period of several years, but in a small minority of women (10–15 %), the symptoms may persist for extended periods of time (Tice and Grady 2006). A questionnaire study of 846 patients who had undergone risk-reducing oophorectomy showed that the participants had decreased concerns regarding cancer risks, but increasing symptoms of menopause and sexual dysfunction. Despite this, 86 % of responders would choose to undergo the procedure again (Madalinska et al. 2005). Even if these symptoms are short-lived, they can have a significant impact on patient quality of life. Many women who experience early menopause experience vaginal dryness as a result of the loss of estrogen that had been produced by the ovaries. As estrogen decreases, the walls of the vagina become thinner and more fragile, and vaginal pH level may increase. Vaginal dryness can range from a mild annoyance to having a significant negative impact on sexual functioning, ability to sleep, and overall quality of life.

Many women opt to manage hot flashes with hormone therapy; however, there is the possibility of increasing risk of cancer with these medications with long-term (Anderson et al. 2004) but not necessarily short-term use (Rebbeck et al. 2005). For patients who are already at risk of these cancers, it is prudent to treat mild menopausal symptoms with nonhormonal alternatives. More severe symptoms may require short-term hormone use, depending on the individual patient's risk. Prospective research has suggested the safety of short-term HRT (e.g., 1–2 years) regarding cancer risk among *BRCA1/2* mutation carriers following prophylactic oophorectomy (Armstrong et al. 2004; Rebbeck et al. 2005). The benefit of improved quality of life following oophorectomy with HRT may greatly outweigh any potential risk of short-term use. The decision to use HRT or ERT should be based on the severity of patient symptomology and patient-provider discussion about the possible risks and benefits of HRT or ERT as well as other therapies available for menopausal symptoms.

Suggested alternatives are summarized in Table 18.3. As with any medication or treatment, there are benefits and risks that should be discussed between patient and provider. These are only summarized below and do not represent all possible benefits or risks. Not all of the suggestions provided have been clinically proven to

Table 18.3 Selected nonhormonal alternatives for the management of the symptoms of menopause

Medication	Benefits	Risks
Selective serotonin reuptake inhibitors (SSRIs)	SSRIs have been shown to substantially decrease hot flash frequency and severity. Typically, short-term use (1 or 2 weeks) is sufficient to determine if an SSRI is going to be beneficial. More prolonged therapy is generally required to obtain maximum symptom control	Restlessness, fatigue, dry mouth, decreased appetite, constipation, difficulty sleeping, and nausea. Side effects are greater at higher medication doses
Gabapentin	Reported to decrease hot flashes	Side effects may include light-headedness, mild swelling of the ankles, or difficulty achieving orgasm
Clonidine hydrochloride	Decreases hot flashes. It may be an appropriate second-line treatment for women who decline or cannot tolerate SSRI treatment	Side effects may include dry mouth, dizziness, drowsiness, tiredness, light-headedness, constipation, decreased sexual desire, lethargy, low blood pressure, and difficulty sleeping. Some patients find it difficult to take this medication over a long period of time. Among women participating in clinical trials of clonidine, there have been high dropout rates because of its numerous side effects
Belladonna-phenobarbital-ergotamine preparations	Belladonna is reported to decrease hot flashes and is an FDA-approved treatment for menopausal symptoms	This combination medication has the potential for abuse and addiction because it contains a barbiturate. It may be difficult to take during the day because of its sedative effect. Side effects include dry mouth, dizziness, and sleepiness

(continued)

Table 18.3 (continued)

Medication	Benefits	Risks
Phytoestrogens	A recent combined analysis of published randomized controlled studies of isoflavones showed no benefit related to the red clover-derived preparations and provided mixed evidence regarding the effectiveness of the soy-derived preparations, although the benefits from soy are smaller than those seen with HRT (Nelson et al. 2006). Other experts, reviewing these and additional data, have concluded that the overall evidence does not show benefit from phytoestrogens in the treatment of hot flashes (Tice and Grady 2006). Dietary phytoestrogens, such as black cohosh, may be effective to treat menopausal symptoms and are not associated with an increased breast cancer risk (Rebbeck et al. 2007)	Side effects were similar between subjects taking phytoestrogens and those taking placebo in several clinical trials. Although these are considered to be benign, natural, herbal preparations, they do in fact have at least some estrogen-like biologic effects. It is possible that estrogen-like side effects might occur as well. The majority of studies support that these plant-based weak estrogens may not increase risk for breast or ovarian cancer, but the data is not definite
Vitamin E	Vitamin E was associated with one less hot flash/day in one study. This difference was statistically significant, but is unlikely to be of clinically meaningful	The long-term safety of vitamin E intake is unknown, but doses within USDA guidelines have not shown toxicity
Relaxation techniques	Relaxation techniques, including yoga, massage, meditation, leisure bath, and slow, deep, paced respiration, may provide some relief of hot flashes	No known risks
Kegel exercises	Kegel exercises are used to strengthen the muscles of the pelvic floor. These exercises, when done regularly, can increase sensation in the pelvic area and strengthen the muscles that support the bladder	No known risks, but may be only minimally effective
Moisturizers and lubricants	Moisturizers can be used for everyday dryness and during foreplay. *Replens* is a gel that is inserted into the vagina and lasts for 3 days. *Gyne-Moistrin* is another commonly used vaginal moisturizer. To reduce discomfort during sex, couples should use lubricants before vaginal penetration. Water-soluble (not oil-based) lubricants should be used. Examples of these include *KY Jelly*, *Ortho Personal Lubricant*, *Astroglide*, and *ForPlay*. Other useful lubricants include *Lubrin vaginal suppositories* or *Lubafax*, which can be inserted about 5 min before intercourse. Some women also have found that *Vitamin E oil* is useful. Vitamin E capsules can be broken open, and the oil applied directly to the vagina. Vitamin E oil should be applied once a day for 1–2 weeks, then applications should decrease to one or two times per week	No known risks

reduce the symptoms of menopause. Other methods to control the symptoms of menopause include:

- Keeping a diary of when hot flashes and night sweats occur. This will help identify triggers to their occurrence or times when medication loses its effectiveness.
- Keeping the body temperature cool by dressing in layers, using a fan, choosing cold food and drinks, and sleeping in a cool room
- Exercising regularly. Physically active women report fewer hot flashes than do sedentary women.
- Do not smoke.
- Eating a healthy diet and avoiding dietary triggers to hot flash occurrence (such as spicy/hot foods, caffeine, and alcohol).
- Short-term use of hormone replacement therapy has not been associated with an increased risk of cancer (Rebbeck et al. 2005); in some cases, the benefit of improved quality of life with HRT may outweigh the potential risk.

Conclusion

There is a great deal of work yet to be done to develop effective screening modalities for ovarian cancer. It is unclear where or how ovarian cancer develops (e.g., likely a subset arises in the fallopian tube), which is a critical piece of knowledge needed to develop appropriate and effective screening methods for this disease. However, with what is known at this time, the risk of ovarian cancer can be reduced by hormonal manipulation (e.g., oral contraceptive use, multiparity) during the early to middle reproductive years. Maintaining a healthy lifestyle through diet and exercise may also reduce ovarian cancer risk. It is very important that appropriate steps be taken to determine a patient's risk of ovarian cancer. Patients who may be at high risk should be referred to a high-risk clinic and to a genetic counselor for appropriate management. Nutritional and lifestyle counseling are also likely to be beneficial to patients at high risk. The consideration of risk-reducing salpingo-oophorectomy (RRSO) should involve consultation with a gynecologic oncologist and depends on the patient's individual level of risk and completion of all childbearing. For patients at high risk who do undergo RRSO, there is a need to address the quality of life issues that are associated with removal of the ovaries and premature menopause and to be cautious about managing risk of other cancers (e.g., breast, endometrial).

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Endometrial Cancer Prevention

19

Mario M. Leitao Jr. and Richard R. Barakat

19.1 Epidemiology of Endometrial Cancer

Uterine cancer, which carries a higher risk in developed countries, affects approximately 280,000 women worldwide annually (Jemal et al. 2011). The age-standardized rate per 100,000 women is 12.9 in developed areas compared to 5.9 in less developed areas, suggesting some potential environmental influences on the development of the disease (Jemal et al. 2011). Uterine cancer is the most common malignancy of the female genital tract and the fourth most common malignancy overall in women in the USA, with an estimated 50,000 new cases and 8,000 deaths in 2012 (Siegel et al. 2012). The annual incidence rate of uterine cancer has been relatively stable over the last 30 years (Siegel et al. 2012).

The majority of uterine cancers (>90 %) are endometrial carcinomas (Kosary 2007), which are the focus of this chapter. The median age at diagnosis is in the mid 60s, but approximately 3–8 % of cancers will be diagnosed in women less than 40 years of age (Wright et al. 2009). The most common histology is endometrioid, and the majority of patients present with organ-limited disease (>70 %). There are, however, racial disparities in terms of histologic and stage distributions, as well as survival (Kosary 2007; Wright et al. 2009). Endometrial cancers appear to primarily affect white women. Black women accounted for only 7 % of all cases entered in the Surveillance, Epidemiology and End Results (SEER) database (Wright 2009). Black women, however, present with higher risk histologies and later stage at presentation compared to white women. Serous carcinomas accounted for 12 % of all cases in black women compared to only 5 % in white women (Wright et al. 2009).

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19.2 Endometrial Carcinoma Precursors

19.2.1 Atypical Endometrial Hyperplasia

Atypical endometrial hyperplasia (AEH) is considered a precursor to endometrial carcinoma. Kurman et al. retrospectively reviewed 170 untreated patients with any degree of endometrial hyperplasia for at least 1 year (Kurman et al. 1985). The risk of progression to carcinoma was 1 % for simple hyperplasia, 3 % for complex hyperplasia, 8 % for simple AEH, and 29 % for complex AEH. The risk for simple atypical versus complex atypical hyperplasia was not statistically different. The most important determinant of risk for progression to carcinoma was the presence of cytologic atypia, with only 2 % of hyperplasias without atypia versus 23 % of atypical hyperplasias progressing to carcinoma. Degrees of atypia, epithelial stratification, and mitotic activity did not predict progression. The time to progression from hyperplasia to carcinoma is long for both non-atypical and atypical hyperplasias, with median times of 9.5 and 4.1 years, respectively. All but one of the 13 patients who eventually developed carcinoma were diagnosed with stage I disease. All 13 patients, including one with stage IV disease, were alive without evidence of disease 4–25 years after definitive therapy. Detection of this precursor lesion allows for significant intervention in preventing endometrial carcinoma and disease-associated death.

There is also risk of having an underlying "occult" carcinoma once a diagnosis of hyperplasia is made. The Gynecologic Oncology Group (GOG) conducted a large prospective trial in patients with AEH (Trimble et al. 2006; Zaino et al. 2006). Patients with AEH on a preoperative endometrial biopsy underwent an immediate hysterectomy, and the findings in the uterus were analyzed to determine the rate of underlying carcinoma (Trimble et al. 2006). A total of 289 cases with a referring GOG institution diagnosis of AEH in the endometrial biopsy specimen were analyzed in this prospective series (Trimble et al. 2006). Carcinoma was diagnosed in the hysterectomy in 123 (43 %) of the 289 cases. Of these 123 cases with cancer in the hysterectomy, most (115/123 [94 %]) were International Federation of Gynecology and Obstetrics (FIGO) grade 1. Myoinvasion was seen in 18/123 (30.6 %) cases. The authors defined "high-risk" cancer cases as those with any myoinvasion or grade 2/3 lesions. "High-risk" lesions, according to these criteria, were seen in 43 (35 %) of 123 cases. Patient age was significantly associated with a "high-risk" cancer being found in the hysterectomy but not time from biopsy to hysterectomy. However, if "high risk" is defined as cases in which the risk of nodal spread is of concern (i.e., tumors with myoinvasion and grade 2 or 3 or tumors with deep myoinvasion of any grade) (Leitao et al. 2008, 2009), then only 16 (14 %) of the 118 cancer cases would be of concern and possibly necessitate treatment beyond just a simple hysterectomy. Overall, this would translate into approximately 6 % (i.e., 14 % of 43 %) of all AEH patients needing either lymphadenectomy or other adjuvant therapy.

19.2.2 Endometrial Intraepithelial Neoplasia

Endometrial intraepithelial neoplasia (EIN) has been reported to more accurately predict for an underlying carcinoma and may more likely be a true precursor entity (Baak et al. 2005; Hecht et al. 2005). Ideally, all examples of EIN should be AEH, but not all cases diagnosed as AEH would be EIN. In practice, strict application of EIN criteria sometimes results in disordered proliferative endometrium, a physiologic variant of normal in the perimenopausal state, and benign papillary change being categorized as EIN. This EIN classification system is based on a D-score (DS), which takes into account glandular volume, architectural complexity, and nuclear abnormality, and is facilitated with computer software (Baak et al. 2005; Hecht et al. 2005). EIN is diagnosed if DS <1. In a large multicenter retrospective review, EIN seemed to be the strongest predictor of a future diagnosis of carcinoma (Baak et al. 2005). However, this requires further validation in a prospective fashion.

19.2.3 Treatment of Endometrial Hyperplasia

The risk of underlying carcinoma is low in patients with endometrial hyperplasias lacking atypia. A conservative approach is preferred, especially if a patient desires fertility preservation. Weight loss alone may reverse the process. If a patient remains relatively asymptomatic, then close observation without any medical or surgical intervention may be sufficient. Hormonal medications, or possibly a progesterone-containing intrauterine device, may be considered in patients with excessive vaginal bleeding. Hysterectomy is also a reasonable option in postmenopausal women, or in women who have completed childbearing, if they do not desire a more conservative approach.

In postmenopausal women and those in whom childbearing is no longer an issue, hysterectomy is the preferred choice of treatment for all atypical hyperplasias. Removal of both tubes and ovaries is not necessarily required, especially in premenopausal women. Removal of both ovaries in patients without a known gynecologic malignancy may result in increased overall morbidity and mortality in women under the age of 50 (Parker et al. 2009). Therefore, the risks of bilateral oophorectomy must be weighed against the risk of an underlying carcinoma that may require additional surgery to remove the ovaries afterwards. A simple hysterectomy with or without removal of the ovaries and without lymphadenectomy seems to be the most appropriate surgical treatment for AEH. Patients should be informed that additional surgery or therapy may be required in certain situations in which an underlying carcinoma is identified.

In young premenopausal women with AEH who desire future fertility, hysterectomy is not an acceptable option, and a conservative approach may be considered. Also, some patients are simply not fit to undergo any surgical procedure. The most commonly used agents for treating AEH are progestational. In morbidly obese patients, significant weight loss may reverse AEH and, therefore, prevent the development of endometrial cancer, but this remains to be determined.

19.3 Risk Factors and Preventive Strategies

19.3.1 Obesity

The most identifiable and proven risk factor for endometrial hyperplasias and carcinomas is obesity. While obesity is considered a modifiable risk, it remains a challenging health problem, with approximately one-third of Americans being obese (Ogden et al. 2012). Encouraging weight loss is a simple recommendation; however, alternative preventive strategies are being proposed to potentially modify the risk of endometrial carcinoma development in women who continue to struggle with obesity.

The prevalent explanation for obesity's association with increased endometrial cancer risk is the increased rate of conversion of androstenedione to estrone in adipose cells (MacDonald et al. 1978). Aromatase cytochrome P450 is mainly responsible for estrogen biosynthesis and is expressed in a number of tissues, such as the ovaries and testes, but also in adipose tissue (Simpson et al. 2002). There is a complex signaling pathway that stimulates aromatase expression in human adipose stromal cells (Fig. 19.1). This signaling pathway involves class I cytokines, TNFα, and glucocorticoid stimulatory signals. These signals are then mediated via a JAK1/STAT3 pathway. Aromatase is actually expressed in the stromal mesenchymal cells or preadipocytes and not the adipocytes themselves, and various stimulatory as well as inhibitory signals exist (Simpson et al. 2002). These complex interactions likely explain why some obese women develop endometrial cancer and others do not. Aromatase is found in many other tissues, and dysregulations of components of the above signaling pathways may explain why some nonobese women develop endometrial cancer. The various components of this pathway provide interesting potential therapeutic and preventive targets. There are also other peptides and substances secreted by adipose tissue that may potentially increase the risk of developing endometrial cancer.

The Women's Health Initiative (WHI) consisted of an observational study and three clinical trials assessing dietary modifications, hormone therapy, and calcium/vitamin D supplementation in affecting various health outcomes in the USA (The WHI Study Group 1998). Data from this large landmark study were used to assess the correlation of obesity and waist-hip ratio (WHR) to the development of endometrial cancer (Reeves et al. 2011). Data from more than 86,000 women were used and included more than 800 incident cases of endometrial cancer. A body mass index (BMI) $\geq$30 kg/m^2 was associated with a modeled hazard ratio (HR) of 1.68 (95 % CI, 1.33–2.13) of developing endometrial cancer, referenced to a BMI <25 and adjusting for other variables as well as WHR (Reeves et al. 2011). On the other hand, increased WHR was not associated with an increased risk of endometrial cancer when adjusted for BMI. Of note, increasing BMI was not associated with a higher grade, higher stage, or histology in those patients who developed endometrial cancer (Reeves et al. 2011).

In a smaller study from the USA, BMI $\geq$35 kg/m^2 was associated with an adjusted odds ratio (OR) of 3.40 (95 % CI, 1.18–9.78) for developing endometrial cancer

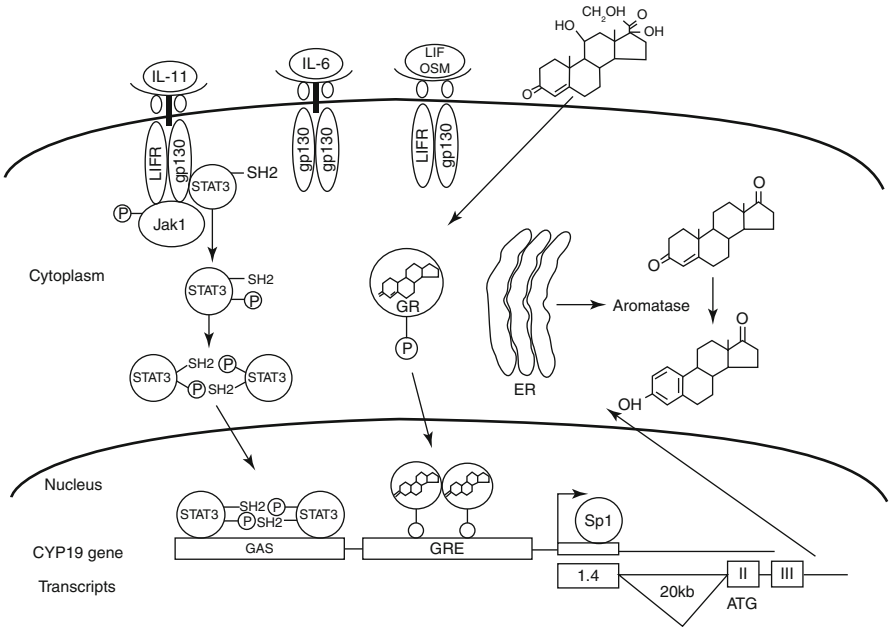

Fig. 19.1 Aromatase expression in human adipose stromal cells. Schematic representation of second messenger signaling pathways whereby class I cytokines stimulate aromatase gene expression in human adipose stromal cells. Jak1 kinase is bound to the common receptor subunit gp130 and activated following ligand binding and receptor dimerization, as a consequence of phosphorylation on tyrosine residues. STAT3 is recruited to binding sites on gp130 and is phosphorylated on tyrosine residues by Jak1. These phosphotyrosine residues are recognized by SH2-homology domains on STAT3, resulting in dimerization followed by translocation to the nucleus and binding to the GAS element of promoter I.4 of the aromatase gene. Following binding of glucocorticoid receptors to the GRE and Sp1 to its site on untranslated exon on I.4, activation of transcription of the aromatase gene from promoter I.4 is initiated. Splicing of the initial transcript results in formation of mature mRNA, which translocates to the ribosomes and is translated to give rise to aromatase protein. *GR* glucocorticoid receptor, *ER* endoplasmic reticulum (With permission from Simpson et al. (2002))

after a prior benign endometrial biopsy (Torres et al. 2012). A personal history of a hereditary nonpolyposis colorectal cancer (HNPCC)-related malignancy and the presence of a polyp on prior benign biopsy were also independently associated with an increased risk. Use of oral contraceptives was found to be protective, with an adjusted OR of 0.18 (95 % CI, 0.08–0.45). Torres and colleagues also demonstrated that the presence of two or more risk factors (lack of oral contraceptive use, presence of polyp in prior biopsy, personal history of HNPCC-associated malignancy, or BMI ≥35) was associated with a nearly 18-fold increased risk of endometrial cancer (Torres et al. 2012). This study provided additional risk factors and also suggested that oral contraceptive use may be protective, but this requires further prospective validation.

A BMI ≥30 kg/m^2 was associated with a 4.5-fold increase in the risk of endometrial cancer in the Netherlands Cohort Study, which analyzed 226 cases of endometrial

cancer matched to 1,739 controls (Schouten et al. 2004). The risk of endometrial cancer was increased even in patients deemed overweight (BMI 25–29.9 kg/m^2) in this study. These investigators also noted that BMI at the age of 20 was associated with an increased risk of endometrial cancer in the future. Additionally, a gain in BMI from the age of 20 significantly increased the risk, whereas a decrease in BMI was protective (Schouten et al. 2004). In a Swedish population-based study, obesity was not associated with cancer development overall (Attner et al. 2012); however, it was significantly associated with the chances of being diagnosed with endometrial cancer.

The increased level of estrogens is one of the main reasons for the increased risk of endometrial cancer in obese patients, but there are other factors that may potentially modify this risk. BMI is associated with levels of CA-125, CA15-3, E-selectin, resistin, adiponectin, IL-8, IGFBP-1, SHBG, leptin, and insulin, among others (Villavicencio et al. 2010; Linkov et al. 2012). Compared to normal-weight cases, obese women will have increased levels of serum estradiol (E2), estrone (E1), leptin, and insulin (Villavicencio et al. 2010). Total androgen levels are unchanged, but the free androgen index is increased in obese patients. The E2 and E1 to progesterone serum ratios are also elevated in obese patients. There is a decrease in SHBG, which likely explains the increased free androgen index and further releases available estrogens (Villavicencio et al. 2010). Markers of increased cellular proliferation, such as ki67 and p-H3, are increased in normal endometrial cells in overweight and obese patients compared to normal-weight patients (Villavicencio et al. 2010). Increased phosphorylation of AKT, ERK1, and ERK2 is also seen in normal endometrial cells from overweight and obese patients (Villavicencio et al. 2010).

Leptin and adiponectin are hormones primarily secreted by adipose tissue and appear to play an important role in the development and progression of endometrial cancer. Leptin is a hormone mainly secreted by adipose tissue and is involved in multiple cellular processes (Catalano et al. 2009). Leptin has also been implicated in growth stimulation, migration, invasion, and angiogenesis in tumor cells (Garofalo and Surmacz 2006). Catalano and colleagues provided evidence that leptin enhances cyclin D1 expression through STAT3 and CREB signaling, leading to the development and progression of endometrial cancer (Catalano et al. 2009). Adiponectin is one of the most abundant serum proteins. Adiponectin levels are inversely correlated with BMI and central obesity (Moon et al. 2011). Adiponectin improves insulin sensitivity, and low levels are associated with the development of metabolic syndrome, type II diabetes mellitus, atherosclerosis, and nonalcoholic fatty liver. Moon and colleagues demonstrated that adiponectin is also involved in cellular proliferation in endometrial cancer cells through its receptors, AdipoR1 and AdipoR2 (Moon et al. 2011). Endometrial cancer tissues seemed to have a higher rate of absent AdipoR1 expression compared to normal endometrial tissue. Adiponectin administration at high concentrations decreased cellular proliferation by 45 % in KLE and RL95-2 endometrial cancer cell lines (Moon et al. 2011). The antiproliferative effects of adiponectin administration were reduced with siRNA silencing of AdipoR1 and AdipoR2 in these cell lines.

Table 19.1 Criteria for the diagnosis of metabolic syndrome

Central obesity as measured by population- and country-specific definitions for elevated waist circumference
Elevated serum triglycerides (≥150 mg/dl)[a]
Reduced serum HDL cholesterol (<40 mg/dl [males]; <50 mg/dl [females])[a]
Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg)[a]
Elevated fasting glucose (≥100 mg/dl)[a]

Modified from reference Alberti (2009)
Require 3 of the above 5 risk factors to establish clinical diagnosis of metabolic syndrome
[a]Drug treatments for elevated triglycerides, reduced HDL cholesterol, hypertension, and elevated glucose can serve as an alternative indicator for the specific criteria

19.3.2 Metabolic Syndrome

Diabetes, hypertension, and lipidemia have been suggested to independently increase the risk of endometrial cancer (Soler et al. 1999; Weiderpass et al. 2000; Anderson et al. 2001); however, this association has not been proven, and large series have reported a lack of association. A large population-based Swedish study showed diabetes was associated with an increased risk of cancer overall (Attner et al. 2012), but not endometrial cancer specifically. Blood lipid levels also were not associated with an increased risk. Torres and colleagues also reported that diabetes and hypertension are not associated with increased endometrial cancer risk (Torres et al. 2012). A recent publication using the Swedish AMORIS database comparing 1,144 endometrial cancer cases to 224,288 non-endometrial cancer cases reported no association of the following serum lipid levels with an increased risk of cancer: total cholesterol, LDL cholesterol, HDL cholesterol, apolipoprotein B, apolipoprotein A-I, total cholesterol/HDL ratio, LDL/HDL ratio, or apoB/apoA-I ratio (Seth et al. 2012). However, serum triglyceride levels >0.9 mmol/l were associated with an increased endometrial cancer risk. It remains unclear whether diabetes, hypertension, or serum lipid levels independently increase the risk for endometrial cancer. It is more plausible that a combination of metabolic derangements increases the risk of endometrial cancer development. This combination of metabolic alterations may also further explain why only certain obese women will actually develop endometrial cancer.

Metabolic syndrome is a grouping of risk factors for cardiovascular disease and diabetes, whose exact pathogenesis remains unknown (Alberti et al. 2009). The factors included in the criteria include dysglycemia, elevated blood pressure, elevated triglyceride levels, low HDL cholesterol levels, and central obesity (Table 19.1). Central obesity is no longer a prerequisite but is a valuable screening tool. The diagnosis of metabolic syndrome can be made in the presence of three of the five harmonized criteria listed in Table 19.1 (Alberti et al. 2009). Therefore, a normal-weight person may be diagnosed with metabolic syndrome. The prevalence of metabolic syndrome using these criteria is approximately 40 % among women in the USA (Alberti et al. 2009). Metabolic syndrome is associated with an increased endometrial cancer risk and may provide some suggestions for optimizing endometrial

cancer risk reduction (Cust et al. 2007; Bjorge et al. 2010; Friedenreich et al. 2011; Rosato et al. 2011).

A recent case-control, population-based study demonstrated that metabolic syndrome, defined by the criteria above, was significantly associated with the risk of endometrial cancer development and more so than any of the individual criteria (Friedenreich et al. 2011). Five hundred and fifteen cases of incident endometrial cancer were matched to 962 controls. The overall multivariable-adjusted OR was 1.66 (95 % CI, 1.26–2.19). When stratified by BMI, the diagnosis of metabolic syndrome was not associated with an increased risk in normal-weight (BMI <25) cases, but this analysis only contained 17 cases and 29 controls. Waist circumference >88 cm was associated with an increased risk in this normal-weight cohort, but there were only 6 cases and 3 controls in this subgroup. Overall, metabolic syndrome was rare in this group of normal-weight women (46/406 [11.3 %]), and the risk stratification in this group of women remains to be determined. In overweight and obese women, metabolic syndrome diagnosis retained an independent association with endometrial cancer risk. Waist circumference and hypertension also were significantly associated but to a lesser degree. This study provides insight into further risk stratification beyond merely the presence of obesity.

Similar findings of an increased risk of endometrial cancer with the diagnosis of metabolic syndrome have been reported in other relatively large series (Cust et al. 2007; Bjorge et al. 2010; Rosato et al. 2011). Most suggest that the presence of metabolic syndrome is of greater concern in an obese population. The risk also increases as the number of applicable criteria for metabolic syndrome increases (Bjorge et al. 2010). The diagnosis of metabolic syndrome may offer better targeted screening, preventive, and therapeutic interventions.

19.3.3 Weight Loss

Obesity is clearly an established risk factor for endometrial cancer. The most obvious preventive strategy is to maintain a normal weight and healthy lifestyle or to lose weight, which would decrease one's risk of developing metabolic syndrome. Weight loss measured as a decline in BMI since age 20 resulted in a 50 % reduction in the risk of endometrial cancer (OR, 0.50 [95 % CI, 0.25–0.97]) in the Netherlands Cohort Study on Diet and Cancer (Schouten et al. 2004). Total baseline non-occupational physical activity of at least 60 min/day was also associated with a significantly decreased risk compared to less than 30 min/day (Schouten et al. 2004). The risk reduction was approximately 40 % even when adjusted for other variables, including BMI. The overall extent of daily physical activity among postmenopausal women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort was also associated with a decreased endometrial cancer risk (Patel et al. 2008). However, this association was not retained once adjusted for BMI. Interestingly, consistently high levels of long-term exercise did retain an independent association with risk reduction (RR, 0.75 [95 % CI, 0.56–0.99]). This was defined as self-reported high levels of exercise in 1982 and again in 1992 in the same person.

Many patients who struggle with obesity go through multiple cycles of weight loss followed by regaining of the lost weight throughout their lifetime. There is concern that this type of weight cycling may increase the risk of endometrial cancer in addition to not improving or actually even worsening other health concerns. Results from the CPS-II Nutrition Cohort demonstrated that such weight cycling is not associated with an increased risk of developing endometrial cancer (Stevens et al. 2012b). Weight cycling was defined as losing at least 10 lb followed by regaining the previously lost 10 lb. The RR of endometrial cancer in the highest cycling group (≥10 cycles) was 1.05 (95 % CI, 0.77–1.42) (Stevens et al. 2012b). Weight loss should still be encouraged, without concern for the inevitable weight gain that many will suffer.

Weight loss is also associated with beneficial alterations in cancer-associated biomarkers. Serum levels of various biomarkers were assessed amongst participants enrolled in the University of Pittsburgh Re-Energize with Nutrition, Exercise, and Weight Loss (RENEW) study (Linkov et al. 2012). Participants lost a mean of 12.8 kg from baseline in this study. At 12 months from baseline, serum levels of E-selectin, VEGF, IL-6, IL-7, and CA-125 decreased. Serum levels of GH, adiponectin, and IGFBP-1 increased. The RENEW study demonstrated that weight loss can be accomplished using an effective intervention and can lead to significant changes in serum biomarkers thought to be associated with cancer development.

19.3.4 Bariatric Surgery

Achieving sustained and healthy weight loss through diet and exercise is often a difficult, lengthy process, and alternative strategies are available. One such strategy, bariatric surgery, is quite expensive and is associated with potential morbidities. However, it may be a consideration and an appropriate, health-improving strategy in appropriately selected and counseled patients who simply cannot lose weight with other nonsurgical approaches.

McCawley and colleagues retrospectively analyzed a cohort of 1,482 women who underwent various bariatric procedures over a 16-year period at their institution (McCawley et al. 2009). The most common invasive cancers among the 53 cancers diagnosed were breast ($n=15$) and endometrial ($N=9$). Of the 9 endometrial cancer cases, all but one were diagnosed before a bariatric procedure. The authors commented that bariatric surgery was associated with beneficial improvements in baseline metabolic derangements.

In contrast, a much larger series from a Swedish, population-based cohort study of obesity surgery did not find a decreased risk of obesity-related cancers after the surgery (Ostlund et al. 2010). Incident obesity-related cancers were diagnosed in 296 patients among a total of 13,123 obesity surgery patients in the cohort. There were 54 endometrial cancers in this cohort for a standardized incidence ratio (SIR) of 2.15 (95 % CI, 1.62–2.81) overall compared to the background Swedish population (Ostlund et al. 2010); this is consistent with the fact that obesity increases the risk of endometrial cancer. However, there was no reduction in the SIR after obesity

surgery with increasing follow-up. Indications for bariatric procedures should be based on other established criteria, and it cannot be recommended as an endometrial cancer risk-reducing strategy at this time.

19.3.5 Endometrial Cancer Screening

Screening obese women for endometrial cancer and its precursor lesions is theoretically reasonable considering their increased risk, with the thought that early detection and treatment of precursor lesions would prevent the subsequent development of endometrial cancer. It may also help detect endometrial cancer at a very early stage. However, there is limited data to support such an approach. Fortunately, women who develop endometrial hyperplasias or cancer will often be symptomatic in terms of abnormal vaginal bleeding patterns. Therefore, any change and/or "abnormal" vaginal bleeding patterns in obese women should prompt immediate diagnostic evaluation. On the other hand, routine screening with transvaginal ultrasound (TVUS) and/or endometrial biopsy in asymptomatic obese patients needs further investigation.

Endometrial screening is not recommended in the general population but is a recommendation in women with Lynch syndrome who desire uterine preservation (Lindor et al. 2006; Vasen et al. 2007). Women from Lynch kindred have a much greater risk of developing endometrial cancer compared to obese women. Further description of hereditary predispositions for endometrial cancer will be discussed later in this chapter. Kwon and colleagues performed Markov decision-analytic modeling in obese patients comparing four strategies: (1) no prevention (reference strategy), (2) oral contraceptives for 5 years starting at age 30, (3) annual screening (physical examination and endometrial biopsy) starting at age 30, and (4) biennial screening starting at age 30 (Kwon and Lu 2008). The RR of endometrial cancer diagnosis was favorable at 0.54 and 0.73 for annual and biennial screening, respectively. However, the risk of death is low, and such screening strategies resulted in a miniscule improvement in survival (+0.0743 years for annual screening and +0.0415 years for biennial screening). The incremental cost-effectiveness ratio (ICER) for these strategies tremendously exceeded the accepted $50,000 benchmark. The ICER for annual screening was $3,879,659 and $1,352,486 for biennial screening. This is prohibitively cost inefficient.

19.3.6 Tamoxifen Use

Tamoxifen is an established adjuvant therapy for patients with estrogen receptor-positive breast cancer. Multiple studies have shown that tamoxifen also increases the risk of endometrial neoplasia. The results of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) study have been recently published (Davies et al. 2013). Tamoxifen use resulted in an RR of 1.74 (95 % CI, 1.30–2.34) for developing an incident endometrial cancer (Davies et al. 2013). Mortality from endometrial cancer

also seems to be higher in patients who develop endometrial cancer with a history of tamoxifen use compared to those with endometrial cancer without prior tamoxifen exposure (Jones et al. 2012). Despite this increased risk, the value of routine screening is limited, and there is insufficient data to support screening in tamoxifen-exposed asymptomatic women (Barakat et al. 2000). It is of utmost importance to consider the false-negative rates of such screening strategies, the need for additional unnecessary evaluations, and the potentially unnecessary morbidities associated with such additional evaluations and surgeries initiated by a "screening" test.

19.3.7 Genetic Syndromes

Two genetic syndromes most associated with an increased endometrial cancer risk are Lynch and Cowden syndromes. However, there may be other rare syndromes that also confer an increased risk. There are extensive investigations that have been published or are still under way to better characterize the molecular basis of endometrial cancer development.

19.3.7.1 Lynch Syndrome

Lynch syndrome is the most recognized syndrome to significantly increase the risk of endometrial cancer. Lynch syndrome is caused by germline mutations in DNA mismatch repair (MMR) genes, primarily *MLH1*, *MSH2*, *MSH6*, and *PMS2* (Guillen-Ponce et al. 2012). Endometrial cancer is the second most common cancer in Lynch syndrome after colorectal cancer and may even be more common in women. The lifetime risk of developing endometrial cancer is at least 40 % (Aarnio et al. 1995). Endometrial cancer is actually the sentinel cancer preceding colorectal cancer diagnosis in half of the women ultimately diagnosed with Lynch syndrome (Lu et al. 2005). The vast majority of endometrial cancers (>95 %) occur in patients with Lynch syndrome who have mutations in *MLH1* and/or *MSH2* (Schmeler et al. 2006; Lu et al. 2007). Nearly 10 % of women 50 years and younger who are diagnosed with endometrial cancer will be found to carry a germline Lynch syndrome mutation (Lu et al. 2007).

The most effective preventive strategy in women with Lynch syndrome is prophylactic total hysterectomy (Schmeler et al. 2006). Bilateral salpingo-oophorectomy must also be performed at the time of prophylactic surgery since the risk of ovarian cancer is also increased in Lynch syndrome (Aarnio et al. 1995). No endometrial cancers were diagnosed after a prophylactic hysterectomy in 61 patients compared to 69 (33 %) of 210 patients who did not undergo prophylactic hysterectomy after a mean follow-up of 13 and 7 years, respectively (Schmeler et al. 2006). This 100 % risk reduction was also seen for ovarian cancer in patients who underwent prophylactic oophorectomy. Decision-analytic modeling has demonstrated that prophylactic surgery is associated with an ovarian or endometrial cancer diagnosis rate of 0.0056 and 0.006 %, respectively, compared to 3.7 and 18.4 % for screening and 8.3 and 48.7 % in women undergoing annual examinations only (Chen et al. 2007). Since mortality from endometrial cancer is relatively low, the survival benefit is not

as pronounced. However, preventing endometrial cancer development will avoid potentially toxic and costly therapies. Clearly, prophylactic risk-reducing total hysterectomy and bilateral salpingo-oophorectomy is the perfect preventive strategy in these patients. This approach should be offered to all women who have completed childbearing, preferably by the age of 40.

Prophylactic total hysterectomy with bilateral salpingo-oophorectomy is not a viable option in some women who wish to preserve fertility, and some women simply will not elect to undergo surgery. Screening for endometrial (and ovarian) cancer is recommended by many in women with Lynch syndrome until total hysterectomy with bilateral salpingo-oophorectomy is performed despite the lack of level 1 evidence demonstrating a survival benefit to screening in these women (Guillen-Ponce et al. 2012). Currently available screening for endometrial neoplasia includes TVUS and endometrial biopsy. In a series of women from HNPCC or HNPCC-like families, 222 women underwent 522 TVUS, and none led to a diagnosis of endometrial cancer (Dove-Edwin et al. 2002). There were two intercurrent cases diagnosed but not through screening; both presented with symptoms of abnormal bleeding. Rijcken and colleagues reported on the use of annual screening, TVUS, and serum CA-125 in 41 women with Lynch syndrome (Rijcken et al. 2003). One hundred seventy-nine TVUS screenings led to 17 biopsies, with only 3 (18 %) having a complex AEH. No endometrial cancers were detected. One case was diagnosed with endometrial cancer outside of the screening interval after presenting with abnormal vaginal bleeding. This suggests that screening may not be clinically beneficial for asymptomatic women with Lynch syndrome. TVUS in conjunction with routine endometrial biopsy detected 14 endometrial cancers, with an additional 14 potentially premalignant lesions, among 175 women undergoing surveillance (Renkonen-Sinisalo et al. 2007). Screening women with Lynch syndrome is considered, but the clinical benefit remains to be determined.

Pharmacologic preventive strategies are of interest in women with Lynch syndrome. Progesterone-based contraceptives, either oral or within intrauterine devices, seem plausible as a means to reduce the risk of endometrial cancer. It seems rational to consider their use in young women seeking effective contraceptive options who also desire retention of future fertility. However, there are no prospective data to routinely support use of these agents for the routine chemoprophylaxis in all women with Lynch syndrome. The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) trial randomized patients with known Lynch syndrome to daily aspirin use versus placebo (Burn et al. 2011). Aspirin use was not statistically associated with a reduction in Lynch-associated cancers. However, per-protocol analysis in cases that used daily aspirin for 2 or more years, there was a statistical association with cancer reduction (HR, 0.45 [95 % CI, 0.26–0.79]). There were not enough endometrial cancers that developed during the trial to make any definitive comment on the use of aspirin for endometrial cancer prevention. There was a non-statistically significant 37 % reduction in endometrial cancer in the aspirin users. Per-protocol use for 2 or more years resulted in a greater than 50 % risk reduction, but again, this was not statistically significant. The use of aspirin in women with Lynch syndrome is of interest and a possible consideration. However, the true clinical benefit remains to be determined, specifically for endometrial cancer prevention.

19.3.7.2 Cowden Syndrome

Cowden syndrome is an autosomal dominant syndrome caused by a germline mutation in *PTEN* (Pilarski 2009). Cowden syndrome is characterized by the development of multiple hamartomatous overgrowths of various tissues as well as multiple cancers, including endometrial cancer (Pilarski 2009). The SIR of developing endometrial cancer was estimated at 42.9 (95 % CI, 28.1–62.8) among 205 women with known germline *PTEN* mutations compared to the incidence of endometrial cancer in a general population (Tan et al. 2012). In other words, women with Cowden syndrome have an approximately 43-fold increased risk of developing endometrial cancer. The estimated lifetime risk of developing endometrial cancer in Cowden syndrome is 28 % (Tan et al. 2012). However, germline *PTEN* mutation carriers represent a very small fraction of all endometrial cancer cases. Peripheral blood lymphocyte genomic DNA analysis of the entire *PTEN* coding region among 240 consecutive endometrial cancer cases failed to identify a single case with a germline mutation (Black et al. 2005).

Prophylactic hysterectomy would be expected to provide a tremendous benefit in women with Cowden syndrome and should be considered based on the above significant risks of developing endometrial cancer. However, there are no robust trials to support this in such a rare syndrome. Annual endometrial screening starting at the age of 30 has also been suggested (Tan et al. 2012). Similarly, robust prospective data are lacking to support screening strategies. Data on pharmacologic preventive strategies specifically in Cowden syndrome are lacking, but extrapolation from data in other high-risk situations may be reasonable.

19.4 Preventive Pharmacologic Interventions

Multiple pharmacologic agents have been proposed as potential preventive strategies in women at increased risk for endometrial cancer. These include oral contraceptives, progesterone intrauterine devices, antiestrogens, and anti-inflammatories, among others. Unfortunately, strong level 1 evidence is lacking for many of these agents, especially in regard to general population use.

19.4.1 Hormone-Based Contraceptives

A systematic review of 19 studies reported an approximate 50 % reduction in the risk of endometrial cancer among women who had ever used a combined oral contraceptive (Mueck et al. 2010). This protective effect increased with duration of use and persisted for years after discontinuation. This protective effect is of great interest. Kwon and colleagues also noted an approximate 20 % risk reduction with the use of oral contraceptives in their cost-effective analysis in obese women (Kwon and Lu 2008). However, the estimated overall life expectancy gain was only 0.0306 years, with an unacceptable ICER of $404,465 (Kwon and Lu 2008). The ICER for contraceptive use was more favorable than that for annual or biennial screening.

Endometrial cancer often leads to recognizable symptoms and is associated with a favorable prognosis overall so that any benefit of a preventive strategy will not translate into a long-term survival benefit. Oral contraceptives are an excellent option for women seeking contraception, and the potential risk reduction in endometrial cancer would just be another positive health benefit. It is difficult though to suggest widespread recommendation to use oral contraceptives merely for endometrial risk reduction.

Levonorgestrel intrauterine systems (LNG-IUS) are also an excellent contraceptive option with potentially fewer systemic side effects. It would also make sense that LNG-IUS use would reduce the risk of endometrial neoplasias. A Cochrane review of two randomized trials assessing LNG-IUS in tamoxifen users reported a significant reduction in the incidence of endometrial polyps (Chin et al. 2009). There was a 70 % reduction in endometrial hyperplasia, but this was not statistically significant (OR, 0.30 [95 % CI, 0.01–7.44]) since the two trials were not powered to assess the protective effect on either hyperplasia or carcinoma. A more recent review of publications using LNG-IUS among various groups of women also reported a significant reduction in the development of endometrial polyps (OR, 0.28 [95 % CI, 0.15–0.55]) (Wan and Holland 2011). LNG-IUS was also associated with a reduction in endometrial hyperplasia risk (OR, 0.14 [95 % CI, 0.02–0.80]). LNG-IUS appears to be a potentially promising endometrial protective agent, especially in high-risk women. However, there is insufficient data to support a recommendation for widespread use as a chemopreventive agent at this time. Large prospective randomized trials should be considered to assess both oral contraceptives and LNG-IUS as endometrial chemopreventive agents in women at high risk for endometrial cancer.

19.4.2 Nonsteroidal Anti-inflammatories (NSAIDs)

Aspirin and other NSAIDs have gained interest as potential chemopreventive and therapeutic agents for various malignancies. This stems from the noted alterations in the inflammatory state seen in patients with malignancies and within the malignant cells themselves. Chronic inflammatory states seem to play a role in carcinogenesis of many malignancies, including endometrial cancers (Coussens and Werb 2002; Wallace et al. 2010). Various publications suggest a protective effect of aspirin and other NSAIDs in endometrial neoplasia prevention.

Results from the VITamins And Lifestyle (VITAL) study have recently become available (Brasky et al. 2013). This was a large prospective cohort study among 22,268 female residents of western Washington state aged 50–76. All participants answered a baseline questionnaire in 2000–2002 and reported their use of various NSAIDs in the prior 10 years. These women were then followed prospectively, and 262 incident invasive endometrial cancers were diagnosed. Use of any NSAID overall was not associated with a reduction in the risk of endometrial cancer. The authors concluded that the use of aspirin did reduce the risk of endometrial cancer. This was based on a *p*-value of 0.03 for the trend comparing endometrial cancer risk in

nonuse, low use, and high use of aspirin. High use of aspirin, defined as use of aspirin at least 4 days/week for at least 4 years, resulted in an RR of 0.83 (95 % CI, 0.56–1.01). While the authors concluded a benefit to high use of aspirin, the conclusion is debatable since the confidence interval crossed 1. The use of other NSAIDs, including ibuprofen and naproxen, did not reduce the risk of endometrial cancer. The only truly significant reduction seen was in a subgroup of never smokers. Every use of aspirin, defined as aspirin use at least 1 day a week for at least 1 year, resulted in an RR of 0.55 (95 % CI, 0.37–0.82). The use of regular-strength aspirin as a chemopreventive agent for endometrial cancer is a potential consideration in women at high risk of endometrial cancer. NSAID use for endometrial cancer prevention warrants further investigation.

19.4.3 Metformin

Metformin is a hypoglycemic agent that is considered a safe and effective monotherapy for the treatment of diabetes (Ali and Fonseca 2012). Metformin has also recently gained interest as a potential cancer chemopreventive agent (Ali and Fonseca 2012). Epidemiologic studies have suggested a benefit of metformin use with cancer prevention and cancer mortality reduction, but the basic mechanism of putative anticancer properties remains to be fully elucidated (Ali and Fonseca 2012). Additionally, level 1 evidence in humans is limited, and no randomized trials specifically addressing endometrial cancer risk reduction have been conducted.

Noto and colleagues recently published the results of their systematic review of metformin use among diabetics as it relates to cancer incidence and mortality (Noto et al. 2012). The pooled RR for all-cancer incidence was 0.67 (95 % CI, 0.53–0.88). This review was limited by the fact that almost all of the included studies were not randomized trials and the incidence of endometrial cancer was not assessed. Metformin was not found to be associated with a reduction in all-cancer incidence in a meta-analysis of 11 randomized trials comparing metformin to other agents in the treatment of diabetes (Stevens et al. 2012a). The summary RR for cancer incidence in people randomized to metformin was 1.03 (95 % CI, 0.82–1.28). This review did not support the use of metformin as a cancer-preventing strategy. However, cancer prevention was not the primary end point in the included randomized trials.

There are limited data specific to the use of metformin and endometrial neoplasia. Cantrell et al assessed cell proliferation, cell cycle progression, and apoptosis after metformin exposure of ECC-1 and Ishikawa endometrial cancer cell lines (Cantrell et al. 2010). Metformin potently inhibited cancer cell growth primarily through cell cycle arrest and not by induction of apoptosis. Metformin exposure also inhibited telomerase activity. Metformin also induced phosphorylation of AMPK with decreased phosphorylation of the S6 protein, with a resultant inhibition of the mTOR pathway (Cantrell et al. 2010). These data provide a basis for continued investigation into the use of metformin as a preventive and therapeutic agent for endometrial neoplasia. However, routine use of metformin as an endometrial cancer chemopreventive agent cannot be recommended at this time.

19.5 Other Preventive Strategies

Other potential endometrial cancer preventive options have been suggested. None have been proven in a properly designed randomized trial. The Multiethnic Cohort (MEC) study is a longitudinal study designed to investigate associations between diet, lifestyle, and genetics with the incidence of cancer. Isoflavone-containing food was associated with a reduced risk of endometrial cancer (Ollberding et al. 2012). Specifically, reduced risk of endometrial cancer was associated with the total isoflavone intake, daidzein intake, and genistein intake but not with legume, soy, tofu, or glycitein intakes. These findings are limited in that they were based on baseline reporting of food intake, and changes in diet over time were not taken into account. Additionally, this is a longitudinal, and a not randomized, study. Endometrial cancer risk reduction has also been reported with the use of vitamin D and green tea (Yu et al. 2010; Kakuta et al. 2009).

Conclusion

Obesity, metabolic syndrome, and genetic predisposition (Lynch and Cowden syndromes) are the greatest risk factors for developing endometrial cancer, with Lynch and Cowden syndromes associated with the greatest lifetime risk. Prevention of endometrial cancer in all women is of great interest. Maintaining a healthy lifestyle in terms of proper diet and exercise in order to avoid weight gain or lose weight is important and may reduce the risk of endometrial cancer. Prophylactic surgery offers the greatest risk reduction in women at highest risk of endometrial cancer (Lynch and Cowden syndromes). However, the morbidity and cost of this surgery cannot be justified in other potentially at-risk women. Multiple chemopreventive strategies have been reported as described above. However, there is a lack of level 1 evidence to provide strong widespread recommendations to use any of these agents. There is an important need to continue the investigation into the carcinogenesis of endometrial cancer and the conduct of randomized trials assessing chemopreventive agents.

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Cancer Survivorship

20

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20.1 Introduction

There is today a greater recognition of symptoms that persist following completion of treatment and those that arise years after primary therapy. Both acute organ toxicities, such as radiation pneumonitis, and chronic toxicities, such as congestive cardiac failure, neurocognitive deficits, infertility, and second malignancies, are being described as the price of cure or prolonged survival.

Generally, long-term cancer survivors are defined as those individuals who are 5 or more years beyond the diagnosis of their primary disease. Long-term effects refer to any side effects or complications of treatment for which a cancer patient must compensate; also known as persistent effects, they begin during treatment and continue beyond the end of treatment. Late effects, in contrast, appear months to years after the completion of treatment. Since tissue damage noted during or at the end of therapy may remain stable or become progressive, late effects refer specifically to these unrecognized toxicities that are absent or subclinical at the end of therapy but manifest later as a result of growth, development, increased demand, or aging. These can be due to any of the following factors: developmental processes, the failure of compensatory mechanisms with the passage of time, or organ senescence.

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Compensatory mechanisms that initially maintain the function of injured organs may fail over time or with organ senescence. Persistent symptoms differ from late effects of treatment because they begin during treatment and continue following treatment rather than appearing months to years after the completion of treatment (Kolb and Poetscher 1997). Some researchers classify cognitive problems, fatigue, lymphedema, and peripheral neuropathy as persistent symptoms. Patients demonstrating signs or symptoms of late or long-term effects may have to undergo major adjustments to a lifestyle for which they are unprepared (Loescher et al. 1989; Welch-McCaffrey et al. 1989; Herold and Roetzheim 1992; Marina 1997; Aziz 2002a, b).

Late effects of cancer treatment occur because effects of therapy on maturing organs may become manifest only with time or with the unmasking of hitherto unseen injury to immature organs by developmental processes (Schwartz 1999; Aziz 2002a, b). The study of late effects, originally within the realm of pediatric cancer, is now germane to cancer survivors at all ages as concerns may continue to surface throughout the life cycle. These concerns underscore the need to follow up and screen survivors of cancer for toxicities in order to prevent or ameliorate these problems (Aziz 2002a, b; Aziz and Rowland 2003).

20.2 Prevalence of Survivorship

There is no universally accepted definition of a cancer survivor. Some regard anyone diagnosed with malignancy as a survivor from the moment of initial diagnosis. Others consider time from diagnosis, or completion of therapy, and disease status as necessary components of defining survivorship. Regardless of the definition, it is well accepted that the number of patients who are living with, or after, a cancer diagnosis has skyrocketed during the past decades. The American Cancer Society estimates that, as of January 1, 2012, there were 13 million cancer survivors alive in the USA; it is projected that there will be nearly 18 million by 2022 (Siegel et al. 2012). According to estimates from the Center for Disease Control, there were 3 million US cancer survivors in 1971 (Fairley et al. 2009).

The most frequent primary sites among survivors include female breast (22 %), prostate (19 %), and colorectal (10 %). More than half of US cancer survivors (54 %) are women and 60 % are 65 years or older. Approximately 65 % of cancer survivors have lived for more than 5 years after diagnosis (Rowland et al. 2011). Results from the 2010 National Health Interview Study found approximately two-thirds of cancer survivors were more than 5 years from diagnosis, 12 % had had a recurrence, and 10 % had two or more cancers. Nearly 70 % of cancer survivors had surgical treatment, 27 % had radiation, 26 % had chemotherapy, and 7 % had hormonal treatment (57). Poor physical health was reported by 24.5 % of survivors and poor mental health by 10 % (Weaver et al. 2012).

Fitzhugh Mullan, a physician diagnosed with and treated for cancer himself, first described cancer survivorship as a concept (Mullan 1985). Definitional issues for cancer survivorship encompass three related aspects. First, who is a cancer survivor? Philosophically, anyone who has been diagnosed with cancer is a survivor, from the time of diagnosis to the end of life (Aziz 2002a, b; Aziz and Rowland 2003).

Caregivers and family members are also included within this definition as secondary survivors. Second, what is cancer survivorship? Mullan described the survivorship experience as similar to the seasons of the year. He recognized three seasons or phases of survival: acute (extending from diagnosis to the completion of initial treatment, encompassing issues dominated by treatment and its side effects), extended (beginning with the completion of initial treatment for the primary disease, remission of disease, or both; dominated by watchful waiting, regular follow-up examinations, and, perhaps, intermittent therapy), and permanent survival (not a single moment; evolves from extended disease-free survival when the likelihood of recurrence is sufficiently low). An understanding of these phases of survival is important for facilitating an optimal transition into and management of survivorship. Third, what is cancer survivorship research? Cancer survivorship research seeks to identify, examine, prevent, and control adverse cancer diagnosis and treatment-related outcomes (such as late effects of treatment, second cancers, and quality of life), to provide a knowledge base regarding optimal follow-up care and surveillance of cancer survivors, and to optimize health after cancer treatment (Aziz 2002a, b; Aziz and Rowland 2003).

Consistent with the shift in our perceptions of cancer as a chronic disease, new perspectives and an emerging body of scientific knowledge must now be incorporated into Mullan's original description of the survivorship experience (Aziz and Rowland 2003). Mullan's comparison of cancer survivorship with seasons of the year had implied that the availability and widespread use of curative and effective treatments would lead to a low likelihood of recurrence and longer survival times. However, the potential impact of late and long-term adverse physiologic and psychosocial effects of treatment was not described. In addition, further advances in survivorship research over the past few years have necessitated the incorporation of other emerging concepts into the evolving paradigm of cancer survivorship research (Aziz 2002a, b; Aziz and Rowland 2003). These include the key role of lifestyle and health promotion in ameliorating adverse treatment and disease-related consequences; the impact of comorbidities on a survivor's health status and their possible interaction with risk for or severity of late effects; the effect of cancer on the family; and the need for incorporating a developmental and life-stage perspective in order to facilitate optimally a cancer patient's journey into the survivorship phase. A developmental or life-stage perspective is particularly important as it carries the potential to affect and modify treatment decisions, the intensity of posttreatment follow-up care, the risk and severity of adverse sequelae of treatment, and the need for or use of technology (e.g., sperm banking, depending on the survivors age at diagnosis and treatment) (Aziz 2002a, b; Aziz and Rowland 2003).

20.3 Survivorship as a Scientific Discipline

The creation of the Office of Cancer Survivorship Program at the US National Cancer Institute (NCI) in 1996 helped to highlight the key importance of cancer survivorship as a research area in its own right and an integral part of the cancer prevention and control spectrum. Research related to cancer survivors, pertaining to

the amelioration or management of adverse late or long-term sequelae of cancer and its treatment; the prevention, control, or management of sources of morbidity; and enhanced length and quality of survival, is a burgeoning area of interest among investigators, practitioners, survivor advocacy groups, and policy makers. Several highly successful research initiatives have been released over the past 8 years by the Office of Cancer Survivorship in order to lay the foundation for and stimulate growth in key areas of cancer survivorship research. The large numbers of successful investigator-initiated grant submissions addressing cancer survivorship relevant research questions who pass through the same stringent scientific criteria for peer review as other grants at the National Institutes of Health (NIH) bear testament to the continued evolution and growth of this scientific discipline, as do the increasing numbers of peer-reviewed manuscripts in leading national and international oncologic, medical, psychosocial, and health-related journals.

20.4 Prevention

The study of cancer prevention focuses on populations who are most at risk of a potential malignancy. Some populations are at such high risk of cancer that more aggressive treatment interventions may be advocated. Examples include patients with Lynch syndrome (familial polyposis syndrome) or who carry mutations in the BRCA-1 or BRCA-2 genes. In these instances, early surgical intervention or intense follow-up is warranted.

Most patients with hereditary breast and ovarian cancer syndrome have germ line mutations in the tumor suppressor genes, BRCA1 or BRCA2. One or the other of these genes is mutated in approximately 3–5 % of breast cancer patients and at least a tenth of ovarian cancer patients. The American College of Obstetrics and Gynecology and the Society of Gynecologic Oncology recommend screening for BRCA mutations based on personal and family cancer history. In particular, women with both breast and ovarian cancers and those who are young at the time of diagnosis are at high risk. An elevated prevalence of BRCA mutations is seen on patients of Ashkenazi Jewish ancestry. Women who are found to have BRCA1 or 2 mutations should be considered for surgical or pharmacologic risk reduction strategies (Lynen 2009).

Two percent of colorectal cancers occur in patients with Lynch syndrome, resulting from defects in mismatch repair genes. The cumulative risk of colon cancer in patients with high-risk mutations is 70 % by age 70. In addition to colorectal cancers, Lynch syndrome is associated with higher frequencies of endometrial cancer and less commonly cancers of the ovary, stomach, skin, brain, small bowel, and urinary and hepatobiliary tracts (Lindor et al. 2006). Women with Lynch syndrome-related colorectal cancer are considered for risk-reducing hysterectomy and salpingo-oophorectomy dependent upon age, menopausal status, and desire for fertility. Women with Lynch syndrome who have not had hysterectomy/salpingo-oophorectomy should be offered annual endometrial biopsy beginning at age 30–35 and merit prompt evaluation with endometrial sampling for any irregular, heavy, or postmenopausal uterine bleeding (Lindor et al. 2006).

20.5 Smoking Cessation and Survivorship

An understudied but significant issue for cancer survivors is smoking cessation. Changes in diet, tobacco use, and exercise may lead to better physical and emotional quality of life for cancer survivors (Demark-Wahnefried et al. 2005). Despite this, recent studies suggest that many cancer survivors do not change their smoking, diet, and exercise behaviors after diagnosis (Bellizzi et al. 2005; Caan et al. 2005; Coups and Ostroff 2005). A recent review found that two-thirds of cancer survivors continued smoking after diagnosis (Tseng et al. 2012), and many more regularly are exposed to secondhand smoke (Evangelista et al. 2003).

Reasons why smokers continue to smoke after a diagnosis of cancer is complex. Smokers may feel ambivalent to quit when they have already had the greatest perceived risk of smoking cancer (especially lung cancer) (Weinstein et al. 2004). They also may feel it is the most difficult time to quit related to the stress of having a new diagnosis of cancer, undergoing difficult treatments, and continued follow-ups. Unfortunately, many smokers may not perceive the risks of continuing to smoke or may choose to ignore them.

Smoking during treatment for cancer may delay surgery, impair wound healing, cause lung infections, and contribute to other comorbidities. Furthermore, continuing to smoke may have serious negative effects on cancer survivors' general health and quality of life—a significant concern for this population, in which there is a high rate of survivorship. In addition to the concerns about secondary cancers and other health issues caused by tobacco use, smoking during cancer treatment has been shown to reduce long-term survival of breast cancer and to increase the possibility of developing distant metastases (Nguyen et al. 2003). Smoking in prostate cancer patients treated with radiation has been linked to lower survival rates (Pahlajani et al. 2004) and to higher genitourinary and gastrointestinal toxicity (Pahlajani et al. 2006).

Those diagnosed with head, neck, or lung cancers—cancers clearly linked to tobacco use—are most likely to quit smoking after a diagnosis (Schnoll et al. 2003). Researchers have found that location and severity of disease (Ostroff et al. 1995), alcohol use, and previous quit attempts (Chan et al. 2004) affect patients' likelihood of stopping smoking. For example, Ostroff and colleagues (1995) found that head and neck cancer patients with less severe disease were more likely to continue smoking following diagnosis. While health concerns may inspire someone to quit, social support and physician encouragement play a major part in the process (Duncan et al. 1992; Gilpin et al. 1993; Shoham et al. 2007; Shoham et al. 2006). Furthermore, cancer patients may have special issues to be considered, such as physical mobility, depression, and possible pharmacologic interactions in nicotine replacement therapy (Gritz et al. 2006). Since research has revealed a link between depression, anxiety, and smoking in the general population (Tsoh et al. 2000; Morrell and Cohen 2006), cessation interventions for cancer patients must be especially sensitive to this in a group dealing with serious disease.

Smoking during treatment for any type of cancer, even those with cancers that have less linkage to tobacco, can lead to significant health complications and can

delay certain procedures, such as surgery. Smoking before and after surgery can have negative effects on wound healing (Warner 2007), and breast reconstruction after mastectomy may be delayed due to cigarette smoking (Krueger and Rohrich 2001). Basic science research reveals that nicotine affects the efficacy of chemotherapeutic drugs, including doxorubicin, which is used to treat breast cancer (Zhou et al. 2007). In addition, smoking along with radiation therapy to the breast may contribute to the development of primary cancer of the lung (Ford et al. 2003). It has been shown that the risk of tobacco-related malignancies in survivors of cervical cancer was double than among patients who had been treated for female breast or colorectal cancer (Underwood et al. 2012). Smoking is related to higher prostate cancer mortality (Gong et al. 2008) and in prostate cancer patients who undergo radiation therapy in particular (Pantarotto et al. 2006). Furthermore, smoking while undergoing chemotherapy may contribute to increased pulmonary infections (Chelghoum et al. 2002).

20.6 Acute Effects of Cancer Treatment

Acute effects of treatment are those that occur during and soon after treatment. Patients suffer many side effects that need to be addressed throughout their course of therapy. Supportive care in the acute setting is focused on known side effects of treatments and, if possible, preemptively treating these problems. Surgical, radiation therapy, and chemotherapy techniques continue to make significant improvements that lead to better quality of life (QOL) for cancer survivors. For example, minimally invasive surgical techniques may reduce pain and postoperative rehabilitation. Use of high-dose brachytherapy for some sarcoma can simplify therapy such that patients are less isolated during these treatments. Oral agents (e.g., 5-FU) enable a much simpler and less uncomfortable administration of chemotherapy for colorectal cancer patients.

20.6.1 Chemotherapy

There are many acute systemic effects related to chemotherapy. Presently, many of these can be adequately treated with medications to reduce the toxicity associated with current chemotherapy regimens. Gastrointestinal complications, such as nausea, vomiting, and diarrhea, have historically been a major difficulty related to chemotherapy, as well as immunotherapy. They may be effectively treated with multiple medical strategies.

20.6.1.1 Nausea and Vomiting

Certain chemotherapeutics carry higher risks of nausea and vomiting, including doxorubicin, cisplatin, ifosfamide, and dacarbazine. Other risk factors may include chronic alcohol use, female gender, and a history of poor control of nausea and vomiting (Bartlett and Koczwara 2002). While persistent difficulties throughout

therapy can lead to altering chemotherapy dosing or discontinuing treatments, prescribing prechemotherapy antiemetics frequently can control, or eliminate, symptoms. Highly effective, combination, prophylactic regimens have been shown to completely control acute emesis in most patients treated with highly emetogenic chemotherapy. Current guidelines from the American Society of Clinical Oncology recommend use of dexamethasone along with 5-HT3 and NK-1 receptor antagonists for all patients treated with highly emetogenic chemotherapy regimens. Patients treated with moderately emetogenic regimens may be well treated with a 5-HT3 receptor antagonist and dexamethasone. The preferred 5-HT3 receptor antagonist is palonosetron. Dexamethasone alone is recommended as prophylaxis with low emetogenic regimens (Basch et al. 2011). Although primary prevention of vomiting is quite successful, nausea may be more difficult to control and delayed and highly effective treatments for anticipatory and delayed nausea and vomiting have not been developed. Treatment with lorazepam, olanzapine, metoclopramide, or a dopamine antagonist may be considered as needed (Basch et al. 2011).

20.6.1.2 Asthenia

Asthenia is a problem with multiple potential etiologies (Von Hoff 1998). If related to anemia, multiple strategies can be attempted, the most straightforward being transfusional therapy. This is most useful for patients who have extremely low hemoglobin or those that are unresponsive to other treatments. Treatment with recombinant human erythropoietin, three times a week or weekly, has been shown to have response rates of 50–60 % (Gordon 2002). Darbepoetin alfa, a newer erythropoiesis-stimulating protein, can be dosed weekly or every other week and may show improved response rates (Gordon 2002). Increased hemoglobin levels are correlated with an improvement in symptoms of fatigue. While there are other mechanisms which can contribute to fatigue (i.e., other medical problems such as congestive heart failure, depression, hormonal abnormalities, or cytokine production), it seems that anemia may play an important role and correction may improve symptoms. A recent comprehensive review of clinical trials concluded that transfusion requirements were reduced and quality of life was improved by administration of erythropoietic growth factors to cancer patients. However, the authors found evidence of increased risks of mortality, thromboembolic events, and hypertension in patients treated with recombinant human erythropoiesis-stimulating agents (Tonia et al. 2012). Therefore, the risks and benefits of use of these agents must be carefully considered.

20.6.1.3 Anorexia and Cachexia

Anorexia and cachexia are frequently mentioned along with asthenia based on potentially similar pathophysiologies (Von Hoff 1998). Poor appetite and wasting frequently coexist in a patient, either causally or due to similar etiologic mechanisms. Anorexia and cachexia are problems not only for patients but are also stressful for families that watch loved ones become thinner and less energetic. Cachexia consists of a constellation of metabolic and symptomatic changes. These include a reduction in lean body tissues and fatty tissues, hypoglycemia, hypercalcemia,

as well as asthenia and anorexia. Progressive weight loss is a common problem faced by cancer patients and is responsible not only for a reduced QOL and poor response to chemotherapy but also a shorter survival time as compared to patients with comparable tumors who do not suffer from weight loss (Tisdale 1999). Medications such as megestrol acetate (Splinter 1992; Downer et al. 1993; Mantovani et al. 1995, 1998; Neri et al. 1997; De Conno et al. 1998), medroxyprogesterone acetate (Splinter 1992; Downer et al. 1993; Mantovani et al. 1995, 1998; Neri et al. 1997; De Conno et al. 1998), and potentially thalidomide (Bruera et al. 1999) can be helpful for some patients, but further study is warranted.

20.6.1.4 Immunosuppression and Risk of Infection

These factors play an overwhelming role in a patient's QOL. The risk of infection mandates lifestyle changes for patients and as well as for families to protect their loved ones. This may include minimal contact with people, careful and frequent washing of hands, and the use of masks. Judicious use of antibiotics, along with cytokine therapy to enhance white blood cell counts, lessens infection (ASCO 1994). Granulocyte colony-stimulating factor has also been shown to reduce hospitalization and antibiotic therapy (Garcia-Carbonero et al. 2001). Patients who maintain or achieve adequate white blood cell counts have an improved QOL and may be better able to tolerate chemotherapy (Jones et al. 1996), although this is not always seen (Steward et al. 1998).

Guidelines from the American Society of Clinical Oncology (Smith et al. 2012), the National Comprehensive Cancer Network (Crawford et al. 2009), the European Organisation for Research and Treatment of Cancer (Aapro et al. 2011), and the Infectious Diseases Society of America (Freifeld et al. 2011) support the prescription of prophylactic colony-stimulating factors for patients considered at a 20 %, or higher, risk of chemotherapy-related febrile neutropenia. Risk of febrile neutropenia is greatest in the initial course of treatment, and there is data showing that overall survival can be improved with use of colony-stimulating factor support for chemotherapy in a number of primary tumor sites (Kuderer and Lyman 2011).

20.6.2 Surgery

Operative therapies are frequently curative and QOL-improving in a number of cancers (i.e., breast cancer, colon cancer, and melanoma). Improvement in QOL may be related to the removal of a potentially painful or problematic tumor-related wound (e.g., from a breast or skin cancer), or the removal of a tumor in the colon that had been causing bleeding or obstruction. For a tumor that is unlikely to be cured via an operation, such as esophageal or gastric cancers, surgical approaches have been shown to improve the ability to swallow for many patients, which can in turn improve QOL (Branicki et al. 1998). Surgical procedures can also lead to multiple acute morbidities. Risks associated with each surgical procedure must be carefully considered, as complications will still occur even with the most fastidious care, especially if the patient is debilitated related to the cancer or underlying conditions.

First, surgical morbidity may include complications unrelated to the surgical site, such as pneumonia, deep venous thrombosis, ileus, and heart failure. With meticulous care, these can often be avoided. Related to the procedure itself, pain is a major issue that occurs in the postoperative setting, and may persist. Epidural, patient-controlled analgesia, and local anesthetic pumps may improve pain control and ultimate outcomes. Improved outcomes can be seen as less impairment of pulmonary, bowel, mental, coagulation, and immune functions and nutritional status, along with an increased risk of chronic pain (Karanikolas and Swarm 2000; Reid 2001; Fotiadis et al. 2004). Acceptance of disfigurement and lifestyle changes are most pronounced in the immediate postoperative setting. For example, for many patients undergoing surgery related to colorectal cancer, the shock of a permanent stoma may be overwhelming. In fact, this may be the overwhelming issue of concern for patients with a new cancer, possibly even leading to delay in treatment (Cohen et al. 1997). Recent evidence suggests that QOL problems related to ostomies may diminish with time but nevertheless remain a significant factor in the postoperative setting (Krouse et al. 2004).

Wound complications must always be considered in the setting of cancer-related surgical procedures. This is certainly true of lymph node dissections; wound problems have been noted to be 47 % for axillary node and 71 % after inguinal node dissections (Serpell et al. 2003). Seromas and infections may take from several weeks to months to heal. Lymphatic leaks may necessitate procedures to isolate the offending lymphatic vessel. Therefore, when considering any surgical procedure, whether for curative or palliative intent, these issues must be discussed prior to the operation. As new innovations are utilized, outcomes will continue to improve for surgical patients.

Application of minimally invasive approaches to the surgical management of malignant disease is of considerable interest and the frequency of such procedures is rising. Use of endoscopic procedures has been studied in endometrial (Walker et al. 2009, 2012), prostate (Cathcart et al. 2011), colorectal (Kang et al. 2012a, b), and other cancers (Yu et al. 2013). Minimally invasive techniques have been associated with favorable short-term outcomes, including lower rates of several complications (Walker et al. 2009; Kang et al. 2012a, b; Yu et al. 2013) and shorter hospitalizations (Walker et al. 2009). There is limited data available on long-term outcomes.

20.6.3 Radiation Therapy

There are many acute effects of radiation therapy. These are based on the location of the treatment. If treatment is directed into the peritoneal cavity, the most likely problems will be related to cramping, abdominal pain, and diarrhea. Fatigue is also a common problem for patients undergoing radiation therapy (Irvine et al. 1998). Radiation of the upper aerodigestive tract may lead to edema and inability to swallow. Localized skin irradiation can lead to painful burns. These symptoms may be very difficult to control initially, but frequently improve with time. Newer

treatments are being tested to reduce the acute effects of radiation, such as silver leaf nylon dressings for perineal irradiation (Vuong et al. 2004). Other promising treatments include glutamine, to protect against radiation-induced injury (Savarese et al. 2003), and hyperbaric oxygen therapy for radiation-induced osteoradionecrosis, soft tissue necrosis, cystitis, proctitis (Bui et al. 2004), or breast skin burns (Borg et al. 2001). Other treatments for skin damage, such as transparent, hydrocolloid, and hydrogel dressings, have demonstrated some benefit, as have sucralfate cream and corticosteroid cream. Aloe vera may be beneficial and has no known side effects (Wickline 2004).

Alternatives to standard external beam radiation and to low-dose rate brachytherapy have been increasingly applied to cancer treatments. Both intensity-modulated radiation (IMRT) and proton beam therapy are being used in order to spare radiation injury to normal surrounding tissues. It is estimated that, at present, over 95 % of patients with localized prostate cancer, who are treated with radiation, are treated with IMRT (Sheets et al. 2012). IMRT, when used for gynecologic (D'Souza et al. 2012) and breast (Dayes et al. 2012) cancer patients and for the radical treatment of prostate cancer (Bauman et al. 2012), is associated with fewer acute adverse effects. A single institution study found that lower GI toxicity is reduced when IMRT is used to treat rectal cancer (Samuelian et al. 2012). High dose rate brachytherapy is indicated for the treatment of certain gynecologic, thoracic, gastrointestinal, breast, urologic, and head and neck cancers (Erickson et al. 2011).

Recently, the American Society for Radiation Oncology and the American College of Radiology have jointly published guidelines for IMRT and high dose rate brachytherapy (Erickson et al. 2011; Hartford et al. 2012).

20.7 Long-Term and Late Effects of Cancer Treatment

Most cancer treatments carry substantial risk of adverse long-term or late effects, including neurocognitive problems, premature menopause, cardiac dysfunction, sexual impairment, infertility, chronic fatigue, pain, peripheral neuropathy, and second malignancies for both adult and childhood cancer survivors (Schwartz et al. 1993; Kolb and Poetscher 1997; Aziz 2002a, b; Aziz and Rowland 2003). One-fourth to one-third of breast and lymphoma survivors who receive chemotherapy may develop detectable neurocognitive deficits (Cimprich 1992; Ganz 1998a, b; Brezden et al. 2000; Ahles et al. 2002). Late clinical cardiotoxicity, often life threatening, may occur in 5–10 % of long-term pediatric cancer survivors even 5–10 years after therapy (Simbre et al. 2001).

Late effects of radiotherapy and chemotherapy are related to organ dysfunction and impact a patient's life by altering functional abilities. The lifestyle changes required by patients are associated with specific drugs used in the treatment regimen, which are frequently prescribed dependent on the location of a solid tumor. Combinations of chemotherapy and radiation therapy have a higher incidence of late effects of treatment (Aziz 2002a, b; Aziz and Rowland 2003). In addition, long-term effects on organ systems may lead to mortality. This has been noted by

investigators to account for one-fourth of late deaths of cancer survivors. The most common causes of late deaths among survivors of pediatric cancer include secondary cancer or cardiac dysfunction (Sklar 1999).

Late effects can be classified further as (a) system-specific (i.e., damage, failure or premature aging of organs, immunosuppression or compromised immune systems, and endocrine damage), (b) second malignant neoplasms (i.e., increased risk of a certain cancer associated with the primary cancer and a second cancer associated with cytotoxic or radiological cancer therapies), (c) functional changes (lymphedema, incontinence, pain syndromes, neuropathies, and fatigue), (d) cosmetic changes (i.e., amputations, ostomies, and skin and hair alterations), and (e) associated comorbidities (i.e., osteoporosis, arthritis, scleroderma, and hypertension) (Aziz 2002a, b; Aziz and Rowland 2003). The risk of a recurrence of the primary malignancy, while not a late effect, is also ever present and affects surveillance, monitoring, and posttreatment follow-up management decisions.

20.7.1 Generalizations

Certain types of late effects can be anticipated from exposure to specific therapies, age of the survivor at the time of treatment, combinations of treatment modalities, and dosage administered (Aziz 2002a, b). Susceptibility differs for children and adults. Generally, chemotherapy results in acute toxicities that can persist, whereas radiation therapy leads to sequelae that are not immediately apparent. Combinations of chemotherapy and radiation therapy are more often associated with late effects. Risk of late death from causes other than recurrence is greatest among survivors treated with a combination of chemotherapy and radiotherapy. Toxicities related to chemotherapy, especially those of an acute but possibly persistent nature, can be related to proliferation kinetics of individual cell populations because these drugs are usually cell cycle dependent. Organs or tissues most susceptible have high cell proliferation rates and include the skin, bone marrow, gastrointestinal mucosa, liver, and testes. The least susceptible organs and tissues replicate very slowly or not at all and include muscle cells, neurons, and connective tissue. However, neural damage may be caused by commonly used chemotherapeutic drugs such as methotrexate, taxanes, platinums, vinca alkaloids, and cytosine arabinoside, bone injury may be caused by methotrexate, and cardiac sequelae can occur after treatment with Adriamycin. Injuries in tissues or organs with low repair potential may be permanent or long-lasting.

20.7.2 Issues Unique to Certain Cancer Sites

The examination of late effects for childhood cancers such as leukemia, Hodgkin's lymphoma, and brain tumors has provided the foundation for this area of research. A body of knowledge on late effects of radiation and chemotherapy is also now appearing for adult cancer sites such as breast cancer. For example, neurocognitive deficits that may develop after chemotherapy for breast cancer are an example of a

late effect that was initially observed among survivors of childhood cancer receiving cranial irradiation, chemotherapy, or both (Kreuser et al. 1988; van Dam et al. 1998; Ahles et al. 2002; Aziz 2002a, b; Aziz and Rowland 2003). Breast cancer radiotherapy has been associated with an elevated risk of death from circulatory diseases; cardiac doses have been decreased in modern treatment planning in an effort to limit long-term morbidity (Stein et al. 2008). Increased risk of treatment-related cardiovascular death has also been reported among testis cancer survivors treated with subdiaphragmatic and mediastinal radiotherapy (Stein et al. 2008). Breast cancer survivors also report pain and edema in the radiation field (Stein et al. 2008). Late effects of bone marrow transplantation have been studied for both adult and childhood cancer survivors as have sequelae associated with particular chemotherapeutic regimens for Hodgkin's lymphoma and breast cancer (Sankila et al. 1996; Schwartz 1999; Greendale et al. 2001; Aziz 2002a, b). The side effects of radiotherapy, both alone and with chemotherapy, have been reported quite comprehensively for most childhood cancer sites associated with good survival rates. Most cancer treatment regimens consist of chemotherapy in conjunction with surgery or radiation, and multidrug chemotherapeutic regimens are the rule rather the exception. As such, the risk of late effects must always be considered in light of all other treatment modalities to which the patient has been exposed.

Psychological sequelae of cancer treatment also bear consideration. Prevalence of depression has been estimated to be as high as 50 %, or higher, in some series. Anxiety has been reported in up to a quarter of cancer survivors and post-traumatic stress in up to a third (Arriagada et al. 2009). Informational, inter- and intrapersonal, and tangible resources are felt to have impact on the patient's ability to cope with a cancer diagnosis (Arriagada et al. 2009).

20.7.3 Special Considerations Related to Age at Diagnosis

Long-term cancer survivors are faced with different effects of treatment depending on the age at diagnosis. Children face growth, neurocognitive, and hormonal imbalance related to cancer treatment. Young adults frequently face issues such as reproductive function and risks for second cancers. Middle-age patients face problems related to chronic disease due to the effects of treatment and early menopause, and older patients frequently suffer from additional comorbidities, making long-term complications potentially more deleterious (Aziz 2002a, b; Aziz and Rowland 2003).

20.7.4 Special Considerations when Primary Diagnosis and Treatment Occur in Childhood

Cancer therapy during childhood may interfere with physical and musculoskeletal development (Blatt et al. 1988; Furst et al. 1989; Sklar et al. 1993; Ogilvy-Stuart et al. 1994; Didi et al. 1995), neurocognitive and intellectual growth (Ochs et al. 1991; Haupt et al. 1994), and pubertal development (Kreuser et al. 1988). These effects may be most notable during the adolescent growth spurt. Prevention of second cancers is also a key issue (Mullan 1985; Aziz 2002a, b).

A report from the Childhood Cancer Survivor Study described the late effects of radiation therapy from a group of over 14,000 subjects. Increased risks of all-cause and late mortality were associated with therapeutic radiation during childhood. Cardiac death was significantly more frequent in those who had total body irradiation or radiation to the spine or chest. A more than sixfold increased risk of second neoplasms was also reported. The most common secondary cancers were those of the breast and thyroid. Obesity is more frequent after cranial radiation, and pulmonary, cardiac, and thyroid dysfunction are also reported more commonly in childhood cancer survivors (Armstrong et al. 2010).

Some late effects of chemotherapy may assume special importance depending on the adult patient's age at the time of diagnosis and treatment (Schwartz 1999; Aziz 2002a, b; Aziz and Rowland 2003). Diagnosis and treatment during the young adult or early reproductive years may call for a special cognizance of the importance of maintaining reproductive function and the prevention of second cancers (Shahin and Puscheck 1998). Cancer patients who are diagnosed and treated around 30–50 years of age may need specific attention for premature menopause; issues relating to sexuality and intimacy; the use of estrogen replacement therapy; prevention of neurocognitive, cardiac, and other sequelae of chemotherapy; and prevention of coronary artery disease and osteoporosis (Herold and Roetzheim 1992; Marina 1997; Schwartz 1999; Aziz 2002a, b). Sexual dysfunction may persist after breast cancer treatment and may include vaginal discomfort, hot flashes, and alterations in bioavailable testosterone, luteinizing hormone, and sex hormone-binding globulin (Ganz et al. 2000; Greendale et al. 2001). Menopausal symptoms such as hot flashes, vaginal dryness, and stress urinary incontinence are very common in breast cancer survivors and cannot be managed with standard estrogen replacement therapy in these patients. The normal life expectancy of survivors of early-stage cancers during these years of life underscores the need to address their long-term health and QOL issues (Herold and Roetzheim 1992; Marina 1997; Schwartz 1999).

Although older patients (65 years of age or more) bear a disproportionate burden of cancer, advancing age is also associated with increased vulnerability to other age-related health problems, any of which could affect treatment choice, prognosis, and survival. Hence, cancer treatment decisions may have to consider preexisting or concurrent health problems (comorbidities). Measures that can help to evaluate comorbidities reliably in older cancer patients are warranted. Little information is available on how comorbid age-related conditions influence treatment decisions and the subsequent course of cancer or the comorbid condition. It is also not known how already compromised older cancer patients tolerate the stress of cancer and its treatment and how comorbid conditions are managed in light of the cancer diagnosis (Yancik et al. 2001; Aziz 2002a, b).

20.8 Physiologic Sequelae of Cancer and Its Treatment

20.8.1 Second Cancers

Second cancers may account for a substantial number of new cancers. A second primary cancer is associated with the primary malignancy or with certain cancer therapies (e.g., breast cancer after Hodgkin's lymphoma, ovarian cancer after

primary breast cancer) (Ho and Frei 1971; Zimm et al. 1983; Meadows et al. 1985; Hawkins et al. 1987; Hildreth et al. 1989; Sankila et al. 1996). Commonly cited secondary malignancies include (a) approximate 20 % risk of myelodysplastic syndromes, acute leukemia, and non-Hodgkin's lymphoma due to the chemotherapy combinations for Hodgkin's lymphoma (alkylating agents and podophyllotoxins); (b) solid tumors such as breast, bone, and thyroid cancer in the radiation fields in patients treated with radiotherapy; and (c) bladder cancer after cyclophosphamide. Secondary solid malignancies have been associated with chemotherapy treatments of Hodgkin's lymphoma up to 20 years after therapy (Foss Abrahamsen et al. 2002). Secondary cancers may also include risks of squamous cell cancer of the skin and sarcoma in radiation fields, such as with breast cancer patients. Within 20 years, survivors of childhood cancer have an 8–10 % risk of developing a second cancer (Draper et al. 1986). This can be attributed to the mutagenic risk of both radiotherapy and chemotherapy, which is further compounded in patients with genetic predispositions to malignancy. The risk of a second cancer induced by cytotoxic agents is related to the cumulative dose of drug or radiotherapy (Herold and Roetzheim 1992; Marina 1997; Schwartz 1999; Aziz 2002a, b).

The risk of malignancy with normal aging may be a result of cumulative cellular mutations. The interaction of the normal aging process and exposure to mutagenic cytotoxic therapies may result in an increased risk of second malignancy, particularly after radiotherapy and treatment with alkylating agents and podophyllotoxins. Commonly cited second cancers include leukemia after alkylating agents and podophyllotoxins; solid tumors, including breast, bone, and thyroid cancer in radiation fields; and bladder cancer after cyclophosphamide. Second cancers may also occur in the same organ site (e.g., breast, colorectal); thus, there is definite need for continued surveillance (Herold and Roetzheim 1992; Marina 1997; Schwartz 1999; Aziz 2002a, b).

Therapeutic doses of radiation have been reported to be associated with increased incidence of secondary cancers after treatment for breast, prostate, and thyroid cancers as well as lymphomas (Armstrong et al. 2010). Because of the sometimes extended period before presentation, the risk of radiation-induced cancer has been underestimated in the past. With higher rates of cure and long-term survival after cancer diagnosis, the probability of treatment-related secondary cancers is becoming better understood. Included among the reported secondary malignancies are lung, esophageal, and colon cancers, leukemias, and soft tissue sarcomas (Armstrong et al. 2010). Modern improvements in dosimetry and patient selection are targeted at reducing the risk (Armstrong et al. 2010).

The risk of secondary malignancy can have long-term psychological impact for patients, as well as overwhelming life changes should a second malignancy occur. In efforts to prevent secondary cancers, treatments may be offered that are associated with other risks on patient QOL. For example, oophorectomy in a breast cancer patient may lead to early menopause and the risks associated with surgery. If antihormonal treatments are implemented, such as tamoxifen to prevent another breast cancer, risks include cardiac toxicity, thrombotic events, or endometrial cancer. These risks must be considered by practitioners and patients prior to initiating treatment. Some patients may initiate alternative medical approaches, which frequently carry unknown risks and unclear benefits (Aziz 2002a, b).

20.8.2 Neurocognitive Function

Most data related to the long-term neurocognitive effects of treatments have focused on brain tumors, especially in children as well as among long-term survivors of breast cancer. A 2011 review found frequent decreased cognitive function among ovarian cancer survivors as well (Correa and Hess 2011). Neurocognitive deficits may be related to surgery, radiation therapy, or chemotherapy. Chemotherapeutics have been associated with long-term neurocognitive deficits for non-CNS tumors (Hess and Insel 2007). While in adults this has been primarily investigated among breast cancer survivors (Schagen et al. 1999; Ahles et al. 2002; Schagen et al. 2002; Castellon et al. 2004), neurocognitive decline is likely to occur in many patients who have been treated with chemotherapeutics (Ahles et al. 2002). For breast cancer survivors, neurocognitive compromise is most profound when tamoxifen was added to chemotherapeutic regimens (Castellon et al. 2004). Despite the preliminary state of this field of research, studies have consistently demonstrated a decline in verbal memory, executive function, and motor function among cancer patients (Anderson-Hanley et al. 2003). It has been estimated that up to 75 % of cancer patients experience a degree of cognitive impairment (Janelsins et al. 2011). Although our understanding of the mechanisms involved is limited, a number of possible etiologies have been considered including genetics, hormonal status, inflammatory response to cancer, and therapy as well as psychological factors (Janelsins et al. 2011). Most commonly affected are executive function, processing speed, and memory (Wefel and Schagen 2012). Imaging studies of breast cancer patients treated with chemotherapy have shown brain atrophy and microstructural damage and that white matter may be particularly vulnerable (Wefel and Schagen 2012). Future research efforts including longitudinal studies, neuroimaging, and animal studies should help us better understand these neurocognitive changes so that preventive or treatment strategies can be developed (Wefel and Schagen 2012).

20.8.3 Gastrointestinal Dysfunction

Radiation therapy has been found to cause fibrosis and stricturing along the alimentary tract and is caused by both brachytherapy (Hishikawa et al. 1986) and external beam (DeCosse et al. 1969; Palmer and Bush 1976). This problem has also been noted with the utilization of photodynamic therapy (McCaughan et al. 1996; Overholt and Panjehpour 1996). The alimentary tract is at risk in the primary or adjuvant treatment of esophageal or rectal tumors; small bowel injury may also occur in the treatment of other intra-abdominal processes, such as pre- or postoperative radiation therapy for retroperitoneal sarcomas. A long-term study of prostate cancer survivors treated with radiotherapy demonstrated that the higher mean absorbed anal sphincter dose is associated with fecal leakage (Alsadius et al. 2012). Large or small bowel strictures can lead to obstruction, the symptoms of which include nausea, vomiting, pain, and bloating. Esophageal strictures can also cause difficulty or inability to swallow. For esophageal or colonic strictures, endoscopic approaches utilizing stents may be beneficial. This approach is not applicable for

most of the small bowel, which may necessitate an operative approach, usually either a bypass or resection. Some surgeons utilize minimally invasive laparoscopic techniques, although this may not be possible if there are abundant adhesions. Long-term gastrointestinal dysfunction is also common among patients suffering from gynecologic cancers. One common example is related to radiation enteritis in the setting of radiation therapy for cervical cancers. In addition, 5–51 % of patients with ovarian cancers present with a bowel obstruction, either as an initial presentation or as a recurrence (Davis and Nouneh 2001). Treatment in both of these settings may be difficult and there is no obvious standard of care.

20.8.4 Pulmonary Dysfunction

Pulmonary dysfunction may be related to major resections, radiation injury, or chemotherapeutic injury. This may be enhanced if the patient has preexisting pulmonary problems. The incidence of lung injury after breast irradiation and after lumpectomy is minimal, but not irrelevant (Kimsey et al. 1994; Dolsma et al. 1997; Theuws et al. 2000). In the context of the large number of women undergoing lumpectomy and radiation therapy as a primary treatment for breast cancer, this problem may be significant, and even more so among women who have underlying lung disease (Theuws et al. 1998). There are many chemotherapeutic agents that can cause pulmonary injury. Bleomycin may be the most well known, but others including cyclophosphamide, mitomycin, carmustine, methotrexate, vinorelbine, gemcitabine, docetaxel, and ifosfamide also increase risk (Makris et al. 2007).

Whenever using these medications, this complication should be anticipated. Therefore, it is recommended to assess pulmonary function tests at baseline and every 3 months while on therapy and carefully follow patients for signs of impending problems such as dyspnea and hypoxia (Ignoffo et al. 1998).

Molecularly targeted anticancer agents are being prescribed with increasing frequency; several are associated with diffuse interstitial lung disease. The tyrosine kinase inhibitors gefitinib and erlotinib have been reported to carry increased risk. In addition, there is a growing body of information associating anti-EGFR antibodies, mTOR inhibitors, multi-kinase inhibitors, and bortezomib with interstitial lung injury (Gemma 2012). Finally, major resections, such as pneumonectomy, may leave patients debilitated and unable to carry out normal functions.

20.8.5 Cardiac Dysfunction

Injury to the heart from chemotherapy, most notably doxorubicin, or from chest wall irradiation is a known risk of cancer treatment. It has been reported that heart disease is the most common cause of death among breast (Patnaik et al. 2011) and endometrial cancer (Ward et al. 2012) patients. Clinical manifestations of anthracyclines include reduced cardiac function, arrhythmia, and heart failure (Lipshultz et al. 1991; Ganz 1998a, b; Lipshultz et al. 2002). Radiation therapy can lead to

valvular damage, pericardial thickening, ischemic heart disease (Lipshultz et al. 1991, 2002), and a decreased ejection fraction (Mukherjee et al. 2003). Left ventricular dysfunction has been associated with other drugs as well, including alkylating agents, antimetabolites, docetaxel, bevacizumab, Herceptin, bortezomib, and several small-molecule tyrosine kinase inhibitors (dasatinib, imatinib, lapatinib, and sunitinib) (Yeh and Bickford 2009). Angiotensin-converting enzyme inhibitors and beta-blockers have been reported to be effective in treating anthracycline-induced heart failure in some patients (Yeh and Bickford 2009).

Cardiac ischemia is associated with antimetabolites, antimicrotubule agents, bevacizumab, and small-molecule tyrosine kinase inhibitors (erlotinib and sorafenib) (Patnaik et al. 2011). Hypertension has been reported in up to 35 % of patients treated with bevacizumab and even more frequently in those receiving sorafenib or sunitinib; discontinuing the drug and treatment with angiotensin-converting enzyme inhibitors may be beneficial Yeh and Bickford (2009). Finally, bradycardia is associated with paclitaxel and thalidomide and prolonged QT interval with vorinostat, arsenic, dasatinib, lapatinib, and nilotinib (Yeh and Bickford 2009).

Cardiac adverse effects may have long-term impact on a patient's QOL and ability to lead an active life. Protective agents, such as dexrazoxane or amifostine, may be given during chemotherapy in an effort to reduce the risk of cardiac damage. Other cardioprotective agent therapies are being studied (Olson et al. 2003; Oliveira et al. 2004). Myocardial injury at the time of radiotherapy may be lessened by breathing techniques (Sixel et al. 2001) and tailored radiation fields. Despite these preventive measures, heart damage is not completely avoidable in patients undergoing these treatments and may cause considerable long-term morbidity. European Society of Medical Oncology (ESMO) guidelines suggest that baseline left ventricular ejection fraction be obtained before administration of potentially cardiotoxic therapy (Curigliano et al 2012). In addition, ESMO notes that baseline and periodic troponin I or BNP measurements may be helpful to indicate when patients on treatment should have further cardiac evaluation. Cardiac evaluation 4 and 10 years after completion of anthracycline therapy is also recommended (Curigliano et al. 2012). Patients receiving more than 30 Gy of radiotherapy to cardiac structures are also recommended for periodic posttreatment cardiac evaluations (Curigliano et al. 2012).

20.8.6 Endocrine Dysfunction

There are multiple potential endocrine problems related to cancer prevention and treatment (Sklar 1999). One common disorder is related to thyroid cancer, whereby total thyroidectomy will necessitate lifelong thyroid replacement therapy. In the case of pancreatic surgery, deficiencies of pancreatic hormones, such as insulin, are treatable, yet they may severely alter a patient's life. This may include the need to control diet, use oral diabetes medications, or take insulin. Perhaps the most common hormonal difficulty is related to the surgical or medical ablation of estrogen in female patients. This will lead to temporary or permanent menopause symptoms. Hot flashes related to tamoxifen can be debilitating and necessitate discontinuing this medication.

Tamoxifen blocks estrogen receptors in most hormonal tissues but is a selective estrogen receptor modulator with estrogenic effects in some tissues and antiestrogenic effects in others. Other medications that block estrogen effects, or activity, are aromatase inhibitors, progestins, and fulvestrant; some of these medications are used for treatment of breast cancer (Osipo et al. 2004). However, control of symptoms does not also compensate for the loss of hormones with regard to bone loss. Strategies to prevent or treat osteopenia are of considerable interest (Coleman 2004).

Several anticancer treatments, including hormonal therapies, corticosteroids, and a number of chemotherapy drugs, accelerate bone loss and increase risk of fracture (Guise 2006). Cancer treatment-induced bone loss has been studied most extensively in patients with breast and prostate cancer as a result of oophorectomy or orchiectomy and administration of selective estrogen receptor modulators, aromatase inhibition, or antiandrogenic treatments. However, methotrexate, alkylating agents, cisplatin, and radiotherapy, used for a number of other malignancies, also are associated with osteopenia (Hu et al. 2010). Bisphosphonates and lifestyle changes (including exercise, vitamin D, and calcium supplementation) historically have been the cornerstones of management. In 2011, denosumab, a monoclonal antibody against RANK ligand (RANKL), was approved for treatment of certain types of cancer-induced bone loss. RANKL is an important component of certain conditions characterized by bone loss, and it is anticipated that denosumab therapy will help in maintaining bone health among cancer survivors (Goessl et al. 2012).

Another hormone dysfunction that can severely alter a patient's QOL is related to advanced neuroendocrine tumors. These can include the carcinoid syndrome, glucagonoma, and insulinoma. There are multiple techniques that can limit the effects of these tumors. These include somatostatin, alpha-interferon, ablative techniques (e.g., radiofrequency ablation, hepatic artery chemoembolization), and surgical extirpation (Krouse 2004). These techniques have shown benefit in multiple instances. The rarity of these tumors makes large prospective studies for these cancers very difficult.

20.8.7 Intestinal Stomas

While intestinal stomas will clearly lead to QOL difficulties as described above, some patients will have long-term problems that may continue to affect daily life. Many issues of concern include problems with travel, intimacy, and satisfaction with appearance. For patients with colostomies and ileostomies, health-related QOL seems to improve with time (Grant M, 2000, unpublished data), although the evidence is not consistent in all studies (Klopp 1990). Many studies have documented additional issues of concern for ostomates, including sexuality (Hojo et al. 1991; Grunberg 1986; Ofman and Auchincloss 1992; Fazio et al. 1980; Yeager and Van Heerden 1980; Borwell 1997; Sprangers et al. 1995), psychological problems (Thomas et al. 1987; Hurny and Holland 1985; Keyes et al. 1987; Wirsching et al. 1975; Sutherland et al. 1952; Krouse et al. 2007a, b), and interference with work, recreational, and sporting activities (Sprangers et al. 1995; Wirsching et al. 1975; Krouse et al. 2004, 2007a, b). Reasons for continued problems may be due to lack of

perioperative teaching, poor stoma placement, stoma-related complications such as hernia or prolapse, or lack of a familial or support group assistance. Research is still needed to better understand the nature and cause of many of these problems so that appropriate interventions may be designed.

20.8.8 Lymphedema

The long-term effects of lymph node dissection are frequently related to disruption of nerves or lymphatics. Nerve disruption may lead to pain syndromes, numbness, or other effects such as paresthesias (Nagel et al. 2003). There is a large spectrum of presentations of lymphedema from axillary dissection, from arm heaviness to elephantiasis. Reported lymphedema rates are variable but likely around 27 % (Beaulac et al. 2002; Golshan et al. 2003; Voogd et al. 2003; Bani et al 2007). This rate may be as high as 49 % for long-term survivors (Petrek et al. 2001). Sentinel node mapping decreases this risk (Haid et al. 2002; Golshan et al. 2003; Schijven et al. 2003; Lucci et al. 2007). It is likely that many patients (38–93 %) will also have other limb symptoms such as pain, numbness, poor range of motion, and weakness (Ververs et al. 2001; Engel et al. 2003; Nagel et al. 2003; Schijven et al. 2003). In addition, newer technologies will assist in the early diagnosis of lymphedema, which will also potentially lead to greater numbers of patients diagnosed with this disorder.

Lymphedema is a risk for patients who have radiation therapy to lymph node basins (Erickson et al. 2001; Meric et al. 2002; Bani et al. 2007). This is especially accentuated if there is a previous lymph node dissection in the same basin. Lymphedema may occur early or many years from treatment and is especially problematic if lymph node basins have been irradiated in addition to having been dissected (Kissin et al. 1986; Ryttov et al. 1988). Preventive strategies, such as limiting the extent of node dissections and use of sentinel node biopsy, in lieu of complete lymphadenectomy, when appropriate are important.

Treatments such as complete decongestive therapy, compression therapy, manual lymphatic drainage, and closed-controlled suction drainage all have been applied with varying degrees of success. Limb elevation, use of compression garments, and massage are frequently used in combination. There are increasing reports of successes with active treatment approaches (Kim et al. 2007; Vignes et al. 2007; Moseley et al. 2007; Hamner and Fleming 2007) (Beck et al. 2012) and research is ongoing.

Historically, surgical techniques for massive lymphedema have primarily focused on debulking procedures. Liposuction, along with compression therapy, has been reported to be beneficial in this setting (Brorson et al. 2006). In addition, microvascular surgical techniques may provide patients with other options to address this debilitating problem (Campisi et al. 2007). Possible adverse effects of exercise have been postulated; however, a recent review of the literature in breast cancer survivors found evidence to support the safety of resistance exercise without increasing lymphedema (Kwan et al. 2011).

20.8.9 Pain

The issue of pain related to cancer and its treatment is quite common and plays an overwhelming role in a patient's life. Nearly 75 % of patients with advanced cancer have pain, with most having moderate or greater levels of pain (ACS 2001). Chronic pain may be related to nerve disruption at the time of surgery, tumor-related persistent pain, or other treatment-related issues. Frequently, these may not be well described by the patient or well understood by the medical team. The psychological health of the patient may have a significant role in the perception of pain, and chronic pain may also severely negatively impact a patient's psychological health (ACS 2001). If a patient has recurrence, pain may be more pronounced compared to a patient who is without disease.

Pain may follow surgery or radiation and can exacerbate other symptoms including depression, fatigue, and insomnia. Postmastectomy and post-thoracotomy pain are reported in up to 50 % of patients so treated. Radiation fibrosis may lead to pain associated with diminished range of motion or nerve injury. Antidepressants, anticonvulsants, opioids, and topical preparations each has a role in pain control. Often a multidisciplinary approach, incorporating pharmacologic, psychological, and rehabilitative methods, is beneficial (Pachman et al. 2012).

A focus on pain has brought anesthesia pain specialists, palliative care specialists, and others together to study optimal approaches to the myriad of pain syndromes faced by long-term cancer survivors. Clearly, there are many approaches to the treatment of pain. The etiology, type, intensity, location, and time course of pain, as well as a patient's tolerance to pain, may all impact the choices of care. For example, bone metastases may be treated with the use of opioids, steroids, radiation therapy, radiofrequency ablation, or nerve blockade. Based on a thorough understanding of the pain experienced by the patient, the optimal approach or approaches can be initiated. The recent use of radiofrequency ablation to treat soft tissue pain (Locklin et al. 2004) is a novel attempt to treat pain based on a new technology. The use of complementary nondrug techniques may play an increasing role as they are studied. For example, it has recently been reported that massage therapy is an effective and safe adjuvant therapy for the relief of acute postoperative pain after a major operation (Mitchinson et al. 2007).

20.8.10 Cosmesis

Cosmetic problems are noted with many surgical procedures, such as amputations, neck dissections, major facial tumor resections, mastectomies, and placement of intestinal stomas. Scarring can be psychologically debilitating for a patient. Minimally invasive procedures have provided improved cosmetic results. This may include laparoscopic colectomies for colon cancer, with smaller incisions and thus smaller scars, and limb-sparing approaches for sarcomas. These approaches are either not applicable or attempted for many surgical procedures due to size of tumor, location of tumor, experience of the surgeon, or inability to achieve surgical objectives such as negative margins.

Cosmetic problems are most notable with head and neck cancers. Surgical treatment, or effects of the tumor itself, may result in facial nerve injury. Major reconstruction may be necessary, and results are most obvious to patients, families, and onlookers. In fact, about 50 % of patients who undergo procedures on head and neck cancers feel that this is a moderate to severe problem (List and Bilir 2004). Survival is not diminished with breast-sparing lumpectomies followed by radiation (Fisher et al. 1995). Cosmesis is generally good and breast-sparing treatment is standard of care for appropriate patients. Nonetheless, self-reported data from women who have undergone breast-conserving treatment show that 30 % felt that the cosmetic result was either "fair" or "poor" (Hill-Kayser et al. 2012). For those who choose to have mastectomy, or those for whom a mastectomy is recommended, reconstruction approaches are available to improve body image.

Radiation therapy may also leave cosmetic results that can be quite disturbing to the patient and family. Cosmetic damage due to radiation may lead to trismus when treating head and neck cancers or alterations of the breast. While these problems may improve with time, there may be long-term or even lifetime difficulties.

20.8.11 Phonation

The ability to speak may be impaired with many head and neck cancers and brain tumors (primary and metastatic). This may be due to recurrent laryngeal nerve invasion or injury during a surgical procedure, laryngectomy, or tongue resections. Recurrent laryngeal injury will lead to a hoarse voice and inability to yell, although this frequently improves with time. Removal of the larynx will leave the patient unable to speak, requiring that a patient communicate by writing or through a device pressed against the submental area. This device gives the patient a robotic voice, which may be unacceptable for many patients. Loss of the tongue will make it difficult or impossible to enunciate words, although many patients will frequently be able to be understood in conversation. Radiotherapy has been utilized to preserve the larynx in some patients with laryngeal cancer. In a small pilot study, it was found that patients treated with radiation for larynx cancer retained functional voice (Lau et al. 2010).

20.8.12 Swallowing

The ability to swallow, imperative for the ability to eat, has significant social impact of a person's QOL (List and Bilir 2004). The inability to swallow and the need for a feeding tube have been noted to be the most important QOL issues among head and neck cancer patients (Terrell et al. 2004). The ability to preserve swallowing function is likely the most important outcome of esophageal surgery. Curative surgery is generally unlikely in the setting of esophageal cancer, but maintaining the ability to eat is an attainable goal by removing the tumor and maintaining gastrointestinal continuity via a surgically created neoesophagus (Branicki et al. 1998).

20.8.13 Sexual Dysfunction

Sexual function is important to most people, yet estimates of the prevalence of sexual dysfunction in persons with cancer range from 20 to 90 % (Ganz 1998a, b, 2001; Varricchio and Aziz 2000; Aziz 2002a, b). It is estimated that among women with breast cancer who were 45 years of age or younger at diagnosis, 45 % have some degree of sexual dysfunction after completion of treatment. In women currently on treatment, 64 % report sexual dysfunction (Kedde et al. 2012). Sexuality encompasses a spectrum of issues ranging from how one feels about one's body to the actual ability to function as a sexual being. Sexual dysfunction has been reported as a persistent effect of cancer treatment. Dysfunction may be related to multiple factors, including nerve injury, physical and physiologic changes, disfigurement, perceived loss of sexuality, and loss of libido. Preexisting sexual dysfunction may also be exacerbated by cancer and its treatment (Ganz et al. 1992).

Nerve injury has implications for both males and females, although these issues have been studied much more for males. Without rehabilitation, approximately 85–90 % of men with prostate cancer suffer erectile impotence secondary to surgery or radiation (Stoudemire et al. 1985; McKenna et al. 1995). For pelvic cases in males, surgical strategies employing sharp dissection of the mesorectum will allow visualization of the sympathetic and parasympathetic nerves, thus preserving erectile and ejaculatory function in most cases (Meuleman and Mulders 2003). These strategies are being explored in radical pelvic surgery for gynecologic cancers as well. While radiation therapy has less incidence of nerve injury than surgical interventions, it nevertheless still carries some risk (Goldstein et al. 1984).

Emotional response to the diagnosis or treatment of cancer can have dramatic effects on sexuality issues (Varricchio and Aziz 2000). Loss of perceived sexuality, by either the patient or the partner, can lead to loss of sexual interactions that once were active and fulfilling. These perceptions may be related to bodily changes, such as creation of a stoma or removal of a breast. These changes can limit interest in sex and interfere with sexual arousal and satisfaction. Pain or bodily function problems may not allow the patient to relax and enjoy sex. By learning what cancer means to the patient and their loved ones, the clinician can correct misinformation and facilitate the patient's adjustment to the illness (Ell et al. 1988).

Gonadal dysfunction or failure can lead to infertility for both male and female cancer survivors (Sklar 1999; Ganz 2001; Aziz 2002a, b). Recovery of gonadal function will depend on type of therapy (such as radiation, chemotherapy, or hormone therapy) dosing and social and psychological factors. Cryopreservation of sperm, ova, or embryos may be considered. Androgen deprivation therapy (ADT) is frequently prescribed for treatment of prostate cancer and is associated with compromised sexuality. It is estimated that 600,000 men in North America are treated with ADT. Adverse impacts include erectile dysfunction, decreased libido, anatomic changes in penis and testes, difficulties with ejaculation, and depression (Higano 2012). Women with gynecologic malignancy have elevated incidence of female sexual dysfunction, often exacerbated by menopause (Ratner et al. 2010). Medical management and psychotherapy have central roles in management of sexual dysfunction in survivors and their partners.

20.8.14 Xerostomia

Dry mouth is a common effect of head and neck irradiation including the parotid nodal field. Improved radiation therapy techniques have focused on lessening the effects of this condition, but this remains a problem for many patients. Patients who suffer from xerostomia frequently must have water nearby at all times. This problem is usually a lifetime issue for patients (August et al. 1996; Liem et al. 1996; Kosuda et al. 1999; Johansson et al. 2002). While it has been shown that many patients adequately adapt to this problem, it remains a serious morbidity of head and neck irradiation. Salivary flow can be stimulated by the use of cholinergic pharmaceutical preparations. Pilocarpine may lead to symptomatic improvement (Hawthorne and Sullivan 2000), but research is necessary to improve this treatment-related survivorship issue. If these treatments fail, mouthwash and saliva substitutes are secondary options (Nieuw Amerongen and Veerman 2003). Bioactive saliva substitutes and mouthwashes are currently under investigation for application in the clinic. These contain antimicrobial peptides to protect the oral tissues against microbial colonization and to suppress and to cure mucosal and gingival inflammation (Nieuw Amerongen and Veerman 2003).

20.8.15 Asthenia/Anorexia/Cachexia

Overwhelming fatigue, loss of appetite, and wasting are difficult issues that affect the long-term as well as the short-term QOL of cancer survivors. Asthenia impacts all phases of life and therefore must be addressed over time. Severe fatigue is a problem for almost 40 % of breast cancer survivors (Servaes et al. 2002). Breast cancer patients who experienced severe fatigue suffered from problems with psychological well-being, functional impairment, sleep disturbance, physical activity, social support, and neuropsychological and social functioning as compared with breast cancer survivors who did not have persistent fatigue. Therefore, it is imperative to address all known etiologies, including depression, anemia, and drug and alcohol use. For patients who are Hodgkin's lymphoma survivors, one-half of the fatigue cases have psychological distress that may respond to treatment (Loge et al. 2000). Related to chronic anorexia, progestational drugs can somewhat stimulate appetite, food intake, and energy level; they promote weight gain in some patients and often decrease nausea and vomiting severity; however, pharmacologic treatment of cancer cachexia remains disappointing (Body 1999).

Cachexia is the most common paraneoplastic syndrome of malignancy, causing the death in as many as 20 % of patients with cancer (Ottery 1994). While frequently considered for patients undergoing treatment or those near the end of life, these problems may persist among cancer survivors (Body 1999). Patients with advanced or chronic disease may live for years and suffer slow wasting over time. There are few current treatment options.

Recent research has suggested a multifactorial etiology for the cancer anorexia-cachexia syndrome leading to treatment strategies including appetite stimulation and short-term corticosteroid administration. Other potentially beneficial therapies

include inhibition of cyclooxygenase-2, ghrelin, to stimulate growth hormone secretion and promote food intake and insulin, branched chain amino acids, oxandrolone, and olanzapine. Investigations of these approaches are currently underway (Mantovani and Madeddu 2010).

20.8.16 Neuropathy

With the successful use of growth factor support, the frequency and severity of myelotoxicity has decreased and chemotherapy-induced peripheral neuropathy (CIPN) has become a dose-limiting toxicity for a number of agents. Unlike hematologic toxicities, successful interventions, prevention and treatment, for CIPN have been elusive. Presently, there is no standard therapy and prevention is primarily based on dose modification and discontinuation of neurotoxic agents.

CIPN is primarily sensory and, generally, is associated with increasing cumulative doses. Two exceptions are oxaliplatin and taxanes, which may cause immediate neurotoxicity. In addition to platinums and taxanes, vinca alkaloids, epothilones, bortezomib, suramin, and thalidomide are known to be neurotoxic. The mechanism of neurotoxicity differs between the classes of agents; this may be one reason why a single effective preventative or therapeutic intervention has not been identified. Diabetes and other medical conditions causing neuropathy may exacerbate the effects of chemotherapy. Paresthesias, dysesthesias, and pain are prominent and management is primarily symptomatic (Grisold et al. 2012; Argyriou et al. 2012). On occasion, neurotoxicity can worsen for up to 6 months after cessation of treatment, a phenomenon called "coasting." CIPN also may improve spontaneously after chemotherapy is stopped.

20.8.17 Fertility

With the increasing numbers of reproductive-age cancer survivors comes great concern regarding future fertility. Surgery, chemotherapy, and radiation each may adversely affect fecundity. The American Society of Clinical Oncology (ASCO) recommends options for preserving fertility as early as is possible during planning anti-cancer therapy (Lee et al. 2006). A number of factors impact the gonadotoxicity of chemotherapy agents (Blumenfeld 2012); alkylating agents are destructive to oocytes, and anthracyclines and platinums are female-specific mutagens (Bauman et al. 2012). In males, alkylating agents, nitrosoureas, and platinums cause azoospermia (Lee et al. 2006). Treatment options known to be effective are limited. Oophoropexy can move the ovaries out of a planned radiation filed, sperm and embryo cryopreservation are available. Ovarian suppression and testicular and ovarian tissue cryopreservation are being investigated (Jensen 2011). The Oncofertility Consortium, an NIH-funded multidisciplinary project, has been established. The consortium is active in research and teaching directed at preserving fertility for young people with cancer (Woodruff 2010).

20.8.18 Employment and Financial

Cancer diagnosis frequently is associated with substantial adverse financial outcomes. Even patients with health insurance may incur relatively expensive out-of-pocket expenses for co-pays, prescription, and nonprescription medicines, transportation, and other needs. In addition, absence from work, for at least a period of time, is frequent and may be associated with decreased income.

A review of the literature finds a wide range of probabilities that a cancer survivor will return to work. It has been estimated that 64 % (ranging from 24 to 94 %) of survivors will resume working (Mehnert 2011). It does not appear that education, marital status, gender, or income are predictive; however, certain prognostic factors have been identified (Spelten 2002). Older age at diagnosis, head and neck cancer, nonsupportive work environment, having surgical treatment, and having a manual labor job each is associated with a lower probability of working after diagnosis (Mehnert 2011). One study found that after completion of a rehabilitation program, the odds of returning to work were significantly higher with an intent, at baseline, to return to work, perceived employer accommodations, and a job with high-level requirements (Mehnert 2011). The odds of returning to work were lowered with cancer recurrence or progression, baseline sick leave absence, and problematic social interactions (Mehnert 2011). It is estimated that after returning to work, 56 % of cancer survivors will experience a change in job responsibilities and view of their work (Mehnert 2011). Interventions to increase successful return to work have been studied in small series; results have been mostly inconclusive (Tamminga 2010). Research in this area is ongoing.

20.8.19 Fatigue

Nearly all patients on anticancer treatment experience some degree of fatigue; however, many survivors report troublesome fatigue months and years after completion of treatment. The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as "tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with normal functioning" (NCCN 2012). NCCN guidelines recommend that every cancer patient be screened for fatigue (NCCN 2012).

The etiology of cancer-related fatigue is complex and multifactorial. Medications, other physical symptoms, emotional distress, nutritional disorder, medical comorbidities, sleep disturbance, and physical limitations all contribute (Horneber et al. 2012) to CRF. Several specific clinical risk factors for CRF have been delineated including pain, nausea, preexisting depression, and other emotional disturbance and stressors (Horneber et al. 2012). It has been estimated that nearly half of cancer survivors report CRF 2 years after completion of therapy (Horneber et al. 2012).

Several non-pharmacologic interventions show promise for management including exercise, education, acupuncture, healing touch, massage therapy and psychological support, intensive rehabilitation, and several complementary therapies (Mitchell 2010). Medications including ATP, bupropion, methylphenidate,

paroxetine, vitamins C and D, thyrotropin-releasing hormone, and others may also improve cancer-related fatigue (Mitchell 2010).

20.9 Survivorship Care Planning

Following the 2006 Institute of Medicine recommendation that cancer patients be provided with survivorship care plans (SCP) as they complete primary treatment, there has been growing interest and research directed toward this goal (Earle 2007). The IOM recommends that the survivorship plan should, at minimum, contain information about diagnosis, treatment and dates received, supportive services provided, contact information for all institutions and providers, and recommended surveillance (Earle 2007). Patients and their primary care providers should receive copies (Earle 2007).

At this time, the format and content of survivorship care plans are being developed. A 2009 survey of comprehensive cancer centers found that only 43 % used SCPs for breast and colorectal cancer patients (Salz et al. 2012) and that key elements were missing in all the plans (Salz et al. 2012). Reasons vary but include availability of financial resources, time, and institutional commitment. In addition, it has been postulated that some of the IOM recommendations are vague and broad in scope which may make interpretation and implementation challenging (Salz et al. 2012). A survey of cancer physicians in Massachusetts found similar results; 56 % of practices prepared treatment summaries and similar barriers to adoption were reported (Merport et al. 2012). It seems clear that additional work is needed in order to provide all cancer survivors with SCPs to help them transition after treatment is complete.

20.10 Grading of Late Effects

The assessment and reporting of toxicity, based on the toxicity criteria system, plays a central role in oncology. Grading of late effects can provide valuable information for systematically monitoring the development, progression, or regression of late effects (Trotti 2002). While multiple systems have been developed for grading the adverse effects of cancer treatment (Ganz 1998a, b), there is no current universally accepted grading system (Aziz 2002a, b; Trotti 2002; Aziz and Rowland 2003). In contrast to the progress made in standardizing the measurement of acute effects, the use of multiple grading systems for late effects hinders the comparability of clinical trials, impedes the development of toxicity interventions, and encumbers the proper recognition and reporting of late effects. The wide adoption of a standardized criteria system can facilitate comparisons between institutions and across clinical trials (Trotti 2002; Aziz and Rowland 2003).

Multiple systems have been developed and have evolved substantially since first introduced more than 20 years ago (Hoeller et al. 2003). Garre and colleagues (1994) developed a set of criteria to grade late effects by degree of toxicity as follows: grade 0, no late effect; grade 1, asymptomatic changes not requiring any corrective measures and not influencing general physical activity; grade 2, moderate symptomatic changes

interfering with activity; grade 3, severe symptomatic changes that require major corrective measures and strict and prolonged surveillance; and grade 4, life-threatening sequelae. A similar system, the Swiss Pediatric Oncology Group (SPOG) grading system, has not yet been validated. The SPOG system also ranges from 0 to 4: grade 0, no late effect; grade 1, asymptomatic patient requiring no therapy; grade 2, asymptomatic patient, requires continuous therapy, continuous medical follow-up, or symptomatic late effects resulting in reduced school, job, or psychosocial adjustment while remaining fully independent; grade 3, physical or mental sequelae not likely to be improved by therapy but able to work partially; and grade 4, severely handicapped and unable to work independently (von der Weid et al. 1996).

The NCI Common Toxicity Criteria (CTC) system was first developed in 1983. The most recent version, Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.03 was released in June 2010), is a comprehensive, multimodality grading system for reporting both acute and late effects of cancer treatment. CTCAE consists of a list of event terms and a five-point severity scale to characterize treatment-related adverse events. Version 4.03 incorporates MedDRA (Medical Dictionary for Regulatory Activities) terminology. MedDRA is a taxonomy used by regulatory agencies and the pharmaceutical industry, and its incorporation into the CTCAE is expected to improve congruence of clinical trial outcomes with regulatory processes (NCI 2010). CTCAE facilitates standardized reporting of adverse events and comparisons of outcomes between trials and institutions (Trotti 2002).

Tools for grading late effects of cancer treatment are available for validation in larger populations and to examine their utility in survivors of adult cancers. Oncologists, primary care physicians, and ancillary providers should be educated and trained to effectively monitor, evaluate, and optimize the health and well-being of a patient who has been treated for cancer. Additional research is needed to provide adequate knowledge about symptoms that persist following cancer treatment or those that arise as late effects especially among survivors diagnosed as adults. Prospective studies that collect data on late effects will provide much needed information regarding the temporal sequence and timing of symptoms related to cancer treatment. It may be clinically relevant to differentiate between onset of symptoms during treatment, immediately following treatment, and months to years later (Aziz 2002a, b; Aziz and Rowland 2003). Continued, systematic follow-up of cancer survivors will result in information about the full spectrum of damage caused by cytotoxic or radiation therapy and possible interventions that may mitigate these adverse effects.

The role of comorbidities on the risk for, and development of, late effects of cancer treatment among, especially, adult cancer survivors has yet to be fully understood. Practice guidelines for follow-up care of cancer survivors and evaluation and management of late effects also have yet to be developed so that effects can be mitigated whenever possible (Aziz 2002a, b; Aziz and Rowland 2003).

In 2004, NIH, recognizing the limitations of existing reporting systems for evaluating the day-to-day functioning of patients with a wide spectrum of diseases, began working on the Patient-Reported Outcomes Measurement Information System (PROMIS). PROMIS is comprised of a number of item banks/instruments in the domains of physical, mental, and social health. Item banks are assessed for reliability, precision, and construct validity and eleven currently are available for use in

clinical research. PROMIS item banks provide a common, precise, and reliable platform for evaluation of self-reported outcomes (Cella et al. 2010). Patient-reported outcome measurements add a critical dimension to the radiographic and laboratory tests used to evaluate and compare treatments.

20.11 Advanced Illness

Care for patients with incurable disease has been recognized as an important component of quality care for cancer patients (Foley and Gelband 2001). Patients with advanced illness face many of the same issues of other survivors, although issues may be magnified. The most common problem for patients with advanced cancer is asthenia (Verger et al. 1992). There are many other specific pain and symptom management issues that present for patients with advanced illness that must be better understood so that improved treatments can be developed. Examples include malignant bowel obstruction, malignant ascites, fungating breast tumors, and painful bony metastasis. These are just some of the many problems that cancer patients frequently face with advanced disease. While there are many explanations as to why there is a paucity of data in many of these situations, there is an opportunity for researchers to explore best practices of care in these situations (Krouse et al. 2004). Research goals and standards equivalent to those for other medical specialties will provide a solid framework for end-of-life care (Casarett 2002).

End-of-life (EOL) care is a complex subject and a focus on QOL of patients and their families is of utmost importance. There are many areas of need for patients and families, and resources are often available. However, EOL care in the USA may be substandard in a significant proportion of cases (U.S. end-of-life care gets a (barely) passing grade 2003). Patients frequently die in the hospital; hospice services may not be readily available, or not consulted until late in the patient's course, and too few palliative care specialists are available. Late hospice consultation may be related to multiple factors, including over optimistic prognosis (Lamont and Christakis 2001). Although increasing numbers of hospitals have palliative care services, such services are still lacking in many centers (Billings and Pantilat 2001), and there are gaps in education of cancer specialists related to EOL care (McCahill et al. 2002; Cherny and Catane 2003). This is a specific area of needed focus for researchers and educators. Communication skills, knowledge of resources, planning for death, pain and symptom management, and advanced directives are all factors that must be considered in the optimal care for the patient facing death. There are multiple ethical dilemmas related to EOL care and research in this population, although opportunities are available to expand research in this population (Krouse et al. 2003; Krouse et al. 2004). A meeting was convened to augment research in this population, focused on malignant bowel obstruction (MBO) as a model (Krouse 2007). This was chosen as it is a relatively common problem (Krouse et al. 2002; Fainsinger et al. 1994; Ripamonti and Mercadante 2004; Davis and Nouneh 2001) and has disparate treatment approaches that may be effective. Cultural, ethical, and implementation issues were noted to mandate special care in clinical trials of palliative and EOL care (Fineberg et al. 2007; Laneader et al. 2007; Whalen et al. 2007). In addition, methods of measuring outcomes and benefit of treatments may differ from those in other types of studies (Mularski et al. 2007; Anthony et al. 2007).

Analysis of data recorded from participants in ASCO's Quality Oncology Practice Initiative indicates that less than half of cancer patients enroll in hospice prior to death (Kuehn 2011). Coupled with the growing body of information demonstrating the benefits of timely and comprehensive end-of-life and palliative care practices (Smith et al. 2012; Peppercorn et al. 2011), this finding suggests a substantial unmet need. An epidemiologic study of hospitalized cancer patients in Germany reported that 7 % have palliative care needs, including 28 % with head and neck cancers, 26 % with melanoma, and 18 % with brain tumors (Weaver et al. 2012). It is generally advisable to involve families and significant others in decision-making processes.

20.12 Future Directions

A large and growing community of cancer survivors is one of the major achievements of cancer research over the past three decades. Both length and quality of survival are important end points. Many cancer survivors are at risk for and develop physiologic and psychosocial late and long-term effects of cancer treatment that may lead to premature mortality and morbidity. As in the past when treatments were modified to decrease the chance of toxicities in childhood cancer survivors, the goal of future research and treatment should also be to evaluate these adverse consequences systematically and further modify toxicities without diminishing cures. Interventions and treatments that can ameliorate or manage effectively both persistent and late medical or psychosocial effects of treatment should be developed and promoted for use in this population. Oncologists, primary care physicians, and ancillary providers should be educated and trained to effectively monitor, evaluate, and optimize the health and well-being of a patient who has been treated for cancer.

Additional research is required to provide adequate knowledge about symptoms that persist after cancer treatment or arise as late effects and interventions that are effective in preventing or controlling them. Continued, systematic follow-up of survivors will result in information about the full spectrum of damage caused by cytotoxic and radiation therapy and possible interventions that may mitigate the effects. Interventions, both therapeutic and lifestyle, that carry the potential to treat or ameliorate these late effects must be developed and should be investigated in larger populations of cancer survivors, those with understudied cancer sites and ethnocultural minority or medically underserved groups.

The relative lack of knowledge that currently exists about the physical health and quality-of-life outcomes of cancer survivors represents a clear area of challenge. It is also one for exciting opportunity and growth. Cancer is expected to become the leading cause of death in the future as a result of our aging population, reduced death rates from cardiovascular disease, and efficacious treatment and screening methodologies. Effective strategies to prevent and delay treatment-related physiologic and psychosocial sequelae must be developed, tested, and disseminated (if found to be effective) to achieve not only the goal of higher cancer cure rates but also a decreased risk of adverse health and social outcomes. As survivorship issues are increasingly explored and mandates are promoted from the survivor community, research in each of the areas described in this chapter should increase in the future (Tables 20.1 and 20.2). Ethical dilemmas and barriers to care and research must be

Table 20.1 Domains and priority areas for cancer survivorship research

Survivorship research domain	Definition and potential research foci
Descriptive and analytic research	Documenting for diverse cancer sites the prevalence and incidence of physiologic and psychosocial late effects, second cancers, and their associated risk factors *Physiologic outcomes of interest* include late and long-term medical effects such as cardiac or endocrine dysfunction, premature menopause, and the effect of other comorbidities on these adverse outcomes *Psychosocial outcomes of interest* include the longitudinal evaluation of survivors' quality of life, coping and resilience, spiritual growth
Intervention research	Examining strategies that can prevent or diminish adverse physiologic or psychosocial sequelae of cancer survivorship Elucidating the impact of specific interventions (psychosocial, behavioral, or medical) on subsequent health outcomes or health practices
Examination of survivorship sequelae for understudied cancer sites	Examining the physiologic, psychosocial, and economic outcomes among survivors of colorectal, head and neck, hematologic, lung, or other understudied sites
Follow-up care and surveillance	Examining the impact of high-quality follow-up care on early detection or prevention of late effects Elucidating whether the timely introduction of optimal treatment strategies can prevent or control late effects Evaluating the effectiveness of follow-up care clinics/programs in preventing or ameliorating long-term effects of cancer and its treatment Evaluating alternative models of follow-up care for cancer survivors Developing a consistent, standardized model of service delivery for cancer-related follow-up care across cancer centers and community oncology practices Assessing the optimal quality, content and frequency, setting, and provider of follow-up care for survivors
Economic sequelae	Examining the economic effect of cancer for the survivor and family and the health and quality-of-life outcomes resulting from diverse patterns of care and service delivery settings
Health disparities	Elucidating similarities and differences in the survivorship experience across diverse ethnic groups Examining the potential role of ethnicity in influencing the quality and length of survival from cancer
Family and caregiver issues	Exploring the impact of cancer diagnosis in a loved one on the family and vice versa
Instrument development	Developing instruments capable of collecting valid data on survivorship outcomes and developed specifically for survivors beyond the acute cancer treatment period Developing/testing tools to evaluate long-term survival outcomes and those that (1) are sensitive to change, (2) include domains of relevance to long-term survivorship, (3) and will permit comparison of survivors to groups of individuals without a cancer history and/or with other chronic diseases over time. Identifying criteria or cutoff scores for qualifying a change in function as clinically significant (e.g., improvement or impairment)

Table 20.2 Future areas of research emphasis in long-term cancer survivorship research

Area of research emphasis	Potential research questions
(A) *Research related to specific survivor groups*	What are the late or persistent effects of cancer and its treatment in *older* adult (65 years or older) long-term cancer survivors?
(i) Those treated for previously understudied cancer sites (e.g., colorectal, gynecologic, hematologic, head and neck, lung)	What is the health status, functioning, and quality of life of long-term cancer survivors belonging to diverse cancer sites?
(ii) Those belonging to understudied or underserved populations (adult, elderly, rural, low education/income, and diverse racial and ethnic populations)	Which are the most common chronic and late effects among survivors across diverse cancer sites and which may be unique to subsets of different cancer survivor groups? What are the characteristics of long-term survivors from rural communities and those from low income and educational backgrounds? What are the similarities and differences in the survivorship experience among underserved cancer survivors and Caucasian survivors?
(B) *Research addressing specific gaps in our knowledge*	(i) *Physiologic late or long-term effects*
In particular as related to	Who is at risk for late and long-term effects and can they be protected? Are there specific, modifiable risk factors (other than exposure to treatment) for the development of late effects?
(i) *Physiologic late or long-term effects*	Which subgroups of adult cancer survivors are at elevated risk for declines in functional status? What are the most common late physiologic sequelae of cancer and its treatment among adults and their effect on physical and psychosocial health? To what extent does cancer treatment accelerate age-related changes? Do comorbidities affect risk for, development of, severity and timing of late effects of cancer treatment among adult cancer survivors? What proportion of survivors will experience recurrent or second malignancies?
(ii) *Psychosocial effects*	(ii) *Psychosocial effects* What are the psychosocial and behavioral consequences of late and/or long-term physiologic sequelae for survivors' health and well-being? Which factors promote resilience and optimal well-being in survivors and their families?
(iii) *Interventions*	(iii) *Interventions* Which interventions (medical, educational, psychosocial, or behavioral) are most effective in preventing or controlling late or long-term physiologic or psychosocial effects? When in the course of illness or recovery should they be delivered and by whom? Can interventions delivered years after treatment control, reduce, or treat chronic or late cancer-related morbidity?

(continued)

Table 20.2 (continued)

Area of research emphasis	Potential research questions
(iv) *Health behaviors*	(iv) *Health behaviors* Does regular physical activity after cancer (or avoidance of weight gain after hormonally dependent cancers) increase length and quality of survival? Does having a cancer history alter cancer risk behaviors among long-term survivors (e.g., smoking, alcohol consumption, sunscreen use)?
(v) *Impact of cancer on family members*	(v) *Impact of cancer on family members* What long-term impact does cancer have on the functioning and well-being of family members of survivors?
(vi) *Posttreatment follow-up care, surveillance, and health-care utilization*	(vi) *Posttreatment follow-up care, surveillance, and health-care utilization* Who is currently following cancer survivors for disease recurrence and cancer treatment-related late and long-term effects? What is the optimal frequency, content, and setting of posttreatment medical surveillance of cancer survivors, especially for those who are adults, and by whom should it be delivered? How does cancer history affect subsequent health-care utilization, both cancer related and that associated with comorbidities?
(C) *Research that takes advantage of existing survivor cohorts or study populations*	Comparison of survivors' functioning over time and/or with other non-cancer populations (e.g., cohort or nested case-control studies)

addressed so that optimal follow-up and/or supportive care for cancer survivors across the trajectory of their experience post diagnosis continues to be studied and improved as patients live longer with the effects of cancer and its treatments.

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