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Breast Cancer Epidemiology

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Foreword by Janet R. Daling, PhD

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ISBN 978-1-4419-0684-7 e-ISBN 978-1-4419-0685-4
DOI 10.1007/978-1-4419-0685-4
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2009930938

Printed on acid-free paper

Springer is part of Springer Science + Business Media (www.springer.com)

To Janet Daling, a wonderful mentor, friend, and breast cancer epidemiologist

and

to the millions of women throughout the world who have contributed to finding cures for breast cancer by volunteering their time to research studies

Foreword

Breast cancer is one of the most common and feared health problems for women worldwide. While breast cancer has been the most common incident and fatal female cancer in the world for sometime now, breast cancer incidence and mortality rates have changed profoundly worldwide over the past several decades. Developed countries experienced a rapid rise in incidence rates starting in the 1980s that continued through the 1990s, largely as a result of the widespread adoption of screening mammography. While incidence rates have historically been higher in developed compared to developing countries, rates have also increased among populations in developing countries. This was seen initially among women from developing countries who upon immigrating to developed countries quickly assumed breast cancer incidence rates at or near those of women in their new country. As Western lifestyles have become increasingly adopted, rapid increases in rates have been observed in a variety of African, Asian, and Latin American countries. What these changes emphasize is the critical component of lifestyle factors in the etiology of breast cancer, which is strongly supported by results from a long and rich history of breast cancer epidemiology studies.

Also quite striking is the dramatic reduction in breast cancer mortality rates that has occurred in developed countries over the past two decades. This is due to both advances in targeted therapies for breast cancer and to earlier detection of disease when it is most treatable through widespread screening. However, breast cancer mortality rates remain high in developing countries and so opportunities to enhance the delivery of screening, diagnostic, and treatment services to these countries could have a powerful impact on reducing the global burden of breast cancer.

The purpose of this book is to provide a comprehensive review and critical assessment of the epidemiology literature on breast cancer etiology and outcomes. Our understanding of exposures that may contribute to breast cancer, as well as the biology and molecular basis for this common disease, has greatly increased over the past few decades. Most epidemiologic research studies currently collect not only detailed histories of exposures that may increase a woman's chances of developing breast cancer but include the collection of blood samples and tumor tissue. These samples have been used

to classify breast cancers into distinct subtypes, each with its own risk factors, as well as molecular prognostic markers that often dictate the most effective therapies. Blood samples are used to determine a woman's inherited susceptibility to breast cancer and prospectively collected samples are used to assess how concentrations of various factors in the blood, such as endogenous hormones, are related to risk.

In this book, Dr. Christopher Li enlisted leading experts to write a timely and comprehensive review of various aspects of breast cancer epidemiology. Chapters focus on the roles of traditional etiologic risk factors, as well as more recently evaluated exposures, and when available how risks vary by demographic factors (e.g., age, menopausal status, and race/ethnicity) and tumor characteristics (e.g., stage and hormone receptor status). The inclusion of chapters on screening, diagnosis and treatment, and survival make this the most up-to-date and comprehensive book on breast cancer available. The content is written in a manner to be informative to the scientific community, trainees, and the general public.

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Chapter 1
Global Burden of Breast Cancer

Jacques Ferlay, Clarisse Héry, Philippe Autier, and Rengaswamy Sankaranarayanan

Introduction

Breast cancer in women is a major public health problem throughout the world. It is the most common cancer among women both in developed and developing countries. One in ten of all new cancers diagnosed worldwide each year is a cancer of the female breast. It is also the principal cause of death from cancer among women globally. More than 1.1 million cases are diagnosed and more than 410,000 patients die of it worldwide (Ferlay et al. 2004). It is the second most common cancer now, after lung cancer, when ranked by cancer occurrence in both sexes. About 55% of the global burden is currently experienced in developed countries, but incidence rates are rapidly rising in developing countries. We review the global burden of breast cancer, focusing on patterns of disease in terms of incidence and mortality and their geographical and temporal variations in different regions of the world. We also discuss briefly the sources and methods of estimation, validity and completeness of available data, and possible explanations for the observed patterns of incidence and mortality.

Measurements of Cancer Burden

The most commonly used indicators of cancer burden are incidence and mortality (Ferlay et al. 2004; Parkin et al. 2005). Cancer incidence is expressed as the absolute number of new cases occurring in a defined population per year or as a rate in terms of number of new cases per 100,000 persons per year. Incidence rates provide an approximation of the average risk of developing a cancer and, since this is strongly associated with age, comparison of incidence rates across different populations should use age-standardized incidence rates to allow for the differences in age structures. A reduction in cancer incidence is the appropriate statistic to use when evaluating primary prevention strategies.

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_1,

Cancer mortality refers to the absolute number of people who die from a specific cancer per year, and may be expressed as a rate in terms of cancer deaths per 100,000 persons. Mortality is the product of incidence and case fatality (the proportion of cancer patients that die). Mortality rates measure the average risk of dying from a given cancer in a given population, while fatality reflects the probability of an individual with cancer dying from it. Mortality rates are influenced by the trends in incidence rates as well as by the natural history of the disease, the efficacy of treatment interventions and of health services delivery. It is inappropriate to use mortality rate as a proxy measure of breast cancer incidence when comparing different populations because survival rates vary markedly across countries.

Survival time refers to the time period between diagnosis and death. Observed survival refers to the probability that a patient will survive to a particular point in time (e.g., 5 years) after the date of diagnosis. However, not all deaths among cancer patients are caused by the given cancer. Deaths from causes other than cancer reduce the observed survival time and complicate comparison between population groups with different probabilities of death. The relative survival, obtained by dividing the observed survival by the expected survival of a comparable group of the general population with respect to age, sex, and calendar period of time, should be used for comparison purposes.

Sources of Cancer Incidence and Mortality Data

Incidence, mortality, and survival estimates discussed in this chapter are derived primarily from the comprehensive global cancer statistics published by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) (Ferlay et al. 2004). The methods involved in compiling these data have been described in detail elsewhere (Parkin et al. 1999; Pisani et al. 1999, 2002, 2005) and are outlined briefly below.

Incidence data are obtained from population-based cancer registries which systematically collect information on a continuing basis on all new cancer cases diagnosed by all means (histological or clinical) in a defined population in a given geographical region (Armstrong 1992; Parkin 2006a). The establishment of population-based cancer registries began in the first half of the twentieth century and since then there has been a steady growth in the number of such registries globally. Some cancer registries, in addition to describing cancer patterns and trends, follow up ascertained cases to assess survival and mortality, thereby contributing to the planning and evaluation of cancer control activities (Armstrong 1992; Parkin 2006a). Although the registration of cancer has expanded into a global activity, cancer registries cover only about 16% of the world population, encompassing 64% of all populations in developed countries and 5% of all populations in developing countries. Thus, cancer

registries do not exist in many areas, particularly in sub-Saharan Africa and certain regions of Asia (e.g., Central Asia) and Latin America (e.g., Central America). Cancer incidences based on registries that meet a certain level of quality are included in the series "*Cancer Incidence in Five Continents*" (Parkin et al. 2005).

Cancer mortality data are derived from death certificates collected by the vital events (births, marriages, deaths) registration systems of countries. These are collated and made available through the World Health Organization (WHO). Mortality data are available for around 33% of the world population. However, the completeness, quality, accuracy, and validity of mortality data available from different countries are highly variable. In most developing countries, particularly in sub-Saharan Africa and certain areas of Asia and Latin America, the coverage of populations by death registration is grossly incomplete, and the mortality rates reported from these regions are low and unreliable. For countries where mortality data were of poor quality or unavailable, they are estimated from incidence, using survival data specific to a country or region.

Survival data are widely available for developed countries, but are only available for limited regions in a few developing countries. The sources of these population-based survival data include the population-based cancer registries that participate in the Surveillance, Epidemiology, and End Results (SEER) program which now covers 26% of the US population, the EUROCARE-3 project providing survival data for registries in several European countries (EUROCARE 2003), the "*Cancer Survival in Developing Countries Monograph*" providing survival data for selected populations in China, Cuba, India, the Philippines, Thailand (Sankaranarayanan et al. 1988), Singapore (Chia et al. 2001), Uganda (Gondos et al. 2005), and Zimbabwe (Gondos et al. 2004). From the above description, it is evident that the estimates of cancer burden for different countries vary in accuracy and completeness, depending upon the extent and validity of the data available for each country or region of the world.

Geographical Burden and Variations Worldwide

Breast cancer is the most common cancer among women with an estimated 1.15 million incident cases diagnosed in 2002, comprising of one fifth of the estimated 5.0 million cancer cases diagnosed each year in the world; it accounted for 410,000 deaths and 4.4 million 5-year prevalent cases (Table 1.1). More developed countries accounted for 641,600 cases and 190,900 deaths while less developed countries accounted for 509,700 cases and 219,600 deaths. The projections of breast cancer cases for the year 2030 for different regions of the world are shown in Table 1.2. Assuming current trends in incidence rates hold constant, there will be 2.7 million new cases in the world in 2030, with more than

Table 1.1 Estimated incidence, mortality, and prevalence worldwide, 2002

	Incidence		Mortality		Prevalence		
	Numbers	ASR(W)	Numbers	ASR(W)	1 year	3 years	5 years
World	**1,151,300**	**37.4**	**410,500**	**13.2**	**1,060,200**	**2,883,400**	**4,406,200**
Northern America	229,600	99.4	48,200	19.2	231,000	665,000	1,058,200
Europe	360,700	62.3	129,000	19.7	349,500	967,100	1,488,800
Australia and New Zealand	13,500	84.6	3,300	19.4	12,200	35,000	56,000
Japan and Korea	37,800	30.0	10,400	7.5	36,400	103,700	164,800
More developed	**641,600**	**67.8**	**190,900**	**18.1**	**629,100**	**1,770,800**	**2,767,800**
China	126,200	18.7	36,600	5.5	107,200	283,300	426,100
India	83,000	19.1	44,800	10.4	71,500	183,900	269,500
Latin America and Caribbean	96,600	40.3	32,800	13.9	88,800	223,900	317,600
Northern Africa and western Asia	41,800	28.6	22,500	15.5	32,800	84,100	124,400
Sub-Saharan Africa	48,600	23.5	32,600	16.0	30,200	71,600	102,200
Other developing	113,500	23.6	50,300	12.0	100,600	265,800	398,600
Less developed	**509,700**	**23.8**	**219,600**	**10.3**	**431,100**	**1,112,600**	**1,638,400**

Table 1.2 Estimated (2002) and projected (2030) numbers of new breast cancer cases

		2030		
	2002	No trend	Recent trends (CI 5 I-VIII)	
Northern America	229,600	354,500	354,500	0.00%
Europe	360,700	420,000	482,900	0.50%
Australia and New Zealand	13,500	20,900	24,000	0.50%
Japan and Korea	37,800	44,900	111,400	3.30%
More developed	**641,600**	**840,300**	**972,800**	
China	126,200	190,300	288,700	1.50%
India	83,000	155,700	249,600	1.70%
Latin America and Caribbean	96,600	200,800	265,400	1.00%
Northern Africa and western Asia	41,800	91,500	198,300	2.80%
Sub-Saharan Africa	48,600	93,200	123,100	1.00%
Other developing	113,500	227,600	596,200	3.50%
Less developed	**509,700**	**959,100**	**1,721,300**	
World	**1,151,300**	**1,799,400**	**2,694,100**	

60% of the cases (1.72 million) occurring in the less developed regions of the world. This projection conservatively assumes that current rates will remain constant, which given the recent rise in breast cancer incidence rates across many developing countries is unlikely to be the case. Thus, in the future the worldwide burden of breast cancer, particularly in less developed countries, is likely to continue to grow.

The estimated age-standardized incidence and mortality rates, incident cases and deaths, as well as prevalent cases in the different regions of the world are given in Table 1.1. Breast cancer incidence and mortality vary considerably by world region (Figs. 1.1 and 1.2). The estimated age-standardized rates varied from 18.7 per 100,000 women in China to 99.4 per 100,000 women in North America (Table 1.1, Figs. 1.1 and 1.2). In general, the incidence is high (greater than 80 per 100,000) in developed regions of the world and low (less than 30 per 100,000) in developing regions; the range of mortality rates is much less (approximately 6–23 per 100,000) because of the more favorable survival of breast cancer in (high-incidence) developed regions.

The highest incidence rates of breast cancer are observed in northern and western Europe, North America, Australia, New Zealand, and in southern countries of South America, notably Uruguay and Argentina (Ferlay et al. 2004) (Fig. 1.1). Clear geographical differences in risk are apparent within Europe, with elevated rates in northern and western Europe, whereas rates in most southern and eastern European countries are low to intermediate. In general, the high rates of breast cancer in developed countries are the consequence of a higher prevalence of the known risk factors for the disease, many of which – early age at menarche, nulliparity, late age at first birth, late age at any birth, low parity, exposure to exogenous hormones (e.g., oral contraceptives and menopausal hormone therapy), obesity, and late menopause – relate to the hormonal (largely estrogen) milieu to

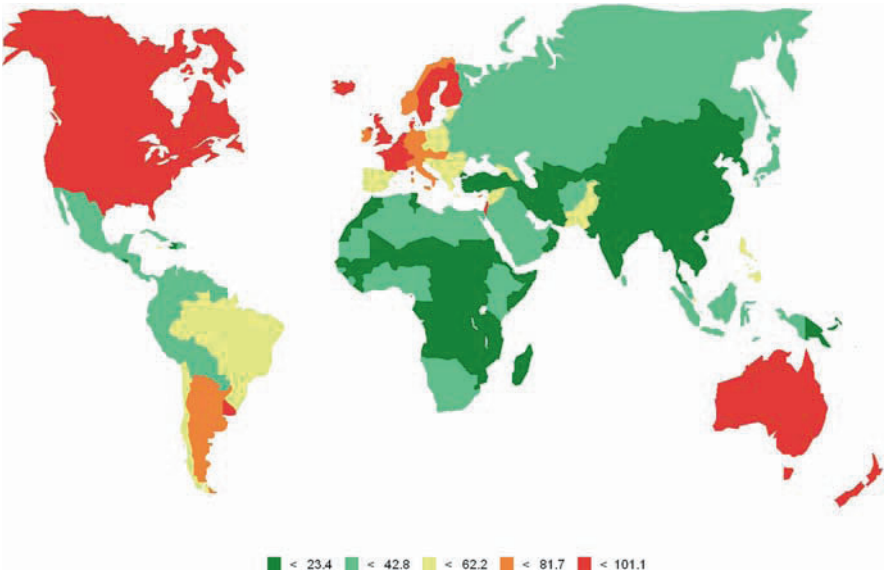

Fig. 1.1 The global burden of breast cancer in 2002: age-standardized incidence rates per 100,000

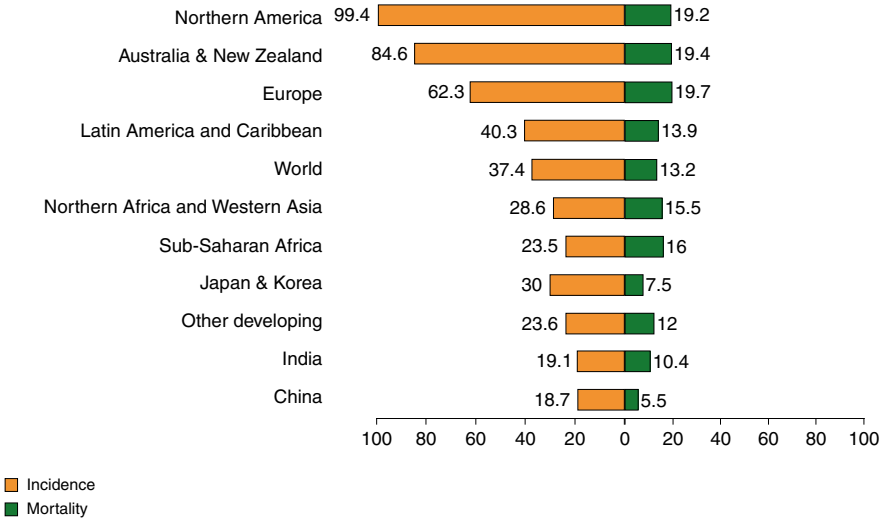

Fig. 1.2 Breast cancer incidence and mortality in 2002: rates per 100,000 by region

which the breast is exposed from menarche to the cessation of ovulation at menopause. While incidence rates are less than 40 per 100,000 women in most less developed countries, breast cancer is still the most common cancer among women in the majority of less developed countries (Parkin et al. 2005).

Incidence rates are intermediate (30–60 per 100,000) in several Asian populations such as Hong Kong, Singapore, and the Philippines as they are in Puerto Rico and Brazil, and most eastern European populations (Parkin et al. 2005). Comparatively lower rates (10–30 per 100,000) are seen in several Chinese populations, in eastern African populations in Zimbabwe and Uganda, Algeria in North Africa, several Southeast Asian countries (Thailand and Vietnam), and several registries in India. Koreans living in the USA have retained a relatively low breast cancer incidence rate (about 28 per 100,000) not dissimilar to that of Koreans living in Korea (21 per 100,000 in Seoul), in comparison with the high rates now seen in other US-born races of Asian descent, notably Japanese, Chinese, and Filipinas.

Age-Specific Variations in Incidence of Breast Cancer

A distinct age-specific incidence pattern is observed for breast cancer, as shown in Fig. 1.3. It is characterized by a rapid increase in incidence rate before menopause (up to age 50 years) and the rate of increase in incidence rates is much lower thereafter. This pattern may be due to the diminishing levels of

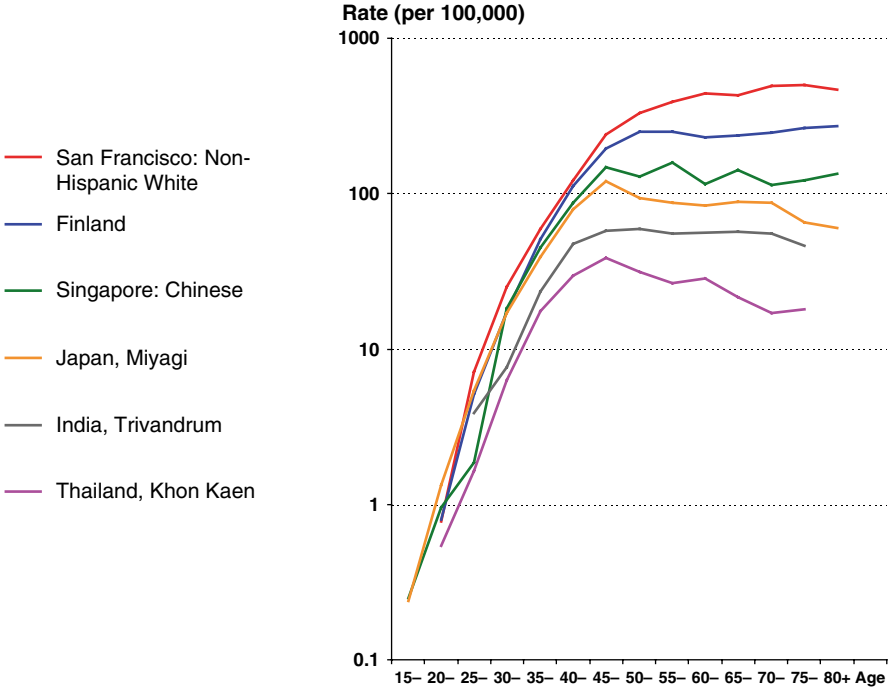

Fig. 1.3 Age-specific incidence of breast cancer around 1995

circulating estrogens after menopause (Henderson et al. 1988). Interestingly, in low-incidence developing countries, the slope of the curve after the menopause may be flat, indicating no increase in incidence rates following menopause or may be even negative, implying lower rates after menopause. This is a consequence of increasing risks of occurrence in consecutive generations of women rather than a real decline in risk with age (Moolgavkar et al. 1979). The comparatively younger age structure of populations and a flat age–incidence curve after menopause result in lower mean age at diagnosis of breast cancer cases in developing countries than that observed in European and American populations.

Trends in Incidence and Mortality

The trends in breast cancer incidence and mortality over time are complex. Over the past several decades the incidence of breast cancer has increased almost everywhere. In general terms, the largest increases in incidence have been seen in populations with historically low-incidence rates, often in developing countries, whereas relatively recent departures from the long-term trend of increasing rates have only recently been observed in several, mainly western countries. The changing patterns of breast cancer screening, childbearing and breastfeeding, exogenous hormonal intake, and lifestyle factors including obesity and reduced physical activity have certainly contributed to trends in incidence. Pinpointing the particular factors that have contributed in different populations worldwide has proved a major challenge, and the underlying reasons are certain to be multiple and interactive. On the other hand, mortality is now decreasing in many high-risk countries due to a combination of the introduction of mammographic screening, and improved awareness and intensified early clinical diagnosis resulting in the diagnosis of more small, early stage tumors; and advances in both primary and adjuvant treatments for breast cancer.

Trends in Developed Countries

Europe

A substantial increase in incidence rates was observed across various European countries through the mid-1990s (Fig. 1.4). These upward trends in incidence were most dramatic for women $\geq$50 years of age indicating that mammography screening may be a primary contributor to these trends (Figs. 1.5 and 1.6). A mean global increase of 56.5% was observed between 1990 and 2002 across all age groups, and the greatest increase was observed across central and eastern European countries (Héry et al. 2008). In the Nordic countries, England, Finland, and Norway, breast cancer incidence rates were increasing even before the

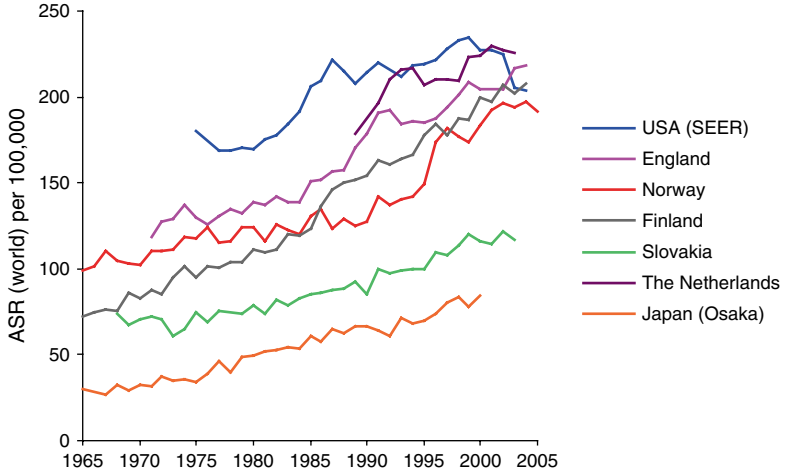

Fig. 1.4 Breast cancer incidence rates (age 35–74) in selected developed countries

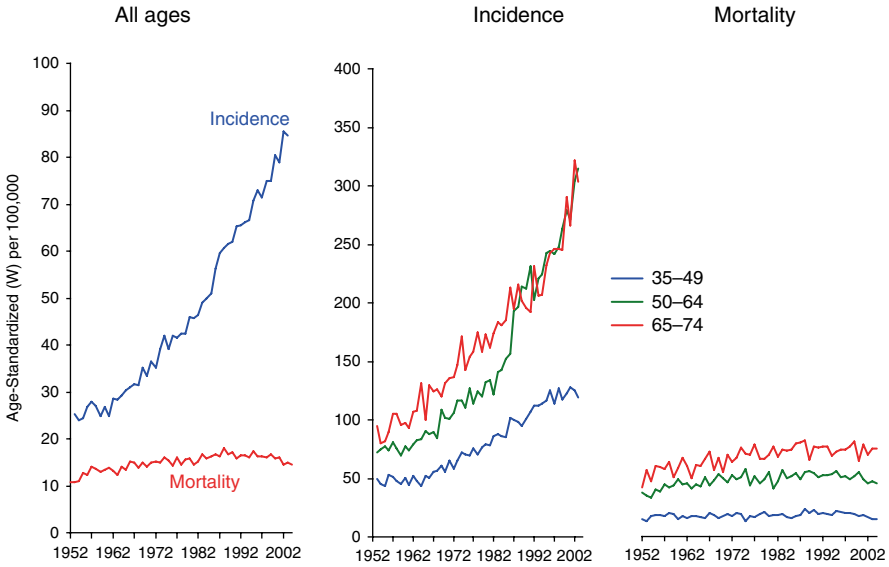

Fig. 1.5 Incidence and mortality trends by age group in Finland

beginning of organized screening activity in the mid-1980s (Fig. 1.4). Increases in incidence greater than 2% per year up to the mid-1990s were also seen in several countries without comprehensive screening programs (Botha et al. 2003). In Spain, Iceland, Norway, Finland, Sweden, Germany, and Ireland at present

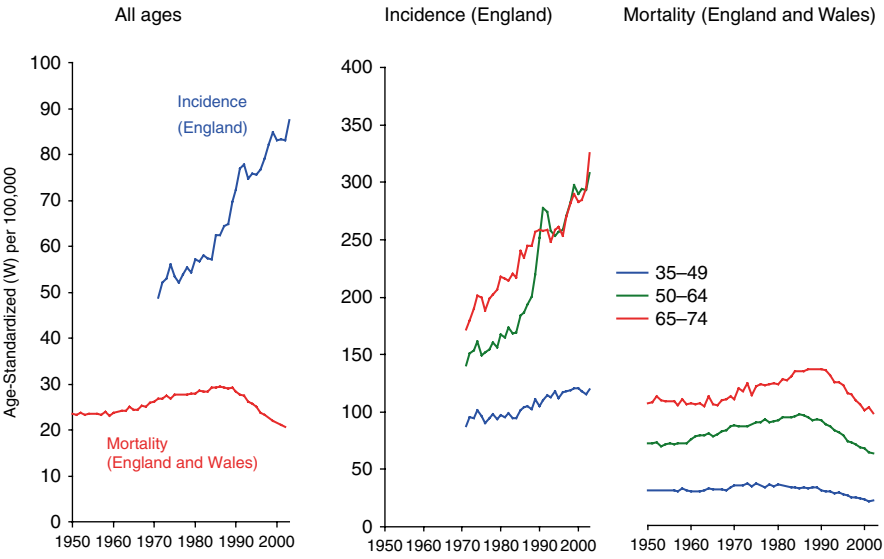

Fig. 1.6 Incidence and mortality trends by age group in England

incidence rates among 50–69-year-olds reach or surpass the rates among women ≥70 years of age (Héry et al. 2008).

Mortality rates from breast cancer increased in most European countries (Fig. 1.7), particularly in southern and eastern European countries, from 1950 to 1980. A leveling off of rates, followed by a decline in mortality has occurred since the early 1990s in the United Kingdom (Fig. 1.7) and this trend is now observed in several other European countries (Fig. 1.7) (Hermon et al. 1996;

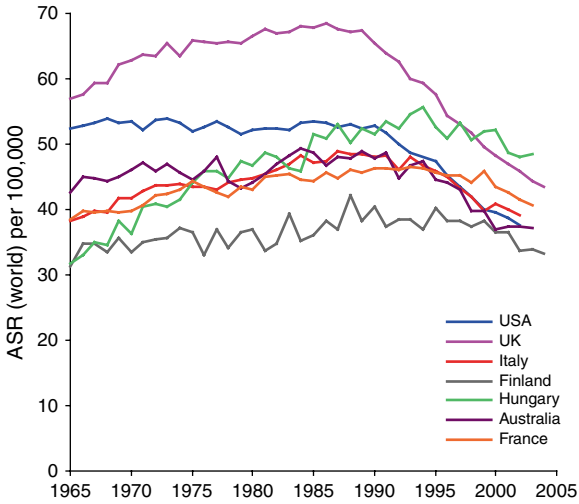

Fig. 1.7 Breast cancer mortality rates (age 35–74) in selected developed countries

Peto 1998; Botha et al. 2003). However, changes in mortality were highly variable across European countries, overall percent changes ranged from −30.5% (England and Wales) to +25.5% (Estonia). The magnitude of mortality changes was not related to mortality levels observed 13 years before. In all countries, there was a strong age gradient in mortality trends: mortality decreased more in the 35–49 agegroup and decreased less in the 70+ age group. The age differences in mortality changes were particularly marked in eastern and central European countries (Héry et al. 2008).

North America

The trends observed in the USA (Fig. 1.4) and Canada are similar to those in Europe, with similar increases in incidence in both white and black women, with most of the increase observed between 1980 and 1987, with the overall rate of increase slowing down since the late 1980s (Wun et al. 1995; Lacey et al. 2002; Weir et al. 2003). This is related to a rise in screen-detected incident cases as a result of the increasingly widespread use of mammographic screening over this period (Wun et al. 1995). Recent US data reveal a statistically significant decline in female breast cancer incidence rates from 2002 to 2003 in the SEER cancer registries (Fig. 1.4) of the USA (Jemal et al. 2007). A plot of the age-specific rates of invasive breast cancer showed a decrease in all 5-year age groups from 45 years and above between 1999 and 2003. This is possibly due to a period effect consistent with saturation in screening mammography and/or to the sharp reductions in menopausal hormone therapy use that followed the publication of the Women's Health Initiative trial showing that the harms of hormone therapy outweighed its benefits. On further analyses by tumor size and stage, incidence rates decreased for small tumors (2 cm) by 4.1% per year from 2000 through 2003 and for localized disease by 3.1% per year from 1999 through 2003. No decrease in incidence was observed for larger tumors or advanced-stage disease during the corresponding periods. Rates for in situ disease were stable from 2000 through 2003 after increasing rapidly since 1981.

Mortality rates in the USA (Fig. 1.7) and Canada have declined since 1990 (Smigel et al. 1995; National Cancer Institute of Canada 1998). Although the trends were similar from the 1970s to the mid-1980s in both US whites and blacks, they diverged thereafter, with white women experiencing a decline in mortality rates since 1990, whereas they have increased slightly among black women (Lacey et al. 2002). Birth cohort trends for US and Canadian women were similar until about 1940, with a reduction in mortality risk beginning in about 1924. Marked declines in mortality by birth cohort were observed for US white women born after 1950, whereas stable or slightly decreasing trends were observed for US black women and Canadian women. In the last calendar period, in the early 1990s, a trend of decreasing mortality rates was found for US white and Canadian women.

Other Developed Countries

Breast cancer incidence rates have been steadily increasing in Australia and New Zealand since the early 1980s (Armstrong and Borman 1996; Giles et al. 2003). Breast cancer mortality in Australia rose steadily from the early 1970s to the late 1980s (Smith et al. 1998). Between 1985–1989 and 1990–1994, breast cancer mortality fell by 3.2% in women 50–69 years of age and by 4.2% in 25–49-year-olds, with little change (−0.2%) in breast cancer mortality in older women in this period. The proportion of women screened in all age groups in Australia increased substantially between 1988 and 1994, and by 1994 nearly 65% of women in the target age group had had at least one mammogram.

Although breast cancer incidence rates in Japan (Fig. 1.8) are lower than those in North America and Europe, both incidence and mortality have been rising rapidly in successive generations of women since the mid-1970s; and in recent years, the increase in incidence has been much larger than for mortality, demonstrating improving prognosis over time (Wakai et al. 1995; Nagata et al. 1997).

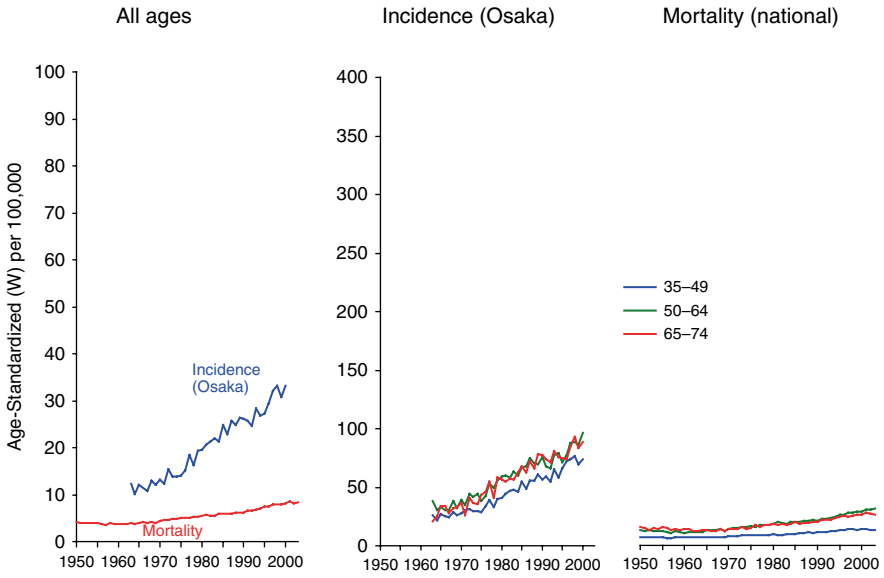

Fig. 1.8 Incidence and mortality trends by age group in Japan

Explanations for Reductions in Breast Cancer Mortality Rates in Developed Countries

Mammographic screening for women aged 50–69 years is effective in reducing breast cancer mortality (IARC 2002), and the declining trends in mortality in

developed countries could be partly attributed to increased mammographic screening. One of the indirect beneficial effects of screening might have been a shift toward earlier diagnosis of breast cancer and better organization of breast cancer management, as a result of the publicity surrounding the disease and its prevention.

Reductions in mortality before the introduction of screening, and in those countries without screening activity, indicate that several improvements in disease management, including the establishment of treatment protocols, adjuvant treatment policies, improved chemotherapeutic and hormonal treatment options, and better therapeutic guidelines, could have accounted for part of the observed declines in mortality. Mathematical modeling of data from the USA suggests that both screening and adjuvant therapy were near equal contributors to the significant decline in breast cancer mortality observed between 1975 and 2000 (Barry et al. 2005).

Trends in Developing Countries

Most developing countries from where incidence data are available have low to moderate rates of breast cancer occurrence compared to developed countries (Parkin 1994; Coleman et al. 1993). High-quality data over a long period of time are available for few developing countries. However, definite increases in breast cancer incidence and mortality (Figs. 1.9, 1.10 and 1.11), particularly in recent birth cohorts, are apparent in populations where rates can be assessed. Studies comparing the risks in migrants from Asian countries to the USA and their offsprings born have revealed substantial increases in risk between first, second, and third generations This indicates that the increase in the prevalence of risk

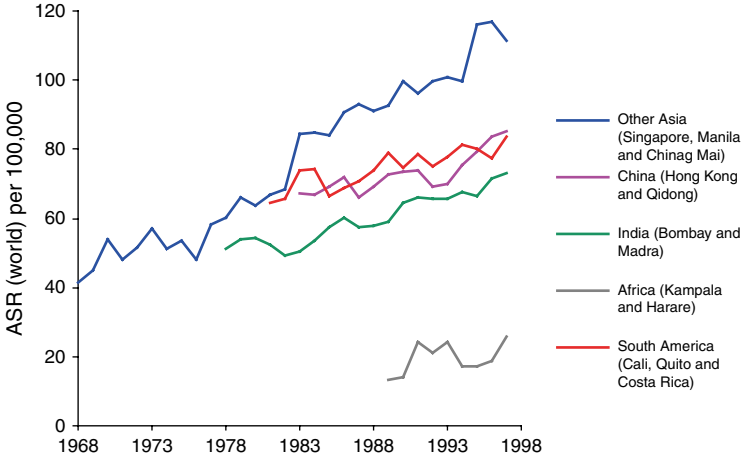

Fig. 1.9 Breast cancer incidence rates (age 35–74) in selected developing countries

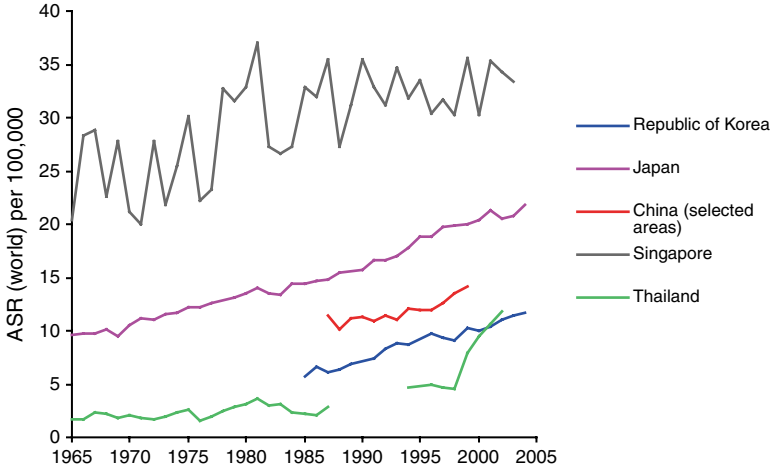

Fig. 1.10 Breast cancer mortality rates (age 35–74) in selected developing countries and Japan

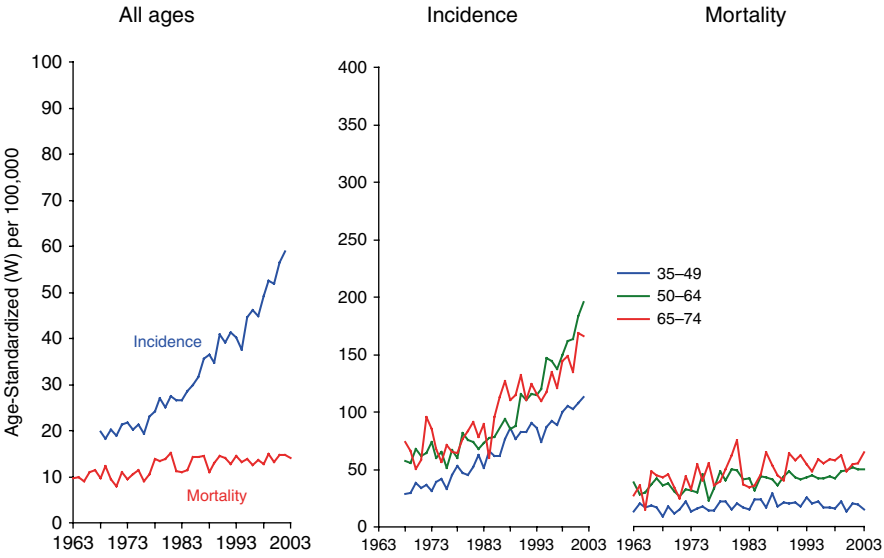

Fig. 1.11 Incidence and mortality trends by age group in Singapore

factors associated with a "western" lifestyle has had a major influence on this increase in countries where incidence was historically low.

Asia

Age-adjusted incidence is low in most Asian countries, although rates exceeding 40 per 100,000 are observed in the Philippines and Pakistan. Rates in Singapore,

particularly among the Chinese population, are also relatively high for the region (Parkin et al. 2005). Rising incidence has been observed in India (Fig. 1.9) and in Singapore (Fig. 1.11), with average annual increases of 3.6% between 1968 and 1992, attributed mainly to birth cohort effects (Yeole et al. 2003; Seow et al. 1996). From 1968 to 2002, Singapore experienced an almost threefold increase in breast cancer incidence. The extent of the mean annual rate of increase in Singapore ranged from 4.4% in Malays to 1.4% in Indians (Seow et al. 1996). In China, mortality increased over the period 1987–1999 in both rural and urban areas (Fig. 1.10), the change being more evident in rural areas although the rates have remained lower than in urban females (Yang et al. 2003). The twofold increase in mortality in Taiwan between the 1960s and the 1990s has been attributed to both period and cohort influences (Chie et al. 1995), whereas in Hong Kong increases of the same order of magnitude were considered to be primarily the result of cohort effects (Leung et al. 2002).

Africa

In Africa, breast cancer ranks as the second most frequent cancer after cervical cancer (Ferlay et al. 2002; Parkin et al. 2003). However, it is the most common malignancy in North Africa and in urban settings within the sub-Saharan region (Echimane et al. 2000). In the few data sets available for the study of time trends in Africa, increases in incidence are apparent. There have been twofold increases in breast cancer incidence in Ibadan, Nigeria, and in Kampala, Uganda, between the 1960s and the late 1990s (Chokunonga et al. 2000; Parkin et al. 2003; Wabinga et al. 2000). Steady increases in breast cancer mortality rates of the same order of magnitude have also been noted from the early 1960s in Mauritius (Parkin et al. 2003).

Latin America

Most countries in Latin America have intermediate rates of breast cancer occurrence, exceeding age-standardized rates of 50 per 100,000 women. Incidence and mortality rates have been increasing in most countries; incidence has at least doubled, for instance, in Cali, Colombia, and in Puerto Rico between the early 1970s and the mid-1990s (Parkin 1994; Coleman et al. 1993; Bray et al. 2004; Parkin and Fernandez 2006). In Uruguay, Argentina, and Chile, incidence rates are intermediate to high, and mortality rates in younger women have been reported to be more or less constant over time.

Conclusion

Due to changing exposures to reproductive and lifestyle characteristics over time, women are at increasingly high risk of breast cancer, with incidence rates increasing in most countries in the past few decades, making cancer of the breast in women a major health problem worldwide. Breast cancer incidence and mortality patterns are influenced by numerous known and unknown risk factors. The most rapid increase in burden is observed in developing countries, where breast cancer risk has historically been low relative to western countries. This increase is widely attributed to the "westernization" of lifestyles, an ill-defined surrogate for changes in factors such as childbearing, anthropometric attributes, and lifestyle characteristics. With respect to mortality, the introductions of screening and substantial improvements in treatment have led to recent dramatic reductions in breast cancer mortality rates in developed countries. While several ongoing trials are investigating a range of preventive regimens (Cuzick 2003) and the primary risk factors for breast cancer are not easily modifiable, continued improvements in strategies to detect breast cancer early, when it is most treatable, could translate into improved survival worldwide. However, in order to effectively curb the emerging epidemic of breast cancer in developing countries where survival rates are currently much poorer than those in developed countries (Fig. 1.12), strategies to deliver screening and treatment strategies in a cost effective and culturally appropriate manner will be needed.

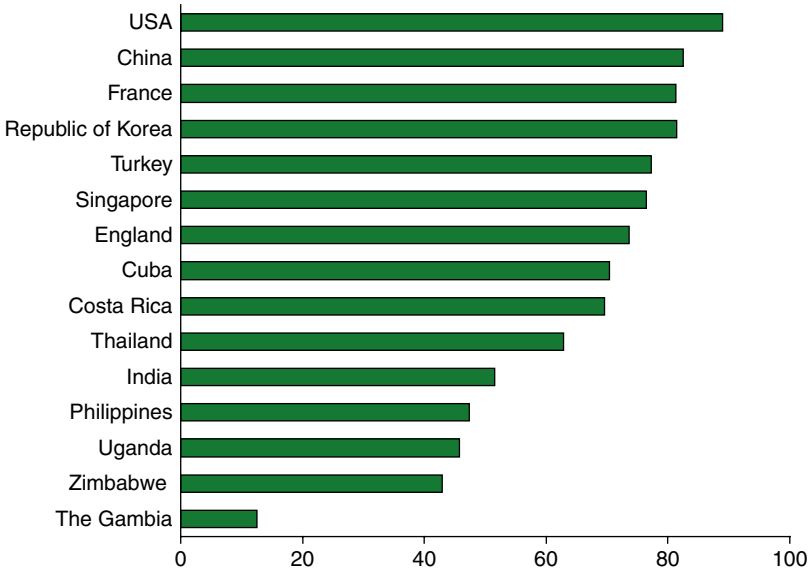

Fig. 1.12 Breast cancer: 5-year relative survival (percent) around 1995

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Chapter 2
Breast Cancer Biology and Clinical Characteristics

Amanda I. Phipps and Christopher I. Li

Introduction

While breast cancer is often studied as a single disease, advances in our understanding of the epidemiology, biology, and molecular basis for breast cancer indicate that it is a heterogeneous disease that can be divided into several distinct subtypes. Proper classification of breast tumors into relevant subtypes is important for studying breast cancer etiology, predicting clinical course, and making decisions related to breast cancer treatment. Distinctions between subtypes of breast cancer can be made on the basis of patient characteristics or according to phenotypic or genotypic characteristics of the tumor itself, such as tumor stage, grade, histology, and genetic profile. While the motivation and methodology behind these different classification systems varies, there is great overlap between the subtypes of disease they describe. Nevertheless, the distinctions between subtypes of disease highlighted by these classifications not only translate to differences in clinical outcome, they also imply important differences in tumor etiology.

Tumor Classification Schemes

Patient Characteristics

The nature, incidence, and prognosis of breast cancer have been observed to vary according to a variety of patient characteristics. Perhaps the strongest epidemiologic distinctions can be made on the basis of patient age, menopausal status, and family history of breast cancer. Observed differences between premenopausal and postmenopausal disease and between familial and

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_2,

sporadic disease are supported by differences in underlying tumor biology which translate to distinct prognostic profiles.

Age at Diagnosis/Menopausal Status

As with most types of cancer, increasing age is the strongest risk factor for female breast cancer. Less than 2% of invasive breast cancers are diagnosed in women aged less than 35 years (Ries et al. 2007a), but incidence rates increase by a factor of almost 100 between the ages of 30 and 50 years (Pike et al. 1993). Although comparatively rare, breast cancer in young women is associated with a markedly poorer overall survival and shorter recurrence-free survival relative to disease in older women (Chung et al. 1996; Winchester et al. 1996; Maggard et al. 2003). In part, this discrepancy in survival may be attributed to the fact that breast cancer is significantly less likely to be diagnosed at an early stage in young women than in older women (Althuis et al. 2003; Maggard et al. 2003; Anderson et al. 2006). However, evidence also exists to suggest that breast tumors diagnosed in young women have a biology distinct from breast tumors diagnosed in older women (Walker et al. 1996; Anderson and Matsuno 2006; Benz 2008). Closely related to the distinction of breast cancer cases according to age, but perhaps more germane to differences in tumor biology, breast cancers are commonly distinguished according to a woman's menopausal status at the time of breast cancer diagnosis. This distinction is relevant not only because of differences in the age of premenopausal vs. postmenopausal women, but also because of the very different hormonal milieus of premenopausal vs. postmenopausal women (Verkasalo et al. 2001). Unlike postmenopausal women, premenopausal women are exposed to cycling ovarian hormones. Endogenous hormone levels in postmenopausal women are comparatively much lower, with adipose tissue serving as the primary source of endogenous estrogen (van den Brandt et al. 2000; Hankinson 2005–2006).

Premenopausal breast cancers are associated with a more aggressive tumor biology relative to breast cancer in older, postmenopausal women. Approximately 38–64% of breast cancers diagnosed in women aged <40 years have a high grade, compared to only 17–38% in women aged ≥ 60 years (Sidoni et al. 2003; Anderson et al. 2007a). Consistent with these differences in tumor grade, breast cancers in younger, premenopausal women are also more likely to be estrogen receptor (ER) negative (42–46% vs. 17–20% of postmenopausal cases) (Zavagno et al. 2000; Sidoni et al. 2003; Anderson et al. 2007a; Dunnwald et al. 2007), progesterone receptor (PR) negative (45–50% vs. 21–31%) (Sidoni et al. 2003; Anderson et al. 2007a; Dunnwald et al. 2007), and exhibit high Ki-67 expression (48% vs. 26%) (Sidoni et al. 2003); these differences persist even after adjusting for differences in tumor grade (Talley et al. 2002). Furthermore, tumors in premenopausal women are more likely than tumors in postmenopausal women to overexpress HER2-neu (HER2) (Sidoni et al. 2003; Hartley et al. 2006), have a basal-like molecular phenotype (Millikan et al. 2008), and overexpress p53 (Breast Cancer Linkage Consortium 1997; Sidoni et al. 2003).

Premenopausal disease is also more likely to be familial (Claus et al. 1990; Sidoni et al. 2003) and, specifically, is strongly associated with *BRCA1* mutations (John et al. 2007). These differences in tumor biology contribute to differences in disease survival: 5-year relative survival rates for women diagnosed prior to age 40 years are approximately 78–84% compared to >90% among women diagnosed at age 60 years or older (Ries et al. 2007b).

Epidemiologic studies indicate that, in addition to differences in tumor biology, risk factors for premenopausal breast cancer differ from those for postmenopausal disease (Gilliland et al. 1998; Titus-Ernstoff et al. 1998; Enger et al. 2000; van den Brandt et al. 2000; Clavel-Chapelon and the E3N-EPIC Group 2002). For example, obesity is associated with a reduced risk of premenopausal but an increased risk of postmenopausal breast cancer (Huang et al. 1997; Enger et al. 2000; van den Brandt et al. 2000; Anderson et al. 2007b), and oral contraceptive use is associated with an increased risk of premenopausal but not postmenopausal disease (Anderson et al. 2007b; Shantakumar et al. 2007). Similarly, nulliparous women have a reduced risk of breast cancer relative to parous women at a young age, but after age 40 nulliparous women have a higher risk of breast cancer compared to parous women (Pathak 2002; Anderson et al. 2007b). Taken together, these differences in disease epidemiology, prognosis, and tumor biology highlight the important distinction between premenopausal and postmenopausal breast cancers.

Family History of Breast Cancer

Approximately 15% of breast cancers arise in women with a history of the disease in first-degree relatives (i.e., mothers, sisters, or daughters) (Collaborative Group on Hormonal Factors in Breast Cancer 2001), and approximately 5–10% of breast cancers may be directly attributable to heredity (Madigan et al. 1995; Newman et al. 1998; Hemminki and Czene 2002). While the heredity of breast cancer susceptibility is not fully understood, it is assumed that the majority of familial breast cancers are attributable to a small number of high penetrance susceptibility genes. To date, two breast cancer susceptibility genes have been well described: *BRCA1* (Miki et al. 1994) and *BRCA2* (Wooster et al. 1995). Familial breast cancers in general, and *BRCA1*-associated breast cancers in particular, are characterized by an epidemiologic, phenotypic, and clinical profile that distinguishes them from sporadic breast tumors. (A detailed discussion of the relationship between family history and breast cancer risk is provided in Chapter 13.)

The phenotypic characteristics of familial tumors are similar to those of premenopausal tumors in that they tend to exhibit a more aggressive biology. Although differences in tumor stage at diagnosis are not pronounced (Eerola et al. 2001; Rennert et al. 2007), *BRCA1*-associated and *BRCA2*-associated breast cancers are characterized by a higher tumor grade relative to sporadic tumors (Marcus et al. 1996; Breast Cancer Linkage Consortium 1997; Palacios et al. 2005). With respect to other markers of tumor aggressiveness, few

distinctions have been noted between *BRCA2*-associated tumors and sporadic tumors (Lakhani et al. 2002). However, compared to sporadic tumors, *BRCA1*-associated breast tumors are more likely to be hormone receptor negative [68–90% of *BRCA1*-associated tumors are ER negative (ER–) compared to only 20–35% of sporadic tumors], HER2 negative (Lakhani et al. 2002; El-Tamer et al. 2004; Palacios et al. 2005; Rennert et al. 2007), overexpress p53 (Lakhani et al. 2002; Palacios et al. 2005), and have higher Ki-67 expression levels (Marcus et al. 1996; Palacios et al. 2005).

Tumor Characteristics

As previously suggested, observed differences in the nature and prognosis of breast cancer according to patient characteristics are largely explained by differences in tumor characteristics, and distinctions between subtypes of breast cancer may also be made on the basis of clinical and molecular tumor characteristics. Molecular and genetic studies of breast cancer provide evidence supporting the classification of breast cancer subtypes according to tumor appearance, histology, tumor marker expression, and gene expression profiles.

Clinical Characteristics

Tumor stage and tumor grade are commonly used by pathologists to describe the severity and aggressiveness of breast cancers. These two attributes are interrelated and often correlated, but are distinct in important ways. Both measures are independently informative in predicting disease course and are commonly used to guide breast cancer treatment decision-making with respect to surgical and adjuvant therapies. Similarly, the histological type of a tumor is useful in characterizing tumor biology and is increasingly being documented as a significant parameter in defining and describing disease epidemiology.

Stage

The staging of breast tumors provides a description of the extent and spread of a tumor. Specifically, tumor stage is determined by the size of the tumor, whether the lymph nodes are involved (and how many lymph nodes are involved), and whether the cancer has spread to other parts of the body. Breast tumors may be classified as stage 0–IV according to the American Joint Committee of Cancer (AJCC) staging system, with increasing stage corresponding to increasing tumor size and spread. Stage 0 breast cancer (i.e., in situ breast cancer) is characterized by an accumulation of malignant cells that have not invaded into surrounding tissue. Breast tumors designated as stage I, II, III, or IV involve some invasion of tumor cells beyond the basement membrane, and

are thus referred to as invasive tumors. Stage I breast cancer is confined to the breast tissue and has a maximum diameter of less than 2 cm while stage IV breast cancer involves distant metastases.

In general, it is presumed that most breast tumors will progress through these stages over time if left undetected. Consistent with this assumption, the epidemiologic literature suggests that risk factors for in situ disease are similar to those for invasive disease (Kerlikowske et al. 1997; Trentham-Dietz et al. 2000; Gill et al. 2006; Reinier et al. 2007), and laboratory studies indicate that patterns of genetic alterations and imbalances observed in in situ tumors are nearly identical to those observed in invasive breast cancers (Buerger et al. 1999; Hwang et al. 2004). Also consistent with progression through breast cancer stages, the distribution of tumor stage at diagnosis has shifted toward earlier stages in countries where mammographic screening has become widespread (Anderson et al. 2004; Li et al. 2005): age-adjusted incidence rates for ductal carcinoma in situ (DCIS) increased by approximately 660% between 1973 and 2000, while incidence rates for invasive breast cancer increased by only 36% over the same time period (Anderson et al. 2004). Not all early stage tumors, however, will progress to advanced stages and in situ breast cancer is thus generally considered a non-obligate precursor to invasive disease. Factors determining which in situ tumors will or will not progress to invasive disease if left untreated are largely unknown because there are few studies on the natural history of breast cancer. Follow-up studies of patients with in situ breast cancer originally misdiagnosed as benign breast disease (and thus treated only with biopsy) suggest that approximately 20–53% of patients with in situ breast cancer treated with biopsy alone will go on to develop invasive breast cancer within 3–31 years (Rosen et al. 1980; Page et al. 1982, 1995; Collins et al. 2005).

As might be inferred from the criteria used to stage breast tumors, disease prognosis is inversely associated with tumor stage in developed countries. Breast cancers diagnosed at stage 0 or stage I are very responsive to available therapies and are associated with 5-year disease-specific survival rates approaching 100% (Ernster et al. 2000; Ries et al. 2007b). Disease diagnosed at a more advanced stage is associated with a less favorable prognosis; 5-year relative survival rates are approximately 86%, 57%, and 20% when disease is diagnosed at stage II, III, and IV, respectively (Ries et al. 2007b).

The majority of breast cancer cases diagnosed in developed countries are diagnosed at an early stage. Based on US breast cancer incidence data from 1988 to 2001, approximately 16%, 40%, 34%, 6%, and 4% of breast cancers are diagnosed at stages 0–IV, respectively (Ries et al. 2007b). Given the relationship between cancer stage and access to health care and screening, stage distributions can vary substantially between countries as well as within countries by various demographic and socioeconomic factors. For example, in the United States, African-American, Hispanic white, and Native American women with breast cancer are about two times more likely to be diagnosed at an advanced stage relative to non-Hispanic white women (Li et al. 2003; Smigal et al. 2006). The distribution of stage is also shifted toward more advanced stages with

decreasing age at diagnosis (Anderson et al. 2007b; Ries et al. 2007b). Thus, tumors in younger, premenopausal women are more likely to have spread beyond the primary site at the time of diagnosis relative to breast cancers diagnosed in postmenopausal women, contributing to the previously described differences in the survival between premenopausal vs. postmenopausal breast cancer.

Differences in the distribution of tumor stage by demographic factors may be largely attributable to differences in the prevalence of breast cancer screening (Blanchard et al. 2004) and access to medical care (Bradley et al. 2002), but are also likely to reflect differences in tumor biology and, in particular, tumor aggressiveness. Specifically, tumors diagnosed at stage III or stage IV are more likely than tumors diagnosed at earlier stages to have a lobular histology (14% vs. 9%) (Li et al. 2005), to be high grade (65% vs. 39%) (Ries et al. 2007b), and to be hormone receptor negative (31% vs. 19%) (Dunnwald et al. 2007). As discussed below, these markers of tumor aggressiveness are strong predictors of disease course and are associated with differences in tumor etiology.

Grade

Tumor grade provides a description of how closely breast tumor cells resemble normal breast tissue when viewed microscopically. One commonly used measure for defining tumor grade for breast cancer is the Bloom–Richardson Scale (Bloom and Richardson 1957). Using this semi-quantitative measure, grade is defined according to three morphologic features of breast tumor cells: (1) the degree of tumor tubule formation, (2) mitotic activity, and (3) nuclear pleomorphism. Tumors are assigned a grade of 1–3 based on the combination of these three characteristics, with an assignment of grade 1 indicating a tumor composed of well-differentiated breast cells that generally appear normal and are not growing rapidly, grade 2 indicating a tumor composed of moderately differentiated breast cells, and grade 3 indicating a tumor of poorly differentiated breast cells that tend to grow and spread more aggressively. Several modifications and amendments to the original Bloom–Richardson Scale have been proposed over the years (Haybittle et al. 1982; Contesso et al. 1987; Meyer et al. 2005) but overall, tumor grade is inversely correlated with the degree of differentiation and proliferation in tumor cells. Thus, across grading scales, lower grade is indicative of slower growing cancer that is less likely to spread and higher grade is indicative of more aggressive, rapidly progressive disease.

Consistent with the slower growth rate of low-grade tumors, there is a high level of correlation between grade and stage at diagnosis: approximately 73% of invasive low-grade tumors are diagnosed as stage I disease compared to only 32% of high-grade tumors (Ries et al. 2007b). The distribution of tumor grade also varies substantially with other tumor characteristics. In particular, although the distribution of tumor grade does not appear to be significantly different between breast cancers of ductal vs. lobular histology (Li et al. 2005), tumors of high grade are more likely to be hormone receptor negative

(Dunnwald et al. 2007) and are more likely to exhibit a "triple-negative" (i.e., ER–/PR–/HER2–) (Rakha et al. 2006; Bauer et al. 2007) or basal-like (Carey et al. 2006; Yang et al. 2007) phenotype.

Tumor grade is also associated with a number of patient characteristics. Specifically, breast cancers diagnosed at an early age (Sidoni et al. 2003; Anderson et al. 2007a) or prior to menopause (Zavagno et al. 2000) tend to be of higher grade relative to breast cancers in older, postmenopausal women: <4% of low-grade but >9% of high-grade breast cancers are diagnosed in women aged <40 years (Anderson et al. 2007a). Additionally, in the United States, breast cancers diagnosed in non-Hispanic white women tend to be of lower grade, on average, than breast cancers diagnosed in women of other racial/ethnic groups (Li et al. 2003). Familial breast cancers also tend to be of higher grade relative to sporadic breast cancers (Marcus et al. 1996; Breast Cancer Linkage Consortium 1997; Lakhani et al. 2000; Palacios et al. 2005). Specifically, *BRCA1*-associated breast cancers demonstrate significantly greater pleomorphism and higher mitotic count than sporadic tumors and *BRCA2*-associated tumors are characterized by significantly lower tubule formation than sporadic tumors (Breast Cancer Linkage Consortium 1997; Lakhani et al. 2000). With respect to other epidemiologic risk factors, a number of studies have found that use of combined estrogen plus progestin menopausal hormone therapy (CHT) is more strongly associated with an increased risk of low-grade than high-grade breast cancer (Manjer et al. 2001; Garcia-Closas et al. 2006; Borgquist et al. 2007); few studies, however, have examined differences in other risk factors for low vs. high-grade breast cancer.

Tumor grade is of particular relevance with respect to the clinical course of breast cancer. Although closely correlated with stage at diagnosis, grade is a significant independent predictor of disease prognosis (Warwick et al. 2004; Rosenberg et al. 2005; Arriagada et al. 2006; Ries et al. 2007b; Soerjomataram et al. 2008) and an important predictor of response to adjuvant therapy (Pinder et al. 1998; Page et al. 2001). Among women with incident invasive breast cancer, overall 5-year relative survival rates are close to 100% for low-grade disease, but less than 80% for high-grade disease (Collaborative Group on Hormonal Factors in Breast Cancer 2001); prognosis is best for women with low-grade, early-stage disease (approximately 100%) and worst for women with high-grade, advanced-stage disease (<20% 5-year relative survival). While grade is a strong predictor of survival in the first 5 years after breast cancer diagnosis (Warwick et al. 2004; Arriagada et al. 2006; Ries et al. 2007b), there is evidence to suggest that this tumor characteristic may continue to have an impact on survival many years after diagnosis (Contesso et al. 1987; Warwick et al. 2004; Rosenberg et al. 2005).

Histology

Breast cancers are also characterized by pathologists according to tumor histology: the microscopic organization and growth pattern of cancer cells. The

two most common histological types of breast cancer are ductal and lobular carcinomas. Although the majority of breast cancers are ductal cancers, the distribution of histological types varies between in situ vs. invasive disease. With respect to in situ lesions, ductal carcinoma in situ (DCIS) constitutes 80–85% while lobular carcinoma in situ (LCIS) accounts for only about 5% of all in situ tumors (Li and Daling 2007). DCIS incidence rates have risen dramatically over the past few decades in developed countries because these tumors can be detected by mammography (Levi et al. 1997; Barchielli et al. 1999; Kricker et al. 2004; Li et al. 2005). With respect to tumor biology, DCIS is considered a precursor of invasive breast cancer (Franceschi et al. 1998; Warnberg et al. 2001a; Li et al. 2006; Soerjomataram et al. 2006). In contrast, LCIS is generally considered to be a marker of invasive breast cancer risk, rather than as a true precursor lesion. However, recent data indicate that invasive tumors diagnosed after LCIS are much more likely to be lobular than to be ductal (Li et al. 2006). LCIS is challenging to study epidemiologically because it lacks clinical signs and is typically only found incidentally on procedures performed for another reason. While it has long been thought that LCIS is not associated with any specific mammographic findings, there is evidence that calcifications are seen in 21–67% of LCIS cases (Carson et al. 1994; Crisi et al. 2003; Arpino et al. 2004a).

With respect to invasive disease, approximately 70–73% of invasive breast cancers in developed countries are invasive ductal carcinomas (IDC) and 13–16% are invasive lobular carcinomas (ILC) (Levi et al. 2003; Li et al. 2003; Verkooijen et al. 2003). The remaining ~15% of invasive cases is composed of a heterogenous group of several histological variants, each of which accounts for no more than 2% of all invasive cases and none of which have been particularly well characterized. In order of most to least frequent (based on US cancer registry data) these rarer histological subtypes include: mucinous (2.3%), comedo (1.6%), inflammatory (1.5%), tubular (1.4%), medullary (1.2%), and papillary (0.4%) carcinomas (Li et al. 2005). Analyses using US SEER registry data indicate that there are several clinical differences across these subtypes. Compared to ductal carcinomas, mucinous, comedo, tubular, and medullary carcinomas are less likely to present at an advanced stage; mucinous, tubular, and papillary carcinomas are less likely, and comedo, medullary, and inflammatory carcinomas are more likely to be ER–/PR– and high-grade (Li et al. 2005). With respect to prognosis, data in recent years have shown that mucinous and tubular carcinomas have 31% and 52% lower risks of mortality, respectively, compared to ductal tumors (Li et al. 2003).

Several recent studies have more clearly described the distinct descriptive epidemiology and risk factor profiles of IDC vs. ILC. Incidence rates of ILC (including both pure lobular and mixed ductal–lobular tumors) were observed to increase more rapidly over the 1990s compared to incidence rates of IDC in both the United States and Switzerland. In the United States, ILC rates increased 65% from 1987 to 1999, while rates of IDC increased only 3% (Li et al. 2003). A similar incidence trend was observed in Geneva, Switzerland,

where ILC rates increased 14.4% per year between 1976 and 1999 compared to an increase of only 1.2% per year for IDC rates (Verkooijen et al. 2003). More recent data from the United States indicate that, since 1999, both IDC and ILC rates have declined at a rate of about 4% per year. The reasons for these changing incidence patterns are unclear, but it may be related to saturation of breast cancer screening in developed countries and/or to the abrupt cessation of CHT use that occurred after the Women's Health Initiative randomized trial reported that the risks of hormone therapy outweighed its benefits.

Pathologically, the growth patterns of ILC and IDC are distinct. ILC is characterized by tumors that grow as sheets or linear strands of cancer cells that are microscopically quite different from the discrete solid masses that are characteristic of IDC (Davis et al. 1979). As a result of this difference, ILC is more difficult to palpate on a clinical exam and to detect by mammography compared to IDC (Dixon et al. 1982). Despite the fact that ILC is more likely to present at an advanced stage than IDC, in recent years ILC has been associated with a 26% lower risk of mortality compared to IDC (Li et al. 2003), likely due to the fact that it is almost always hormone receptor positive (Li et al. 2005) (and thus amenable to treatment with adjuvant hormonal therapy). Consistent with the growth pattern of ILC, expression of the cell–cell adhesion molecule E-cadherin is almost universally absent in ILC, while it is almost universally present in IDC (Acs et al. 2001). For this reason, E-cadherin expression is sometimes used clinically to distinguish ILC from IDC. Recent studies have also identified numerous other molecular differences between ILC and IDC through the use of various array platforms, further suggesting that there are important differences in the origins and etiologies of these two histological types of breast cancer (Aldaz et al. 1995; Nishizaki et al. 1997; Gunther et al. 2001; Coradini et al. 2002; Korkola et al. 2003; Arpino et al. 2004b; Loo et al. 2004). As discussed in Chapter 5, the epidemiologic risk factor most consistently observed to differentially impact risk of ILC vs. IDC is CHT use, which is much more strongly related to risk of ILC than it is with risk of IDC.

Molecular/Genetic Profile

Molecular and genetic markers are also widely used to discriminate subtypes of breast cancer. The distinction of tumor subtypes on the basis of tumor marker expression, particularly the distinction between tumors that express ER (ER+) and those that do not (ER–) correlates well with previously described phenotypic classifications and has prognostic significance. Individual assays for tumor markers, including PR, HER2, p53, epidermal growth factor receptor (EGFR), and especially ER, have become common clinical practice because of their utility in selecting targeted therapies and in predicting clinical course. Specifically, breast tumors that are ER+ are most likely to benefit from hormonal therapies such as selective estrogen receptor modulators (SERMs, e.g., tamoxifen) and aromatase inhibitors, while tumors that are HER2+ are most likely to benefit from trastuzumab therapy. Recently, however, advances

in gene expression profiling technology have made it possible to evaluate a large number of tumor markers and genetic alterations in concert. While breast cancer subtypes identified through gene expression profiling reflect many previously established differences according to individual tumor markers and other tumor characteristics, these newly identified subtypes also reflect a more complex interplay of a variety of transcriptional programs. Here we consider the significance of breast cancer subtypes distinguished on the basis of ER expression status alone as well as subtypes distinguished by more refined gene expression profiles.

Estrogen Receptor (ER) Status

In normal breast tissue, estrogen is the predominant controller of cell proliferation and its activity is mediated by the estrogen receptor (ER). Although there are two forms of ER (ERα and ERβ), ERα is the predominant form in breast tissue; we refer to ERα simply as ER throughout this chapter. In developed countries where tumor ER expression is routinely assessed on breast cancer patients, approximately 75% of breast tumors are ER+ (Li et al. 2003). Pronounced differences in the epidemiology and clinical profiles of ER+ and ER– breast cancers have been noted for decades (McGuire 1975; Leclercq et al. 2002) and suggest vastly different tumor etiologies. Breast cancer risk factors related to endogenous hormone exposure, such as parity and age at first live birth, are more strongly associated with risk of ER+ breast cancer, while risk factors for ER– disease are more likely to involve non-hormonal mechanisms (Potter et al. 1995; Huang et al. 2000; Ma et al. 2006; Rosenberg et al. 2006). Clinically, ER+ breast cancers are associated with a much more favorable prognosis than ER– tumors: the estimated 5-year survival probability for patients with ER+ breast cancer is approximately 90%, compared to only 77% for patients with ER– disease (Grann et al. 2003). These tumor types are also clinically distinguished by the fact that hormonal therapies (including selective estrogen receptor modulators and aromatase inhibitors) offer significant improvement in disease survival among patients with ER+, but not ER–, breast cancer (Rutqvist and Johansson 2007).

Increasing evidence suggests that ER expression is strongly correlated with a number of other tumor markers, including many that are not regulated by estrogen (Lacroix et al. 2004). ER expression is strongly correlated with PR expression, with greater than 80% of ER+ tumors also being PR+ and greater than 90% of ER– tumors being PR– (Surveillance Epidemiology and End Results Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 17 Regs Limited-Use). ER expression is also associated with genes and protein products involved in cell cycle regulation and proliferation: ER+ tumors exhibit higher expression of cyclin-dependent kinase inhibitors p21 and p27 (Reed et al. 1999; Oh et al. 2001), cyclin D1 (Reed et al. 1999; Oh et al. 2001), and apoptosis inhibitor bcl-2 (Callagy et al. 2003), while ER– tumors exhibit higher expression of p53 (Sorlie et al. 2001; Callagy et al. 2003), cyclin

E (Callagy et al. 2003), and proliferation indicator Ki-67 (Molino et al. 1997; Ruiz et al. 2006). These differences in cell biology may largely explain the pronounced phenotypic and clinical differences between ER+ and ER– tumors.

As may be gathered from the differences described above, distinctions between ER+ and ER– tumors overlap with previously described classification systems. With respect to patient characteristics, ER– tumors are more common among patients diagnosed at a young age (Anderson et al. 2006) and among patients with a genetic predisposition for breast cancer (Palacios et al. 2005). ER+ and ER– tumors also exhibit differences in the distribution of tumor grade (Callagy et al. 2003): approximately 75% of ER+ tumors are low-grade, while approximately 75% of ER– tumors are high-grade (Surveillance Epidemiology and End Results Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 17 Regs Limited-Use). With respect to histology, approximately 25% of ductal tumors are ER– while lobular tumors are almost never ER– (Korhonen et al. 2004). Additionally, while ER– tumors are most likely to exhibit patterns of gene expression associated with myoepithelial lineage, ER+ tumors are strongly associated with luminal cell lineage (Jones et al. 2004; Lacroix et al. 2004).

The relevance of ER expression as a major discriminator of breast cancer subtypes has been confirmed by gene expression profiling studies (Perou et al. 2000; Sorlie et al. 2001; van't Veer et al. 2002; van de Vijver et al. 2002; Sorlie et al. 2003; Farmer et al. 2005; Hu et al. 2006). Importantly, however, these studies also reveal a substantial amount of heterogeneity within ER+ and ER– subtypes of breast cancer.

Molecular Subtypes of Breast Cancer

Gene expression profiling technology has been used to identify and discriminate between subtypes of breast cancer (Perou et al. 2000; Sorlie et al. 2001; van't Veer et al. 2002; van de Vijver et al. 2002; Farmer et al. 2005). cDNA microarrays have been used to assay gene expression in breast tumors which allows the hundreds of genes involved in cell growth, death, and proliferation to be analyzed concurrently. Hierarchical clustering is then employed to group together those tumors with similar "molecular portraits." Studies utilizing this approach have discovered and validated several molecular subtypes of breast cancer. While different investigators have used different sets of genes to characterize breast cancer subtypes, the gene expression profiles that have been most widely utilized and validated are those identified by the Perou and Sorlie groups (Perou et al. 2000; Sorlie et al. 2001, 2003; Fan et al. 2006; Hu et al. 2006; Sorlie et al. 2006). These groups identified five subtypes of breast cancer with distinct molecular profiles: luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like (also called unclassified). Of note, ER status alone can reliably distinguish between broad groups of these subtypes as almost all luminal

A and luminal B tumors are ER+ and the vast majority of HER2-overexpressing, basal-like, and normal-like tumors are ER–. Although there is little population-based data to approximate the distribution of these subtypes, it is clear that the majority of breast cancers belong to the luminal A subtype (41–69%), and the HER2-overexpressing and normal-like phenotypes are the least common (5–10%) (Sorlie et al. 2001; Carey et al. 2006; Yang et al. 2007). Existing epidemiologic evidence also suggests that the distribution of the five subtypes varies with demographic and genetic factors: breast cancers diagnosed in premenopausal women or African-American women are more likely to be basal-like or HER2-overexpressing (Carey et al. 2006; Yang et al. 2007), and *BRCA1*-related breast cancers are almost always basal-like (Foulkes et al. 2003). Additional differences in the epidemiologies of luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like tumors remain to be understood although, consistent with the previously described association between reproductive history and risk of ER+ breast cancer, hormonal factors appear most strongly associated with risk of luminal A breast cancer (Yang et al. 2007; Millikan et al. 2008; Phipps et al. 2008a, b).

The primary factors discriminating between luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like subtypes of breast cancer reflect the cellular origin of these tumors within the breast: luminal A and luminal B subtypes express genes characteristic of luminal cell lineage (particularly ER), while HER2-overexpressing, basal-like, and normal-like subtypes demonstrate no such expression. Within the group of luminal-like tumors, luminal A tumors are characterized by a higher level of expression of luminal-specific genes (e.g., ER, GATA-binding protein 3 [GATA3], hepatocyte nuclear factor 3 alpha [HNF3A], X-box-binding protein 1 [XBP1]), and a lower level of expression of proliferative genes (e.g., cyclin B1, proliferation-associated antigen Ki-67) as compared to luminal B tumors (Sorlie 2004). Among the group of non-luminal tumors, HER2-overexpressing tumors are characterized by a high level of HER2 expression, while basal-like tumors exhibit the gene expression pattern most similar to that of basal epithelial cells, generally including a lack of ER, PR, and HER2 expression (the so called "triple-negative" phenotype) accompanied by expression of EGFR and/or basal cytokeratins (e.g., cytokeratin 5/6) (Nielsen et al. 2004). Normal-like tumors demonstrate strong expression of genes characteristic of adipose and other non-epithelial cells, although it remains to be seen whether this tumor subtype represents a clinically relevant group or simply poorly sampled tumor tissue (Sorlie 2004).

Existing data from gene expression-based studies, and from studies using simplified IHC-based definitions of luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like tumor subtypes, indicate that the observed genotypic differences between these subtypes translate to distinctive clinical profiles (Table 2.1). Consistent with the fact that luminal A tumors are ER+, tumors of this type are most commonly low-grade and are associated with an early stage at diagnosis and favorable prognosis (Carey et al. 2006; Kim et al.

Table 2.1 Characteristics of breast cancer subtypes defined by gene expression profiles

	Luminal A	Luminal B	HER2-overexpressing	Basal-like	Normal-like
Approximate distribution:	55–65%	7–12%	6–10%	10–15%	5–10%
Tumor biology/appearance:					
Presumed cellular origin	Luminal epithelial	Luminal epithelial	Basoluminal	Basal epithelial	Non-epithelial
Predominant tumor marker expression pattern:	ER + and/or PR +, HER2-	ER + and/or PR +, HER2 +	ER–, PR–, HER2 +	ER–, PR–, HER2–, cytokeratin 5/6 + and/or EGFR +	ER–, PR–, HER2–, cytokeratin 5/6–, EGFR–
Stage at diagnosis:					
I	44%	39%	28%	24%	48%
II	47%	54%	53%	62%	39%
III–IV	9%	6%	19%	13%	13%
Grade:					
Poorly differentiated	58%	56%	70%	82%	81%
Mod./well-differentiated	42%	44%	30%	18%	19%
Clinical characteristics:					
Average 5-year survival:	75–90%	45–90%	20–75%	30–80%	50–87%
Targeted therapies:	Tamoxifen	Tamoxifen, possibly trastuzumab	Trastuzumab	None available	None available

2006; Stark et al. 2007). In comparison, basal-like and HER2-overexpressing tumors are more likely to present at an advanced stage, to be of high-grade and, therefore, are associated with a markedly worse survival: the average 5-year survival among patients with luminal A disease is approximately 90%, while estimates for patients with HER2-overexpressing or basal-like breast cancer may be as low as 20–30% (Sorlie et al. 2001, 2003; Carey et al. 2006; Hu et al. 2006). Patients with luminal B disease appear to experience a slightly, but not significantly poorer prognosis than patients with luminal A tumors, but patients with tumors of either luminal subtype may be expected to benefit from targeted hormonal therapy. Although patients with HER2-overexpressing, basal-like, and normal-like breast cancers have a poorer prognosis than patients with luminal disease, it is suggested that they may respond more favorably to anthracycline-based neoadjuvant chemotherapy (Banerjee et al. 2006; Kim et al. 2006; Carey et al. 2007).

Understanding the different patterns of gene expression evident in different subtypes of breast cancer has helped to explain differences in clinical profiles. The classification of subtypes according to genetic and molecular characteristics correlates well with differences in prognosis, tumor aggressiveness, and response to available therapies. These subtypes have now been identified and validated in a number of different study populations and on a number of different platforms (Fan et al. 2006; Hu et al. 2006). The fact that these five disease subtypes reflect much of what has long been known about different aspects of disease, such as age at diagnosis and menopausal status, genetic predisposition, tumor stage and grade, histology, and individual tumor marker expression illustrates the benefit of jointly considering multiple tumor characteristics. Although technology will undoubtedly change and progress, it is certain that any attempts to classify subtypes of breast cancer in the future will need to concurrently consider a wide variety of genotypic and phenotypic factors in their characterization.

Origins of Breast Cancer Subtypes

The previously described distinctions between subtypes of breast cancer imply differences in tumor etiology. However, while the phenotypic and genotypic differences between disease subtypes have been well characterized, the biology underlying the initiation, progression, and divergence of these subtypes is not fully understood. Given the magnitude of the genomic, genetic, and epigenetic differences between subtypes of breast cancer defined by gene expression profiles and by tumor grade, it is likely that distinctions between these subtypes are fixed at tumor inception (Lacroix et al. 2004). For example, loss of genomic material in chromosome 16q is observed in approximately 65% of low-grade tumors but in less than 20% of high-grade tumors (Roylance et al. 1999); because the recovery of lost genomic material is an unlikely event in cancer

progression, this suggests that low and high-grade tumors arise through different etiologic pathways (Bergamaschi et al. 2006). Consistent with such a hypothesis, there is increasing evidence to suggest that breast cancers are relatively genetically stable throughout progression (Lacroix et al. 2004) and that tumor grade and tumor marker expression are highly concordant between in situ, invasive, and metastatic components of a breast cancer (Warnberg et al. 2001b).

In order for cancer to occur, a normal cell must accumulate several genetic and/or epigenetic changes including an activation or amplification of oncogenes, mutation or loss of tumor suppressor function, and the ability to proliferate indefinitely (Hanahan and Weinberg 2000). While the specific set of acquired alterations leading to the transformation of a normal cell could, in part, determine the makeup or subtype characterization of a cancer, the characteristics of the cell of origin itself are also thought to be relevant to subtype distinctions. The cancer stem cell model provides one framework under which the characteristics of a breast cancer are directly tied to its cellular origin (Dontu et al. 2003; Campbell and Polyak 2007; Stingl and Caldas 2007; Melchor and Benitez 2008).

Adult stem cells are tissue-specific, self-renewing cells capable of differentiating into all cell types in their tissue of origin. Given that the human breast undergoes many morphological changes throughout life, particularly during pregnancy, the existence of mammary stem cells has long been postulated (Daniel and Deome 1965; Dulbecco et al. 1982). Recent studies have been able to confirm that such cells exist in the normal adult breast (Shackleton et al. 2006) and characterize these cells in breast tumor tissue (Stingl et al. 2001; Al-Hajj et al. 2003; Shipitsin et al. 2007). The model of how these mammary stem cells generate different epithelial cell lineages is assumed to involve a hierarchy of proliferation similar to other epithelial cell systems (Villadsen 2005). Under such a system, self-renewing mammary stem cells give rise to progenitor cells which, in turn, give rise to terminally differentiated luminal and myoepithelial cells (Fig. 2.1). Unlike stem cells, progenitor cells have a finite division capacity and are more differentiated. Some progenitor cells appear to be bipotent, capable of giving rise to either luminal or myoepithelial cell lineages (Stingl et al. 2001), while others appear to be restricted to luminal lineages (Dontu et al. 2004; Stingl and Caldas 2007). The fact that tumor cells exhibit many properties of normal adult stem cells, such as self-renewal, high proliferative capacity, and longevity, has led to the hypothesis that breast tumors originate in stem cells which have undergone some genomic transformation (i.e., "cancer stem cells"). In contrast to stem and progenitor cells, the terminally differentiated cells which comprise the majority of breast tissue rarely proliferate and are continuously replaced; thus, there is some question as to whether terminally differentiated cells have adequate opportunity to accumulate the multiple genetic/epigenetic changes necessary to initiate oncogenesis.

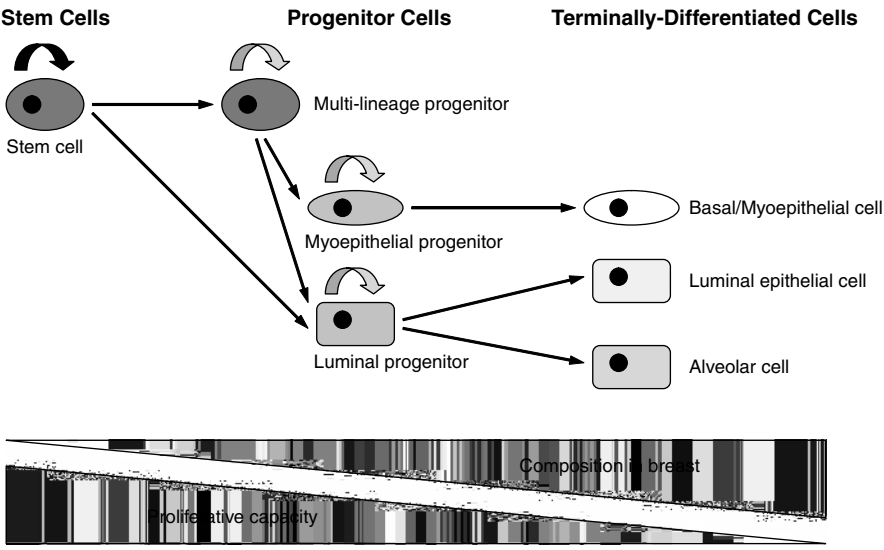

Fig. 2.1 Hierarchy of mammary epithelial cells in the normal adult breast

The tumorigenicity of mammary stem cells is supported by a landmark paper by Al-Hajj et al. (2003), who demonstrated that cells from a solid human breast tumor exhibiting a $CD44^{+}/CD24^{-/low}$ phenotype could induce breast tumors in immunocompromised mice with transfection of as few as 200 cells, and that induced tumors demonstrated an array of cell types similar to those found in the original tumor. In contrast, injecting thousands of cancer cells that came from the same human tumors but that had an alternate phenotype (i.e., not $CD44^{+}/CD24^{-/low}$) failed to induce any tumors. Further studies have confirmed the oncogenic properties of $CD44^{+}/CD24^{-/low}$ cells (Ponti et al. 2005) and have demonstrated that the gene signatures for these cells are enriched for stem cell markers (Shipitsin et al. 2007). Specifically, $CD44^{+}/CD24^{-/low}$ cells exhibit increased expression of genes involved in cell motility and genes in the TGF-β pathway and a lack of ER expression. While it is generally considered that the $CD44^{+}/CD24^{-/low}$ phenotype, in conjunction with epithelial-specific antigen (ESA) expression, characterizes cancer stem cells, these biomarkers are not highly specific (Honeth et al. 2008) and there is a great need to develop more specific cancer stem cell markers.

Under the cancer stem cell model of breast oncogenesis, cancer-inducing mutations and/or alterations in protein expression affect either mammary stem cells or progenitor cells, giving rise to cancer stem cells which are able to self-renew and differentiate into the other cells that comprise a tumor. In contrast to more traditional models of clonal evolution and multistep oncogenesis, the cancer stem cell model posits that only a small subset of cells within a breast tumor (i.e., cancer stem cells and their progenitor cells) are able to drive

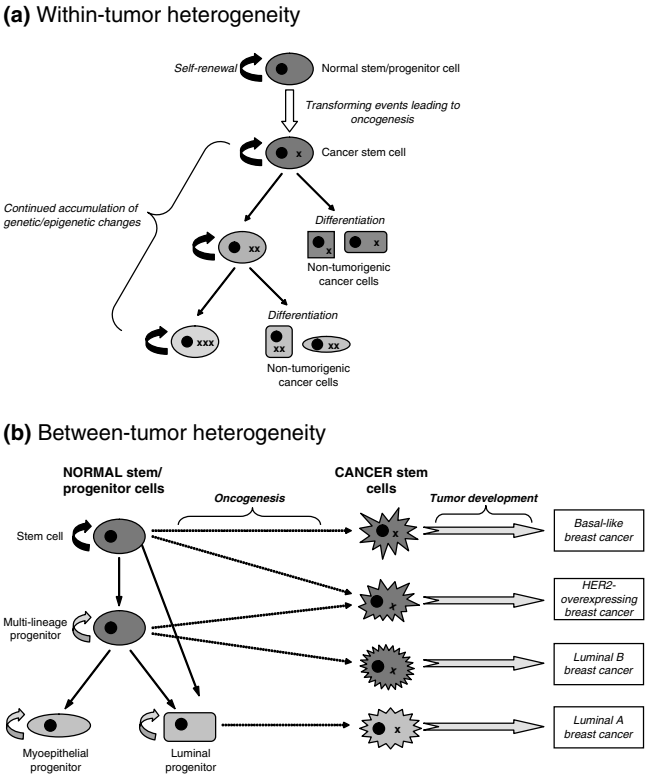

Fig. 2.2 Possible sources of heterogeneity under the cancer stem cell model

proliferation and accumulate genetic and/or epigenetic changes (Campbell and Polyak 2007; Stingl and Caldas 2007). As a result, heterogeneity within a tumor is expected to arise as the result of aberrant differentiation of cancer stem cells and the continued accumulation of genetic and epigenetic changes in cancer stem cells (Fig. 2.2a).

With respect to heterogeneity between tumors, the cancer stem cell model implies that breast tumor characteristics, including grade and tumor marker expression largely reflect the type of stem cell or progenitor cell in which the tumor arose (Fig. 2.2b). For example, basal-like breast tumors exhibit a gene expression profile similar to that of mammary stem cells (Yehiely et al. 2006) but differ from differentiated myoepithelial cells in that they do not express smooth muscle actin (Livasy et al. 2006); based on these observations, it has been suggested that basal-like tumors are derived directly from mammary stem cells (Stingl and Caldas 2007) or from ER– bipotent progenitor cells (Stingl et al. 2001). Conversely, given the lack of ER expression in mammary stem cells (Asselin-Labat et al. 2006; Shipitsin et al. 2007), it has been proposed that luminal breast tumors must arise from ER+ luminal progenitor cells (Dontu et al. 2004). The underlying implications of this model are thus that the basic

patterns of gene expression, specific to different types of stem or progenitor cells within the breast, are largely maintained throughout the pathway leading to breast cancer and are fundamentally responsible for distinctions between subtypes of breast cancer (Korsching et al. 2002). Accordingly, differences between subtypes of breast cancer defined on the basis of biological characteristics such as grade, tumor marker expression, and/or gene expression pattern, are suggested to be fixed at tumor inception.

Conclusions

Evidence suggests that the distinction between different subtypes of breast cancer arises early in cancer development. A number of classification systems have been utilized to distinguish subtypes of breast tumors according to epidemiologic, morphologic, genetic, and molecular characteristics. While the specific subtypes identified through each of these classification systems highlight important distinctions in clinical outcome and tumor etiology, there is great overlap between tumor subtypes identified on the basis of patient characteristics and various tumor characteristics. The classification system most recently proposed from gene expression profiling studies appears to offer the most refined system of classification, and has been shown to have both epidemiologic and clinical relevance. Given the heterogeneity of breast cancer, distinguishing breast cancers into relevant subtypes is often critical when studying the disease's etiology, predicting disease prognosis, and making appropriate treatment decisions.

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Chapter 3
In situ Breast Cancer

Brian L. Sprague and Amy Trentham-Dietz

Introduction

Breast carcinoma in situ (BCIS) is the penultimate step in the progression of normal epithelium from hyperplasia to invasive breast cancer. There are two types of BCIS: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Most BCIS of both types originate in the terminal duct lobular unit, with the type of cells and their growth pattern providing the distinguishing features. DCIS is a proliferation of presumably malignant epithelial cells confined to the mammary ducts and lobules without demonstrable evidence of invasion through the basement membrane into the surrounding stroma (Harris et al. 1997). DCIS is typically detected by mammography, as it is frequently associated with microcalcifications (Damiani et al. 2002). LCIS is a solid proliferation of generally small and often loosely cohesive cells with small, uniform, round to oval nuclei (Harris et al. 1997). The overall lobular architecture is maintained and the cells are contained within the basement membrane. LCIS is often multicentric and bilateral and is most commonly diagnosed incidentally by a breast procedure performed for another reason (Damiani et al. 2002).

In this chapter, we will summarize trends in BCIS incidence, describe the natural history of BCIS, and review factors associated with its incidence, recurrence, and survival. Important differences between the epidemiology of invasive breast cancer and BCIS will be noted, with additional attention to differences according to histologic subtype of BCIS.

Incidence Trends

Prior to 1980, BCIS was a rare diagnosis, comprising about 4% of all newly diagnosed breast cancer in the United States (Ries et al. 2008). Most cases were detected as palpable masses or lumps. A dramatic increase in the incidence of

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_3,

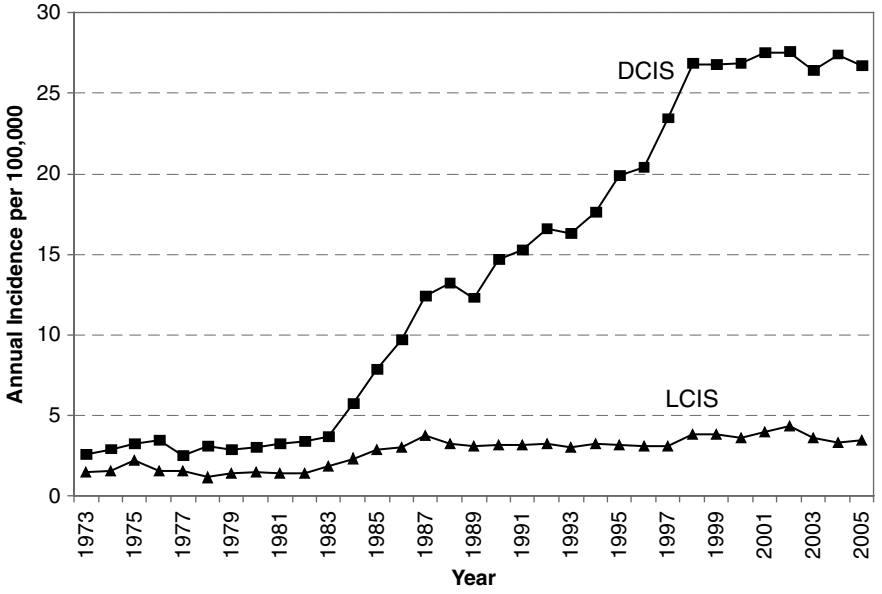

Fig. 3.1 Annual age-adjusted incidence of DCIS and LCIS, SEER*Stat Database: Incidence – SEER 9 Regs Limited-Use, November 2007 Sub (1973–2005), Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), United States

BCIS, and particularly DCIS, began in the early 1980s, concurrent with the adoption of widespread screening mammography (Fig. 3.1) (Ernster et al. 1996). By 2005, the annual incidence of BCIS in the United States was 32.0 per 100,000 women, constituting 20.5% of all breast cancers (Ries et al. 2008). The rise in incidence has been dominated by DCIS which currently comprises 85–90% of diagnosed BCIS, although increases in LCIS have also been observed (SEER Program 2007).

Similar patterns of increasing BCIS incidence following the adoption of screening mammography have been observed internationally. In South Australia, the incidence of BCIS rose 7-fold between 1985 and 2000, then leveled off from 2000 to 2004 as population screening reached a plateau (Luke et al. 2006). BCIS incidence rose 2.6-fold and 4.5-fold in areas of Italy and Switzerland, respectively, following the introduction of mammography in the 1980s (Levi et al. 1997; Barchielli et al. 1999). These increases were largest for DCIS as opposed to LCIS and within age groups who were targeted for screening.

The increase in BCIS incidence in the United States has been most pronounced among women over the age of 55 years (Fig. 3.2). In 2005, approximately 74% of BCIS cases were women over the age of 50 (SEER Program 2007). The age-specific pattern of incidence for BCIS shows a broad peak among women 45–84 years old (Fig. 3.3) (Young et al. 2001). The rate of increase in incidence with advancing age slows near age 50, likely reflecting

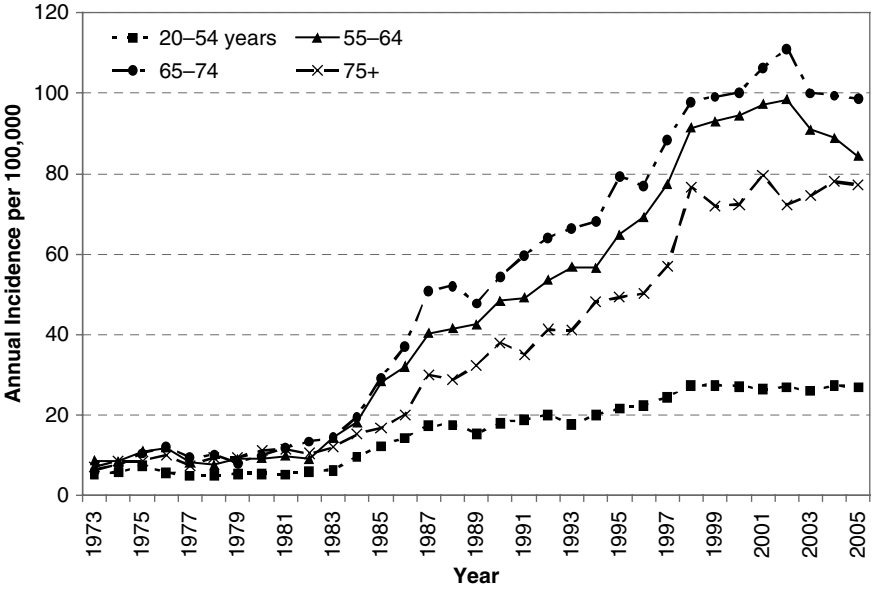

Fig. 3.2 Annual incidence of BCIS by age, SEER*Stat Database: Incidence – SEER 9 Regs Limited-Use, November 2007 Sub (1973–2005), Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), United States

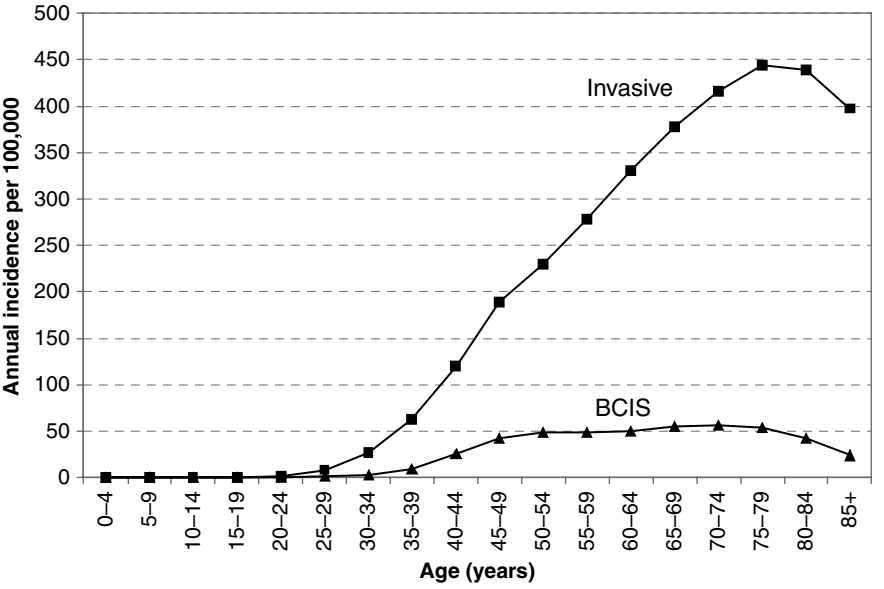

Fig. 3.3 Annual age-specific incidence of BCIS, 1973–2005, SEER*Stat Database: Incidence – SEER 9 Regs Limited-Use, November 2007 Sub (1973–2005), Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), United States

the role of reproductive hormones in breast cancer etiology (Pike et al. 1993). In contrast to invasive breast cancer incidence, however, which continues to increase among progressively older age groups up to age 85, incidence of BCIS levels off at age 50.

BCIS incidence rates among the SEER 17 Registries in 2001–2005 were highest in non-Hispanic whites (33.1 per 100,000), followed by blacks (26.1 per 100,000), Asian/Pacific Islanders (25.7 per 100,000), Hispanics (18.7 per 100,000), and American Indians/Alaska natives (14.7 per 100,000) (Ries et al. 2008). However, the rise in BCIS incidence has generally been consistent across all races and ethnicities (SEER Program 2007).

Substantial geographic variation in BCIS incidence has been observed across SEER 17 Registries, ranging from 20.7 per 100,000 in New Mexico to 43.1 per 100,000 in Connecticut for the 2001–2005 period (Ries et al. 2008). Much of this variation in breast cancer stage at diagnosis can likely be attributed to patterns in mammography utilization (McCarthy et al. 2000).

Since 2001, breast cancer incidence has declined in the United States. This has provoked a number of hypotheses regarding the underlying cause, including a reduction in the number of women taking postmenopausal hormones, fewer women utilizing screening mammography, and saturation of the pool of detectable cancers by screening (Ravdin et al. 2007; Jemal et al. 2007). If reduced mammography screening was responsible, one would have expected larger declines in the incidence of in situ as compared to invasive cancers, which has not been the case (Fig. 3.1), leading some authors to conclude that postmenopausal hormone use and saturation of screening are more likely explanations (Colditz 2007; Kerlikowske et al. 2007; Li and Daling 2007).

Many clinics are converting from film to digital mammography following the results of the Digital Mammographic Imaging Screening Trial, which suggested increased accuracy with digital mammography for women under the age of 50 years (Pisano et al. 2005). The potential effects of this transition on trends in BCIS incidence remain unclear.

Natural History

Biological Markers

DCIS and LCIS differ in important respects regarding their natural history. Though not all DCIS cases will progress, DCIS is considered a true precursor to invasive breast cancer. Histological examination reveals that DCIS lies in the middle of a spectrum of progressive changes in nuclear features from normal breast tissue to invasive breast cancer (Mommers et al. 2001). Additionally, DCIS and invasive breast cancer share many of the same patterns of expression of biological markers (Burstein et al. 2004). The most widely studied markers are HER-2/neu, p53, and the estrogen receptor (ER), though

several other molecular markers have received attention, including the progesterone receptor, p21, p27, bcl-2, cyclin D1, Ki-67, E-cadherin, and TGF-beta (Zagouri et al. 2007; Mommers et al. 2001). Little evidence has arisen to establish that any of these markers are differentially upregulated in BCIS compared to invasive tumors. Given the large variability of expression in both in situ and invasive breast cancers, moderate differences may be difficult to detect.

High correlations have been observed between expressions of ER, PR, HER-2/neu, and p53 in primary DCIS and in local recurrences after breast-conserving surgery, suggesting that local recurrence reflects an outgrowth of residual DCIS (Bijker et al. 2001). Similarly, in lesions with both a DCIS and invasive component, tumor marker expression is similar in both components (Warnberg et al. 2001). Notably, tumor grade has been strongly related to tumor marker expression in both DCIS and invasive breast cancers (Mommers et al. 2001; Warnberg et al. 2001). Thus it has been hypothesized that well-differentiated DCIS progresses toward well-differentiated invasive cancer and poorly differentiated DCIS progresses toward poorly differentiated invasive cancer.

Though fewer studies of molecular markers in LCIS have been conducted, there appear to be marked differences in comparison with DCIS and invasive breast cancer, including less overexpression of HER-2/neu and p53 (Mohsin et al. 2005). Loss of E-cadherin expression appears to be an early event in lobular carcinogenesis, as both invasive and in situ lobular carcinomas typically show complete loss of membranous expression (Acs et al. 2001). Since ductal carcinomas continue to express E-cadherin, immunohistochemical staining for E-cadherin provides an important diagnostic tool for distinguishing between DCIS and LCIS (Lerwill 2004).

Survival and Recurrence

While BCIS may be a direct precursor of invasive disease, it is not an obligate precursor lesion, and therefore its potential for recurrence is variable. Notably, in most studies of recurrence, the term "subsequent breast cancer diagnosis" may be more appropriate, since it is difficult to establish whether a breast cancer arose directly from a previously identified BCIS lesion.

Overall relative survival after a BCIS diagnosis approaches 100% regardless of choice of therapy (Ernster et al. 2000; Fisher et al. 1999; Fisher et al. 1991), thus the goal of treatment for BCIS is prevention of local recurrence in the form of invasive breast cancer. Compared to the general population, women diagnosed with BCIS have an approximately 4-fold higher risk overall of developing invasive breast cancer (Warnberg et al. 2000). Among women diagnosed with BCIS, less than 1% die from breast cancer within 5 years and less than 2% die within 10 years (Ernster et al. 2000; Schairer et al. 2004).

The natural history of BCIS in the absence of treatment is not well understood. A few small studies of DCIS cases which were mistakenly labeled as benign and left untreated beyond biopsy have reported follow-up results. The percent of women that were diagnosed with subsequent in situ or invasive breast cancer varied from 20 to 77% among the studies with up to 30 years of follow-up; however, these estimates are based on small numbers of cases (Collins et al. 2005; Page et al. 1982; Rosen et al. 1970; Betsill 1978; Eusebi et al. 1994). LCIS patients with no treatment beyond biopsy have a 10-fold risk of invasive breast cancer as compared to the general population, and retrospective studies suggest that 13–31% of untreated LCIS patients will ultimately develop invasive breast tumors (Levi et al. 2005; Posner and Wolmark 1992; Page et al. 2003, 1991; Goldschmidt and Victor 1996).

Given the restricted location of BCIS within the basement membrane, complete excision should completely prevent further morbidity or mortality. Despite this theoretical paradigm, recurrences and second primaries do occur after surgical treatment of BCIS, but in a minority of patients. Disease-free survival after BCIS may be related to (1) an invasive component (perhaps micro-metastasis) unrecognized at the time of the BCIS diagnosis, (2) the progression of BCIS that was inadequately excised or unrecognized, or (3) the development of an independent lesion (Burstein et al. 2004, Ernster et al. 2000).

Current practice guidelines for DCIS treatment recommend mastectomy or breast-conserving surgery with radiation and consideration of tamoxifen (National Comprehensive Cancer Network Inc. 2007). No clinical trials have compared breast-conserving treatment to mastectomy in DCIS patients; however, a benefit for tamoxifen for estrogen receptor positive DCIS has been supported (Fisher et al. 1999). Women who choose mastectomy have approximately a 98% chance of remaining disease-free (Boyages et al. 1999; Hwang and Esserman 1999; Cutuli et al. 2001). Higher recurrence rates have been observed among women who undergo breast-conserving treatment (Julien et al. 2000; Fisher et al. 1998; Solin et al. 2001; Kerlikowske et al. 2003). Among women with breast-conserving treatment for DCIS, 2–3% annually will experience an ipsilateral recurrence of breast cancer, about half of which are invasive. Approximately 4–7% of DCIS cases will develop a contralateral in situ or invasive breast cancer within 10 years following diagnosis (Habel et al. 1997; Li et al. 2006).

Fewer studies have evaluated the impact of treatment on disease-free survival after an LCIS diagnosis. Although risk of any recurrence may be lower among women diagnosed with LCIS than DCIS, the risk of subsequent invasive breast cancer is similar (Levi et al. 2005; Habel et al. 1997; Fisher et al. 2001; Sasson et al. 2001). One prospective study found that about 22% of LCIS cases experienced recurrence within 12 years of local excision and about half were invasive (Fisher et al. 2004). Given the often multicentric and bilateral nature of LCIS, the treatment choice is thus typically one of two extremes: either no surgery beyond biopsy and counseling regarding risk reduction with tamoxifen or bilateral mastectomy (National Comprehensive Cancer Network Inc. 2007).

The risk of developing invasive breast cancer after LCIS is higher in women treated with partial mastectomies compared to total, modified radical, or radical mastectomies (Chuba et al. 2005). Invasive breast cancers subsequent to LCIS are more often of lobular histologic type (~23%) compared to first primary invasive breast cancers (~7%) (Sasson et al. 2001; Chuba et al. 2005). However, since a subsequent breast cancer after LCIS is equally likely to appear in the ipsilateral or contralateral breast (Warnberg et al. 2000; Chuba et al. 2005; Habel et al. 1998), and because many of these recurrences are ductal in histology, the malignant potential of this tumor type is less certain than for DCIS (Li et al. 2006; Haagenson 1986; Schnitt and Morrow 1999). Thus, rather than a true precursor, LCIS is regarded to be a marker of risk, reflecting the mixture of risk factors of the woman – her family history of breast cancer and genetic predisposition, hormone use, reproductive history, etc.

Prognostic Factors

Besides type of treatment, most studies of factors related to recurrence after BCIS have focused on DCIS tumor characteristics. Comedo type architecture, high grade, larger size, and detection by palpation rather than mammography are associated with an increased likelihood of recurrence after DCIS (Boyages et al. 1999; Kerlikowske et al. 2003; Li et al. 2006; Habel et al. 1998). Following breast-conserving surgery for DCIS, negative margins are associated with a reduced risk of recurrence (Fisher et al. 1999; Solin et al. 2005).

Few studies have examined patient factors in relation to recurrence after BCIS. Women who are younger and/or premenopausal at diagnosis have a higher rate of recurrence after a DCIS or LCIS diagnosis (Kerlikowske et al. 2003; Chuba et al. 2005; Habel et al. 1998; Solin et al. 2005; Vicini and Recht 2002). Limited and conflicting evidence exists regarding the association between recurrence and body mass index at diagnosis or postmenopausal hormone use after a DCIS diagnosis (Kerlikowske et al. 2003; Habel et al. 1998).

Concern with Overtreatment

Randomized trials have demonstrated that screening mammography reduces breast cancer mortality (Humphrey et al. 2002). However, the dramatic rise in BCIS incidence which has accompanied the widespread adoption of mammography has provoked concerns regarding the potential for "overdiagnosis" and "overtreatment" (Ernster and Barclay 1997). It has been estimated that 37% of DCIS cases detected in women attending screening for the first time are non-progressive (Yen et al. 2003). Autopsy studies of women with no known diagnosis of breast cancer reveal the potential reservoir of cases that could be

detected by advanced screening tools, as well as the prevalence of apparently non-life threatening lesions. While LCIS appears to be a rare finding on autopsy (Alpers and Wellings 1985; Nielsen et al. 1987), a comprehensive review concluded that DCIS is not uncommon, with a median prevalence of 9% (range 0–15%) (Welch and Black 1997). If the median prevalence is applied to the US population, one would expect over 2 million women to have DCIS (Welch and Black 1997). Such a large reservoir suggests that increasing detection sensitivity may reveal many cases that would never progress into invasive breast cancer.

Thus some women may suffer the physical and mental effects of a breast cancer diagnosis and its treatment despite having a clinically insignificant disease. Without reliable methods to identify BCIS tumors that will progress or recur, the optimal treatment approach for BCIS remains controversial (Hwang and Esserman 1999; Schwartz et al. 1999).

Summary

DCIS appears to be a true precursor to invasive breast cancer, whereas LCIS may serve instead as a marker of risk. For both forms of BCIS, relative overall survival approaches 100% regardless of treatment choice. Mastectomy provides better protection against a future recurrence than breast-conserving treatment. It is important that better tumor and/or patient predictors of recurrence are identified so that women with BCIS do not undergo unnecessary treatment for an increasingly common disease that may often be clinically insignificant.

Risk Factors

Patterns in breast cancer incidence have been extensively studied to identify a number of reproductive, menstrual, lifestyle, and genetic risk factors (Hankinson and Hunter 2002). This epidemiologic evidence indicates that estrogen exposure plays a primary role in breast cancer etiology (Hankinson et al. 2004). Fewer studies have evaluated risk factors for BCIS separately from invasive breast cancer. The extent to which BCIS and invasive breast cancer share the same risk factors can inform our knowledge regarding the natural history of breast cancer.

Studies of BCIS risk encounter a number of unique challenges. First, the consistency of a BCIS diagnosis should be considered. One randomized trial implementing centralized pathology review noted that among the cases initially diagnosed as DCIS, 1.5% were re-classified as invasive breast cancer and 4.7% were re-classified as atypical hyperplasia (Fisher et al. 1993). Another study of approximately 2,000 patients with non-palpable breast lesions diagnosed after core needle biopsy reported 96% concordance overall between local and centralized review, with diagnostic agreement varying according to the type of

lesion: 53% for LCIS, 83% for DCIS, 97% for invasive breast cancer, and 99% for benign diagnoses (Collins et al. 2004). Thus, the use of uniform diagnostic criteria is particularly important for LCIS.

Due to the preponderance of BCIS cases identified by mammography, it is imperative to adequately control for utilization of screening mammography. This is of particular concern when the risk factor of interest may also be associated with screening utilization (e.g., postmenopausal hormone use).

Length bias must also be considered in interpreting studies of BCIS risk, as screening mammography is more likely to detect slow-growing BCIS tumors. Factors that act as promoters may reduce the time spent as BCIS before progression to invasive breast cancer, and thus may appear to be associated with invasive breast cancer but not BCIS. That is, the factor may truly be associated with BCIS incidence but the short time spent as a BCIS lesion may prevent this association from being observed.

Below we review the current knowledge regarding risk factors for BCIS. We give particular attention to how the relation between each factor and BCIS compares to that for invasive breast cancer, and whether there is any evidence for differential risk patterns by histologic subtype (i.e., DCIS vs. LCIS).

Menstrual and Reproductive Factors

In general, menstrual and reproductive risk factors are thought to influence breast cancer risk through their effects on the duration of exposure to high estrogen levels and their effects on breast tissue differentiation (see Table 3.1).

Age at Menarche

In contrast to invasive breast cancer, most studies have reported null associations between age at menarche and risk of BCIS. Studies examining BCIS risk concurrently with invasive breast cancer risk have found that women with earlier age at menarche had increased risk of invasive breast cancer but not BCIS (Brinton et al. 1983; Weiss et al. 1996; Trentham-Dietz et al. 2000;). There is some evidence that an inverse relation between age at menarche and BCIS risk may exist among premenopausal women (Longnecker et al. 1996; Kerlikowske et al. 1997). In the only study to examine this relation by histologic type, no relation was observed between age at menarche and either LCIS or DCIS risk (Claus et al. 2001).

Age at Menopause

Few studies have examined BCIS risk in relation to age at menopause. Three of four studies to do so have reported a positive association, with odds ratio ranging between 1.3 and 2.9 for women at least 55 years old at menopause

Table 3.1 Studies of menstrual, reproductive, and lifestyle risk factors for BCIS

Citation	Dates of diagnosis	Study population	Number of cases/controls	Number of DCIS/LCIS	Age at menarche	Age at menopause	Age at first birth	Parity	Lactation	Body weight	Physical activity	Alcohol	Smoking	Exogenous hormones	Diet
Cross-sectional studies															
Kerlikowske et al. (1997)	1985–1995	UC-San Francisco Screening Program	102/39,177	102/0	x		x	x[b]		x					
Case-control studies															
Lambe et al. (1998)	1958–1990	Sweden	1,368/6,837	NS			x	x							
Brinton et al. (1983, 1986)	1973–1980	BCDDP screening cohort	254/2258	NS	x		x	x[b]		x				x	
Nasca et al. (1994)	1982–1984	New York state	153/1,617	139/14								x			
Longneckeret al. (1996)	1983–1989	Los Angeles County	233/2,203	158/42	x	x	x	x		x				x	
Henrich et al. (1998)	1987–1992	Yale Screening Mammography Program	32/545	NS										x	
Ross et al. (2000)	1987–1996	Los Angeles County	186/1,637	NS										x	
Stanford et al. (1995)	1988–1990	Washington State	87/492	NS										x	
Trentham-Dietz et al. (2000)	1988–1990	Wisconsin	301/3,999	238[a]/63	x	x	x	x	x	x	x	x		x	x
Weiss et al. (1996); Swanson et al. (1996); Gammon et al. (1998); Brinton et al. (1995); Potischman et al. (2002)	1990–1992	Multi-site, USA	227/2,009	NS	x		x	x	x	x		x	x	x	x
Claus et al. (2001, 2003a, b)	1994–1998	Connecticut	998/999	875/123	x	x	x	x				x	x	x	
Bernstein (Meeske et al. 2004; Patel et al. 2003; Gill et al. 2006)	1995–1998	Los Angeles County	567/616	479/58	x		x	x	x	x	x			x	
Trentham-Dietz et al. (2007); Sprague et al. (2007); Nichols et al. (2007)	1995–2001	Multi-site, USA	1871/8,041	1471[a]/223	x	x	x	x			x	x	x	x	
Terry et al. (2006)	1996–1998	Long Island, NY	NS	NS								x			
Reeves et al. (2006)	1996–2002	United Kingdom	1913/1,017,122	1,443/86										x	

Table 3.1 (continued)

Citation	Dates of diagnosis	Study population	Number of cases/controls	Number of DCIS/LCIS	Age at menarche	Age at menopause	Age at first birth	Parity	Lactation	Body weight	Physical activity	Alcohol	Smoking	Exogenous hormones	Diet
Cohort studies															
Schairer et al. (1994, 2000)	1980–1995	BCDDP screening cohort	255/44,273	NS										x	
Gapstur et al. (1999)	1986–1996	Iowa	175/35,585	175/0										x	
Feigelson et al. (2003)	1992–1997	USA	NS	NS								x			
Bernstein (Dallal et al. 2007)	1995–2002	California	593/106,441	538[a]/55											
Vacek (Reinier et al. 2007)	1996–2002	Vermont screening cohort	300/60,653	NS			x	x[b]		x				x	
Clinical trials															
Rossouw et al. (2002)	1993–2002	Multi-site, USA	NS	NS										x	
Stefanick et al. (2006)	1993–2004	Multi-site, USA	55/10,447	NS										x	

NS, not specified.

[a]Includes ductal and other nonlobular subtypes. [b]Examines nulliparous vs. parous only.

compared to women less than 45 years old at menopause (Trentham-Dietz et al. 2000; Longnecker et al. 1996; Claus et al. 2001; Trentham-Dietz et al. 2007). Limited evidence suggests that the positive association between BCIS and age at menopause is similar for both LCIS and DCIS (Claus et al. 2001).

Age at First Birth

Age at first birth is consistently observed to be related to BCIS risk, with odds ratios around 1.5–2.0 for women at least 30 years old at first birth compared to women less than 20 years old at first birth (Claus et al. 2001; Trentham-Dietz et al. 2007; Lambe et al. 1998). This relation may be stronger for BCIS than invasive breast cancer risk (Longnecker et al. 1996; Kerlikowske et al. 1997), though this difference is not consistently observed (Brinton et al. 1983; Trentham-Dietz et al. 2000). There is some evidence that this relation may be strongest in premenopausal women (Longnecker et al. 1996; Reinier et al. 2007). No clear pattern has emerged in analyses stratified by BCIS histology (Weiss et al. 1996; Trentham-Dietz et al. 2000; Claus et al. 2001).

Parity

A 10–20% reduction in BCIS risk per pregnancy is generally reported, such that women with four or more pregnancies are typically half as likely to develop BCIS as nulliparous women (Weiss et al. 1996; Trentham-Dietz et al. 2000; Longnecker et al. 1996; Claus et al. 2001; Trentham-Dietz et al. 2007; Lambe et al. 1998). Each study that has evaluated both BCIS and invasive breast cancer in relation to parity has reported that the relation appears to be stronger with BCIS (Brinton et al. 1983; Weiss et al. 1996; Trentham-Dietz et al. 2000; Longnecker et al. 1996; Kerlikowske et al. 1997; Reinier et al. 2007). The two studies which have evaluated the relation between parity and BCIS risk stratified by histological type suggest that parity is positively associated with DCIS but not LCIS (Weiss et al. 1996; Claus et al. 2001).

Lactation

Despite much attention, the relation between lactation and invasive breast cancer is unclear. Overall, the evidence suggests that long-term breastfeeding appears to provide a protective effect against invasive breast cancer among premenopausal women (Lipworth et al. 2000). Very few studies have examined BCIS risk in relation to lactation. Weiss et al. (1996) reported no relation between BCIS risk and duration of breastfeeding. Trentham-Dietz et al. (2000) found that women who had breastfed for at least 24 months were at a reduced risk of BCIS compared to parous women who never breastfed, although this did not reach statistical significance (OR=0.73, 95% CI: 0.4–1.3) and there was not a trend in risk with the continuous number of months of lactation. In contrast, Meeske et al. (2004) found that duration of

breastfeeding was positively associated with BCIS risk: women who breastfed for at least 24 months were twice as likely to develop BCIS as those who never breastfed (95% CI: 1.1–3.6). Further research will be required to determine if lactation plays a role in BCIS initiation or the progression of BCIS to invasive breast cancer.

Lifestyle Factors

Body Size

The relation between body weight and invasive breast cancer risk varies by menopausal status. Body mass index (BMI) is inversely associated with risk among premenopausal women and positively associated with risk among postmenopausal women (McTiernan 2003). Obese premenopausal women are more likely to have irregular menstrual cycles and ovulatory infertility (Rich-Edwards et al. 1994), whereas after menopause, adipose tissue becomes the primary source of estrogen synthesis (Siiteri 1987). Notably, body weight reflects both lean body mass and adipose tissue. Weight gain in women after young adulthood is more likely to reflect an increase in adipose tissue. Accordingly, weight gain from adolescence to adulthood appears to be a more powerful determinant of postmenopausal invasive breast cancer risk than current BMI (Friedenreich 2001).

With some exceptions (Brinton et al. 1983; Reinier et al. 2007), most studies have reported significant inverse associations between BMI and BCIS risk in premenopausal women, with risk reduced by approximately 50% in the highest compared to lowest BMI categories (Weiss et al. 1996; Longnecker et al. 1996; Kerlikowske et al. 1997; Meeske et al. 2004; Swanson et al. 1996). Weiss et al. (1996) found that this relation was stronger for DCIS compared to LCIS. It has been suggested that the inverse association between BMI and BCIS risk in premenopausal women may be attributable at least in part to a difficulty in detecting in situ lesions in younger women with high BMI (Longnecker et al. 1996). However, Swanson et al. (1996) suggests that the degree of detection bias is likely to be minimal, as the inverse association between BMI and BCIS risk persists even when limited to cancers detected by mammography, the sensitivity of which is unlikely to be reduced in overweight women.

The relation between BMI and BCIS risk in postmenopausal women is less clear. Four of six studies have reported a null association (Brinton et al. 1983; Trentham-Dietz et al. 2000; Kerlikowske et al. 1997; Reinier et al. 2007), whereas Longnecker et al. (1996) found a positive association and Meeske et al. (2004) found an inverse association. Only one study has examined postmenopausal BCIS risk in relation to weight gain. Trentham-Dietz et al. (2007) found that women who gained more than 50 pounds since age 18 were 50% more likely to develop BCIS than women with 0–15 pounds of weight gain.

Little evidence has been published regarding the relation between BCIS risk and other anthropometric measures. In the only study to examine height in relation to BCIS risk, Brinton et al. (1983) did not find a clear association, in contrast to the positive association observed between height and invasive breast cancer.

Physical Activity

Physical activity is now recognized as a protective factor which decreases invasive breast cancer risk through a variety of potential mechanisms (IARC 2002). Though data are limited, three studies have observed a similar inverse relation with BCIS risk, with up to a 40% reduction in risk for women in the highest categories of activity (Trentham-Dietz et al. 2000; Patel et al. 2003; Dallal et al. 2007). In contrast, Sprague et al. (2007) found no association between physical activity and BCIS risk, despite finding an inverse relation with invasive breast cancer risk.

Alcohol

Alcohol consumption is an established risk factor for invasive breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2002). Studies examining alcohol consumption in relation to BCIS risk have reported conflicting results. The majority of studies have reported a null relation, yet three found risk increases of 25–55% for more than 15 grams of alcohol intake per week compared to abstainers (Trentham-Dietz et al. 2000; Nasca et al. 1994; Feigelson et al. 2003). In the only one of these studies to stratify by histology, Trentham-Dietz et al. (2000) observed that the increase in BCIS risk associated with alcohol intake was limited to DCIS.

Smoking

Breast cancer has not consistently been found to be associated with smoking, although risk may vary across different subgroups (Collaborative Group on Hormonal Factors in Breast Cancer 2002). This may be due to a balance between the carcinogenic and antiestrogenic properties of cigarette smoke. Carcinogens in cigarette smoke may initiate tumors while the antiestrogenic components may prevent progression to an invasive stage. Alternatively, the antiestrogenic effects of smoking could prevent the promotion of benign breast disease to in situ cancer. The evidence examining the relation of smoking to BCIS risk is sparse. Two studies have reported a null association (Claus et al. 2001; Gammon et al. 1998), whereas a recent study found a weak inverse association between smoking and BCIS risk (OR = 0.8 for current vs. never smokers) (Trentham-Dietz et al. 2007).

Postmenopausal Hormones

Observational studies and clinical trials have demonstrated an increased risk of breast cancer in women who have used postmenopausal hormones (Collaborative Group on Hormonal Factors in Breast Cancer 1997; Rossouw et al. 2002). Risk appears to be most increased among current users and women using combined estrogen and progesterone rather than estrogen-only regimens (Collaborative Group on Hormonal Factors in Breast Cancer 1997; Stefanick et al. 2006). Notably, the Women's Health Initiative reported no increase in BCIS risk with either combined or estrogen-only regimens, although there was likely insufficient power to detect a weak association (Rossouw et al. 2002; Stefanick et al. 2006). In contrast, the majority of observational studies have found that ever use of postmenopausal hormones is associated with increased BCIS risk, with odds ratios ranging from 1.2 to 2.4 (Longnecker et al. 1996; Claus et al. 2001; Trentham-Dietz et al. 2007; Brinton et al. 1986; Schairer et al. 1994; Ross et al. 2000; Reeves et al. 2006). A handful of studies have examined BCIS in relation to postmenopausal hormone use by regimen type, but with limited power no clear pattern has emerged (Longnecker et al. 1996; Schairer et al. 1994; Ross et al. 2000; Stanford et al. 1995; Henrich et al. 1998). In general, similar risk estimates have been obtained for both LCIS and DCIS (Trentham-Dietz et al. 2000; Claus et al. 2001), although Reeves et al. (2006) found a higher risk of LCIS than DCIS among current users of postmenopausal hormones.

Oral Contraceptives

A pooled analysis of 54 studies suggested a small increase in overall breast cancer risk associated with oral contraceptive use, with the relative risk declining from 1.24 in current users to 1.01 in women who discontinued use over 10 years ago (Collaborative Group on Hormonal Factors in Breast Cancer 1996). Relatively few studies have examined oral contraceptives in relation to BCIS risk specifically, with nearly all of them finding no association (Trentham-Dietz et al. 2000; Claus et al. 2001; Brinton et al. 1995; Claus et al. 2003; Gill et al. 2006). Only Nichols et al. (2007) observed a weak positive association, with ever users having an 11% increase in risk compared to never users. The two studies which examined both BCIS and invasive breast cancer risk in relation to oral contraceptive use found no relation to BCIS but a modest positive association with invasive breast cancer (Trentham-Dietz et al. 2000; Brinton et al. 1995).

Diet

A variety of dietary components, notably dietary fat, fruits and vegetables, vitamin C, and beta-carotene have been investigated in relation to breast cancer, with generally inconclusive findings (Hunter et al. 1996; Gandini et al. 2000). There is a paucity of published data relating diet to BCIS risk specifically. Trentham-Dietz et al. (2000) found a decreased risk of DCIS, but not LCIS,

among women in the highest quartile of beta-carotene intake. Additionally, Potischman et al. (2002) have reported that women in the highest quartile of "sweets" intake were at a 53% increased risk of developing BCIS (see Table 3.1).

Genetics, Personal, and Family History of Breast Disease

BRCA1/2

Women with mutations in either *BRCA1* or *BRCA2* have a lifetime breast cancer risk of about 80%, as well as an increased ovarian cancer risk (King et al. 2003). The role of BCIS in the inherited breast/ovarian cancer syndrome associated with these mutations remains unclear. An early study found that among 36 families carrying *BRCA1* mutations, 202 invasive breast cancers but only 4 cases of BCIS were diagnosed (Sun et al. 1996). The Breast Cancer Linkage Consortium reported that DCIS and LCIS components were 29% and 62% less likely, respectively, to be present in breast cancers of *BRCA1* carriers compared to patients unselected for family history (Lakhani et al. 1998). Additionally, two recent studies found that while proliferative fibrocystic changes were more common in high risk women with *BRCA* mutations, no differences in BCIS were observed (Adem et al. 2003; Hwang et al. 2007). These findings have led some researchers to suggest that tumorigenesis in *BRCA1/2* mutation carriers may be accelerated compared to that in non-carriers, such that tumors pass quickly through pre-invasive stages.

Indeed, Kauff et al. (2003) found that DCIS was 13 times more common in prophylactic mastectomy specimens from women with *BRCA* mutations than in mastectomy specimens obtained at autopsy from a control group. In the only population-based study to examine the prevalence of *BRCA* mutations in women diagnosed with BCIS, Claus et al. (2005) found that *BRCA1* and *BRCA2* mutations were found in 0.8% and 2.4% of DCIS cases, respectively. This prevalence is very similar to that estimated for invasive breast cancers among unselected populations (Peto et al. 1999; Syrjakoski et al. 2000). This provides some evidence that diagnoses of BCIS should be considered in *BRCA* risk assessment and that BCIS may be included as part of the inherited breast/ovarian cancer syndrome associated with *BRCA* mutations. Continued research on the relation between *BRCA* mutations and BCIS risk, particularly in population-based studies, will be necessary to better inform genetic testing and counseling, as well as to better understand breast cancer progression.

Genetic Polymorphisms

Few studies have examined single nucleotide polymorphisms (SNPs) in relation to BCIS risk separately from invasive breast cancer. Jacobs et al. (2006) reported a 41% reduction in BCIS risk, but no difference in invasive breast cancer risk, for women with a *VEGF* polymorphism that is thought to be

associated with increased *VEGF* expression. Other studies have reported that certain SNPs in *HER2* and *BRCA2* are more common in women with in situ than invasive breast cancer, though little difference was seen in comparison to controls without breast cancer (Millikan et al. 2003; Gorski et al. 2005). Null relations have been reported for *MnSOD* and *TP53* SNPs (Millikan et al. 2004; Sprague et al. 2007).

Benign Breast Disease

Benign breast disease is generally classified into three primary categories: non-proliferative breast disease, proliferative breast disease without atypia, and proliferative breast disease with atypia (Dupont and Page 1985). Risk of invasive breast cancer increases with these successive categories of disease. Studies examining BCIS risk in relation to benign breast disease have used previous breast biopsy or cyst aspiration as an indicator of benign disease. Risk of BCIS is approximately twice as high in women with a history of benign breast disease as in those without (Weiss et al. 1996; Longnecker et al. 1996; Trentham-Dietz et al. 2007). Two studies have suggested that this relation is somewhat stronger for LCIS than DCIS (Trentham-Dietz et al. 2000; Claus et al. 2001).

Family History

Similar to invasive breast cancer, women with at least one first degree relative with breast cancer are approximately twice as likely to develop BCIS as those with no family history (Trentham-Dietz et al. 2007; Meeske et al. 2004; Claus et al. 2003). This relation appears to be slightly stronger in premenopausal than postmenopausal women (Longnecker et al. 1996; Kerlikowske et al. 1997; Reinier et al. 2007). No substantial differences have been observed between the association of family history with LCIS and DCIS risk (Weiss et al. 1996; Trentham-Dietz et al. 2000; Claus et al. 2003).

Biomarkers of Risk

Endogenous Hormones

The positive association between plasma steroid hormones and invasive breast cancer risk is well documented (Endogenous Hormones and Breast Cancer Collaborative Group 2002). Only two studies have specifically examined BCIS risk in relation to endogenous hormone levels. Missmer et al. (2004) found that estradiol, estrone, and testosterone were positively associated with BCIS risk in the Nurses Health Study and that these relations were generally stronger than those observed for invasive breast cancer. In contrast, Zeleniuch-Jacquotte et al. (2005) found no relation between estradiol, estrone, testosterone, or other sex hormones and BCIS risk. The authors speculate that length

time bias could at least in part explain these findings in a heavily screened population, as in situ tumors exposed to higher endogenous hormone levels may progress more rapidly to invasive stages.

Mammographic Breast Density

Mammographic breast density is emerging as one of the strongest risk factors for invasive breast cancer (Boyd et al. 2005). Most DCIS lesions arise from areas of dense tissue, with one report documenting that 17 of 22 DCIS tumors arose in the mammographic quadrant with the highest density (Ursin et al. 2005). An early study by Boyd et al. (1992) indicated that women with greater than 75% breast density had a 9.7-fold increase in risk of developing BCIS or atypical hyperplasia compared to those with no areas of density. Subsequent studies have found less extreme increases in risk, generally reporting odds ratios of 1.5–5.0 for the highest density categories compared to the lowest (Reinier et al. 2007; Gill et al. 2006; MacKenzie et al. 2007). In the two studies that examined density in relation to BCIS and invasive breast cancer risk concurrently, a 10–25% stronger association was observed for BCIS (Reinier et al. 2007; Gill et al. 2006).

Environmental Pollution

Few studies have evaluated BCIS risk in relation to environmental pollutants. The Long Island Breast Cancer Study Project has reported no relation between BCIS risk and blood levels of bis(4-chlorophenyl)-1,1-dichloroethane (DDE), polychlorinated biphenyls (PCBs), or chlordane (Gammon et al. 2002a). However, a borderline significant association with polycyclic aromatic hydrocarbons (PAH) was observed, with a 50% increase in BCIS risk among women with detectable blood levels of PAH–DNA adducts (Gammon et al. 2002b). This relation was similar to that reported for invasive breast cancer.

Summary of BCIS Risk Factors

Overall, few significant differences in direction or magnitude of effect have been established in risk factors for BCIS as compared with invasive breast cancer. Possible exceptions include age at menarche, for which most studies have reported null associations with BCIS, and parity and breast density, which appear to be more strongly related to BCIS than invasive breast cancer. Given the moderate effect sizes associated with most breast cancer risk factors, increased precision in BCIS studies will be necessary to distinguish subtle differences from invasive breast cancer.

There is some suggestion that the association between BCIS risk and parity, alcohol, diet, and *BRCA* mutations may be limited to or stronger for DCIS compared to LCIS. In contrast, benign breast disease may be more strongly related to LCIS. Unfortunately, there have been too few studies to fully establish these differences by BCIS histology.

Conclusion

Persistent uncertainty remains regarding the natural history of BCIS as a nonobligate precursor to invasive breast cancer. Differences in tumor markers and recurrence patterns have been observed between DCIS and LCIS, such that LCIS is regarded as a marker of breast cancer risk rather than a true precursor. Further study of disease-free survival and risk factors for LCIS in particular could help to clarify potential differences in the natural history of BCIS according to histologic subtype.

BCIS and invasive breast cancer appear to a large extent to share the same risk factors, though insufficient data are available to rule out small differences. The current evidence suggests that most breast cancer risk factors are associated similarly with both BCIS and invasive breast cancer, such that they likely act most critically in the carcinogenic process prior to the development of BCIS (i.e., rather than during the promotion of BCIS to invasive cancer).

The incidence of BCIS has risen dramatically over the past 20 years, across all ages and races. There is an ever growing number of BCIS survivors making this diagnosis of growing public health concern. Relative survival following a BCIS diagnosis is high, but women with BCIS often face the same anxiety and physical side effects associated with the diagnosis and treatment of invasive breast cancer. To prevent overtreatment, there is a real need to distinguish those cases that require intensive treatment similar to invasive breast cancer, and those that could be treated similar to benign breast diseases. A combination of approaches, including further molecular characterization of BCIS tumors, follow-up of BCIS cohorts, computer simulation of detection and treatment regimens, and randomized trials may be useful in achieving this goal.

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Chapter 4
Endogenous Hormones

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Introduction

Given the consistent associations between various reproductive and hormonally related factors and breast cancer risk, sex hormones have long been implicated as key players in breast cancer etiology. However, early studies assessing the association between levels of circulating hormones and breast cancer risk primarily used case–control study designs, which may incorporate bias if hormone levels at the time of breast cancer diagnosis do not reflect levels prior to cancer development. More interpretable evidence regarding the types of hormones related to breast cancer risk and the magnitudes of these associations is increasingly available from large prospective studies with high quality biological samples. As described herein, there is now consistent evidence regarding the influence that endogenous estrogens and androgens have on breast cancer risk, particularly postmenopausal disease. Only a handful of studies have assessed the association between breast cancer risk and circulating levels of progesterone and prolactin. In contrast, a relatively extensive literature has been devoted to the association between the IGF axis and breast cancer risk, but with inconsistent findings.

Estrogens

Estrogen is critical to normal breast development, but the proliferative effects of estrogen have also been implicated in breast carcinogenesis and tumor promotion (Feigelson and Henderson 1996). The two types of estrogen that have been most closely studied in relation to breast cancer risk are estradiol and estrone sulfate. Estradiol is the most biologically active form of endogenous estrogen and circulates in the blood either bound to sex

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_4,

hormone-binding globulin (*SHBG*), bound to albumin, or "free" (i.e., unbound). Estradiol that is either bound to albumin or "free" is termed bioavailable since it can have its maximal biological effects in these forms. Estrone sulfate is the most abundant circulating estrogen and, in postmenopausal women, it is the main source of estradiol derived primarily through its peripheral conversion in adipose tissue.

Perhaps the most compelling evidence regarding the relationship between endogenous sex hormone levels and breast cancer risk among postmenopausal women comes from a pooled analysis of nine prospective studies conducted by The Endogenous Hormones and Breast Cancer Collaborative Group (*EHBCCG*) (Key et al. 2002). This analysis included 663 women who developed breast cancer and 1,765 who did not, none of whom were using exogenous hormones at the time of blood collection. This study observed that breast cancer risk increased with increasing blood concentrations of total estradiol, free estradiol, bioavailable estradiol, estrone, and estrone sulfate, with evidence of marked dose–response relationships for all estrogen forms (all p-values for trend < 0.001) (Table 4.1). Comparing women in the highest quintiles of concentration to the lowest quintiles, relative risk estimates were

Table 4.1 Relative risk of breast cancer associated with levels of various hormones in prospective analyses (2002–2009)

Hormone	First author (year)	Comparison	Cases/ controls	Risk estimate	p for trend
Estrogens – postmenopausal breast cancer					
Estradiol	Key (2002)	Highest vs. lowest quintile	656/1,709	2.0 (1.5–2.7)	<0.001
	Manjer (2003)	High vs. low	172/436	1.7 (1.0–2.9)	0.04
	Kaaks (2005b)	Highest vs. lowest quintile	672/1,297	2.3 (1.6–3.2)	<0.0001
	Gunter (2009)	Highest vs. lowest tertile	384/436	1.6 (1.0–2.6)	0.04
	Sieri (2009)	Highest vs. lowest quartile	165/642	1.5 (0.9–2.5)	0.216
Free estradiol	Key (2002)	Highest vs. lowest quintile	478/980	2.6 (1.8–3.8)	<0.001
	Kaaks (2005b)	Highest vs. lowest quintile	671/1,295	2.1 (1.5–3.0)	<0.001
Bioavailable estradiol	Key (2002)	Highest vs. lowest quintile	474/972	2.4 (1.6–3.5)	<0.001
Estrone	Key (2002)	Highest vs. lowest quintile	469/1,188	2.2 (1.5–3.2)	<0.001
	Manjer (2003)	Highest vs. lowest quartile	171/436	2.6 (1.5–4.4)	<0.01
	Kaaks (2005b)	Highest vs. lowest quintile	630/1,188	2.1 (1.4–3.0)	0.0001
Estrone sulfate	Key (2002)	Highest vs. lowest quintile	310/651	2.0 (1.3–3.2)	<0.001

Table 4.1 (continued)

Hormone	First author (year)	Comparison	Cases/ controls	Risk estimate	*p* for trend
Estrogens – premenopausal breast cancer					
Estradiol	Kaaks (2005a)	Highest vs. lowest quartile	283/551	1.0 (0.7–1.5)	0.89
	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	185/368	2.7 (1.3–5.4)[a]	0.07
		Luteal phase	175/349	0.9 (0.4–1.9)[a]	0.91
Free estradiol	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	177/347	2.7 (1.4–5.3)[a]	0.01
		Luteal phase	170/344	1.3 (0.7–2.7)[a]	0.56
Estrone	Kaaks (2005a)	Highest vs. lowest quartile	283/550	1.2 (0.7–1.9)	0.46
	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	193/381	1.4 (0.8–2.6)[a]	0.25
		Luteal phase	193/392	0.7 (0.4–1.3)[a]	0.30
Estrone sulfate	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	181/361	1.1 (0.6–2.0)[a]	0.66
		Luteal phase	182/364	0.8 (0.4–1.6)[a]	0.23
Androgens – postmenopausal breast cancer					
Androstenedione	Key (2002)	Highest vs. lowest quintile	375/1,000	2.2 (1.4–3.2)	<0.001
	Manjer (2003)	Highest vs. lowest quartile	154/419	1.6 (0.9–2.7)	0.11
	Kaaks (2005b)	Highest vs. lowest quintile	663/1,267	1.9 (1.4–2.7)	<0.0001
DHEA	Key (2002)	Highest vs. lowest quintile	231/423	2.0 (1.2–3.5)	0.018
DHEAS	Key (2002)	Highest vs. lowest quintile	578/1,230	1.8 (1.3–2.4)	0.002
	Manjer (2003)	Highest vs. lowest quartile	155/419	1.6 (0.9–3.0)	0.31
	Kaaks (2005b)	Highest vs. lowest quintile	661/1,267	1.7 (1.2–2.3)	0.0002
Testosterone	Key (2002)	Highest vs. lowest quintile	585/1,574	2.2 (1.6–3.1)	<0.001
	Manjer (2003)	Highest vs. lowest quartile	154/417	1.9 (1.1–3.3)	0.13
	Kaaks (2005b)	Highest vs. lowest quintile	668/1,280	1.9 (1.3–2.6)	<0.0001
	Sieri (2009)	Highest vs. lowest quartile	165/643	3.3 (1.9–5.6)	<0.001
Free testosterone	Kaaks (2005b)	Highest vs. lowest quintile	667/1,278	2.5 (1.8–3.6)	<0.0001
	Sieri (2009)	Highest vs. lowest quartile	165/643	2.9 (1.7–4.9)	<0.001

Table 4.1 (continued)

Hormone	First author (year)	Comparison	Cases/ controls	Risk estimate	*p* for trend
Androgens – premenopausal breast cancer					
Androstenedione	Kaaks (2005a)	Highest vs. lowest quartile	370/724	1.6 (1.1–2.3)	0.01
	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	193/385	1.5 (0.8–2.9)[a]	0.23
		Luteal phase	196/392	1.7 (0.8–3.4)[a]	0.52
Testosterone	Kaaks (2005a)	Highest vs. lowest quartile	367/713	1.7 (1.2–2.6)	0.01
	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	190/374	1.8 (0.9–3.4)[a]	0.17
		Luteal phase	192/390	2.0 (1.1–3.6)[a]	0.05
Free testosterone	Micheli (2004)	Highest vs. lowest tertile	50/142	3.5 (1.2–10.5)	0.02
	Eliassen (2006)	Highest vs. lowest quartile:			
		Follicular phase	189/372	1.5 (0.8–2.8)[a]	0.25
		Luteal phase	191/388	1.9 (1.0–3.8)[a]	0.08
DHEA	Tworoger (2006)	Highest vs. lowest quartile	208/422	1.0 (0.6–1.8)	0.82
DHEAS	Kaaks (2005a)	Highest vs. lowest quartile	370/725	1.5 (1.0–2.1)	0.10
	Tworoger (2006)	Highest vs. lowest quartile	208/421	1.3 (0.8–2.1)	0.08
Progesterone – postmenopausal breast cancer					
Progesterone	Missmer (2004)	Highest vs. lowest quartile	270/530	0.8 (0.5–1.3)[a]	0.77
Progesterone – premenopausal breast cancer					
Progesterone	Micheli (2004)	Highest vs. lowest tertile	50/142	0.4 (0.1–1.2)	0.10
	Kaaks (2005a)	Highest vs. lowest quartile	277/524	0.6 (0.4–1.0)	0.06
	Eliassen (2006)	Highest vs. lowest quartile, luteal	195/391	0.9 (0.5–1.7)[a]	0.74
Prolactin – postmenopausal breast cancer					
Prolactin	Manjer (2003)	Highest vs. lowest quartile	173/438	1.3 (0.8–2.2)	0.28
	Tworoger (2007)	Highest vs. lowest quartile	915/1,410	1.3 (1.1–1.7)	0.01
Prolactin – premenopausal breast cancer					
Prolactin	Tworoger (2007)	Highest vs. lowest quartile	492/1,001	1.4 (1.0–1.9)	0.05

[a]Relative risks are for invasive breast cancer only.

similar across all five of these forms of estrogen, ranging from 2.00 to 2.58. The strongest association was seen with free estradiol where, compared to women in the lowest quintile of free estradiol concentration, women in the highest quintile had a 2.58-fold [95% confidence interval (CI): 1.8–3.8] increased risk of breast cancer. Associations did not vary according to the time between blood draw and case diagnosis or with stratification by age at diagnosis, parity, type of menopause, body mass index, or history of oral contraceptive use. However, the relative risk associated with a doubling of endogenous hormone concentration did vary by past use of menopausal hormone therapy (*HT*). Among never users of HT, relative risks across the five forms of estrogen evaluated ranged from 1.32 to 1.67, and all were statistically significant. In contrast, associations in past HT users ranged from 1.04 to 1.15 and were not statistically significant, though it is important to note that none of the comparisons between never users of HT and past HT users reached statistical significance. In contrast to this result, a more recent analysis of data from the Nurses' Health Study (*NHS*) indicated that concentrations of free estradiol, but not total estradiol, may be related to risk of breast cancer among HT users (Tworoger et al. 2005): women in the highest quartile of free estradiol concentration had a 1.7-fold (95% CI: 1.1–2.7; p for trend $= 0.06$) increased risk of breast cancer compared to women in the lowest quartile. Although other studies have not reported on this possible effect modification by HT use, similar associations in postmenopausal women overall were reported by the Women's Health Initiative Observational Study (*WHI-OS*) (Gunter et al. 2009), the European Prospective Investigation into Cancer and Nutrition (*EPIC*) cohort study (Kaaks et al. 2005b), and a pooled analysis of two prospective cohorts in Sweden (Manjer et al. 2003).

While data on postmenopausal women and endogenous estrogen are largely consistent across numerous studies, the literature focused on premenopausal women is quite limited. Since hormone levels in premenopausal women vary cyclically, these studies are challenging to conduct and most have been limited by small sample sizes. Given such limitations, it is not surprising that published results have been inconsistent. The two largest studies to assess these relationships are the Nurses' Health Study II (*NHS II*) (197 cases/394 controls) (Eliassen et al. 2006) and the EPIC study (285 cases/555 controls) (Kaaks et al. 2005a). The NHS II collected blood during both the early follicular and the mid-luteal phases of the menstrual cycle and observed that risk of invasive breast cancer tended to increase across increasing quartiles of plasma hormone concentration for total estradiol, free estradiol, and estrone during the follicular but not the luteal phase. However, only the trend for free estradiol concentration during the follicular phase reached statistical significance (p for trend $= 0.01$); women in the highest concentration quartile for free estradiol had a 2.7-fold (95% CI: 1.4–5.3) increased risk of invasive breast cancer relative to women in the lowest quartile. In contrast, the EPIC cohort did not observe relationships between estrone or estradiol plasma concentrations and risk of premenopausal breast cancer; however, blood samples were collected from

EPIC study participants without consideration of menstrual cycle timing, and had limited power to assess risk during different segments of the menstrual cycle. Thus, further work is needed to confirm the results of the NHS II.

Few studies have comprehensively evaluated the association between circulating estrogen levels and breast cancer risk by estrogen receptor (*ER*) and progesterone receptor (*PR*) status. In an analysis of data from the NHS, Missmer et al. (2004) observed that estrogen levels were only strongly positively associated with risk of postmenopausal ER+/PR+ breast cancer (OR = 3.3, 95% CI: 2.0–5.4, for highest vs. lowest quartile), but not with risks of either ER+/PR– or ER–/PR– tumors (OR = 1.0, 95% CI: 0.4–2.6 and OR = 1.0, 95% CI: 0.4–2.4, respectively). Results from two recent prospective studies also suggest a stronger association between estradiol levels and risk of postmenopausal hormone receptor-positive than receptor-negative breast cancer (Gunter et al. 2009; Sieri et al. 2009). Consistent with these results in postmenopausal women, analyses from the NHS II in premenopausal women suggested that associations between breast cancer risk and levels of circulating total and free estradiol were stronger for ER+/PR+ tumors than they were for breast cancer overall (Eliassen et al. 2006).

Several studies have also evaluated the relationship between levels of estrogen metabolites, which have the potential to generate reactive oxygen species that can cause oxidative damage, and risk of postmenopausal breast cancer (Cauley et al. 2003; Wellejus et al. 2005; Eliassen et al. 2008). Of particular interest are the 2-OH and 16α-OH estrone metabolites, which are thought to have particular genotoxic potential (Cavalieri et al. 2000). To date, however, studies have found no association between concentrations of these metabolites in either blood or urine and breast cancer risk.

Androgens

Given the observed influence of androgens on breast cancer growth and proliferation and the fact that androgens are necessary precursors to all endogenous estrogens, it is plausible that circulating levels of androgens could either directly or indirectly influence breast cancer risk (Nicolas Diaz-Chico et al. 2007). Indeed, androgen levels have been shown to be positively related to breast cancer risk in postmenopausal women across numerous studies. In the most comprehensive of these analyses, the EHBCCG reported that several androgens including androstenedione, dehydroepiandrosterone (*DHEA*), DHEA sulfate (*DHEAS*), and testosterone were all positively related to breast cancer risk with *p*-values for trend all <0.02 and relative risks comparing the highest vs. lowest quartiles of concentration ranging from 1.75 to 2.22 (Key et al. 2002) (Table 4.1). The strongest association was seen with testosterone: compared to women in the lowest quintile of testosterone concentration, women in the highest quintile had a 2.22-fold (95% CI: 1.6–3.1) increased risk

of breast cancer. In contrast to estrogen data from the EHBCCG pooled analysis, risk estimates did not vary substantially when results were stratified according to history of HT use. Associations reported by other studies have been similar in magnitude, all indicating a significant trend of increasing risk of postmenopausal breast cancer with increasing circulating androgen levels (Missmer et al. 2004; Kaaks et al. 2005b; Sieri et al. 2009). Only two studies have carefully evaluated the risk associated with androgen levels in postmenopausal women by tumor ER/PR status (Missmer et al. 2004; Sieri et al. 2009). In an analysis based on data from the NHS, Missmer et al. (2004) observed that testosterone, androstenedione, DHEA, and DHEAS concentrations were strongly positively associated with risk of ER+/PR+ but not ER–/PR– breast cancer. In slight contrast to these findings, Sieri et al. (2009) observed similar associations between circulating free testosterone levels and risks of ER+/PR+ and ER–/PR– breast cancers, and only a slightly stronger association with total testosterone levels and risk of ER+/PR+ vs. ER–/PR– tumors.

With respect to premenopausal women, again the NHS II and EPIC cohorts are the largest two studies in which the relationship between androgen levels and risk of premenopausal breast cancer has been evaluated. Unlike with estrogen, results from the NHS II indicate that testosterone, free testosterone, and androstenedione are positively associated with breast cancer risk in both the follicular and luteal phases, though none of the trends across quartiles were statistically significant for risk of breast cancer overall (Eliassen et al. 2006). However, when analyses were restricted to ER+/PR+ breast cancer, both testosterone and free testosterone measured in the luteal phase were positively related to risk with borderline statistically significant trends. In a separate report based on the NHS II cohort, DHEA and DHEAS levels were not found to be related to risk of premenopausal breast cancer overall, though they were both positively associated with ER+/PR+ tumors (Tworoger et al. 2006). Consistent with these results, serum concentrations of testosterone, androstenedione, and DHEAS were all positively related to risk of premenopausal breast cancer in the EPIC cohort (Kaaks et al. 2005a). Despite the consistency of these findings, the biological mechanisms underlying the relationship between androgens and premenopausal breast cancer are largely unknown.

Progesterone

Endogenous progesterone also serves a critical role in normal breast development and in driving cellular proliferation within the breast, thus implying a possible role for this hormone in breast cancer development (Feigelson and Henderson 1996). The relevance of exogenous progesterone to breast cancer risk has been highlighted by the Women's Health Initiative randomized trials and several observational studies documenting that the use of combined

estrogen–progestin HT increases breast cancer risk considerably more than the use of estrogen-only HT (Collaborative Group on Hormonal Factors in Breast Cancer 1997; Writing Group for the Women's Health Initiative Investigators 2002; Li et al. 2003; The Women's Health Initiative Steering Committee 2004). However, compared to the literature on endogenous estrogens and androgens, the literature on endogenous progesterone is considerably more sparse. The only large prospective study of postmenopausal women to evaluate this relationship is the NHS: in a nested case–control study including 270 cases and 530 controls, no relationship between progesterone levels and breast cancer risk was observed overall or when stratified by ER/PR status or estradiol level (Missmer et al. 2004) (Table 4.1).

Evidence for an association between circulating progesterone levels and breast cancer risk in premenopausal women is similarly limited and based on small numbers. The largest prospective study in premenopausal women conducted to date (285 cases/555 controls), conducted within the EPIC cohort, suggested an inverse association between progesterone levels and breast cancer risk: compared to women in the lowest progesterone level quartile, those in the highest had a 0.61-fold (95% CI: 0.4–1.0) reduced risk of breast cancer (p for trend = 0.06) (Kaaks et al. 2005a). Although the results of two smaller prospective studies are consistent with these findings (Thomas et al. 1997; Micheli et al. 2004), no association between progesterone levels during the luteal phase and premenopausal breast cancer risk was noted by the NHS II (Eliassen et al. 2006). Given the limited available data, further studies are needed before conclusions can be drawn regarding the relationship between endogenous progesterone levels and risks of both premenopausal and postmenopausal breast cancer.

Prolactin

Prolactin is synthesized and secreted by the pituitary gland as well as the mammary gland, and acts synergistically with estrogen to regulate levels of cyclin D1 and other cell cycle proteins (Clevenger et al. 2003; Gutzman et al. 2004). A role of prolactin in mammary tumorigenesis is suggested by findings from animal and in vitro studies that prolactin can inhibit apoptosis and promote proliferation of mammary tumor cells (Freeman et al. 2000; Clevenger et al. 2003). The epidemiologic literature assessing an association between prolactin levels and breast cancer risk is less extensive than that with respect to steroid sex hormones. However, there is increasing evidence to suggest a positive association between levels of circulating prolactin and breast cancer risk, particularly with respect to postmenopausal women and ER+ breast cancer.

The largest analysis of prolactin in relation to breast cancer risk conducted to date is based on data pooled from the NHS and NHS II: overall, Tworoger et al. (2007) reported a 1.3-fold (95% CI: 1.1–1.6) higher breast cancer risk among women in the highest vs. lowest quartile of serum prolactin concentration, with similar associations noted with respect to postmenopausal (OR = 1.3, 95%

CI: 1.1–1.7) and premenopausal women (OR = 1.4, 95% CI: 1.0–1.9) (Table 4.1). Consistent with these data, a prior study conducted within a Swedish cohort reported a 1.3-fold (95% CI: 0.8–2.2) higher breast cancer risk in the highest vs. lowest quartile of prolactin concentration for postmenopausal women (Manjer et al. 2003); two much smaller prospective studies reported slightly stronger but not statistically significant associations in postmenopausal women (Wang et al. 1992; Kabuto et al. 2000). Evidence from additional prospective studies for an association between serum prolactin levels and breast cancer risk in premenopausal women is weaker but based on small numbers (Wang et al. 1992; Helzlsouer et al. 1994; Kabuto et al. 2000). Similarly, several small retrospective case–control studies support a positive association between circulating prolactin levels and breast cancer, particularly among postmenopausal women (Cole et al. 1977; Rose and Pruitt 1981; Meyer et al. 1986; Bernstein et al. 1990; Ingram et al. 1990; Abu-Bedair et al. 2000).

Only one epidemiologic study has explored the association between prolactin levels and risk of ER+ vs. ER– breast cancer. In their analysis of data pooled from the NHS and NHS II, Tworoger et al. (2007) observed that the association between serum prolactin and breast cancer risk was limited to ER+ disease (OR = 1.6 vs. OR = 1.0 for ER+ vs. ER– disease, respectively). This association is consistent with the observed synergism between estrogen and prolactin in mammary gland growth and differentiation (Freeman et al. 2000; Gutzman et al. 2004), and with the finding that endogenous prolactin increases protein levels of ER-alpha (Gutzman et al. 2004).

Insulin-Like Growth Factors

The insulin-like growth factor (*IGF*) axis includes two peptide growth hormones (IGF-I and IGF-II), two cell-surface receptors (IGF1R and IGF2R), and six known binding proteins (IGFBP-1 through IGFBP-6). The IGF axis serves both mitogenic and anti-apoptotic roles in normal cells, and has been implicated in the etiology of several types of cancer (Renehan et al. 2004). With respect to breast cancer, the associations between disease risk and circulating levels of IGF-I and IGFBP-3 have been studied most extensively.

IGF-I has been most consistently associated with breast cancer risk in premenopausal women. Meta-analyses and systematic reviews of the epidemiologic literature on IGF-I and breast cancer risk have reported a 1.4 to 2.1-fold increased risk of breast cancer among premenopausal women with high IGF-I serum concentrations relative to women with low IGF-I levels (Renehan et al. 2004; Shi et al. 2004). Findings from more recent prospective studies, however, are not entirely consistent with these summary estimates, as they indicate little or no association between IGF-I levels and breast cancer in premenopausal women (Rinaldi et al. 2005b; Rinaldi et al. 2006; Schernhammer et al. 2006; Vatten et al. 2008) (Table 4.2). In the largest study conducted to date, Vatten

Table 4.2 Relative risk of breast cancer associated with hormones in the IGF axis, large prospective analyses (N>100 cases)

Hormone	Study (publication year)	Comparison	Cases/ controls	Risk estimate	*p* for trend
Postmenopausal breast cancer					
IGF-I	Gronbaek et al. (2004)	Per 25 unit increase	411/397	1.0 (0.9–1.1)	
	Rinaldi et al. (2006)	Highest vs. lowest quintile	609/1,179	1.3 (0.9–1.9)	0.06
	Baglietto et al. (2007)	Highest vs. lowest quartile	220/8,885 person-years	1.6 (1.0–2.4)	0.05
	Gunter et al. (2009)	Highest vs. lowest quartile	838/810	1.2 (0.9–1.7)	0.92
Free IGF-I	Gunter et al. (2009)	Highest vs. lowest quartile	806/780	1.1 (0.8–1.5)	0.67
IGFBP-3	Gronbaek et al. (2004)	Per 500 unit increase	411/397	1.1 (1.0–1.3)	
	Rinaldi et al. (2006)	Highest vs. lowest quintile	609/1,179	1.5 (1.0–2.1)	0.06
	Baglietto et al. (2007)	Highest vs. lowest quartile	215/8,705 person-years	1.9 (0.1–3.7)	0.06
	Gunter et al. (2009)	Highest vs. lowest quartile	839/809	0.8 (0.6–1.1)	0.26
Premenopausal breast cancer					
IGF-I	Rinaldi et al. (2005b)	Highest vs. lowest quintile	217/333	1.4 (0.8–2.6)	0.15
	Rinaldi et al. (2006)	Highest vs. lowest quintile	242/477	1.2 (0.8–1.8)	0.61
	Schernhammer et al. (2006)	Highest vs. lowest quartile	239/478	0.9 (0.6–1.4)	0.48
	Baglietto et al. (2007)	Highest vs. lowest quartile	151/6,352 person-years	0.8 (0.5–1.4)	0.29
	Vatten et al. (2008)	Highest vs. lowest quintile	323/641	1.5 (0.9–2.3)	0.15
IGFBP-3	Rinaldi et al. (2005b)	Highest vs. lowest quintile	217/341	1.8 (1.0–3.2)	0.09
	Rinaldi et al. (2006)	Highest vs. lowest quintile	242/477	1.0 (0.6–1.6)	0.70
	Schernhammer et al. (2006)	Highest vs. lowest quartile	239/478	1.2 (0.8–1.8)	0.79
	Baglietto et al. (2007)	Highest vs. lowest quartile	145/6,185 person-years	0.7 (0.4–1.3)	0.20
	Vatten et al. (2008)	Highest vs. lowest quintile	323/641	0.8 (0.5–1.2)	0.12

et al. (2008) reported a 1.46-fold (95% CI: 0.9–2.3, p for trend=0.15) increased risk among premenopausal women in the highest quintile of IGF-I; however, results from the EPIC (Rinaldi et al. 2006) and NHS II (Schernhammer et al. 2006) studies indicated no association (OR=1.18 and OR=0.92, respectively).

In contrast to findings in premenopausal women, meta-analyses indicate a lack of an association between IGF-I levels and breast cancer risk in postmenopausal women (Renehan et al. 2004; Shi et al. 2004), while more recent prospective studies are suggestive of a null to modest positive association (Rinaldi et al. 2005b; Rollison et al. 2006; Baglietto et al. 2007; Gunter et al. 2009). Results from the WHI-OS study constitute the largest analysis conducted to date in postmenopausal women (Gunter et al. 2009): women in the highest quartile of circulating IGF-I concentration had a 1.21-fold (95% CI: 0.9–1.7) increased risk of postmenopausal breast cancer relative to women in the lowest quartile, with no evidence of a linear trend ($p = 0.92$). No association was observed with respect to concentrations of free IGF-I (HR = 1.09, 95% CI: 0.8–1.5) and no significant differences in associations with total IGF-I or free IGF-I were noted according to HT use. Results from the EPIC study, the largest previous prospective analysis, similarly indicated a 1.29-fold (95% CI: 0.9–1.8) increased risk among women in the highest vs. lowest quintile of circulating total IGF-I (Rinaldi et al., 2006).

Studies on the relationship between circulating IGFBP-3 levels and breast cancer risk have also been inconsistent. Overall, no significant association between IGFBP-3 levels and breast cancer in premenopausal women has been observed, and risk estimates from prospective studies comparing women in the highest vs. lowest levels of circulating IGFBP-3 range from 0.49 (95% CI: 0.2–1.1) (Allen et al. 2005) to 5.28 (95% CI: 1.1–24.7) (Krajcik et al. 2002). Results from the largest study to date fall within the lower end of this range: Vatten et al. (2008) reported an odds ratio of 0.78 (95% CI: 0.5–1.2) comparing premenopausal women in the highest and lowest quintiles of serum IGFBP-3 (383 cases/641 controls). Reported associations in postmenopausal women are similarly variable but, when considered together, imply no association between IGFBP-3 and postmenopausal breast cancer (Gronbaek et al. 2004; Renehan et al. 2004; Shi et al. 2004; Allen et al. 2005; Rinaldi et al. 2006; Baglietto et al. 2007; Gunter et al. 2009). There is some suggestion that the substantial variability between studies of IGFBP-3 may stem from the use of different IGFBP-3 assays with differing capabilities to measure the functional forms of the protein (Rinaldi et al. 2005a).

In light of the cross-talk between IGF-I and estradiol (Martin and Stoica 2002), it is plausible that the relationship between IGF-I, IGFBP-3, and breast cancer risk could vary according to tumor hormone receptor status; however, few studies have explored potential differences. In a prospective analysis among postmenopausal women, one study reported an increased risk of ER+ but not ER– breast cancer among women in the highest vs. lowest quartile of IGF-I [OR = 1.12 (95% CI: 1.0–1.2) and OR = 0.87 (95% CI: 0.7–1.1), respectively], with similar variability noted in associations with IGFBP-3 levels [OR = 1.19

(95% CI: 1.1–1.3) and OR = 0.96 (95% CI: 0.8–1.1), respectively] (Gronbaek et al. 2004). In contrast, results from the NHS II suggested no difference in the association between circulating IGF-I levels and risk of ER+ or ER– breast cancer in premenopausal women [OR = 1.14 (95% CI: 0.7–1.9) and OR = 1.25 (95% CI: 0.5–3.2), respectively] (Schernhammer et al. 2006). To date, no additional studies have reported on the association between breast cancer risk and IGF-I or IGFBP-3 according to hormone receptor status.

Summary

Blood concentrations of estrogens and androgens rank among the strongest risk factors for postmenopausal breast cancer given the magnitudes of their associated risk estimates. Estrogen and androgen levels may also be important with respect to premenopausal breast cancer risk, though the available data are considerably more sparse. The relationships between levels of these hormones and breast cancer are not surprising given the large volume of evidence linking hormones to breast cancer. However, measurement of these hormones to aid in breast cancer risk prediction has not gained wide clinical use. The roles of progesterone and prolactin on breast cancer risk remain unclear given the scarcity of studies focusing on them. Many studies have investigated the influence of IGF growth hormones and binding proteins on breast cancer risk, but have yielded largely inconsistent results. The potential clinical and public health utility of measuring hormones like progesterone, prolactin, and members of the IGF family is dependent on the roles and influences of these hormones being further clarified.

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Chapter 5
Exogenous Hormones

Christopher I. Li and Elisabeth F. Beaber

Introduction

Women worldwide have been prescribed medications containing female steroid sex hormones for the past several decades. These medications primarily containing various derivatives of estrogen and/or progesterone have been used for two main purposes, as menopausal hormone therapy (HT) and as contraceptives [primarily in the form of oral contraceptives (OCs)]. Given the central role of hormones in the etiology of breast cancer and the widespread uses of these preparations, numerous studies have evaluated the relationship between both HT and various hormonal contraceptives and breast cancer risk. These relationships have been and continue to be of considerable interest to epidemiologists, physicians, and the general population. A summary of this large body of work is provided below including assessments of the impact different types of hormones have on different types of breast cancer.

Menopausal Hormone Therapy

Patterns of Use

When menopausal HT started to be used more than 50 years ago, most HT users took preparations containing estrogen alone. Use of combined estrogen and progestin hormone therapy (CHT) increased rapidly over the 1980s when it was established that unopposed estrogen hormone therapy (EHT) increases endometrial cancer risk, but that HT regimens containing progestin do not. In the 1980s use of HT, and CHT specifically, increased steadily. For example, from 1982 to 1992 the number of prescriptions containing estrogen increased 2.3-fold ($p = 0.001$) and the number of prescriptions

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_5,

containing progestin increased 4.9-fold ($p = 0.001$) in the United States (Wysowski et al. 1995). Use of HT also became increasingly common in Europe. In the United Kingdom, from 1996 to 2001, 53% of postmenopausal women had ever used HT (Million Women Study Collaborators and Beral 2003), and in Geneva, Switzerland, by 1996 more than 50% of women 45–59 years of age had ever used HT (Olsson et al. 2003). The primary reason why HT use became increasingly common was the perception that its benefits outweighed its risks. In addition to relieving many menopausal symptoms, including hot flashes, sweating, and vaginal dryness, there was also evidence that HT may have important systemic benefits, most notably cardioprotective effects and the ability to prevent fractures by reducing bone loss. However, as described below, epidemiological data have consistently shown that HT use is positively related to breast cancer risk. HT use peaked in 2002 when in the United States an estimated 15 million women were using some form of HT, but then dropped precipitously (Buist et al. 2004; Clarke et al. 2006; Wei et al. 2005) following the publication of the results of the Women's Health Initiative randomized controlled trial of oral conjugated estrogen and medroxyprogesterone acetate (MPA) which observed that the risks of CHT outweighed its benefits. In particular, contrary to observational studies it was found that CHT users had elevated risks of coronary heart disease, stroke, and pulmonary embolism and confirmed that CHT use increases breast cancer risk. Even though rates of CHT use have dropped considerably since the publication of the WHI trials, studies of the risks associated with CHT use remain of critical importance given that HT is still widely used. For example, in the United States an estimated 57 million HT prescriptions continue to be filled each year (Hersh et al. 2004).

Types of Estrogen and Progesterone Used

The study of the relationship between HT and breast cancer has been challenging because of changes in formulations and patterns of HT use over time both within and across countries. In addition to the shift from use of EHT to CHT among postmenopausal women with an intact uterus, there has also been considerable variation in the types of estrogens and progestins used, patterns of CHT use, methods of delivery, and doses prescribed. In the United States, the types of estrogen and progestin used are fairly homogenous, as 84% of estrogens used in HT regimens are conjugated estrogens and 78% of the progestins used are MPA (Wysowski et al. 1995). Alternatively, there is much greater heterogeneity throughout Europe. For example, in the United Kingdom, among estrogen users 46% use ethinyl estradiol and 43% use conjugated estrogen, and among progestin users 47% use norgesterol/levonorgesterol, 34% use norethisterone, and 17% use MPA (Million Women Study Collaborators and Beral 2003). With respect to different patterns of use, CHT can be used either in a continuous (use of estrogen and progestin daily) or in a sequential

(use of estrogen daily and progestin in an interrupted manner, typically a certain number of days per month) manner. In the United States, approximately 70% of CHT users are continuous CHT users and 30% are sequential CHT users (Weiss et al. 2002). Alternatively, in the United Kingdom, 35% of CHT users are continuous users and 61% are sequential users (Million Women Study Collaborators and Beral 2003), while in Sweden, equal proportions of women use continuous and sequential CHT (Olsson et al. 2003). There are also different types of ways that hormones can be taken. Pills are the most commonly used method, though other options include patches, creams, injectables, and suppositories. Use of these different methods varies widely by country. Finally, HT doses have also changed over time, and in general doses have been decreasing. Previously unpublished data from our group suggest that in the Seattle area the proportion of EHT users taking >1.2 mg/day of conjugated estrogen has decreased steadily from 44% among users before 1980 to 17% among users since 1995. Thus, all of these variations in the ways that HT has been used over time, both within and across countries, have made studying its relationship with breast cancer challenging.

Observational Studies of the Relationship Between HT Use and Breast Cancer Risk

One means of understanding the results of the numerous observational studies that have evaluated the association between HT use and breast cancer risk is to take into account the time period in which different studies were conducted. As described above, in the 1970s and 1980s EHT and higher dose regimens predominated, while in the 1990s CHT and use of lower doses of estrogen were more common. With respect to studies conducted through the early 1990s, the Collaborative Group on Hormonal Factors in Breast Cancer conducted a comprehensive pooled analysis of 51 epidemiologic studies published from 1980 to 1997, and the median year of diagnosis for cases in these studies was 1984 (Collaborative Group on Hormonal Factors in Breast Cancer 1997). This study found that use of HT in general, and use of EHT and CHT specifically, for less than 5 years was not associated with altered risks of breast cancer. However, use for more than 5 years was associated with elevated risks, a 1.35-fold increased risk for EHT users and a 1.53-fold increased risk for CHT users. Similarly, in follow-up of the Nurses' Health Study (a large cohort of 121,700 US nurses established in 1976) through 1992, recent EHT use was associated with a 1.32-fold increased risk of breast cancer, and recent CHT use was associated with a 1.41-fold increased risk (Colditz et al. 1995). So based on studies conducted throughout the world from the 1970s to the early 1990s, both EHT and CHT have consistently been shown to be associated with an increased risk of breast cancer, particularly among current users for 5 years or longer.

Studies conducted during the 1990s have yielded somewhat different though generally consistent results, finding that CHT is associated with a greater increased risk of breast cancer than is unopposed EHT. Nine recent observational studies evaluating the relationship between EHT and CHT (including both sequential and continuous use) and breast cancer risk that included breast cancer cases diagnosed in the mid- to late-1990s are summarized in Table 5.1 (Million Women Study Collaborators and Beral 2003, Olsson et al. 2003, Weiss et al. 2002, Chen et al. 2002, Li et al. 2003, Newcomb et al. 2002, Porch et al. 2002, Ross et al. 2000, Fournier et al. 2005). All nine of these studies found that CHT was more strongly associated with breast cancer risk than was EHT. Further, seven of these studies found that EHT was not associated with an altered risk of breast cancer (Olsson et al. 2003, Weiss et al. 2002, Chen et al. 2002, Li et al. 2003, Porch et al. 2002, Ross et al. 2000, Fournier et al. 2005), with one also finding that even EHT use for 25 years or longer did not increase risk (Li et al. 2003). The other two studies observed a modest 20–30% increased risk of breast cancer associated with EHT (Million Women Study Collaborators and Beral 2003, Newcomb et al. 2002).

Of the eight recent studies evaluating continuous vs. sequential CHT use, four observed that both sequential and continuous CHT were associated with elevations in breast cancer risk that were similar in magnitude (Million Women Study Collaborators and Beral 2003, Chen et al. 2002, Li et al. 2003, Newcomb et al. 2002); three observed that continuous but not sequential CHT was associated with breast cancer risk (Olsson et al. 2003, Weiss et al. 2002, Porch et al. 2002); and one found that sequential but not continuous CHT increased risk (Ross et al. 2000). Variations across these studies may be due to numerous factors including the age range studied, varying proportions of women who used sequential CHT and continuous CHT, and differences in the distributions of durations of use across studies. As previously described, use of these regimens also varies widely by country, as do the types of estrogens and progestins used.

Different types of estrogen and progestin have not been well studied in the United States given the homogeneity of the hormones used, but results from the Million Women Study, based in the United Kingdom, suggest that there may be minimal differences in the risk of breast cancer associated with the use of different types of hormones (Million Women Study Collaborators and Beral 2003). Specifically, among EHT users, use of conjugated estrogen was associated with a 1.29-fold increased risk of breast cancer and use of ethinyl estradiol was associated with a 1.24-fold increased risk. Among users of CHT for 5 years or longer there were minimal differences in risk across women who used MPA, norethisterone, or norgestrel/levonorgestrel (relative risks of 2.42, 2.10, and 2.23, respectively). In contrast, data from the French E3N cohort indicate that there may be considerable differences in the risks of breast cancer associated with use of different types of progestagens. France is a unique setting for such studies given the considerable heterogeneity in the types of hormone therapies used there. Specifically, in the E3N cohort women who used estrogen and progesterone or estrogen and dydrogesterone had no elevations in their risk

Table 5.1 Summary of studies evaluating the relationship between unopposed estrogen (EHT) and combined estrogen and progestin (CHT) [including sequential (seq CHT) and continuous (cont CHT) regimens] postmenopausal hormone therapies and breast cancer risk

First author (journal, year)	Age	Diagnosis years	Setting	Study type	Number of cases	Type of HT use	Duration of use	RR/OR EHT	RR/OR CHT	RR/OR seq CHT	RR/OR cont CHT
Prior studies											
Collaborative Group (Lancet, 1997)	32–69[a]	1974–1992[a]	51 studies, worldwide	Pooled analysis	52,705	Current	5+ years	1.34	1.53	–	–
Colditz (NEJM, 1995)	<72	1976–1992	Nurses' Health Study, USA	Cohort	1,935	Current	Lifetime	1.32*	1.41*	–	–
Recent studies											
Ross (JNCI 2000)	55–72	1987–1996	Los Angeles, USA	Case–control	1,897	Ever	Each 5 years	1.06	1.24*	1.38*	1.09
Weiss (Ob Gyn 2002)	<65	1994–1998	Multicenter, USA	Case–control	1,870	Current	5+ years	0.81	1.37*	1.00	1.54*
Newcomb CEBP (2002)	50–79	1992–1994	Multicenter, USA	Case–control	5,298	Ever	Lifetime	1.2*	1.4*	1.0–1.6[b]	1.5*[,b]
Porch (CCC, 2002)	≥60	1993–2000	Multicenter, USA	Cohort	411	Ever	Lifetime	0.96	1.37*	1.04	1.82*
Chen (JAMA 2002)	50–74	1990–1995	Seattle, USA	Case–control	1,995	Current	Lifetime	1.17	1.49*	1.62[a,c]	1.85[c]
Olsson (Cancer 2003)	50–74	1990–2001	Sweden	Cohort	556	Ever	4+ years	0.58	–	1.44	3.13*
Li (JAMA 2003)	65–79	1997–1999	Seattle, USA	Case–control	975	Current	Lifetime	1.0	1.8*	2.0*	1.8*
Million Women's Study (Lancet, 2003)	50–64	1996–2001	United Kingdom	Cohort	9,364	Ever	5+ years	1.30*[,d]	2.21*	2.12*	2.40*

Table 5.1 (continued)

First author (journal, year)	Age	Diagnosis years	Setting	Study type	Number of cases	Type of HT use	Duration of use	RR/ OR EHT	RR/ OR CHT	RR/OR seq CHT	RR/OR cont CHT
Chlebowski (JAMA, 2002)	50–79	1993–2002	Multicenter, USA	Randomized trial	430	Current	5.2 years (mean)	–	–	–	1.24
Stefanick (JAMA, 2004)	50–79	1993–2004	Multicenter, USA	Randomized trial	218	Current	6.8 years (mean)	0.77	–	–	–
Fournier (IJC, 2005)	≥40	1992–2000	France	Cohort	948	Ever	Lifetime	1.1	1.3*	–	–

[a]Ranges of median ages and years of diagnosis across the studies.
[b]In this study CHT use was categorized into three patterns, use of progestin for <10, 10–21, and >21 days/month. The OR for <10 days/month of progestin was 1.57, for 10–21 days was 0.92, and for >21 days was 1.48. For the purposes of this table use of progestin for ≤21 days was considered seq CHT, and use for >21 days was considered cont CHT.
[c]OR for seq CHT is for 36+ months of seq CHT use in the past 5 years, and the OR for cont CHT is for 20+ months of cont CHT in the past 5 years.
[d]OR is for ever lifetime EHT, not only for ever use for ≥5 years.
*$p < 0.05$.

of breast cancer (RR = 1.00, 95% CI: 0.8–1.2 and RR = 1.16, 95% CI: 0.9–1.4, respectively) while users of estrogen in combination with other types of progestagens, including progestins such as MPA, had a 1.69-fold (95% CI: 1.5–1.9) increased risk of breast cancer (Fournier et al. 2008). While these results require confirmation, synthetic progestins such as MPA may confer a higher risk of breast cancer compared to progesterone and dydrogesterone (a retroprogesterone chemically and pharmacologically very similar to progesterone) because these progestins have a higher degree of androgenicity which has been hypothesized to elevate breast cancer risk (Campagnoli et al. 2005).

The Million Women Study also provides some of the only data on risk by formulation. Among EHT users women using oral, transdermal, and implanted estrogen had 1.32-fold (95% CI: 1.2–1.5), 1.24-fold (95% CI: 1.1–1.4), and 1.65-fold (95% CI: 1.3–2.2) increased risks of breast cancer, respectively. Given the degree to which the 95% CI's of these risk estimates overlap, there is no strong evidence from this study that risk of breast cancer varies substantially by route of HT administration.

Although uncommonly used, HT regimens containing both estrogen and testosterone are used by some women to manage menopausal symptoms. There are few published studies with sufficient statistical power to assess this association, though data from the Nurses' Health Study indicate that current users of estrogen and testosterone have a 2.48-fold (95% CI: 1.5–4.0) increased risk of breast cancer compared to never users of HT (Tamimi et al. 2006).

Women's Health Initiative Randomized Trials of EHT and CHT

Perhaps the most compelling data regarding the differences between EHT and CHT in relation to breast cancer risk come from the Women's Health Initiative (WHI) randomized trials of these two therapies. The WHI trial of continuous CHT (an oral combination of conjugated equine estrogen and MPA) was stopped early in 2002 because overall health risks exceeded benefits after 5.2 years of follow-up (Writing Group for the Women's Health Initiative Investigators 2002). One of the risks identified was a 24% increase in breast cancer risk. Further, it was found that the breast cancers that CHT users developed compared to placebo users were larger (1.7 cm vs. 1.5 cm, $p = 0.04$), more likely to have nodal involvement (25.9% vs. 15.8% of cases, $p = 0.03$), and to be of a regional/metastatic stage (9.4% vs. 5.4% of cases, $p = 0.04$) (Chlebowski et al. 2003). CHT was also found to be associated with an increased likelihood of having an abnormal mammogram, as the proportion of subjects with an abnormal mammogram after 1 year was 9.4% vs. 5.4% among CHT vs. placebo users ($p < 0.001$). Thus, the WHI provided evidence indicative of a causal relationship between CHT use and breast cancer and that the breast cancers developed among CHT users are more advanced at diagnosis. The EHT arm of WHI was stopped on February 29, 2004, because users of EHT were

observed to have an increased risk of stroke (The Women's Health Initiative Steering Committee 2006). However, unlike CHT, EHT was not found in this trial to increase breast cancer risk (RR = 0.80; 95% CI: 0.6–1.0), providing strong evidence that use of EHT for a duration of 7.1 years or less does not alter breast cancer risk (Stefanick et al. 2006). Thus, the WHI trial results are quite consistent with the recent observational studies in finding that while CHT increases breast cancer risk, EHT does not.

Understanding Differences in EHT Findings Across Studies

There are a few hypothesized reasons why the results of the more recent studies detailed above differ from those conducted earlier with respect to the risk associated with EHT. First, the pooled analysis conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer 1997) had certain limitations. Specifically, data on the type of HT used were only available for 39% of the eligible women, and the analysis was not restricted to women who were exclusive EHT users. Though this pooled analysis began with a very large sample size, only 58 cases and 86 controls were current CHT users for 5 years or longer, limiting the power of its EHT vs. CHT analyses. Further, some of the association that was observed with EHT may have been due to a mixing of CHT's effects with EHT's, as there is now clear evidence that use of CHT is a stronger risk factor for breast cancer than is use of EHT. It is also noteworthy that earlier results from the Nurse's Health Study from 1976 to 1986, a time period prior to the widespread use of CHT, are consistent with these more recent studies as it found that even use of EHT for $\geq$15 years was not associated with an increased risk of breast cancer (Colditz et al. 1990). Since studies conducted in the 1980s often failed to distinguish between women who had used both EHT and CHT and because many HT users during this time switched from using EHT to CHT as a result of the risk of endometrial cancer associated with EHT use, the associations observed with EHT in these studies may be biased. Thus, the more recently conducted studies of HT use conducted over periods when women were less likely to have first used EHT and then switched to CHT, likely provide clearer evidence regarding how EHT and CHT differ in their association with breast cancer risk, and the majority indicate that EHT is not positively related to breast cancer risk, even when used for long durations (Li et al. 2003, Colditz et al. 1990).

Another reason why results may be different across time periods is because of changes in HT doses over time as described above. Dose of EHT appears to be related to breast cancer risk as the study by Porch et al. (2002) found that increasing doses of estrogen were associated with increasing risks of breast cancer (compared to never HT users, users of $\leq$0.30 mg/day, 0.625 mg/day, and $\geq$0.9 mg/day had 0.87-fold (95% CI: 0.4–1.7), 1.26-fold (95%

CI: 1.0–1.7), and 1.43-fold (95% CI: 0.9–2.3) altered risks of breast cancer, respectively, p-trend = 0.06). Similarly, in the Million Women Study (a cohort of 1,084,110 UK women recruited from 1996 to 2001), use of ≤ 0.625 mg/day was associated with a lower risk of breast cancer than was use of > 0.625 mg/day of conjugated estrogen (relative risk [RR] = 1.25, 95% CI: 1.1–1.4, and RR = 1.36, 95% CI: 1.1–1.6, respectively) (Million Women Study Collaborators and Beral 2003). Thus, the increasing use of lower dose estrogens in HT regimens, particularly in the United States, may account for the differences observed across studies.

Relationship Between HT Use and Different Breast Cancer Subtypes

Increasing attention has been directed toward understanding how HT use influences risk of different types of breast cancer. Recent studies have primarily focused on differences in risk by histological type and by hormone receptor status. Work related to histological type was initially motivated by the observation that incidence rates of invasive lobular carcinoma (the second most common histologic type of breast cancer) have increased steadily since the late 1980s, particularly among postmenopausal women, while rates of invasive ductal carcinoma (the most common histologic type of breast cancer) have remained relatively constant in the United States (Li et al. 2000). Specifically, from 1987 to 1999 lobular carcinoma rates increased 65%, while ductal carcinoma rates increased only 3%, such that in the United States, the total proportion of breast cancer cases that were lobular increased from 9.5% to 15.6% over this time period (Li et al. 2003). These trends have also been observed in two areas of Switzerland. In Geneva and Vaud lobular carcinoma rates have increased 14.4% and 10.0% per year, respectively, from 1976–1979 to 1995–1996 while ductal carcinoma rates have increased only 1.2% and 0.9% per year, respectively (Levi et al. 2003, Verkooijen et al. 2003).

Eleven epidemiologic studies have now been published evaluating the relationship between EHT and CHT use and risk of lobular and ductal carcinomas (Chen et al. 2002, Li et al. 2003, Newcomb et al. 2002, Daling et al. 2002, Lee et al. 2006, Li et al. 2000, Newcomer et al. 2003, Reeves et al. 2006, Rosenberg et al. 2006, Ursin et al. 2002, Li et al. 2008). There is reasonable consistency across these studies as seven found no association between EHT use and risk of ductal carcinoma (Chen et al. 2002, Li et al. 2003, Daling et al. 2002, Li et al. 2000, Newcomer et al. 2003, Ursin et al. 2002, Li et al. 2008) and eight found no association between EHT and risk of lobular carcinoma (Chen et al. 2002, Li et al. 2003, Newcomb et al. 2002, Daling et al. 2002, Lee et al. 2006, Li et al. 2000, Newcomer et al. 2003, Ursin et al. 2002, Li et al. 2008). Five of the eleven found no association between CHT use and risk of ductal carcinoma (Newcomb et al. 2002, Stefanick et al. 2006, Colditz et al. 1990, Li et al.

2000). Nine of these studies also observed that CHT use was more strongly related to risk of lobular carcinoma than it was to risk of ductal carcinoma (Chen et al. 2002, Li et al. 2003, Daling et al. 2002, Li et al. 2000, Newcomer et al. 2003, Reeves et al. 2006, Rosenberg et al. 2006, Ursin et al. 2002, Li et al. 2008). Specifically, risk estimates associated with CHT use ranged from 0.7 to 2.0 for ductal carcinoma and from 1.2 to 3.9 for lobular carcinoma. All but two of these lobular carcinoma risk estimates were < 2.0, and all but two of the ductal carcinoma risk estimates were >1.6. With respect to the WHI trials, it is notable that the CHT trial did not find a difference in risk by histology, though the trial was underpowered to assess this relationship given that it accrued only 61 lobular cases across both arms of the study (Chlebowski et al. 2003). In the EHT WHI trial, EHT use reduced risk of ductal carcinoma (RR = 0.71, 95% CI: 0.5–1.0) but was not related to risk of lobular carcinoma (Stefanick et al. 2006). Based on the available evidence, EHT use does not appear to increase risk of either ductal or lobular carcinomas, but CHT use does seem to be more strongly related to risk of lobular carcinoma than it is to risk of ductal carcinoma.

Several recent studies have evaluated the relationship between HT use and risk of breast cancer subtypes defined by estrogen receptor (ER) and/or progesterone receptor (PR) status. The data consistently indicate that HT use, and particularly CHT use, is related to risk of hormone receptor positive breast cancer, but not to risk of hormone receptor-negative breast cancer (Chen et al. 2002, Li et al. 2003, Ursin et al. 2002, Chen et al. 2004, Stahlberg et al. 2004, Rosenberg et al. 2006). In particular, four studies evaluating joint ER/PR status and EHT and CHT use separately all observed that CHT use is associated with 1.9-fold to 2.3-fold increases in risk of ER+/PR+ tumors, but is not related to risk of ER−/PR− tumors (Li et al. 2003, Ursin et al. 2002, Chen et al. 2004, Rosenberg et al. 2006). In these studies EHT use has consistently been found not to be related to risk of ER−/PR− tumors, but two found that EHT was also not related to risk of ER+/PR+ tumors (Li et al. 2003, Ursin et al. 2002) and two found that it was associated with a modest 1.4-fold to 1.7-fold increased risk of ER+/PR+ tumors (Chen et al. 2004, Rosenberg et al. 2006).

Clinical Implications

Though certain aspects of the relationship between HT and breast cancer are still unclear, our understanding of this relationship has progressed in recent years and the issue of how to advise women contemplating HT use today remains. Clearly it is important to make sure that patients are aware of HT's risks and benefits, particularly in light of the WHI results, which dramatically altered our understanding of this balance. The main reasons why patients may consider HT are to relieve menopausal symptoms and to slow bone loss. Prior to WHI it was also thought that CHT may have numerous other benefits

including protecting against cardiovascular disease and possibly Alzheimer's disease. However, based on WHI, increased risks of coronary heart disease, stroke, and pulmonary emboli and deep vein thrombosis must also be tallied as risks of CHT use. Fewer risks are associated with the use of EHT, but for healthy postmenopausal women its risks still likely outweigh its benefits. Based on the available data, for women who choose to use HT the US Food and Drug Administration (FDA) recommends that it be used at the lowest beneficial dose and for the shortest period of time needed. These recommendations may change though as the study of HT and breast cancer is likely to remain an active area of research as different, including newer, HT regimens are used by women throughout the world. However, the impact of recent studies documenting the adverse effects of HT has been dramatic. In the United States CHT use rates dropped 38–68% (Buist et al. 2004, Clarke et al. 2006, Wei et al. 2005) following the publication and dissemination of the results of the WHI CHT trial in 2002 (Writing Group for the Women's Health Initiative Investigators 2002).

Oral Contraceptives

There are multiple types of hormonal contraception available by prescription, including OCs, injectable contraceptives, hormonal intrauterine devices (IUDs), implants, vaginal rings, and transdermal contraceptive patches. OCs are the most common type of hormonal contraception used, though their availability and frequency of use vary considerably worldwide. Rates of use are generally higher in developed countries, for example, in the United States approximately 82% of women have ever used OCs and in 2002 approximately 11.6 million women of reproductive age were currently using OCs (Mosher and Martinez 2004). The majority of OCs contain both estrogen and progestin components and regimens can be monophasic (i.e., the estrogen and progestin doses do not vary during a monthly cycle), biphasic, or triphasic, with the doses of progestin and/or estrogen varying over a monthly cycle. Sequential OCs have not been used for the past several decades (they were removed from the US market around 1977) (Piper and Kennedy 1987) and at present progestin-only OCs are rarely used (<1% of US women use them) (Mosher and Martinez 2004), and therefore this chapter will not discuss either of these OC regimens.

OC formulations are remarkably heterogeneous. For example, at present there are eight different synthetic progestins used in OCs in the United States and a wide range of doses and potencies of the hormones included. The progestins used in OCs are derivatives of 19-nortestosterone, with the exception of drospirenone, which is a derivative of 17-α-spironolactone (first approved for use in OCs by the FDA in 2001). The 19-nortestosterone derivatives can be grouped into estranes and gonanes (Hatcher et al. 2007, Schindler et al. 2003). Estrane progestins currently used in OC formulations in the United States

include norethindrone, norethindrone acetate, and ethynodiol diacetate. Gonane progestins include norgestrel, levonorgestrel, norgestimate, and desogestrel. In addition to structural differences between estrane and gonane progestins, there are also differences in estrogenic, androgenic, and progestational activity (Dickey 2007). Estranes have varying degrees of estrogenic activity, whereas gonanes have no estrogenic activity. In general, gonane progestins have increased progestational potencies and greater androgenic activity than estrane progestins (Dickey 2007, Benagiano et al. 2004). In contrast, the 17-α-spironolactone derivative drospirenone has no estrogenic activity, lower progestational activity than both estranes and gonanes, and no androgenic activity (Dickey 2007, Benagiano et al. 2004). The estrogen component for the majority of OC formulations is ethinyl estradiol; however, some contain the estrogen mestranol, which is metabolized to ethinyl estradiol (Dickey 2007). Mestranol has approximately 67% estrogenic activity of ethinyl estradiol and there is evidence that OCs containing 35 micrograms (μg) of ethinyl estradiol are approximately bioequivalent to those containing 50 μg of mestranol (Dickey 2007, Brody et al. 1989).

In addition to the use of new synthetic progestins in OCs over time, there has also been considerable changes in dose since OCs were first introduced in the 1960s (Dickey 2007, Brody et al. 1989, David et al. 2006). Estrogen dose has decreased from 150 μg in the 1960s to as low as 20 μg in OCs currently available, with pills containing 20–35 μg of ethinyl estradiol being the most commonly prescribed OCs at present (Casey et al. 2008). OCs with >50 μg of ethinyl estradiol have not been sold in the United States since 1988 (Dickey 2007). Since the early 1990s, OC formulations and patterns of use have continued to change, including increased use of OCs with the progestins desogestrel and norgestimate, the development of the synthetic progestin drospirenone, increased popularity of OCs with lower estrogen dose (e.g., 20 μg of ethinyl estradiol), and the introduction of extended- and continuous-use OCs (David et al. 2006, Althuis et al. 2003, Burkman et al. 2001).

Epidemiologic Evidence Assessing Oral Contraceptive Use and Breast Cancer Risk

A multitude of case–control studies, cohort studies, and pooled analyses have assessed the relationship between OC use and risk of breast cancer among pre- and postmenopausal women, including recent studies that have focused on timing of use, specific durations of use, and hormonal content. Table 5.2 summarizes 16 studies published since 1995. Overall, the evidence supports that recent use of OCs is associated with a modest increased risk of breast cancer among premenopausal women and that this relationship is strongest among very young women (Althuis et al. 2003, Brinton et al. 1995, Kahlenborn et al. 2006, Newcomb et al. 1996, Wingo et al. 1991). Recently, case–control

studies have further examined the relationship between OC use and breast cancer by assessing risk of in situ breast cancer and risk of invasive breast cancer according to histologic type and expression of different tumor markers.

Age at Diagnosis, Timing of Oral Contraceptive Use, and Duration of Use

Evidence from numerous case–control and cohort studies shows that OC use is associated with a modest increased risk of breast cancer in premenopausal/younger women, but not postmenopausal/older women (Althuis et al. 2003, Brinton et al. 1995, Kahlenborn et al. 2006, Newcomb et al. 1996, Wingo et al. 1991, WHO 1990, Nyante et al. 2008, Romieu et al. 1989, 1990, Rookus and van Leeuwen 1994). In observational studies and pooled analyses that included both pre- and postmenopausal women, the risk estimates for the effect of ever using OCs on risk of breast cancer range from approximately 0.9 to 1.3 (Newcomb et al. 1996, Collaborative Group on Hormonal Factors in Breast Cancer 1996, Dumeaux et al. 2003, Hankinson et al. 1997, Kumle et al. 2002, Marchbanks et al. 2002, Rossing et al. 1996, Van Hoften et al. 2000) (Table 5.2). However, when restricting to premenopausal/younger women, the risk estimates range from approximately 0.8 to 2.1 (Althuis et al. 2003, Brinton et al. 1995, Kahlenborn et al. 2006, Newcomb et al. 1996, Hankinson et al. 1997, Marchbanks et al. 2002, Rosenberg et al. 1996, Ursin et al. 1998, Lee et al. 2008). With respect to timing of OC use, there is consistent evidence that the modest increased risk observed among women younger than 45 years of age is specifically associated with recent use of OCs (Althuis et al. 2003, Brinton et al. 1995, Newcomb et al. 1996). The most comprehensive single evaluation of much of the world's data is the pooled analysis conducted by the Collaborative Group on Hormonal Factors in Breast Cancer. It included both pre- and postmenopausal women with a median age at diagnosis of 49 years and observed a modest increased risk of breast cancer associated with OC use within the prior year (RR = 1.2, 95% CI: 1.2−1.3), within the prior 5 years (RR = 1.2, 95% CI: 1.1−1.2), and 5–9 years prior (RR = 1.1, 95% CI: 1.0−1.1), but no significant increased risk among those who used OCs $\geq$10 years prior (Collaborative Group on Hormonal Factors in Breast Cancer 1996). When restricting to premenopausal women, use of OCs within the prior 5 years was associated with a statistically significant 1.2-fold increased risk of breast cancer compared to never users based on 4,417 cases and 7,929 controls (Collaborative Group on Hormonal Factors in Breast Cancer 1996).

Among studies subsequent to the publication of these results some (Althuis et al. 2003, Brinton et al. 1995, Newcomb et al. 1996), but not all (Marchbanks et al. 2002, Ursin et al. 1998, Lee et al. 2008), have observed a relationship between OC use and breast cancer risk among premenopausal/younger ($\leq$49-year-old) women. These variations may be related to the age range included

Table 5.2 Overview of studies evaluating the relationship between oral contraceptive (OC) use and breast cancer risk

First author (journal, year)	Diagnosis years	Setting	Study type	Age	Number of cases	Type of OC use	Duration of use[b]	RR/OR	Duration effect?	E dose effect?
Premenopausal/younger (≤49 years of age) women										
Brinton (JNCI, 1995)	1990–1992	Multi-center, USA	Population-based case–control	<35	268	Ever	≥6 mo	1.7*	<5 y: 1.6 5–9 y: 1.8* ≥10 y: 2.3*	–
						Recent	<5 y	2.0*	–	–
				<45	1,648	Ever	≥6 mo	1.3*	<5 y: 1.3* 5–9 y: 1.3 ≥10 y: 1.3	–
						Recent	<5 y	1.5*	–	–
Collaborative Group (Lancet, 1996)	Median = 1984[a]	54 studies, worldwide	Pooled analysis	Pre-meno	4,417	Recent	w/in 5 y	1.2*	–	–
Newcomb (CCC, 1996)	1988–1991	Multi-center, USA	Population-based case–control	<35	167	Ever	≥3mo	1.4	N	–
						Recent	<2 y	1.3	–	–
				35–44	883	Ever	≥3 mo	1.0	N	–
						Recent	<2 y	2.0*	–	–
Rosenberg (AJE, 1996)	1977–1992	Multi-center, USA	Hospital-based case–control	25–34	318	Ever	≥1 y	1.7*	1–4 y: 1.6* 5–9 y: 1.7* ≥10 y: 2.5*	N
				35–44	1,073	Ever	≥1 y	0.9	N	N
Hankinson (CCC, 1997)	1976–1992	Nurses' Health Study, USA	Cohort	<45	515	Ever	<1 y	1.1	N	–
							≥10 y	1.1		
Ursin (BCRT, 1998)	1983–1988	Los Angeles County, USA	Population-based case–control	≤40	744	Ever	Any use	0.8	>12 y: 1.4	>12 y using ≥50 μg: 1.6
						Recent	w/in 1 y	1.1	–	–
							>1–3 y	0.8		
							>3–<5 y	0.8		
							≥5 y	0.8		

Table 5.2 (continued)

First author (journal, year)	Diagnosis years	Setting	Study type	Age	Number of cases	Type of OC use	Duration of use[b]	RR/OR	Duration effect?	E dose effect?
Marchbanks (NEJM, 2002)	1994–1998	Multicenter, USA	Population-based case–control	35–44	1,447	Ever	Any use	1.0	N	N
						Current	w/in 6 mo	1.1	–	–
						Recent	7 mo–<5 y	0.9	–	–
						Former	>6 mo	1.0	–	–
Althuis (CCC, 2003)	1990–1992	Multicenter, USA	Population-based case–control	<35	265	Ever	≥6 mo	2.0*	–	–
						Recent	w/in 5 y	2.3*	–	–
							5–9 y	1.9*		
							10+ y	1.4		
				35–44	1,214	Ever	≥6 mo	1.1	–	–
						Recent	w/in 5 y	1.3*	–	–
							5–9 y	1.2		
							10+ y	1.1		
Althuis (Br J Cancer, 2003)	1990–1992	Multicenter, USA	Population-based case–control	<35	267	Ever	≥6 mo	2.1*	–	–
						Recent	w/in 5 y	2.2*	–	–
							6–10 y	2.0*		
							>10 y	1.5		
					193	Dose used for longest duration w/in 5 y	≥6 mo	–	–	≤35 μg: 1.9* >35 μg: 3.6*
				35–44	1,373	Ever	≥6 mo	1.1	–	–
						Recent	w/in 5 y	1.3	–	–
							6–10 y	1.2		
							>10 y	1.1		
					487	Dose used for longest duration w/in 5 y	≥6 mo	–	–	≤35 μg: 1.0 >35 μg: 1.5

Table 5.2 (continued)

First author (journal, year)	Diagnosis years	Setting	Study type	Age	Number of cases	Type of OC use	Duration of use[b]	RR/OR	Duration effect?	E dose effect?
Kahlenborn (Mayo Clinic Pro, 2006)	1980–1998	34 case–control studies, worldwide	Pooled analysis	Pre-meno or <50	16,181	Ever	Any use	1.2*	N	–
Folger (CCC, 2007)	1994–1998	Multicenter, USA	Population-based case–control	Pre-meno	497	Ever	Short-term (<6 mo)	1.3*	–	–
Lee[c] (CEBP, 2008)	1998–2003	Los Angeles County, USA	Population-based Case–control	20–49	1,375	Ever	Any use	0.8	N	Low dose: 0.6* High dose: 1.2
Pre- and postmenopausal women										
Collaborative Group (Lancet, 1996)	Median = 1984[a]	54 studies, worldwide	Pooled analysis	Median = 49[a]	53,297	Ever	Any use	1.1*	N	N
						Current	w/in 1 y	1.2*	–	–
						Recent	>1-<5y	1.2*	–	–
						Former	5–9 y	1.1*	–	–
Van Hoften (Int J Cancer, 2000)	1982–1996	Utrecht area, Netherlands	Nested case–control	≤55	208	Ever	Any use	1.3	N	–
Marchbanks (NEJM, 2002)	1994–1998	Multicenter, USA	Population-based case–control	35–64	4,575	Ever	Any use	0.9	N	N
						Current	w/in 6 mo	1.0	–	–
						Recent	7 mo–<5 y	0.7*	–	–
						Former	>6 mo	0.9*	–	–

Table 5.2 (continued)

First author (journal, year)	Diagnosis years	Setting	Study type	Age	Number of cases	Type of OC use	Duration of use[b]	RR/OR	Duration effect?	E dose effect?
Kumle (CEBP, 2002)	1991–1999	Norway and Sweden	Prospective cohort	30–57 Median = 47[a]	1,008	Ever	Any use	1.3*	<5 y: 1.2 5–9 y: 1.2 10–14 y: 1.4* 15+ y: 1.3 $p = 0.005$	–
						Current	w/in 1 y	1.6*	–	–
						Former	>1 y	1.2*	–	–
Dumeaux (Int J Cancer, 2003)	1991–1999	Norway	Prospective cohort	30–70	851	Ever	Any use	1.3*	<5 y: 1.3* 5–9 y: 1.2 10+ y: 1.4* $p = 0.007$	Cumulative dose (mg): <50: 1.4* 50–99: 1.3 100+: 1.5* $p = 0.002$
Postmenopausal/older (≥45 years of age) women										
Collaborative Group (Lancet, 1996)	Median = 1984[a]	54 studies, worldwide	Pooled analysis	Post-meno	433	Recent	w/in 5 y	1.1	–	–
Rossing (AJE, 1996)	1988–1990	Western WA, USA	Population-based case–control	50–64	537	Ever	Any use	1.1	N	–
Rosenberg (AJE, 1996)	1977–1992	Multicenter, USA	Hospital-based case–control	45–59	2,076	Ever	≥1 y	1.2	N	N
Newcomb (CCC, 1996)	1988–1991	Multicenter, USA	Population-based case–control	45–54	1,315	Ever	≥3 mo	1.1	N	–
						Recent	<2 y	1.4	–	–
				≥55	4,386	Ever	≥3 mo	1.0	N	–
Hankinson (CCC, 1997)	1976–1992	Nurses' Health Study, USA	Cohort	≥45	2,868	Ever	<1 y	1.0	N	–
							≥10 y	1.1		

Table 5.2 (continued)

First author (journal, year)	Diagnosis years	Setting	Study type	Age	Number of cases	Type of OC use	Duration of use[b]	RR/OR	Duration effect?	E dose effect?
Van Hoften (Int J Cancer, 2000)	1982–1996	Utrecht area, Netherlands	Nested case–control	>55	101	Ever	Any use	1.5	1–10 y: 1.3 >10 y: 2.1*	–
Althuis (CCC, 2003)	1990–1992	Multicenter, USA	Population-based case–control	45–54	271	Ever	≥6 mo	0.7	–	–
						Recent	w/in 5 y	0.1*	–	–
							5–9 y	1.0		
							10+ y	0.8		
Folger (CCC, 2007)	1994–1998	Multicenter, USA	Population-based case–control	Post-meno	729	Ever	Short-term (<6 mo)	0.8	–	–

[a]Median age or year at diagnosis.
[b]For recent exposure, this column refers to how recent use was defined.
[c]OR compares controls to *BRCA1/2* mutation non-carrier cases (number of cases listed); low dose = OC use 1975 and after; high dose = OC use before 1975.
*$p < 0.05$.
Abbreviations: RR = relative risk; OR = odds ratio; E = estrogen; N = no effect; mo = months; y = year(s); w/in = within; pre-meno = premenopausal; post-meno = postmenopausal

since studies focusing on women <35 years of age observe the most pronounced risks (Althuis et al. 2003, Rosenberg et al. 1996). They also could be the consequence of changes in the types of OCs used over time since more recent formulations with lower doses and different hormonal constituents may have a different impact on risk compared to older formulations. With respect to the effect of age at initiating OCs, a large US multicenter case–control study among women 35–44 years of age found that beginning OCs at a young age was not associated with an increased risk of breast cancer (Marchbanks et al. 2002). In contrast to the findings among premenopausal/younger (≤49-year-old) women, neither the Collaborative Group on Hormonal Factors in Breast Cancer or any of the seven subsequent studies restricted to postmenopausal/older (≥45-year-old) women observed any relationship between OC use and breast cancer risk among these older women. This is consistent with the evidence that only recency of OC use confers a modest elevation in breast cancer risk.

In general, the evidence does not support an association between increasing duration of OC use and increasing risk of breast cancer. Among studies that included both pre- and postmenopausal women, some found an increasing risk of breast cancer associated with using OCs for a longer duration (Dumeaux et al. 2003, Kumle et al. 2002), but most found no association with duration of OC use (Newcomb et al. 1996, Collaborative Group on Hormonal Factors in Breast Cancer 1996, Hankinson et al. 1997, Marchbanks et al. 2002, Rossing et al. 1996). The large pooled analysis by the Collaborative Group found no significant differences in risk of breast cancer among categories of total duration of OC use (<1, 1–4, 5–9, 10–14, ≥15 years of use), though there was a suggestion of a trend of increasing risk with increasing duration of OC use ($p = 0.05$) (Collaborative Group on Hormonal Factors in Breast Cancer 1996). Among premenopausal women, most (Brinton et al. 1995, Kahlenborn et al. 2006, Newcomb et al. 1996, Hankinson et al. 1997, Marchbanks et al. 2002, Lee et al. 2008), but not all (Ursin et al. 1998), studies have found no effect of duration of OC use on risk of breast cancer. However, when restricting to women <35 years of age, two studies found an increasing risk of breast cancer associated with an increasing duration of OC use (Brinton et al. 1995, Rosenberg et al. 1996). In both studies women <35 years of age who used OCs for ≥10 years had a greater than 2-fold increased risk of breast cancer (OR = 2.3, 95% CI: 1.2–4.1; OR = 2.5, 95% CI: 1.4–4.8) compared to never users (Brinton et al. 1995, Rosenberg et al. 1996). A recent multicenter case–control study found that ever using OCs for <6 months was associated with a statistically significant increased risk of breast cancer among premenopausal women (OR = 1.3, 95% CI: 1.0–1.7), but a reduced risk among postmenopausal women (OR = 0.8, 95% CI: 0.6–1.0) (Folger et al. 2007); however, this association is likely due to differences in the underlying characteristics of users or unmeasured factors related to both short-term OC use and risk of breast cancer. In addition to assessing duration of use in relationship to risk of breast cancer, it is important to consider the progestin and estrogen components of different pills because of the high amount of variation among OC formulations.

Oral Contraceptive Use According to Progestin and Estrogen Content

There is evidence that estrogen and 19-nortestosterone-derived progestins can stimulate breast cell mitotic activity on breast cells in vivo and that 19-nortestosterone derivatives alone can stimulate the growth of multiple breast cancer cell lines (Isaksson et al. 2001, Jeng et al. 1992). Although it is known that different types of progestins have different estrogenic, progestational, and androgenic activities (Dickey 2007, Benagiano et al. 2004), relatively few studies have assessed the effect of specific OC formulations on breast cancer risk (Brinton et al. 1995, Ursin et al. 1998, Jick et al. 1989, White et al. 1994). In terms of risk by type of progestin, a large multicenter US case–control study of women 35–64 years of age found that current use of both ethynodiol diacetate and norgestrel progestins increased breast cancer risk (OR = 3.5, 95% CI: 1.1–10.7; OR = 1.4, 95% CI: 0.8–2.5, respectively), but use of OCs containing other types of progestins, such as levonorgestrel, did not (Marchbanks et al. 2002). With respect to progestin dose, a Norwegian cohort study of women 30–70 years of age found that both low (<0.3 g) and high (≥0.3 g) cumulative doses of the progestins levonorgestrel or norgestrel were similarly related to risk (RR for both dose groups = 1.3, 95% CI: 1.0–1.7) (Dumeaux et al. 2003). However, both of these studies included pre- and postmenopausal women, rather than focusing on a younger age group. In an effort to address the limitations of previous studies, Althuis et al. (2003) evaluated the risks associated with recent exposure to OC formulations available prior to 1993 by hormonal content and potency using a population-based case–control study among women 20–44 years of age. They found similar risks across types of progestins recently used, but an elevated risk of breast cancer among women <35 years of age who recently used OCs with high progestin potency (OR = 8.1, 95% CI: 2.1–31.6) (Althuis et al. 2003). Other studies examining progestin dose in OCs and breast cancer risk among young women have observed mixed results, with some finding an increased risk of breast cancer associated with use of OCs with high progestin potency or content (White et al. 1994, Pike et al. 1983) and others finding no association (Miller et al. 1986, Stadel et al. 1985).

With respect to dose of estrogen, some studies have found a greater risk of breast cancer associated with higher doses of estrogen in OC formulations (Althuis et al. 2003, Dumeaux et al. 2003, Ursin et al. 1998, Lee et al. 2008), while others have not (Collaborative Group on Hormonal Factors in Breast Cancer 1996, Marchbanks et al. 2002, Rosenberg et al. 1996). Althuis et al. (2003) found that among women <35 years of age, those who recently used an OC formulation with >35 μg of ethinyl estradiol per pill had a significantly higher risk of breast cancer than those who never used OCs (OR = 3.6, 95% CI: 1.7–7.9) (Althuis et al. 2003). The increased risk associated with using a higher dose of estrogen was attenuated for women who were 35–44 years of age

(OR = 1.5, 95% CI: 0.8–2.8) (Althuis et al. 2003). When examining cumulative dose of estrogen rather than recently used dose of estrogen per pill, Dumeaux et al. (2003) found that women with ≥100 mg-months of estrogen exposure had an increased risk of breast cancer compared to never users (OR = 1.5, 95% CI: 1.1–2.0). Because of the dramatic decrease in estrogen dose in OCs since they were introduced, the relations observed in previous studies between recent OC use and risk of breast cancer may be attributed to the higher doses of estrogen used in past OCs, yet it is largely unknown the extent to which lower estrogen doses and more recent OC formulations are related to breast cancer risk.

Oral Contraceptive Use and Risk of Breast Cancer by Tumor Characteristics

There is strong evidence that use of combined estrogen and progestin menopausal hormone therapy is more strongly related to risks of lobular breast carcinomas and hormone receptor positive tumors than it is with risks of ductal carcinomas and hormone receptor-negative tumors (Benz et al. 2003, Chen et al. 2002, Daling et al. 2002, Li et al. 2000, 2003, 2008, Newcomer et al. 2003); therefore, it is plausible that risk of breast cancer related to OC use would also vary by histologic type and hormone receptor status. In general, the results from case–control studies examining the relationship between characteristics of OC use and different histologic types of breast cancer have been mixed and have included both pre- and postmenopausal women, and no clear picture of which breast cancer subtypes may be more strongly related to OC use has emerged (Claus et al. 2003, Gill et al. 2006, Li et al. 2003, Newcomer et al. 2003, Nichols et al. 2007). With respect to histology, one study found a statistically significant increased risk of invasive lobular carcinoma associated with recent use of OCs (OR = 2.6, 95% CI: 1.0–7.1), with an increasing risk with more recent use ($p = 0.02$), but no significant association with invasive ductal carcinoma (OR = 1.2, 95% CI: 0.8–1.9) (Newcomer et al. 2003). Another study found an increased risk of invasive lobular carcinoma associated with using OCs for at least 5 years that was not statistically significant (OR = 1.6, 95% CI: 1.0–2.6) (Li et al. 2003). Both of these studies included either primarily or exclusively postmenopausal women. Results from a recent study focusing on premenopausal women suggest that ever using OCs has a similar effect on risk of ductal and lobular cancer (invasive or in situ), while recent use of OCs is associated with an increased risk of ductal carcinoma (invasive or in situ), but not lobular carcinoma (Nyante et al. 2008). When restricting to invasive cases in this study, there was a slightly increased risk associated with ever using OCs and ductal carcinoma (OR = 1.3, 95% CI:

1.1–1.6), but no increased risk associated with lobular carcinoma (OR = 0.9, 95% CI: 0.5–1.6) (Nyante et al. 2008).

Few studies have focused exclusively on the effect of OCs on risk of in situ breast cancer (Claus et al. 2003, Gill et al. 2006, Nichols et al. 2007). Gill et al. (2006) found no excessive risk of breast carcinoma in situ (BCIS) associated with ever using OCs among women 35–64 years of age. However, when stratifying by histologic type of in situ carcinoma, another large case–control study found a statistically significant increased risk of ductal carcinoma in situ (DCIS) (OR = 1.2, 95% CI: 1.0–1.3), but not lobular carcinoma in situ (LCIS) (OR = 1.0, 95% CI: 0.8–1.4) among women 20–74 years of age (Nichols et al. 2007). In contrast, a study assessing the risk of DCIS associated with ever using OCs found no association among pre- or postmenopausal women (Claus et al. 2003). Further studies among premenopausal women are needed to clarify potential differences in the relationship between use of OCs and risk of invasive ductal cancer, invasive lobular cancer, DCIS, and LCIS.

In addition to histology, the relationship between OC use and risk of breast cancer according to ER and/or PR status has been examined. In general, the evidence relating to ER and PR suggests that ever using OCs is associated with an increased risk of either ER− or ER−/PR− breast cancer among premenopausal women (Althuis et al. 2003, Britton et al. 2002); however, there are studies that found either no differences in risk by ER/PR expression (Largent et al. 2005) or the suggestion of an increased risk of ER+/PR+ and not ER−/PR− breast cancer (Huang et al. 2000). In a review of breast cancer risk factors according to ER/PR status, Althuis et al. (2004) concluded that there is modest evidence supporting that use of OCs has a stronger association with ER− breast cancer than with ER+ breast cancer.

Injectable Contraceptives

Depo-medroxyprogesterone acetate (DMPA), also commonly known as Depo-Provera, was developed as an injectable contraceptive in the late 1950s and was first evaluated in clinical trials in 1963. It was subsequently approved for use throughout the world, and it is currently approved in more than 100 countries. DMPA is commonly used, particularly in developing countries, because it has low failure rates for both typical and perfect use (3 and 0.3%, respectively, compared to 8 and 0.3% for OC use), it is convenient to use, it is less user dependent than OCs, and it suppresses menstrual bleeding. The most common complication associated with its use is weight gain (an average of 5.4 lbs in the first year). DMPA is also associated with bone density loss because it decreases endogenous estrogen levels, but this effect appears to be reversible (Scholes et al. 2002).

With respect to its pharmacokinetics, serum concentrations of MPA are maintained at approximately 1.0 ng/mL for 3 months following a DMPA

injection. MPA levels then decline to 0.2 ng/mL in the fifth and sixth months and become undetectable 7.5–9 months after injection (Ortiz et al. 1977). Ovulation resumes once MPA levels fall below 0.1 ng/mL (Mishell 1996). So based on its pharmacokinetics, even a single dose of DMPA results in a relatively lengthy exposure time.

The literature on the relationship between DMPA use is limited as only four observational studies have assessed it (Table 5.3) (Lee et al. 1987, Paul et al. 1989, WHO 1991, Shapiro et al. 2000). Of the three studies assessing recency of DMPA use, all three found that current DMPA use is associated with a 60–70% increase in breast cancer risk (Paul et al. 1989, WHO 1991, Shapiro et al. 2000). However, only two of these studies found that ever use of DMPA was related to risk (Lee et al. 1987, WHO 1991), and only one observed that women who started using DMPA at a young age had an increased risk (Paul et al. 1989).

Newer Forms of Hormonal Contraceptives and Patterns of Use

Recent developments in combined hormonal contraceptives include the transdermal patch (Ortho Evra) containing the progestin norelgestromin and the vaginal ring (Nuva Ring) containing the progestin etonogestrel. Both were approved for marketing in the United States in 2001. New regimens for taking combined OCs, such as extended-cycle and continuous-use regimens have also been recently marketed in the United States. Extended-cycle pill regimens typically involve 84 pills containing both estrogen and progestin followed by 7 placebo or low-dose estrogen pills, while continuous-use combined OCs are taken without any hormone-free time periods. Additionally, newer progestins, such as drospirenone, have been added to OC formulations and there have been changes in the frequency of OC use according to type of progestin. These recent changes in mode of combined hormone delivery, pattern of use, and type of progestin used require follow-up studies because it is plausible that different types and doses of progestin could have different relationships with risk of breast cancer. Furthermore, because recent developments in types and patterns of hormonal contraceptive use are marketed to young women in the United States and because there is existing evidence of a small increased risk of breast cancer associated with recent use of OCs among premenopausal women (Althuis et al. 2003, Brinton et al. 1995, Newcomb et al. 1996, Collaborative Group on Hormonal Factors in Breast Cancer 1996), future studies are needed to assess the relationships of these newer forms of hormonal contraception with risk of breast cancer in young women. At present, there is insufficient or no available evidence to document these relationships yet, given how recently they have been introduced and their relatively limited use in most populations.

Table 5.3 Overview of studies evaluating the relationship between DMPA use and breast cancer risk

First author (year)	Country(ies)	Study type	No. of cases/ controls	Age range	Percentage of controls ever using DMPA (%)	Odds ratio (95% confidence interval)		
						Ever use	Ever use by age at diagnosis	Current use
Lee (1987)	Costa Rica	Population-based case–control	148/773	25–54	6.3	2.6 (1.4–4.7)*	N/A	N/A
Paul (1989)	New Zealand	Population-based case–control	891/1,864	25–54	13.5	1.0 (0.8–1.3)	25–34: 2.0 (1.0–3.8)* 35–44: 0.9 (0.7–1.4) 45–54: 1.0 (0.6–1.4)	1.6 (1.0–2.5)*, [a]
WHO (1991)	Kenya Mexico Thailand	Hospital-based case–control	869/11,890	<63	12.2	1.2 (1.0–1.5)*	≤34: 1.4 (0.9–2.2) 35–44: 1.1 (0.8–1.6) ≥45: 1.0 (0.7–1.5)	1.7 (1.1–2.5)*
Shapiro (2000)	South Africa	Hospital-based case–control	419/1,625	20–54	71.0	0.9 (0.7–1.2)	≤34: 1.1 (0.5–2.4) 35–44: 1.1 (0.7–1.6) 45–54: 0.8 (0.6–1.1)	1.6 (1.1–2.3)*

[a]Last used DMPA <5 years ago.
*$p<0.05$.

Summary

There is clear and consistent evidence that recent use of CHT, particularly for 5 years or longer, increases risk of breast cancer in postmenopausal women. This relationship appears to primarily be confined to increases in risk of hormone receptor-positive tumors and is more pronounced for lobular carcinomas. There is also consistent evidence that recent OC use, and perhaps current DMPA use, increases risk of breast cancer among premenopausal women, but their impact on overall breast cancer burden is substantially lower than that of CHT, given the comparatively much lower incidence rates of breast cancer among premenopausal women. Future studies evaluating the relationships between new forms of menopausal hormone therapy and hormonal contraception that are now on the market will continue to be important given the clear history that numerous forms of exogenous hormones are related to breast cancer risk.

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Chapter 6
Reproductive Factors

Mats Lambe

Introduction

A large body of experimental and epidemiological evidence points to a major influence of ovarian hormones on breast cancer risk. In particular, estrogens have been shown to induce and promote mammary tumors in rodents, though the exact role of progesterone remains unclear (Henderson et al. 1982, Bernstein and Ross 1993, Hankinson and Eliassen 2007). Steroid hormones affect the risk of breast cancer by stimulating cellular replication and mitotic activity in breast epithelium, processes which are believed to be crucial in the pathogenesis of mammary cancer. A high rate of cell division increases both the frequency and the likelihood of propagation of copying errors and DNA changes (Pike et al. 1983). The stimulative effect may be either direct or indirect, possibly exerted through different growth factors. Results from animal studies indicate that estrogen metabolites have genotoxic properties (Yager and Davidson 2006). One manifestation of the relationship between hormones and breast cancer is the numerous reproductive factors that are well established or suspected modulators of breast cancer risk.

Reproductive Factors

Age at Menarche and Menopause

Perhaps the most compelling evidence regarding the influence of endogenous hormones on breast cancer risk is found in the leveling off in the age-specific incidence curve of breast cancer after menopause when ovarian production of steroid hormones ceases. The ages at menarche and menopause, milestone events that determine the period over which women are exposed to endogenous

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_6,

ovarian hormones, have repeatedly been shown to be related to the risk of breast cancer (Shapiro et al. 1973, Tulinius et al. 1978, Kvåle and Heuch 1988, Hsieh et al. 1990). Estimates based on a pooled analysis of the results from 21 studies show that for each additional year, age at menarche is postponed; pre- and postmenopausal breast cancer risk decreases 9% and 4%, respectively (Clavel-Chapelon and Gerber 2002). Each additional year natural menopause is delayed increases risk by an estimated 2.8% (Collaborative Group on Hormonal Factors in Breast Cancer 1997). Thus, the risk of breast cancer in women with a natural menopause before the age of 45 years is up to half that of women who stop menstruating after the age of 55 years (Pike et al. 2004). There is also convincing evidence of an age-dependent protective effect of early surgical menopause (bilateral oophorectomy) (Lubin et al. 1982, Brinton et al. 1988, Irwin et al. 1988).

Childbearing

The risk of developing breast cancer varies widely between religious and social groups with different childbearing patterns. For example, Parsi women in India, who on average are wealthy, marry late, and have few children, have an age-adjusted incidence rate of breast cancer that is more than twice that of Hindu women living in the same geographical area who as a group are poorer, marry earlier, and have more children (Jussawalla et al. 1981). Similarly, in most Western countries, there is a social gradient in breast cancer risk with markedly higher incidence in women with high education compared to women with low education (Faggiano et al. 1997). While these patterns cannot exclude genetic and lifestyle influences, they likely reflect an influence of reproductive history where each pregnancy and the timing of birth serve as markers for cumulative exposure to ovarian hormones and possibly other, some yet-to-be-identified, risk-modifying factors associated with childbirth.

Parity

It has long been recognized that parity reduces the risk of breast cancer (Kelsey et al. 1993). In the 18th century, Ramazzini of Padua observed what appeared to be an epidemic of breast cancer among nuns (Ramazzini 1743). One hundred years later, it was noted that breast cancer was at least three times as frequent in nuns as in other women (Rigoni-Stern 1842). In a study published in 1926, Lane-Claypon reported an association between reproductive history and breast cancer risk (Lane-Claypon 1926), findings which were confirmed in the early 1930s (Wainright 1931), and later in British vital statistics' data which revealed a high breast cancer mortality in unmarried and childless women (Gilliam 1951). Similar risk-modifying effects of parity were found in a number of early investigations (Stocks 1957, Wynder et al. 1960). In these studies, however, the effect of number

of births was not adequately separated from the possible influence of other aspects of reproductive history, such as age at first birth.

There is also evidence from subsequent epidemiological studies indicating that the timing of pregnancy is relevant to breast cancer risk. For example, compared to single women, the risk of breast cancer is lower in older married women, but not in younger married women, with an approximate crossover of the effect around age 40 (Janerich and Hoff 1982, Pathak et al. 1986). Others reported a higher breast cancer risk among young parous compared to young nulliparous women (Woods et al. 1980, Layde et al. 1989) and an increased risk of breast cancer in the years following childbirth (Layde et al. 1989, Bruzzi et al. 1988, Williams et al. 1990).

More recent studies have clarified pregnancy's dual effect on breast cancer risk, documenting that it confers a short-term increase in risk followed by a long-term decrease (Hsieh et al. 1994, Lambe et al. 1994, Leon et al. 1995, Chie et al. 2000, Albrektsen et al. 2005, Liu et al. 2002). Results from these studies show that the crossover effect of parity can be explained in terms of a transient increase in breast cancer risk following birth. In some studies, the duration of the increased risk following childbirth was longer than that reported previously, lasting up to 15 years with a peak at around 5 years (Lambe et al. 1994, Liu et al. 2002). Taken together, these epidemiological findings corroborate predictions made in mathematical models based on the hypothesis of a central role of rate of breast tissue aging in breast cancer etiology (Pike et al. 1983, Rosner and Colditz 1996, Rosner et al. 1994). In their models of breast cancer incidence rates Rosner and Colditz (1996) incorporated an immediate, one-time increase in breast cancer risk at the time of childbirth. Also, these observations and mathematical models are compatible with experimental data showing that pregnancy induces both transient and permanent structural changes in the breast tissue of laboratory animals (Russo et al. 1990a, b, 1982). The short-term increase in risk that follows a first birth likely reflects a growth-enhancing effect of high estrogen levels during pregnancy on tumor cells whose malignant transformation has already begun (Henderson and Bernstein 1991), while the long-term protective effect likely results from pregnancy-induced differentiation of mammary gland stem cells that become resistant or less sensitive to carcinogenic stimuli. Some, but not all, studies have found a more pronounced short-term increase among women who were older at first pregnancy which could reflect the prolonged exposure of their undifferentiated breast parenchyma to carcinogenic stimuli (Lambe et al. 1994, Liu et al. 2002).

Age at First Birth

In a 1970 landmark study, MacMahon and colleagues concluded that the observed protective effect of parity at least in part can be attributed to an earlier age at first birth in women with many children (MacMahon et al. 1970). It is now estimated that for each additional year of age at first birth, the risk of

premenopausal breast cancer increases by 5%, and increases by 3% for breast cancers diagnosed after menopause (Clavel-Chapelon and Gerber 2002). Compared to nulliparous women, women with a first full-term pregnancy before age 20 years have about half the risk of breast cancer (Kelsey et al. 1993). Women with an older age at first birth ($\geq$35 years) have the same risk of breast cancer as nulliparous women.

The exact mechanism by which an early first birth protects against breast cancer remains incompletely understood, but has primarily been attributed to shortening of the time window of high susceptibility beginning at the start of the proliferation of breast cells at menarche and ending at the pregnancy-induced differentiation of breast cells. There is also some evidence that the interval between age at menarche and age at first birth may be relevant to breast cancer risk (Clavel-Chapelon 2002, Andrieu et al. 1998, Andrieu et al. 2000, Li et al. 2007), with a recent study reporting that the length of this interval was positively related to risk and particularly to risk of hormone receptor-positive tumors (Li et al. 2007).

Age at Subsequent Births and Birth Spacing

A woman's risk of breast cancer appears to be related not only to timing of first birth but also to age at subsequent births. In a reanalysis of MacMahon's data, older age at any birth was found to be an independent risk indicator (Trichopoulos et al. 1983). In an Italian case–control study, breast cancer risk increased 0.7% per year subsequent births were delayed (Decarli et al. 1996). Similarly, results from a large Danish cohort study indicated that early timing of any additional birth beyond the first induces an additional long-term protection. Per 5 years delay in maternal age at first, second, third, and fourth birth, the risk increase was 9%, 7%, 5%, and 14%, respectively (Wohlfahrt and Melbye 2001). Taken together, it appears that the effect of parity is determined by the age of occurrence of component pregnancies and that the closer the births are together, the lower the risk. A likely explanation is that pregnancies occurring close together in time provide less time for breast cells to accumulate DNA damage and that every new pregnancy affords additional protection by recruiting more of the remaining undifferentiated cells (Russo and Russo 1993).

Pregnancy Interruption: Induced and Spontaneous Abortions

The question whether an incomplete pregnancy affects future breast cancer risk has been under much debate. Based on findings from animal studies, it has been hypothesized that an increase in breast cancer risk may follow if the hormonal surge occurring during the first trimester is not followed by the protective components of breast tissue maturation and terminal differentiation of lobular

structures during the second and third trimester (Russo et al. 1982). Findings from early case–control studies indicated that induced abortions were associated with an increased risk of breast cancer (Michels and Willett 1996). However, other studies where data on abortions were collected prospectively have found no such associations (Harris et al. 1989, Tang et al. 2000, Goldacre et al. 2001, Erlandsson et al. 2003, Melbye et al. 1997).

Taken together, the collective evidence to date points to no association between pregnancy interruption and subsequent breast cancer risk. In 2003, a National Cancer Institute expert panel concluded that neither spontaneous nor induced abortions are associated with an increased risk of breast cancer (http://www.cancer.gov/cancerinfo/ere-workshop-report), a conclusion supported by more recent findings from a large cohort study that was able to adjust for established breast cancer risk factors (Michels et al. 2007).

Breast-Feeding

Already in the 1920s, it was observed that the children of women with breast cancer were less likely to have been breast-fed for 1 year than the children of control women (Lane-Claypon 1926). Attempts to assess this postulated association have been hampered by the somewhat low prevalence of long-term breast-feeding in Western women. However, results from a study combining epidemiological data on more than 50,000 women from 47 studies conducted in 30 countries confirm that breast-feeding lowers breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer 2002). In this large study, including more than 80% of the studies worldwide to date on lactation and breast cancer, the relative risk of breast cancer was reduced 4.3% for each year that a woman breast-feeds. The magnitude of the decline was consistent across age at breast cancer diagnosis, race/ethnicity, different reproductive patterns, and various personal characteristics. The authors concluded that the limited time women in developed countries breast-feed is likely to be one of the reasons for their higher incidence rates of breast cancer.

A protective effect of lactation may be mediated by several mechanisms (Kelsey et al. 1993). Breast-feeding may result in further terminal differentiation of the breast epithelium, making it more resistant to carcinogenic change. Also, breast-feeding may reduce risk since it can prolong anovulation and delay the reestablishment of the menstrual cycle and ovarian hormone production.

Reproductive Factors and Risk of Different Subtypes of Breast Cancer

Epidemiological evidence indicates that invasive lobular carcinomas of the breast (ILC) may be more hormonally responsive than the most common histological subtype of breast cancer, invasive ductal carcinomas (IDC) (Li

et al. 2000, Chen et al. 2002, Newcomb et al. 2002, Daling et al. 2002, Newcomer et al. 2003, Li et al. 2003). To date, however, few studies have evaluated possible associations between reproductive factors and different subtypes of breast cancer. In a Danish cohort study a reduction in risk by each additional birth was seen for most histological types, but not for tumors of lobular origin. On the other hand, lobular carcinomas appeared to be more strongly associated with a late first birth compared to other histological subtypes (Wohlfahrt et al. 1999).

In a case–control study restricted to older women, no difference was found in the influence of age at first birth or number of children on the risk of developing invasive lobular carcinoma or invasive ductal carcinomas. However, lifetime duration of ovarian function was more strongly associated with increased risks of ductal carcinomas compared to lobular carcinomas (Li et al. 2003). In a Canadian study, no significant differences were observed in risk-factor profiles for ER+/PR+ and ER−/PR− breast cancers (Cotterchio et al. 2003). Results from a large US-based multicenter case–control study found no difference in the protective influence of reproductive factors between tumors of ductal or lobular origin (Ursin et al. 2005). In the same study, lactation was associated with a reduction in the risk for both ER+/PR+ and ER−/PR− tumors, while multiparity and early age at first birth were associated with a reduced risk for ER+/PR+ tumors only. Thus, there is little consistent evidence to suggest that reproductive factors differ in their associations with different types of breast cancer defined either by hormone receptor status or histology.

Postulated Biological Mechanisms Underlying the Observed Relationships Between Reproductive Factors and Breast Cancer Risk

While associations between reproductive history and subsequent risk of breast cancer are one of the most thoroughly investigated areas in cancer epidemiology, surprisingly little is known about the underlying biological mechanisms by which parity and age at first birth influence the risk of breast cancer. Childbearing may modify the subsequent risk by having lasting effects on levels of endogenous hormones. Following exposure to very high levels of hormones during pregnancy, long-term changes in non-pregnancy levels occur, including a reduction of bioavailable estrogens (Bernstein et al. 1985, Musey et al. 1987). It is also possible that protection is afforded by a permanent decrease in the production of the anterior pituitary hormone prolactin after a first full-term pregnancy (Musey et al. 1987). Results from animal and in vitro models indicate that prolactin plays a role in carcinogenesis (Clevenger et al. 2003). Taken together, available epidemiologic evidence suggests that high prolactin levels are associated with an increased breast cancer risk (Tworoger and Hankinson 2008). A reduced risk of breast cancer in mothers of twins has been attributed to

the anti-estrogenic properties of alpha-fetoprotein, which is present at increased concentrations in twin pregnancies (Wald et al. 1991).

Childbearing, especially a first pregnancy, causes a permanent modification of the structural characteristics of the breast. Epithelial cells reach full differentiation, a process which makes them more resistant to neoplastic transformation (Russo et al. 1982, Murphy et al. 1998). Results from animal experiments indicate that a term pregnancy induces a permanent differentiation of terminal end buds and a substantial reduction in breast cancer induced by 7,12-dimethylbenzanthracene (DMBA) (Russo et al. 1991). The risk of malignant change may also be reduced through a slowing down in the subsequent rate of cell proliferation and possibly also a decrease in the carcinogen-binding capacity (Russo and Russo 1994). The process of differentiation is probably not uniform (Russo et al. 1990) and it has been hypothesized that every new pregnancy "recruits" more of the remaining undifferentiated cells, explaining why each pregnancy, particularly those at an early age, imparts additional protection. A more speculative hypothesis is that each pregnancy causes a reduction in the number of estrogen receptor-positive cells, thereby reducing the sensitivity of the breast to the influence of estrogens (Kvåle 1992).

With regard to the transiently increased risk following birth, it has been suggested that lasting immune alterations may also play a role. In addition to the mechanisms discussed earlier, pregnancy-associated immunosuppression and increased inflammatory responses may increase the risk of breast cancer, effects that may be particularly pronounced in women with a late age at first birth (Shakhar et al. 2007). Proinflammatory processes in the tissue microenvironment take place during mammary gland involution, events that have been proposed to contribute to the initiation and progression of breast cancer (Schedin 2006).

Pregnancy Characteristics and Breast Cancer Risk

Several characteristics of pregnancy may be associated with altered exposure to gestational hormones and may influence breast cancer risk. Parameters or conditions of interest include birth weight, placental weight, preterm birth, gender of offspring, multiple births, and preeclampsia and/or pregnancy-related hypertension. Compared to the multitude of studies addressing the associations between reproductive history, in general, and breast cancer risk, there are few studies that have assessed these exposures with often little consistency across them.

Birth Weight

One large Danish study found evidence of an increased risk of breast cancer among women with children weighing over 3,750 g at birth (Wohlfahrt and Melbye 1999), while other studies have found no association (Mogren et al. 2001, Smith et al. 2000) or a tendency toward a reduced risk among women with

heavy firstborn children (Innes and Byers 2004). Interpretation of results regarding the influence of infant birth weight on breast cancer risk is difficult since high birth weight is associated with obesity, which is itself a breast cancer risk factor.

Placental Weight

Since pregnancy hormones are primarily produced in the placenta, indicators of placental size or function may serve as indirect markers of hormone exposure during pregnancy. One study found evidence of a lower breast cancer risk in women with low placental weight, small placental diameter, and maternal floor infarction of the placenta (Cohn et al. 2001). Swedish investigators have reported a positive association between placental weight and premenopausal breast cancer risk (Cnattingius et al. 2005); compared with women who had low placental weight in successive pregnancies, the risk of breast cancer was twice as high among mothers whose placentas weighed 700 g or more in both pregnancies. In the same study, high birth weight was associated with an increase in risk of breast cancer before, but not after, adjusting for placental weight and other covariates. Based on these findings, placental weight may represent a better indicator of the internal hormonal milieu during pregnancy than birth weight and possibly also other birth parameters.

Preterm Birth

Only a handful of studies have assessed the possible influence of prematurity (Innes and Byers 2004, Troisi et al. 1998, Melbye et al. 1999, Hsieh et al. 1999, Polednak and Janerich 1983). Of these five studies, only two found evidence of an increased breast cancer risk among women who had delivered before 32 weeks gestation (Innes and Byers 2004, Melbye et al. 1999). Proposed mechanisms behind an increased risk include increased susceptibility to neoplasia due to exposure to high levels of estrogens during first and second trimester that is not followed by terminal differentiation of breast cells in the third trimester. However, given the lack of consistent data the relationship between preterm birth and breast cancer risk remains unclear.

Preeclampsia and/or Pregnancy-Related Hypertension

With varying design, sample size, and focus, several epidemiological studies have examined the association between preeclampsia and/or hypertension and risk of breast cancer (Cohn et al. 2001, Troisi et al. 1998, Polednak and Janerich 1983, Thompson et al. 1989, Vatten et al. 2002, Vatten et al. 2007, Terry et al.

2007). Taken together, the results of these studies indicate that maternal risk of breast cancer is reduced following preeclampsia. Postulated mechanisms include altered hormonal profiles, such as lower level of estrogens and insulin-like growth factor and higher levels of androgens and alpha-fetoprotein. In one of these studies, the lowered risk was restricted to women giving birth to a son in the preeclamptic pregnancy (Vatten et al. 2007). Terry et al. (2007) reported stronger risk reductions in women with multiple occurrences of preeclampsia and that the overall association between preeclampsia and breast cancer was more pronounced for postmenopausal breast cancer.

Gender of Offspring

The possible role of gender of children on subsequent breast cancer risk in the mother has received little attention. In one study, no overall association was found between offspring gender and maternal breast cancer risk (Albrektsen et al. 1995). In another study, number of boys was inversely associated and number of girls was positively associated with breast cancer risk: women who gave birth to two or more boys but no girls were at a significantly lower risk of breast cancer in comparison with women who gave birth to two or more girls, but no boys (Hsieh et al. 1999). However, in this study the apparent protective effect of male pregnancies was limited to women younger than 40 years. A risk-modifying effect of offspring gender may result from physiological changes specifically associated with a male rather than a female fetus. Again though, the literature on this topic is too sparse to draw any firm conclusions.

Multiple Births

With contradictory results, several studies have examined the possible associations between twinning and risk of maternal breast cancer. In two studies no association was found (Nasca et al. 1992, Dietz et al. 1995, Neale et al. 2004), two studies reported weak indications of an increased breast cancer risk in mothers of twins compared to singleton mothers (Wyshak et al. 1983, Hsieh et al. 1993), and five studies have found some evidence that mothers of twins have a lower risk of breast cancer (Albrektsen et al. 1995, Jacobson et al. 1989, Lambe et al. 1996, Murphy et al. 1997, Neale et al. 2005).

Multiple births have several features that might influence subsequent maternal breast cancer risk. Compared to singleton mothers, pituitary activity is increased in mothers of twins (Milham 1964, Short 1984, Thomas et al. 1998). A twin pregnancy entails higher levels of several placental hormones, probably as a result of a higher total placental mass (Thomas et al. 1998, Wald et al. 1991). While our understanding of the long-standing hormonal profiles of mother of twins is limited, one study reported higher concentrations of steroid

hormone globulins in women with a history of twinning, compared to singleton mothers, a difference that was of the same magnitude as that between nulliparous and parous women (Murphy et al. 1990). Also, some of the known or suspected long-standing characteristics of women with proneness to twin births may affect breast cancer risk. These include a larger body size (Doherty 1988), a better nutritional status (Hollenbach and Hickok 1990), a higher social status (Morton et al. 1953), an earlier menarche, a larger cumulative number of menstrual cycles during fertile life (Wyshak 1981), and older age when giving birth (Hollenbach and Hickok 1990). However, a prospective cohort study examining social, biological, and reproductive characteristics found no evidence that mothers of twins differed markedly from other parous women with regard to height, family history of breast cancer, use of hormone replacement therapy or other hormones, age at menarche, length of menstrual cycles, or age at child birth (Murphy et al. 1998). Overall, the evidence regarding the relationship between twin pregnancies and breast cancer risk remains inconclusive.

Implications for Prevention

Reproductive patterns are not readily amenable to change; it is unlikely that a majority of women would actively choose to have their first child at an earlier age or prolong breast-feeding for the sake of reducing future health risks. In many Western countries there is a dramatic trend toward delayed childbearing. In the United States, the number of first births per 1,000 women 35–39 years of age increased by 36% between 1991 and 2001, and the rate among women 40–44 years increased 70% (Heffner 2004). The mean age at first birth among Swedish women increased from 24 years in 1970 to 28.7 years in 2006 (www.scb.se. [cited 2006]). One reproductive factor that is somewhat more modifiable is breast-feeding. Among the numerous advantages of breast-feeding to both infants and mothers, the reduced risk of breast cancer it confers to mothers can certainly be tallied as a benefit.

Since the breast tissue undergoes rapid changes and is believed to be at peak vulnerability to mutagenesis between menarche and first birth (Russo and Russo 1994, Colditz and Frazier 1995), this period represents a window of opportunity for primary prevention. This may include efforts to delay exposure to suspected mutagens during adolescence and the early introduction of possible protective lifestyle components (Colditz and Frazier 1995); theoretically, age at menarche could be delayed by encouraging or removing obstacles for physical activity in young girls. Another proposed strategy is to artificially manipulate the secretion of hormones that underlie or affect the involved risk predictors (Harris et al. 1992). Results from animal studies indicate that the placental hormone human chorionic gonadotropin (hCG) may inhibit both the initiation and the progression of breast cancer (Russo et al. 1990). Theoretically, this could include the administration of hCG to young nulliparous

women in order to mimic a first pregnancy and achieve differentiation of breast cells (Russo and Russo 1994). One observational study has found evidence of a reduced breast cancer risk in young women treated with hCG as a part of weight loss regimen (Bernstein et al. 1995). Furthermore, gonadotropin hormone agonists given at a very low dose of estrogens may decrease the risk of breast cancer by reducing the circulating levels of endogenous estrogens. However, such chemopreventive strategies have not been evaluated in a clinical trial and so the risk/benefit ratio of such treatments is unknown.

Also of recent interest is the proposed risk-modifying role of alpha-fetoprotein (AFP), a small glycoprotein produced by the fetal liver and the yolk sac (Jacobson et al. 1989), levels of which are elevated during multiple births and preeclampsia. Laboratory findings show that AFP has important anti-estrogenic properties with an ability to inhibit growth of estrogen-dependent human breast cancer cells in animal models (Jacobson et al. 1990, Bennett et al. 1998, Bennett et al. 2002). Epidemiological evidence of a biologically important role of AFP comes from the finding from a large Danish case–control study that found a markedly lower risk of breast cancer among women with high compared to low AFP concentrations during pregnancy (Melbye et al. 2000). Recombinant AFP is available today (Bennett et al. 1997), and recent evidence indicates that chronic oral administration of AFPep – AFP-derived peptides – appears to be safe and effective for the treatment or prevention of breast cancer in animal models (Bennett et al. 2006). However, the potential applicability and suitability of such an approach in humans has not been evaluated.

Summary

Reproductive factors are among the first and most consistently observed risk factors for breast cancer. While we have some understanding of the biological mechanisms underlying these relationships, additional research is needed to further elucidate the pathways through which an early first birth, breast-feeding, and multiparity protect against breast cancer. Another area of interest is to improve our understanding of how reproductive factors may differentially influence risk of various clinical, pathological, and molecular subtypes of breast cancer. Taken together, improved knowledge in these areas could point to new directions for breast cancer prevention research.

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Chapter 7
Physical Activity and Anthropometric Factors

Katherine D. Henderson, Jennifer Prescott, and Leslie Bernstein

Introduction

Physical activity and certain anthropometric factors have been proposed as independent risk factors for breast cancer. Increased physical activity appears to be associated with decreased breast cancer risk, and this association is independent of the influence of anthropometric factors on risk. Conversely, anthropometric factors such as body mass index (BMI), weight change, and height appear to have effects on breast cancer risk that are independent of physical activity. The International Agency for Research on Cancer (IARC) published a systematic review of the available epidemiologic literature on physical activity and weight control and concluded that sufficient evidence exists that physical activity lowers breast cancer risk and that among postmenopausal women, weight gain increases risk (IARC 2002). These findings have been confirmed in another recently published monograph (WCRF/AICR 2007). In this chapter, we first review some of the epidemiological literature linking physical activity to breast cancer risk. We then consider the literature surrounding the relationship between anthropometric factors and breast cancer risk. Finally, we discuss possible mechanistic pathways which may mediate these relationships.

Physical Activity

As summarized in an IARC review, most observational studies have shown that increased levels of physical activity are associated with lower breast cancer risk (IARC 2002). Women in the highest categories of physical activity have a 20–40% reduced risk when compared to women in the lowest activity group.

Bernstein et al. published results of a landmark case–control study of young women (545 case/control pairs) in 1994 designed specifically to determine

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_7,

whether women who regularly participated in physical exercise during their reproductive years had a reduced risk of breast cancer. The investigators collected lifetime histories of regular exercise activities from participants and created an average activity measure (hours/week/year) over the years from menarche to a reference date that, for the incident breast cancer patients, was 1 year prior to diagnosis with a comparable date used for the control participants. Women who averaged at least 3.8 hours of activity per week had a substantially lower risk of breast cancer than women who were relatively inactive (those who never exercised as much as 2 hours per week in any year of their lives). The risk reduction was 58% [odds ratio (OR) = 0.42, 95% confidence interval (CI) 0.3–0.6] and risk declined across categories of activity (p-trend 0.0001) (Bernstein et al. 1994). A study of similar design conducted by these investigators among postmenopausal women found comparable reductions in risk for women who maintained their physical activity for most of their lives (Carpenter et al. 1999).

Results from the Women's Contraceptive and Reproductive Experiences (CARE) Study, a multicenter population-based case–control study of invasive breast cancer among 3,251 black women (1,605 case patients and 1,646 control participants) and 5,966 white women (2,933 case patients and 3,033 control participants) aged 35–64 years, affirmed the dose–response effect between increasing level of average annual lifetime exercise activity and decreasing breast cancer risk (Bernstein et al. 2005). Risk was approximately 20% lower among women who averaged at least 2 hours of strenuous or 3 hours of moderate activity per week. With the exception of a first-degree family history (mother or sister with breast cancer), no other factors modified the observed association. The statistically significant trend between increasing physical activity and decreasing breast cancer risk was apparent only among women with no first-degree family history of breast cancer. Among women with a family history, the results for all categories of activity except the highest were similar to those for women with no family history. In the highest activity category, no reduction in risk was observed. Although the results for black and white women did not differ in a statistically significant manner in the Women's CARE Study, the breast cancer risk reduction conferred by physical activity appeared to be marginally stronger among black women than among white women.

Several case–control studies have documented reductions in risk of breast cancer associated with physical activity in other population subgroups. In a study of Asian-American women, breast cancer risk decreased progressively (p-trend <0.0001) with increasing level of lifetime physical activity. Women who averaged at least 1 hour per week of strenuous activity (or 1.5 hours per week of moderate-level activities) had a 40–50% lower breast cancer risk than relatively inactive women (Yang et al. 2003). Three studies have shown that physical activity (a combination of recreational, occupational, and household) lowers risk of breast cancer among Latina women in the western United States (Gilliland et al. 2001, John et al. 2003, Slattery et al. 2007). Studies conducted

elsewhere in the world have reported an inverse relationship between physical activity and breast cancer risk (Patel and Bernstein 2006).

Results from some, but not all, prospective cohort studies, such as the California Teachers Study (CTS) cohort, have supported evidence for a protective effect of physical activity on breast cancer risk (IARC 2002). One of the issues for cohort studies of physical activity is that most provide information on a woman's activity at only one or two time points during her adult years. Although it is difficult to capture long-term physical activity in cohort studies, this was done in the CTS, a cohort of more than 133,000 women who were current or recent public school professionals in California (Bernstein et al. 2002). In this study, information on strenuous activities and moderate activities was collected from high school onward through age 54 years or, if younger than 54 years when data were collected, up to a woman's current age at that time. CTS results indicate that long-term strenuous activity is associated with decreased risks of both invasive and in situ breast cancer (Dallal et al. 2007). Women who averaged more than 5 hours of strenuous activity per week had a 20% lower risk of invasive disease when compared to women who averaged less than 30 minutes per week (relative risk [RR] = 0.80, 95% CI: 0.7–0.9, p-trend 0.02). For in situ breast cancer, the risk reduction for more than 5 hours per week of strenuous activity was 31% (RR = 0.69, 95% CI: 0.5–0.9, p-trend 0.04). The risk reductions for both invasive and in situ disease appeared stronger for strenuous than for moderate levels of physical activity. Although numbers were small in a stratified analysis, effect modification by estrogen receptor status was evident in this study; the protective effect of increasing long-term strenuous activity on invasive breast cancer was evident only among estrogen receptor-negative disease.

Physical activity was also assessed in the Women's Health Initiative observational study, a prospective cohort of 74,171 women aged 50–79 years who were recruited between 1993 and 1998 (McTiernan et al. 2003). Women reported whether they were regularly physically active at a strenuous or moderate activity level at age 18 years, at age 35 years, and at age 50 years. With an average follow-up of 4.7 years, 1,780 women were diagnosed with incident invasive or in situ breast cancer. Those who engaged in regular strenuous activity at age 35 years had a 14% lower risk of breast cancer compared to women who were inactive at that age. Risk was also lower among those who engaged in at least 1–1.5 hours of moderate-level activity per week at the time they were enrolled in the cohort.

Not all studies find that recreational physical activity impacts risk. In the European Prospective Investigation into Cancer and Nutrition (EPIC) (Lahmann et al. 2007), increased physical activity in the form of household activity (highest vs. lowest quartile) was associated with a reduction in breast cancer risk among postmenopausal and premenopausal women, but neither leisure time activity nor occupational activity was significantly associated with risk.

A meta-analysis of 19 cohort and 29 case–control studies published prior to the EPIC and CTS studies has provided strong evidence for an inverse association between physical activity and postmenopausal breast cancer risk (Monninkhof et al. 2007). For premenopausal breast cancer risk the evidence is weaker, but most studies have limited numbers of younger women participating. Evidence for a dose–response relationship, on the order of a 6% decrease in risk for each additional hour of physical activity per week, is observed among those studies considered to be of "higher quality" (top 50%).

In summary, the average annual level of physical activity over a woman's lifetime appears to be an important determinant of breast cancer risk. This association also appears to be consistent across subgroups of the population. Whether physical activity is preferentially protective for estrogen receptor-negative invasive breast cancer, as was recently shown in the CTS (Dallal et al. 2007), requires further study. Factors such as family history of breast cancer, parity, use of menopausal hormone therapy, and obesity have been implicated as potential effect modifiers of the association between physical activity and breast cancer risk in some, but not all, studies (Patel and Bernstein).

A number of issues need to be considered in reviewing the literature on physical activity and breast cancer risk. One of the most important is variability in questionnaire design. Questions regarding physical activity range from general to very detailed reconstructed histories based on calendars recording important events throughout the woman's life, and assess type, duration, frequency, and intensity of physical activity. Many studies only obtain recent activity or activity at a particular age (e.g., ages 18, 35, 50 years). Many questions about the relationship between physical activity and breast cancer risk remain to be answered. No prescription exists to tell women what type of activity, intensity of energy expenditure, and duration of participation is needed to lower their breast cancer risk. Further, it is not known whether participating in activity at certain ages (e.g., during a woman's reproductive years) is sufficient to provide protection against breast cancer. Yet, although many details remain to be explained, there is sufficient evidence to conclude that a physically active lifestyle that persists over a woman's lifetime lowers her breast cancer risk, relative to an inactive woman.

Anthropometric Factors and Breast Cancer Risk

The physiological manifestation of energy balance in humans can be measured by indices of nutritional status or body fatness such as BMI, weight change, waist–hip ratio (WHR), and height. BMI is measured as weight in kilograms (kg) divided by the square of height in meters (m^2). Although an imperfect measure, BMI is highly correlated with percentage of body fat (Deurenberg et al. 1991). The World Health Organization has defined the following cut-points for BMI (WHO 1995): BMI less than 18.50 is considered underweight;

BMI between 18.50 and 24.99 is described as normal or healthy; BMI between 25.00 and 29.99 is grade 1 overweight or overweight; BMI between 30.00 and 39.99 is grade 2 overweight or obese; BMI greater than or equal to 40.00 is grade 3 overweight or morbidly obese. Weight change differs from other measures of body size in that it reflects a change in energy balance over a specified time period rather than providing a measure that applies to a single time point. WHR is an index of intra-abdominal fat, one of the two general categories of fat distribution which occur in humans, the other being subcutaneous fat; subcutaneous fat and intra-abdominal fat are each characterized by a specific metabolic profile. Attained height has been proposed as a measure of early life nutrition, regulated by growth hormone, and is firmly established as a breast cancer risk factor (WCRF/AICR 2007).

Body Mass Index

The relationship between BMI and breast cancer risk has been extensively studied. Evidence for an association between BMI and breast cancer risk differs by menopausal status in that high BMI may be associated with a lower risk of premenopausal breast cancer, but is strongly associated with a higher risk of postmenopausal breast cancer (WCRF/AICR 2007). In an IARC review on this topic, it was concluded that high-quality case–control studies and cohort studies reflected a 30–40% reduction in premenopausal breast cancer risk with high BMI, but that no association was observed below a BMI of 28 kg/m^2 (IARC 2002). A more current meta-analysis, limited to cohort studies providing adequate dose–response data, shows an approximate 15% decreased risk of premenopausal breast cancer per 5 kg/m^2 increase in BMI (WCRF/AICR 2007); the decrease observed in case–control studies is somewhat less than that observed for cohort studies. Data from the Nurses' Health Study II, which recruited women of ages 25–42 years in 1989 and followed them through 2003, indicate a strong inverse association between BMI at age 18 years and premenopausal breast cancer; risk was 39% lower among women with a BMI greater than or equal to 27.5 kg/m^2 than among lean women (BMI of 20.0–22.4 kg/m^2) (Michels et al. 2006). In this study, current BMI was also associated with breast cancer risk among premenopausal women; however, this effect was explained by women's BMI at age 18 years. This suggests that higher body mass during adolescence accounts for at least some of the reduction in premenopausal breast cancer risk among women with high current BMI. Generally the reduction in risk of premenopausal breast cancer with increasing BMI has been attributed to the association between amenorrhea and high BMI (Key and Pike 1988); however, history of infertility, polycystic ovary disease, and menstrual irregularities were considered in the analysis of the Nurses' Health Study and had little impact on the results. Thus, other mechanisms may account for the protective effect of high BMI in premenopausal breast cancer.

High BMI has been clearly associated with risk for breast cancer diagnosed during the postmenopausal period. A meta-analysis of prospective studies examining the relationship between BMI and postmenopausal breast cancer risk found a 12% increase in risk per 5 kg/m^2 increase in BMI (Renehan et al. 2008). Case–control studies have shown similar reductions (WCRF/AICR 2007). Of the factors considered as possible effect modifiers of the association between BMI and postmenopausal breast cancer risk, menopausal hormone therapy has the clearest impact. Investigators with the EPIC study have reported that among non-hormone therapy users, those in the highest BMI category have 31% greater risk for postmenopausal breast cancer than those in the lowest BMI category (Lahmann et al. 2004). Among menopausal hormone therapy users in this study, BMI was not significantly associated with breast cancer risk. Hormone users already will have high exposures to estrogen and, likely, a progestin, which will override any impact of high BMI on breast cancer risk. Further, evidence has suggested that higher current BMI may be associated with increased risk for estrogen receptor and progesterone receptor-positive tumors (Enger et al. 2000, Ahn et al. 2007); this differential effect on receptor status was notably observed among non-current menopausal hormone therapy users (Ahn et al. 2007). A large population-based case–control study has also provided evidence that the association between BMI and postmenopausal breast cancer risk is modified by first-degree family history of breast cancer (Carpenter et al. 2003). In this study, among postmenopausal women with at least one first-degree relative with breast cancer, those whose current BMI was 27.1 kg/m^2 or greater had breast cancer risk that was 2.9 times greater than that of women whose current BMI was less than 21.7 kg/m^2 (95% CI: 1.9–4.5, p-trend <0.0001). A modest non-significant 20% increase in risk was observed for women in these same BMI categories who had no family history of breast cancer (p-trend 0.08) (Carpenter et al. 2003).

Weight Change

Weight change reflects a positive energy balance over time. Most studies investigating the association between weight change and breast cancer risk have measured adult weight gain, meaning weight gain from early adulthood (often weight at age 18 years) to current weight; this measure, however, may ignore weight loss or reveal an overall loss of weight loss. Further, the majority have focused on postmenopausal women. A recent meta-analysis reported a 5% increase in postmenopausal breast cancer risk per 5 kg of weight gained over the adult period (WCRF/AICR 2007). In the Nurses' Health Study I, adult weight gain of 25 kg or more since age 18 years conferred a 45% increased risk of breast cancer after menopause (95% CI: 1.3–1.7, p-trend <0.001) relative to stable weight (weight gain or loss of less than 2 kg) (Eliassen et al. 2006). Furthermore, women who gained at least 10 kg after menopause had a significantly elevated

risk of breast cancer (RR = 1.18, 95% CI: 1.0–1.4, p-trend 0.002) compared to women with stable weight during that time period. Within the Nurses' Health Study, weight loss appeared to be modestly protective (p-trend 0.02) (Eliassen et al. 2006).

Menopausal hormone therapy use is an important effect modifier of the weight gain association. Among Nurses' Health Study I participants who had used menopausal hormone therapy after menopause, weight change had little impact on their risk (Eliassen et al. 2006). Among those who gained at least 25 kg during their adult years, risk was only 20% higher (95% CI: 1.0–1.4) than among women with stable weight. In contrast, among women who never used menopausal hormone therapy, risk for those who gained 25 kg was nearly two-fold greater than that for women with stable weight. Similar results were observed in the American Cancer Society (ACS) Cancer Prevention Study-2 (CPS-2) (Feigelson et al. 2004). Furthermore, among women who were not current users of menopausal hormone therapy at baseline, BMI did not predict risk of breast cancer among postmenopausal women when weight gain was included in the model (Feigelson et al. 2004).

Several studies have evaluated the effect of weight gain in postmenopausal women by estrogen receptor and progesterone receptor status (Enger et al. 2000, Feigelson et al. 2004, Rosenberg et al. 2006, Han et al. 2006). Results from a case–control study in which percent weight gain rather than absolute weight gain was assessed showed that risk associated with high weight gain during the adult years did not differ substantially between women with receptor-positive and receptor-negative tumors (Enger et al. 2000). Case–control studies that have looked at absolute weight gain have shown that increases in risk with increasing weight gain are restricted to hormone receptor-positive tumors (Rosenberg et al. 2006, Han et al. 2006). Results from the ACS CPS-2 cohort study have not completely confirmed these findings (Feigelson et al. 2006). Among postmenopausal women who were not taking menopausal hormone therapy, weight gain was associated with increased risk of estrogen receptor-positive/progesterone receptor-positive breast cancer in a marked dose-dependent manner (p-trend <0.0001), whereas the trend in risk was not as strong for estrogen receptor-negative/progesterone receptor-negative breast cancer (p-trend 0.09). In the most extreme weight gain group (>60 pounds), the risks relative to women who gained between 5 and 20 pounds since age 18 years were 2.42 (95% CI: 1.8–3.2) for estrogen and progesterone receptor-positive and 1.78 (95% CI: 1.0–3.2) for estrogen and progesterone receptor-negative breast cancer.

Waist–Hip Ratio

Results of studies looking at the association between 'waist–hip ratio' (WHR), a measure of central adiposity, and breast cancer risk have been mixed; those

studies focusing on postmenopausal women who have not used menopausal hormone therapy are the most consistent, showing an increase in risk with increasing WHR. In the Iowa Women's Health Study cohort, in which both current BMI and weight change from age 18 to baseline were positively associated with breast cancer risk, particularly for women 65 years or older, the relative risks for the association between highest quartile of WHR and breast cancer were 1.38 (95% CI: 1.1–1.8), 1.34 (95% CI: 1.2–1.6), and 1.49 (95% CI: 1.2–1.9) for women who were 55–64, 65–74, and 75–84 years of age, respectively (Sweeney et al. 2004). Ahn et al. showed in their cohort, the National Institutes of Health-American Association for Retired Persons Diet and Health Study, that high WHR was significantly associated with increased breast cancer risk among women who were non-users of menopausal hormone therapy, but not among current hormone therapy users (Ahn et al. 2007). Non-users of menopausal hormone therapy with a WHR greater than 0.94 were at nearly 90% greater risk for breast cancer than were women with a WHR of less than 0.70 (RR = 1.88, 95% CI: 1.1–3.2; p-trend <0.001). In contrast, current users of menopausal hormone therapy with a WHR greater than 0.94 were at no greater risk of breast cancer than the reference group (RR = 1.00, 95% CI: 0.7–1.5; p-trend 0.18). A recent meta-analysis of cohort data reported a 19% increase in breast cancer risk per 0.1 unit increase in WHR and labels abdominal fatness, whether measured by WHR or simply waist circumference, as a probable cause of postmenopausal breast cancer (WCRF/AICR 2007).

Height

Two meta-analyses of prospective cohort studies addressing the association between attained adult height and breast cancer risk have reported summary increases in risk per 5 cm increase in attained height of 9% and 11% for premenopausal breast cancer and postmenopausal breast cancer, respectively (WCRF/AICR 2007). Results from the Nurses' Health Study II are consistent with these findings; women with an attained height of at least 175 cm had a 57% increased risk of premenopausal breast cancer compared to women with an attained height of 160 cm or less; further, each 5 cm of additional height corresponded to an 11% higher risk (Baer et al. 2006). Assessments of whether factors like race/ethnicity (Palmer et al. 2001, Okobia et al. 2006), breast cancer family history (Carpenter et al. 2003, Cerhan et al. 2004), tumor histology (Li et al. 2006), hormone receptor status (Rosenberg et al. 2006, Colditz et al. 2004, Iwasaki et al. 2007), or history of menopausal hormone therapy use (Lahmann et al. 2004) modify these associations with height have been inconclusive.

The age when maximum height is achieved may also be associated with breast cancer risk. In a cohort study, women who achieved their maximum height at age 12 or younger had 40% greater risk (95% CI: 1.0–1.8) than women

who achieved their maximum height at age 17 or older (p-trend 0.04); of interest, this association was limited to estrogen receptor-negative breast cancer and to those cancers diagnosed at an advanced stage (Li et al. 2007). Growth rates during childhood as well as birth weight are also associated with breast cancer risk. These effects are complex; for example, Ahlgren et al. have modeled growth curves in a large cohort of Danish women for whom annual school health records of height and weight were available and showed that high birth weight, height at age 8 years, being tall at age 14 years, having a low BMI at age 14 years, having early peak growth, and rate of growth between the ages of 8 and 14 years were all associated with subsequent breast cancer risk (Ahlgren et al. 2006).

Biological Mechanisms

The relationship between physical activity, anthropometric factors, and breast cancer risk may be mediated by several pathways including the steroid hormone, insulin, and insulin-like growth factor pathways. Evidence regarding steroid hormones is particularly convincing. Examination of the age–incidence curves for breast cancer, where rates increase rapidly during a woman's reproductive years, but level off after menopause, implicate the ovarian hormones estradiol and progesterone in breast cancer risk (MacMahon et al. 1973). The link between estradiol and breast cancer has been supported by in vitro (McManus and Welsch 1984, Laidlaw et al. 1995) and in vivo (Chang et al. 1995) studies showing that estradiol increases the mitotic activity of breast epithelial cells. Cumulative lifetime exposure to estrogen is thought to be a key factor in determining a woman's breast cancer risk (Henderson et al. 1985, Henderson et al. 1988). The importance of progesterone in breast cancer risk has been highlighted by several recent observational studies and most notably the Women's Health Initiative randomized trials that have shown that combined estrogen plus progestin hormone therapy increases breast cancer risk while use of estrogen alone does not (Chlebowski et al. 2003, Ross et al. 2000).

Physical activity appears to have a direct physiological effect on steroid hormone levels, most clearly during the pubertal and premenopausal periods. Increased physical activity has been directly associated with reduced circulating levels of endogenous estradiol and progesterone among normally cycling women (Shangold et al. 1979, Ellison and Lager 1986). In addition, physical activity has an indirect effect on exposure to ovarian steroid hormones, in that high levels of moderate and vigorous physical activity result in delayed menarche, irregular or anovulatory menstrual cycles, a shortened luteal phase, and in the extreme, secondary amenorrhea (Warren 1980, Frisch et al. 1981, Bernstein et al. 1987). Results of studies looking at physical activity and circulating hormone levels in postmenopausal women have not been as consistent (Verkasalo et al. 2001, Newcomb et al. 1995, Atkinson et al. 2004).

Table 7.1 Summary of risk estimates characterizing the relationships between physical activity and anthropometric factors and risk of breast cancer

Risk factor	Summary risk estimate
Physical activity	
High vs. low average lifetime activity [≥3.0 hours per week vs. Inactive (<2 hours per week)]	~20–40 decrease in risk
Dose–response effect (per each additional hour of physical activity per week)	~6% decrease in risk
Anthropometric factors	
Body mass index, premenopausal women Dose–response effect (per each additional 5 kg/m^2 of body mass index)	~15% decrease in risk
Body mass index, postmenopausal women Dose–response effect (per each additional 5 kg/m^2 of body mass index)	~12% increase in risk
Weight change, postmenopausal women Dose–response effect (per each additional 5 kg of weight gained)	~5% increase in risk
Waist–hip ratio Dose–response effect (per each additional 0.1 unit of waist-hip ratio)	~19% increase in risk
Height, premenopausal women Dose–response effect (per each additional 5 cm of attained height)	~9% increase in risk
Height, postmenopausal women Dose–response effect (per each additional 5 cm of attained height)	~11% increase in risk

Exposure of breast tissue to estrogen may also explain the association between adiposity and breast cancer risk among postmenopausal women. The adrenal androgen, androstenedione, is converted to estrone in adipose tissue through an aromatization process (Grodin et al. 1973). Estrone, in turn, is metabolized to estradiol, a more potent estrogen. Testosterone is also elevated with higher BMI. Further, sex hormone-binding globulin (SHBG) is inversely associated with body mass; SHBG binds circulating estradiol and testosterone, thereby limiting their bioavailability to tissues (Anderson 1974). Thus, in the postmenopausal period, when ovarian production of estradiol and progesterone has ceased, substantially overweight and obese women will have higher circulating levels of estrone, estradiol and testosterone compared to leaner women. Although physical activity has independent effects on hormone levels after menopause (Cauley et al. 1989), these effects may not be as great as the impact of physical activity on body size measures, particularly BMI. By reducing adiposity or maintaining a constant weight during adulthood (that is, preventing weight gain), physical activity may have an indirect effect on circulating hormone levels, thereby reducing breast cancer risk.

Both the insulin and insulin-like growth factor pathways, which have been implicated in carcinogenesis because of their roles in stimulating cell proliferation and inhibiting apoptosis (Pollak et al. 2004), may also mediate the associations between physical activity as well as adiposity and breast cancer risk. History of diabetes, a condition marked by sustained, high insulin levels, has been associated with increased breast cancer risk (Wu et al. 2007). Obesity is associated with insulin resistance and higher risk of diabetes; conversely, physical activity is associated with increased insulin sensitivity and lower diabetes risk (for review see Rao 2001). Increased levels of insulin may increase breast cancer risk by down-regulating SHBG, resulting in higher bioavailable estradiol (Nestler et al. 1991) or alternatively by down-regulating insulin-like growth factor-binding protein-1, resulting in increased bioavailable insulin-like growth factor-I (IGF-I) (Conover et al. 1992). High IGF-I levels have been associated with increased risk of premenopausal breast cancer (Hankinson et al. 1998), and recent results from the EPIC study implicate IGF-I in postmenopausal breast cancer risk (Rinaldi et al. 2006). IGF-I acts as a mitogen in breast cell lines; it may also play roles in promoting breast cell differentiation, breast cell transformation, and suppression of apoptosis (Jones and Clemmons 1995).

Other mechanisms with less compelling supporting evidence have been proposed to explain the associations between physical activity and breast cancer risk and obesity and breast cancer risk. These include regulation of the immune system (for review, see Hoffman-Goetz et al. 1998) and lipid peroxidation (Vincent and Taylor 2006).

Conclusions

A substantial body of evidence has accumulated showing that physical activity reduces breast cancer risk among premenopausal women and among postmenopausal women. Measures of lifetime activity and participation in more vigorous forms of activity appear to be better predictors of these associations than activity measured at a single time point or moderate intensity activities. In addition, both excess adiposity after menopause and weight gain during a woman's adult years have been consistently associated with increased risk of breast cancer in postmenopausal women. These relationships with breast cancer have been established through observational studies, and despite the consistency of findings, one cannot rule out bias as a possible explanation. Because of this, establishing the mechanisms that account for these associations is important. Although several mechanisms provide plausible explanations for the associations, none has been definitively established. Breast tissue is hormonally responsive, and alterations in steroid hormones associated with physical activity and with adiposity provide credible explanations for the observed relationships. Evidence also exists to support a mediating role for insulin and insulin-like growth factor pathways in these relationships. The positive

association between height and breast cancer risk suggests that nutrition during childhood is important.

Few established breast cancer risk factors are modifiable. However, increasing physical activity and maintaining weight during a woman's adult years offer both individual and population-based opportunities for lowering women's risk of breast cancer.

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Chapter 8
Diet and Nutrition

Martin Lajous and Shumin M. Zhang

Introduction

The incidence of breast cancer varies dramatically across different populations (Parkin et al. 1999), and migrants from low-incidence geographic areas take on the incidence rates of the new area to which they migrate (Ziegler et al. 1993). Lifestyle appears to be a strong determinant of breast cancer risk and diet composition and nutritional status are important candidates. Understanding the role of diet in breast cancer is important because dietary factors are potentially modifiable risk factors on which preventive efforts may focus. New insights into breast cancer etiology have revealed additional complexities of the potential relevance of diet. Breast cancer has traditionally been viewed as one disease; however, recent data suggest that phenotypically distinct breast tumors characterized by hormone receptor status may also differ with respect to risk factors (Colditz et al. 2004). Additionally, several determinants of breast cancer differ in premenopausal and postmenopausal women. Exposures occurring at various stages of life, from as early as in utero up to age at diagnosis, can potentially have an important impact on breast cancer risk; early life environment may contribute to breast cancer risk because the mammary tissue may be particularly susceptible to environmental influence at that time (Land et al. 2003).

When evaluating the wealth of epidemiologic data on the relation between nutrition and breast cancer, careful consideration of the study design and implementation and accuracy of dietary assessment is required. Case–control studies of nutrition may afford important insights, but are susceptible to both recall bias and selection bias. Affected individuals may associate their malignancy with foods perceived to be poor in nutritional value and overreport them relative to unaffected controls. In addition, controls may not represent the

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_8,

population from which the cases arose. Prospective studies, in contrast, assess diet before breast cancer diagnosis and, therefore, address some of the inherent limitations of case–control studies. However, they typically provide only a snapshot of dietary intake, and so it can be challenging to accurately assess an individual's diet over prolonged periods of time. The current review is a summary of the available evidence relating dietary composition and nutrition and breast cancer that will focus on dietary factors that have been extensively evaluated in an effort to characterize them better and on emerging factors that may prove to be of relevance in the future.

Dietary Fat

The potential role of fat intake as a risk factor for breast cancer received widespread attention after a report of dramatic differences in fat consumption and breast cancer incidence across countries (Armstrong and Doll, 1975). High-fat diets have been shown to induce mammary tumors in rodents (Fay and Freedman, 1997). However, there is controversy over the value of these results for humans (Holmes and Willett, 2004). Experimental studies do suggest that fat intake may accelerate formation of arachidonic acid and prostaglandins and alter cell membrane function (Woutersen et al. 1999). Lowering dietary fat intake has also been associated with a decrease in estradiol levels (Wu et al. 1999a), though the biological mechanism underlying this association is unclear (Wu et al. 1999b).

Observational studies evaluating dietary fat intake and breast cancer have yielded mixed results: most case–control studies find significant positive associations (Boyd et al. 2003) while most large prospective cohort studies are null (Table 8.1) (Mills et al. 1989; Howe et al. 1991; Graham et al. 1992; Kushi et al. 1992; van den Brandt et al. 1993; Gaard et al. 1995; Wolk et al. 1998; Velie et al. 2000; Horn-Ross et al. 2002; Cho et al. 2003b; Gago-Dominguez et al. 2003; Mattisson et al. 2004b; Kim et al. 2006; Thiebaut et al. 2007). A meta-analysis of 14 cohort studies showed no association with total fat intake, but the relative risk for the highest category of saturated fat intake compared to the lowest was 1.15 (95% CI: 1.0–1.3) (Boyd et al. 2003). A pooled analysis of eight prospective cohorts, with 351,821 women and 7,329 cases, found that total fat intake was not related to risk of either pre- or postmenopausal breast cancer, but observed a modest association with saturated fat intake [RR = 1.09 (95% CI: 1.0–1.2)] (Smith-Warner et al. 2001a). Different types of fat may have different effects on the breast. Olive oil, which has a high content of monosaturated fat, has been shown to lower breast cancer risk in some studies (Martin-Moreno et al. 1994; Wolk et al. 1998; Voorrips et al. 2002).

More recently, the National Institutes of Health-AARP Diet and Health Study (NIH-AARP) prospective cohort reported a relative risk for the highest versus the lowest quintile of total fat intake of 1.11 (95% CI: 1.0–1.2) after an

Table 8.1 Results from large prospective studies on total fat and saturated fat intake and breast cancer risk.

Study	Reference	Cohort size	Years of follow-up	Breast cancer cases	Relative risk (95%CI)[a] Total fat	Relative risk (95%CI)[a] Saturated fat
NIH-AARP Diet and Health Study	Thiebaut et al. (2007)	188,736	15	3,501	1.1 (1.0–1.2)	1.2 (1.1–1.3)
Nurses' Health Study	Kim et al. (2006)	80,375	20	3,537	1.0 (0.95–1.0)	1.0 (0.9–1.0)
Malmo Diet and Cancer Cohort	Mattison et al. (2004)	11,726	10	342	1.4 (1.0–1.9)	
Nurses' Health Study II	Cho et al. (2003)	90,655	8	714	1.3 (1.0–1.6)	1.2 (0.9–1.5)
The Singapore Chinese Health Study	Gago-Dominguez et al. (2003)	35,298	7	314	1.0 (0.7–1.3)	0.9 (0.7–1.3)
California Teachers' Study	Horn-Ross et al. (2002)	115,526	2	711	0.8 (0.6–1.2)	0.8 (0.6–1.2)
Breast Cancer Detection Demonstration Project	Velie et al. (2000)	40,022	5	996	1.1 (0.9–1.3)	1.1 (0.9–1.5)
Swedish Mammography Screening Cohort	Wolk et al. (1998)	61,471	6	674	1.0 (0.8–1.3)	1.1 (0.8–1.4)
Iowa Women's Health Study	Kushi et al. (1995)	32,080	4	408	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Norwegian National Health Screening	Gaard et al. (1995)	31,209	6	248	1.3 (0.9–1.8)	1.0 (0.8–1.6)
Netherlands Cohort Study	van den Brandt et al. (1993)	62,573	3	471	1.1 (0.7–1.6)	1.4 (0.9–2.1)
Canadian National Breast Screening Study	Howe et al. (1991)	56,837	5	519	1.3 (0.9–1.9)	1.1 (0.7–1.6)
New York State Cohort	Graham et al. (1991)	17,401	7	344	1.0 (0.6–1.7)	1.1 (0.8–1.2)
Adventists' Health Study	Mills et al. (1989)	20,341	6	215	–	1.2 (0.8–1.8)

[a]Relative risk comparing the highest versus the lowest category of intake

average follow-up of 4.4 years (Thiebaut et al. 2007). These results contrast those of an updated analysis in the Nurses' Health Study (NHS), the longest prospective study of fat intake and breast cancer (Kim et al. 2006). After 20 years of follow-up with repeated dietary measures and correction of measurement error, no association for total and specific types of fat intake was observed. These results should be considered in light of the large Women's Health Initiative (WHI) randomized trial (Prentice et al. 2007). The WHI trial assigned 19,541 women to a low-fat diet and 29,294 to a comparison group; results are suggestive of a 9% lower risk of breast cancer in the intervention group. Interpretation of these results is complex: by the end of follow-up the actual difference in fat intake between groups was much smaller than expected, and fruit and vegetable intake was increased and a reduction of weight was observed in the intervention group.

Concern that fat intake may affect breast cancer risk in developmentally important stages has been raised. Fat intake in adolescence affects levels of circulating hormones and may affect subsequent breast cancer risk by exposing the mammary gland to elevated estrogen levels at a key moment in breast tissue development (Dorgan et al. 2003). Relatively few studies have evaluated childhood and adolescent fat intake and subsequent breast cancer; those that have do not support an association with either total fat or saturated fat (Pryor et al. 1989; Frazier et al. 2003, 2004; Michels et al. 2006).

The modest association, if any, between dietary fat and breast cancer observed in epidemiological studies and the WHI randomized trial do not advocate for a restriction of fat intake in midlife as a strategy for cancer prevention. Recommendations on quantity and type of fat to be consumed should be driven primarily by the important effects of these nutrients on cardiovascular health.

Dietary Carbohydrates

Interest in the possible role of carbohydrate intake as a potential risk factor for breast cancer stems from the concern that chronically raised insulin levels may increase carcinogenesis by stimulating insulin receptors in breast tissue or through the mitogenic effects of insulin growth factor-1 (IGF-1) (Calle and Kaaks, 2004). In experimental settings, IGF-1 has shown strong proliferative and antiapoptotic effects on human mammary cells (Yanochko and Eckhart, 2006). However, experimental data on the insulin pathway and breast carcinogenesis are not fully supported by observational studies. Even though diabetics appear to be at an increased risk of breast cancer (Larsson et al. 2007b) and elevated fasting glucose levels have been associated with breast cancer (Muti et al. 2002; Rapp et al. 2006), insulin resistance, as measured by glycosylated hemoglobin (Lin et al. 2006) or serum fructosamine (Platek et al. 2005), is not

associated with subsequent breast cancer risk. Furthermore, circulating IGF-1 levels are not strongly related to risk of postmenopausal breast cancer and may only be modestly relevant for premenopausal breast cancer (Fletcher et al. 2005).

Carbohydrate intake and carbohydrate quality, as measured by glycemic index and glycemic load, have been evaluated in five case–control studies (Yu et al. 1990; Augustin et al. 2001; Dos Santos Silva et al. 2002; Levi et al. 2002; Romieu et al. 2004; Lajous et al. 2005) and 12 prospective cohorts (Table 8.2) (Knekt et al. 1990; Kushi et al. 1992; Barrett-Connor and Friedlander, 1993; Horn-Ross et al. 2002; Sieri et al. 2002; Cho et al. 2003a; Folsom et al. 2003; Jonas et al. 2003; Higginbotham et al. 2004; Holmes et al. 2004; Nielsen et al. 2005; Silvera et al. 2005; Giles et al. 2006; Sieri et al. 2007). Carbohydrate intake appears to have only a minimal role in breast carcinogenesis. Only one case–control study (Romieu et al. 2004), an analysis on a prospective cohort of adolescent diet and subsequent risk of breast cancer (Frazier et al. 2004), and a small prospective study (Barrett-Connor and Friedlander, 1993) found an overall positive association between carbohydrate intake and breast cancer risk.

Nevertheless, there is an indication that quality rather than quantity of carbohydrates may be the more relevant exposure particularly when assessing this relationship by menopausal status (Holmes et al. 2004; Silvera et al. 2005; Sieri et al. 2007), lifestyle factors (Cho et al. 2003a; Jonas et al. 2003; Higginbotham et al. 2004; Sieri et al. 2007; Lajous et al. 2008), and hormone receptor status (Kushi et al. 1995; Nielsen et al. 2005). One prospective study found a strong association when comparing the highest to the lowest level of glycemic index [RR = 1.57 (95% CI: 1.0–2.4)] and glycemic load [RR = 2.53 (95% CI: 1.5–4.2)] (Sieri et al. 2007). Among postmenopausal women only, the NHS found a relative risk of 1.15 (95% CI: 1.0–1.3) (Holmes et al. 2004) and the Canadian National Breast Screening Study observed an increased risk of close to 90% (RR = 1.87; 95% CI: 1.2–3.0) (Silvera et al. 2005) when comparing extreme levels of glycemic index. There is also some suggestion that carbohydrate intake may be primarily relevant among overweight (Cho et al. 2003a; Lajous et al. 2008) and sedentary women (Higginbotham et al. 2004) and that it may primarily affect estrogen receptor (ER) negative tumors (Kushi et al. 1995; Nielsen et al. 2005). A large prospective study in France found a relatively strong association comparing the highest to the lowest level of glycemic index and breast cancer among overweight women [RR = 1.35 (95% CI: 1.0–1.8)]; similar results were found among women in the highest category of waist circumference [RR = 1.35 (95% CI: 1.0–1.8)]. This same study found a strong association between carbohydrate intake and ER-negative breast cancer [RR = 1.78 (95% CI: 1.2–2.6)] comparing the highest to the lowest intake (Lajous et al. 2008).

Table 8.2 Results from prospective studies on carbohydrate intake, glycemic index, and glycemic load and breast cancer risk

Study	Reference	Cohort size	Years of follow-up	Breast cancer cases	Relative risk (95%CI)[a]		
					Carbohydrate	Glycemic index	Glycemic load
E3N Study (France)	Lajous et al. (2008)	62,739	9	1,812	1.0 (0.9–1.2)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
ORDET Study (Italy)	Sieri et al. (2007)	8,926	12	289		1.6 (1.0–2.4)	2.5 (1.5–4.2)
Melbourne Collaborative Cohort Study	Giles et al. (2006)	12,273	9	324	1.3 (1.0–1.8)[b]	1.0 (0.9–1.1)[b]	1.2 (1.0–1.5)[b]
Danish Diet, Cancer and Health Study	Nielsen et al. (2005)	23,870	7	634	1.1 (1.0–1.2)[c]	0.9 (0.8–1.1)[c]	1.0 (0.9–1.2)[c]
Canadian National Breast Screening	Silvera et al. (2005)	49,613	17	1,461	1.0 (0.8–1.1)	0.9 (0.6–1.2)	0.9 (0.7–1.2)
Nurses' Health Study	Holmes et al. (2006)	88,678	18	4,092	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.0 (0.9–1.1)
Women's Health Study	Higginbotham et al. (2004)	39,879	7	946	–	1.0 (0.8–1.3)	1.0 (0.8–1.4)
Nurses' Health Study II	Cho et al. (2003)	90,655	8	714	0.9 (0.6–1.3)	1.1 (0.8–1.3)	1.1 (0.8–1.5)
Cancer Prevention Study II	Jonas et al. (2003)	63,307	5	1,442	–	1.0 (0.9–1.2)	0.9 (0.8–1.1)
Iowa Women's Health Study	Folsom et al. (2003)	34,703	15	2,031	–	1.0 (NA)	1.0 (NA)
California Teachers' Study	Horn-Ross et al. (2002)	111,526	2	711	0.8 (0.5–1.2)	–	–
ORDET Study (Italy)	Sieri et al. (2002)	3,367	6	56	0.4 (0.2–1.0)	–	–
Iowa Women's Health Study	Kushi et al. (1992)	34,388	4	459	0.9 (0.7–1.1)	–	–
Rancho Bernardo Study	Barrett-Connor et al. (1992)	590	15	15	1.9 (1.2–3.2)[d]	–	–
Finish Mobile Clinic Examination Survey	Knekt et al. (1990)	3,988	20	54	0.4 (0.2–1.0)	–	–

[a]Relative risk comparing the highest versus the lowest category of intake unless otherwise noted
[b]Relative risk for one standard deviation increase
[c]Relative risk for 50 g/day increase in carbohydrate intake, 10 units/day increase in glycemic index, and 100 units/day increase in glycemic load
[d]Relative risk for 66 g/day increase in carbohydrate intake

Dietary Fiber

Fiber has been postulated to lower circulating levels of estrogens by inhibiting their intestinal reabsorption (Cohen, 1999) and to increase serum levels of insulin growth factor binding protein-3 (IGFBP-3), the main protein carrier for IGF-1 (Probst-Hensch et al. 2003). While case–control studies found an inverse association (Howe et al. 1990; Freudenheim et al. 1996; Challier et al. 1998; Ronco et al. 1999; Dos Santos Silva et al. 2002), the results from most prospective cohorts are null (Terry et al. 2002b; Cho et al. 2003a; Holmes et al. 2004; Giles et al. 2006). The NHS evaluated this relationship using a cumulative average of total fiber and fiber fraction intake based on six dietary questionnaires over an 18-year period and found no association with premenopausal and postmenopausal breast cancer (Holmes et al. 2004). Nevertheless, the Malmo Diet and Cancer prospective cohort in Sweden noted a statistically significant inverse association among postmenopausal women with a relative risk of 0.58 (95% CI: 0.4–0.8) for the highest quintile of fiber intake as compared to the lowest (Mattisson et al. 2004a).

Alcohol

Alcohol intake is the dietary factor associated with breast cancer for which the evidence is most consistent and the biological mechanisms are the most clearly established. Alcohol intake increases mammary tissue exposure to estrogen, induces mutagenesis through its metabolites, increases free radical-mediated DNA damage, and may influence DNA metabolism and gene expression by affecting one-carbon metabolism (Dumitrescu and Shields, 2005; Seitz and Stickel, 2007). However, the best supported mechanism is related to circulating hormonal levels. In vitro, addition of alcohol to breast cancer cells resulted in ER signaling and cell proliferation of ER+ but not ER− cells (Fan et al. 2000; Singletary et al. 2001). In addition, controlled feeding trials have shown that moderate alcohol intake increases circulating estrogen levels in both premenopausal (Reichman et al. 1993) and postmenopausal (Dorgan et al. 2001) women.

Most studies report a moderate linear increase in the risk of breast cancer with increasing alcohol consumption (Fig. 8.1). For an increase of roughly one additional drink per day (10 g) a pooled analysis of six prospective cohorts found a 9% (95% CI: 4–13%) increase in breast cancer risk (Smith-Warner et al. 1998). The European Prospective Investigation Into Cancer and Nutrition (EPIC) study found a 3% (95% CI: 1–5%) increase in risk per drink per day among 274,688 women, 4,285 of whom were incident breast cancer cases (Tjonneland et al. 2007). The association is present in both premenopausal and postmenopausal women, does not vary by type of alcoholic beverage (Smith-Warner et al. 1998; Tjonneland et al. 2007), and does not seem to depend on drinking frequency (Tjonneland et al. 2003; Horn-Ross et al. 2004). Recent

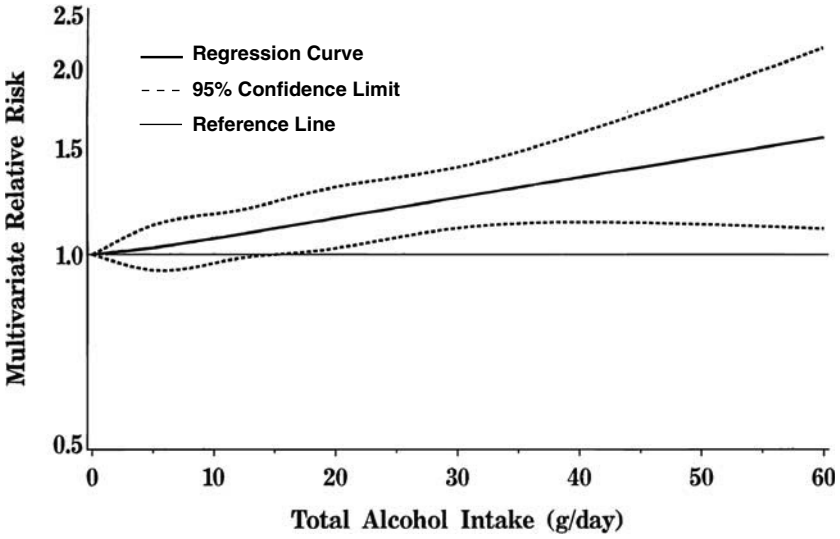

Fig. 8.1 Non-parametric regression curve for the relationship of total alcohol intake and breast cancer risk (Smith-Warner et al. 1998, 537, Copyright © (1998), American Medical Association. All rights reserved.)

alcohol intake seems to be more relevant than past intake. Alcohol intake in adolescence is not associated with subsequent breast cancer risk (Holmberg et al. 1995; Marcus et al. 2000), and in EPIC a null association between alcohol intake during a woman's twenties, thirties, and forties and breast cancer risk was observed after adjustment for current alcohol intake (Tjonneland et al. 2007). These observations are supported by some (Holmberg et al. 1995; Horn-Ross et al. 2004), but not all (Garland et al. 1999), studies.

Four large prospective studies have evaluated alcohol intake and breast cancer risk classified jointly by ER and PR status (Potter et al. 1995; Colditz et al. 2004; Suzuki et al. 2005; Zhang et al. 2007b). Results are not entirely consistent; however, the pooled estimate comparing non-drinkers to individuals consuming one or more drinks per day for three of these studies yielded a relative risk of 1.30 (95% CI: 1.1–1.5) for ER + /PR + , 1.02 (95% CI: 0.7–1.5) for ER − /PR − , and 1.65 (95% CI: 0.8–3.5) for ER + /PR − (Zhang et al. 2007b). This observation further supports the notion that alcohol intake may affect breast cancer risk through an estrogen-dependent pathway.

Vitamins A, C, and E

Vitamin A is a family of fat-soluble nutrients that include both preformed vitamin A (retinol) from animal sources and certain carotenoids (α- and β-carotenes and β-cryptoxantin) from fruits and vegetables. α-Carotene,

β-carotenes, β-cryptoxantin, lycopene, and lutein/zeaxanthin are abundant dietary carotenoids that circulate in humans. Vitamin A is involved in cell proliferation and differentiation and carotenoids act as antioxidants that limit oxidative DNA damage by free radicals (Krinsky and Johnson, 2005). Retinoic acid inhibits cell growth through early cell cycle arrest and induction of apoptosis in mammary tumor cell lines (Donato et al. 2007) and β-carotene has been shown to inhibit mammary carcinogenesis in rat models (Maillard et al. 2006). Evidence for a role of vitamin A intake on breast cancer risk is inconclusive. In contrast to case–control studies (Howe et al. 1990), most cohort studies yield little evidence of an association between total vitamin A intake and breast cancer risk (Graham et al. 1992; Kushi et al. 1996; Jarvinen et al. 1997; Verhoeven et al. 1997; Michels et al. 2001; Terry et al. 2002a; Nissen et al. 2003). However, others have found vitamin A and carotenoids to be inversely related to breast cancer (Shibata et al. 1992; Hunter et al. 1993). In an updated analysis of the NHS, among premenopausal women, a weak inverse association between cumulative intake of vitamin A and carotenoids and breast cancer risk was observed (Zhang et al. 1999a). These nutrients may be of relevance to breast cancer among smokers who may have lower retinol stores (Cho et al. 2003c). However, a large clinical trial that randomized 39,876 women to β-carotene supplementation or placebo found no evidence of a protective effect of β-carotene on breast cancer risk over a median of 4.1 years of follow-up (2.1 years' treatment plus another 2.0 years' follow-up) (Lee et al. 1999). Some studies that have evaluated pre-diagnostic circulating levels of retinol and individual carotenoids and subsequent breast cancer suggest an inverse association with some of these nutrients (Dorgan et al. 1998; Toniolo et al. 2001; Sato et al. 2002), particularly with respect to ER− breast cancer (Tamimi et al. 2005). Others have not confirmed these associations (Hulten et al. 2001; Sesso et al. 2005).

Vitamin C, a water-soluble compound, has been shown to induce apoptosis in breast cancer cells (Hong et al. 2007) and reduce oxidative DNA damage and mutations (Sowell et al. 2004). Most case–control studies find a strong inverse association between vitamin C intake and breast cancer (Howe et al. 1990; Graham et al. 1991; Freudenheim et al. 1996; Negri et al. 1996; Adzersen et al. 2003; Singh et al. 2005). However, prospective cohorts do not support this association (Graham et al. 1992; Rohan et al. 1993; Kushi et al. 1996; Jarvinen et al. 1997; Verhoeven et al. 1997; Zhang et al. 1999a; Cho et al. 2003c), and a nested case–control study of plasma vitamin C and breast cancer yielded null results (Wu et al. 2000). Another cohort study observed an increased risk of breast cancer with increasing intake of vitamin C (Nissen et al. 2003).

Vitamin E or tocopherol is a lipid-soluble vitamin that is found in seeds, nuts, and vegetables. It is an antioxidant that may participate in cell signaling and gene regulation (Tucker and Townsend, 2005). There is little evidence to support an inverse association between vitamin E intake and breast cancer risk from prospective studies (Graham et al. 1992; Rohan et al. 1993; Kushi et al.

1996; Jarvinen et al. 1997; Verhoeven et al. 1997; Zhang et al. 1999a; Michels et al. 2001). Similarly, nested case–control studies have not confirmed the hypothesis that increasing circulating levels of α- or γ-tocopherol reduce breast cancer risk (Dorgan et al. 1998; Hulten et al. 2001; Sato et al. 2002; Tamimi et al. 2005). In addition, a large randomized trial among 39,876 US female health professionals found that 600 IU of vitamin E taken every other day had no effect on the incidence of breast cancer over a median of 10 years of treatment and follow-up (Lee et al. 2005). Nevertheless, results from a population-based case–control study in China observed a significant reduction of risk for vitamin E supplement use among women with the lowest intake from food (Dorjgochoo et al. 2007).

Folate, Vitamin B_6, and Vitamin B_{12}

Inadequate folate levels have been related to several cancers, including cancers of the colon and pancreas (Giovannucci, 2003; Larsson et al. 2006). Folate, vitamin B_6, and vitamin B_{12} participate in DNA metabolism in the synthesis of purines and thymidylate. In addition, vitamin B_{12} serves as a cofactor in the synthesis of *S*-adenosylmethionine from folate, a methyl donor for DNA methylation reactions, and vitamin B_6 participates in the synthesis of gluthathione, one of the most powerful intracellular antioxidants (Stover, 2004). Low levels of these vitamins may result in a disruption of DNA repair and replication processes and in abnormal methylation and gene expression (Mason and Choi, 2000).

Two meta-analyses have evaluated the association of folate intake and breast cancer risk (Lewis et al. 2006; Larsson et al. 2007a). Summary results for both analyses indicate a discrepancy between prospective and case–control studies. Prospective studies do not provide evidence of an association, while case–control studies show a 9–27% lower risk of breast cancer when comparing high versus low dietary folate intake. In prospective studies, there is a suggestion that high folate levels may be associated with a lower risk of breast cancer among moderate to high alcohol drinkers. In the Nurses' Health Study, folate intake seemed to attenuate the negative effect of alcohol intake dramatically (Fig. 8.2) (Zhang et al. 1999b), particularly for ER− breast cancer (Zhang et al. 2005). In a prospective study in France where moderate alcohol intake is very common, the relative risk for the highest versus the lowest quintile of dietary folate intake was 0.78 (95% CI: 0.7−0.9) (Lajous et al. 2006b) and in Sweden where folate intake is low a strong inverse association was observed (Ericson et al. 2007). It is possible that the benefit of folate may only be observable in individuals with low folate status and that ethanol may produce a physiologic deficiency that affects one-carbon metabolism by reducing folate absorption in the gastrointestinal tract or by inhibiting enzymatic activity (Mason and Choi, 2005). The suggestion of a protective effect contrasts with

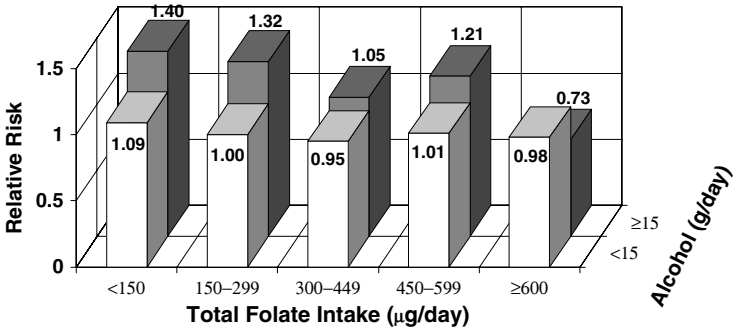

Fig. 8.2 Relative risk of breast cancer by total folate intake and alcohol consumption. The reference group for all comparisons was women who consumed 150–299 μg/day of total folate and less than 15 g/day of alcohol. (Zhang et al. 1999b, 1635, Copyright © (1999), American Medical Association. All rights reserved.)

a screening trial in the United States that found a significant increase in risk with increasing folate intake. The relative risk for the highest level of intake as compared to the lowest was 1.32 (95% CI: 1.0–1.7); folic acid supplement use was also significantly associated with breast cancer risk (Stolzenberg-Solomon et al. 2006). Total folate intake in this population was several times higher than what was observed in other studies and it was mainly in the folic acid form from supplements and fortified foods. It has been suggested that folate may play a dual role and protect in early carcinogenesis but promote cancer growth if administered later in the carcinogenic process.

Circulating levels of folate have been evaluated in four prospective studies (Wu et al. 1999b; Zhang et al. 2003; Rossi et al. 2006; Lin et al. 2008). Results from the Nurses' Health Study and Australia are suggestive of an inverse association; it also confirmed the observation that folate status may be of particular relevance for breast cancer among women who regularly consume alcohol (Zhang et al. 2003). A common polymorphism in the 5,10 methylenetetrahydrofolate reductase (MTHFR), the enzyme responsible for nucleic acid methylation, has been studied in relation to breast cancer and results remain inconclusive (Lewis et al. 2006). More recently, polymorphisms in other enzymes in this pathway have been evaluated and suggest that some variants may be inversely associated with breast cancer primarily in individuals with adequate dietary folate intake (Lissowska et al. 2007).

Few epidemiologic studies have evaluated the role of vitamin B_6 and B_{12} intake and breast cancer risk, and reports are inconsistent (Wu et al. 1999b; Levi et al. 2001; Shrubsole et al. 2001; Zhang et al. 2003; Lajous et al. 2006a; Lajous et al. 2006b). One prospective study in France found a null association between vitamin B_{12} intake and breast cancer (Lajous et al. 2006b), while a case–control study in a population with low levels of intake (Lajous et al. 2006a) and two nested case–control studies looking at circulating levels found

evidence of an inverse association with breast cancer risk (Wu et al. 2000; Zhang et al. 2003). As noted above, vitamin B_{12} is a cofactor in the methyl transfer of methyltetrahydrofolate to homocysteine to form methionine. Similar to what is observed with folate deficiency, low levels of vitamin B_{12} may affect DNA methylation (Friso and Choi, 2005). A prospective study (Lajous et al. 2006b) and two case–control studies (Shrubsole et al. 2001; Lajous et al. 2006a) have observed that adequate levels of vitamin B_{12} may be necessary for folate to have a protective effect for breast cancer, and a recent genetic study found that a polymorphism in the vitamin B_{12}-dependent methionine synthase was associated with breast cancer risk (Lissowska et al. 2007). In two studies, high vitamin B_6 levels were associated with lower breast cancer risk among postmenopausal women (Zhang et al. 2003).

Vitamin D and Calcium

Vitamin D is a fat-soluble vitamin and a hormone present in food in two forms: cholecalciferol (D_3) from animal sources and ergocalciferol (D_2) from plant sources. The main source of vitamin D_3 in humans is epidermally generated through the exposure of 7-dehydrocholesterol to UV light (Welsh, 2007). Vitamins D_2 and D_3 are metabolized to 25-hydroxyvitamin D [25-(OH) D] in the liver and then transformed, mainly in the kidneys through 1-alpha-hydroxylase, Into the biologically active and closely regulated 1,25-dihydroxyvitamin D [1,25-(OH_2) D] (Holick, 2007). As a hormone, vitamin D is involved in calcium and bone metabolism. Ionized calcium in plasma is maintained at a narrow range in part through a 1,25-(OH_2) D-mediated mechanism that increases intestinal absorption of calcium by enhancing the expression of epithelial calcium channels and calcium-binding proteins. Calcium participates in a negative-feedback loop that controls 1,25-(OH_2) D in the kidney. Changes in calcium intake result in only minor fluctuations in circulating levels of 1,25-(OH_2) D and are unlikely to have a significant biologic effect (Bonjour et al. 2007). Experimental studies have shown that 1,25-(OH_2) D can inhibit cellular proliferation, induce differentiation and apoptosis, and inhibit angiogenesis in normal and malignant breast cells; 1,25-(OH_2) D modulates gene expression in specific tissues through its binding to the nuclear vitamin D receptor (VDR) and to specific DNA sequences (Cui and Rohan, 2006). In mice, vitamin D and calcium intake suppress epithelial cell proliferation (Xue et al. 1999) and a synthetic vitamin D analog induced apoptosis in transformed mammary gland cells (Mehta et al. 2003).

Epidemiologic assessment of the role of vitamin D intake in breast carcinogenesis is based on evaluations of dietary and supplemental vitamin D intake, studies on circulating levels of vitamin D, on sunlight exposure, and vitamin D receptor (VDR) polymorphisms. Five prospective studies have evaluated vitamin D intake and breast cancer risk (Table 8.3) (John et al.

Table 8.3 Results from prospective studies on vitamin D, calcium and dairy intake, and breast cancer risk

	Reference	Cohort size	Years of Follow-up	Breast cancer cases	Relative risk (95%CI)[a] Premenopausal	Relative risk (95%CI)[a] Postmenopausal
Vitamin D						
Iowa Women's Health Study	Robien et al. (2007)	34,321	8	2,440	–	0.9 (0.8–1.0)
Women's Health Study	Lin et al. (2007)	31,487	10	1,019	0.7 (0.4–1.0)	1.3 (1.0–1.7)
CPS II Nutrition Cohort	McCullough et al. (2005)	68,567	9	2,855	–	1.0 (0.8–1.1)
Nurses' Health Study	Shin et al. (2002)	88,621	16	3,172	0.7 (0.6–0.9)	0.9 (0.8–1.1)
NHANES	John et al. (1999)	5,009	21	190	–	0.9 (0.6–1.2)
Calcium						
Women's Health Study	Lin et al. (2007)	31,487	10	1,019	0.6 (0.4–0.9)	1.2 (0.9–1.5)
CPS II Nutrition Cohort	McCullough et al. (2005)	68,567	9	2,855	–	0.9 (0.8–1.1)
Nurses' Health Study	Shin et al. (2002)	88,621	16	3,172	0.8 (0.6–1.1)	0.9 (0.8–1.1)
SUVIMAX	Kesse-Guyot et al. (2007)	3,627	1.5	92	0.3 (0.1–0.7)	
Dairy						
Women's Health Study	Lin et al. (2007)	31,487	10	1,019	0.6 (0.4–1.0)	1.1 (0.8–1.4)
CPS II Nutrition Cohort	McCullough et al. (2005)	68,567	9	2,855	–	0.8 (0.7–1.0)
Nurses' Health Study	Shin et al. (2002)	88,621	16	3,172	0.8 (0.6–1.0)	1.0 (0.9–1.1)
SUVIMAX	Kesse-Guyot et al. (2007)	3,627	1.5	92	0.3 (0.1–1.0)	–

[a]Relative risk comparing the highest versus the lowest category of intake

1999; Shin et al. 2002; McCullough et al. 2005; Lin et al. 2007; Robien et al. 2007). Overall, results are suggestive of an inverse association between vitamin D intake and breast cancer, particularly among premenopausal women. An analysis in the NHS showed a significant inverse association for the highest category of vitamin D intake as compared to the lowest among premenopausal women [RR = 0.72 (95% CI: 0.6–1.0)], but not among postmenopausal women [RR = 0.93 (95% CI: 0.8–1.1)] (Shin et al. 2002). These results were confirmed in the Women's Health Study (WHS), where the relative risk of premenopausal breast cancer in the highest quintile of total vitamin D intake as compared to those in the lowest quintile was 0.65 (95% CI: 0.4–1.0) (Lin et al. 2007). Findings from a few studies that have evaluated the association between vitamin D intake and hormone receptor-defined breast cancer are inconsistent (McCullough et al. 2005; Lin et al. 2007; Robien et al. 2007). A pooled analysis of a nested case–control study (Bertone-Johnson et al. 2005) and a case–control study (Lowe et al. 2005) found a strong linear inverse association between serum 25(OH)D and breast cancer risk (Garland et al. 2007). Results for 1,25-(OH_2) D are less clear, the case–control nested in the Nurses' Health Study found only a modest association, while a study in the Kaiser Permanente system reported null results (Hiatt et al. 1998). Even though 25(OH)D levels are more sensitive to diet and sunlight, they may not reflect circulating levels of 1,25-(OH_2) D; 1-alpha-hydroxylase has been shown to be present in breast tissue and 25(OH)D may be hydroxylated Into the biologically active form locally (de Lyra et al. 2006; Friedrich et al. 2006). Studies that find an inverse association between sunlight exposure and breast cancer risk (Gorham et al. 1990; John et al. 1999; Freedman et al. 2002; Knight et al. 2007) and the associations found with VDR polymorphisms (Chen et al. 2005) afford additional insights and strengthen the support for an important role of vitamin D in breast cancer. Vitamin D has potentially emerged as an important determinant of breast cancer, yet information is still scant and a more detailed understanding of its physiologic underpinnings is warranted.

Some studies have evaluated calcium intake and breast cancer risk (Table 8.3). The WHS found an inverse association among premenopausal women, the relative risk for the group in highest quintile of calcium intake relative to the lowest one was 0.61 (95% CI: 0.4–0.9) and additional adjustment for vitamin D did not change the results (Lin et al. 2007). In the NHS (Shin et al. 2002) and in the Cancer Prevention Study II (McCullough et al. 2005) results were not conclusive. In a small prospective study in France, where dairy is not fortified with vitamin D, a very strong inverse association was observed between calcium intake and breast cancer (Kesse-Guyot et al. 2007), and an analysis of pre-diagnostic serum calcium in Sweden observed a strong inverse dose−response relation among premenopausal women, but not among postmenopausal women (Almquist et al. 2007).

Selenium

Selenium is an essential trace element and a constituent of proteins involved in several biologic processes. Selenium may be involved in mammary carcinogenesis through growth inhibition, induction of apoptosis, reduction of angiogenesis, and oxidative stress reduction (Whanger, 2004). Epidemiological evidence lends little support to an inverse association between selenium and breast cancer risk. Prospective studies, three of which used toenail selenium as an indicator of long-term exposure (Coates et al. 1988; Hunter et al. 1990; van den Brandt et al. 1994; van Noord et al. 1993), and most case–control studies indicate no association with breast cancer (Willett et al. 1983; van't Veer et al. 1990, 1996; Strain et al. 1997; Ghadirian et al. 2000).

Coffee and Tea

Initial interest in coffee as a risk factor for breast cancer stemmed from the observation that women who reduced consumption of coffee experienced a regression of fibrocystic breast disease, a known risk factor for breast cancer (Marshall et al. 1997). Tea has also been hypothesized to be associated with a reduced risk of breast cancer through the anticarcinogenic effect of polyphenolic flavonoids (Yang et al. 2002). Several case–control studies and seven large prospective cohort studies have evaluated coffee and caffeine consumption and subsequent risk of breast cancer (Snowdon and Phillips, 1984; Jacobsen et al. 1986; Vatten et al. 1990; Graham et al. 1992; Hunter et al. 1992; Folsom et al. 1993; Michels et al. 2002). Most large prospective cohorts have found no evidence of an overall association. In Sweden, the largest per capita consumer of coffee, women who consumed four or more cups of coffee a day had a relative risk of 0.94 (95% CI: 0.8–1.3) as compared to women who had one cup a week or less (Michels et al. 2002). The Iowa Women's Health Study evaluated the association between caffeine consumption and risk of breast cancer according to history of benign breast disease, and no significant association was observed in any category of benign breast disease history (Folsom et al. 1993). A meta-analysis found an inverse association between green tea and breast cancer, the summary odds ratio for the highest versus the lowest exposure level was 0.78 (95% CI: 0.6–1.0) (Sun et al. 2006). In addition, a recent case–control study in China that looked at different measures of green tea exposure found a significant dose–response inverse association [odds ratio = 0.57 (95% CI: 0.5–0.7) for women who had two or more cups per day as compared to women who did not consume green tea] (Zhang et al. 2007a). Results for black tea have been consistently null and a prospective analysis of total polyphenol intake did not yield significant findings (Adebamowo et al. 2005a; Baker et al. 2006; Sun et al. 2006). Polyphenol content in green tea is far greater than that in black tea; many prospective studies in Western populations may lack the power to detect an association because of low total polyphenol consumption.

Soy and Phytoestrogens

Interest in evaluating soy and phytoestrogens as possible determinants of breast cancer originated from the relatively low incidence of breast cancer in some eastern populations where soy is regularly consumed (Parkin et al. 1999) and from the estrogenic properties of some of the nutrients found in soy products (Barnes, 2004). Phytoestrogens considered to be relevant to human nutrition are isoflavonoids (daidzein, genistein, biochanin A), coumestrol, and lignans (enterolactone, enterodiol) and are mainly found in soybeans, cereals, and grains (Dixon, 2004). Phytoestrogens have been hypothesized to affect breast cancer risk by acting as weak estrogen agonists or antagonists (Messina et al. 2006). In a meta-analysis on 12 case–control and 5 prospective analyses, the pooled relative risk estimate comparing high and low soy intake was 0.86 (95% CI: 0.8–1.0) (Trock et al. 2006). More recently, a large prospective study in France observed that lignan intake may lower ER+/PR+ postmenopausal breast cancer (Touillaud et al. 2007), but not premenopausal breast cancer (Touillaud et al. 2006). Furthermore, urinary (Zheng et al. 1999; Dai et al. 2001; den Tonkelaar et al. 2001) and circulating biomarkers of phytoestrogen intake and breast cancer risk (Pietinen et al. 2001; Kilkkinen et al. 2004; Olsen et al. 2004; Zeleniuch-Jacquotte et al. 2004; Piller et al. 2006; Verheus et al. 2007) have been evaluated and results are not fully consistent with an inverse association.

Dietary Patterns and Foods

Empirically derived dietary patterns have been used to investigate diet–breast cancer associations in an effort to explore more closely the complex combinations of nutrients and foods observed in an usual diet. The NHS and the NHS II identified a prudent pattern (vegetables, fruit, legumes, fish, low-fat dairy) and a Western pattern (refined grains, meats, French fries, high-fat dairy) (Adebamowo et al. 2005b; Fung et al. 2005). These studies did not find an association between these patterns and overall breast cancer risk. However, among postmenopausal women the prudent diet was inversely associated with ER− breast cancer (Fung et al. 2005). A report from a large Greek study supports a risk reduction in all-cause mortality, cardiovascular disease mortality, and cancer mortality associated with adherence to a Mediterranean diet (abundance of plant food – fruits, vegetables, whole-grain cereals, nuts, and legumes; olive oil as the principal source of fat; fish and poultry consumed in low-to-moderate amounts; a low intake of red meat; and moderate consumption of wine, normally with meals) (Trichopoulou et al. 2003). However, both a pooled analysis of cohorts (Smith-Warner et al. 2001b) and the EPIC study (van Gils et al. 2005) did not observe an association between fruit and vegetable intake and breast cancer.

Milk and dairy products are the main sources of dietary vitamin D and calcium in many populations. Few studies have evaluated dairy intake in relation to breast cancer. Among several published prospective studies, there appeared to be an inverse association with high dairy intake for premenopausal breast cancer, but mixed results for postmenopausal breast cancer (Table 8.3) (Shin et al. 2002; McCullough et al. 2005; Kesse-Guyot et al. 2007; Lin et al. 2007). A pooled analysis of cohort studies did not find an association between dairy intake and breast cancer (Missmer et al. 2002). Milk intake may also be of relevance at earlier ages, an inverse association has been observed for milk intake in childhood (Hjartaker et al. 2001) and in adolescence (van Gils et al. 2005).

Meat intake as a possible risk factor for breast cancer was initially evaluated because of the concern that saturated fat may influence breast cancer incidence. A meta-analysis found a summary relative risk of 1.17 (95% CI: 1.1–1.3) for highest versus lowest meat intake (Boyd et al. 2003). Nevertheless, the pooled analysis mentioned earlier found no evidence of an association (Missmer et al. 2002). Interest in meat intake has now shifted toward the possible carcinogenic effect of heterocyclic amines, compounds that are created during high-temperature cooking of meat (Snyderwine et al. 2002). Several studies have evaluated the role of well-cooked meat (Knekt et al. 1994; De Stefani et al. 1997; Zheng et al. 1998; Kotsopoulos et al. 2006; Steck et al. 2007). In the Iowa Women's Study, women who ate well-done meat had fivefold increased risk of breast cancer as compared to those who ate rare- or medium-done meats [RR = 4.62 (95% CI: 1.4–15.7)] (Zheng et al. 1998).

Conclusions

Elucidating the relationship between diet and breast cancer is of public health importance because of the potential to intervene with preventive strategies. When evaluating the evidence to establish a diet–breast cancer relationship, it is important to take into account both the strengths and the limitations of an individual study due to the employment of a specific study design. Although using a randomized, double-blinded, placebo-controlled design minimizes biases and confounding that observational studies are prone to, results from randomized clinical trials should be interpreted with consideration of the restrictions imposed by this design such as only single or few doses, duration of intervention, and compliance to intervention. The validity of meta-analyses and pooled analyses should also be considered only with regard to the quality of their component studies. Compared with studies using a case–control design, prospective studies are less likely to be susceptible to biases. In addition, studies in populations where the distribution of exposure may differ substantially from that of the majority of studies can provide some insight into the dose–response relationship between diet and cancer.

To date, the only established dietary factors consistently related to breast cancer is alcohol and the association with alcohol intake is fairly modest. Some evidence suggests that vitamin D may be of relevance but findings are not fully conclusive and deserve further consideration. Fat intake in adulthood is not consistently associated with breast cancer and fat intake restriction should not be considered as a primary preventive measure for breast cancer. So despite the wide international variation in breast cancer rates and the higher incidence rates of breast cancer in countries where so-called "Western" diets predominate, evidence implicating "Western" diets in relation to breast cancer is weak. Nevertheless, given that diet is a promising target for prevention, additional studies of diet with improved means of assessing exposures and relevant biomarkers are certainly warranted.

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Chapter 9
Environmental and Occupational Exposures

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Introduction

Breast cancer incidence rates have increased substantially over the past several decades in most Westernized countries, with great variation in incidence rates between countries (Kamangar et al. 2006). Given such patterns of breast cancer incidence and the fact that established risk factors for breast cancer explain less than half of all incident cases (Madigan et al. 1995), it has been widely suggested that the environment may play an important role in breast cancer etiology. Several classes of environmental exposures have been investigated in relation to breast cancer risk, with sources of exposure as diverse as the proposed mechanisms linking exposure to breast cancer risk. Among the hypothesized environmental risk factors are unintended byproducts of industrial processes and industrialization: environmental pollutants (such as organochlorines, polycyclic aromatic hydrocarbons, dioxins, and bisphenol A) and extremely low-frequency (ELF) magnetic fields have been linked with breast cancer risk in animal studies and may plausibly be associated with risk in humans. Exposure to some naturally occurring trace elements and heavy metals has also been suggested to influence breast cancer risk, although existing evidence is sparse. Perhaps the strongest evidence exists for an association between exposure to ionizing radiation and breast cancer risk. Here we explore the existing evidence linking these environmental exposures with risk of breast cancer.

Ionizing Radiation

Ionizing radiation, including x-rays, gamma rays, cosmic rays, and radioactive particles, has the potential to induce carcinogenesis in humans by inducing DNA damage in exposed cells. The breast is one of the most sensitive organs in

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_9,

the body to the carcinogenic action of ionizing radiation. Quantitative estimates of the risk of breast cancer associated with exposure to ionizing radiation are derived principally from studies of survivors of the atomic bombings of Hiroshima and Nagasaki and persons exposed to radiation medically for diagnostic or therapeutic purposes. Studies of persons exposed in occupational settings have generally been less informative, particularly with respect to quantitative risk estimates. Although some studies have attempted to determine whether persons exposed to ionizing radiation from natural environmental sources (e.g., naturally occurring radon gas, uranium and thorium in soil, and cosmic rays) are at an increased risk of developing cancer, such studies are primarily descriptive and do not contain quantitative information on radiation dose on an individual basis. We focus here on evidence provided by studies of ionizing radiation in atomic bomb survivors as well as women exposed medically and occupationally to ionizing radiation.

Japanese Atomic Bomb Survivors

Extensive information from the Japanese atomic bomb survivors has demonstrated not only that the risk of breast cancer is increased in these exposed populations but also that the risk increases in a linear manner with increasing radiation dose (Land et al. 2003; Preston et al. 2003). Observations regarding dose–response in atomic bomb survivors suggest an influence of age at exposure and attained age. Specifically, risk is highest for exposures occurring before age 20, although there is little variation under age 20 (Tokunaga et al. 1994); risk declines with increasing age at exposure and is low in women exposed after age 40. Excess risk does not appear until at least 10 years after exposure and not before age 30. The relative risk (RR) associated with exposure is roughly constant over time, except with respect to early-onset disease (i.e., before age 35) among women who were exposed before age 20 [RR = 14.5 at 1 Sievert (Sv)] (Land et al. 1993, 2003). Based on data from this exposed population, the RR associated with a unit increase in exposure is estimated to be 2.6 per gray (Gy), and the absolute risk has been estimated at 6.7 excess cases per 10^4 person-years per Gy (Thompson et al. 1994). Early age at first birth, parity, and lactation are associated with a reduced risk of both baseline and radiation-induced breast cancer (Land et al. 1994). Risk appears to be relatively constant with time since exposure, and dose fractionation seems to have little influence on the risk per unit dose.

Medical Exposures

Several studies of medical exposures to ionizing radiation have even longer follow-up than the cohort of atomic bomb survivors. One of the most informative of these medical cohorts is a study of 2,573 women in Massachusetts who

received frequent x-ray fluoroscopy exams to monitor lung-collapse treatments for tuberculosis from 1935 to 1954 (average cumulative dose to the breast 0.79 Gy). An increased risk of breast cancer has been observed in this group, with the excess incidence related to increasing dose in a linear manner (Boice and Monson 1977; Boice et al. 1991). This excess risk appears 10–15 years after the exposure and has persisted over 50 years of follow-up. Follow-up data from this cohort indicate an excess absolute risk (EAR) of 10.7 cases per 10^4 person-years per Gy and an RR of 1.61 per Gy; exposures during adolescent and teenage years were associated with the highest risk while exposure after age 40 was associated with the lowest risk. Results from another extended follow-up study of tuberculosis patients who received multiple chest fluoroscopies are consistent with these findings (Miller et al. 1989; Howe and McLaughlin 1996). Findings from this cohort indicate a strong linear dose–response relationship between radiation dose and breast cancer mortality and also suggest that women exposed at younger ages experienced the greatest risk; additionally, after adjusting for age at exposure, data from this study suggest that the excess relative risk (ERR) may be lower between 40 and 57 years after exposure as compared with the earlier period, although not significantly so (Miller et al. 1989; Howe and McLaughlin 1996).

Several other studies have also investigated breast cancer in persons treated with radiation for Hodgkin's disease and have generally found a significant increase in breast cancer following radiation doses of 4 Gy or more. Bhatia et al. reported a high incidence of breast cancer in an international study of breast cancer among patients treated for Hodgkin's disease in childhood [standardized incidence ratio (SIR) = 75.3, 95% confidence interval (CI): 44.9–118.4] (Bhatia et al. 1996). Similar results have been reported in studies in Nordic countries (Sankila et al. 1996), France and the United Kingdom (de vathaire et al. 1999), and the United States (Hancock et al. 1993; Travis et al. 1996; van Leeuwen et al. 2003). Bhatia et al. (1996) reported evidence of a dose–response trend: compared to women with radiation doses to the mantle region of less than 20 Gy, exposures of 20–40 and greater than 40 Gy were associated with 5.9-fold (95% CI: 1.2–30.3) and 23.7-fold (95% CI: 3.7–152) increased risks of breast cancer, respectively. Differences in risk according to age at radiation exposure have not been documented in studies of Hodgkin's disease survivors.

With respect to radiation treatment for breast cancer, Boice et al. observed an increased risk of second primary contralateral breast cancer following radiation therapy for first primary breast cancer (Boice et al. 1992): in a cohort of over 41,000 women with a first primary breast cancer in Connecticut (average dose to the contralateral breast 2.8 Gy), risk of contralateral breast cancer was increased only among those treated with radiation before age 45 (RR = 1.59, 95% CI: 1.1–2.4). Alternatively, no significant increase in risk for contralateral breast cancer associated with radiotherapy was observed in a cohort of 14,000 cancer survivors in Denmark (Basco et al. 1985) or in a case–control study based on cases identified through the Danish Cancer Registry from 1943 to 1978 (Storm et al. 1992).

Women may also be exposed to medical radiation directed at the breast for the treatment of conditions other than breast cancer, such as postpartum mastitis and benign breast disease. One study of 601 women treated with radiation for postpartum mastitis in New York (average dose to the breast 3.8 Gy) and 1,239 women who had not been irradiated reported an excess of breast cancer in irradiated patients that began to emerge 10 years after exposure and increased in a linear manner with increasing radiation dose (ERR = 0.74, 95% CI: 0.2–0.7) (Shore et al. 1986). In another cohort, 1,216 women in Sweden irradiated for benign breast disease (average dose to the breast 5.8 Gy) and 1,874 women treated by other means were followed for 27 years for the incidence of breast cancer (Mattsson et al. 1995): an ERR of 1.63 per Gy (95% CI: 0.8–2.9) was reported, suggesting an increased risk of radiation-induced breast cancer in women with benign breast disease.

Several studies have focused on exposure to medical radiation during infancy. One such study was conducted in 1,200 women who had received x-ray treatment as infants for thymus enlargement between 1926 and 1957 (estimated average dose to the breast 0.69 Gy) and their 2,469 non-irradiated siblings (Hildreth et al. 1989): a linear dose–response was found in relation to breast cancer risk, with an ERR of 3.48 per Gy (95% CI: 2.1–6.2) and an EAR of 5.7 per 10^4 person-years per Gy (95% CI = 2.9–9.5). Two cohort studies in Sweden similarly assessed breast cancer risk in women treated with radiation for skin hemangioma as infants (estimated average dose to the breast 0.39 Gy): in a pooled analysis of data from these two cohorts, a significant linear dose–response was reported for breast cancer (ERR = 0.35 per Gy, 95% CI: 0.2–0.6) (Lundell et al. 1996). This relationship was not modified by age at exposure or time since exposure. Another study suggested an elevated breast cancer risk following scattered radiation received from radiotherapy for retinoblastoma during infancy (Wong et al. 1997); however, this association was based on a small number of cases, and the possible role of both chemotherapy and genetic susceptibility in the development of the tumors is unclear.

Some studies have also assessed exposure to medical radiation during childhood and adolescence. Between 1948 and 1960, more than 20,000 children in Israel received radiation treatments for tinea capitis (ringworm of the scalp). Modan et al. reported an increased breast cancer incidence in this cohort in an analysis based on follow-up through 1986 (estimated average dose to the breast 0.016 Gy), but only among those aged 5–9 years at the time of exposure (Modan et al. 1989). Another study of almost 5,500 women with scoliosis exposed to multiple diagnostic x-rays during adolescence (estimated average dose to the breast 0.11 Gy) also reported an increased risk of developing breast cancer (Hoffman et al. 1989; Doody et al. 2000). Risk increased significantly with increasing cumulative dose, with an ERR of 5.4 per Gy (95% CI: 1.2–14.1). After excluding 644 women from this cohort who had scoliosis but for whom there were no recorded radiographic exams, the ERR was reduced to 2.7 (95% CI: -0.2–9.3) (Doody et al. 2000).

Studies have also investigated breast cancer risks among patients given ^{131}I (i.e., radioiodine) for medical purposes. A study in Massachusetts showed a higher risk of breast cancer among women treated for hyperthyroidism with ^{131}I compared with patients treated by other methods, but there was no consistent trend in risk with the amount of ^{131}I administered (Goldman et al. 1988). Similar conclusions were reached in a larger study including these and other hyperthyroid patients in the United States (Ron et al. 1998). In contrast, a study of patients treated for hyperthyroidism in Sweden (Holm et al. 1991; Hall et al. 1992) did not show an elevated breast cancer risk overall, nor did it indicate a trend in risk according to the level of radiation administered. It is worth noting, however, that the mean dose to the breast in the Swedish study was estimated to be 0.06 Gy (Holm et al. 1991): studies assessing exposures of such low levels are unlikely to have sufficient statistical precision to detect an elevated risk. This problem also applies to studies of patients exposed to ^{131}I for diagnostic purposes (where the number of cases was larger but the doses substantially smaller) (Holm et al. 1989) or for the treatment of thyroid cancer (where doses were higher but the number of breast cancers was lower) (Hall et al. 1991).

Occupational Exposures

Studies of occupational exposure to ionizing radiation have generally not been very informative in generating quantitative estimates of the risk of female breast cancer. This is because most occupational cohorts that have been studied for radiation effects are predominantly male and because the radiation doses received by female workers are quite low (generally less than 0.1 Gy). Most of the information to date regarding the risk of breast cancer associated with occupational exposure to radiation comes from studies of radiation workers in the medical field. Boice et al. conducted a case–control study (528 cases) of breast cancer nested within a cohort of approximately 79,000 female radiological technologists who had worked in the United States since 1926 (Boice et al. 1995). Results from this study provided no evidence of an association with jobs involving radiotherapy, radioisotopes, or fluoroscopic equipment or with the number of years worked in such jobs. However, dosimetry records were available for only 35% of the study subjects and were mostly available for those who had worked in more recent years (and were thus likely to have lower doses than earlier workers). A subsequent mortality analysis based on a larger number of the same occupational cohort showed a standardized mortality ratio (SMR) of 1.5 (95% CI: 1.2–1.9) compared with national rates for women certified before 1940, although no increased risk was evident for women certified to work in the field more recently (Doody et al. 1998). An elevated risk of breast cancer has also been reported among radiological technologists and radiologists in China. Although radiation doses were not known for this study, measured blood counts suggested that doses were generally high (Wang et al. 1990).

There has also been some indication of an excess in breast cancer mortality among female dial painters in the United Kingdom who had used a paint containing radium (Baverstock et al. 1981; Baverstock and Papworth 1989), although the cohort included not only dial painters but also women who carried out other tasks in this workplace and another study failed to document such an association (Stebbings et al. 1984). Another study restricted to the dial painters in the United States provided some suggestion of a raised breast cancer incidence rate (Rowland et al. 1989). However, any effect of radiation in this context is more likely to be due to external irradiation of the breast from paint in containers than to exposures arising from intakes of ^{226}Ra.

Conclusions

It is clearly established that exposure to ionizing radiation is an important risk factor for breast cancer. Most of the information available regarding the risk of breast cancer associated with ionizing radiation comes from studies of the survivors of the atomic bombings of Hiroshima and Nagasaki and long-term follow-up of cohorts of people receiving radiation exposure for medical reasons (either for diagnosis or treatment procedures). Although there is considerable evidence to indicate that the risk of breast cancer increases in a linear manner with increasing radiation dose to the breast, the characteristics of the dose–response relationship are not well established. This is because there is little consistency in the studies that have been conducted to date regarding which factors influence the dose–response, and in what manner. Age at exposure appears to be an important determinant of risk, with exposure around the time of puberty conferring the highest risk. However, there are very few studies that have investigated this directly, and the most compelling findings come primarily from the atomic bomb survivor studies. Unfortunately, there is also very little information regarding the dose–response at low doses; this is a long-standing limitation of the studies of medical exposures and atomic bomb survivors, which are generally characterized by high doses and dose rates. Studies of low-dose exposures in occupational and environmental settings have not been very informative in describing dose–response relationships. Similarly, the most informative studies of dose rate and fractionation of dose have been limited to primarily higher dose rates and instantaneous (atomic bomb survivors) or relatively short-term exposure (medical exposures). Finally, studies of medical radiation exposures have included populations with a large variety of underlying conditions or diseases, which may or may not be directly related to the development of breast cancer.

Overall, there is little question that exposure to radiation is associated with an increased breast cancer risk. The current challenge is to better understand which factors that characterize the nature of the radiation exposure are most important in determining the subsequent risk of breast cancer. Future efforts should focus

on exposure circumstances that are more relevant for the current time, including low doses, low dose rates, and etiologically relevant time periods of exposure.

Environmental Pollutants

Based largely on evidence from experimental models in animals and cancer cell lines, the International Agency for Research on Cancer (IARC) considers a number of environmentally abundant chemicals, chemical compounds, and their metabolites to be either known (IARC 1983, 1997b) or suspected (IARC 1997a, 1998) human carcinogens (Table 9.1). Among these, organochlorines, polycyclic aromatic hydrocarbons (PAHs), dioxins, and bisphenol (BPA) have received particular attention with respect to breast cancer. The specific mechanisms by which exposure to environmental pollutants could impact breast cancer risk are varied and, as described in Table 9.1, the sources of exposure to these pollutants are similarly variable. What organochlorines, PAHs, dioxins, and BPA share in common, however, are their persistence in the environment and their tendency to accumulate in adipose tissue, including the fatty tissue in the breast. Concerns that exposure to these pollutants could influence a woman's risk of breast cancer stem primarily from the fact that many of these chemicals are "endocrine disruptors," mimicking or blocking the effects of specific hormones (Rudel et al. 2007). Given that some of these pollutants mimic the activity of estrogen in particular (i.e., environmental estrogens), it is hypothesized that they could influence the initiation or progression of breast cancer in humans through estrogenic effects (Soto et al. 1995; Connor et al. 1997; Shekhar et al. 1997). Additionally, the metabolism of some environmental pollutants, such as organochlorines and PAHs, can produce free radicals and bulky DNA adducts which may directly or indirectly contribute to carcinogenesis by contributing to DNA damage (Peltonen and Dipple 1995; Oakley et al. 1996).

Organochlorines

Compounds falling under the category of organochlorines are diverse in their uses, toxicities, and presence in nature. Epidemiologic studies assessing the relationship between organochlorine exposure and breast cancer risk in humans have focused primarily on polychlorinated biphenyls (PCBs), dichloro-diphenyl-trichloroethane (DDT), and its metabolite dichloro-diphenyl-dichloroethylene (DDE) (Falck et al. 1992; Moysich et al. 1999; Millikan et al. 2000; Laden et al. 2001a, b; Gammon et al. 2002; Laden et al. 2002; Zhang et al. 2004; Li et al. 2005; Raaschou-Nielsen et al. 2005). The epidemiologic literature on organochlorine exposures and breast cancer risk is extensive and diverse, with studies using a number of different methodologies and diverse populations; the vast majority of studies, however, are consistent in indicating no association.

Table 9.1 Summary of environmental pollutants and sources of exposure

Compound/agent	Uses/sources of exposure	IARC classification
Organochlorines:		
Polychlorinated biphenyls (PCBs)	(**Production banned in 1970s*) *Uses:* Previously used in industrial applications as coolants, flame retardants, sealants, adhesives, and plasticizers in paints/cements *Sources of exposure*: Persistent in the food chain, primarily fish	IARC (1998) Group 2A (probably carcinogenic)
Dichloro-diphenyl-trichloroethane (DDT) and dichloro-diphenyl-dichloroethane (DDE)	(**Use and production banned in most developed countries in the 1970s–1980s*) *Uses:* Previously used as a nonsystemic insecticide, particularly for the control of vectors of malaria, typhus, and yellow fever *Sources of exposure*: Persistent in the food chain, primarily fish and fatty meat. Also persistent in soil and sediment in some regions	IARC (1997a) Group 2B (possibly carcinogenic)
Polycyclic aromatic hydrocarbons (PAHs)	*Uses*: No direct uses, these compounds are formed as the unintentional byproduct of combustion *Sources of exposure*: Found in soil and sediment, and as particulate matter suspended in the air (air pollution, vehicular exhaust); formed by combustion of fossil fuels, wood, coal, and tobacco, and grilling or smoking or meat or fish; occupational exposure prevalent in some industries	IARC (1983) Group 1 (known human carcinogen): Occupational exposures during coal gasification, coke production, coal-tar distillation, chimney sweep, paving and roofing with coal-tar pitch, aluminum production; benzo[a]pyrene Group 2A (probably carcinogenic): Occupational exposures during calcium electrode manufacture; creosotes; cyclopenta[cd]pyrene; dibenz[a,h]anthracene; dibenzo[a,l]pyrene

Table 9.1 (continued)

Compound/agent	Uses/sources of exposure	IARC classification
		Group 2B (possibly carcinogenic): benz[j]aceanthrylene; benz[a]anthracene; chrysene; dibenzo[a,h]pyrene; 5-methylchrysene
Dioxins	*Uses*: No direct uses, these compounds are formed as unintentional byproducts of combustion, chlorine bleaching, and certain manufacturing processes *Sources of exposure*: Persistent in the food chain, particularly meat, fish, milk, and eggs; occupational exposure primarily as a result of herbicide production and use	IARC (1997b) Group 1 (known carcinogen): tetrachlorodibenzo-p-dioxin (TCDD) Group 3 (not classifiable): polychlorinated dibenzo-para-dioxins other than TCDD; polychlorinated dibenzofurans
Bisphenol A	*Uses*: Used in the production of epoxy resins that line food and beverage cans, and in the production of shatter-proof polycarbonate plastics *Sources of exposure*: Dietary exposures due to leaching of bisphenol A from food and beverage cans and polycarbonate plastic bottles and containers	No IARC evaluation at present

Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are classified as Group 2A carcinogens (probably carcinogenic to humans) by IARC (IARC 1998) and were widely used for a variety of industrial applications in the 1940s–1970s. Production of PCBs was banned in 1977, although these compounds have persisted in the environment and bioaccumulate in the food chain (Brody et al. 2007). While often studied as a single entity, a total of 209 unique PCB congeners have been identified. Based on structural properties, it has been suggested that PCB congeners can be subdivided into three distinct groups with differing biologic activity (Wolff and Toniolo 1995; Connor et al. 1997): Group I congeners may have estrogenic effects, Group II congeners appear to be anti-estrogenic, and Group III congeners induce CYP1A and CYP2B activity.

In a study conducted in the early 1990s, it was found that women with breast cancer had higher levels of PCBs in adipose tissue relative to women with benign breast disease (Falck et al. 1992). In the years since these initial findings, however, the many studies that have assessed the relationship between PCB exposure and breast cancer risk have been relatively consistent in suggesting no such association (Helzlsouer et al. 1999; Hoyer et al. 2000; Laden et al. 2001a, b; Gammon et al. 2002; Laden et al. 2002; Bosetti et al. 2003; Raaschou-Nielsen et al. 2005). Table 9.2 provides an overview of the results from recent studies of breast cancer risk in relation to PCB exposure. Large prospective studies, such as the Nurses' Health Study (Laden et al. 2001b), large retrospective studies, such as the Long Island Breast Cancer Study (Gammon et al. 2002), and cohorts of occupationally exposed women (Bosetti et al. 2003) have all failed to detect any association between overall PCB levels and breast cancer risk. Studies examining associations between levels of specific PCB congeners or congener subgroups and breast cancer risk have also been null (Hoyer et al. 2000; Laden et al. 2001a; Raaschou-Nielsen et al. 2005).

In conducting more sensitive subgroup-specific analyses, most studies find null associations across subgroups defined on the basis of age or menopausal status, although there is some suggestion that breast cancer risk in relation to PCBs is slightly higher among nulliparous women (Millikan et al. 2000; Laden et al. 2001a; Gammon et al. 2002), African-American women (Millikan et al. 2000), and lean women (Laden et al. 2001a; Gammon et al. 2002). Studies assessing the potential for gene–environment interactions have consistently indicated that the effect of PCB exposure on breast cancer risk is likely to be influenced by *CYP1A1* genotype and, specifically, by the presence of *CYP1A1* exon 7 valine for isoleucine substitution alleles (Moysich et al. 1999; Laden et al. 2002; Zhang et al. 2004; Li et al. 2005). Individuals who carry a *CYP1A1* exon 7 valine for isoleucine substitution allele may be particularly susceptible to the effects of PCBs due to the fact that this variant genotype has been linked with greater inducibility of *CYP1A1* (Cosma et al. 1993). Although there is little evidence of a relationship between polymorphisms in *CYP1A1* and breast cancer risk overall (Masson et al. 2005), women who carry a *CYP1A1* exon 7

Table 9.2 Overview of recent studies and relevant subgroup analyses on the relationship between polychlorinated biphenyls (PCB) and breast cancer risk

First Author (year)	Years	Location	Study design	Subgroup	OR (95% CI)[a]
Overall associations					
Raaschou-Nielsen (2005)	1993–2000	Denmark	Nested case–control (409 cases/409 controls)		1.1 (0.7–1.7)
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)		0.8 (0.5–1.3)
Laden (2001b)	1989–1994	USA	Nested case–control (370 cases/370 controls)		0.8 (0.5–1.2)
Hoyer (2000)	1976–1992	Denmark	Nested case–control (155 cases/274 controls)		1.6 (0.8–3.3)
Millikan (2000)	1993–1996	USA	Case–control (748 cases/659 controls)	African-American	1.7 (1.0–3.0)
				White	1.0 (0.7–1.6)
Helzlsouer (1999)	1974–1994	USA	Nested case–control (346 cases/346 controls)	*Year of collection:*	
				1974	1.1 (0.6–2.2)
				1989	0.8 (0.4–1.5)
Moysich (1999)	1986–1991	USA	Case–control (154 cases/191 controls)		1.3 (0.8–2.1)
Subgroup analyses: age/menopausal status					
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	Premenopausal	0.9 (0.5–1.7)
				Postmenopausal	0.7 (0.5–1.1)
Helzlsouer (1999)	1974–1994	USA	Nested case–control (346 cases/346 controls)	*Collection 1974:*	
				Premenopausal	2.2 (NA)
				Postmenopausal	0.6 (NA)
				Collection 1989:	
				Premenopausal	2.1 (NA)
				Postmenopausal	0.7 (NA)
Subgroup analyses: parity/breast-feeding					
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	*Parous:*	
				Never breastfed	0.8 (0.5–1.3)
				Ever breastfed	1.1 (CI: 0.6–2.0)
				Nulliparous	1.2 (0.4–3.5)

Table 9.2 (continued)

First Author (year)	Years	Location	Study design	Subgroup	OR (95% CI)[a]
Laden (2001b)	1989–1994	USA	Nested case–control (370 cases/370 controls)	*Parous:*	
				Never breastfed	0.7 (0.4–1.3)
				Ever breastfed	1.0 (0.7–1.7)
				Nulliparous	5.3 (1.1–26.6)
Millikan (2000)	1993–1996	USA	Case–control (748 cases/659 controls)	*Parous:*	
				Never breastfed	1.3 (0.8–2.1)
				Ever breastfed	0.8 (0.5–1.4)
				Nulliparous	1.6 (0.6–4.6)
Subgroup analyses: body mass index					
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	*Tertile of BMI:*	
				Lowest	1.2 (0.7–1.9)
				Middle	0.7 (0.4–1.3)
				Highest	0.9 (0.4–1.8)
Laden (2001b)	1989–1994	USA	Nested case–control (370 cases/370 controls)	*BMI* (kg/m^2):	
				<25	1.4 (0.8–2.4)
				25–29.9	1.2 (0.6–2.3)
				≥30	0.3 (0.1–0.8)
Millikan (2000)	1993–1996	USA	Case–control (748 cases/659 controls)	*Tertile of BMI:*	
				African-American	
				Lowest	0.8 (0.3–2.1)
				Middle	2.5 (0.9–7.5)
				Highest	4.5 (1.6–14.8)
				White	
				Lowest	0.7 (0.4–1.5)
				Middle	0.8 (0.4–1.7)
				Highest	1.8 (0.8–4.2)

Table 9.2 (continued)

First Author (year)	Years	Location	Study design	Subgroup	OR (95% CI)[a]
Subgroup analyses: ER status					
Raaschou-Nielsen (2005)	1993–2000	Denmark	Nested case–control (409 cases/409 controls)	ER +	1.4 (0.8–2.5)
				ER–	0.3 (0.1–0.9)
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	ER + PR +	1.0 (0.6–1.5)
				ER–PR–	0.5 (0.2–0.9)
Helzlsouer (1999)	1974–1994	USA	Nested case–control (346 cases/346 controls)	*Collection 1974:*	
				ER +	0.8 (NA)
				ER–	1.3 (NA)
				Collection 1989:	
				ER +	1.2 (NA)
				ER–	0.1 (NA)
Subgroup analyses: CYP1A1 exon 7 variant genotype					
Li (2005)	1993–2000	USA	Case–control (612 cases/599 controls)	*White women:*	*Genotype/high vs. low PCB:*
				Premenopausal	WT–WT/low: 1.0 (ref)
					WT–WT/high: 0.6 (0.4–1.0)
					Variant/low: 0.3 (0.1–0.8)
					Variant/high: 2.1 (0.4–10.6)
				Postmenopausal	WT–WT/low: 1.0 (ref)
					WT–WT/high: 0.8 (0.5–1.2)
					Variant/low: 0.7 (0.1–3.1)
					Variant/high: 0.7 (0.3–1.9)
Zhang (2004)	1994–1997	USA	Case–control (374 cases/406 controls)	*White women:*	*Genotype/high vs. low PCB:*
				Premenopausal	WT–WT/low: 1.0 (ref)
					WT–WT/high: 1.1 (0.2–5.0)
					Variant/low: 1.3 (0.7–2.3)
					Variant/high: 2.2 (0.4–12.0)

Table 9.2 (continued)

First Author (year)	Years	Location	Study design	Subgroup	OR (95% CI)[a]
				Postmenopausal	WT–WT/low: 1.0 (ref) WT–WT/high: 1.8 (0.7–4.5) Variant/low: 1.1 (0.8–1.6) Variant/high: 4.3 (1.6–12.0)
Laden (2002)	1989–1994	USA	Nested case–control (367 cases/367 controls)	*Postmenopausal*	*Genotype/tertile of PCB:* WT–WT/low: 1.0 (ref) WT–WT/middle: 1.0 (0.6–1.6) WT–WT/high: 1.0 (0.6–1.7) Variant/low: 0.5 (0.2–1.4) Variant/middle: 1.3 (0.5–3.2) Variant/high: 2.8 (1.0–7.8)
Moysich (1999)	1986–1991	USA	Case–control (154 cases/191 controls)		*Genotype/high vs. low PCB:* WT–WT/low: 1.0 (ref) WT–WT/high: 1.1 (0.6–1.9) Variant/low: 0.9 (0.3–2.7) Variant/high: 2.9 (1.2–7.5)

[a]Odds ratio comparing the highest versus lowest category of PCB exposure unless otherwise noted. PCB levels in blood were assessed in all studies except for the study by Raaschou-Nielsen et al. (2005) which used adipose tissue.

valine for isoleucine substitution allele who also have a high PCB body burden appear to have a two- to four-fold increased risk of breast cancer relative to women with two wild-type alleles and/or low PCB body burden (Moysich et al. 1999; Laden et al. 2002; Zhang et al. 2004; Li et al. 2005). The magnitude of this association and the fact that approximately 10–15% of Caucasians carry at least one such polymorphism (Shields et al. 1993) reinforce the need to consider gene–environment interactions in evaluating the associations between environmental pollutants and breast cancer risk.

Dichloro-diphenyl-trichloroethane (DDT) and Dichloro-diphenyl-dichloroethane (DDE)

Dichloro-diphenyl-trichloroethane (DDT) was used widely as an agricultural insecticide in the years following World War II, until its use was banned in the United States in 1972. Due in part to evidence from animal studies, DDT and its associated compounds have been classified as Group 2B carcinogens (possibly carcinogenic) by IARC (IARC 1997a). Similar to PCBs, DDT is ubiquitous in nature and accumulates in the food chain, particularly in fish and fatty foods. Also similar to some PCBs, DDT has estrogenic effects (Soto et al. 1995; Dees et al. 1997; Shekhar et al. 1997); in particular, studies have documented that DDT can regulate estrogen receptor (ER)-mediated cellular responses and stimulate cell cycle progression in ER-positive (ER+) breast cancer cell lines (Dees et al. 1997; Shekhar et al. 1997). The primary metabolite of DDT, dichloro-diphenyl-dichloroethane (DDE), is more prevalent and more persistent in the environment than DDT itself; therefore, studies often measure DDE levels as a surrogate for past exposure to DDT. However, the estrogenic effects of DDE appear to be weak (Shekhar et al. 1997), adding complexity to the interpretation and measurement of past DDT exposure.

More than 25 epidemiologic studies have examined the potential association between exposure to DDE and breast cancer risk (Laden et al. 2001a; Snedeker 2001; Lopez-Cervantes et al. 2004; Raaschou-Nielsen et al. 2005; Cohn et al. 2007). Table 9.3 provides an overview of recent studies examining the potential association between DDE exposure and breast cancer risk. Although most studies have been small in size and many are limited by a narrow range of exposure levels, a large meta-analysis of 22 studies found no evidence of any association between DDE levels and breast cancer risk [odds ratio (OR) = 1.0, 95% CI: 0.9–1.1, highest vs. lowest category of exposure] (Lopez-Cervantes et al. 2004). Stratified analyses suggest that this lack of association between DDE levels and breast cancer risk is consistent across parity (Laden et al. 2001a, b; Gammon et al. 2002), body mass index (Laden et al. 2001a, b; Gammon et al. 2002), age (Gammon et al. 2002), and menopausal status (Gammon et al. 2002).

Table 9.3 Overview of recent studies and relevant subgroup analyses on the DDT and DDE relationship between and breast cancer risk

First Author (year)	Years	Location	Study design	Subgroup	Odds ratio (95% CI)[a]
Overall associations					
Cohn (2007)	1959–1998	USA	Nested case–control (129 cases/129 controls)		DDT: 2.8 (1.2–6.7)
Raaschou-Nielsen (2005)	1993–2000	Denmark	Nested case–control (409 cases/409 controls)		DDT: 0.6 (0.3–1.0)
					DDE: 0.7 (0.5–1.2)
Charlier (2004)	1999–2000	Belgium	Hospital-based case–control (159 cases/250 controls)		DDT: 5.6 (1.8–17.7)
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)		DDT: 1.2 (0.7–1.8)
					DDE: 1.2 (0.8–1.9)
Laden (2001b)	1989–1994	USA	Nested case–control (372 cases/372 controls)		DDE: 0.8 (0.5–1.4)
Hoyer (2000)	1976–1992	Denmark	Nested case–control (155 cases/274 controls)		DDT: 3.6 (1.1–12.2)
					DDE: 1.4 (0.7–2.8)
Millikan (2000)	1993–1996	USA	Case–control (748 cases/659 controls)	African-American	DDE: 1.4 (0.9–2.3)
				White	DDE: 1.0 (0.7–1.4)
Romieu (2000)	1990–1995	Mexico	Case–control (120 cases/126 controls)		DDE: 3.8 (1.1–12.8)
Helzlsouer (1999)	1974–1994	USA	Nested case–control (346 cases/346 controls)	*Year of collection:*	
				1974	DDE: 0.7 (0.4–1.3)
				1989	DDE: 0.6 (0.3–1.2)
Subgroup analyses: age/menopausal status					
Cohn (2007)	1959–1998	USA	Nested case–control (129 cases/129 controls)	*Age in 1945:*	
				<4 years	DDT: 11.5 (1.0–138.9)
				4–7 years	DDT: 9.6 (0.7–137.2)
				8–13 years	DDT: 3.9 (0.9–19.2)
				≥14 years	DDT: 0.6 (0.1–3.2)
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	Premenopausal	DDE: 0.9 (0.4–1.7)
				Postmenopausal	DDE: 1.1 (0.7–1.7)
Romieu (2000)	1990–1995	Mexico	Case–control (120 cases/126 controls)	Premenopausal	DDE: 2.4 (0.4–15.8)
				Postmenopausal	DDE: 5.3 (0.8–34.3)

Table 9.3 (continued)

First Author (year)	Years	Location	Study design	Subgroup	Odds ratio (95% CI)[a]
Helzlsouer (1999)	1974–1994	USA	Nested case–control (346 cases/346 controls)	*Collection 1974:*	
				Premenopausal	DDE: 0.9 (NA)
				Postmenopausal	DDE: 0.5 (NA)
				Collection 1989:	
				Premenopausal	DDE: 1.4 (NA)
				Postmenopausal	DDE: 0.5 (NA)
Subgroup analyses: parity/breast-feeding					
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	*Parous:*	
				Never breastfed	DDE: 1.1 (0.7–1.8)
				Ever breastfed	DDE: 1.0 (0.5–1.8)
				Nulliparous	DDE: 0.8 (0.2–2.4)
Laden (2001)	1989–1994	USA	Nested case–control (372 cases/372 controls)	*Parous:*	
				Never breastfed	DDE: 0.7 (0.4–1.3)
				Ever breastfed	DDE: 1.1 (0.7–1.8)
				Nulliparous	DDE: 0.6 (0.1–1.9)
Millikan (2000)	1993–1996	USA	Case–control (748 cases/659 controls)	*Parous:*	
				Never breastfed	DDE: 1.2 (0.8–1.9)
				Ever breastfed	DDE: 0.8 (0.5–1.4)
				Nulliparous	DDE: 1.5 (0.5–4.5)
Subgroup Analyses: Body Mass Index					
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	*Tertile of BMI:*	
				Lowest	DDE: 1.2 (0.7–2.0)
				Middle	DDE: 0.9 (0.5–1.8)
				Highest	DDE: 1.2 (0.5–2.6)
Laden (2001)	1989–1994	USA	Nested case–control (372 cases/372 controls)	*BMI (kg/m^2):*	
				<25	DDE: 1.2 (0.7–1.9)
				25–29.9	DDE: 0.6 (0.3–1.2)

Table 9.3 (continued)

First Author (year)	Years	Location	Study design	Subgroup	Odds ratio (95% CI)[a]
				≥30	DDE: 0.8 (0.3–1.9)
Millikan (2000)	1993–1996	USA	Case–control (748 cases/659 controls)	*Tertile of BMI:*	
				African-American	
				Lowest	DDE: 1.5 (0.6–3.5)
				Middle	DDE: 1.0 (0.5–1.9)
				Highest	DDE: 1.1 (0.4–2.8)
				White	
				Lowest	DDE: 1.3 (0.6–2.6)
				Middle	DDE: 1.9 (0.7–5.1)
				Highest	DDE: 0.9 (0.4–1.8)
Subgroup Analyses: ER Status					
Raaschou-Nielsen (2005)	1993–2000	Denmark	Nested case–control (409 cases/409 controls)	ER +	DDT: 0.6 (0.3–1.1)
					DDE: 1.1 (0.6–1.8)
				ER–	DDT: 0.5 (0.1–2.1)
					DDE: 0.1 (0.0–0.5)
Gammon (2002)	1996–1997	USA	Case–control (646 cases/429 controls)	ER + PR +	DDE: 1.1 (0.7–1.8)
				ER–PR–	DDE: 1.0 (0.5–1.9)
Helzlsouer (1999)	1974–1994	USA	Nested case–control (346 cases/346 controls)	*Collection 1974:*	
				ER +	DDE: 0.8 (NA)
				ER–	DDE: 1.7 (NA)
				Collection 1989:	
				ER +	DDE: 0.6 (NA)
				ER–	DDE: 0.2 (NA)

[a]Odds ratio comparing the highest versus lowest category of exposure unless otherwise noted. Levels of DDT and DDE in blood were assessed in all studies except for the study by Raaschou-Nielsen et al. (2005) which used adipose tissue.

Fewer studies have been able to directly assess DDT levels in relation to breast cancer risk (Hoyer et al. 2000; Romieu et al. 2000; Gammon et al. 2002; Charlier et al. 2004; Raaschou-Nielsen et al. 2005; Cohn et al. 2007) (Table 9.3). While most of these studies suggest no association between DDT exposure and breast cancer risk, the few studies that do find an association indicate that the timing and methodology used for DDT measurement are likely to be important (Hoyer et al. 2000; Charlier et al. 2004; Cohn et al. 2007). One prospective study observed a significant positive association between DDT level and breast cancer risk only when DDT levels were taken as the average of levels from two blood specimens taken 5 years apart, with the suggestion that repeated measures may be necessary to reflect an individual's body burden of DDT (Hoyer et al. 2000). In another study that used stored blood specimens collected between 1959 and 1967 to measure DDT levels, it was observed that women in the highest tertile of serum DDT had a five-fold increased risk of breast cancer in the 20 years following specimen collection relative to those in the lowest tertile of DDT levels (Cohn et al. 2007); however, this association was restricted to women born between 1932 and 1945, suggesting that the timing of exposure plays an important role in the relationship between DDT exposure and breast cancer risk.

Few studies have examined the potential for gene–environment interactions in the relationship between DDT exposure and breast cancer risk (Helzlsouer et al. 1999), although there is likely to be much interindividual variation in the susceptibility to and metabolism of DDT and DDE.

Polycyclic Aromatic Hydrocarbons (PAHs)

Formed as byproducts of combustion, the primary sources of human exposure to polycyclic aromatic hydrocarbons (PAHs) are tobacco smoke, air pollution, vehicle exhaust, and smoked or grilled meat and fish (Brody et al. 2007). A large number of chemicals are individually classified as PAHs, but these chemicals are usually present in complex mixtures, such as soot. Based largely on evidence from studies relating to lung cancer, IARC has classified PAH mixtures as a "known human carcinogen" and considers some individual PAHs to be "probable human carcinogens" (IARC 1983). Animal studies also suggest that exposure to PAHs causes mammary tumors (Rudel et al. 2007).

There are several potential mechanisms by which PAHs could directly or indirectly initiate or promote breast tumor formation. Consistent with the structural similarity of PAHs to steroid hormones, some PAHs are considered environmental estrogens, although their estrogenic effects are generally weak (Santodonato 1997). Other PAHs, however, appear to be ER agonists and bind preferentially to aryl hydrocarbon receptors (Bigelow and Nebert 1982), triggering the induction of cytochrome P450 isoenzymes. Cytochrome P450 transforms PAHs into highly reactive intermediates capable of binding to DNA, forming bulky adducts (Peltonen and Dipple 1995). These bulky

PAH–DNA adducts can disrupt and interfere with DNA replication, repair, and transcription; therefore, it is biologically plausible that the accumulation of PAH–DNA adducts could contribute to carcinogenesis.

Studies comparing levels of PAH–DNA adducts in breast tumors to levels in benign tissue suggest that adduct levels are significantly higher in tumor tissue (Rundle et al. 2000). Case–control studies that have compared PAH–DNA adduct levels in blood or adipose tissue from cases and controls suggest that women with detectable PAH–DNA adduct levels have an increased risk of breast cancer, although no dose–response relationship has been observed (Rundle et al. 2000; Gammon et al. 2004).

Informed by knowledge of the potential biological mechanisms by which PAH exposure and PAH–DNA adducts may contribute to mammary carcinogenesis, a number of studies have assessed interactions with genes involved in DNA repair (*XPA*, *XPC*, *XPD*, *XPF*, *XPG*, *ERCC1*, *IGHMBP2*), apoptosis (*TP53*), estrogen metabolism (*SULT1A1*), and detoxification of PAH metabolites (*GSTM1*) (Rundle et al. 2002; Tang et al. 2003; Terry et al. 2004; Shen et al. 2006; Crew et al. 2007; Gaudet et al. 2008; Shen et al. 2008). While the majority of these studies provide no strong evidence of gene–environment interactions, there is some evidence to suggest that women with a *GSTM1*-null phenotype (Rundle et al. 2002), women homozygous for the Asp312Asn polymorphism in *XPD* (Crew et al. 2007), women homozygous for the 8092C/A polymorphism in *ERCC1* (Crew et al. 2007), and women with a variant Thr671Ala polymorphism in *IGHMBP2* (Shen et al. 2006) may be most susceptible to the effects of PAH exposure. Polymorphisms in these genes may alter a woman's capacity for DNA repair and response to oxidative stress, modifying the effect of PAH exposure on breast cancer risk.

Studies that have assessed the relationship between exposure to air pollution, traffic congestion, or cigarette smoke and breast cancer risk also indirectly assess the effects of PAHs (Lewis-Michl et al. 1996; Terry and Rohan 2002; Bonner et al. 2005; Nie et al. 2007). Using historical measurements of total suspended particulates and traffic congestion, maps of industrial facilities, residential histories, and mathematical modeling to reconstruct exposure histories, studies have suggested that exposure to high levels of PAHs in early childhood (Bonner et al. 2005), at the time of first birth (Nie et al. 2007), or in the past 10–20 years (Lewis-Michl et al. 1996) could increase a woman's risk of postmenopausal breast cancer; associations with risk of premenopausal breast cancer are somewhat less consistent (Bonner et al. 2005; Nie et al. 2007). While only a small number of studies have investigated air pollution as a risk factor for breast cancer, the epidemiologic literature examining the relationship between smoking and breast cancer is extensive (Terry and Rohan 2002). Most such studies suggest little if any association between either active or passive smoking and breast cancer risk (Terry and Rohan 2002); however, tobacco smoke also contains carcinogens other than PAHs (IARC 2002), and any association between PAH exposure from tobacco smoke and breast cancer risk is likely to be modified by genetic factors.

Given the multiple potential sources of exposure to PAHs and interindividual variability in response to PAH exposure, assessing the potential relationship between exposure to PAHs and breast cancer risk is complex. Indirect reconstruction of PAH exposure history using geographical information, smoking and dietary habits, and residential histories is imprecise and may be subject to substantial confounding. Even in measuring PAH exposure more directly through biological measures, interpreting PAH–DNA adduct levels is complicated: elevated adduct levels may imply either high levels of past exposure, a poor response to PAH exposure, or both. However, it is biologically plausible that PAH exposure and the accumulation of PAH–DNA adducts could contribute to breast carcinogenesis either directly or indirectly, and epidemiologic studies conducted to date lend some support to this hypothesis.

Dioxins

Similar to PAHs, dioxins are formed as an unintentional byproduct of combustion and many industrial processes. Of the 211 different dioxin congeners, 17 are considered toxic and many are endocrine disruptors (IARC 1997b). Tetrachlorodibenzo-*p*-dioxin (TCDD), the most widely studied dioxin, is considered by IARC to be a multisite carcinogen in animals and is classified as a Group 1 carcinogen (carcinogenic to humans) (IARC 1997b). Studies using rat models to examine the effects of prenatal exposure to TCDD indicate that early exposure to this toxic dioxin can lead to an altered architecture in the mammary gland: adolescent rats prenatally exposed to TCDD have an increased number of terminal end buds and fewer lobules relative to untreated rats (Brown et al. 1998; Jenkins et al. 2007). This altered architecture could result in greater susceptibility to carcinogenic insult in adulthood. However, while animal studies support the plausibility of TCDD as a mammary carcinogen, human studies have not found strong evidence of an association between dioxin exposure and breast cancer risk. The strongest evidence for the carcinogenicity of TCDD in humans comes from studies looking at cancer overall, rather than specific cancer sites (IARC 1997b).

Most epidemiologic literature on dioxin exposure in relation to breast cancer risk comes from cohorts of occupationally exposed individuals (Manz et al. 1991; Kogevinas et al. 1993) or geographically defined populations exposed as the result of an industrial accident (Warner et al. 2002; Viel et al. 2008). Cohort studies of workers occupationally exposed to dioxins are few, inconsistent, and include only small numbers of women, making it difficult to examine any association with breast cancer risk: in a study pooling 20 cohorts of workers in chemical plants, only 701 of 18,910 workers were women, of whom 169 were exposed to dioxin and 7 developed breast cancer (Kogevinas et al. 1993). An explosion at a trichlorophenol manufacturing plant in Seveso, Italy, in 1976 has

also provided a cohort of highly exposed individuals: measuring dioxin levels from serum samples collected soon after the explosion, a 10-fold increase in TCDD level was associated with a 2.1-fold (95% CI: 1.0–4.6) increased risk of breast cancer after 20 years of follow-up (Warner et al. 2002). Another study employed dispersion models to reconstruct dioxin exposures for women living near a municipal solid waste incinerator (Viel et al. 2008); this study observed a null to moderate inverse association between reconstructed dioxin exposure and breast cancer risk (OR for high vs. very low exposure = 0.9, 95% CI: 0.4–1.8, and OR = 0.3, 95% CI: 0.1–0.9, for women aged 20–59 and women aged 60 years and older, respectively), although the range of dioxin exposures was more narrow than that observed in Seveso. In addition to these studies in highly exposed populations, two small hospital-based case–control studies have compared levels of different dioxin congeners from breast tissue in women with breast cancer and women with benign breast conditions (Hardell et al. 1996; Reynolds et al. 2005). While neither study observed any association with levels of TCDD, the most toxic dioxin, both studies did observe a slightly increased risk associated with elevated levels of another dioxin congener, octachlorodibenzo-*p*-dioxin (OCDD). Overall, however, epidemiologic evidence in support of an association between dioxin exposure and breast cancer risk is limited and weak.

Bisphenol A (BPA)

Bisphenol A (BPA) is an important monomer in the production of the epoxy resins that line food and beverage cans and in the production of the shatterproof polycarbonate plastics that are used in a wide variety of household products and devices. Although no epidemiologic studies have been conducted to assess the relationship between BPA exposure and breast cancer risk in humans, a number of animal and in vitro studies implicate BPA as a potential mammary carcinogen.

Studies in mouse and rat models have suggested that in utero exposure to BPA results in alterations in the architecture of the adolescent and adult breast (Durando et al. 2007; Murray et al. 2007; Moral et al. 2008). Specifically, mammary glands in animals prenatally treated with BPA have an increased number of undifferentiated epithelial structures (Moral et al. 2008), more progesterone receptor-positive (PR+) epithelial cells (Murray et al. 2007), decreased apoptosis (Murray et al. 2007; Moral et al. 2008), and enhanced sensitivity to estradiol (Murray et al. 2007). Prenatally exposed animals also have a greater number of hyperplastic ducts in adulthood (Durando et al. 2007; Murray et al. 2007), are more susceptible to adult exposures to carcinogens (Durando et al. 2007), and are more likely to develop neoplastic lesions in the breast (Murray et al. 2007).

In vitro studies demonstrate the estrogenic properties of BPA (Olsen et al. 2003; Singleton et al. 2004; Iso et al. 2006). Although BPA has only weak binding affinity to the ER, studies treating breast cancer cell lines with BPA suggest that BPA can induce cell growth (Olsen et al. 2003) and cause genotoxicity (Iso et al. 2006) in an ER-dependent manner. There is also evidence to suggest that BPA may modulate the expression of target genes in breast cancer cells (Olsen et al. 2003; Singleton et al. 2004).

In 2008, the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) evaluated the literature on the potential adverse health effects of exposure to BPA (Chapin et al. 2008); in that report, the NTP concluded that there was "minimal concern" for the potential effects of BPA on the mammary gland. Given the widespread use of BPA and concerns raised by animal studies, however, there is likely to be additional research into the potential association between BPA exposure and breast cancer risk in the future.

Conclusions

Animal and in vitro studies suggest that environmental pollutants, such as organochlorines, PAHs, dioxins, and BPA could plausibly contribute to the initiation or promotion of breast cancer. In spite of the well-established carcinogenic potential of some of these compounds, extensive epidemiologic research has failed to find an association between exposure to specific environmental pollutants and overall risk of breast cancer. However, it is conceivable that this failure to document any such relationship stems from methodological limitations of prior studies in terms of quantifying past exposures and consideration of relevant subgroup analyses or gene–environment interactions. In particular, individual variation in metabolism is likely to impact not only detected serum or adipose levels of pollutants but also the risk associated with persistent pollutant exposure; therefore, gene–environment interactions and subgroup-specific effects are likely to be important. Additionally, studies that focus on individual pollutants may fail to detect the impact of exposures in combination, and studies that measure serum or adipose levels of pollutants many years after exposure may fail to account for the potential relevance of timing of exposure. In light of these methodological complications, it is not entirely surprising that the majority of epidemiologic studies have failed to document any association between exposure to specific environmental pollutants and breast cancer risk overall (Snedeker 2001; Lopez-Cervantes et al. 2004; Brody et al. 2007). However, given the biological plausibility of such associations and the fact that these pollutants are ubiquitous, there is a continued interest in the study of environmental pollutants in relation to breast cancer risk.

Extremely Low-Frequency (ELF) Magnetic Fields

Extremely low-frequency (ELF) magnetic fields result from the generation, distribution, and use of electric power, a hallmark of industrialization and modernization. There is considerable evidence from experimental studies in laboratory animals to support a link between ELF magnetic field exposure and decreased melatonin levels (Semm et al. 1980; Wilson et al. 1981; Welker et al. 1983; Olcese and Reuss 1986; Reiter et al. 1988; Stehle et al. 1988; Lerchl et al. 1991; Yellon 1991; Kato et al. 1993; Loscher et al. 1994), as well as limited data to support this link in humans (Semm 1992; Graham et al. 1995; Reif et al. 1995; Davis et al. 2001, 2006). More directly, a number of animal studies have found increased breast cancer incidence under varying conditions of magnetic field exposure (Beniashvili et al. 1991; Loscher et al. 1993; Mevissen et al. 1993; Loscher and Mevissen 1994; Loscher et al. 1994; Baum et al. 1995; Loscher and Mevissen 1995). It has been hypothesized that the disruption of the normal nocturnal rise in melatonin resulting from exposure to ELF magnetic fields could confer an increased risk of breast cancer through mechanisms similar to those described in Chapter 10 regarding shift work and circadian rhythm dysregulation (Stevens 1987; Stevens et al. 1992). As described below, ELF magnetic field exposure can come from residential or occupational sources but, regardless of the source, there is limited evidence of an association between magnetic field exposure and breast cancer risk overall.

Residential ELF Magnetic Field Exposure and Breast Cancer

There have been a number of studies of residential exposure to magnetic fields and the risk of breast cancer [reviewed in (Brainard et al. 1999; Caplan et al. 2000)]. Several studies have employed self-reported usage of bed-warming devices (e.g., electric blankets) as the primary exposure measure (Vena et al. 1991, 1994; Gammon et al. 1998; Laden et al. 2000; Zheng et al. 2000; McElroy et al. 2001; Kabat et al. 2003); of these, only two found an association with breast cancer risk, but the results were not statistically significant. However, these studies are all limited by the inability to account for ambient residential and occupational magnetic field exposure from other sources and are subject to recall bias. Other studies have used characteristics of power distribution and/or transmission lines surrounding participants' current and historical residences as an indirect method to estimate ambient exposure to residential magnetic fields in a more objective manner (Wertheimer and Leeper 1982; McDowall 1986; Wertheimer and Leeper 1987; New York State Department of Health Bureau of Environmental and Occupational Epidemiology 1992; Schreiber et al. 1993; Verkasalo et al. 1996; Li et al. 1997; Coogan and Aschengrau 1998; Feychting et al. 1998; Davis et al. 2002; London et al. 2003), two of which also employed magnetic field measurements in the home at diagnosis to estimate ambient

exposure (Davis et al. 2002; London et al. 2003). Of these, seven studies found no evidence that exposure to residential magnetic fields is associated with an increased risk of breast cancer (McDowall 1986; Schreiber et al. 1993; Verkasalo et al. 1996; Li et al. 1997; Coogan and Aschengrau 1998; Davis et al. 2002; London et al. 2003), with definitions of high exposure to magnetic fields varying from use of distance to transmission lines [30–500 m] to a classification of high current configuration using a wire coding technique originally developed by Wertheimer and Leeper (1979).

In contrast to these seven studies finding no association, three other studies have reported an increased risk of breast cancer associated with exposure to residential magnetic fields using characteristics of wiring configuration as the primary exposure metric (Wertheimer and Leeper 1979; Wertheimer and Leeper 1987; New York State Department of Health Bureau of Environmental and Occupational Epidemiology 1992; Feychting et al. 1998). Wertheimer and Leeper found an increased risk of breast cancer among women with high current configuration, relative to matched controls (C-ratio = 164, $p < 0.01$), and this relationship was slightly more pronounced in premenopausal than postmenopausal women; however, the coder of all addresses was aware of the case–control status of the subjects adding the potential for bias (Wertheimer and Leeper 1982, 1987). A study in New York State found slightly increased age-adjusted incidence rates of breast cancer among women who resided in census tracks containing 138 kV transmission lines at the time of diagnosis [incidence rate (IR): 102.9 in exposed vs. 96.3 in not exposed, Nassau and Suffolk counties] (New York State Department of Health Bureau of Environmental and Occupational Epidemiology 1992); however, women living in these "exposed" census tracks had higher average income levels and more localized staging of breast cancer. Feychting et al. (1998) reported an association between magnetic field exposure as estimated from surrounding residential power lines and breast cancer risk among young women (aged <50 years at diagnosis) [RR = 1.8, 95% CI: 0.7–4.3, for calculated magnetic field level $\geq$0.2 vs. <0.1 μT]. Using the same exposure measure, risk was highest with respect to ER+ breast cancer in young women, but these results were based on only six exposed cases and one exposed control (RR = 7.4, 95% CI: 1.0–178.1) (Feychting et al. 1998).

A number of studies have assessed magnetic field exposure to individual study participants in various ways and have generally found mixed results regarding breast cancer risk. In a cohort study conducted in England, McDowall (1986) defined exposure as living within 30 m of either electrical installation equipment or an overhead power cable. An OR of 1.06 (95% CI: 0.7–1.6) was reported based on 22 cases. Schreiber et al. defined high exposure as living within 100 m from electrical transmission equipment and reported an OR of 0.96 (95% CI: 0.3–2.2) based on 14 cases in the Netherlands (Schreiber et al. 1993). In a much larger cohort study conducted in Finland, Verkasalo et al. defined high exposure as living within 500 m from overhead transmission lines with calculated magnetic field exposure >0.01 μT and reported an OR of 0.95 (95% CI: 0.9–1.0) based on

1,229 cases (Verkasalo et al. 1996). In a case–control study conducted in Taiwan, Li et al. reported OR's of 1.0 (95% CI: 0.9–1.3) and 1.2 (95% CI: 0.9–1.5) associated with living within 50 m and 50–99 m of transmission lines, respectively, based on a total of 1,980 cases and 1,880 controls (Li et al. 1997). In a case–control study conducted in Massachusetts, Coogan and Aschengrau (1998) reported a non-significant increase in breast cancer risk for participants who lived within 152 m of a transmission line or substation, but the confidence interval of the OR was quite large (OR = 1.5, 95% CI: 0.6–3.3). The authors acknowledged the study was limited by small numbers and exposure misclassification and concluded that their study did not support the hypothesis that exposure to 60-Hz magnetic fields increases the risk of breast cancer.

Two studies employed direct measurements of magnetic field levels in the home at diagnosis to estimate exposure. In a population-based case–control study conducted in the Seattle area, Davis and colleagues found no relationship between exposure to residential magnetic fields and increased breast cancer risk, using both current wire configuration and measured magnetic fields in the home to estimate residential exposure (Davis et al. 2002). A similar study by London et al. used both wiring configuration of current and historical residences and measured magnetic fields in the current residence to estimate exposure to residential magnetic fields (London et al. 2003). Relative to low-current configuration, high-current configuration was not associated with risk; stronger measured magnetic fields were also not associated with increased risk.

Occupational ELF Magnetic Field Exposure and Breast Cancer

There is also little epidemiological evidence that occupational magnetic field exposure increases the risk of breast cancer overall [reviewed in (Brainard et al. 1999; Caplan et al. 2000)]. However, many of the occupational studies assessing this potential association are limited by small numbers and crude estimations of exposure. Several of the more recent studies that attempted to address these limitations reported slightly increased breast cancer risk associated with occupational magnetic field exposure, but none have demonstrated a clear dose–response relationship (Floderus et al. 1999; Kliukiene et al. 1999; Forssen et al. 2000; Van Wijngaarden et al. 2001; Labreche et al. 2003; Kliukiene et al. 2004). Additionally, several studies that have been able to conduct subgroup analyses have found suggestive effects among premenopausal women, particularly with respect to ER+ breast cancer (Loomis et al. 1994; Coogan et al. 1996; Kliukiene et al. 1999; Forssen et al. 2000; Van Wijngaarden et al. 2001; Labreche et al. 2003; Kliukiene et al. 2004).

Most of the initial studies of occupational magnetic field exposure and breast cancer risk relied on job title as an indicator of exposure. Vagero et al. found no evidence of an increased risk in a cohort of telecommunications workers in Sweden (SIR = 0.6, 95% CI: 0.3–1.3) (Vagero et al. 1985); however, results

were based on just seven breast cancer cases. Guenel et al. conducted a much larger cohort study in Denmark in which exposure was defined as belonging to an occupational group with potential for magnetic field exposure above 0.3 μT (Guenel et al. 1993); there was no evidence of a relationship between breast cancer risk and occupational magnetic field exposure. In a large case–control study of 28,434 cases and 113,011 controls conducted in the United States by Loomis et al., in which exposure classification was based solely on having an "electrical worker" job title, the OR was 1.38 (95% CI: 1.0–1.8) based on 68 exposed cases (Loomis et al. 1994). Kliukiene and colleagues reported a slight but statistically non-significant increase in the risk of breast cancer associated with occupational magnetic field exposure as indicated by job title (OR = 1.13, 95% CI: 0.9–1.4, highest exposure vs. no exposure) (Kliukiene et al. 2004). Using a job title exposure matrix, Cantor et al. reported a slightly increased breast cancer risk with medium but not high exposure in a large case–control study in the United States (Cantor et al. 1995).

Several studies have evaluated breast cancer risk from occupational magnetic field exposure according to menopausal status (Coogan et al. 1996; Kliukiene et al. 1999; Forssen et al. 2000; Van Wijngaarden et al. 2001; Labreche et al. 2003). Coogan et al. (1996) used job title classification to determine exposure in a large case–control study of 6,888 cases and 9,529 controls in the United States and reported an overall OR of 1.43 (95% CI: 1.0–2.1) associated with the highest exposure level; the risk among premenopausal women in the highest exposure category (OR = 1.98, 95% CI: 1.0–3.8) was higher than for postmenopausal women (OR = 1.33, 95% CI: 0.8–2.2). Kliukiene et al. (1999) classified participants according to potential exposure to magnetic fields based upon determination by an "expert panel" in a population-based cohort study in Norway. They reported an overall RR of 1.14 (95% CI: 1.1–1.2) in the highest exposure category, relative to the lowest; risks were slightly higher when limited to women <50 years of age (RR = 1.20, 95% CI: 1.1–1.3). Forssen and colleagues (2000) used a job exposure matrix based on magnetic field measurements in a case–control study conducted in Sweden and reported no association overall (OR = 1.0, 95% CI: 0.6–1.7) but an elevated risk in women under age 50 (OR = 1.5, 95% CI: 0.6–3.5), particularly with respect to ER+ breast cancer (OR = 3.2, 95% CI: 0.5–18.9). Using data from a job measurement survey, Van Wijngaarden et al. (2001) reported increased risk associated with intermediate levels of exposure accumulated 20 or more years prior (OR = 1.5, 95% CI: 1.1–2.0), but not for higher levels of exposure or more recent exposure; associations were higher for premenopausal and for ER+ breast cancer, but no consistent dose–response pattern was observed. In a case–control study of postmenopausal women, Labreche et al. (2003) found a slight but not statistically significant increased risk of breast cancer overall in participants with an occupational history of jobs determined to have medium or high magnetic field exposure (OR = 1.21, 95% CI: 1.0–1.5), but among participants with such exposure prior to age 35, the risk of PR+ breast cancer was greater (OR = 1.56, 95% CI: 1.0–2.4).

Conclusions

In summary, there have been a considerable number of studies investigating the possible relationship between exposure to ELF magnetic fields and an increased risk of breast cancer. These studies have employed different study designs, have defined exposure both directly and indirectly (for individuals as well as groups), and have considered exposures in residential and occupational settings. On balance, there is little consistent and reproducible evidence of an association between residential exposure to ELF magnetic fields and the risk of breast cancer. In contrast, there is some intriguing evidence that risk of ER + breast cancer and/or breast cancer in premenopausal or younger women may be increased with exposure to ELF magnetic fields in some occupational settings.

Trace Elements and Heavy Metals

In addition to the exposures described above, exposure to trace elements and heavy metals occurring naturally in the environment may influence a woman's risk of developing breast cancer. As with environmental pollutants, exposure to these naturally occurring trace elements and heavy metals can come from a variety of sources, including drinking water, air, food, and occupational exposure, with substantial geographic variation. Some trace elements such as arsenic (IARC 1987) and some heavy metals such as cadmium (IARC 1993) and lead (IARC 1987) are considered by IARC to be either known or suspected human carcinogens at specified doses of exposure. Others, such as selenium, copper, iron, and zinc, may plausibly be associated with breast cancer risk given their biological roles. However, evidence associating exposure to these elements with breast cancer risk is limited (Navarro Silvera and Rohan 2007).

With respect to trace element exposure and breast cancer risk, the most extensive literature is that regarding selenium. Selenium is an essential element and has been hypothesized to lower cancer risk by counteracting oxidative stress. While biologically plausible, however, existing studies do not support an association between selenium levels and breast cancer risk, regardless of whether selenium exposure is ascertained through toenail specimens, blood, or dietary questionnaires (Navarro Silvera and Rohan 2007). Another trace element, arsenic, is classified as a Group 1 carcinogen (carcinogenic to humans) by IARC; however, evidence for the carcinogenicity of this trace element is largely limited to lung and bladder cancer (Navarro Silvera and Rohan 2007). Only one prior study has examined arsenic exposure levels in relation to breast cancer risk: in a nested case–control study, no differences in arsenic levels from toenail specimens were observed for breast cancer cases relative to controls (OR for highest vs. lowest quintile of exposure = 1.1, 95% CI: 0.7–1.9) (Garland et al. 1996).

Studies examining the relationship between exposures to heavy metals and breast cancer risk are also limited and predominantly null. While a positive

association between cadmium levels and lung cancer risk has been repeatedly observed (Navarro Silvera and Rohan 2007), only one study has assessed the relationship between exposure to this Group 1 carcinogen and breast cancer risk (McElroy et al. 2006): in a case–control study with measurement of urinary cadmium, a significant positive relationship was observed between cadmium levels and breast cancer risk (OR for highest vs. lowest quartile of exposure = 2.3, 95% CI: 1.3–4.2). The relationship between urinary lead levels and breast cancer risk was assessed by the same study with no evidence of an association after excluding women who were users of nonsteroidal aromatase inhibitors (OR for highest vs. lowest quartile of exposure = 1.1, 95% CI: 0.9–1.3) (McElroy et al. 2008). Studies of copper, iron, and zinc levels in relation to breast cancer vary in their findings and in their methods of exposure ascertainment. Given that zinc has antioxidant properties similar to selenium, it has been proposed that zinc exposure could be inversely associated with breast cancer risk; however, one study measuring zinc from breast tissue observed a suggestive positive association between zinc levels and breast cancer risk (Cui et al. 2007), while another study measuring zinc levels from toenail specimens observed no association (Garland et al. 1996), and two other studies measuring exposure from serum and dietary questionnaires observed a suggestive inverse relationship with breast cancer risk (Navarro Silvera and Rohan 2007). Both copper and iron are biologically important in the production of reactive oxygen species, such that excessive exposure to these metals could contribute to oxidative stress and, potentially, carcinogenesis. With respect to copper, however, one study indicated no association between copper levels measured from toenail specimens and breast cancer risk (Garland et al. 1996), while another suggested a U-shaped relationship between plasma copper levels and breast cancer risk (Overvad et al. 1993). With respect to iron, most studies have found no evidence of a relationship with breast cancer risk (Kabat and Rohan 2007), with the exception of one study that suggested a positive association between levels of iron in benign breast tissue and subsequent breast cancer risk (OR for highest vs. lowest exposure quintile = 1.6, 95% CI: 1.0–2.4) (Cui et al. 2007).

Overall, associations between exposure to naturally occurring elements and breast cancer risk are biologically plausible even if evidence from epidemiologic studies is sparse and inconsistent. The overall carcinogenicity of arsenic and cadmium in particular are well established; however, the role that these elements may play specifically in breast carcinogenesis remains uncertain.

Conclusions

Many methodological issues complicate the study of past exposure to ionizing radiation, environmental pollutants, ELF, and trace elements and risk of breast cancer in humans. Methodologies for reconstructing doses of exposure are varied, complex, and imperfect. Even when dose is well measured, dose–response

relationships are likely to be influenced by a variety of individual-level factors such as the timing of exposure, duration of exposure, and individual variation in susceptibility to the effects of exposure. While there is biological plausibility for associations between all the exposures described herein and breast cancer in humans, epidemiologic evidence is currently limited. Overall, evidence is particularly strong in support of an association between exposure to ionizing radiation and breast cancer risk, although factors influencing a dose–response relationship have not been well described and the role of low-level long-term exposures have not been characterized. Evidence in support of associations between exposure to environmental pollutants, ELF, trace elements, and heavy metals is weaker and less consistent; however, studies exploring gene–environment interactions and subgroup-specific associations suggest that the failure to observe associations with breast cancer risk overall may be due to a lack of sensitivity. Additional studies paying particular attention to dose rates, the timing of exposure, gene–environment interactions, and subgroup-specific effects are needed to better elucidate the role of all these environmental factors in relation to breast cancer risk.

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Chapter 10
Shift Work and Circadian Disruption

Scott Davis and Dana K. Mirick

Introduction

There is increasing interest in the possible role of environmental factors that can alter normal endocrine function, often referred to as "endocrine disruptors," in the etiology of cancer. Because the release of nearly all hormones exhibits a circadian timing patterned on approximately a 24-h cycle, agents that disrupt circadian rhythm may also alter endocrine function and thereby the regulation of reproductive hormones (Czeisler and Klerman 1999). Of particular interest regarding breast cancer is the potential influence of both light at night and sleep disruption on the regulation of estrogen release and levels of circulating estrogen. Persons who engage in night shift work are subject to the influence of both factors and may exhibit altered hormone profiles as a result that could increase their risk of hormone-related diseases, including breast cancer. Epidemiologic studies are now beginning to emerge which suggest that women who work shifts at night, and consequently may experience sleep deprivation, circadian disruption, and exposure to light at night, are at an increased risk of breast cancer.

A substantial number of employed women work in jobs involving some degree of night shift work. Broadly speaking, the definition of "shift work" encompasses work that occurs outside of the typical 8-h day. Examples include permanent evening or night shifts, rotating shifts, and split shifts. According to the Bureau of Labor Statistics within the US Department of Labor, approximately 12.4% of female full-time wage and salary workers were employed in a job with some amount of shift work in 2004 (Anonymous 2005). Among non-married women, the percentage is higher: 16.0% of the female workforce was employed in shift work in 2004. In Canada, approximately 26% of employed Canadian women worked some type of shift work in 2000–2001 (Anonymous 2002). In both countries, the majority of workers reported having

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_10,

little choice in working non-standard shifts, with shift work being most common in blue-collar, sales, and service workers (Anonymous 2002, 2005). Although there is now considerable evidence that night shift workers experience a variety of physical symptoms and adverse health effects, most notably those associated with gastrointestinal dysfunction (Angersbach et al. 1980, Colligan et al. 1980, Minors et al. 1986), cardiovascular morbidity (Knutsson et al. 1999, Steenland and Fine 1996, Tuchsen 1993, Knutsson et al. 1986, Kawachi et al. 1995, Alfredsson et al. 1982, Tenkanen et al. 1997), and some aspects of reproductive health (e.g., preterm births and low birth weight (Mamelle et al. 1984, McDonald et al. 1988, Nurminen 1989, Arendt and Deacon 1997, Axelsson et al. 1989, Xu et al. 1994, Armstrong et al. 1989, Zhu et al. 2004), spontaneous abortion (McDonald et al. 1988, Axelsson et al. 1996, 1984, Hemminki et al. 1985, Uehata and Sasakawa 1982, Zhu et al. 2004, Infante-Rivard et al. 1993), and reduced fecundity (Uehata and Sasakawa 1982, Ahlborg et al. 1996, Bisanti et al. 1996)), evidence is just beginning to emerge to suggest that breast cancer risk may be increased in women who work night shifts. Underlying biological mechanisms which could provide an explanation for the observed associations between night shift work and breast cancer risk may be related directly to the effects of light exposure and/or sleep disruption, or more fundamentally to altered pineal function and the resulting effects on hormonal regulation. This chapter summarizes the epidemiologic evidence and considers possible underlying biological mechanisms that might help to explain the associations observed.

Epidemiological Evidence: Breast Cancer and Night Shift Work

A number of studies have investigated a potential link between night shift work and cancer. Four publications (Table 10.1) report results from studies that have directly investigated the association between night shift work and the development of breast cancer (Hansen 2001, Davis et al. 2001, Schernhammer et al. 2001, 2006). Hansen (2001) reported an increased risk of breast cancer associated with occupational shift work exposure (primarily women working in catering jobs or as flight attendants) in a large cohort study (over 6,000 cases) in Denmark. In this study, shift work was defined as being employed for at least 6 months in one or more of the trades in which at least 60% of the female responders had nighttime schedules, based on information provided in a prior nationwide survey. To take induction time into account, the 5-, 10-, or 15-year periods prior to breast cancer diagnosis for cases and an equivalent period for controls were disregarded. The odds ratio (OR) for women who worked at night for at least a half year was 1.5 (95% CI: 1.2–1.7), and there was a trend of increasing risk with increasing duration of employment. A case–control study conducted by Davis et al. observed an increased risk of breast cancer in women who engaged in graveyard shift work (Davis et al. 2001), where graveyard shift

Table 10.1 Observational studies of night shift work and breast cancer risk

First Author (Year)	Type of study	Population	Years of accrual	Occupation	Source of exposure information	Definition of exposure	No. of breast cancer cases	OR or RR[a]	95% CI
Hansen (2001)	Case–control	Age 30–54, Denmark	1964–1999	Various	Individual employment histories from national pension fund files	Employed ≥ 6 months in trades in which 60% of women had nighttime schedules	7,035	1.5	1.3–1.7
Davis (2001)	Case–control	Age 20–74, Seattle, USA	1992–1995	Various	In-person interview, occupational and sleep history	Ever worked graveyard shift in 10 years prior to diagnosis	813	1.6	1.0–2.5
Schernhammer (2001)	Prospective cohort	Nurses Health Study, USA	1988–1998	Nurses	Interview of work history and number of years of night shift work	Employed ≥ 30 years on rotating night shifts	2,441	1.36	1.0–1.8
Schernhammer et al. (2006)	Prospective cohort	Participants in the Nurses Health Study II	1989–2001	Nurses	Interview of work history including number of years of night shift work	Employed ≥ 20 years on rotating night shifts	1,352	1.79	1.1–3.0
Tynes et al. (1996)	Cohort	Norwegian Telecom cohort of female radio and telegraph operators	1961–1991	Radio and telegraph operators	Individual job histories of years worked on each ship	Cumulative years of employment	2619	1.5	1.1–2.0
Lie et al. (2006)	Nested case–control	Norwegian nurses educated between 1914–1980	1960–1982	Nurses	Individual reconstruction of employment history	Assigned to night work for ≥ 30 years	537	2.21	1.1–4.5
All combined								1.51	1.4–1.7

[a]Odds ratio or relative risk comparing the highest versus lowest category of exposure.

work was defined as beginning work after 7 p.m. and leaving work before 9 a.m. Specifically, working graveyard shift during the 10 years prior to diagnosis was associated with increased breast cancer risk (OR = 1.6, 95% CI: 1.0–2.5), with a significant trend of increasing risk with increasing years and with more hours per week of graveyard shift work. Schernhammer et al. (2001, 2006) reported similar results in nurses who worked rotating shifts (where "rotating" was defined as working at least three nights per month in addition to days or evenings that same month), particularly among those who worked on rotating night shifts for 30 or more years (OR = 1.36, 95% CI: 1.0–1.8).

In contrast to these studies which were based on information about an individual's history of shift work, most studies have relied on job title as a surrogate indicator of shift work to more indirectly assess the effects of night shift work on breast cancer risk. Tynes et al. (1996) reported increased risks of breast cancer among a cohort of female Norwegian radio and telegraph operators working the night shift at sea, relative to the Norwegian female population (SIR = 1.5; 95% CI: 1.1–2.0). Lie et al. also reported findings from a nested case–control study within a cohort of Norwegian female nurses, based on a reconstruction of work histories (2006). The adjusted OR of breast cancer among nurses who worked nights for 30 or more years was 2.21 (95% CI: 1.1–4.5) compared with those who did not work nights after graduation from nursing school ($p_{\text{trend}} = 0.01$). Increased risks have also been reported among flight attendants from seven studies (Table 10.2) (Pukkala et al. 1995, Rafnsson et al. 2001, Haldorsen et al. 2001, Reynolds et al. 2002, Linnersjo et al. 2003, Lynge 1996, Wartenberg and Stapleton 1998). Results from these studies are reasonably consistent, as all but one of the risk estimates (standardized incidence ratios) are between 1.3 and 2.0. These studies, however, were based on population comparisons and did not have individual information regarding a woman's work schedule.

A recently published meta-analysis (Megdal et al. 2005) combined data from 13 studies conducted to date, including all of the studies discussed above. Eligible for inclusion in the analysis were observational studies that looked at any type of night shift work and breast cancer; animal studies, reviews, studies that did not provide separate risk estimates for breast cancer, and studies that did not separate women from men were excluded. Of the 13 included studies, seven were of flight attendants, and the remaining six studies, four of which were cohort studies and two of which were case–control studies, included other forms of night work. Three of these six studies were of nurses. The results of the meta-analysis found an aggregate risk estimate of 1.48 (95% CI:1.4–1.6) for all 13 studies; similar results were found among female flight attendants (SIR = 1.44, 95% CI:1.3–1.7) and non-flight attendant female night workers (relative risk (RR) = 1.51, 95% CI: 1.4–1.7). The study concluded that studies of night shift work and breast cancer risk collectively show an increased breast cancer risk among women who work in occupations that typically involve some degree of shift work and that formal testing indicates publication bias is unlikely to have influenced the results (Megdal et al. 2005).

Table 10.2 Breast cancer incidence studies of flight attendants

First Author (Year)	Population studied	Comparison group	Years of follow-up	Number of cases	Standardized incidence rate (SIR)	95% confidence interval
Haldorsen (2001)	3105 Norwegian flight attendants	Norwegian national breast cancer rates	1953–1996	38	1.1	0.8–1.5
Linnersjo (2003)	2324 Swedish Scandinavian Airline System flight attendants	Swedish national breast cancer rates	1961–1996	33	1.30	0.9–1.7
Lynge (1996)	915 Danish flight attendants	Danish breast cancer rates	1970–1996	14	1.61	0.9–2.7
Pukkala (1995)	1577 Finnish flight attendants	Finnish national breast cancer rates	1967–1992	20	1.87	1.2–2.2
Rafnsson (2001)	1532 Icelandic flight attendants	Icelandic national breast cancer rates	1955–1997	26	1.5	1.0–2.1
Reynolds (2002)	44201 California Association of Flight Attendants	Breast cancer rates in the state of California	1988–1995	60	1.42	1.1–1.8
Wartenberg (1998, 2005)	287 retired US flight attendants	US national breast cancer rates	Unspecified	7	2.00	1.0–4.3
All combined					1.44	1.3–1.7

In summary, there is reasonable consistency in findings of an increased risk of breast cancer associated with working at night. The magnitude of this increase is approximately 1.5-fold, and the consistency of findings is striking given the different definitions of shift work used.

Epidemiological Evidence: Breast Cancer and Light-at-Night Exposure

Also of potential concern regarding the risk of breast cancer is exposure to light at night, and the corresponding disruption of normal circadian rhythms. Epidemiologic studies of exposure to light at night in relation to cancer risk are exceedingly difficult to conduct. In the night shift work study conducted by Davis et al. (2001) described above, investigators looked at exposure to light at night somewhat indirectly by categorizing women according to whether they did not sleep during the period of the night when melatonin levels are typically at their highest (defined as 1–2 am). They reported a 14% increase in breast cancer risk for each night per week they were awake during this interval, and a trend of increasing risk with increasing number of years of frequently not sleeping when melatonin levels are at their highest. In a recently published study that looked at light-at-night exposure and breast cancer incidence on a population level, an approximately 73% higher breast cancer incidence was reported among communities with the highest light-at-night exposure, compared to the lowest light-at-night exposed communities, using nighttime satellite images to estimate levels of light at night (Kloog et al. 2008).

An alternative approach to investigating light-at-night exposure in sighted women or in the general population has been to investigate whether profoundly blind women, who generally do not perceive light, are at a reduced risk of breast cancer. Using more than 100,000 US hospital discharge records, Hahn identified women with a primary diagnosis of breast cancer and a comparison group of women with stroke or cardiovascular disease. Among the comparison group, 0.26% were profoundly blind, whereas among the women with breast cancer, only 0.15% were profoundly blind (Hahn 1991). Thus, after accounting for a number of potential confounding factors, they found that women with breast cancer were approximately half as likely to be profoundly blind as the comparison group (OR = 0.57; 95% CI: 0.4–0.9). Further, the magnitude of this association increased with decreasing age at diagnosis. Feychting et al. (1998) reported similar findings based on a cohort study in Sweden. They found the risk of cancer (all combined) was lower among blind persons, including female breast cancer. Pukkala et al. (1999) also observed that blind women in Finland have a reduced risk of breast cancer, although their risk of other cancer types was higher, in contrast to the Swedish study. In an extension of the Finnish study, Verkasalo et al. (1999) included additional breast cancer cases and further refined the definition of visual impairment to include five categories

from moderate low vision to total blindness. Over the period 1983–1996, there were 124 cases of breast cancer among approximately 11,000 women with some degree of visual impairment. The standardized incidence ratio declined from 1.05 in women with "moderate low vision" to 0.47 in totally blind women; the decrease was monotonic and statistically significant. A recent report from Norway (Kliukiene et al. 2001) also suggests a lower risk of breast cancer in blind women.

Possible Biological Mechanisms

The Pineal Gland and Actions of Melatonin

Melatonin is a primary circadian pacemaker; its purpose is to synchronize the internal hormonal environment to the light–dark cycle of the external environment. It is produced and secreted by the pineal gland, a neuroendocrine transducer that is stimulated by darkness and suppressed by light as perceived by the retina (Wurtman and Axelrod 1965). The retinohypothalamic tract carries information from the retina to the suprachiasmatic nuclei (SCN), which generates the signal to the pineal gland to regulate melatonin production accordingly. In effect, melatonin secretion acts as the "arm" of the biologic clock: the timing of the melatonin rhythm indicates the status of the internal clock, with regard to phase position (the internal clock time vs. external clock time) and amplitude (Pandi-Perumal et al. 2007). Further, melatonin acts as a chemical code for the night: the longer the night, the longer the duration of secretion (Claustrat et al. 2005). Hence, during the typical sleep–wake period of the non-night shift worker, circulating melatonin concentrations are low during the day and higher at night, exhibiting a characteristic rise in concentration after darkness and a peak near the midpoint of the dark interval (Czeisler et al. 1999).

Melatonin as a Regulator of Gonadal Function

Melatonin appears to be involved in the regulation of gonadal function by influencing the hypothalamic–pituitary–gonadal axis. Animal studies indicate that melatonin can modify the firing frequency of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator, thereby affecting the release of gonadotropins (LH and FSH) from the pituitary (Bittman et al. 1985, Yellon and Foster 1986, Robinson et al. 1986, Robinson 1987) and stimulating testicular testosterone or ovarian estrogen production and release. LH and FSH, in turn, are critical in the biosynthesis of steroid hormones in the ovary, including estradiol (Catt and Dafau 1991, Adashi 1991). Consequently, pineal function, through the secretion and action of melatonin, may exert an important modulatory effect on ovarian function and estrogen production.

Human studies indicate that decreased concentrations of circulating melatonin (such as those brought about by circadian disruption) can result in increased release of the gonadotropins LH and FSH from the pituitary and estrogen release by the ovaries (Sandyk 1992, Anonymous 1981, Yie et al. 1995, Penny et al. 1987, Voordouw et al. 1992). Conversely, melatonin secretion appears to be unaffected by fluctuations in ovarian steroid production. Thus, through its control over gonadal hormone production, melatonin may have an inhibitory effect on hormone-dependent tumors.

Melatonin as a Direct Oncostatic Agent

In addition to the potential inhibitory effect of melatonin on hormone-dependent tumors through its control of gonadal hormone production, melatonin may also have a direct effect on the development of cancer. Growth-inhibitory and oncostatic properties of melatonin have been well described (reviewed in Blask et al. 2005). A number of in vitro studies have reported a reduction in the growth of malignant cells and/or tumors of the breast (Hill and Blask 1988, Cos et al. 1996, 1998, 2002, Mediavilla et al. 1999), prostate (Siu et al. 2002, Rimler et al. 2002, Marelli et al. 2000, Xi et al. 2000, Moretti et al. 2000, Philo and Berkowitz 1988), and other tumor sites (Sze et al. 1993, Ying et al. 1993, Petranka et al. 1999, Shiu et al. 1999, Kanishi et al. 2000) by both pharmacological and physiologic doses of melatonin, although such findings are not always consistent (Panzer et al. 1998). In rodent models, pinealectomy has been found to enhance tumor growth (Tamarkin et al. 1981), and exogenous melatonin administration has demonstrated anti-initiating (Musatov et al. 1999) and oncostatic activity (Anisimov et al. 1997, 1999, Cini et al. 1998, Mocchegiani et al. 1999) in various chemically induced cancers as well as in virus-transmitted tumors in mice (Subramanian and Kothari 1991). It has recently been reported that exposure of rats with hematomas or human breast cancer xenographs to light during each 12-h dark phase resulted in a dose-dependent suppression of nocturnal melatonin blood levels and a stimulation of tumor growth (Blask et al. 2005). Further, tumors from these same rats perfused in situ with nocturnal, physiologically melatonin-rich blood collected from healthy premenopausal women exhibited markedly suppressed proliferative activity compared with tumors perfused with daytime-collected melatonin-deficient blood. Tumors perfused with melatonin-deficient blood collected following exposure to light at night exhibited the daytime pattern of high proliferative activity. Sainz et al. (2005) have also recently shown that treatment of prostate cancer cells with pharmacological concentrations of melatonin significantly reduced the number of prostate cancer cells and stopped cell cycle progression in both androgen-dependent (LNCaP) and androgen- independent (PC3) epithelial prostate cancer cells and induced cellular differentiation. Although not directly related to breast cancer, these findings are consistent with similar results regarding breast cancer and further support

the possible role of direct action of melatonin on hormone-related tumor development.

A number of mechanisms have been proposed to explain melatonin's potential direct anti-cancer activity: melatonin may have anti-mitotic activity through its direct effect on hormone-dependent proliferation via interaction with nuclear receptors; it may affect cell cycle control; and it may increase the expression of the tumor-suppressor gene p53 (Mediavilla et al. 1999, Brzezinski 1997). Furthermore, some clinical trials suggest that melatonin, either alone or in combination with standard therapy regimens, helps promote a favorable response in the treatment of human cancers (Vijayalaxmi et al. 2002).

Whether low nocturnal melatonin levels predisposes one to an increased risk of cancer is difficult to determine; several studies of breast cancer in women have been attempted to answer this question. Three studies measured urinary melatonin levels in women prior to their development of breast cancer (Schernhammer and Hankinson 2005, Schernhammer et al. 2008, Travis et al. 2004). Two of the three reported decreased pre- and post-menopausal breast cancer risk among women with higher melatonin levels, using nocturnal or "first morning void" urine samples (Schernhammer and Hankinson 2005, Schernhammer et al. 2008). The third study found no relationship between melatonin level and breast cancer risk (Travis et al. 2004); however, this study used a 24-h urine sample to assess melatonin levels, which has a number of concerns as described by Hrushesky and Blask (2004). There is evidence that melatonin levels are decreased in patients with breast cancer, although in each of these studies melatonin levels were measured after diagnosis and therefore it is uncertain whether the disease itself and/or treatment might have affected melatonin levels among the cases (Bartsch et al. 1981, 1989, 1991, 1997, Tamarkin et al. 1982, Skene et al. 1990). Nighttime plasma melatonin levels have been reported to be lower in women with estrogen receptor positive (ER+) breast cancer than in ER– breast cancer, which in turn are lower than in healthy control women, and that women with the lowest peak melatonin concentrations had tumors with the highest concentrations of estrogen receptors (Tamarkin et al. 1982). Melatonin levels have also been found to be lower among women with malignant breast cancer vs. those with benign breast disease (Bartsch et al. 1989, Skene et al. 1990). Although these findings are consistent with the results of laboratory studies and melatonin levels are in the direction of what might be predicted, it is difficult to assess their biological relevance due to the presence of disease and its possible effect on blood melatonin levels.

Light-at-Night Exposure and Breast Cancer in Laboratory Animals

Light exposure has been investigated directly in relation to breast cancer in laboratory studies. Jöchle (1964) reported that spontaneous mammary tumors in C3H-A mice increased with constant illumination. Early experiments wherein rats were initiated with high doses (20–30 mg) of DMBA and exposed to extended

or constant-light photoperiods yielded mixed results (Jull 1966, Hamilton 1969, Aubert et al. 1980). Later, Shah et al. (1984) reported that constant light increased DMBA-induced mammary tumorigenesis in rats. At 55 days of age, rats exposed to constant light from before birth (beginning in utero) showed a greater concentration of terminal end buds and alveolar buds in mammary tissue than did rats raised on a 10-h light:14-h dark regimen. Constant light animals also showed greater DNA synthesis activity in the mammary tissue and higher levels of circulating prolactin. A suggested mechanism for these effects is that reduced melatonin resulted in increased circulating estrogen and prolactin, and, consequently, increased turnover of the breast epithelial stem cells thus increasing the risk of malignant transformation (Mhatre et al. 1984). Recent experimental evidence suggests that light exposure during the dark cycle increases the progression of cancer (Blask et al. 1999, 2002), and that dim light is as effective in this regard as bright and constant light (Dauchy et al. 1997, 1999).

Light-at-Night Exposure and Melatonin Levels in Humans

It is also well established that ocular light exposure in humans can affect melatonin secretion, either acutely as a direct response to the presence or absence of retinal light exposure, or indirectly as a result of the influence of light on circadian mechanisms. Light is the most powerful circadian synchronizer in humans (Czeisler and Wright 1999) and can exert a profound effect on the phase and amplitude of the human circadian pacemaker (Czeisler and Khalsa 1999). Of particular interest in the context of cancer etiology is the effect of light on pineal function in humans. Several features have been identified that are relevant to potential long-term health effects (Wetterberg 1993): (1) the effect of light at night (LAN) is qualitatively similar to the effect in other mammals in that sufficient intensity (~2,500 lux) of nocturnal illumination completely suppresses melatonin production (Lewy et al. 1980, Lynch et al. 1984); (2) some people are much more sensitive to LAN (~200 lux) than others (McIntyre et al. 1990); (3) there appears to be a dose–response to LAN in that the brighter the light the greater the reduction in nocturnal circulating melatonin (McIntyre et al. 1989), with evidence of a maximum effect at wavelengths of less than 500 nm (Brainard et al. 2001); and (4) light quality during the day affects night time melatonin production (McIntyre et al. 1990, Lewy et al. 1987, Wehr et al. 1995, Boivin et al. 1996) as well as the human circadian pacemaker (Czeisler et al. 1986).

Effects of Night Shift Work on Sleep

The effects of night shift work on sleep may also contribute importantly to biologic mechanisms that could affect the development of cancer. A pervasive and severe consequence of the desynchronosis that occurs with shift work is a

decrease in the quantity and quality of sleep (Winget et al. 1984, Akerstedt 1990, Dement et al. 1986, Santhi et al. 2005). Night workers typically get less sleep than those who work during the day, and regular night work is associated with chronic sleep deprivation (Tepas 1982, Tepas and Sullivan 1982). It is well known that sleep exerts a profound effect on endocrine function and hormones such as melatonin and cortisol (Czeisler and Klerman 1999). However, sleep is a complicated, multifaceted process and hormonal responses most certainly vary. Although considerable evidence exists that sleep affects melatonin levels, less information in humans is available regarding the effects of sleep interruption or deprivation on reproductive hormones. Some studies have found increased melatonin levels during sleep deprivation at night (Salin-Pascual et al. 1988, Akerstedt et al. 1979), but a number of other studies suggest that elevated plasma melatonin levels are associated with increased sleep propensity (Czeisler and Klerman 1999). Quera-Salva et al. (1996) found a rapid change in sleep time and melatonin acrophase in some night shift workers, but not others, suggesting that some people have a physiological ability to readily adapt to rotating shift schedules and showing for the first time a corresponding rapid shift in melatonin secretion. Touitou et al. (1990) found that fast-rotating shift work modifies peak or trough values and rhythm amplitudes of melatonin, prolactin, testosterone, and cortisol. Schernhammer et al. (2004) reported reduced melatonin and elevated estrogen levels in nurses with a history of rotating night shifts. In support of the possible link between adverse effects of sleep quantity and risk of cancer, Verkasalo et al. (2005) have recently published results showing that the risk of breast cancer was lower in women who sleep longer ($\geq$9 h) compared to average sleepers (7–8 h) in a study of women in the Finnish Twin Cohort.

Night Shift Work and Breast Cancer Risk: Potential Role of Genetics

A number of genes have now been identified that are believed to be important in the regulation of circadian rhythms (Reppert and Weaver 2001). The *Period* (*Per*) gene family is central to this mechanism, as is the *h*CLOCK gene. Recently, specific polymorphisms in these genes have been found to be associated with a number of sleep-related conditions, including diurnal preference (*h*CLOCK, Katzenberg et al. 1998); *Per3*, (Johansson et al. 2003); delayed sleep phase syndrome and extreme diurnal preference (*Per3*, Archer et al. 2003, Ebisawa et al. 2001); and insomnia in mood disorders (*h*CLOCK, Parry and Newton 2001). Regarding reproductive function, a recent series of mouse experiments have demonstrated that *h*CLOCK mutants have disrupted estrous cyclicity and maintenance of pregnancy (Miller et al. 2004). Of particular interest is new evidence that a polymorphism of *Per3* is associated with the development of breast cancer (Zhu et al. 2005), and an alteration in *Per2* has been shown to affect tumor suppression and DNA damage response in mice

(Fu et al. 2002). Thus, there may be a genetic component that affects an individual's ability to adapt to circadian disruption, for example, as a result of working at night. If so, specific genotypes may define groups that are more or less susceptible to the effects of working night shifts, including the effects on melatonin and reproductive hormones, and consequently the risk of developing hormone-related cancer such as breast cancer. This work is in a very early stage, however. The associations observed thus far require confirmation, and much work remains to be done to establish the role of genetic susceptibility in relation to developing hormone-related cancer.

Summary and Future Directions

In summary, recent efforts to better understand the role of environmental influences in the etiology of breast cancer have increasingly focused on elucidating the possible effects of circadian disruption on the regulation of hormones most directly involved in the growth and development of breast tissue. Epidemiologic studies have begun to suggest that women who work night shifts are at an increased risk of developing breast cancer. Women who work at night can experience sleep deprivation, circadian disruption, and are exposed to light at night. These factors have been shown to affect pineal function and the normal nocturnal release of the hormone melatonin. Melatonin, in turn, can affect the production of reproductive hormones, and may also have a direct role in the carcinogenic process. Future research should focus on determining the direct effects of night shift work on melatonin and the reproductive hormones of most interest in the etiology of breast cancer.

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Chapter 11
Non-Hormonal Medications and Chronic Diseases

Patricia F. Coogan

Introduction

This chapter explores the relation between breast cancer risk and the use of non-hormonal medications and chronic diseases. Many drugs and diseases have been linked with breast cancer in case reports and epidemiologic studies. This chapter covers those major medications and diseases where there is adequate epidemiologic evidence for evaluation.

Statins

The cholesterol-lowering statins exhibit anti-proliferative, anti-angiogenic, and pro-apoptotic properties in various cell types including breast cancer cells (Seeger, Wallwiener and Mueck 2003; Demierre et al. 2005). Statins are among the top-selling drugs in many developed countries and even modest chemopreventive effects would have important public health implications. However, isolated epidemiologic findings of reduced breast cancer risk in statin users, including a relative risk of 0.37 in one small cohort study (Cauley et al. 2003), have not been replicated in larger studies. Several large data linkage studies wherein pharmacy and cancer registry databases are merged have found no association between breast cancer risk and statin use, including the United Kingdom's General Practice Research Database (Kaye and Jick 2004) and databases in Europe (Friis et al. 2005; Graaf et al. 2004), Canada (Blais, Desgagne and LeLorier 2000; Beck et al. 2003), and the United States (Setoguchi et al. 2007).

Three large case–control studies (Boudreau et al. 2004; Coogan, Rosenberg and Strom 2007; Pocobelli et al. 2008) found no statistically significant association between overall statin use and breast cancer risk although in one of them there was a non-significant 30% decrease in risk among women who had used

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_11,

statins for 5 or more years (Boudreau et al. 2004). In two major cohort studies, the Women's Health Initiative (Cauley et al. 2006) and the Nurses' Health Study (Eliassen et al. 2005), there was no association between statin use and breast cancer risk even among women who used statins for at least 4 years. Furthermore, in up to 10 years of follow-up of participants in the original statin clinical trials, no difference in breast cancer incidence has been observed between treatment and control groups (Dale et al. 2006).

Due to differing pharmacokinetics and effects on cell proliferation, a protective effect may be more apparent among the hydrophobic statins (i.e., simvastatin, lovastatin, fluvastatin) (Duncan, El-Sohemy and Archer 2007). In the Women's Health Initiative, there was a statistically significant 18% reduction in breast cancer risk among users of hydrophobic statins (Cauley et al. 2006). However, this finding was not confirmed in three other studies (Boudreau et al. 2007; Duncan, El-Sohemy and Archer 2007; Pocobelli et al. 2008). In the one study that assessed statins' effects on breast cancer recurrence, there was a non-significant 33% reduction in risk of recurrence among breast cancer survivors who used mostly hydrophobic statins (i.e., lovastatin and simvastatin) post-diagnosis compared to those who used no statins (Kwan et al. 2008).

As of this writing, two phase II clinical trials are underway, one evaluating the effect of simvastatin on breast cancer biomarkers (e.g., circulating estrogen levels) and the other the effect of lovastatin on abnormal breast duct cytology in women at high breast cancer risk (National Cancer Institute, 2007).

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs inhibit cyclooxygenases (COX) 1 and 2 which play a key role in the proliferation of tumor tissue (Taketo 1998); COX-2 is overexpressed in breast cancer (Ristimaki et al. 2002). Inhibition of COX-2 decreases aromatase activity which may suppress estrogen synthesis (Singh-Ranger et al. 2008). In one cross-sectional study of postmenopausal women, levels of estradiol, an established breast cancer risk factor, were lower among current NSAID users than nonusers (Hudson et al. 2008). In a second similar study, there was no association between current NSAID use and estradiol, but prolactin levels were significantly lower among current NSAID users than nonusers (McTiernan et al. 2008); prolactin is a possible risk factor for breast cancer (Tworoger et al. 2004).

Most case–control studies show reduced odds ratios for breast cancer among NSAID users (reviewed in Gonzalez-Perez, Garcia Rodriguez and Lopez-Ridaura (2003)), and three meta-analyses reported pooled odds ratio estimates of 0.7 to 0.8 (Khuder and Mutgi 2001; Gonzalez-Perez, Garcia Rodriguez and Lopez-Ridaura 2003; Mangiapane et al. 2008). Results from eight large cohort studies are less consistent. Aspirin use had no significant effect in the Nurses Health Study (Egan et al. 1996), in the Cancer Prevention Study II Nutrition

cohort (Jacobs et al. 2007), or in the NIH-AARP Diet and Health Study (Gierach et al. 2008). In the Danish Diet, Cancer and Health cohort there was a significant 34% increase in breast cancer risk among users of any NSAID and a 38% increase in risk among users of aspirin (Friis et al. 2008). In the Women's Health Initiative (Harris et al. 2003), the use of all NSAIDs reduced breast cancer risk by 20% with the greatest reduction in long-term ibuprofen users; in contrast, in the California Teachers Study (Marshall et al. 2005), there was no effect among all NSAID users and risk was increased 24% among ibuprofen users. In the Iowa Women's Health Study (Johnson et al. 2002), risk was reduced by 30% among users of aspirin but not among users of other NSAIDs. In the Multiethnic Cohort study there was no effect of aspirin but a 30% reduction in risk among women who had used non-aspirin NSAIDs for 6 or more years (Gill et al. 2007).

Five recent studies considered the hormone receptor status of the tumors. In two studies, one of which found no effect of NSAIDs (Zhang et al. 2005) and one of which found an increased risk associated with NSAIDs (Friis et al. 2008), there was no difference in the risk estimates by hormone receptor status (Zhang et al. 2005; Friis et al. 2008). In the California Teacher's Study, there was an increased risk of hormone receptor negative tumors (and no effect in hormone receptor positive tumors) among NSAID users (Marshall et al. 2005). In two other studies, a reduced risk associated with NSAID use was associated only with hormone receptor positive tumors (Terry et al. 2004; Gierach et al. 2008).

The conflicting details of the relationship undermine a causal interpretation. There is evidence that regular NSAID users are more likely than nonusers to report regular mammograms (Johnson et al. 2002; Marshall et al. 2005; Gierach et al. 2008) and to take multivitamins (Egan et al. 1996; Johnson et al. 2002) suggesting that a healthy user effect plays a role in observed risk reductions.

One randomized placebo-controlled trial of low-dose aspirin and cancer incidence in women has been conducted: in the Women's Health Study over an average of 10 years of follow-up, 608 women developed breast cancer among the 19,934 women randomized to receive 100 mg of aspirin every other day and 622 occurred among the 19,942 women randomized to placebo ($p = 0.68$) (Cook et al. 2005). These results cannot rule out an effect of higher aspirin doses or of non-aspirin NSAIDs. At this time the evidence does not support a recommendation for aspirin or any NSAID to be taken to prevent breast cancer.

Hypertension and Antihypertensive Therapy

Some studies suggest that hypertension increases the risk of all malignancies (Grossman, Messerli and Goldbourt 2001) via hypothesized pathways relating to abnormalities of vascular smooth muscle proliferation, carcinogen binding to DNA, or angiogenesis (Felmeden and Lip 2001). While some small early studies reported a positive association between hypertension and breast cancer

(reviewed in Largent et al. (2006)), there was no difference in breast cancer risk between hypertensive and normotensive women in four prospective cohort studies with up to 27 years of follow-up (Michels et al. 1998; Peeters et al. 2000; Manjer et al. 2001; Lindgren et al. 2007).

Treatment for hypertension has also been associated with breast cancer risk in a number of studies although the evidence is inconsistent (Grossman, Messerli and Goldbourt 2001). Early reports that the Rauwolfia derivative, reserpine, increased breast cancer risk were later judged to be in error (Horwitz and Feinstein 1985).

More recently attention has focused on calcium channel blockers (CCBs) which inhibit apoptosis in certain cells lines (Daling 1996). In one cohort study the hazard ratio for CCB use was 2.6 and it was 4.5 for joint CCB and estrogen use (Fitzpatrick et al. 1997). These findings were not confirmed in subsequent studies including large cohort (Michels et al. 1998; Fryzek et al. 2006) and case–control (Rosenberg et al. 1998; Meier et al. 2000; Li et al. 2003) studies.

Increased breast cancer risk has also been reported among users of diuretics (Li et al. 2003; Largent et al. 2006). Odds ratios of 1.8 for use of any diuretic (Largent et al. 2006), 1.4 for thiazide, and 1.6 for potassium-sparing diuretics (Li et al. 2003) were reported in two case–control studies but not confirmed in two cohort studies (Fitzpatrick et al. 1997; Fryzek et al. 2006).

While there is some laboratory evidence that angiotensin-I-converting enzyme (ACE) inhibitors may affect tumorigenesis (Volpert et al. 1996; Lindberg et al. 2004), an initial report of reduced risk of breast cancer among users (Lever et al. 1998) was not confirmed (Rosenberg et al. 1998; Friis et al. 2001; Meier, Schmitz and Jick 2002; Gonzalez-Perez, Ronquist and Garcia Rodriguez 2004; Van der Knaap et al. 2008).

As for other antihypertensive drugs, angiotensin-II receptor antagonists did not affect breast cancer risk in one study (Fryzek et al. 2006) nor have beta-blockers increased the risk in four studies (Rosenberg et al. 1998; Meier et al. 2000; Li et al. 2003; Fryzek et al. 2006). Limited data on methyldopa and hydralazine were null (Grossman, Messerli and Goldbourt 2001).

In conclusion, most observational epidemiologic data do not support an association between antihypertensive use and breast cancer. Furthermore, there was no association between risk of any cancer and antihypertensive treatment among participants of several large randomized clinical trials followed for an average of 5 years (SHEP Cooperative Research Group 1991; Lindholm et al. 2001; ALLHAT Collaborative Research Group 2002).

Antidepressants and Depression

In 1992 a study was published wherein the antidepressants fluoxetine and amitriptyline promoted the growth of mammary tumors in rodents (Brandes et al. 1992) but these data were not replicated (Volpe et al. 2003).

Evidence from at least 12 case–control and cohort studies does not support an association between any particular antidepressant drug class and breast cancer (reviewed in Coogan (2006)). Risk increases reported for tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) were based on small numbers and not confirmed in larger studies. For example, one case–-control study reported an odds ratio of 7.2 among paroxetine users (Cotterchio et al. 2000) that was not confirmed in six subsequent studies (Coogan 2006). Likewise studies that showed increased risks among tricyclic antidepressant users are far outnumbered by studies that showed no relation (Coogan 2006).

Two studies have examined the effect of antidepressants on secondary breast cancer, which is important since 10–20% of oncology patients are prescribed antidepressants (Ashbury et al. 2003). In one study of 1467 oncology patients, of whom 57% had breast cancer, there was no association between antidepressant use and cancer recurrence or second primary cancer (Weiss et al. 1998). In another study of 1306 breast cancer patients there was no difference in risk of breast cancer recurrence or death between users and nonusers of antidepressants (Chubak et al. 2007). The SSRIs are in fact proving useful as treatment for hot flashes in breast cancer survivors (Bordeleau et al. 2007). As regards the hypothesis that depression itself predisposes to breast cancer, no compelling biological mechanism has been proposed and the epidemiological evidence does not support it (McKenna et al. 1999).

Retinoids

Retinoids are derivatives of vitamin A and have been shown to inhibit the growth of mammary cancer in rodents and human breast cancer cells in vitro (Brtko 2007). They have a key role in cellular differentiation but the precise mechanism of growth inhibition has not been elucidated (Bonanni, Lazzeroni and Veronesi 2007; Brtko 2007). Data are available from one phase III secondary prevention trial that assessed breast cancer recurrence among 2867 women with previous breast cancer (Veronesi et al. 1999). After median follow-up of 8 years, there was a statistically significant 35% reduction in breast cancer recurrence among premenopausal women but no effect among postmenopausal women. After 15 years of follow-up of a subgroup (60%) of the original participants, the risk reduction among premenopausal women persisted, with a hazard ratio of 0.62 (Veronesi et al. 1999). A phase II trial of bexarotene, a retinoid X receptor agonist, is testing whether the drug suppresses breast epithelial cell growth in women at high risk of breast cancer (Arun et al. 2005; Uray and Brown 2006).

Antibiotics

In a small cohort study published in 2000, the risk of breast cancer was elevated among women who had ever been treated for a urinary tract infection (Knekt et al. 2000). The effect was confined to women under age 50 where the relative

risk was a statistically significant 1.74. Two subsequent case–control studies (Velicer et al. 2004; Tamim et al. 2008) showed a consistent risk increase among users of all classes of antibiotics. In one study there was an increasing trend in risk over number of days of use for six subgroups of antibiotics (Velicer et al. 2004); the risk was increased twofold among women with more than 100 days of use. In the other study the odds ratio for subjects with 14 or more antibiotic prescriptions was a significant 1.79; odds ratios were increased for each class of antibiotics (Tamim et al. 2008). The fact that an effect was observed for all classes of antibiotics argues against a causal interpretation, since antibiotics have different mechanisms of action (Tamim et al. 2008). In the largest study to evaluate the relationship, which included 8,521 women who developed breast cancer out of 2 million women in the Kaiser Permanente Medical Program of Northern California, hazard ratios were compatible with 1.0 for 14 antibiotic classes with the exception of tetracyclines (HR = 1.23, 95% CI: 0.9–1.1) (Friedman et al. 2006). The latter estimate was adjusted only for age and use of hormone therapy. Four other studies (Didham et al. 2005; Garcia Rodriguez and Gonzalez-Perez 2005; Kaye and Jick 2005; Sorensen et al. 2005; Friedman et al. 2006) found no effect of all antibiotics or of any specific class. Although biological mechanisms have been proposed, including antibiotics' effects on estrogen metabolism and on immune and inflammatory factors, they are speculative. Observed positive associations between antibiotic use and breast cancer may reflect confounding by indication (e.g., use for conditions that reflect excess androgen or underlying inflammation) or by insufficient control for potential confounders.

Diabetes Mellitus Type 2

Type 2 diabetes is currently epidemic in the United States as is obesity, a risk factor for both type 2 diabetes and breast cancer. The pathways by which diabetes might cause breast cancer involve the insulin pathway, activation of the insulin-like growth factor pathway, and altered regulation of endogenous sex hormones (Wolf et al. 2005). The latter two pathways are thought to be key mechanisms linking obesity and breast cancer. As reviewed by Wolf et al. (2005) and Xue and Michels (2007), many epidemiological studies of diabetes and breast cancer are limited by failure to distinguish types 1 and 2 diabetes, small numbers, and poor control for body weight and other confounders. In the Nurses' Health Study, which largely overcame these limitations, the risk of breast cancer was increased by a statistically significant 17% among postmenopausal women with type 2 diabetes (Michels et al. 2003). Although this is the largest study to date with the longest follow-up (over 22 years), self-reported body weight and lack of data on central obesity could have

resulted in residual confounding. In 16 years of follow-up in the Cancer Prevention Study II, the relative risk for breast cancer mortality among women with diabetes was a statistically significant 1.27 (Coughlin et al. 2004). However, this study did not differentiate types 1 and 2 diabetes, and mortality reflects factors associated with survival as well as incidence. For example, women with diabetes may present with breast cancer at a more advanced stage (Wolf et al. 2005). In addition, the high prevalence of undiagnosed diabetes in the population may lead to substantial misclassification. In studies that evaluated pre- and postmenopausal women separately, risk increases associated with diabetes were confined to postmenopausal women (Xue and Michels, 2007).

Eight studies that used objective measures of insulin resistance (e.g., fasting plasma concentrations of glucose, insulin, and C-peptide) did not yield consistent evidence of a positive relation between the measures and breast cancer risk (Wolf et al. 2005). In conclusion, data from some case–control and cohort studies suggest that diabetes carries a moderate increase in the risk of breast cancer; one meta-analysis that included 20 studies calculated a summary risk ratio of 1.15 (95% CI: 1.1–1.2) (Xue and Michels, 2007). Nevertheless, the overall evidence is weak due to the difficulty of adequate control of confounders, especially body weight and fat distribution.

Autoimmune Diseases

It has been hypothesized that the persistent immune system stimulation that characterizes autoimmune diseases may inhibit carcinogenesis; conversely, the long-term exposure of patients to immunosuppressive drugs might increase the risk (Achiron et al. 2005). Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), primary biliary cirrhosis (PBC), and autoimmune thyroid disease are the major autoimmune diseases suspected to influence the incidence of malignancies.

Rheumatoid Arthritis and Systemic Lupus Erythematosus

At least six cohorts of patients with prevalent RA have been followed for malignancy with the risk quantified as standardized incidence ratios (SIRs). There was a 20% deficit in the SIR for breast cancer in four of the cohorts (Gridley et al. 1993; Mellemkjaer et al. 1996; Askling et al. 2005; Wolfe and Michaud 2007) which included up to 37,882 women (Askling et al. 2005) and 18 years of follow-up (Gridley et al. 1993). In two other cohorts, one large (19,543 women) (Thomas et al. 2000) and one small (6200 women) (Setoguchi et al.

2006), SIRs were near 1.0. In one cohort of incident RA, where 2,589 female patients entered the cohort within 1 year of diagnosis, the SIR was 0.6 (95% CI: 0.3–1.0), based on 13 cases (Askling et al. 2005).

The cohort studies did not control for reproductive and other hormonal factors, or for the use of NSAIDs, which might differ between RA patients and healthy women.

Tumor necrosis factor α (TNF-α) has been associated with an increased risk of lymphoma and increased risk of solid tumors has been feared due to the drug's effect on the immune system. Two studies have evaluated TNF-α and risk of solid tumors. In one cohort there was no difference in breast cancer risk between RA patients treated with TNF-α and those treated with methotrexate (Setoguchi et al. 2006) although statistical power was low. In a second cohort, the SIR comparing breast cancer incidence among 3,112 patients treated with TNF-α with national Swedish incidence rates was 0.4 (95% CI: 0.2–0.9), based on eight cases (Askling et al. 2005). Thus at this time data are too sparse to conclude that TNF-α treatment influences the risk of breast cancer.

There have been at least nine single-center cohorts of patients with SLE followed for cancer incidence; in five of these the risk of total cancers was significantly increased, mostly due to increases in the risk of non-Hodgkin's lymphoma (Bernatsky et al. 2005a). However, the cohorts have been so small that estimates of breast cancer risk, when given, were imprecise and heterogeneous (Bernatsky et al. 2005a). Although some increased risks ranging from 1.2 to 2.9 have been observed in several small cohorts (Bernatsky et al. 2005b), a reduced risk was reported from the largest cohort amassed to date (Bernatsky et al. 2005a). That cohort was many times larger than previous cohorts and included 9,547 SLE patients (90% female) from six countries; over an average of 8 years of follow-up, the SIR for breast cancer was 0.76 (95% CI: 0.6–1.0), based on 73 observed cases (Bernatsky et al. 2005a). Exposure to exogenous and endogenous estrogens may differ between SLE patients and women without the disease; for example, in one SLE cohort from Quebec, patients had a lower prevalence of current use of oral contraceptives, and a greater prevalence of obesity and nulliparity, than the general population (Bernatsky et al. 2002). These differences may mediate any observed associations between SLE and breast cancer risk.

In conclusion, in both RA and SLE cohorts, risk estimates for breast cancer have been heterogeneous. This contrasts with consistently observed elevations in risks for hematopoietic cancers in these patients (Extermann 2007). Observed reductions in breast cancer risk in RA and SLE patients may reflect confounding by hormonal factors or NSAID use. For both RA and SLE, the prevailing concern has been that immunosuppressive drugs might increase the risk of malignancy. Limited evidence thus far does not implicate these drugs as a cause of breast cancer but more data are needed to adequately address the question.

Multiple Sclerosis

Four cohort studies of MS patients have presented risk estimates for breast cancer (Moller et al. 1991; Midgard et al. 1996; Achiron et al. 2005; Nielsen et al. 2006). In the largest population-based cohort yet assembled, including 7,188 Danish female MS patients followed for an average of 13 years, the SIR for breast cancer was 1.21 (95% CI: 1.1–1.4) (Nielsen et al. 2006). A database of reproductive history allowed for adjustment for parity and age at first birth in a subset of 3,318 women in the cohort; among them the adjusted relative risk was 1.54 (95% CI: 1.2–2.0). A previous hospital-based cohort of Danish MS patients that included 3,165 women followed for a mean of 5 years yielded an SIR for breast cancer of 1.3 ($P>0.5$), but among women younger than age 50 the SIR was 1.9 (95% CI: 1.2–3.1) (Moller et al. 1991). Among 741 Norwegian MS patients with mean follow-up of 14 years the SIR was a significant 1.70 (Midgard et al. 1996). In contrast, in a cohort of 892 Israeli MS patients the SIR was 0.97 (Achiron et al. 2005) (duration of follow-up not given). MS patients may be advised against childbirth and lack of control for reproductive factors might explain the increased risk observed in three of the four cohorts (Moller et al. 1991; Midgard et al. 1996; Nielsen et al. 2006), although in one of them the risk increase persisted after control for parity and age at first birth (Nielsen et al. 2006). Nevertheless, the distribution of other risk factors could differ between women with MS and healthy women leading to bias in the risk estimates. Surveillance bias might also play a role, although in the most recent cohort, MS patients had larger tumors at diagnosis than did other women (Nielsen et al. 2006).

There are little data on the effect of MS treatment on breast cancer risk. Authors of the Israeli study assessed risk among patients treated with glatiramer acetate, β-interferons, and IgG immunoglobulins, but numbers were too few to be informative (Achiron et al. 2005). Two studies have assessed cancer risk from azathioprine therapy but numbers were small and no specific data on breast cancer were presented (Amato et al. 1993; Confavreux et al. 1996).

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease. Estrogens may be involved in the pathogenesis of PBC; the sex hormone serum profile is similar in postmenopausal women with PBC and with breast cancer and there is a marked expression of estrogen receptors in both PBC and in breast cancer (Bergasa 1998). Early reports of increased incidence of breast cancer among patients with PBC have not been confirmed in more recent and larger studies (reviewed in Howel et al. (1999) and Nijhawan et al.(1999)). The most recent study, published in 1999, observed no excess of breast cancer among 1,692 patients with PBC presenting to the Mayo Clinic from 1976 to 1985 (Nijhawan et al. 1999).

Thyroid Diseases

Observations of high levels of thyroid disease in breast cancer cases and higher breast cancer risk in areas of endemic goiter have long fueled the notion that thyroid hormones influence breast cancer risk (Goldman 1990). Both mammary and thyroid epithelial cells concentrate iodine, and thyroid hormones appear to have a role in the regulation of breast epithelial cell growth (Simon et al. 2002). Although almost every type of thyroid condition has been associated with breast cancer, the evidence, reviewed in Goldman (1990) and Simon et al. (2002), is not compelling. The most commonly reported association is between autoimmune hypothyroidism and breast cancer (Smyth 2000). Results from the two largest and most recent case–control studies of hypothyroidism and breast cancer were conflicting: the largest (4,575 cases), based on self-reported thyroid disease, found no association (Simon et al. 2002) and the other (1136 cases), based on medical record review, reported a strong protective effect (OR = 0.44, 95% CI: 0.3–0.6) (Cristofanilli et al. 2005). Results from clinical studies wherein measures of thyroid function were compared between cases and controls have also been inconsistent (Goldman 1990).

Evidence linking hyperthyroidism with breast cancer is equally equivocal, but concern is focused on the effect of its treatment, radioactive iodine (^{131}I). Results from follow-up of patients treated with ^{131}I, reviewed in Goldman (1990), have been mixed. However, there was no increase in breast cancer risk among treated women in what is by far the largest cohort of hyperthyroid patients followed ($n = 33{,}748$), of whom 76% had 10 or more years of follow-up (Ron et al. 1998). In conclusion, despite decades of study the relation between thyroid disorders and breast cancer risk remains controversial.

Conclusion

Lack of demonstrated biological mechanisms and a dearth of consistent clinical and epidemiologic data argue against a causal interpretation for observed associations between breast cancer and the diseases reviewed above. A summary of the evidence is shown in Table 11.1. For some diseases (e.g., type 2 diabetes, primary biliary cirrhosis), the most convincing explanation for reported risks increases may be that they share well-established breast cancer risk factors (e.g., obesity, perturbations in estrogen levels). Confounding is likely to distort most effect estimates to some degree, particularly in studies where information on breast cancer risk factors is minimal or lacking and where the estimates are of modest magnitude. None of the evidence linking breast cancer to the reviewed diseases is as persuasive as that for established disease–cancer associations such as Sjogren's disease and lymphoma, where 5% of patients with that disease develop the malignancy (Tzioufas and Voulgarelis

Table 11.1 Summary of evidence for associations between non-hormonal medications and chronic diseases and breast cancer risk

Non-hormonal medications			
Medication	Direction of hypothesized association	Range of risk estimates for ever use[a]	Summary of evidence[b]
Statins	Decreased risk	~30% decrease to ~20% increase	Favors the null
NSAIDs	Decreased risk	~40% decrease to ~30% increase	Weak but possible
Antihypertensive therapy			
CCBs	Increased risk	No increase to ~160% increase	Favors the null
Diuretics	Increased risk	No increase to ~80% increase	Favors the null
ACE inhibitors	Decreased risk	~30% decrease to ~80% increase	Favors the null
Beta blockers	Increased risk	No increase	Favors the null
Antiotensin-II receptor antagonists	Decreased risk	Data available from 1 study only (non-significant 30% increase)	Inadequate for summary
Antidepressants			
Tricyclics	Increased risk	~50% decrease to ~10% increase	Favors the null
SSRIs	Increased risk	~30% decrease to ~30% increase	Favors the null
Any	Increased risk	~50% decrease to ~180% increase	Favors the null
Retinoids	Decreased risk of recurrence	Data available from 1 trial only (significant 35% reduction in recurrence)	Inadequate for summary
Antibiotics	Increased risk	No increase to ~70% increase	Favors the null
Tumor necrosis factor α	Increased risk	~40% decrease to no increase	Data inadequate for summary
^{131}Iodine	Increased risk	No increase to ~90% increase	Favors the null

Table 11.1 (continued)

Chronic diseases			
Condition	Direction of hypothesized association	Range of risk estimates for history of the condition	Summary of evidence
Hypertension	Increased risk	No increase to ~40% increase	Favors the null
Diabetes type 2	Increased risk	~30% decrease to ~100% increase	Weak but possible
Rheumatoid arthritis	Decreased risk	~40% decrease to no decrease	Weak but possible
Systemic lupus erythematosus	Increased risk	~25% decrease to ~190% increase	Too inconsistent to support conclusion
Multiple sclerosis	Increased risk	No increase to ~90% increase	Weak but possible
Primary biliary cirrhosis	Increased risk	No increase to ~ 340% increase	Favors the null
Autoimmune thyroid diseases	Increased risk	~55% decrease to ~120% increase	Too inconsistent to support conclusion

[a]Range of reported estimates regardless of statistical significance.
[b]Summary of evidence: Favors the null – the majority of studies finds no association; inadequate for summary – the data are too sparse to support any conclusion; too inconsistent to support conclusion – the data are so conflicting that even the direction of a potential association is not clear; weak but possible – the studies showing an association are not compelling but are not entirely outweighed by null studies.

2007), and primary biliary cirrhosis and hepatobiliary cancers, where relative risks of greater than 40 have been consistently observed (Nijhawan et al. 1999).

As regards medication use and breast cancer, the totality of the evidence is not as convincing as for the more consistently observed medication–cancer associations such as thiazide diuretics and renal cell cancer (Grossman, Messerli and Goldbourt 2001) and NSAIDs and colorectal cancer (Baron 2003), where epidemiologic studies are more consistently positive and are buttressed by clinical and experimental data. Interest in chemoprevention is keen for a cancer as common as breast cancer because even a modest protective effect could prevent thousands of cases per year. However, current data do not suggest that current practice as regards the use of the reviewed drugs should be modified to prevent breast cancer.

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Chapter 12
Male Breast Cancer

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Introduction

The aim of studying the epidemiology of breast cancer is to identify risk factors that could be eliminated or inhibited. Unfortunately, the two major risk factors are gender and increasing age, neither of which can be avoided. Nevertheless, the relative rarity of male breast cancer (MBC) has prompted investigations in the hope that the disease in men can give clues to the etiology of the more common female form. One of the evident differences is the age frequency distribution of the disease: in women it is bimodal, with peaks at 52 and 71 years whereas in MBC it is unimodal, peaking at age 71 (Anderson et al. 2004). In a recent report from the Veterans' Affairs Central Cancer Registry the mean age at diagnosis for females with breast cancer was 57 whereas for men it was 67 (Nahleh et al. 2007). The clinical behavior of MBC is similar to that of postmenopausal breast cancer in women (Fentiman et al. 2006).

The focus of this chapter is on the epidemiology of MBC. Among men, germline mutations of the *BRCA2* and *CYP17* genes play a significant role but account for only a small minority of cases. Men with Klinefelter's syndrome have a risk of breast cancer similar to that in females. Testicular damage, whether from mumps orchitis, high ambient working temperature, use of estrogens, or undescended testes, increases risk of MBC, but gynecomastia is not a risk factor. No consistent endocrine abnormalities have been identified in case–control studies. Both obesity and excess alcohol consumption are risk factors, as is diabetes mellitus, but the situation with regard to radiation is unclear: electromagnetic field may increase risk but ionizing rays almost certainly play a role in the evolution of male breast cancer.

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_12,

Geographic Variation in Incidence

In Europe and the United States, <1% of all breast cancer patients are male, giving an annual incidence of 1 in 100,000 (Sasco et al. 1993). The incidence and mortality rates in Europe remained fairly stable between 1955 and 1989 (La Vecchia et al. 1992) but more recent results from the United States indicate an increase in incidence (Giordano et al. 2004). Similarly, data from the Florida Cancer Data System suggest an annual increase in incidence from 0.9/100,000 in 1990 to 1.5/100,000 in 2000 (Hodgson et al. 2004). This latter finding may reflect an increase in longevity in the population with age being the major determinant of risk for the majority of solid tumors (Fentiman et al. 1990).

International incidence rates vary widely such that in Uganda and Zambia 5% and 15%, respectively, of all breast cancer cases diagnosed in these countries occur among men (Ojara 1978, Bhagwandin 1972). This has been attributed to endemic infectious diseases causing liver damage leading to hyperestrogenism. In contrast, the incidence of MBC in Japan is <5/million, reflecting the environmental factors lowering the incidence of female breast cancer in that country (Waterhouse et al. 1976). Jewish men living in Israel (Steinitz et al. 1981) or the United States (Mabuchi et al. 1985) have a particularly high incidence of MBC (2.3/100,000). However, rates do not appear to vary substantially by race/ethnicity. In Tanzania, there has been a significant drop in incidence of MBC since the HIV/AIDS epidemic because of the consequent reduction in life expectancy (Amir et al. 2000).

Laterality of Disease

Breast cancer in females occurs more frequently on the left side (1:1.2) and the same phenomenon has been observed in MBC: in a report from Iceland the ratio was 1:1.9 (Jonasson et al. 1996). The reason for this is uncertain. One possibility is a slightly larger target group of breast epithelial cells on the left side due to preferential vascular supply during intrauterine cardiac development (Fentiman 1998).

The risk of contralateral MBC in Swedish men was examined by Dong and Hemminki and they reported a standardized incidence ratio (SIR) of 93 (Dong and Hemminki 2001) as shown in Table 12.1. This elevated SIR was maintained for more than 10 years after diagnosis. Auvinen et al. (2002) used data from the Surveillance, Epidemiology and End Results (SEER) Program based on 1,788 cases of MBC, followed for a mean of 5.6 years. Contralateral cancers developed in 12 (SIR = 30). There was no increase in incidence of other non-mammary cancers.

In contrast, a study from the California Cancer Registry of 1,926 MBC cases showed a significantly increased risk of other cancers (SIR = 1.16) (Safram-Hoang et al. 2007). For contralateral breast cancer the SIR was 52.1. Risk was

Table 12.1 Risk of contralateral breast cancer in men with breast cancer

First Author (year)	*N*	Mean follow-up	2nd cancers	Standardized incidence ratio (95% CI)
Dong (2001)	552	6.8 years	8	93.1 (39.8–184.3)
Auvinen (2002)	1,788	3.9 years	12	30 (15–52)
Safram-Hoang (2007)	1,926	4.39 years	20	1.2 (1.0–1.3)

inversely related to age at onset: the SIR for those diagnosed at <60 years was 1.42 falling to 1.24 between ages 60–69 and 1.01 in those aged ≥70 years at diagnosis. Rather than reflecting an alteration of the biology of MBC in older men it is likely that risk is masked due to other causes.

Synchronous bilateral MBC is a very rare occurrence and in two large series was reported in only 0.2–0.5% of cases (Giordano et al. 2004, Donegan et al. 1998). Although synchronous bilateral MBC has been reported following estrogen therapy for prostate cancer, this is a rare event (McClure and Higgins 1951, Coard and McCartney 2004). Another reported association with bilateral breast cancer in males is prolactin-secreting pituitary adenoma (Volm et al. 1997, Forloni et al. 2001). There is usually not an identifiable risk factor in men with bilateral breast cancer (Kahla et al. 2005, Lambley et al. 2005).

Genetics

Men with a first-degree family history of either male or female breast cancer have a relative risk of developing MBC of 2.5 (Sasco et al. 1993). Approximately 10% of MBC cases have a first-degree relative with the disease (Ribeiro et al. 1980). Some individuals have rare mutations in high-penetrance genes, such as *BRCA1* and *BRCA2*, placing them at high risk whereas others more commonly have low-penetrance mutations conferring a smaller increase in risk.

BRCA1/2

Between 5 and 10% of breast cancers are due to autosomal dominant inheritance, particularly *BRCA1* and *BRCA2* mutations (Martin and Weber 2000). MBC is much more common in *BRCA2* compared with *BRCA1* families. In a US series no *BRCA1* mutations were found among 54 cases of MBC whereas 2 (4%) had a *BRCA2* mutation (Friedman et al. 1997). A UK study of 94 MBC cases reported no germline *BRCA1* mutations, but 5 (6%) cases had *BRCA2* mutations and 20% reported a first-degree relative with breast cancer (Basham et al. 2002). Both studies found no correlation between the location of the mutations within the *BRCA2* gene and MBC risk.

In contrast, of 76 MBC cases tested commercially, deleterious *BRCA1* mutations were found in 8 and *BRCA2* mutations in 14 (Frank et al. 2002). Men with *BRCA1* mutations were diagnosed at a mean age of 52 years compared with a mean age of 59 years in those with *BRCA2* mutations, which was the same age for males without mutations in this study. In a comprehensive analysis of point mutations and large genomic rearrangement in 41 MBC cases, deleterious *BRCA1* point mutations were found in 4 cases and deleterious *BRCA2* point mutations were found in 11 cases, but large genomic rearrangements were not observed in any cases (Tchou et al. 2007).

A study of 269 MBC cases, diagnosed in Israel, reported mutations of *BRCA1* in 8 (3%) and *BRCA2* in 21 (8%) (Chodick et al. 2008). There was no significant difference in the frequency of mutations among Ashkenazi and non-Ashkenazi Jews (13% versus 9%). Carriers of both *BRCA1* and *BRCA2* mutations in the United States were shown to have higher rates of MBC compared with non-carriers (Tai et al. 2007). The accumulated risk at 70 years was greater in *BRCA2* than in *BRCA1* mutation carriers (6.8% versus 1.2%)

Other High-Penetrance Genes

Cowden syndrome (CS), characterized by multiple hamartomas, especially in the skin, mucous membranes, breast, and thyroid gland confers a 25–50% life risk of breast cancer in affected females (De Jong et al. 2002). This rare disease with an estimated incidence of 1 in 250,000 is caused by mutations in the *PTEN* tumor-suppressor gene. There have been two reported cases of MBC in CS families, both of whom had early onset disease and germline *PTEN* mutations (Fackenthal et al. 2001). *PTEN* mutations are not associated with MBC in those having no phenotypic abnormalities of CS. No cases of MBC have been reported in Li–Fraumeni syndrome families.

Low-Penetrance Genes

CHEK2

The cell cycle checkpoint kinase *CHEK2* is involved in DNA repair together with *BRCA1* and *BRCA2* and the *CHEK2**1100delC variant affects kinase activity (Meijers-Heijboer et al. 2002) A tenfold increase in risk of MBC was found in families harboring the *CHEK2**1100delC mutations but without *BRCA1/2* mutations (The CHEK2 Breast Cancer Consortium 2002). However, a study from Finland comprising 114 MBC cases reported *CHEK2**1100delC in 1.8% of cases compared with 1.4% in population controls (Syrjäkoski et al. 2004), and a study of 54 Israeli cases revealed that none had *CHEK2**1100delC mutations (Ohayon et al. 2004) suggesting that this mutation plays a minor role

in MBC. Support for this has come from an Italian study of 102 unrelated cases of MBC in which no mutations were found in *BRCA1/2* or *CHEK2*.

Androgen Receptor Gene

Mutations in the androgen receptor (AR) gene within the DNA-binding domain were reported in two brothers with MBC and androgen insufficiency (Wooster et al. 1992). In a subsequent study of 13 MBC cases a guanine–adenine point mutation in the second zinc finger of the AR gene was found in one man with partial androgen insensitivity (Lobaccaro et al. 1993).

Within exon 1 of the AR gene there is a polymorphic region containing a variable number of cytosine–adenine–guanine (CAG) repeat sequences. The shorter CAG repeats increase transactivation of the receptor (Chamberlain et al. 1994). In an analysis of length of CAG repeats in 53 BC cases and controls, no overall difference in median CAG repeat length was reported but none of the controls had >28 repeats whereas 2 MBC cases had 29 and 30 repeats (Young et al. 2000a). Similar results were reported in another study which found a higher incidence of CAG repeats ($\geq$24) in 41 MBC samples compared to a control population (Maclean et al. 2004). In contrast, a Finnish study screened the entire AR coding region together with CAG repeat lengths in 32 Finnish MBC cases and found no germline mutations and no difference in CAG repeat lengths so they concluded that mutations of the AR gene do not contribute significantly to the risk of MBC (Syrjäkoski et al. 2003).

CYP17 Gene

CYP17 gene codes for the cytochrome P450c17α enzyme that is responsible for steroid 17α-hydroxylation and 17,20-lyase activity and is central to the regulation of steroid synthesis. A polymorphic T to C substitution creates an additional prompter site that increases both gene transcription and steroid synthesis (Carey et al. 1994). In a case–control study of 64 MBC cases and 81 controls, the C allele of the *CYP17* gene was present more frequently in the cases with an odds ratio of 2.1 (Young et al. 1999). In an Icelandic study of 39 cases of MBC, 15 of whom had a BRCA2 mutation, the CC genotype was found more frequently in the carriers of 999del5 mutation (33% versus 17%) (Gudmundsdottir et al. 2003). When Young et al. (2000b) examined polymorphic tetranucleotide repeats in the *CYP19* gene which controls the rate-limiting step for estrogen synthesis from precursors they found no significant difference between DNA specimens from 64 MBC cases and 79 healthy males.

Klinefelter's Syndrome

Patients with Klinefelter's syndrome (KS) have at least one X chromosome added to the normal XY karyotype (usually 47XXY) (Klinefelter et al. 1942). This is associated with testicular dysgenesis, gynecomastia, low testosterone levels, and increased gonadotropins. The prevalence of KS is 1 in 1,000 newborn boys (Jacobs et al. 1974). There is a 20 to 50-fold increased risk of breast cancer in these individuals compared with 46XY men (Harnden et al. 1971, Hultborn et al. 1997).

Cancer incidence and mortality have been reported on a cohort of 3,518 British men with cytogenetically confirmed KS who were followed for an average of 15 years (Swerdlow et al. 2005). The standardized incidence ratio (SIR) for MBC was significantly elevated at 19.2 and the standardized mortality rate also greatly increased at 57.8. When men with 47XXY karyotype were compared with men having a 47XXY/46XY mosaic karyotype, the latter group had a higher SMR for MBC (223 versus 29). Death rates from breast cancer in men with KS are similar to those in the female population (Price et al. 1985).

Gynecomastia

Gynecomastia, a benign enlargement of male breast tissue, is common in boys going through puberty after which it declines. There is an increase in incidence in later life but the condition has a high rate of spontaneous regression (Treves 1958). In a report on mammography in 212 males, gynecomastia was present in 62%. At the histological level, the incidence of gynecomastia in mastectomy specimens from MBC cases was 21%, which is less than the incidence of 40–55% reported at autopsy of unselected cases (Andersen and Gram 1982). Several studies have examined the relationship between gynecomastia and MBC and no linkage has been found (Sasco et al. 1993, Carlsson et al. 1981). In a cohort of 446 Swedish with gynecomastia followed for a mean of 18.7 years no cases of breast cancer were diagnosed (Olsson et al. 2002). Thus, there is no evidence to support a link between gynecomastia and MBC.

Occupation

There are consistent data from case–control studies linking increased frequency of MBC among men with a history of working in hot environments, such as blast furnaces, steel works, and rolling mills (Mabuchi et al. 1985, McLaughlin et al. 1988, Lenfant-Pejovic et al. 1990, Cocco et al. 1998). Some evidence also suggests that occupational exposure to petrol and exhaust fumes is a risk factor. In a Danish study of 12,880 controls and 230 MBC cases, with an estimated lag time of >10 years there was a 2.5-fold increase in risk in men with >3 months

employment in such work (Hansen 2000). This rose to 5.4 among men aged <40 when first employed with exposure to gasoline and combustion products.

Although Florida fire fighters were reported to have lower than expected overall mortality from cancer, they suffered more deaths from MBC (Ma et al. 2005). The putative carcinogens are polycyclic aromatic hydrocarbons (PAH), benzene, toluene, and 1,3-butadiene which are present in exhaust emissions. PAH–DNA adducts have been found in both tumors and benign tissue, the latter with a greater frequency in cases compared with controls (27% versus 13%) (Rundle et al. 2000). The wide variation in levels of DNA adducts may partly result from polymorphism of DNA repair genes (Smith et al. 2003).

Palli et al. (2005) examined the relationship between occupation and genetic susceptibility using the protein truncation test and single-strand conformational polymorphism assay to determine the entire coding sequence of *BRCA1 and BRCA2*. Additionally a detailed occupational history was taken from 23 cases of MBC. In this case–case study, of the 4 BRCA carriers, 3 were or had been truck drivers compared with 2/19 non-carriers: a 25-fold interaction.

Increased exposure to electromagnetic fields can inhibit pineal function with decreased melatonin production, leading to breast tumorigenesis in animal models (Brainard et al. 1999). Despite this a study of 127 female breast cancer cases and 353 matched controls showed no significant association between levels of 6-sulfatoxy melatonin and breast cancer risk (Travis et al. 2004). Early reports suggested an increased risk in men exposed to high electromagnetic fields (Demmers et al. 1991, Tynes and Andersen 1990) but a larger case–control study of 250 men who died of MBC showed that 4 had worked in the electrical industry (odds ratio 0.9)(Loomis 1992). Of these, three were >65 years old (odds ratio 2.2), that is twice the expected rate for this age group.

Pollan et al. (2001) reported a 1.31 relative risk in men with an electromagnetic field exposure above the first quartile, but no clear trend of exposure and risk. There was a suggestion of an exposure response effect in those who had intermittent exposure to electromagnetic fields. The studies are confounded by imprecise quantification of electromagnetic field exposure both at work and at home.

Overall, the evidence regarding the relationship between various occupational exposures and MBC is largely limited due to the rarity of MBC and the small groups of exposed men.

Endocrine Risk Factors

Men who take estrogens for prostate cancer (McClure and Higgins 1951), or because they are transsexuals (Symmers 1968), are at an increased risk of both unilateral and bilateral breast cancers. In terms of exposure to a range of endogenous hormones the evidence is mixed. Obesity is the commonest cause of hyperestrogenization in males and as a result has been implicated in MBC (D'Avanzo and La Vecchia 1995, Hsing et al. 1998, Ewertz et al. 2001, Johnson

Table 12.2 Risk of male breast cancer in relation to obesity

Author	Variable	Cases	Controls	OR	95% CI
D'Avanzo (1993)	Current weight (kg)				
	<70	1	23	1.0	ref
	70–79	4	33	2.1	0.4–11.1
	≥80	16	26	3.4	0.7–15.7
				P-for trend not statistically significant	
Hsing (1998)	Usual weight (kg)				
	<70	25	26	1.0	ref
	≥70–77	35	115	0.5	0.8–2.6
	78–86	50	137	1.2	1.0–2.9
	87–158	57	102	3.5	1.5–4.6
				P-for trend < 0.01	
Ewertz (2001)	Weight (kg) 10 years before diagnosis				
	<70	28	92	1.0	ref
	70–79	47	176	1.7	1.1–2.6
	80–89	44	133	1.1	0.6–2.0
	≥90	33	49	2.3	1.2–4.4
				P -for trend = 0.02	
Johnson (2002)	Weight (kg)				
	<73	13	508	1.0	ref
	73–<81	18	466	1.47	0.5–2.3
	81–90	25	506	1.89	0.6–2.8
	>90	25	425	2.16	1.3–5.0
				P -for trend = 0.02	

et al. 2002). As Table 12.2 shows, all studies report at least a doubling of risk of MBC among obese men. In a study of 21 cases and 82 controls, cases were heavier than controls but this association diminished after controlling for height (D'Avanzo and La Vecchia 1995).

In a cohort study of 73,847 Swedish diabetics, there was a doubling of risk of MBC (SIR = 2; 95% CI: 1–3.4) (Weiderpass et al. 1997). A Danish study of 156 cases and 468 controls also reported that diabetes increased risk of MBC (OR = 2.6; 95% CI: 1.3–5.3) (Ewertz et al. 2001). Benchellal et al. (2002) reported a French series of 19 cases of MBC in which there was a high incidence of diabetes, obesity, and hypertension. This association may relate to the age of those being diagnosed with MBC which was a mean of 65.3 years in the French study. It may also be that the peripheral vascular disease consequent upon diabetes may lead to testicular atrophy.

In the case–control studies that have measured serum and urinary hormones in MBC results have been contradictory (Table 12.3) (Scheike et al. 1973, Calabresi et al. 1976, Ribeiro et al. 1980, Nirmul et al. 1982, Casagrande et al. 1988, Ballerina et al. 1990). The reasons for this include different assay methodologies, often small numbers of cases, and most importantly the failure of some studies to take into account the influence of body weight on steroid metabolism.

Table 12.3 Case–control studies of endogenous urinary and serum hormones in male breast cancer

Author	Cases	Controls	Hormones	Results
Scheike (1973)	19	24	Urine: E2	No difference observed
Calabresi (1976)	17	17	Serum: andro, E1, E2, E3, T	E1, E2, E3 ↑ in cases
Ribeiro (1980)	10	31	Serum: E2, LH, FSH	No differences observed
Nirmul et al. (1982)	8	8	Serum: E2	E2 ↑ in cases
Casagrande et al. (1988)	75	75	Serum: E1, E2 Free E2, SHBG Urine: E1, E2, E3	No differences observed but cases were significantly heavier
Ballerini (1990)	10	10	Serum: T, E2, DHEA, Pr, LH, FSH, SHBG Urine: T, 5α A, 17OHC, Preg	No differences observed

Andro = androstendione, E1 = estrone, E2 = estradiol-17β, E3 = estriol, T = testosterone, LH = luteinizing hormone, FSH = follicle stimulating hormone, free E2 = biologically available estradiol-17β, SHBG = sex hormone-binding globulin, DHEA = dehydroepiandrosterone sulphate, Pr = prolactin, 5α A = 5α androstenediol, preg = pregnanediol

Testicular damage resulting in low testosterone levels is an uncommon but important risk factor for MBC. Causes include mumps orchitis aged >20 (Mabuchi et al. 1985), undescended testes (12-fold), congenital inguinal hernia or unilateral or bilateral orchidectomy (2-fold) (Thomas et al. 1992). Cases are more likely childless with an odds ratio of 5.5 (CI 1.6–19.9) compared with fathers (D'Avanzo and La Vecchia 1995). Using another indicator of testicular function a Greek study found that MBC cases had less frequent orgasms per month compared with normal controls (Petridou et al. 2000).

First pregnancies are associated with higher levels of total and percentage-free estradiol compared with subsequent ones (Bernstein et al. 1986). This led Trichopoulos (1990) to hypothesize that some breast cancers might arise in daughters as a result. In a Greek case–control study of MBC there was a significant inverse relationship between birth order and risk of breast cancer, that is, significantly more of the cases were firstborn (Petridou et al. 2000). A study from Denmark with 77 MBC cases and 288 population controls reported the relative risk of MBC for firstborn compared with later-born men was 1.7 (95% CI: 1–2.9) (Sørensen et al. 2005).

Twinship is also associated with elevated estradiol levels in pregnancy (Thomas et al. 1998) and increased risk of postmenopausal breast cancer has been reported in female dizygotic twins (Cerhan et al. 2000). Since MBC behaves in many ways like postmenopausal breast cancer in females it could be hypothesized that a similar effect would be seen in male twins. This was refuted in a joint

analysis of four twin cohorts from Denmark, Finland, Sweden, and the United States (Whiteman et al. 2000). The cohort comprised 115,235 male twins with a total of >3.5 million person-years of risk and 11 cases of MBC were reported compared with 16 expected. The authors concluded that any influence of intrauterine estradiol on risk of MBC is likely to be small.

Prolactin

Prolactin plays a central role in the growth and differentiation of normal breast tissue and inhibition of prolactin synthesis reduces S-phase fraction (SPF) of established breast cancers (Fentiman et al. 1988). Several MBC cases developing both unilaterally and bilaterally in men with hyperprolactinaemia due to pituitary adenomas have been reported (Haga et al. 1993, Volm et al. 1997, Forloni et al. 2001, Okada et al. 2003). However, in a comparison of 59 women and 3 men with breast cancer 83% of the females had detectable prolactin receptors but only 1 of the 3 cases of MBC (Gill et al. 2001). No significant difference has been found in levels of circulating prolactin in case–control studies (Ballerina et al. 1982, Nirmul et al. 1990, Thomas et al. 1992, Cocco et al. 1998).

Diet

Hsing et al. interviewed next of kin of 178 men who had died of MBC and 512 men who had died of other diseases to obtain data on diet, exercise, height, weight, occupation, and use of alcohol and tobacco (Hsing et al. 1998). A non-significant trend was found of increased risk with consumption of red meat and a decrease with higher intake of fruit and vegetables. Using data from 10 cancer registries, Rosenblatt et al. (1999) conducted a study of diet in 220 cases of MBC and 291 controls. No association was found between intake of fat, carbohydrate, protein fiber, or vitamins, other than vitamin C, consumption of which appeared to lead to an increase in risk. It is not surprising that these results are contradictory given the contradictory evidence available for most dietary exposures and risk of female breast cancer which come from multiple studies with much larger sample sizes.

Alcohol

Evidence is now accumulating that alcohol consumption is a risk factor for MBC. Earlier studies of cirrhotic males had shown no increased risk but this result may have been confounded by the high mortality from cirrhosis and the rarity of MBC (Thomas et al. 1992, Hsing et al. 1998, Weiderpass et al. 2001). A

European multicenter study with 74 cases and 1432 population controls reported a significant relationship between alcohol consumption and risk of MBC (Guenel et al. 2004). Consumers of >90 g/day of alcohol had a 5.89-fold (95% CI: 2.2–15.7) increased risk of MBC compared to men who consumed <15 g/day. The risk of MBC rose by 16% per 10 g of daily alcohol intake. Similarly, in a larger study of 1457 MBC cases and 3,374 population controls a 17% increased risk per 10 g of alcohol consumed per day was observed (Lynge et al. 2005).

Ionizing Radiation

Exposure of the breast to ionizing radiation increases risk of breast cancer in women and there is some evidence of a similar effect in men undergoing therapeutic or diagnostic radiation (Schottenfeld et al. 1963). In a study of 73 cases of MBC using neighborhood controls matched for age and race there were no significant differences in exposure to fluoroscopy, repeated chest x-rays or upper body irradiation, although there was an excess risk associated with 10 or more fluoroscopies (Casagrande et al. 1988). Thomas et al. reported a modest increase in risk associated with repeated chest x-rays or upper body irradiation in a case–control study of 227 men with breast cancer (Thomas et al. 1994). The effect emerged 20–35 years after exposure and declined after 40 years.

The Late Effects Study Group reported on a cohort of 1,380 children who had received radiotherapy for Hodgkin's disease and after 11.4 years median follow-up there was a significant increase in risk of female breast cancer (SIR 75.3, 95% CI: 44.9–118.4) (Bhatia et al. 1996). There were, however, no cases of MBC in this cohort of which 65% were males. Using data from the Hiroshima and Nagasaki Tumor Registries, Ron et al. (2005) reported 9 cases of MBC among 45,880 male atomic bomb survivors. There was a dose–response relationship with a significant eightfold increase in risk per sievert. These conflicting data may result from a long latent period from exposure so that differences in length of follow-up may miss a significant effect of radiation on risk of MBC.

Conclusions

The major similarity between breast cancer in females and males is that the majority of cases have none of the recognized risk factors, underlining the paucity of epidemiological knowledge concerning this disease. Germline mutations of the *BRCA2* and *CYP17* genes play a significant role in a small group of men. Individuals with Klinefelter's syndrome have a risk of breast cancer similar to that in females. Testicular damage, whether from mumps orchitis, high ambient working temperature, consumption of estrogens, or undescended testes, leads to an increase in risk of MBC, whereas gynecomastia is not a risk

factor. No consistent endocrine abnormalities have been identified in case–-control studies. However, obesity, alcohol consumption, diabetes mellitus, and radiation do all appear to be related to MBC risk, similar to female breast cancer.

The lacunae in our knowledge of this rare disease are the result of often small studies that are underpowered to elucidate small but significant risk factors. National and international investigations are needed so that the influence of lifestyle and endocrine factors on both risk and prognosis of MBC can be determined in order that rational preventive and therapeutic strategies can be pursued.

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Chapter 13
Inherited Predisposition: Familial Aggregation and High Risk Genes

Kathleen E. Malone and Kerryn W. Reding

Introduction

The heritable component of breast cancer has been long recognized, as illustrated in the 1866 report, by a French physician of 10 breast cancer cases in four generations of his wife's family (Broca 1866). Family history of breast cancer is the single most well-established risk factor for breast cancer and confers some of the strongest effects seen among known breast cancer risk factors. The accumulation of epidemiologic evidence has clarified that the increased risk of breast cancer conferred by a positive family history varies with the degree of kinship, the number of affected relatives, and the onset ages in relatives and/or the women under study.

Familial Aggregation of Breast Cancer

Family History of Breast Cancer

The vast majority of studies have observed 1.5- to 3-fold increased risks of breast cancer in relation to a first-degree family history of breast cancer (i.e., mother, sister, or daughter) and elevated but generally lower increases in risk in relation to a second-degree (i.e., aunt or grandmother) family history alone (Table 13.1). A 52-study meta-analysis observed for first-degree family history a 2- to 3-fold range of increased risks across the majority of studies (pooled relative risk (RR) = 2.1, 95% CI = 2.0–2.2.); in the 10 studies with second-degree family history data, 1.2- to 1.9-fold increased risks were observed (pooled RR = 1.5, 95% CI = 1.4–1.6) (Pharoah et al. 1997).

Breast cancer risk increases steadily with the number of affected first-degree relatives as reported in a pooled analysis of 52 studies including 58,209 cases and

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_13,

Table 13.1 Summary of the association between family history of breast cancer and risk of breast cancer

Family history of breast cancer	Range of RR estimates across studies	Summary risk estimates from pooled/meta-analyses (95% CI)[a]			
Affected first- or second-degree relative[b]	1.2 - 4.0	1.9 (1.7–2.0)[b]			
Affected first-degree relative[b]	2.0 - 4.0	Probands age: All ages	< 50	≥ 50	
		2.1 (2.0–2.2)	2.4 (2.2–2.7)	1.9 (1.8–2.0)[b]	
Affected second-degree relative[b]	1.2 - 2.0	1.5 (1.4–1.6)[b]			
Number of first-degree affected relatives[b]					
1		1.8 (1.7–1.9)	2.1 (1.9–2.4)	1.7 (1.5–1.8)	
2		2.9 (2.4–3.6)	3.8 (2.6–4.2)	2.6 (1.5–1.8)	
3+		3.9 (2.0–7.5)	12.1 (1.7–85.2)	2.7 (1.3–5.5)	
Age of relative's diagnosis					
Among women with two affected first-degree relatives[b]					
• At least one diagnosed < age 40			13.5 (3.4–53.9)	3.9 (1.8–8.6)	
• Both diagnosed age ≥40			7.8 (2.4–25.0)	2.6 (1.8–3.7)	
Among women with one affected first-degree relative[b]		Probands age <40	40–49	50–59	≥60
• Relative diagnosed < age 40		5.7 (2.7–11.8)	3.0 (1.8–4.9)	2.0 (1.2–3.4)	1.4 (0.9–2.1)
• Relative diagnosed age 40–49		2.9 (1.9–4.4)	2.0 (1.5–2.8)	2.2 (1.6–3.0)	1.4 (1.0–2.0)
• Relative diagnosed age 50–59		2.8 (1.7–4.5)	2.3 (1.7–3.2)	1.6 (1.2–2.1)	1.5 (1.2–2.0)
• Relative diagnosed age ≥60		2.0 (1.2–3.2)	1.7 (1.3–2.1)	1.6 (1.3–2.0)	1.4 (1.2–1.7)

[a]These summary risk estimates are drawn from a prior meta-analysis and a pooled analysis (Pharoah et al. 1997, Collaborative Group on Hormonal Factors in Breast Cancer 2001)

[b]First-degree relatives include mother, sister, and daughter; second-degree relatives include aunt and grandmother

101,896 controls conducted by the Collaborative Group on Hormonal Factors and Breast Cancer (Table 13.1). Breast cancer risk also tends to be higher for women with a relative diagnosed with breast cancer at a young age (i.e., <50 or 45 years) (Sattin et al. 1985, Byrne et al. 1991, Colditz et al. 1993, Schwartz et al. 1985, Tulinius et al. 1992). The Collaborative Group analysis showed that among women diagnosed with breast cancer under age 60 the risk associated with family history was generally greater, the younger their relative was diagnosed (Table 13.1) (Collaborative Group on Hormonal Factors in Breast Cancer 2001). The magnitude of the increase in risk associated with a family history of breast cancer is also dependent on the age of the proband or index woman, in that the increased risk associated with family history is higher in younger women and lower among older women (Sattin et al. 1985, Ottman et al. 1986, Claus et al. 1990, Roseman et al. 1990). In the Collaborative Group analysis, the RRs in relation to having one affected first-degree relative ranged from a high of 2.9 (99% CI 2.1–4.1) among women <35 years of age to a low of 1.5 (99% CI 1.2–1.7) among women 60–64 years of age (Collaborative Group on Hormonal Factors in Breast Cancer 2001).

Additional familial characteristics have also been implicated as risk factors although they are less studied and/or involve less consistent associations. Many but not all studies have observed an increased risk of breast cancer in relation to family history of bilateral breast cancer (Sattin et al. 1985, Byrne et al. 1991, Ottman et al. 1986, Sakamoto et al. 1978, Anderson and Badzioch 1985, de Bock et al. 2008). Family history of ovarian cancer has also been implicated as a risk factor for breast cancer although these studies pre-dated the discovery of the *BRCA1* and *BRCA2* genes and it is unclear to what extent this association persists outside of mutation carriers (Schildkraut et al. 1989, Thompson and Schildkraut 1991). Positive family history has been observed to be more frequent and also to be associated with higher risks of breast cancer in Jewish women, another observation which is at least partly intertwined with effects of the *BRCA1*/*BRCA2* genes (Egan et al. 1996). It is also worth noting that 2- to 4-fold increased risks of male breast cancer have been observed in relation to family history and this association is heightened with increased numbers and earlier onset ages in relatives (Casagrande et al. 1988, Ewertz et al. 2001, Rosenblatt et al. 1991).

Family History of Breast Cancer and Interaction with Other Factors

A number of studies have evaluated whether non-familial risk factors (i.e., exogenous, lifestyle, or personal factors) have a differential effect on the risk of breast cancer according to family history. Results have been mixed and difficult to interpret due to power limitations and the crude nature of family history which can reflect underlying genes, shared exposures, high background incidence rates, and chance. Although several factors have been observed in one

or more studies to have heightened effects in women with a positive family history, such as oral contraceptive (OC) use (Grabrick et al. 2000, UK National Case-Control Study Group 1990), body weight (Sellers et al. 1992, Carpenter et al. 2003), and recency of pregnancy (in younger women) (Colditz 1996, Wohlfahrt et al. 2002), these results have not been consistently replicated. For example, with respect to the increased risk observed in relation to OCs in a few studies, two other large studies, the Nurses' Health Study (Colditz 1993) and the CASH Study (Murray et al. 1989), found no evidence of an increased risk. The largest assessment of risk factors by family history to date, the Collaborative Group's pooled analysis, found little evidence that the effects of other established risk factors, including parity, age of first birth, OC use, HRT use, body mass index, and alcohol, varied by the presence or absence of first-degree family history of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2001). However, it is worth noting that when examined by age (an important consideration given that the magnitude of the risk associated with family history varies by age and that associations with certain breast cancer risk factors are well known to vary by age/menopausal status) some risk factors were assessed in cruder ways (i.e., ever/never use of OCs) rather than by the finer delineations (i.e., recency or duration of OC use) that have been observed to be most pertinent to breast cancer risk. As a result, some important interactions may have been overlooked. Regardless, given that women with positive family history have a higher absolute risk of developing breast cancer, even relative risks which are identical for women with and without a family history would have a greater absolute impact on disease incidence among those with a family history.

BRCA1 and BRCA2 Genes

Discovery of BRCA1 and BRCA2

Multiple segregation analyses conducted in the 1980s and early 1990s, first in high-risk families and subsequently in population-based studies, substantiated that familial breast cancer transmission was likely best accounted for by one or more rare but highly penetrant, autosomal dominant alleles (Williams and Anderson 1984, Bishop et al. 1988, Newman et al. 1988). Years of investigation culminated in the localization on chromosome 17q of the first major breast cancer susceptibility gene, *BRCA1*, in a linkage study of rare, high-risk breast cancer families with multiple affecteds and early-onset ages (Hall et al. 1990); *BRCA1* was also found to co-segregate with ovarian cancer. In 1994, *BRCA1* was cloned and sequenced (Miki et al. 1994), and soon after, a second gene, *BRCA2*, was localized to chromosome 13q, cloned and sequenced (Wooster et al. 1995).

Biology and Function of BRCA1 and BRCA2

The proteins encoded by the *BRCA1* and *BRCA2* genes are involved in maintaining genomic integrity (Kinzler and Vogelstein 1997). While *BRCA1* and *BRCA2* do not share similarities in DNA sequence, they are believed to share a similar role in the cell (Kinzler and Vogelstein 1997). These tumor-suppressor genes were originally thought to serve as cell gatekeepers (e.g., stopping cellular proliferation); subsequently, evidence emerged demonstrating an additional role in DNA repair (Kinzler and Vogelstein 1997).

Observations implicating both genes in the repair of DNA double-strand breaks (DSB), perhaps as a component of homologous directed repair (HR) which is the least error prone of the DSB repair mechanisms, includes the finding that *BRCA1* and *BRCA2* proteins are at their highest expression levels during the phase of the cell cycle when HR occurs (Scully et al. 1997, Venkitaraman 2002). Additionally, *BRCA1* and *BRCA2* proteins have been observed to bind to other DNA repair proteins, including Rad51, CHK2, and ATM, in order to assemble into a multiprotein complex which repairs the DSB through HR (Weinberg 2007). Studies have demonstrated that in the absence of *BRCA1* or *BRCA2* proteins, Rad51 is not recruited to a DSB within the cell (Weinberg 2007). Under this scenario, chromosomal aberrations such as translocations may occur (Venkitaraman 2002). Further, in the absence of HR, base pairs may be omitted when single strands of DNA are used to rejoin the double strand in non-homologous end joining (Weinberg 2007). Thus, the hypothesis has developed that *BRCA1* and *BRCA2* proteins are crucial for the DSB repair process with the highest repair fidelity (Venkitaraman 2002).

Multiple studies have also reported that *BRCA1* appears to be involved in cell cycle regulation via inhibition of steroid hormone receptor signaling (Venkitaraman 2002, Heine and Parvin 2007, Fan et al. 1999, Mote et al. 2004). In particular, wild-type *BRCA1* protein has been shown to inhibit the estrogen receptor's transcriptional activation mechanisms (Fan et al. 1999). It has been proposed that *BRCA1* estrogen receptor signaling may explain the tissue specificity of *BRCA1* mutations; however, more information is needed to fully understand this relationship (Venkitaraman 2002, Eakin et al. 2007, Monteiro 2003).

Prevalence and Predictors of BRCA1/BRCA2 Mutations

The prevalence of deleterious *BRCA1*/*BRCA2* mutations has been shown to vary according to study population type. Initial assessments in the same types of rare, high-risk families used to localize these genes found that *BRCA1*/*BRCA2* mutations accounted for the majority of breast (and ovarian) cancers in such families (Shattuck-Eidens et al. 1997, Ford et al. 1998). In the Breast Cancer Linkage Consortium (BCLC), among 237 families with at least four breast cancer cases,

disease was linked to *BRCA1* or *BRCA2* in approximately 84% of families (Ford et al. 1998). Compared to the aforementioned, rare, linkage-type families, high-risk cancer genetic clinic populations have been observed to have lower but still substantially increased mutation prevalences ranging as high as 20 to 55% (Couch et al. 1997, Martin et al. 2001, Shih et al. 2002, Simard et al. 2007).

Population-based assessments in the unselected, more general population of breast cancer cases have found lower overall mutation prevalences than those from family and clinic-based studies (Peto et al. 1999, Malone et al. 2000, Loman et al. 2001, Anglian Breast Cancer Study Group. 2000, Malone et al. 2006). The first to examine both genes, a population-based study of 617 British cases under age 45, found 2.6% and 2.3% carried a *BRCA1* and *BRCA2* mutation, respectively (Peto et al. 1999). In a US population-based study, 5.9% and 3.4% of 203 cases under age 36 carried a *BRCA1*and *BRCA2* mutation, respectively, (Malone et al. 2000), and in a Swedish population-based study of 234 cases diagnosed before age 41, 6.8% and 2.1%, respectively, carried a mutation in *BRCA1* and *BRCA2* (Loman et al. 2001). The Anglian population-based study of breast cancer in women up to age 54 observed 0.7% and 1.3%, respectively, with a *BRCA1* and *BRCA2* mutation (Anglian Breast Cancer Study Group 2000). The NICHD CARE Study, the first population-based study to examine both genes in women up to age 64, observed *BRCA1* and *BRCA2* mutations, respectively, in 2.4% and 2.3% of cases (Malone 2006). In all of the above studies which included women over age 35, mutation prevalence decreased with increasing age, and in general, most studies found *BRCA1* mutations to be more frequent than *BRCA2*.

Within population-based studies, as would be expected, mutations are more common in women with a family history of breast (or ovarian) cancer compared to those with no family history and mutation proportions increase in relation to the extent of family history. A number of factors have been observed to correlate with the presence of a *BRCA1* or *BRCA2* mutation in breast cancer cases, including early-onset disease, and familial features such as number of affected relatives, onset ages, and ovarian cancer family history as well as Jewish ancestry. Multivariate approaches have been used in a few studies to evaluate potential predictors of mutation carriership, initially in higher risk populations defined either by family history features or Jewish ancestry (Hartge et al. 1999, Apicella et al. 2003, Ozcelik et al. 2003), and more recently in the CARE population-based study (Malone 2006). A young age of breast cancer diagnosis in a proband or a relative, first-degree family history of breast cancer, any ovarian cancer family history, and Jewish ancestry were each independent and powerful predictors of carrying a *BRCA1* mutation among women with breast cancer diagnosed at ages 34–64 in multivariate predictive models in the CARE Study (Malone 2006). Only two factors were significant predictors of *BRCA2* status, early onset in the case and early onset in a relative, and the magnitude of these associations were considerably more modest.

Population-based studies have shown that mutation prevalence is much lower in unselected series of breast cancer cases overall and that the majority

of women with a positive family history, particularly those with fewer affected relatives and later-onset ages, do not carry a deleterious mutation in either gene. For example, in the CARE Study, among those reporting first-degree and second-degree only family histories of breast cancer, 5.6% and 3.1% carried *BRCA1* mutations and another 5% and 1.9% carried *BRCA2* mutations, respectively. This translates into more than 90% of the cases with a first-degree family history and 95% of those with only a second-degree family history not carrying a mutation. Although they account for relatively high proportions of breast or breast–ovarian families with extreme high-risk profiles, deleterious mutations in *BRCA1*/*BRCA2* appear to account for less than 10% of breast cancers overall.

Multiple series of male breast cancer cases have been assessed for *BRCA1*/*BRCA2* mutation prevalence. *BRCA2* mutations have been observed in less than 5% to more than 30% of male breast cancer cases with some suggestion that design features (i.e., population-based or high-risk family-based) contribute to variation in results (Basham et al. 2002, Couch et al. 1996, Friedman et al. 1997, Haraldsson et al. 1998). *BRCA1* mutations appear to have little involvement in male breast cancer.

Founder Effects and Race-Specific Results

Early on, mutations in *BRCA1*/*BRCA2* were observed to occur at particularly high frequencies in Ashkenazi Jewish women and three founder mutations, the *BRCA1* 185delAG, the *BRCA1* 5382insC, and the *BRCA2* 6174delT, are estimated to constitute a 2.6% prevalence in the Jewish population (Struewing et al. 1995, Roa et al. 1996, Neuhausen et al. 1996) as compared to an estimated 0.15–0.3% *BRCA1*/*BRCA2* mutation prevalence in the general population (Peto et al. 1999, Anglian Breast Cancer Study Group. 2000 Malone et al. 2007, Whittemore et al. 2004). It is worth noting that the estimates outside of Jewish populations are statistical extrapolations because of the absence of any large population prevalence surveys of *BRCA1*/*BRCA2* mutations in other groups. Founder mutations have also been identified in Iceland, Norway, Finland, and Holland (Ferla et al. 2007).

Studies of any notable size have focused almost exclusively on women of European or Ashkenazi Jewish descent, resulting in a paucity of information on other racial/ethnic groups. To date, three population-based studies have provided mutation prevalence data in African-American breast cancer cases, two on *BRCA1* and a third on both genes (Malone et al. 2006, Newman et al. 1998, John et al. 2007). No *BRCA1* mutations were observed in a North Carolina series of 88 African-American cases (Newman et al. 1998) and 1.3% were found in 341 African-American cases in a California study (John et al. 2007). The CARE Study examined both genes among 483 African-American cases and found that *BRCA1* mutations were twice as common in White (2.9%) versus

Black (1.4%) cases and *BRCA2* mutations were slightly more common in Black (2.6%) than White (2.1%) cases (Malone et al. 2006). The California study by John et al. (2007) observed *BRCA1* mutations in 3.5% of 393 Hispanic cases and 0.5% in 444 Asian-American cases.

Penetrance Estimates

Germline mutations in *BRCA1* and *BRCA2* have been reported to confer 26–84% lifetime risks of breast cancer (Ford et al. 1998, Easton et al. 1995, Risch et al. 2006, Satagopan et al. 2001, Struewing et al. 1997). This variability in results can likely be ascribed in part to variation in populations and study designs. In general, penetrance estimates have been higher in high-risk family settings (Ford et al. 1998, Easton et al. 1995). In BCLC families with at least four breast cancer cases, breast cancer penetrance by age 70 was estimated as 87% for *BRCA1* and 84% for *BRCA2*(Ford et al. 1998, Ford et al. 1994). A meta-analysis of 10 published estimates of penetrance from a mix of selected high-risk families, population-based series of early-onset breast cancer cases, and Ashkenazi Jewish women reported pooled penetrance estimates by age 70 of 57% (47%–66%) for *BRCA1* and 49% (40%-57%) for *BRCA2* (Chen et al. 2006). A pooled analysis of 22 studies involving unselected case series, a mix of hospital and population-based studies, reported summary breast cancer penetrance estimates of 65% (51%-75%) and 45% (33%-54%) for *BRCA1* and *BRCA2* mutation carriers, respectively (Antoniou et al. 2003). Although earlier reports (Satagopan et al. 2001) had suggested penetrance might be lower in Ashkenazi Jewish women, a second report from the group of 22 studies found that the three Jewish founder mutations appeared to carry similar penetrance estimates to the study as a whole (Antoniou et al. 2005). A recent population-based study of contralateral breast cancer found penetrance estimates of 36% and 47% for *BRCA1* and *BRCA2*, respectively, in the families of women with unilateral breast cancer; these rose to 48% and 59% in families of contralateral breast cancer cases (Begg et al. 2008). There was also strong evidence of residual variation in risk between mutation carrying families, possibly attributable to additional risk factors, either genetic or environmental, and/or heterogeneity in risk associated with unique variants.

Variants of Unknown Significance

Most work to date on *BRCA1*/*BRCA2* sequence variants has focused on relatively rare, unambiguous, clearly deleterious mutations, which for the most part involve protein truncation through premature termination codons, along with a smaller portion of splice site mutations, large rearrangements, and missense variants in functional motifs. However, a larger portion of sequence

variants detected in these two large genes (roughly 10–15% of those tested) are currently classified as variants of unknown significance (VUS), presenting substantial challenges to women and clinicians. The vast majority of VUS consist of missense variants while a smaller portion includes intronic variants in frame deletions and insertions (IFDIs). Classification of *BRCA1*/*BRCA2* VUS is hindered by the low population frequency of most individual variants, which precludes evaluation through disease segregation, and the scarcity of assays that can directly and reliably assess functional significance. Extensive efforts involving functional assays, in silico approaches based on evolutionary sequence conservation (i.e., highly conserved invariant changes are more often deleterious), degree of chemical change (Tavtigian et al. 2006), and multifactorial models (Goldgar et al. 2004, Easton et al. 2007), are underway to improve VUS classification.

Gene–Environment Interaction Studies of BRCA1 and BRCA2

A number of studies have investigated the impact of risk factors for breast cancer among *BRCA1* and *BRCA2* mutation carriers although many of these studies have been constrained by limited power due to the rare nature of these mutations. Many analyses therefore have combined *BRCA1* and *BRCA2* mutation carriers in attempts to overcome power limitations despite potential differences in the etiology of *BRCA1*- and *BRCA2*-associated breast cancers. Additionally, most studies to date have focused on mutation carriers identified via high-risk cancer genetics clinics and high-risk families, a population for which results may well be applicable to high-risk families in general but may not be generalizable to mutation carriers in the general population.

Pregnancy has a complex role in sporadic as well as inherited breast cancer. While overall pregnancy confers a decreased risk of breast cancer over time, increased risk of breast cancer in the years immediately following a pregnancy have been reported (Albrektsen et al. 1995). In *BRCA1*/*BRCA2*-positive women, this dual nature of pregnancy presents an added layer of complexity given the generally younger age of onset for *BRCA1*/*BRCA2*-related breast cancers. Multiple studies have not observed a decreased breast cancer risk in *BRCA1*/*BRCA2* mutation carriers in relation to an early age at first birth (Cullinane et al. 2005, Kotsopoulos et al. 2007, Hartge et al. 2002, Ursin et al. 1997), nor with parity (Kotsopoulos et al. 2007, Ursin et al. 1997, Andrieu et al. 2006). However, the role of increasing numbers of live births is less clear. Two of the three largest studies have shown a marginally decreased risk for each additional birth in *BRCA1* mutation carriers with most of the effect being observed in women with 4+ live births (Cullinane et al. 2005, Gronwald et al. 2006, Andrieu et al. 2006). The third study observed a 1.2-fold increased risk with increasing parity but only 9% of women had more than three births (Gronwald et al. 2006). For *BRCA2* mutation carriers, there was no association

between numbers of live births and breast cancer risk, although the number of *BRCA2* mutation carriers in these studies was much smaller (Cullinane et al. 2005, Andrieu et al. 2006). Overall, there is no convincing evidence that pregnancy affords the same protection in *BRCA1*/*BRCA2* mutation carriers as in non-carriers. It has been proposed that without a functioning *BRCA1* or *BRCA2* protein, the protective effect of pregnancy may be absent (Russo et al. 2001, Narod 2006).

With respect to other reproductive factors, the impact of breastfeeding on breast cancer risk may differ between *BRCA1* and *BRCA2* carriers. A 44–50% reduction in breast cancer risk was observed for more than 1 year of breastfeeding in women with *BRCA1* mutations in two of three studies assessing this question (Gronwald et al. 2006, Jernstrom et al. 2004), while breastfeeding was found not to impact risk among *BRCA2* mutation carriers (Kotsopoulos et al. 2007, Andrieu et al. 2006, Jernstrom et al. 2004). Similarly, a decreased breast cancer risk associated with a later age of menarche was restricted to *BRCA1* mutation carriers, with two studies reporting 10–15% reductions in risk associated with later age at menarche, similar to effects seen in breast cancer studies overall; no association was observed in *BRCA2* mutation carriers (Gronwald et al. 2006, Kotsopoulos et al. 2005, Chang-Claude et al. 2007).

Multiple studies have reported increased risks ranging from 1.3- to 2.1-fold for long-term use of OCs among *BRCA1*/*BRCA2* mutation carriers, with particularly increased risks associated with OC use before a first pregnancy (Narod et al. 2002, Brohet et al. 2007, Haile et al. 2006) (Table 13.2). A few studies have observed no association in relation to ever use of OCs but were limited by either small numbers of mutation carriers or small numbers of carriers with long-term OC use, precluding analyses of detailed OC features (Gronwald et al. 2006, Figueiredo 2008). It is plausible that a modestly elevated risk of breast cancer is associated with long-term use of OCs among *BRCA1*/*BRCA2* mutation carriers as similar to sporadic breast cancer (Casey et al. 2008), and further, risk may be largely confined to OC use before first pregnancy.

With respect to anthropometric characteristics, two studies reported a 1.4- and 3.6-fold increased risk, respectively, for women with a *BRCA1*/*BRCA2* mutation who gained more than 10 pounds after age 18 and one also observed a 30% reduction in breast cancer risk for mutation carriers who lost at least 10 pounds after age 18 (Kotsopoulos et al. 2005, Nkondjock et al. 2006). Together, these studies suggest that weight gain may increase the risk of breast cancer among *BRCA1*/*BRCA2* mutation carriers.

Several other well-established breast cancer risk factors have not been shown to be associated with risk among *BRCA1*/*BRCA2* mutation carriers including alcohol (Nkondjock et al. 2006, McGuire et al. 2006), CHT use (Rebbeck et al. 2005, Armstrong et al. 2004), BMI (Kotsopoulos et al. 2005, Nkondjock et al. 2006), and smoking (Gronwald et al. 2006, Ghadirian et al. 2004), though it is important to acknowledge that many of these studies had limited sample sizes.

Table 13.2 Summary of reports on the risk of breast cancer associated with oral contraceptive use among *BRCA1* and *BRCA2* mutation carriers

Author and year of publication	Ursin (1997)	Narod (2002)		Haile (2006)		Gronwald (2006)	Brohet (2007)	Figueiredo (2008)	
Study population[a]	Ashkenazi Jewish cases < age 40	Women from high-risk clinics		Women from high-risk families		Women from high-risk clinics	International *BRCA1/2* Carrier Cohort	Population-based study of contralateral breast cancer	
Mutation carriers	3 *BRCA1/2* founder mutations	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA1/2*	*BRCA1*	*BRCA2*
Sample size	14 carriers, 37 non-carriers	981	330	497	307	1,482	1,593	109	72
Categories of oral contraceptive use	**Relative risk estimates and 95% confidence intervals**								
Ever use	–	1.2 (1.0–1.4)	0.9 (0.7–1.2)	0.8 (0.5–1.1)	1.6 (0.9–2.9)	0.8 (0.5–1.2)	1.5 (1.2–1.9)	2.4 (0.7–7.8)	0.8 (0.2–3.1)
Short-term use[b]	1.6 (0.2–10.9)	1.1 (0.9–1.3)	0.9 (0.7–1.2)	0.7 (0.4–1.1)	1.2 (0.6–2.3)	0.9 (0.5–1.5)	1.3 (1.0–1.8)	2.9 (0.8–11.3)	0.9 (0.2–3.6)
Long-term use[c]	4.3 (0.5–24.6)	1.4 (1.1–1.7)	0.8 (0.6–1.9)	0.8 (0.5–1.2)	2.1 (1.1–3.9)	0.8 (0.5–1.4)	1.6 (1.2–2.2)	2.1 (0.6–7.1)	2.0 (0.5–7.8)
Short-term use before first pregnancy	1.9 (0.3–13.2)	–	–	0.8 (0.5–1.2)	1.5 (0.9–2.7)	–	1.3 (1.0–1.8)	1.1 (0.3–4.2)	1.4 (0.3–6.0)
Long-term use before first pregnancy	7.8 (1.1–55.0)	–	–	0.9 (0.6–1.3)	3.5 (2.1–5.7)	–	1.8 (1.2–2.9)	1.0 (0.4–2.5)	1.7 (0.5–6.0)

[a]With the exception of Ursin, all studies compared breast cancer cases to controls within *BRCA1/2* subsets; Ursin compared *BRCA1/2* mutation carrier cases to non-carrier cases

[b]Short-term use was defined as 12–48 months in Ursin; >0–4 years in Narod, Haile, and Figueiredo; 1–3 years in Brohet

[c]Long-term use was defined as ≥49 months in Ursin; 5–9 years in Narod; >9 years in Brohet; ≥5 years in Haile and Figueiredo

Prevention, Treatment, and Outcomes in Mutation Carriers

Tumor Features of BRCA1- and BRCA2-Associated Breast Cancers

Tumor characteristics differ between *BRCA1*- and *BRCA2*-associated breast cancers. *BRCA1* breast cancers tend to be estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, of basal-like phenotype, high histologic grade, and medullary histology, whereas *BRCA2* breast cancers are, in general, more similar to sporadic breast cancers with the majority being ER-positive and PR-positive, and of similar histologic grade and morphology to sporadic breast cancers (Brekelmans et al. 2007, Honrado et al. 2006). Similarities between *BRCA1*- and *BRCA2*-associated breast cancers include the lack of HER2 expression and the greater proportion of tumors that are poorly differentiated (Honrado et al. 2006, Robson 2007). Overall, these characteristics have implications for breast cancer prevention and treatment.

Prevention of First Primary Breast Cancer

Women with a *BRCA1*/*BRCA2* mutation experience the greatest reduction in breast cancer risk after undergoing a bilateral mastectomy. Prophylactic bilateral mastectomy in *BRCA1*/*BRCA2* carriers confers an estimated 85–100% reduction in breast cancer risk (Hartmann et al. 2001). It is estimated that 36% and 18% of mutation carriers in the United States and worldwide, respectively, have undergone a prophylactic bilateral mastectomy (Metcalfe et al. 2008).

Multiple studies have observed 47–68% reductions in breast cancer risk in *BRCA1*/*BRCA2* mutation carriers following a prophylactic bilateral oophorectomy (Eisen et al. 2005, Kauff et al. 2002, Kauff 2008, Rebbeck et al. 2002). The use of tamoxifen and other anti-estrogenic drugs for prevention of breast cancer among *BRCA1*/*BRCA2* mutation carriers is not widespread with an estimated 8% and 12% in the United States and worldwide, respectively, using tamoxifen or raloxifene (Metcalfe et al. 2008). This low level of use is likely due to the lack of clear evidence demonstrating an associated reduction in breast cancer. Within randomized trials assessing the effectiveness of tamoxifen as chemoprevention for breast cancer in mutation carriers, one study reported some suggestion of a reduced risk associated with tamoxifen use (King et al. 2001) and another reported no reduction in risk (Kote-Jarai et al. 2007), although both were constrained by small numbers of mutation carriers.

Breast Cancer Treatments for BRCA1 and BRCA2 Mutation Carriers

Current American Society of Clinical Oncology and National Comprehensive Cancer Network recommendations regarding adjuvant therapy do not distinguish between *BRCA1*/*BRCA2* mutation carriers and non-carriers because thus far, the evidence to recommend differential systemic therapies based on carrier

status has been insufficient (Robson 2007, Domchek and Weber 2006, Nusbaum and Isaacs 2007, National Comprehensive Cancer Network 2008). Currently, breast conservation surgery and radiotherapy are widely used in the management of early-stage disease (Nusbaum and Isaacs 2007).

With laboratory studies demonstrating that in vitro *BRCA1*-positive tumors are sensitive to agents targeting DNA double-strand breaks, such as cyclophosphamide- and anthracycline-based (CA) regimens, but not responsive to regimens containing taxanes (Robson 2007, Domchek and Weber 2006), clinical studies have begun to test the hypothesis that CA-based chemotherapeutic regimens are better suited for breast cancer patients carrying *BRCA1* mutations. Multiple small clinical studies have observed differential responses to chemotherapy between *BRCA1*/*BRCA2* carriers and non-carriers in that carriers were more responsive to CA regimens (Chappuis et al. 2002, Kennedy et al. 2004) but less responsive to taxane regimens compared to non-carriers (Byrski et al. 2008).

Ipsilateral and Contralateral Breast Cancer

The risk of subsequent breast cancer among women with a first primary breast cancer is substantially greater than the risk of unilateral breast cancer among women in the general population. Multiple studies have observed that among those treated with lumpectomy and radiotherapy the risk of ipsilateral recurrence is higher in *BRCA1*/*BRCA2* mutation carriers compared to non-carriers (Haffty and Lannin 2004, Pierce et al. 2000, Robson et al. 2005). However, the risk of ipsilateral recurrence was observed to be the same between non-carriers and carriers who had undergone a bilateral oophorectomy in addition to the lumpectomy and radiotherapy (Pierce et al. 2000).

Multiple studies have observed a 40–70% reduction in the risk of contralateral breast cancer (CBC) among *BRCA1*/*BRCA2* mutation carriers who use tamoxifen (Gronwald et al. 2006, Metcalfe et al. 2004, Narod et al. 2000, Pierce et al. 2006, Reding 2008). Results have been inconsistent regarding the effect of chemotherapy on CBC risk among *BRCA1*/*BRCA2* mutation carriers. Two studies observed a 50–60% reduced risk of CBC associated with chemotherapy among *BRCA1*/*BRCA2* mutation carriers, while two others observed no reduction in risk (Metcalfe et al. 2004, Narod et al. 2000, Pierce et al. 2006, Reding 2008). Differences in findings across studies may be due to the heterogeneity of chemotherapeutic regimens. One of these studies reported the suggestion of a difference in CBC risk for different regimens between mutation carriers and non-carriers with CA regimens providing a greater reduction in risk of CBC in mutation carriers (RR = 0.3, 95% CI: 0.1–0.8) compared to non-carriers (RR = 0.8, 95% CI: 0.5–1.2), although these analyses had limited power (Reding 2008).

Breast Cancer Mortality

Many studies have investigated breast cancer-specific and overall mortality among *BRCA1*/*BRCA2* mutation carriers and non-carriers (Robson 2007).

Collectively, these studies have not demonstrated a difference between mutations carriers and non-carriers (Robson 2007). Furthermore, despite the poorer prognostic tumor features associated with *BRCA1* mutations, there appeared to be no differences in survival between *BRCA1* and *BRCA2* mutation carriers (Kriege et al. 2008).

Remaining Unexplained Heritable Component

BRCA1/*BRCA2* mutations appear to account for the bulk of breast cancers in rare, high-risk type families; however, the majority of women with positive family history in the general population do not carry a *BRCA1*/*BRCA2* mutation. Segregation analyses in the families of breast cancer cases under age 55 and under age 40, respectively, have suggested that residual familial aggregation which persists after accounting for *BRCA1*/*BRCA2* mutations could be potentially explained by (i) a large number of common, low-penetrant genes with multiplicative effects (Antoniou et al. 2002) and (ii) unidentified major dominant and recessive genes (Cui et al. 2001). Efforts are ongoing to identify and evaluate additional genes contributing to breast cancer. Chapter 14 addresses the role of common, low-penetrant genes.

Several cancer genetic syndromes have been shown to include an increased risk of breast cancer. Very rare germline mutations in *p53* are associated with the Li–Fraumeni syndrome which involves high risks of several cancers including breast cancer at a young age (Garber et al. 1991, Sidransky et al. 1992, Arcand et al. 2008, Malkin et al. 1990). Other identified cancer syndrome-related genes which have been associated with high risks of breast cancer include *PTEN* (Cowdens syndrome) (Nelen et al. 1996), *LKB1*/*STK11* (Peutz–Jeghers syndrome) (Boardman et al. 1998, Hemminki et al. 1998, de Jong et al. 2002), and *CDH1*/E-cadherin (hereditary diffuse gastric cancer syndrome) (Pharoah et al. 2001, Suriano et al. 2005). Although mutations in these genes appear to carry high, 10- to 20-fold increased risks compatible with an autosomal dominant inheritance mode, they are also quite rare and account for a negligible portion of breast cancer incidence.

Several other genes have been shown or have been hypothesized to carry somewhat less rare and less-penetrant mutations than the rare, highly penetrant mutations in *BRCA1*/*BRCA2*. *ATM* and *CHEK2*, both of interest because of involvement in DNA damage response and evidence of interaction in the *BRCA1*/*BRCA2* pathways, have been the subject of considerable investigation with inconsistent results. *ATM* homozygote mutation carriers are afflicted with the autosomal recessive condition, ataxia-telangiectasia (AT), a disease characterized by progressive cerebellar ataxia, telangiectasias, immunodeficiency, ionizing radiation hypersensitivity, and a greatly increased cancer risk. *ATM*

carriers or heterozygotes, although asymptomatic for AT, have been shown within family studies to have an increased risk of breast cancer (Swift et al. 1991, Pippard et al. 1988, Olsen et al. 2001); however, results in studies outside of ATM families have been mixed (Broeks et al. 2000, Chenevix-Trench et al. 2002, Fitzgerald et al. 1997, Renwick et al. 2006, Tamimi et al. 2004, Concannon et al. 2008). Mutations in *CHEK2*, a critical G2 checkpoint kinase, have been observed in 5–11% of multicase families not linked to *BRCA1*/*BRCA2* (Meijers-Heijboer et al. 2002, Vahteristo et al. 2002, Oldenburg et al. 2003) and are suggested to pose 2-fold increased risks (Meijers-Heijboer et al. 2003, CHEK2 Breast Cancer Case-Control Consortium 2004). A more recently identified gene, *PALB2*, was discovered as a *BRCA2*-associated protein and has been less studied to date although a modest increased risk has been observed in several studies (Rahman et al. 2007, Erkko et al. 2007). Clear truncating-type mutations in these genes appear to be rare (<1%) and risks for carriers of mutations in these genes, although still fraught with uncertainty due in part to power limitations in most studies, appear to be far less than those seen in *BRCA1* and *BRCA2*, with 1.5- to 3-fold increased risks (Oldenburg et al. 2007, Stratton and Rahman 2008).

Summary

Extensive epidemiologic research has substantiated that breast cancer risk is increased in relation to increased numbers of affected relatives and the presence of relatives with an early age of diagnosis, and that risk related to family history is greater in younger versus older breast cancer cases. Two major breast cancer susceptibility genes, *BRCA1* and *BRCA2*, have been identified. The prevalence of *BRCA1*/*BRCA2* mutations is low in the general population overall and somewhat more common in Ashkenazi Jewish women. *BRCA1*/*BRCA2* mutations account for the majority of breast cancers in rare high-risk-type families but the majority of women with breast cancer in population-based studies who have a family history of breast cancer do not carry *BRCA1*/*BRCA2* mutations. *BRCA1*/*BRCA2* mutation carriers face a greater lifetime risk of breast cancer ranging from 26% to 84% and an increased risk of contralateral breast cancer ranging from 18% to 40%. Prophylactic bilateral mastectomy and bilateral oophorectomy have been shown to greatly reduce the risk of breast cancer among *BRCA1*/*BRCA2* mutation carriers. While *BRCA1* and *BRCA2*-associated breast cancers differ in tumor characteristics, it is unclear if there are differences in survival. Although a number of other genes have been identified as potentially involved in breast cancer, thus far a considerable component of familial aggregation remains unexplained.

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Chapter 14
Common Genetic Susceptibility Loci

Mikkel Z. Oestergaard and Paul Pharoah

Introduction

Common genetic variants, that is, variants with greater than 5% frequency in the population, are likely to contribute greatly to inherited genetic susceptibility to breast cancer. As with many other common diseases, the success of recent genome-wide association scans has revived research into genetic susceptibility to breast cancer and ended a decade of largely unsuccessful candidate-gene association studies. All eight common genetic variants with confirmed association with breast cancer have been identified between 2007 and 2008. Seven variants were identified from genome-wide association studies (Easton et al. 2007; Stacey et al. 2008,2007) and one from a candidate-gene study (Cox et al. 2007) (see Table 14.2).

The success of genome-wide association scans has sparked hopes that common susceptibility variants responsible for the majority of genetic risk for breast cancer will be discovered in the near future. The scans have confirmed the predicted polygenic component with many low-penetrant variants influencing genetic susceptibility to breast cancer. Though individual variants have a small effect, their combined effect can have great impact on an individual's lifetime risk. The immediate value of common susceptibility variants lies in understanding their biological effects. By mapping susceptibility genes to biological pathways and networks, functional studies can be defined. Furthermore, these studies are expected to accelerate the identification of further breast cancer genes, for example, by identifying future candidate genes (Ponder, 2001; Todd, 2006).

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_14,

The Search for Common Susceptibility Variants

Breast cancer is known to aggregate in families, that is, family relatives of breast cancer cases are at an increased risk of developing breast cancer compared to the general population. The familial relative risk (FRR) is most often used to estimate this aggregation. FRR measures the ratio of risk for a particular type of relative (offspring, sibling, etc.) to the risk in the general population (Risch, 1990). The risk of breast cancer in first-degree relatives of breast cancer cases is approximately two-fold greater than in the general population (Collaborative Group on Hormonal Factors in Breast Cancer, 2001).

When a disease aggregates in families, it suggests that family members are more likely to be exposed to a causal factor than the general population. The causal factor could be inherited genetic factors and/or shared environmental factors. Twin studies suggest that the majority of the familial aggregation is due to inherited genetic susceptibility (Lichtenstein et al. 2000). Simulation studies have shown that even if an environmental factor is perfectly correlated among relatives, it needs to confer at least a 10-fold increase in risk to result in even modest increases in familial relative risk (Hopper and Carlin, 1992; Khoury et al. 1988). None of the known or expected breast cancer risk factors confer risks of this magnitude. Of the known environmental risk factors, geographical location confers the highest relative risk, with Western countries conferring a five-fold higher risk than Far Eastern countries (McPherson et al. 2000).

During the last decade, research into inherited genetic susceptibility of breast cancer has increasingly focused on common variants. This has partly been in response to the increasing evidence that the majority of the unexplained familial risk of breast cancer is likely to be due to low-penetrant variants. Linkage analyses have failed to identify further moderate- to high-penetrant variants using multiple-case families (Smith et al. 2006), and twin studies and segregation analyses have suggested a polygenic component with many low-penetrant genetic variants (Antoniou et al. 2002, 2001; Peto and Mack, 2000). The expected genetic architecture for breast cancer susceptibility is, thus, similar to many other common diseases with an expected L-shaped distribution of effect sizes with few variants with high penetrances and many variants with low penetrances (Wang et al. 2005).

The genetic association study is the most powerful approach to identify common low-penetrant disease susceptibility alleles (Houlston and Peto, 2004; Risch and Merikangas, 1996). Most breast cancer candidate-gene association studies have attempted to test variants in genes located in various pathways suspected to be important in breast cancer carcinogenesis. These include genes involved in sex hormone synthesis, DNA repair genes, genes involved in cell death (apoptosis), and carcinogen metabolism. These studies have either tested putative functional variants in genes or approximated coverage of known common variants in genes by using tagging SNPs (Pharoah et al. 2004). However, candidate–gene studies have been largely unsuccessful with many false-positive findings. The Breast Cancer Association Consortium (BCAC) was

founded in 2005 in recognition of the low power of individual association studies to detect low-penetrant variants and the need for validation of findings from single small studies. The BCAC now includes more than 30 research groups from Europe, the United States, Australia and Asia and has a combined sample size of over 30,000 cases and 30,000 controls. The high false-positive rate from candidate-gene studies is exemplified by the small proportion of variants validated across the BCAC out of all initially significant associations from individual studies. Of the 22 variants tested in the BCAC before August 2007, only 1 (rs1045485 in *CASP8*) was later validated as true positive. This corresponds to a false-positive rate of ~95% in the initial studies. Replication of genotype–phenotype association is now considered absolutely essential and a focus point for association studies to secure the needed credibility of initial findings (Chanock et al. 2007; Todd, 2006). The formation of a consortium is one way of seeking validation. The diversity of study designs used by consortium members and the range of populations studied furthermore improve the generalizability and robustness of the results.

The irreproducibility of initial findings from candidate-gene association studies over the last decade can partly be understood as a result of low prior probabilities for association of any given SNP and inappropriate levels for *p*-values considered as statistically significant. This is similar in concept to the "screening paradox" (Manly et al. 2004). The candidate-gene testing paradox is illustrated in Table 14.1. The posterior error rate (PER) is defined for a single hypothesis test as the probability of the null hypothesis being true, given that the test resulted in a rejection of the null hypothesis. For a randomly selected hypothesis test, the PER is equal to the proportion of false-positives for the family of tests. PER depends on the prior probability of the alternative hypothesis (π_1), the significance level (α) and false-negative error (β) for a hypothesis test. PER is given by

$$\frac{1}{1+\frac{(1-\beta)\pi_1}{\alpha(1-\pi_1)}} \tag{14.1}$$

and is indicative of the probability of replicating an initial positive finding. The lower the PER is for a family of tests the more likely it is that a significant association is true. For our illustration of the candidate-gene testing paradox,

Table 14.1 The candidate-gene testing paradox. Assume that 10 markers are tested per candidate gene and that the research community defines 500 candidate genes in which 50 markers are true breast cancer susceptibility variants. Furthermore, assume each of the 5,000 tests to be independent, the power for testing a marker to be 80% and set $\alpha = 5\%$. Given that a randomly picked hypothesis test rejects $\mathbf{H}_0$, the probability that $\mathbf{H}_0$ is actually true is 86% ($\frac{250}{290}$) and, thus, reflects a very high false-positive rate and low chance of replication

Markers	Accept H_0	Reject H_0	Total
Non-disease marker, H_0	4700	250	4950
Disease marker, H_1	10	40	50
Total	4710	290	5000

the PER is high (86%) and, thus, reflects low chances of replication. To achieve an acceptably low PER, the ratio of the prior probability (π_1) to α is required to be high (Manly et al. 2004). For example, assuming that we accept PER values smaller than 20% and have a power of 80% ($\beta = 20\%$), the ratio needs to be greater than 4. If we set $\alpha = 5\%$, then π_1 needs to be greater than 0.2, which means that our candidate gene needs very strong prior evidence, which may include data from functional studies or from previous association studies. Similarly, to obtain large ratios of $\frac{\pi_1}{\alpha}$, a *p*-value threshold of 10^{-4} for marker association from candidate-gene studies has been used to select SNPs for replication across the BCAC.

An inherent difficulty with candidate-gene studies is in the selection of genes. The selection is based on current biological knowledge, which might be limited. The main advantage of genome-wide association studies over candidate-gene association studies is the unbiased coverage of genes. The selection of tagging SNPs for genome-wide studies solely aims to cover known common variants. Of the known susceptibility regions from the two genome-wide breast cancer association studies, only one region contains a breast cancer candidate gene (*FGFR2*). This would suggest that breast cancer candidate-gene studies have simply tested the wrong pathways and genes, which reflects the limited understanding of breast cancer carcinogenesis.

Commmon susceptibility variants

All known common susceptibility variants for breast cancer have been identified between 2007 and 2008. Table 14.2 lists the eight known variants, all of which are single nucleotide polymorphisms (SNPs). The rs numbers are for SNPs originally confirmed by each study to be associated with breast cancer. Only for the susceptibility locus *FGFR2*, have functional variants been identified, whereas for the seven other SNPs the actual causative variant is unknown, as it cannot be excluded that the association is only observed because of high linkage disequilibrium (LD) with a causative variant. Extensive fine-mapping and functional analyses are now being carried out to identify causative variants.

The candidate-gene study by Cox et al. (2007) identified rs1045485 in *CASP8*. Two previous studies had also suggested a reduction in breast cancer risk associated with rs1045485 (Frank et al. 2005; MacPherson et al. 2004), but the finding by Cox et al. with replication across the BCAC validates the association. The seven other known SNPs were identified with two genome-wide studies by Easton et al. (2007) and Stacey et al. (2007, 2008). Both identified rs3803662 as associated with breast cancer.

For all eight variants, effect sizes are small. rs1045485 in *CASP8* is the only SNP for which the minor allele reduces the risk of breast cancer (odds ratios (95% confidence intervals): 0.89 (0.85–0.94) and 0.74 (0.62–0.87) for

Table 14.2 Common susceptibility loci for breast cancer. Odds ratio in heterozygotes (HetOR) and rare homozygotes (HomOR) compared to common homozygotes with 95% confidence intervals (CI). *TOX3* is also known as *TNRC9*

Locus	Region[a]	Position[b]	MAF[c]	HetOR (95% CI)	HomOR (95% CI)	FRR[d]	PAR[e]	First author (year)
rs2981582[f]	*FGFR2*	10 123342307	0.38 (0.30)	1.2 (1.2–1.3)	1.6 (1.5–1.7)	2.0	17	Easton (2007), Hunter (2007)
rs13387042	2q	2 217614077	0.50	1.1 (1.0–1.2)	1.4 (1.3–1.6)	1.3	14	Stacey (2007)
rs3803662[f]	*TOX3* *LOC643714*	16 51143842	0.25 (0.60)	1.2 (1.2–1.3)	1.4 (1.3–1.5)	1.0	10	Easton (2007), Stacey (2007)
rs10941679x[g]	*MRPS30*	5 44742255	0.24	1.2 (1.1–1.3)	1.4 (1.2–1.7)	0.9	9	Stacey (2008)
rs889312	*MAP3K1* *MGC33648* *MIER3*	5 56067641	0.28 (0.54)	1.1 (1.1–1.2)	1.3 (1.2–1.4)	0.4	7	Easton (2007)
rs1045485	*CASP8*	2 201857834	0.13	0.9 (0.8–0.9)	0.7 (0.6–0.9)	0.2	23	Cox (2007)
rs13281615	8q	8 128424800	0.40 (0.56)	1.1 (1.0–1.1)	1.2 (1.1–1.3)	0.2	5	Easton (2007)
rs3817198x	*LSP1*	11 1865582	0.30 (0.14)	1.1 (1.0–1.1)	1.2 (1.1–1.3)	0.2	4	Easton (2007)

[a] Chromosome region or genes associated with region if any.
[b] Chromosome and base position (build 36.2).
[c] Minor allele frequency. The combined allele frequency across Asian studies in Easton et al. (2007) in parenthesis.
[d] Percentage of excess familial risk attributable to SNP assuming that the overall familial relative risk to offspring is 2, a codominant model at each locus and that disease loci combine multiplicatively.
[e] Population attributable fraction. The PAR assumes that the susceptibility allele is causal for disease, such that the observed association with disease is fully explained by the disease variant and not due to a confounding risk factor.
[f] Estimates are from Easton et al. (2007) and were similar in Hunter et al. (2007) (for rs2981582) and Stacey et al. (2007) (rs3803662).
[g] HetOR and HomOR were inferred from published per-allele odds ratio and MAF in cases and controls respectively (Stacey et al. 2008).

heterozygotes and rare homozygotes, respectively). The greatest increase in risk is for rs2981582 in *FGFR2* (odds ratios: 1.2 (1.2–1.3) and 1.6 (1.5–1.7) for heterozygotes and rare homozygotes, respectively). With the exception of rs13387042, all SNPs fit a multiplicative or dose-dependent model. For rs13387042, both heterozygotes and rare homozygotes are at significantly elevated risk, but the risk for rare homozygotes is greater than expected under a dose-dependent model.

Table 14.2 also lists the population attributable fraction (PAR) and excess familial relative risk (FRR) of common susceptibility loci. The PAR for a genetic locus is the proportional reduction in average disease risk in the population if the disease-allele was eliminated, or, equivalently, the proportion of cases that could be prevented if the whole population was homozygous for the non-disease allele. Because susceptibility variants are common in the population, the PARs are relatively high with greater than 9% for the majority of loci. However, because of the small effect sizes, each of the variants explains only a minor proportion of the excess familial risk to breast cancer. Assuming a co-dominant model at each locus and that risk across susceptibility loci combines multiplicatively, the eight common variants explain an estimated 6.2% of the excess familial risk. It is estimated that known rare variants for breast cancer explain approximately 20% (Easton, 1999; Easton et al. 2007). Thus, in total, approximately 26% of the excess familial risk is explained (see Fig. 14.1). These estimates are lower bounds for the proportion of genetic susceptibility explained, as estimates are based on the assumption that all the excess familial relative risk can be explained by inherited genetic variants.

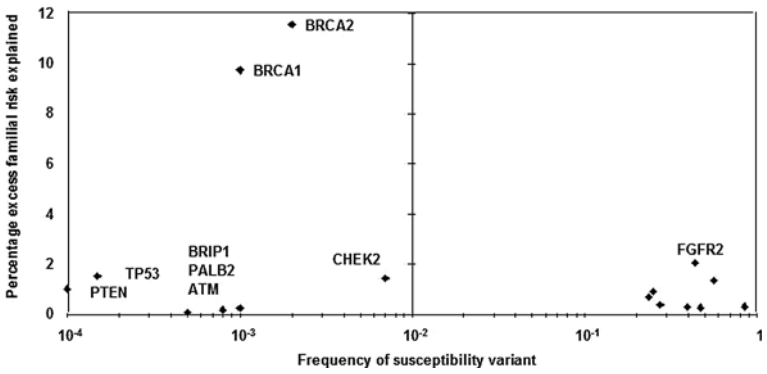

Fig. 14.1 Excess familial risk explained. The figure illustrates the percentage of the excess familial risk explained by genetic susceptibility variants for breast cancer, as plotted against the frequency of the susceptibility variant

Heterogeneity in Risk of Common Susceptibility Variants

Breast cancer tumors differ in their genetic risk profile, that is, some susceptibility loci confer higher risk to a particular tumor subgroup than to other subgroups. The characteristics of tumors that most often have been used to test for such subgroup heterogeneity are estrogen receptor status (ER-positive or ER-negative); progesterone receptor status (PR-positive or PR-negative); whether the cancer is in situ or invasive at diagnosis; and grade, nodes, size, histology and stage of tumor at diagnosis. A difference in genetic risk profiles between tumors suggests that tumors differ in their a etiologic pathway rather than representing different states in tumor progression of a shared pathway. Only ER-status has shown convincing heterogeneity in risk for the common susceptibility variants. For rs2981582, rs13387042, rs3803662, rs13281615 and rs10941679, the risk of breast cancer is significantly higher in ER-positive than in ER-negative tumors, and for rs13387042, rs13281615 and rs10941679, the risk is suggested to be specific to ER-positive cases (see Table 14.3). However, only for rs2981582 has this heterogeneity been confirmed. For the other SNPs (rs13387042, rs3803662, rs13281615 and rs10941679), follow-up studies are needed for confirmation of the suggested heterogeneity. The major impediment for ER-status subgroup analyses is that ER-negative cases are much rarer than ER-positive cases in the general population and estimates of risk in ER-negative cases are often based on small observations. In the largest of these subgroup analyses, Garcia-Closas et al. (2008) showed that for rs2981582, women homozygous for the disease variant had a 1.74

Table 14.3 Heterogeneity in risk for asssociation with estrogen receptor status

		ER-positive cases		ER-negative cases		
SNP	Controls	*n*	OR (95% CI)	*n*	OR (95% CI)	P-het[a]
rs2981582						
Garcia-Closas (2008)	26,058	13,069	1.3 (1.3–1.4)	3,813	1.1 (1.0–1.1)	10^{-13c}
Stacey (2008)	31,409	2,354	1.3 (1.2–1.4)	657	1.0 (0.9–1.1)	2.9×10^{-5}
rs13387042						
Stacey (2007)	16,536	2,124	1.2 (1.1–1.3)	589	1.1 (0.9–1.2)	0.036
rs3803662						
Garcia-Closas (2008)	25,026	12,974	1.2 (1.2–1.3)	3,765	1.1 (1.1–1.2)	0.015[c]
Stacey (2007)	16,575	2,128	1.3 (1.2–1.4)	589	1.1 (0.9–1.2)	0.0098
rs13281615						
Garcia-Closas (2008)	22,105	11,700	1.1 (1.1–1.2)	3,384	1.0 (1.0–1.1)	0.001[c]
rs10941679						
Stacey (2008)	32,090	2,736	1.3 (1.2–1.4)	744	1.1 (0.9–1.2)	0.0042

[a] *p*-value for heterogeneity in per-allele odds ratio of ER-positive and ER-negative cases.
[b] Estimates are for rs1219648, which is perfectly correlated with rs2981582 ($r^2 = 1$).
[c]Garcia-Closas et al. adjusted for multiple testing. Adjusted *p*-het: rs2981582, >0.001; rs3803662, 0.43; and rs13281615, 0.038.

(95% CI: 1.6–1.9) times greater risk of ER-positive tumors than women homozygous for the non-disease variant.

Antoniou et al. (2008) recently examined whether genetic variants that modify risk of breast cancer in the general population also carry an increased risk for *BRCA1* and *BRCA2* mutation carriers. They tested the common loci rs2981582, rs3803662 and rs889312 in a sample of 10,358 mutation carriers and found that all SNPs confer similar risks in *BRCA2* mutation carriers as in the general population. However, in *BRCA1* mutation carriers, rs2981582 and rs889312 showed no association and the risk conferred by rs3803662 was reduced compared to the general population. Interestingly, 90% of breast cancer tumors with *BRCA1* mutations are ER-negative, whereas *BRCA2* breast cancer tumors have a similar proportion of ER-positive and ER- negative tumors as in the general population (Lakhani et al. 2005). These results warrant functional studies to examine whether the cellular phenotype(s) driving the increase in cancer propensity of *BRCA1* mutations differ from phenotypes of both *BRCA2* mutations and common susceptibility variants. However, given the heterogeneity in risk for ER-status, one hypothesis is that *BRCA1* cellular alterations are distinct from alterations of the other loci (observed in *BRCA1* non-carriers) and that *BRCA1*-induced alterations mask alterations by rs2981582 and rs889312.

The common susceptibility loci have further been tested for heterogeneity in effects by age of diagnosis and family history of breast cancer. No association with age of diagnosis has been found for any of the SNPs (Cox et al. 2007; Easton et al. 2007; Stacey et al. 2008, 2007). Under the polygenic susceptibility model, the frequency of the risk allele at common susceptibility loci is expected to be slightly higher in cases with a family history of breast cancer compared to cases from the general population (Antoniou and Easton, 2003). Cox et al. found no association with family history for rs1045485 and Stacey et al. (2008) found rs10941679 to be borderline significant for association with family history. Easton et al. found that the three SNPs rs2981582 ($p = 0.02$), rs3803662 ($p = 0.03$) and rs13281615 ($p = 0.05$) showed association with family history, with the susceptibility allele more common in women with a first-degree relative with the disease than in those without.

The common susceptibility variants were all identified in study populations of predominantly European descent. The effect of rs1045485 was consistent across the 14 studies in the BCAC. However, the locus is not polymorphic in Korean, Han Chinese or Japanese populations (Cox et al. 2007). For rs13387042, rs3803662 and rs10941679, the observed associations were consistent across five populations of European descent, but were not observed in populations of recent African ancestry in samples of approximately 600 cases and 600 controls (Stacey et al. 2008, 2007). This discrepancy between ethnicities suggests that these SNPs are not the

causative variants. Most likely, these three SNPs are only in weak LD with the causative variants in African populations. The difference in LD patterns and observed effect estimates between populations was applied by Easton et al. for fine-mapping purposes. In general, a weaker LD pattern in a population will allow more variants to be excluded and, thus, provide a higher resolution for identifying the causal variant. For example, the per-allele odds ratio for rs2981582 was significantly smaller ($p = 0.04$), though still elevated, in Asians compared to the European populations in the BCAC. The difference supported the hypothesis by Easton et al. that rs2981582 is not the functional variant at the *FGFR2* locus.

Functional Insight into Susceptibility

Of the eight known SNPs, four lie in regions with one gene (rs1045485, rs2981582, rs10941679 and rs3817198), two in regions with more than one gene (rs3803662 and rs889312) and two SNPs in regions without known genes (rs13281615 and rs13387042) (see Table 14.2). The gene mapping is based on mapping each SNP to a haplotype block and then associating genes in the block to the SNP. Therefore, these gene mappings are constrained by the set of currently identified coding regions in the human genome and the set of currently identified genetic variants that define haplotype block construction. Also, it cannot be excluded that the causative variant in the block actually lies in a regulatory region of a gene outside the block. Interestingly, rs13281615 resides within an approximately 1 Mb region on chromosome 8q that contains no known genes, but nine cancer-associated SNPs have been reported in this region. At the region's centromeric end is *FAM84B* and at its telomeric end is *MYC* (also known as *c-Myc*), both candidate cancer susceptibility genes. Ghoussaini et al. (2008) showed that five different haplotype blocks within the region were specifically associated with risks of different cancers. One block was specific to risk of breast cancer; three others were solely associated with risk of prostate cancer; and a fifth haplotype block was associated with risk of prostate, colorectal and ovarian cancers.

CASP8 (caspase 8) is an important initiator of apoptosis which is activated by external death signals to the cell and in response to DNA damage (Hengartner, 2000). The SNP rs1045485 in *CASP8* results in a substitution of aspartic acid to histidine, but the functional consequences of the substitution are not known (Cox et al. 2007). rs3817198 maps to *LSP1* (lymphocyte-specific protein 1), that encodes an intracellular F-actin-binding protein and is expressed in lymphocytes, neutrophils, macrophages and endothelium. rs10941679 lies in the same haplotype block as *MRPS30* (mitochondrial ribosomal protein s30), which is also known as *PDCD9* (programmed cell death protein 9) and has been implicated in pro-apoptotic events (Stacey 2008). rs3803662 lies in a region with two known

genes (*TOX3*, *LOC643714*). The product of *LOC643714* is a hypothetical protein (LOC643714). *TOX3* (also known as *TNRC9*) is a more attractive candidate for the association with breast cancer. rs3803662 lies 8 kb upstream of *TOX3* (TOX high-mobility group box family member 3) that contains a putative high-mobility group box motif, which suggests that it might act as a transcription factor (Easton et al. 2007). Increased expression of *TOX3* is associated with metastasis of breast cancer to bone (Smid et al. 2006).

An early insight into the mechanisms by which *FGFR2* (fibroblast growth factor receptor 2) affect susceptibility to breast cancer has recently come from a functional study by Meyer et al. (2008), the first functional study of the known common susceptibility loci. *FGFR2* encodes a transmembrane tyrosine kinase, which can function as a mitogenic or angiogenic factor, depending on the cell type and/or the microenvironment of the cell (Dickson et al. 2005). Mouse models of mammary carcinogenesis have long established the fibroblast growth factor pathway as a major contributor to tumorigenesis (Grose and Dickson 2005). In human breast cancer, *FGFR2* is known to be overexpressed in ER-positive tumors (Luqmani et al. 1992; Rhodes et al. 2007,2004), and functional studies in cell lines implicate *FGFR2* in tumorigenesis, with an alternative splicing in the C-terminal domain of FGFR2 to give rise to a more strongly transforming isoform (Tannheimer et al. 2005). Fine mapping of the *FGFR2* susceptibility locus in Europeans narrowed down the causative locus to a haplotype of eight strongly linked SNPs (Easton et al. 2007). These SNPs span a region of 7.5 kb in the second intron of *FGFR2* and reside in a haplotype block with no linkage disequilibrium with coding regions of *FGFR2*. Gene expression analyses showed that rare homozygotes of rs2981582 have higher expression of *FGFR2* compared to common homozygotes (Blenkiron et al. 2007; Meyer et al. 2008; Naderi et al. 2007). Meyer et al. (2008) further showed that genotype of *FGFR2* does not correlate with expression of *FGFR2* ligands FGF-7, FGF-10 and FGF-22 or splicing forms of *FGFR2* and that of the eight putative causative SNPs in *FGFR2*, only two (rs7895676 and rs2981578) affect affinity of transcription factors Oct-1/Runx2 and C/EBPβ. Meyer et al. propose that the disease-associated allele results in increased expression of *FGFR2*, which is hypothesized to increase a cell's probability of tumor formation.

Polygenic Architecture of Susceptibility

What Does Polygenic Imply?

Polygenic susceptibility implies that *many* genetic loci affect susceptibility to disease and that the majority of loci have low penetrances (the relatively low prevalence of breast cancer in the general population rules out the possibility of many common susceptibility loci with large effects). Susceptibility to breast cancer is determined by the combined effect of loci, and susceptibility levels will

be correlated between family members. Current evidence suggests that approximately 80% of the excess familial risk to breast cancer is due to low-penetrant variants and only approximately 20% due to rare mutations with moderate to high penetrances. This means that the causative factor for the majority of women at an increased familial relative risk is likely to be the combined effect of many low-penetrant common genetic variants.

It is expected that at least 100 low-penetrant variants await discovery such that more than 95% of all susceptibility loci are due to low-penetrant variants. The evidence comes from the low coverage of common genetic variants in human populations in the two genome-wide studies and the relatively low statistical power of these studies. For example, the genome-wide scan by Easton et al. only covered approximately 60% of the common variants known at the time (HapMap Phase II), and the future is likely to see many more common variants uncovered, such that future genome-wide scans will have close to complete coverage of common variants. The statistical power was low for most of the identified variants in the study by Easton et al.: 93%, 71%, 25%, 3% and 1% (for rs2981582, rs3803662, rs889312, rs13281615 and rs3817198), which suggests that the number of variants similar in effect and allele frequency awaiting discovery are 0, 0, 3, 32 and 99. Furthermore, Easton et al. only pursued validation in the BCAC for the 30 most significant SNPs from the initial scan, and it is expected that more susceptibility variants await discovery as SNPs lower down the significance ranking are tested in the BCAC.

The first strong evidence for a polygenic component to breast cancer susceptibilty came from segregation analyses carried out in the United Kingdom. The aim of these studies was to identify the best fitting genetic model explaining the observed familial aggregation of breast cancer not due to *BRCA1* and *BRCA2*. Based on the occurrence of breast cancer in relatives of population-based cases, Antoniou et al. (2001) showed that a polygenic component with many common low-penetrant variants acting multiplicatively on disease risk best explained the familial aggregation not due to *BRCA1* and *BRCA2*. The combined effect of a polygenic component and *BRCA1* and *BRCA2* was also found to best explain the occurrence of breast cancer in multiple-case families (Antoniou et al. 2002). Recent inclusion of additional data from both population-based and multiple-case families suggested that the polygenic variance decreases with age. This implies that at least some of the variants in the polygenic component confer higher relative risk at young ages, which is consistent with the observation that the familial relative risk decreases with age (Antoniou and Easton, 2006a).

Combined Effect of Susceptibility Loci

Under a polygenic architecture of susceptibility, individual genetic risk of breast cancer is determined by a multi-locus genotype defined over susceptibility loci. To estimate individual risk, we need to consider both genotype effect at each

susceptibility locus (single-locus effect) and how single-locus effects depend on genotype at other loci.

Let us assume that n bi-allelic loci influence susceptibility (to illustrate the combined effect of loci, n just needs to be greater than one). The genotype effect at each locus is estimated without consideration to genotypes at other loci, that is, the population sample of diseased and healthy individuals is split into three genotype groups. Let $R_{i,j}$ denote risk of disease (for example, lifetime probability of breast cancer) for individuals with genotype j at locus i. The most prevalent effect measures are

Risk ratio

$$M_{i,j} = \frac{R_{i,j}}{R_{i,reference}} \tag{14.2}$$

Risk difference

$$A_{i,j} = R_{i,j} - R_{i,reference} \tag{14.3}$$

Effect estimates are most accurate when the most populous genotype is used as reference group. Then, heterozygotes and rare homozygotes for the minor allele are compared to common homozygotes.

Individuals that share a particular genotype at one locus are likely to have different genetic risks of disease as they most likely differ in genotypes at other susceptibility loci. An estimate of genetic risk based solely on genotype information at one susceptibility locus will always be an average over effects of other susceptibility loci or, equivalently, over all individuals that share the single-locus genotype. In general, the greater the proportion of all susceptibility loci that are used for genetic risk profiles, the more relevant the risk estimates for the individual. However, as more and more susceptibility loci are identified, the number of multi-locus genotypes increases exponentially. Even for large population samples, the number of individuals in each genotype group will quickly become too small for risk estimates to be based on sampling estimates for each group. For example, for the eight currently identified common susceptibility loci, there are 6,561 possible multi-locus genotypes. Based on the minor allele frequencies in Table 14.2, we would only expect one individual out of 400 people in the most common multi-locus genotype group and one out of 400 million in the rarest. Considered over 100 susceptibility loci, there are approximately 10^{47} possible multi-locus genotypes and the probability that each one of us will have a unique multi-locus genotype will be very high (greater than 99%). However, as will be illustrated in the next section, many multi-locus genotypes will carry the same risk of breast cancer, and the distribution of genetic risk in the population will converge to a normal distribution as more and more susceptibility loci are identified.

There is very little understanding of how susceptibility loci combine to influence risk for any common disease. In general, most studies modelling combined effect assume that genotype effects combine either multiplicatively or additively across

susceptibility loci. Then estimates are based solely on combining n genotype effects or single-locus effects to estimate disease risk for a given multi-locus genotype (m)

Multiplicative model

$$M_m = \prod_{i=1}^{n} M_{i,j} \tag{14.4}$$

Additive model

$$A_m = \sum_{i=1}^{n} A_{i,j} \tag{14.5}$$

The multiplicative model applies the n risk ratios, whereas the additive model is based on the n risk differences. Both models assume that each estimated single-locus effect is the same within each of the 3^{n-1} multi-locus genotypes defined over the other loci, and their accuracy depends on the accuracy of single-locus estimates and the true underlying genetic architecture. If common homozygotes are used as reference group at each locus, both measures compare disease risk for people with multi-locus genotype m to people that are common homozygotes at each susceptibility locus. Notice that for a given multi-locus genotype, a purely multiplicative model will give a higher susceptibility estimate than a purely additive model. A multiplicative model will also explain a larger proportion of the total familial aggregation and, thus, require fewer loci to explain the familial aggregation of breast cancer.

In the segregation analyses by Antoniou et al. (2001, 2002) the polygenic component is approximated by the hypergeometric polygenic model, which is equivalent to a fully additive polygenic continuous trait with no dominance and epistatic variance (Antoniou et al. 2001; Lange, 1997, 2002). The hypergeometric polygenic model provides a good approximation to polygenic inheritance, as first described by R.A. Fisher in 1918 (Lange, 1997). The number of disease alleles carried by an individual is assumed to follow a binomial distribution with $2n$ trials and probability $\frac{1}{2}$. The effect of each disease allele on the lifetime risk of breast cancer is assumed to be independent of the number of disease alleles at any locus. This is a great simplification of the genetic architecture for breast cancer susceptibility, as are the multiplicative and additive models. But these simplifications are required for modelling purposes and also serve very useful conceptual tools. Segregation analyses are generally highly underpowered, which only allows likelihoods of simple models of the underlying genetic architecture to be compared. In general, if the true underlying genetic architecture for breast cancer susceptibility deviates only slightly from a given model of the combined effect of susceptibility loci, then the model is likely to provide more accurate estimates of multi-locus disease risks compared to using sampling estimates of risk in each multi-locus genotype. This concept,

often referred to as *model parsimony*, results from model estimates smoothing random sampling fluctuations across the multi-locus genotypes.

If we assume that the eight identified common susceptibility loci combine multiplicatively and if we use the genotype relative risks in Table 14.2, the lifetime risk of breast cancer is an estimated 3.6% in the lowest genetic risk group in the United Kingdom (individuals rare homozygotes at rs1045485 and common homozygotes at other susceptibility loci), but approximately 11 times higher (at 39 %) in the highest risk group (common homozygotes at rs1045485 and rare homozygotes at other loci). One out of approximately 21,000 people will be in the lowest genetic risk group, and only 1 out of 10 million in the highest. The average lifetime risk of breast cancer in the United Kingdom is 9.4% (Pharoah et al. 2008), which means that the relative risk is 0.38 in the lowest risk group and 4.15 in the highest, as compared to the population average. Importantly, these risk estimates are still too uncertain to be used for individual breast cancer prevention. We do not know how each single-locus genotype effect depends on genotype at other susceptibility loci and how great the variation in disease risk is within each multi-locus genotype. Given that more than 100 common susceptibility loci are expected, genetic risk classification based on identified loci would result in too many misclassifications of genetic risks. Particularly, too many women currently classified as having low genetic risks will be truly high risk, and too many women currently classified as high risk will be at relatively low risk. Genetic risk estimates will only turn useful for individual breast cancer prevention when a larger fraction of all susceptibility loci are identified.

Population Distribution of Genetic Risk

The greatest implication from polygenic susceptibility is in the potential for defining high-risk and low-risk susceptibility groups and directing public health and clinical measures to the group of women at highest risk. It is important to base genetic screening policies on reducing the number of screened individuals. Besides an associated reduction in public health spendings, the greatest incentive comes from possible adverse psychosocial effects associated with genetic testing (Davis, 1997). Risk prediction models offer one way of identifying women at highest risk (Antoniou and Easton, 2006b). Based on information such as family history and age of diagnosis of relatives, these models can be used to identify women carrying a particular genotype and evaluate their risk of developing breast cancer. It has been argued that for common low-penetrant variants, the number of people needed to screen to prevent one case makes genetic screening unreasonable (Vineis et al. 2001). However, directed screening in the population reduces this ratio and makes it reasonable and comparable to existing screens for *BRCA1* and *BRCA2* mutations in families with a strong breast cancer history.

A consequence of polygenic susceptibility is that the distribution of relative risk in the population is log-normal. The emerging log-normal distribution is a known result from statistical distribution theory and an often observed biological property. Whenever many factors, each with a small effect, act

independently on a trait, the trait will have either a log-normal or a normal distribution in the population depending on whether effects combine multiplicatively or additively, respectively (Fisher, 1918). If the individual relative risk for breast cancer is the product of relative risks at many susceptibility loci, then the distribution of relative risks (RR) in the population is log-normal and $\log(RR)$ will have a normal distribution.

The normal distribution is characterized by its mean (μ) and variance (σ^2). For the distribution of $\log(RR)$, σ^2 describes the variation in the population and is, thus, an indicator of how well we can genetically define distinct high- and low-risk susceptibility groups of women. In general, the larger the fraction of all susceptibility loci that are identified, the larger the population variance (see Fig. 14.2). Pharoah et al. (2002) showed that the distributions of $\log(RR)$ in the general population and among (future) cases have the same variance and only differ in the mean of the normal distribution of $\log(RR)$. Based on estimates of σ^2 from the segregation analysis by Antoniou et al. (2002), Pharoah et al. estimated that if all susceptibility loci were known and combine multiplicatively, there would be a 40-fold difference in risk between the highest quintile and lowest quintile of the

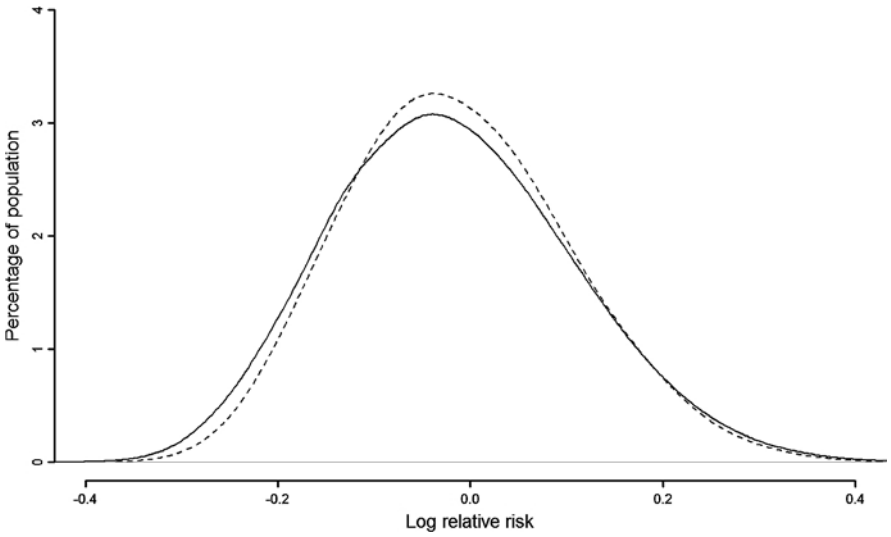

Fig. 14.2 Population distribution of genetic risk. The *solid curve* is the distribution of relative risk based on the eight identified common loci and the *dashed curve* the distribution when only the three SNPs with the largest effects are considered (rs2981582, rs13387042 and rs3803662). The larger the fraction of all susceptibility that are identified (and included in genetic risk calculations), the greater the variance of genetic risk in the population. The following assumptions were made for the calculation of relative risk in each multi-locus genotype: loci combine multiplicatively; we used single-locus genotype effects and minor allele frequencies in individuals with European ancestry as outlined in Table 14.2; estimated odds ratios were assumed to approximate risk ratios; and the risk in each multi-locus genotype was compared to the average lifetime risk in the United Kingdom (9.4%)

distribution, and half of all breast cancer cases would occur among the 12% of the population at highest risk. Recently, Pharoah et al. (2008) estimated the distribution of risk based on seven of the eight known common susceptibility variants (rs10941679 was not included, as the susceptibility locus was not identified at the time of their analysis). Based on these seven variants, half of all breast cancer cases occur among the 40% of the population at highest risk and 15% of all cases occur among the 10% of the population at highest risk.

The identified common susceptibility loci do not provide enough information for individual disease prevention, but the loci can be used for risk stratification in population level screening programmes to make programmes more efficient by targeting women at highest risk (Pharoah et al. 2008). If every woman was genotyped at all susceptibility loci, screening programmes could be personalized by allowing starting age to depend on the person's breast cancer risk profile. For example, the United Kingdom's National Health Service breast-screening programme is currently offered to all women of age 50 years or older. In the general population in the United Kingdom, a 50-year-old woman has a 2.3% risk of breast cancer within the next 10 years of her life. However, based on the risk distribution of the known common susceptibility loci in the United Kingdom, this risk is reached as early as after 41 years of age for women in the 95th percentile of the risk distribution, but never reached for women in the 5th percentile because of competing causes of death (Pharoah et al. 2008).

Future

The cardinal feature of polygenic susceptibility to breast cancer is that most genetic susceptible individuals are at an increased risk because of the combined effect of several alleles. The identification of residual breast cancer susceptibility variants is likely to follow from more genome-wide scans with a larger number of cases and controls that have close to complete coverage of known common variants in several populations. The mapping of the biological effect of known susceptibility variants to pathways and networks is likely to help define new genes for candidate-gene studies and to guide functional studies aiming to elucidate the cellular consequences of susceptibility variants. The "1000 Genomes Project" was recently launched with a focus on uncovering the distribution of rare genetic variants in a variety of populations. Most likely, within 3 years time, genetic association studies will increasingly focus on the contribution of rare low-penetrant variants, which heretofore has been largely unexplored.

Studies of the combined effect of susceptibility loci will be required to adequately understand disease a etiology and for individual disease prediction. Furthermore, theoretical studies have shown that variants with small single-locus effects that only influence disease risk through interactions with other variants are unlikely to be identified with single-locus approaches (Evans et al.

2006; Marchini et al. 2005). Studies of genetic interactions on genome-wide scale have been shown to be computationally tractable, but have so far not identified SNP pairs that deviate from a multiplicative model (Oestergaard et al. 2008a, b).

The coming years will also see new cohorts of women defined and followed for breast cancer incidence to understand the importance of gene–environment interactions, which have been argued to be intrinsic to the way that low-penetrant variants act (Vineis et al. 2001). When a large proportion of breast cancer susceptibility variants are identified (which may vary between populations), these cohorts will also be useful for testing and validating the predictive power of risk prediction models of common genetic variants. It will be interesting to see how high a predictive power information on genotype and environment holds and whether noise or stochasticity in cell processes influence disease development and prediction (Bar-Even et al. 2006; Kaern et al. 2005).

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Chapter 15
Mammographic Density as a Potential Surrogate Marker for Breast Cancer

Norman F. Boyd, Lisa J. Martin, and Salomon Minkin

Introduction

Despite extensive research, the causes of most cases of breast cancer remain unknown, although there is strong evidence that risk of the disease is influenced by both genetic and environmental factors (Veronesi et al. 2005). We consider here the potential role of mammographic density as a surrogate marker in research on the etiology and prevention of breast cancer. Mammographic density refers to variations in the radiological appearance of the breast illustrated in Fig. 15.1. Women with more than 75% of the breast occupied by density (Panel F) have a risk of breast cancer 4–6 times that of women with little or no density (Panel A).

Mammographic density differs from other risk factors for the disease in a number of ways. The differences in the relative risk of breast cancer associated with variations in density are larger than those for almost all other risk factors, and the high-risk appearance of extensive mammographic density is common and may account for a substantial fraction of breast cancer (Byrne et al. 1995, Boyd et al. 2007). Further, unlike most other risk factors, mammographic density directly reflects breast tissue composition and, as discussed below, can be changed. Mammographic density is influenced by several other risk factors for the disease, including by exogenous and endogenous hormones, and growth factors that influence breast cancer risk. However, the risk of breast cancer associated with mammographic density is independent of other risk factors.

These observations raise the possibility that mammographic density might be a suitable surrogate marker for breast cancer. We distinguish here between a surrogate marker and an intermediate phenotype. The latter refers to a phenotypic feature that is a risk factor for disease, and that has a genetic component (Carlson et al. 2004), criteria that mammographic density does meet (Boyd et al. 2005 and see further below). A surrogate marker allows prediction of the effects

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_15,

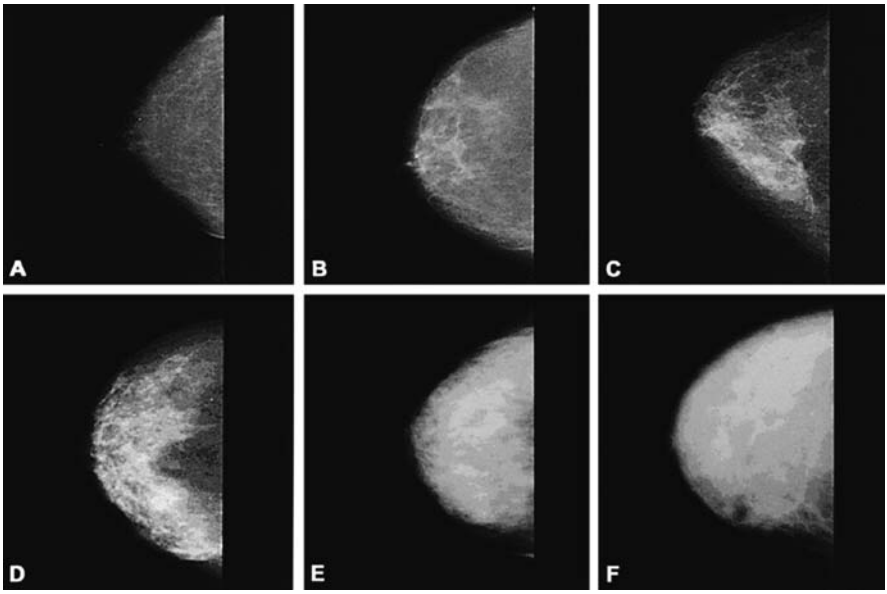

Fig. 15.1 Examples of mammographic density: A: 0%; B:<10%; C: 10<25%; D: 25<50%; E: 50<75%; F: >75%

of an exposure or intervention on a disease outcome by observing the effects on the marker, which can thus be used instead of a disease endpoint in trials (Schatzkin and Gail 2002). A surrogate marker would be especially valuable in the context of research on breast cancer prevention where, if breast cancer is the endpoint, very large numbers of healthy subjects must be enrolled and observed for prolonged periods of time before a large enough number of cancers develop. A surrogate might be used rather than cancer as an endpoint in trials of potential preventive interventions for breast cancer, and allow smaller, shorter, and less costly trials (Schatzkin and Gail 2002).

The criteria that should be met before a marker is accepted as a suitable surrogate have been proposed by Prentice (1988), Schatzkin and Gail (2002), Freedman and Graubard (1992), and others and are summarized as follows: First, the marker should be associated with the disease, second, the exposure or intervention should be associated with the marker, and third, the potential surrogate marker should mediate the entire relation of the intervention to the disease. The third condition is met when the exposure and disease are statistically unrelated once the surrogate is taken into account. This would be demonstrated when adjustment for mammographic density in regression analysis removed the effect of the exposure or intervention on disease risk.

In this chapter we describe briefly the evidence that mammographic density is a risk factor for breast cancer, the histological basis for mammographic density and the principal factors that are associated with variations and with

change in mammographic density. We describe what is known of the clinical significance of change in density and the extent to which mammographic density meets criteria for a surrogate marker for breast cancer.

Mammographic Density and Breast Cancer Risk

In 1976, Wolfe described a method of classifying variations in the appearance of the mammogram comprised of four categories that were associated with different risks of breast cancer (Wolfe 1976a, b). The categories were designated N for a breast comprised mainly of fat, DY for a breast mostly dense, and P1 and P2 for linear densities of different extents, indicating "ductal prominence." Most well-designed epidemiological studies have confirmed that these categories are associated with different risks of breast cancer (McCormack and dos Santos Silva 2006). Other methods of classifying breast tissue as seen on mammography have been introduced, including a Breast Imaging Reporting and Data System (BI-RADS) classification (American College of Radiology 1998) and a classification proposed by Tabar (Gram et al. 1997). Various other approaches have been taken to generate a quantitative measure including estimation of percent density by radiologists, and measurement of the areas of the breast and density by planimetry, or by a computer-assisted method applied to digitized images.

McCormack and dos Santos Silva have reviewed the data on the association of mammographic density with risk of breast cancer in a meta-analysis of aggregate data for >14,000 cases and 226,000 non-cases from 42 studies. Associations were most consistent in studies conducted in the general population, rather than symptomatic women, were stronger for percentage density than for Wolfe categories or the BI-RADS classification, and were stronger in studies of incident than of prevalent cancer. Relative to women with $< 5\%$ density, relative risks (RR) of breast cancer were found to increase linearly with increasing percentage density (5–24%: RR = 1.79, 95% confidence interval (CI): 1.5–2.2; 25–49%: RR = 2.11, 95% CI: 1.7–2.6; 50–74%: RR = 2.92, 95% CI: 2.5–3.4; $\geq$75%: RR = 4.64, 95% CI: 3.6–5.9). No differences in the breast cancer risk associated with mammographic density were observed by age or menopausal status at mammography, or by ethnicity (McCormack and dos Santos Silva 2006). Mammographic density has been shown to influence risk of breast cancer in Caucasians, African-Americans, Asian-Americans, and Asians (Ursin et al. 2003).

Although extensive mammographic density is associated with an increased risk of breast cancer, it also makes the detection of cancer by mammography more difficult. However, studies based on mammographic screening programs have shown that mammographic density is associated with an increased risk of breast cancers detected at screening, as well as cancers detected after a negative screening examination. The increased risks of breast cancer, for both screen detected and non-screen detected breast cancer, persisted for at least 8 years after entry (Boyd et al. 2007). The optimal approach to detecting breast cancer

in women with dense breast tissue remains to be determined, but there is evidence that detection is improved by digital mammography (Pisano et al. 2005).

Mammographic Density and Breast Tissue Composition

Studies based on mastectomy specimens, or biopsies from women with known or suspected breast disease, have shown that greater amounts of epithelial and stromal tissue are associated with more extensive mammographic density (reviewed in Boyd et al. 1998). Li et al. used breast tissue obtained at forensic autopsy and hence unselected for breast disease (Bartow et al. 1997, Li et al. 2005). Randomly selected tissue blocks were taken from breast tissue slices obtained by subcutaneous mastectomy, and quantitative microscopy used to determine the proportions of the biopsy occupied by cells (estimated by nuclear area), glandular structures, and collagen. Percent mammographic density was estimated by a radiologist in the x-ray image of the tissue from which the biopsy was taken.

Greater percent mammographic density was associated with a significantly greater total nuclear area, a greater nuclear area of both epithelial and non-epithelial cells, a greater proportion of collagen, and a greater area of glandular structures. The area of collagen explained 29% of the variance in percent density, and the other tissue measurements accounted for between 4 and 7% of the variance. Age, body weight, parity and number of births, and menopausal status, all factors that are associated with variations in mammographic density in these and other data (discussed below), were all associated with variations in one or more of the measured tissue features (Li et al. 2005). Increasing age was associated with a reduction in the nuclear areas of both epithelial and non-epithelial cells, as well as glandular area and the area of collagen.

Age, Mammographic Density, and the Incidence of Breast Cancer

The average level of percent mammographic density declines with increasing age (Fig. 15.2A), reflecting the age-related differences in breast tissue composition referred to in the previous section, while breast cancer incidence increases with age (Fig. 15.2C). This apparent paradox may, however, be resolved by reference to a model of breast cancer incidence proposed by Pike et al. (1983) that is based on the concept that the rate of "breast tissue ageing," rather than chronological age, is the relevant measure for describing the age-specific incidence of breast cancer. The concept of "breast tissue age" was developed to account for the effects of menstrual and reproductive risk factors on the incidence of breast cancer and is related to the effects of hormones on the kinetics of breast cells and the accumulation of genetic damage.

According to the model, shown in Fig. 15.2B, the rate of "breast tissue ageing" is most rapid at the time of menarche, slows with pregnancy, slows further in the perimenopausal period, and is least after the menopause. After

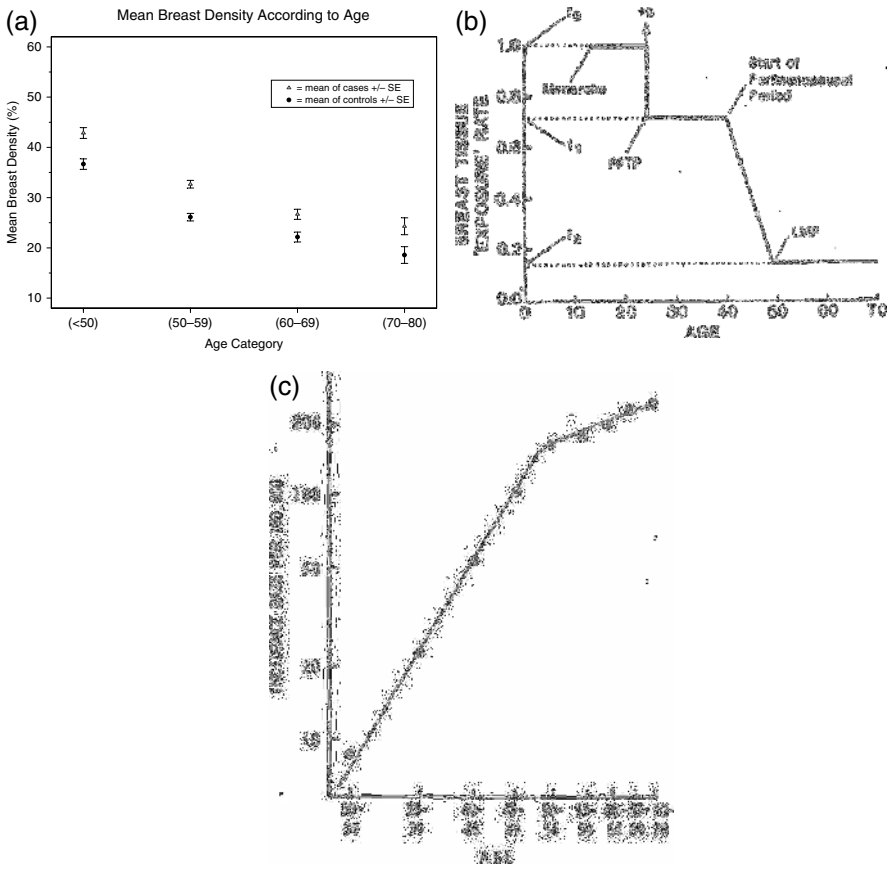

Fig. 15.2 **(A)** Baseline percentage mammographic density according to age at first screening mammogram in women from three mammographic screening programs. Reproduced from Martin and Boyd (2008) with kind permission of BioMed Central. **(B)** Pike model of "breast tissue age," and **(C)** the age-specific incidence of breast cancer. Reproduced from Pike et al. (2005) with permission of Nature Publishing Group

fitting numerical values for these parameters, Pike showed that cumulative exposure to "breast tissue ageing," given by the area under the curve in Fig. 15.2B, described the age–incidence curve for breast cancer in the United States, shown in Fig. 15.2C. The age-specific incidence of breast cancer increases rapidly up to about age 50 and the rate of increase then slows down. The Pike model has been extended by Rosner and Colditz (1996) to include the number and spacing of pregnancies and subsequently other risk factors.

Mammographic density shares many of the features of "breast tissue age" and as discussed below is influenced by similar factors. The study of Li et al. (2005) described above showed that age was inversely associated with the total, epithelial and non-epithelial nuclear areas and with the areas of collagen and glandular tissue in the breast, all features that were also associated with mammographic density.

Detailed descriptions of the associations of established breast cancer risk factors with mammographic density can be found elsewhere (Vachon et al. 2000) and major well-characterized associations are described below. Other factors, including diet (Boyd et al. 1997), vitamin D (Bérubé et al. 2004), and a GHRH agonists (Spicer et al. 1994), have been reported to influence mammographic density but have not yet definitively been shown to affect risk of breast cancer and are omitted here.

Factors Associated with Variation and Change in Mammographic Density

Breast Cancer Risk Factors

Parity

Early age at first live birth and greater number of live births are known to reduce long-term risk of breast cancer, after a short-term increase in risk after the first birth (Kelsey et al. 1993). Women who have had a live birth have a lower average percent density than nulliparous women (Vachon et al. 2000). In the study of Li et al. (2005) the number of births, but not age at first birth, was inversely associated with the area of collagen in the breast tissue examined. The other measured histological features were not influenced by parity. Gertig et al. (1999) studying biopsy material from the Nurses Health Study found that parity was associated with an increase in epithelium and a decrease in stroma. Greater time since last birth was associated with an increase in epithelium but was not associated with stroma.

Menopause

An early menopause, whether natural or artificial, is associated with a reduced risk of subsequent breast cancer (Kelsey et al. 1993), and in the study of Li et al. (2005) menopause was associated with a reduced total of epithelial and non-epithelial areas and reduced areas of collagen and glandular tissue in the breast.

A longitudinal study of the effect of menopause on mammographic density carried out in a screened population compared the density in the mammograms of women who were premenopausal at entry and had undergone menopause with an age-matched group of women who were also premenopausal at entry, had been followed for the same length of time, and had not experienced menopause (Boyd et al. 2002). We found evidence that percent density changed in the years preceding menopause, as density was less extensive in women who were about to become menopausal than in age-matched women who remained premenopausal (Fig. 15.3). We also observed that menopause was associated with a reduction in the area of radiologically dense tissue, an increase in the area of non-dense tissue and total breast area, and a decrease in percent density.

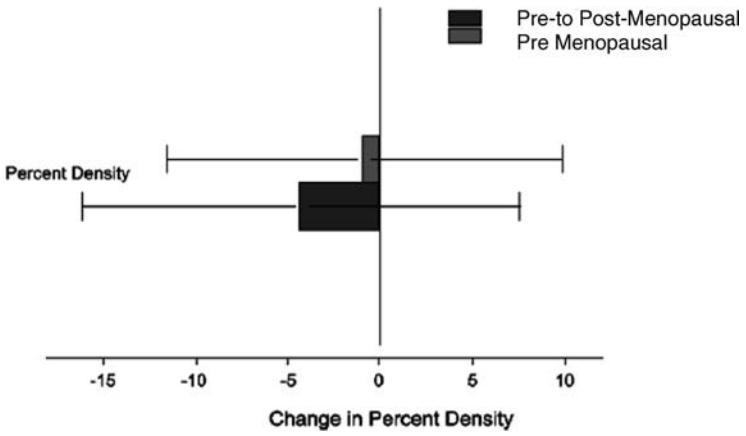

Fig. 15.3 Change in percent density at menopause among a cohort of premenopausal women who underwent menopause vs matched premenopausal women who had not yet experienced menopause (mean and standard deviation of change in percent density). Reproduced with kind permission of Boyd et al., Cancer Epi Bio Prev (2002)

These changes did not, however, account fully for the effects of age on mammographic density seen in cross-sectional data.

Body Mass Index

Height, weight, and body mass index (BMI) are associated with risk of breast cancer. Leanness has been associated with an increased risk of premenopausal breast cancer, but greater body weight or BMI with an increased risk of postmenopausal breast cancer (Hunter and Willett 1993). In the study of Li et al. (2005), BMI was inversely associated with total epithelial and non-epithelial nuclear areas and with reduced areas of collagen and glandular tissue in breast tissue, and with less extensive mammographic density.

The associations of body size, percent mammographic density, and breast cancer risk have been examined in a nested case–control study within a screening program (Boyd et al. 2006). The effects of BMI and mammographic density on risk of breast cancer were examined, before and after adjustment for the other, using logistic regression. The main result is shown in Table 15.1.

In all subjects, before adjustment for mammographic density, breast cancer risk in the highest quintile of BMI, compared to the lowest, was 1.04 (95% CI: 0.8–1.4). BMI was associated positively with breast cancer risk in postmenopausal women and negatively in premenopausal women. After adjustment for density, the risk associated with BMI in all subjects increased to 1.60 (95% CI: 1.2–2.2), became statistically significant and was positive in both menopausal groups. Adjustment for BMI increased breast cancer risk in

Table 15.1 Risk of breast cancer according to quintile of BMI: before and after adjustment for mammographic density[a]

Quintile of BMI (kg/m^2)	<21.79	21.79–23.30	23.30–25.02	25.02–27.64	>27.64	Number	*p*-value[d]
A. All subjects							
Cases	245	218	208	212	231	1,114	
Controls	232	217	220	224	221	1,114	
OR[b] (95% CI) (not adjusted for density)	1.0 (ref)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.0 (0.8–1.4)		0.86
OR[c] (95% CI) (adjusted for density)	1.0 (ref)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	1.2 (0.9–1.6)	1.6 (1.2–2.2)		0.002
B. Premenopausal							
Cases	86	54	49	42	51	282	
Controls	64	59	46	46	52	267	
OR[b] (95% CI) (not adjusted for density)	1.0 (ref)	0.7 (0.4–1.1)	0.8 (0.5–1.3)	0.7 (0.4–1.2)	0.8 (0.5–1.3)		0.37
OR[c] (95% CI) (adjusted for density)	1.0 (ref)	0.9 (0.5–1.5)	1.1 (0.6–2.0)	1.1 (0.6–1.9)	1.5 (0.8–2.7)		0.18
C. Postmenopausal							
Cases	159	164	159	170	180	832	
Controls	168	158	174	178	169	847	
OR[b] (95% CI) (not adjusted for density)	1.0 (ref)	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.0 (0.8–1.4)	1.2 (0.9–1.6)		0.43
OR[c] (95% CI) (adjusted for density)	1.0 (ref)	1.2 (0.8–1.6)	1.1 (0.8–1.6)	1.3 (0.9–1.8)	1.7 (1.2–2.3)		0.004

Reprinted from Boyd et al., Cancer Epi Bio Prev (2006).

[a] Unmatched logistic regression, adjusted for age, age at menarche, age at first birth, parity, number of live births, menopausal status, age at menopause, hormone replacement therapy (ever/never), breast cancer in first-degree relatives (0,1, 2+), study (NBSS, OBSP, SMPBC) and observation time (2 years, 2–4years, >4 years), not adjusted for percent mammographic density. Menopausal status was omitted from the analysis for the separate menopausal groups, and age at menopause from the analysis of the premenopausal group. Quintiles based on the distribution in controls.

[b] Adjusted only for factors listed in footnote (a).

[c] Adjusted for factors listed in footnote (a) and percent mammographic density.

[d] *p*-value for linear trend.

women with 75% or greater density, compared to those with 0%, from 4.25 (95% CI: 1.6–11.1) to 5.86 (95% CI: 2.2–15.6). These effects of adjustment on risk are seen because BMI and percent mammographic density are strongly and negatively correlated (Boyd et al. 2006) and show that BMI and mammographic density are independent risk factors for breast cancer, and likely to operate through different pathways.

Family History

A family history of breast cancer increases risk to first-degree female relatives about two-fold (Beral et al. 2001). Compared to women with no affected relatives, those with a family history of breast cancer have been found to have more extensive mammographic density (Ziv et al. 2005). Ziv et al. determined the association between mammographic density and family history of breast cancer among women in the San Francisco Mammography Registry. Mammographic density was classified using the four BI-RADS categories and analyses were adjusted for various other breast cancer risk factors. Compared to women with BI-RADS 1 readings, women with higher breast density were more likely to have first-degree relatives with breast cancer (BI-RADS 2, odds ratio (OR) = 1.37, 95% CI: 1.0–1.9; BI-RADS 3, OR = 1.70, 95% CI: 1.2–2.4; BI-RADS 4, OR = 1.70, 95% CI: 1.1–2.7). The authors concluded that the genetic factors that determine breast density may also determine breast cancer risk.

Race/Ethnicity

Few studies to date have examined the association of mammographic density with the large international and ethnic differences that exist in breast cancer risk (Muir et al. 1992), but lower mean levels of percent density in Chinese women compared to other ethnic groups with a higher breast cancer incidence have been described (Maskarinec et al. 2001).

Endogenous Hormones and Growth Factors

As the Pike model emphasizes, the effects of hormones and growth factors on cell proliferation in the breast are thought to be of fundamental importance in determining breast cancer risk. The influence of hormones is suggested by the effects on breast cancer risk of ages at menarche and menopause, and of age at first birth, as well as by the effects of exogenous hormones discussed in the following section. Blood levels of estrogens and androgens in postmenopausal women (Key et al. 2003), IGF-1 in premenopausal women (Renehan et al. 2006), and prolactin in both pre- and postmenopausal women (Hankinson et al. 1999, Tworoger et al. 2007) have been found to be associated with risk of breast cancer.

Cross-sectional studies of hormones associated with mammographic density [reviewed in detail in reference (Martin and Boyd 2008)] have shown that growth hormone, IGF-1 and prolactin, all mitogens in the breast, have been associated positively with mammographic density. SHBG has been found to have significant positive association with mammographic density in two studies after adjustment for other variables (Boyd et al. 2002, Bremnes et al. 2007) and in four other studies before adjustment (Noh et al. 2006, Greendale et al. 2005, Tamimi et al. 2005, Verheus et al. 2007).

Most studies to date of blood levels of ovarian hormones have found either no association or an inverse association with percent mammographic density (PMD), in premenopausal or postmenopausal women (Noh et al. 2006, Tamimi et al. 2005, Aiello et al. 2005, Warren et al. 2006, Verheus et al. 2007), or total or free estradiol (Bremnes et al. 2007, Noh et al. 2006, Tamimi et al. 2005, Aiello et al. 2005, Warren et al. 2006, Boyd et al. 2002, Verheus et al. 2007), in premenopausal or postmenopausal women. Only 2 studies in postmenopausal women found a positive association of estrogen levels with PMD (Greendale et al. (2005), Johansson et al. (2008)). Testosterone and androstenedione have not been shown to be associated with mammographic density in postmenopausal women and have not yet been studied in premenopausal women.

In a case–control study nested in the Nurses' Health Study cohort, Tamimi et al. (2007) measured plasma levels of estradiol, free estradiol, testosterone, and free testosterone, and mammographic density in postmenopausal women, who were not using hormones at the time of both blood collection and mammography, and evaluated these factors in relation to risk of breast cancer. Levels of circulating sex steroids and mammographic density were both statistically significant and independently associated with breast cancer risk. The relative risk of breast cancer associated with mammographic density changed little when the analysis was adjusted for circulating estradiol or testosterone. Circulating levels of estradiol and of testosterone were both associated with breast cancer risk, before and after adjustment for mammographic density. In a joint analysis of mammographic density and plasma testosterone, the risk of breast cancer was highest in the highest tertiles of both variables, relative to the lowest tertiles (RR = 6.0, 95% CI: 2.6–14.0). A similar pattern was observed in the joint analysis of estradiol and mammographic density (RR = 4.1, 95% CI: 1.7–9.8). Circulating sex steroid levels and mammographic density thus appear to be strongly and independently associated with the risk of breast cancer in postmenopausal women.

Exogenous Hormones

Combined hormone therapy, but not estrogen alone, is associated with a small increase in risk of breast cancer (Chlebowski et al. 2003), and tamoxifen and raloxifene have been shown to reduce risk (Fisher et al. 1998, Vogel et al. 2006). The effects of hormonal interventions on change in mammographic density are summarized in Table 15.2. Freedman et al. (2001) showed that estrogen alone

Table 15.2 Summary of effects of hormonal interventions on quantitative measures of mammographic density from randomized trials

First author (year)	Intervention	Subjects	Mean change in percent density[a]	Duration
Freedman (2001)	Estrogen	36	+1.2% ($p<0.01$)	2 years
	Raloxifene (60 mg)	45	−1.5%	
	Raloxifene (150 mg)	42	−1.7%	
	Placebo	45	−1.3%	
Greendale (2003)	CEE[b]	99	+1.2% ($p=0.24$)	1 year
	CEE +progesterone[c]	306	+3–5% ($p=0.002$ to < 0.001)	
	Placebo	93	−0.1%	
McTiernan (2005)	CEE + progesterone[d]	202	+4.9%	2 years
	Placebo	211	−0.8% ($p<0.001$)	
Hofling (2007)	Testosterone patch	46	+5.4%	6 months
	Placebo patch	41	+7.4% (NS)	
Eilertsen (2008)	Tibolone	47	0.8%[f] ($p<0.01$)	12 weeks
	Raloxifene	49	0.4% ($p<0.001$)	
	Estrogen + NETA[e] – usual dose	49	2.3% (NS)	
	Estrogen + NETA[e] – low dose	48	2.6%	
Vachon (2007)	Letrozole	35	−0.3%	1 year
	Placebo	33	−1.0% ($p=0.58$)	
Brisson (2000)	Tamoxifen	36	−9.4%	3.3 years
	Placebo	33	−3.6% ($p=0.01$)	
Cuzick (2004)	Tamoxifen	388	−13.7%	4.5 years
	Placebo	430	−7.3% ($p<0.001$)	

[a]Measured using a computer-assisted method, except for Brisson and Cuzick which used visual estimation of percent density. When available, p value is for comparison between treatment and placebo except for Freedman where p value is for comparison of estrogen with all other groups, and for Eilertsen where p values are for comparison of each group with low dose estrogen + NETA.
[b]Conjugated equine estrogens.
[c]Three types of progesterone treatment were tested: cyclic medroxyprogesterone acetate, continuous medroxyprogesterone acetate, and micronized progesterone. Results were similar and the combined mean change in percent density is shown.
[d]Medroxyprogesterone acetate.
[e]Subjects in both groups received continuous oral estrogen plus norethindrone acetate (NETA).
[f]Results shown are for difference in mean PMD between baseline and follow-up but p values refer to comparison of median percent change in PMD.

increased percent density slightly (1.2 percentage points) over 1 year compared to reduction with placebo (1.3 percentage points) and Raloxifene (1.5–1.7 percentage points). Greendale et al. (2003) reported that administration of estrogen alone for 2 years resulted in a small non-significant increase in percent density, while combined HT increased percent density by about 3–5 percentage points, a change that was significantly different from placebo and estrogen use alone. McTiernan reported similar findings for combined hormone therapy (McTiernan et al. 2005), and Decensi found little difference between the effects of estrogen alone, transdermal estrogen with sequential medroxyprogesterone acetate, fenretinide and placebo (Decensi et al. 2004). A testosterone patch did not increase density compared to placebo in women receiving combined hormone therapy (Hofling et al. 2007). Observational studies have also shown that combined HRT use may have a greater effect on mammographic density than estrogen alone (Aiello et al. 2005, Warren et al. 2006, Verheus et al. 2007). Intervention studies have shown that the anti-estrogen tamoxifen reduces mammographic density (Cuzick et al. 2004, Brisson et al. 2000).

We have examined in postmenopausal women the association of hormone therapy at the time of entry to mammographic screening programs, with mammographic density in the mammogram taken at entry, and with subsequent risk of breast cancer (Boyd et al. 2006). Table 15.3 shows the risk of breast

Table 15.3 Hormone use and risk of breast cancer in three screening populations: before and after adjustment for mammographic density

Program	Hormone use	Number of subjects		OR[a] Not adjusted for density	OR[a] Adjusted for density
		Case	Control		
NBSS ($N = 416$)	Never	107	112	1.00 (ref)	1.00 (ref)
	Past	52	59	0.99 (0.61, 1.61)	1.04 (0.64, 1.69)
	Current	45	41	1.13 (0.68, 1.88)	1.12 (0.66, 1.87)
OBSP ($N = 708$)	Never	190	215	1.00 (ref)	1.00 (ref)
	Past	57	44	1.48 (0.95, 2.32)	1.47 (0.93, 2.32)
	Current	103	99	1.20 (0.85, 1.71)	1.12 (0.78, 1.60)
SMPBC ($N = 617$)	Never	171	191	1.00 (ref)	1.00 (ref)
	Past	65	52	1.43 (0.93, 2.22)	1.39 (0.90, 2.16)
	Current	75	63	1.50 (0.99, 2.27)	1.44 (0.95, 2.18)
Combined ($N = 1{,}741$)	Never	468	518	1.00 (ref)	1.00 (ref)
	Past	174	155	1.27 (0.98, 1.64)	1.27 (0.98, 1.65)
	Current	223	203	1.26 (1.00, 1.59)	1.19 (0.94, 1.51)

Reprinted from Boyd et al., Cancer Epi Bio Prev (2006).

[a] Odds ratio adjusted for age, BMI, age at menarche, parity, number of live births,age at first birth, age at menopause, and breast cancer in first-degree relatives (0, 1, 2+). Data shown were obtained in three case–control studies nested in mammographic screening programs: The Canadian National Breast Screening Study (NBSS), Ontario Breast Screening Program (OBSP), and the Screening Mammography Program of British Columbia (SMPBC). Hormoneuse and percent mammographic density at baseline were used in the analysis.

cancer according to hormone use in each of the three screening populations studied. All estimates of risk for the unmatched data are shown after adjustment for the other risk factors for breast cancer, and before and after adjustment for percent mammographic density.

Before adjustment for percent density, current use of hormone therapy was associated, within each population, with a point estimate of risk of breast cancer that was greater than unity, and past use with estimates greater than unity in two populations and in the combined data. Only current use in the combined data was significantly associated with risk of breast cancer, although at a borderline level. The estimates of risk of breast cancer associated with hormone therapy were unchanged, or at most only slightly reduced, by adjustment for percent density.

These results suggest that the pathways that are responsible for the increase in mammographic density following exposure to exogenous hormones, and those that increase risk of breast cancer in women taking hormone therapy, may be different.

Some of the limitations of our study that may have attenuated the effect of adjustment for mammographic density on the breast cancer risk associated with hormone therapy include reliance on cross-sectional differences in density, rather than measurement of change, and the lack of information about the type of hormones used. The preferred design to examine further the issues raised by our findings would be a cohort study with mammograms available before and after the start of hormone therapy of known type. Change in density, according to type of hormone therapy, could then be examined in relation to subsequent risk of breast cancer.

Change in Mammographic Density and Breast Cancer Risk

The potential significance of change in mammographic density can be seen in the context of cumulative exposure to density and its relationship to "breast tissue ageing" and breast cancer incidence as discussed above. If cumulative exposure to mammographic density is related to the incidence of breast cancer in the population, then reduction of cumulative exposure can be expected to reduce breast cancer incidence. As shown above, several of the factors known to reduce mammographic density are also known to influence breast cancer incidence.

The association of change in mammographic density over time with subsequent risk of breast cancer has been examined to date in three longitudinal studies. Vachon et al. (2007) studied 372 incident breast cancer cases and 713 matched controls. All subjects had been examined in the Mayo Clinic mammography screening practice. Cases and controls were matched on age, date of mammogram, residence, menopause, interval between, and number of mammograms. The cranio-caudal view of an average of five mammograms taken over a

period of 10 years before the diagnosis of cancer in the cases were digitized, and measured using a computer-assisted method. Average percent density was greater in cases than controls, but there was no evidence of an association between change in percent density and breast cancer risk. Similar results were seen in users and non-users of hormone therapy (Vachon et al. 2007).

Maskarinec et al. (2006) examined longitudinal changes in mammographic density over a period of more than 20 years. Density from serial mammograms obtained before the diagnosis of breast cancer in 607 cases was compared with 667 frequency-matched using a computer-assisted method. After integrating the area under the percent density curve over time, cumulative percent density was compared with age-specific breast cancer rates in Hawaii. Mammographic density was greater in women who developed breast cancer than in controls, but the rate of change in density was similar in those who developed breast cancer and in controls. Cumulative percent densities and age-specific breast cancer rates were found to increase at very similar rates (Maskarinec et al. 2006).

Neither of these studies provide any evidence that the rate of change in mammographic density is related to risk of breast cancer, but both suggest that the extent of density is related to risk. However, change in mammographic density at young ages, which has not yet been examined, might be relevant to subsequent risk of breast cancer.

Kerlikowske et al. (2007) studied a large number of women undergoing mammographic screening and described an association between an increase or decrease in BI-RADS category in mammograms repeated over an average period of 3.2 years and, respectively, a higher and lower risk of breast cancer. However, no measurements of change were made and the reported changes might be due to technical variations in film production, or to observer variation in the subjective classification of mammograms. Further, there appeared to be no distinction made between change in the affected and unaffected breasts of women who developed breast cancer, and some of the reported changes may have been due to the signs of developing breast cancer rather than a change in mammographic density itself.

Mammographic Density as a Potential Surrogate Marker of Breast Cancer

Mammographic density has been repeatedly shown to be a strong independent risk factor for breast cancer, and thus meets the first of the three criteria referred to in the introduction. Further, as summarized in Table 15.4, mammographic density is also influenced by several exposures or interventions that are also known to influence breast cancer risk. These include parity, menopause, body weight, endogenous levels of IGF-I and prolactin, combined hormone therapy, tamoxifen and raloxifene, and, in general, the directions of the effects of these variables on density are the same as their effects on breast cancer risk. The second of the three criteria is thus also met.

Table 15.4 Summary of variables that influence mammographic density and breast cancer risk

Category	Variable (comparison)	Impact on breast cancer risk	Impact on mammographic density (MD)	Interaction assessed
Risk factors	Parity (parous vs non-parous)	↓	↓	No
	Menopause (early vs late)	↓	↓	No
	BMI (high vs low)	↓ (premenopausal) ↑ (postmenopausal)	↓ ↓	Yes, no evidence of an interaction
	Family history (yes vs no)	↑	↑	No
Endogenous hormones and growth factors	Estradiol (high vs low)	↑	None	Yes, no evidence of an interaction
	Prolactin (high vs low)	↑	↑	No
	IGF-I (high vs low)	↑	↑	No
Exogenous hormones	Combined HT (use vs non-use)	↑	↑	Yes, no evidence of an interaction
	Estrogen (use vs non-use)	None or ↓	None or ↑	NA
	Tamoxifen (use vs non-use)	↓	↓	No
	Raloxifene (use vs non-use)	↓	↓	No

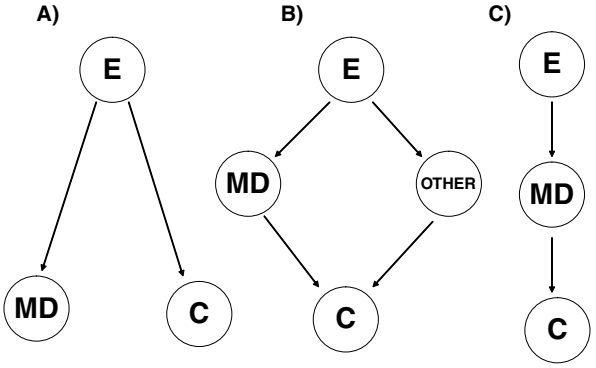

Fig. 15.4 Potential relationships between exposure (E), mammographic density (MD), and breast cancer (C)

The potential relationships between mammographic density and these other influences on breast cancer risk are shown in Fig. 15.4. Risk factors and hormones might influence mammographic density and breast cancer through pathways that are entirely separate (Model A), or through more than one pathway, one of which involves density (Model B), or entirely through a pathway that involves density (Model C).

To date, although the extent of density has repeatedly been shown to be associated with risk of breast cancer, rate of change in mammographic density has not been convincingly shown to be associated with breast cancer risk. Further, none of the factors that influence breast cancer risk have been shown to do so through their associations with mammographic density. This would be shown if adjustment for mammographic density in regression analysis removed the effect of any of the exposures on risk of breast cancer. Such a result would indicate that the effect of the exposure on risk was mediated by the effect of the exposure on mammographic density, as in Model C.

The demonstrated independence from mammographic density of BMI, blood levels of estradiol and testosterone, and hormone therapy, referred to above suggests that Model A best describes the relationship between these factors. The potential mediation of the effects of tamoxifen and raloxifene by their effects on density has not yet been examined. However, their mechanism of action of these drugs in reducing risk of breast cancer is thought to be blockade of the action of estrogen on the breast. Given the evidence that estradiol and mammographc density are independently associated with breast cancer risk, it seems unlikely that an effect on density mediates the effects of these drugs on reducing risk.

We thus find that the available evidence is insufficient to conclude that the mammographic density can be used as a surrogate marker for breast cancer, and further research to examine the potential role of mammographic density as a mediator of the effects of other risk factors is required. Two areas of research that are now in progress may improve prospects for using mammographic density as a surrogate marker for breast cancer. These concern reduction in the error

associated with measurement of density, and increasing our understanding of the biological pathways that are responsible for variations and change in density, and the association of density with risk of breast cancer.

Mammographic density is currently measured with error. All existing methods of assessing mammographic density quantitatively are based on the area of the breast as projected in an image, and none takes into account the volumes of the tissues of interest. Further, computer-assisted methods of measurement require that a dichotomous threshold be placed between dense and non-dense tissue, and no allowance is made for the gradual transition from one tissue type to the other. None of the available methods takes into account variations in the exposure and processing of film images (Boyd et al. 2005). These limitations are likely to lead to underestimation of the risk of breast cancer associated with mammographic density and to increased variance in the assessment of change in density.

Parity, menopause, and the other risk factors discussed above explain only 20–30% of the variance in mammographic density (Vachon et al. 2000, Boyd et al. 1998). Twin studies in Australia and North America have provided a replication of evidence that mammographic density is a highly heritable trait, and that additive genetic factors (heritability) account for 63% (95% CI: 59–67%) of the population variance in the trait, after adjustment for other factors (Boyd et al. 2002). Several large-scale genome-wide linkage and association studies are in progress and can be expected to report their findings within the next few years. Identification of the genes that influence variation and change in mammographic density is expected to provide insights into the biological pathways involved in the breast that determine risk of breast cancer and may suggest potential targets for preventive interventions. The mechanisms that underlie risk are currently unknown, but we have proposed elsewhere that the combined effects of cell proliferation (mitogenesis), and genetic damage to proliferating cells by mutagens (mutagenesis), may underlie the increased risk of breast cancer associated with extensive mammographic density (Martin and Boyd 2008).

Summary

All risk factors for breast cancer must ultimately exert their influence by an effect on the breast, and these findings suggest that, for at least some risk factors, this influence includes an effect on the number of cells and the quantity of collagen in the breast that is reflected in differences in mammographic density. An improved understanding of the biological pathways involved in this risk factor, and improvements in its measurement, may ultimately allow use of mammographic density as a surrogate marker for breast cancer for some exposures.

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Chapter 16
Breast Cancer Screening

Karla Kerlikowske

Introduction

There are few non-pharmacological primary preventive measures that reduce an average-risk woman's breast cancer risk. Strenuous exercise, maintaining ideal body weight, minimizing alcohol intake, breastfeeding, and avoidance of long-term postmenopausal hormone therapy are a few potential modifiable risk factors (Huang et al. 1997, Swanson et al. 1997, Bernstein et al. 1994, Thune et al. 1997, Smith-Warner et al. 1998, Freudenheim et al. 1997, Michels et al. 1996, Newcomb et al. 1994, Kerlikowske et al. 2003, Lahmann et al. 2007, Eliassen et al. 2006, Dallal et al. 2007, Bardia et al. 2006, Zhang et al. 2007, Suzuki et al. 2005, Monninkhof et al. 2007, Chlebowski et al. 2003). Thus, secondary prevention, screening for early-stage disease, is a principal means of reducing breast cancer mortality. Since mass screening for breast cancer involves primarily healthy women, it is important for women and health practitioners to understand the potential benefits as well as the harms and limitations of screening for breast cancer.

Goal of Screening

The primary goal of screening is to avert deaths from breast cancer. In order for that to occur, breast cancer must be identified in the pre-clinical phase and be biologically significant; treatment must be more effective in the pre-clinical phase than in the symptomatic phase; the screening test must have a high sensitivity and specificity; and it must be widely applied in the target population. For a screening to be cost effective, early detection must not only reduce the rate of death from breast cancer but the number of false-positive screening tests should be relatively low and the screening test inexpensive.

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_16,

Breast cancer has a detectable pre-clinical phase that can be identified before women are symptomatic. Survival is over 90% when small breast tumors (less than 10 mm) are identified and treated before women become symptomatic. Mammography, clinical breast exam (CBE), breast self-examination (BSE), and magnetic resonance imaging (MRI) are screening tests that have been evaluated for early detection of breast cancer; the potential benefits, harms, limitations, and cost-effectiveness of these tests are described below.

Efficacy and Accuracy of Screening Mammography

A randomized controlled trial is the most unbiased means to assess whether a screening test reduces the likelihood of death in a person who has the disease and is considered the gold standard when evaluating the efficacy of screening tests. There have been 11 randomized controlled trials conducted to determine whether undergoing screening mammography decreases the chance of dying from breast cancer. There have been several systematic reviews (Kerlikowske et al. 1995, 1997, Elwood et al. 1993, Glasziou et al. 1995, Humphrey et al. 2002, Nystrom et al. 2002) published that combine data from the randomized controlled trials of screening mammography in order to quantify the overall impact of screening on breast cancer mortality and to obtain a more stable estimate of the effect of screening according to age. Meta-analysis results reported over the last 10–12 years have been remarkably consistent (Table 16.1).

Table 16.1 Systematic reviews of randomized controlled trials of screening mammography

	Change in breast cancer mortality (95% CI)	
First author (year)	Women 40–49 years	Women 50–74 years
Kerlikowske (1995, 1997)		
7–9 years from first screen	+2% (–18% to +27%)	–27% (–16% to –37%)
10–14 years from first screen	–16% (–1% to –29%)	–24% (–13% to –33%)
Humphrey (2002)		
14 years from first screen	–15% (–1% to –27%)	–22% (–13% to –30%)
Gotzsche (2007)		
7 years from first screen	–4% (–22% to +18%)	–28% (–15% to –38%)
13 years from first screen	–16% (–1% to –28%)	–23% (–14% to –31%)

Efficacy by Age

Women Aged 40–49 Years

Pooled results from randomized controlled trials have not demonstrated that screening mammography significantly reduces breast cancer mortality in women aged 40–49 years within the first 7–9 years following the initiation of

screening (Table 16.1) (Kerlikowske et al. 1995, Gotzsche and Nielsen 2007). However, there is a trend toward a significant reduction in breast cancer mortality 10–14 years after the start of screening (Kerlikowske 1997, Humphrey et al. 2002, Gotzsche and Nielsen, 2007). Based on a subgroup analysis of women aged 39–49 years, the Gothenburg trial is the only individual study to report a statistically significant reduction in breast cancer mortality 11 years after the initiation of screening (Bjurstam et al. 1997). In contrast, the Canadian National Breast Screening Study (CNBS), designed specifically for women aged 40–49 years, enrolled 50,430 women to undergo either annual mammography, clinical breast examination, and breast self-examination or usual care and found no reduction in breast cancer mortality after 11–16 years of follow-up (+6%, 95% CI: −20% to +20%) (Miller et al. 1997, 2002). The Age trial was designed to study the effect on mortality among women aged 39–41 years screened with annual mammography (Moss et al. 2006). A total of 160,921 women in England, Wales, and Scotland were randomly assigned in a 1:2 ratio to an intervention group of annual mammography or to a control group of usual medical care. At a mean follow-up of 10.7 years there was a −17% (95% CI: −34% to +4%) relative reduction in breast cancer mortality in the intervention group compared to the usual care group, which did not reach statistical significance.

Effectiveness of community-based screening mammography of women aged 40–49 years in the United States has been examined in two case–control studies (Elmore et al. 2005, Norman et al. 2007). Effectiveness for reducing the rate of breast cancer death within 5 years after diagnosis was non-significant at −11% (95% CI: −35% to +23%) among a population of white and black women aged 40–49 years (Norman et al. 2007). There was a similar small, non-statistically significant association between breast cancer mortality and receipt of screening during 3 years prior to diagnosis for women aged 40–49 years enrolled in an organized health plan (−8%, 95% CI: −24% to +13%) (Elmore et al. 2005).

Among 10,000 women 40 years old, an estimated 150 will be diagnosed with invasive breast cancer in the next 10 years and of these 37 will die of the disease. Using results from the pooled analysis of randomized controlled trials (Table 16.1), if 10,000 women get routine mammography over the next 10 years, 4 of the 37 breast cancer deaths may be averted (Table 16.2). This means that for women in their forties, mammography prevents one breast cancer death for every 2,500 women screened annually for 10 years or one death averted per 25,000 mammography examinations performed (Moss et al. 2006, Salzmann et al. 1997). More deaths from breast cancer are not averted because many breast cancers detected by mammography can be diagnosed later and still be cured. Also, some cancers detected on mammography are already too advanced at the time of detection to make a difference. Lastly, since breast cancer is less common in younger than older women, there are fewer potential breast cancer deaths to avert (Esserman and Kerlikowske 1996).

Table 16.2 Annual mammography in 10,000 forty-year-old women for 10 years compared with biennial mammography in 10,000 fifty-year-old women for 20 years[a]

	Age (years)	
	40–49	50–69
Abnormal result	3,000	2,500
Biopsy	750	1,000
Breast cancer		
Invasive	150	580
DCIS	50	220
Die of breast cancer	37	260
Breast cancer deaths averted from screening	4	37
Mammograms performed per breast cancer death averted	25,000	2,700
Cost per year of life saved	$105,000	$21,000

[a]Adapted from reference (Salzmann et al. 1997) Copyright © *1997, Annals of Internal Medicine*. All rights reserved.

Interventions that cost less than $50,000 per life-year saved are generally viewed favorably. For prevention interventions targeted at people of average risk, a gain in life expectancy for the population that received the intervention on the order of 30 days or more is considered to be large (Wright and Weinstein 1998). The incremental cost-effectiveness of screening women aged 40−49 years annually for 10 years is $105,000 per year of life saved and the gain in life expectancy is only 2 days (Salzmann et al. 1997).

Women Aged 50–69 Years

Screening mammography has been shown to reduce mortality from breast cancer 27% among women aged 50 and older 7–9 years after the initiation of screening (Table 16.1) (Kerlikowske et al. 1995, Humphrey et al. 2002, Gotzsche and Nielsen 2007, Fletcher et al. 1993). The mortality reduction begins to appear as early as 4–5 years after the initiation of screening (Humphrey et al. 2002, Nystrom et al. 1993, Shapiro 1988). In the Netherlands, 11 years after screening mammography became available to women aged 50–69 years, there was a 20% reduction in breast cancer mortality among women aged 55–75 years (Otto et al. 2003). A similar 25% reduction has been observed in Denmark with the introduction of screening mammography (Olsen et al. 2005). Effectiveness for reducing the rate of breast cancer death within 5 years after diagnosis in a case–control study was −53% (95% CI: −37% to −65%) among a population of white and black women aged 50–64 years (Norman et al. 2007). Another recent case−control study did not show a significant reduction in breast cancer mortality among women aged 50–65 years that received screening mammography 3 years prior to diagnosis (−13%, 95% CI: −32% to +12%) (Elmore et al. 2005).

Statistical modeling based on population-based cancer screening and treatment patterns has been used to estimate the contribution of screening mammography and adjuvant treatments to observed declines in breast cancer mortality in community practice in the year 2000 in the United States. It appears that screening mammography has contributed 15% to the recent decline in breast cancer incidence and adjuvant therapy 30% (Berry et al. 2005).

Among 10,000 women 50 years old, an estimated 580 will be diagnosed with invasive breast cancer in the next 20 years and of these 260 will die of the disease. If 10,000 women get biennial routine mammography over the next 20 years, 37 of the 260 breast cancer deaths may be averted. This means for women aged 50 and older, routine mammography averts one breast cancer death for every 270 women screened regularly for 20 years, or one death averted per 2,700 examinations performed (Table 16.2) (Salzmann et al. 1997). The cost-effectiveness ratio of screening women aged 50–69 years biennially for 20 years is $21,000 per year of life saved (Table 16.2), a ratio comparable to other recommended screening interventions (Maciosek et al. 2006). The gain in life expectancy of woman 50–69 years screened biennially is modest at 14 days.

Women Aged 70 Years and Older

There are inadequate data from randomized controlled trials to draw a conclusion regarding the benefit of screening mammography in women aged 70 and older. Data from the combined Swedish trials reported a relative risk of 0.78 (95% CI: 0.5–1.2) at 13 years of follow-up (Chen et al. 1995). Small numbers limit the statistical power of this analysis to provide meaningful results. A decision analysis of the utility of screening for breast cancer in women aged 65–85 years reported that, on average, life expectancy would be extended about 2 days for women aged 65–74 years and 1 day for women aged 75–85 years in a screened population (Mandelblatt et al. 1992, Kerlikowske et al. 1999). The cost-effectiveness ratio of screening women aged 69–79 years biennially for 10 years is $73,855 per life-year saved. Continuing mammography screening after age 69 years is thus not generally viewed as cost-effective and results in a small gain in life expectancy because cardiovascular disease is the leading cause of death with more women dying of other causes after detection of breast cancer whether or not they undergo screening mammography (Chapman et al. 2008). Screening mammography may benefit some elderly women through detection of early breast cancers if they do not have co-morbid conditions. However, among elderly women with three or more co-morbid conditions (i.e., hypertension, diabetes, arthritis, history of myocardial infarction, stroke, respiratory disease, or other types of cancer) their risk of death from causes other than from breast cancer is 20-fold more likely within 3 years regardless of the stage at diagnosis of breast cancer (Satariano and Ragland 1994). Given this, performing screening mammography on elderly women whose life expectancy is less than 5 years will not likely impact their overall mortality but may influence their quality of life if they have to live with the knowledge they have cancer, be

subjected to unnecessary diagnostic evaluations of abnormal mammographic results the vast majority (86% to 92%) of which do not represent cancer, and be exposed to surgical treatment of clinically insignificant lesions (Kerlikowske et al. 1999, Welch and Fisher 1998, Smith-Bindman and Kerlikowske 1998, Walter and Covinsky 2001).

Efficacy According to Length of Screening Interval and Whether CBE is Performed

Screening Interval

Three clinical trials screened women aged 40–49 years annually: the Health Insurance Plan trial showed a non-significant 23% reduction in breast cancer mortality 10 years after screening began (Shapiro 1988), the Canadian trial showed a non-significant 6% increase in breast cancer mortality after 11 years (Miller et al. 2002), and the Age trial that showed a non-significant 17% reduction in breast cancer mortality after 11 years (Moss et al. 2006). One community-based study found women aged 40–49 years with a 2-year screening interval were more likely to have late-stage disease at diagnosis than those with a 1-year screening interval (28% versus 21%) (White et al. 2004). This suggests that a greater proportion of invasive breast cancers grow more rapidly in younger women requiring a shorter interval between screening mammographic examinations to detect small occult tumors as early as possible. Thus, if women aged 40–49 years request screening mammography, they probably should be screened annually.

Among women aged 50 and older, screening every 18–33 months results in a 23% (95% CI: 12–32%) reduction in breast cancer mortality; screening annually results in a similar reduction (23%; 95% CI: 0–41%) (Kerlikowske et al. 1995). The estimated breast cancer-specific survival rates for women aged 50–74 years undergoing annual and biennial screening mammography are 95.2 and 94.6% at 5 years and 90.4 and 89.2% at 10 years, respectively (Wai et al. 2005). Thus, screening biennially allows sufficient time to detect breast cancer at a curable stage without affecting survival from breast cancer. Screening more frequently than biennially in this age group does not result in a higher reduction in breast cancer mortality, but does increase the cost of screening (Salzmann et al. 1997). Screening triennially results in unacceptable rates of interval cancers (Asbury et al. 1996).

Clinical Breast Exam

Screening mammography results in a significant reduction in breast cancer mortality regardless of whether clinical breast examination is performed in conjunction with mammography (Kerlikowske et al. 1995). Among women aged 50 and older, breast cancer mortality is decreased 24% among those

who did not receive CBE and 20% among those who did undergo CBE in conjunction with mammography (Kerlikowske et al. 1995).

Efficacy According to Family History of Breast Cancer

There are no clinical trials or subgroup analysis evaluating the efficacy of screening mammography in women who have a family history of breast cancer. Women with a positive family history of breast cancer are at no higher risk for breast cancer mortality than those without a family history of the disease (Yang et al. 1998, Figueiredo et al. 2007, Verkooijen et al. 2006).

The positive predictive value (PPV)[1] of screening mammography is increased two- to three-fold in women aged 40–59 years with a family history of breast cancer because of the higher prevalence of disease in these women (Kerlikowske et al. 1993, 2000). The sensitivity of mammography is similar or slightly lower for women less than 50 years with a family history compared to women who do not have a family history even though women with a family history are at higher risk of breast cancer (Kerlikowske et al. 2000, 1996). Although studies confirming a benefit from screening high-risk young women are lacking, recommendations for screening such women have been made on other grounds, including a high burden of suffering (increased risk of disease and possibly death from breast cancer) and a PPV of mammography similar to that of women aged 50–69 years (Kerlikowske et al. 2000, US Preventive Services Task Force 2002).

Efficacy According to Menopausal Status or Postmenopausal Hormone Therapy

There are no clinical trials or subgroup analyses evaluating the efficacy of screening mammography according to menopausal status or postmenopausal hormone therapy. Studies report that the sensitivity of mammography is lower for premenopausal compared with postmenopausal women (Kerlikowske et al. 1996, Buist et al. 2004) and that the sensitivity and specificity of mammography are lower among women who use postmenopausal hormone therapy compared with those that do not (Laya et al. 1996, Carney et al. 2003). The sensitivity of mammography among hormone users is lower, in part, because cancers are obscured by dense breast tissue (Carney et al. 2003), and because the cancers go from undetectably small on mammography to very large in a short amount of time (Kerlikowske et al. 2003). The lower specificity among hormone users may

[1] The PPV of screening mammography is calculated as the percent of women with abnormal screening results who are subsequently diagnosed with breast cancer.

be because hormone therapy increases breast density in about 16–20% of users (Carney et al. 2003, Greendale et al. 1999, 2003).

Estrogen and progestin postmenopausal hormone therapy use for 5 years or more increases a woman's risk of breast cancer across all stages of disease (Kerlikowske et al. 2003, Chlebowski et al. 2003). The higher rate of advanced stage disease in long-term estrogen and progestin users compared with non-users suggests estrogen and progestin may act synergistically to promote tumorigenesis and more rapid tumor growth (Bigsby 2002, Moore et al. 2000). Postmenopausal women who take estrogen and progestin therapy for more than 5 years should consider undergoing screening mammography annually because of the increased risk of advanced stage disease.

Accuracy of Screening Mammography

Film Screening Mammography

The percentage of screening examinations with abnormal results increases with age (Table 16.3). The PPV of mammography also increases with age with women aged 50–59 years having about a twofold higher PPV of mammography than women aged 40–49 years (Table 16.3). This means for every 100 forty-year-old women with an abnormal mammography result about 2 will have breast cancer compared with 4, 5, and 6 per 100 women in their fifties, sixties, and seventies or older, respectively (Yankaskas et al. 2005). The incidence of breast cancer increases about 1.5-fold every 10 years starting at age 40 up to age 70 with approximately 75% of all invasive breast cancers diagnosed after age 50 (Ries et al. 2007). The observed increase in PPV with increasing age is most likely due to the higher prevalence of breast cancer in older women.

Studies of community-based screening mammography (Buist et al. 2004, Yankaskas et al. 2005) report overall sensitivities of screening mammography (71%–93%) similar to those published for randomized controlled trials

Table 16.3 Performance of screening mammography by age

	Age (years)						
Measures[a]	40–44	45–49	50–54	55–59	60–64	65–69	70–74
Abnormal exams (%)	8.3–9.1	8.7–9.4	7.9–9.3	7.8–9.4	7.2–8.7	6.8–8.0	6.6–7.7
PPV (%)	1.4–1.8	2.2–2.3	2.6–3.4	4.1–4.7	3.5–5.8	4.7–6.8	6.2–7.2
Sensitivity (%)	73–78	65–71	71–88	78–85	73–89	82–86	80–93
Rate per 1,000 exams	1.7–2.0	2.4–2.6	3.3–3.7	5.0–5.3	4.8–6.7	6.8–8.4	9.2–9.3

[a]Data from Breast Cancer Surveillance Consortium, 1996–2000 (adapted from reference (Yankaskas et al. 2005)

(Fletcher et al. 1993). Studies reporting the sensitivity of mammography by age show that sensitivity is lower for women less than age 50 years (71%–78%) compared to women aged 50 and older (71%–93%) (Yankaskas et al. 2005). The sensitivity of mammography is primarily influenced by the ability of radiologists to identify breast cancers on mammography and by the rate at which breast cancers double in size between screening examinations. Consequently, a false-negative examination can occur when a radiologist does not identify a breast lesion that is visible on mammography or when an undetectable breast cancer grows quickly and is discovered clinically before the next screening examination. Mammographic breast density can obscure small tumors and is prevalent in young women (Table 16.4). Mammographic breast density is determined by the relative amounts of epithelial tissue, connective tissue, and fat in the breast. Fat appears radiolucent or dark on a mammogram whereas connective tissue and epithelial tissues are radiologically dense and appear lighter or white. Other than age, mammographic breast density is one of the strongest predictors of breast cancer risk. The rate of cancer increases with

Table 16.4 Breast Cancer Surveillance Consortium (http://breastscreening. cancer.gov/) rates of screen and non-screen detected cancer per 1,000 screening mammography examinations by BI-RADS density and age for 1996–2003

Age at screen	BI-RADS® density[a]	% of screening exams	Screen detected cancer rate per 1,000 exams[b]	Non-screen detected cancer rate per 1,000 exams[c]
40–49	Almost entirely fat	5	1.0	0.1
	Scattered fibroglandular densities	36	1.8	0.4
	Heterogeneously dense	46	2.5	0.9
	Extremely dense	13	2.5	1.5
50–59	Almost entirely fat	8	1.5	0.1
	Scattered fibroglandular densities	45	3.4	0.6
	Heterogeneously dense	40	4.5	1.3
	Extremely dense	7	4.2	2.2
60–69	Almost entirely fat	12	2.4	0.4
	Scattered fibroglandular densities	51	5.0	1.0
	Heterogeneously dense	33	6.4	1.7
	Extremely dense	4	5.3	3.0

[a]American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS®) defined as almost entirely fat (<25% fibroglandular), scattered fibroglandular densities (25–50% fibroglandular), heterogeneously dense (51–75% fibroglandular), extremely dense (>75%)

[b]Breast cancer detected within 12 months of positive screening mammography result

[c]Breast cancer detected with 12 months of negative screening mammography result

Data from Breast Cancer Surveillance Consortium, 1996–2003 (adapted from reference [68]

higher breast density as does the rate of missed cancers obscured by mammographically dense tissue (Table 16.4) (Kerlikowske 2007). It has been suggested that the lower sensitivity of mammography in younger women is because of high breast density and rapid tumor growth rates (Kerlikowske et al. 1996, Buist et al. 2004). (A detailed discussion of breast density is provided in Chapter 15.)

Digital Screen Mammography

The Digital Mammographic Imaging Screening Trial (DMIST) compared the performance of film screening mammography with digital mammography. A total of 49,528 asymptomatic women at 33 sites in the United States and Canada underwent both digital and film mammography. In the DMIST, the overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer was similar. However, digital mammography appears to be more accurate for the following group of women: (1) those under the age of 50 years, (2) those with radiographically dense breasts, and (3) those that are premenopausal or perimenopausal women (Pisano et al. 2005). These three categories of women overlap considerably since the majority of premenopausal women are under the age of 50 years and more than 60% have dense breasts (Carney et al. 2003). Digital screening mammography for women aged 40–49 years and film screen mammography for women aged 50 and older appears to be cost-effective compared with screening all women aged 40 and older with film screen mammography (Tosteson et al. 2008). Given these results, for women aged 40–49 years who elect to undergo screening mammography, if available, should undergo digital screening mammography.

Harms and Limitations of Screening Mammography

Screening mammography may harm women through additional diagnostic evaluations following an abnormal mammography result with associated morbidity and anxiety, the potential detection and surgical treatment of clinically insignificant lesions which may have no impact on mortality (Ernster et al. 2000), and false reassurance resulting from having a normal examination. In addition, a large proportion (up to 91%) of women report having some degree of pain during mammography, with a small proportion of women (less than 15%) reporting intense pain (Kornguth et al. 1996).

Diagnostic Evaluations and Associated Morbidity and Anxiety

One consequence of the low PPV of mammography (Table 16.3) is the high number of diagnostic evaluations. On average, approximately 1.5–2 additional

diagnostic tests are performed per abnormal screening examination (Kerlikowske et al. 1993, Chang et al. 1996). Since the PPV of mammography is low in women aged 40–49 years, these women have the potential to be subjected to the greatest harm since they will undergo the greatest number of diagnostic tests to find the fewest cancers. For example, among 100 average-risk women aged 40–49 years with an abnormal screening examination, about 98 do not have cancer (Table 16.3) and must undergo further diagnostic evaluation that may include tests such as clinical breast examination, additional mammography examinations, ultrasounds, and needle aspirations, core biopsies, or excisional biopsies. Women 40–49 years of age undergo approximately 45 diagnostic tests for every cancer detected by screening mammography compared to 15 for every cancer detected in women aged 50 and older (Kerlikowske et al. 1993). The yield of breast cancer diagnosed per breast biopsy increases with age from 11 to 14% in women aged 40–49 years to 25–55% in women aged 50 and older (Ernster et al. 2000, Kerlikowske and Barclay 1997, May et al. 1998, Weaver et al. 2006). For women less than age 50, only one in seven biopsies will have cancer while one in three will have cancer in older women. The lower yield of cancer per breast biopsy and higher number of diagnostic tests per cancer detected in younger women are due to the lower incidence of breast cancer in these women. Several studies have noted additional outpatient and physician visits to evaluate abnormal results (Elmore et al. 1998, Lidbrink et al. 1996).

Because most mammographic abnormalities are non-palpable, needle localization biopsy or core biopsy is often required. Although risk is low, there are complications associated with biopsies, such as hematomas, infection, and scarring, and from wire localization itself, complications include vasovagal reactions (7%) and rarely prolonged bleeding (1%) and extreme pain (1%) (Dixon et al. 1988). In addition, women with false-positive mammography results experience greater general anxiety or depression or anxiety about breast cancer, compared to women with normal mammographic results though it generally resolves quickly after the evaluation is completed (Lerman et al. 1991, Hofvind et al. 2004, Olsson et al. 1999, Ong et al. 1997, Lampic et al. 2003). False-positive results and the resultant anxiety do not appear to interfere with subsequent adherence to screening (Lerman et al. 1991, Lampic et al. 2003, Burman et al. 1999, Lipkus et al. 2000, Pinckney et al. 2003). Having had a false-positive mammography result has been associated with an increase in the frequency of breast self-examination and of breast and non-breast health-care visits (Lampic et al. 2003, Burman et al. 1999, Barton et al. 2001, Lampic et al. 2001).

The risk of at least one abnormal mammographic examination, false-positive examination, and breast biopsy in women screened annually for 10 years is high for all ages (Table 16.5). If a 40-year-old woman elects to be screened annually for 10 years, i.e., 10 mammographic examinations in 10 years, she should be informed she has a 30% chance of having at least one abnormal screening examination that will require a diagnostic work-up, a 28% chance of

Table 16.5 Risk of at least one abnormal mammographic exam, false-positive exam, and breast biopsy if screened annually for 10 years[a]

	Age (Years)			
Risk	40	50	60	>70
Abnormal exam	30%	26%	23%	26%
False-positive exam	28%	23%	20%	22%
Biopsy	7.5%	10.4%	10.4%	10%
Invasive breast cancer[b]	1.5%	2.4%	3.4%	3.5%
DCIS[b]	0.5%	1.0%	1.2%	1.1%

[a]Adapted from references (Kerlikowske and Barclay 1997) and (Ries et al. 2007) *Copyright © 1997, Oxford University Press.* All Rights reserved.
[b]Risk of invasive breast cancer or ductal carcinoma in situ in the next 10 years.

at least one false-positive examination, and a 7% chance of undergoing at least one breast biopsy (Table 16.5). A 50-year-old woman, who elects to be screened annually for 10 years, should be informed she has a 26% chance of having at least one abnormal screening examination that will require a diagnostic work-up, a 23% chance of at least one false-positive examination, and a 10% chance of undergoing at least one breast biopsy. For all women irrespective of age, the chance of a false-positive test is greater than the risk of breast cancer (Table 16.5). The estimated cumulative risk of a false-positive examination after 10 mammograms has been reported to be as high as 38–56% (Elmore et al. 1998, Hofvind et al. 2004). Three modifiable factors that decrease the chance of a false-positive result include having a comparison film when reading a current examination, time between mammography examinations is less than 3 years, and avoiding postmenopausal hormone therapy (Christiansen et al. 2000).

Increased Detection of Ductal Carcinoma In Situ (DCIS)

DCIS is a breast lesion that is contained within the milk ducts of the breast. DCIS lesions contain some cells with malignant features but not all such lesions behave as cancer, i.e., they will not spread outside the ducts and invade surrounding breast tissue, nor will they be life threatening. (A detailed discussion of in situ breast cancer is provided in Chapter 3).

It is thought that 10–20% of DCIS lesions treated by wide excision alone are associated with a subsequent invasive cancer over 10 years (Kerlikowske et al. 2003). Of breast cancers detected by screening mammography in average-risk women aged 40–49 years, approximately 20–26% are DCIS compared to 14–18% of those detected by mammography in women aged 50 and older (Ernster et al. 2002). The rate of DCIS increases with age from 0.6 per 1,000 screening examinations in women aged 40–49 years to 1.3 per 1,000 screening examinations in women aged 70–84 years (Ernster et al. 2002). The sensitivity of mammography to detect DCIS is high at 86% and varies little with age (Ernster et al. 2002).

Data from the Surveillance Epidemiology and End Results (SEER) program depict over a 300–500% increase in DCIS since the 1980s with the greatest number of DCIS cases detected in women aged 50 and older (Ernster et al. 1996). In 2009, there were an estimated 62,000 cases of DCIS but only a small fraction of these women will ever develop invasive breast cancer or die of breast cancer. Since the vast majority of DCIS is non-palpable (Ernster et al. 2002) and, therefore, detected by screening mammography, the increased use of mammography is the primary reason for the increased incidence of DCIS (White et al. 1990).

Given that the natural history of DCIS is unknown, in particular, the natural history of mammographically detected DCIS, the clinical dilemma lies in not being able to distinguish which lesions will be associated with a subsequent invasive cancer. This results in the vast majority of women with DCIS receiving some surgical treatment. Almost all women who have DCIS detected are currently treated either by mastectomy or lumpectomy with or without radiation and with or without tamoxifen with less than 3% receiving no treatment (Baxter et al. 2004). Mortality from breast cancer is low among women diagnosed with DCIS. Only 1.0–2.6% will die of invasive breast cancer within 8–10 years of diagnosis (Ernster et al. 2000, Kerlikowske et al. 2003, Fisher et al. 1998). Whether the low risk of death from breast cancer is due to very effective treatment or the fact that the majority of DCIS are relatively benign or both is not known. Thus, screening mammography may be benefiting some women whose DCIS would be associated with a subsequent invasive cancer, while it is potentially harming other women whose DCIS would never be associated with subsequent invasive cancer, who, for lack of good prognostic indicators, are almost always treated surgically. Whether or not detection of DCIS by mammography averts breast cancer deaths is unknown.

False Reassurance

Of 100 women aged 40–49 years with breast cancer, about 25 will go undetected by screening mammography, compared with 10–15 of 100 women aged 50–79 years with breast cancer (Table 16.3). This means potentially 25 women aged 40–49 years with breast cancer will be told their screening examination is normal and may be falsely reassured that they do not have breast cancer and not seek medical attention for breast symptoms. Women who have a normal result and do not have breast cancer may be reassured by having a normal screening examination that they do not have breast cancer. For example, the annual risk of invasive breast cancer for a 40-year-old woman is about 1 in 625 (Ries et al. 2007). Having a normal screening examination decreases her risk to about 1 in 2500 (Kerlikowske et al. 1996). Although the very low risk of breast cancer after a normal screening examination may reassure women that they do not have breast cancer, the risk of breast cancer *before* mammography is

already quite low. The need for reassurance from mammography might not be necessary if women understood that the risk of breast cancer prior to mammography is already very low (Black et al. 1995).

Mammography Facilities

High-volume screening mammography programs (greater than 20–35 mammograms per day) offer screening examinations at $85–$135 per film or digital screen (Tosteson et al. 2008). Interpretation of ≥2,500 mammograms by a radiologist per year has been associated with lower abnormal interpretation rates with average or better cancer detection rates (Kan et al. 2000, Smith-Bindman et al. 2005). Other studies have found that increased radiologist experience is associated with higher specificity of mammography in clinical practice (Smith-Bindman et al. 2005, Barlow et al. 2004). Clinicians should refer patients to accredited high-volume mammography programs with well-trained and experienced personnel to insure patients undergo high-quality mammography at a low cost.

Interpreting Mammographic Results

The most common (and most worrisome) mammographic abnormalities are masses and calcifications. Radiologists generally describe both masses and calcifications in terms of location, size, and other characteristics (such as shape, borders, pattern). In addition to describing findings, radiologists make an *assessment and recommendation* (Olson 1993). The American College of Radiology (ACR) recommends one of five assessments for interpretation of a screening mammographic examination (Table 16.6). The ACR quotes a performance benchmark for recall rate of 5–10% with recall examinations defined as

Table 16.6 Frequency of mammographic results in a first screened population and risk of breast cancer based on mammographic result

Mammography assessment	Frequency[a]	Risk of breast cancer[a]	Likelihood ratio[b]
Normal or benign finding	87–93%	0.05–0.1%	0.1
Need additional imaging	6–8%	2–10%	7
Suspicious	0.3–1.4%	10–55%	125
Highly suggestive of malignancy	0.1%	60–100%	2,200

[a]Data from University of California Mobile adapted from references (Kerlikowske et al. 1993, 1996)
[b]Likelihood ratios are the ratio of diseased to non-diseased persons for a given test result.

those screening examinations with an initial Breast Imaging Reporting and Data System (BI-RADS®) assessment of "need additional imaging evaluation," "suspicious abnormality," or "malignant" (American College of Radiology 2003). A higher rate results in a large number of healthy women undergoing additional diagnostic evaluation.

Another test statistic that is clinically useful is the likelihood ratio $(LR)^2$. This test characteristic incorporates both sensitivity and specificity. Likelihood ratios can be used clinically by estimating the "prior" probability of having disease. This "prior" probability is converted to odds then multiplied by the positive likelihood ratio to obtain "posterior" odds and probability. Similarly, negative likelihood ratios can be used to calculate the probability of not having a disease. Very high positive likelihood ratios for screening tests (over 20) or very low negative likelihood ratios (below 0.1) indicate clinically useful screening tests. Likelihood ratios associated with screening mammography interpreted as "suspicious for malignancy" and "malignant" are associated with a substantial increase in the risk of breast cancer, irrespective of age (Table 16.6) (Kerlikowske et al. 1996). However, these interpretations only account for about 4–12% of all abnormal mammographic results.

Efficacy and Accuracy of Clinical Breast Exam

There are no studies that compare the effectiveness of CBE alone compared to screening mammography or CBE alone to no screening. Although mammography plus CBE will detect more breast cancer than clinical breast examination alone (Oestreicher et al. 2005), mammography plus CBE does not decrease breast cancer mortality beyond the reduction achieved by mammography alone for women aged 50–69 years (Kerlikowske et al. 1995). In the Canadian trial of women aged 50–59 years (Miller et al. 2000), mammography and CBE did not decrease breast cancer mortality beyond the reduction achieved by CBE alone. These results can be interpreted in one of two ways; mammography failed to decrease breast cancer mortality or CBE was just as effective as mammography plus CBE suggesting that mammography adds little to decreasing breast cancer mortality if CBE is performed by a trained practitioner. The fact that the number of node-positive tumors was similar in the mammography plus CBE group and CBE alone group and that the sensitivity of mammography in the Canadian trial was similar to or better than in other randomized controlled trials (Fletcher et al. 1993) would suggest that mammography did not fail to decrease breast cancer mortality. Rather, when performed by skilled practitioners, clinical breast exam can be as efficacious as mammography among older women.

The sensitivity of CBE is highest for lesions 1.0 cm or larger (87–88%) and lower for lesions smaller than 1.0 cm (34–55%) (Baines et al. 1989). In one study, mammography sensitivity was 78% and combined mammography–CBE

sensitivity was 82%, thus CBE detected an additional 4% of invasive cancers. Sensitivity increased from adding CBE to screening mammography for all ages (Oestreicher et al. 2005). As with any screening test, there are potential harms. Specificity and positive predictive value decline when CBE is used in conjunction with mammography. The rate of false-positive CBEs is highest for women aged 40–49 years (6%) who undergo screening CBE and declines with age to 3.5% for women aged 50–59 years, 2.5% for women aged 60–69 years, and 2.2% for women aged 70–79 years (Elmore et al. 1998). If a woman elects to undergo annual CBE over 10 years, i.e., 10 screening CBEs in 10 years, she has a 13% chance of having at least one false-positive examination that will require a diagnostic work-up and an estimated cumulative risk of a false-positive CBE of 22% (Elmore et al. 1998). The risk of having at least one biopsy as a result of a false-positive test is 6% after 10 CBEs (Elmore et al. 1998). CBE alone may be most advantageous for women aged 70 and older since CBE results in a lower number of breast biopsies (0.5%) per woman screened compared with mammography (1–2.5%) and lower rates of detection of DCIS. Yet, in proficient hands CBE may detect clinically important lesions that impact on breast cancer mortality (Miller et al. 2000, Baines et al. 1989).

Efficacy and Accuracy of Breast Self-Exam (BSE)

BSE has an overall sensitivity of 26%, which decreases with age from 41% for women aged 35–39 years old to 21% for women aged 60–74 years (O'Malley and Fletcher 1987). In the United Kingdom Trial of Early Detection of Breast Cancer, a non-randomized community trial, there was no reduction in breast cancer mortality in the BSE communities compared to communities that did not perform BSE (UK Trial of Early Detection of Breast Cancer Group 1993). There have been two randomized controlled trials, one in Leningrad of women aged 40–64 years (Semiglazov et al. 1992) and one in Shanghai of women aged 31–64 years (Thomas et al. 1997), that have directly tested the efficacy of BSE to reduce breast cancer mortality. In the Leningrad trial, all women also underwent yearly CBE. After 15 years of follow-up, the Leningrad study reported no difference in the number of breast cancers diagnosed in the BSE group versus the control group and no difference with regard to the size of primary tumors or incidence of metastasis or regional lymph nodes (Semiglazov et al. 1992, 1996, 2003). The Shanghai study reported similar results after 12 years of follow-up. In addition, the authors reported no difference in breast cancer mortality between the BSE-trained group and the control group (Thomas et al. 1997, 2002, Gao et al. 2005). However, in both studies (Semiglazov et al. 1992, Thomas et al. 1997, Semiglazov et al. 2003, Semiglazov et al. 1996, Thomas et al. 2002, Gao et al. 2005) there were increases in physician visits, referrals for further diagnostic evaluations, and twofold greater number of benign breast biopsies among women in the BSE group compared with those in the control

group. The Leningrad study reported 50% more excisional biopsies in the BSE group than control group.

In summary, there is no substantial stage shift from late to earlier stage disease in women who report regular practice of BSE and no reduction in breast cancer mortality. Performing BSE results in additional physician visits and diagnostic tests without identifying more breast cancers or earlier stage disease.

Accuracy of MRI

There are no studies that compare the efficacy of magnetic resonance imaging (MRI) to other breast cancer screening modalities. Studies show MRI compared to screening mammography can detect additional cancers in young women at very high risk of breast cancer. However, the magnitude of this benefit is unknown.

Meta-analysis of data from three studies that compared MRI plus mammography versus mammography alone showed the sensitivity of MRI plus mammography is 94% (95% CI: 86–98%) (Lord et al. 2007). Estimates of the specificity of MRI plus mammography vary widely from 77% to 96%. This variation may be explained, at least in part, by use of different thresholds for classifying positive test results. Screening specificity will be lowest (and sensitivity highest) when all patients referred for further diagnostic imaging or invasive procedure to obtain breast tissue for diagnosis are classified as having a positive test. In contrast, studies that only classify subjects as having a positive test if they had a suspicious or malignant finding requiring biopsy have higher specificities up to 96% and lower sensitivities. Adding MRI to mammography increases a woman's risk of a false-positive result three- to fivefold and of a benign percutaneous biopsy by at least threefold.

Screening MRI is potentially cost-effective for BRCA1 and BRCA2 mutation carriers that are younger than 50–54 years. It is not likely that MRI alone will replace mammography in mutation carriers, as there are breast cancers detected by mammography that are not detected by MRI. In addition, screening women who are known or likely to have an inherited predisposition to breast cancer with both MRI and mammography may rule out cancerous lesions better than mammography alone (Warner et al. 2008). Thus, performing mammography and MRI in BRCA carriers every 12 months is preferable to either test alone. It is not yet clear whether finding additional pre-invasive disease and small node negative invasive tumors on MRI will have an impact on long-term survival rates. It is important to provide counseling and information to these women about the large uncertainty surrounding potential benefits of MRI; the higher risk of unnecessary false-positive findings and the benefits and harms of primary prevention measures as an alternative strategy to screening.

Breast MRI in the general population is not recommended or feasible as currently performed because of the low specificity of MRI that results in additional imaging and tissue biopsies.

Breast Cancer Screening Recommendations

Recommendations for breast cancer screening by five organizations are summarized in Table 16.7. The US Preventive Services Task Force (USPSTF) and Canadian Task Force on the Periodic Health Exam adhere to a high standard of evidence in recommending guidelines for screening and develop such guidelines by conducting an exhaustive review of the literature with explicit linking of the quality of the data to the strength of the recommendation. The American Cancer Society (ACS) and National Cancer Institute (NCI) recommendations are primarily established by group consensus based on expert opinion.

Baseline mammography at age 35 is no longer recommended by any organization. There is disagreement concerning whether the potential mortality benefit of mammography screening in women aged 40–49 years outweighs the known associated harms, which is reflected in differing guidelines about what age routine screening mammography should start (Table 16.7). The American College of Physicians and American Academy of Family Physicians (Qaseem et al. 2007), as well as most European countries (International Agency for Research on Cancer 2002), recommend mammography every 1 to 2 years for women beginning at age 50. The USPSTF and NCI recommend starting at age 40 and also recommend that women should be fully informed of the harms and benefits of screening (Humphrey et al. 2002, National Cancer Advisory Board 1997). The ACS recommends mammography screening begin at age 40 and be performed annually (Smith et al. 2007). Women aged 40–49 years with a family history of a first-degree relative with breast cancer are recommended to undergo routine screening mammography because their risk of disease is similar to that of women aged 50–69 years. There is no evidence to recommend for or against CBE alone in women aged 40–49 years.

For women aged 50–69 years there is universal agreement that they should undergo screening mammography every 1 to 2 years. As noted above, there is no evidence that screening annually is more effective than biennially, but it is more costly. The USPSTF recommends that screening mammography be performed with or without clinical breast examination since there is no evidence that clinical breast examination increases the benefit beyond what is achieved by mammography alone. The age at which to stop performing routine screening mammography has not been determined. A decision regarding screening women beyond age 69 years should be based on a woman's general health, presence of co-morbid conditions, and her willingness to undergo additional tests to find and treat breast lesions that may have no impact on her mortality.

Table 16.7 Recommendations type and frequency of breast cancer screening for average-risk women

Screening modality	US Preventive Services Task Force (USPSTF)	Canadian Task Force on the Periodic Health Exam (CTFPHE)	American Cancer Society (ACS)	National Cancer Institute (NCI)	International Agency for Research on Cancer
Mammography					
40–49	Every 1–2 years	0[a]	Annual	Every 1–2 years	0[a]
50–69	Every 1–2 years	Annual	Annual	Every 1–2 years	Every 1–2 years
≥70[b]	Every 1–2 years[b]	0[a]	Annual	Every 1–2 years	0[a]
Clinical breast exam					
40–49	Optional every 1–2 years with mammography[a]	0[a]	Annual	Every 1–2 years	0[a]
50–69	Optional every 1–2 years with mammography[a]	Annual	Annual	Every 1–2 years	0[a]
Breast self exam	Optional[a]	0[c]	Every month[d]	No recommendation	0[a]

[a]Insufficient evidence to recommend for or against.
[b]USPSTF recommends women aged 70 years and older that have a reasonable life expectancy may consider screening past age 69 years. ACS and NCI recommend screening women aged 40 years and older with no upper age limit on when to stop screening.
[c]Recommends against teaching BSE to women.
[d]ACS recommends monthly breast self-examinations starting at age 20 years without an upper age limit of when to stop.

The USPSTF leaves screening with BSE up to the discretion of the practitioner and woman since there is no evidence to suggest that performing BSE decreases breast cancer mortality. However, the ACS recommends routine BSE starting at age 20.

Informed Decision Making for Screening

All women who request or are offered screening mammography should be informed of the chance of an abnormal result, the chance of a false-positive examination, the chance of undergoing a breast biopsy, the chance of finding breast cancer, and their age-specific risk of breast cancer (Table 16.5). Women should also be informed of the available evidence that screening mammography reduces breast cancer mortality for women in their age group. This is especially important for (1) women aged 40–49 years since the absolute benefit of screening mammography is small, and (2) women aged 70 and older in whom the benefits of screening mammography may not outweigh the costs of screening and treatment of early lesions that may have no impact on mortality. In addition, women should be informed that (1) BSE has a very low sensitivity to detect breast cancer, does not decrease breast cancer mortality, and may result in additional diagnostic procedures including breast biopsies and that (2) CBE alone has a lower sensitivity than mammography to detect breast cancer, there is insufficient evidence to determine whether CBE decreases breast cancer mortality, and CBE may result in additional diagnostic procedures. Health practitioners need to assist women in understanding what factors might influence their choice to undergo or not undergo screening, such as their attitude toward pain, risk of breast cancer, and inconvenience of diagnostic tests, and assist them in understanding the potential benefits, harms, and limitations of breast cancer screening tests (Humphrey et al. 2002, Pauker and Kassirer 1997).

Future Directions

Screening for breast cancer in the near future may be based on risk of breast cancer in the next 5–10 years rather than simply the age of a woman. Risk will likely be determined using clinical risk factors and biomarkers such as quantitative measures of breast density and possibly serum markers such as sex hormones and/or proteins secreted by tumors. Women at highest risk may undergo a combination of screening tests such as mammography and MRI and those at lowest risk may undergo screening mammography less frequently than current recommendations.

Summary

In randomized controlled trials, screening mammography has been shown to reduce mortality from breast cancer about 25–30% among women aged 50–69 years after only 5–6 years from the initiation of screening. The magnitude of the reduction in mortality is similar whether screening is performed annually or biennially or with or without clinical breast examination. Among women aged 40–49 years, trials have reported no reduction in breast cancer mortality after 7–9 years from the initiation of screening; after 10–14 years there is a 16% reduction in breast cancer mortality. Given that the incidence of breast cancer is lower among women aged 40–49 years and the potential benefit from mammography screening smaller and delayed, the absolute number of deaths averted by screening women aged 40–49 years is much less than in screening women aged 50–69 years. There are associated harms with undergoing screening mammography, including additional diagnostic evaluations and the associated morbidity including anxiety, breast discomfort, and complications from biopsies, the potential for detecting clinically insignificant breast lesions, and uncommonly false reassurance resulting from having a normal examination. Performing breast self-examinations results in additional physician visits and diagnostic tests without reducing the risk of death from breast cancer. BRCA carriers are at high risk of breast cancer and mammography and magnetic resonance imaging every 12 months is preferable to either test alone. Health practitioners need to assist women in understanding what factors might influence their choice to undergo or not to undergo breast cancer screening, such as their attitude toward pain, risk of breast cancer, and inconvenience of undergoing diagnostic tests, and to assist them in understanding the potential benefits, harms, and limitations of screening with mammography, clinical breast examination, and breast self-examination.

Acknowledgments This work was supported by an NCI-funded Breast Cancer Surveillance Consortium cooperative agreement (U01 CA 63740) and NCI-funded Breast Cancer SPORE grant (P50 CA58207).

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Chapter 17
Principles of Breast Cancer Therapy

Allison W. Kurian and Robert W. Carlson

Introduction

The treatment of breast cancer is largely determined by stage at diagnosis, hormone receptor status, HER-2/neu level of expression or amplification, patient preference, and comorbidity. Available treatments may be divided into those addressing local–regional disease and those primarily addressing systemic disease. Early breast cancer, generally stages 0, I, II, and III, is treated with curative intent, while metastatic or recurrent breast cancer is generally treated with palliative intent. The treatment of most breast cancers is multidisciplinary, incorporating surgery, radiation therapy, and systemic therapy. In this chapter, we review the prognostic and predictive factors for breast cancer, the treatment of early-stage breast cancer, and the treatment of metastatic disease.

Prognostic and Predictive Factors

Prognostic factors are tumor characteristics that are associated with the risk of breast cancer recurrence and death, and predictive factors are those that provide estimates of the likelihood of benefit from specific therapies (see Table 17.1)

Breast cancer is staged using the Tumor Node Metastasis (TNM) staging system, and TNM subsets are grouped into five stage categories (0–IV) according to the presence or absence of an invasive component, tumor size, regional lymph node involvement, and presence of distant metastasis (Singletary et al. 2002). Ten-year survival estimates in the United States according to breast cancer stage are presented in Fig. 17.1. In patients without distant metastatic disease (M0 disease), the involvement of ipsilateral axillary lymph nodes is the most significant prognostic factor (Fisher et al. 2001, 1983). A number of other

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_17,

Table 17.1 Breast cancer prognostic and predictive factors

Prognostic factor (impact)	Five-year disease-free survival (%) (Reference)
Age ≥50 at diagnosis (favorable (F))	70–85 (EBCTCG 2005)
Age <50 at diagnosis (unfavorable (U))	55–80 (EBCTCG 2005
Estrogen/progesterone receptor (ER/PR) expressed (F)	70–85 (EBCTCG 2005)
ER and PR not expressed (U)	55–75 (EBCTCG 2005)
Axillary lymph nodes not involved by tumor (F)	75–90 (EBCTCG 2005)
Axillary lymph nodes involved by tumor (U)	45–65 (EBCTCG 2005)
Low tumor grade (F)	80–95 (Henson et al. 1991)
High tumor grade (U)	60–85 (Henson et al. 1991)
Tubular or mucinous histology (F)	90–95 (Vo et al. 2007)
HER-2/neu oncogene amplified or overexpressed (U)	60–80 (Romond et al. 2005)
Predictive factors for response to specific therapies	**Specific therapy**
ER and/or PR expressed	Endocrine therapy
ER and PR not expressed	Chemotherapy
High tumor grade	Chemotherapy
HER-2/neu oncogene amplified or overexpressed	Trastuzumab therapy

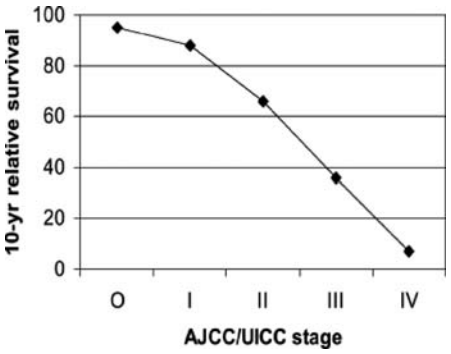

Fig. 17.1 Breast cancer stages of the American Joint Committee on Cancer and International Union Against Cancer (AJCC/UICC), with associated 10-year survival (Source: Singletary and Connolly 2006)

tumor pathologic factors are used to further refine estimates of breast cancer prognosis, including tumor histology, tumor grade, level of steroid hormone receptor expression, and amplification or overexpression of the HER-2/neu oncogene. In developed countries approximately 80% of breast cancers are of ductal histology with approximately 10–15% of tumors being of lobular histology. The less common tubular and mucinous histologies exhibit slower growth and a more favorable prognosis (Fisher et al. 2001, Holland et al. 2001, Talman et al. 2007). The most widely used histologic grading system uses a combined score based on nuclear grade, extent of tubule formation, and number of

mitotic figures and assigns a histologic grade of I (well differentiated), II (moderately differentiated), or III (poorly differentiated). Increasing tumor grade correlates with greater distant recurrence risk and shorter survival (Contess et al. 1987). Higher levels of expression of receptors for estrogen and progesterone associate with improved survival (Kamby et al. 1988) and amplification or overexpression of the HER-2/neu oncogene with early recurrence and worse outcomes (Riou et al. 2001). Age is a prognostic factor, in part, because breast cancers diagnosed before menopause often have unfavorable pathologic features, and young patients, therefore, have shorter survival (Rosenberg et al. 2005).

Tumor grade, estrogen and progesterone receptor (ER/PR), and HER-2/neu status also predict response to specific systemic therapies (EBCTCG 2005, Berry et al. 2006, Pritchard et al. 2006). Tumors that are positive for ER and/or PR respond to a number of endocrine maneuvers, tumors that are HER-2/neu-positive respond to inhibitors of the HER-2/neu growth factor receptor, and higher grade tumors tend to be more responsive to cytotoxic therapy.

Breast cancers are heterogeneous in their pathologic appearance, response to therapies, and clinical course. This heterogeneity is also observed using new molecular classifications of breast cancer. Complementary DNA (cDNA) microarray technology has permitted the assignment of breast cancers into five distinct subtypes: luminal A and B (which are generally ER/PR positive), HER-2/neu overexpressed, basal (which is usually negative for ER, PR, and HER-2/neu), and normal breast like (Sorlie et al. 2001). cDNA microarray technologies have also been used to identify a limited panel of genes prognostic for survival (van de Vijver et al. 2002) and predictive of response to systemic therapy (Paik et al. 2004) and have shown some concordance in outcome prediction between various systems, despite incomplete overlap in the specific genes assessed (Fan et al. 2006).

Loco-regional Therapy for Early-Stage Breast Cancer

The aim of treating early breast cancer is to eradicate any detectable tumor in the breast and lymph nodes with surgery and radiation therapy and to eradicate microscopic tumor cells that have spread systemically at the time of diagnosis using chemotherapy, endocrine therapy, and biological therapy. Loco-regional therapy usually consists of surgery and may also include radiation therapy. Surgical procedures include either removal of the breast (mastectomy) or tumor excision including a surrounding margin of normal tissue, followed by whole-breast irradiation (breast-conserving therapy). Clinical trials have established that modified radical mastectomy, in which the pectoralis muscles are spared, is as effective as more extensive surgical approaches. Randomized trials with 20-year follow-up have established that overall survival does not differ between women undergoing

breast-conserving therapy followed by radiation compared to women undergoing modified radical mastectomy. Based on these studies, contraindications to breast-conserving surgery include a tumor larger than 5 cm, disease sufficiently widespread that it cannot be removed through a single incision, diffuse microcalcifications on mammography suggestive of extensive disease, specimen margins involved by cancer (re-excision may be used to obtain negative pathologic margins), or conditions which preclude radiotherapy, such as previous chest radiation or some connective tissue diseases (Carlson et al. 2007). Women at high inherited risk for a contralateral breast cancer, due to family cancer history or a BRCA1/2 or other cancer susceptibility gene mutation, are often managed with bilateral mastectomy (Stolier and Corsetti 2005). After mastectomy, breast reconstruction may be performed, with the use of autologous tissue from the rectus abdominis or other muscles or with silicone or saline breast implants (Disa and McCarthy 2005).

Axillary lymph node assessment is key to establishing estimates of recurrence or death from breast cancer; consequently, evaluation and treatment of the axilla is an essential component of loco-regional therapy. Axillary lymph node dissection, which removes lymph nodes in the axilla and retropectoralis major regions (levels I and II axillary nodes), remains the standard procedure in women with clinically or pathologically involved axillary lymph nodes (Fisher et al. 2002, Veronesi et al. 2002), but is associated with significant long-term morbidity, including an increased risk of ipsilateral arm lymphedema. Sentinel lymph node biopsy entails injection of blue dye or a radioactive isotope near the breast tumor to identify a limited number of draining lymph nodes for excision. If the identified sentinel node(s) is involved by cancer, an axillary dissection is performed; if the sentinel node is not involved, then an axillary dissection is unnecessary. Randomized trials have demonstrated sensitivity and accuracy in the range of 90–95% with the sentinel node procedure at experienced centers (Goyal et al. 2006, Veronesi et al. 2003) and a lower incidence of lymphedema than with axillary dissection. Based on these results, the sentinel lymph node biopsy has become an accepted treatment option for women without evidence of pathologic axillary lymphadenopathy on physical examination.

Whole-breast radiation therapy routinely follows breast-conserving surgery and chest wall irradiation follows mastectomy in selected circumstances. A meta-analysis of randomized trials demonstrated a threefold reduction in ipsilateral breast tumor recurrence (IBTR) and a trend toward fewer breast cancer deaths, with the addition of whole-breast radiation to breast-conserving surgery (Early Breast Cancer Trialists' Collaborative Group 1995). Reductions in recurrence and death rates with post-mastectomy chest wall and regional lymph node radiation have been observed in some, but not all, clinical trials (Recht et al. 2001). Typical selection criteria for post-mastectomy chest wall and regional lymph node radiation

include a tumor larger than 5 cm, a close or involved tumor margin, and four or more lymph nodes involved by cancer. Controversy remains about the benefits of post-mastectomy chest wall radiation in women with one to three involved nodes (Early Breast Cancer Trialists' Collaborative Group 1995, Ragaz et al. 2005, Chagpar et al. 2003).

Whole-breast or chest wall radiation is delivered in fractionated doses over a course of weeks and generally includes a boost dose to the tumor cavity in breast-conserving therapy. Shorter radiation treatment durations including accelerated partial-breast irradiation and intraoperative radiation are currently under study (Lemanski et al. 2006, Ott et al. 2007).

Determinants of Systemic Therapy for Early Breast Cancer

The primary goals of endocrine, biologic, and chemotherapy of early breast cancer are to prevent distant disease recurrence and improve overall survival. Systemic therapies form a component of the treatment of most patients with early breast cancer, with the exception of those with very small (generally less than 5 mm) node-negative tumors or tumors of favorable histologic subtypes (such as tubular carcinomas) because of their low risk of distant recurrence following local therapy alone. In early breast cancer, systemic chemotherapies are most often administered after surgery and before radiation therapy. Adjuvant systemic therapy is administered to patients who lack evidence of distant disease, with the aim of eradicating microscopic metastasis. The decision to use systemic therapy is made based on estimates of the risk of distant breast cancer recurrence, the likely reduction in this risk from specific therapies, comorbidities which may complicate treatment, expected toxicity experience, and patient preference. Computer models have been developed to calculate an individual patient's likelihood of distant breast cancer recurrence based on the standard prognostic factors of age, comorbidity, tumor size, grade, hormone receptor status, and number of involved axillary lymph nodes; these models also estimate the absolute benefit likely to derive from specific endocrine and chemotherapy regimens. The most widely used model is the Adjuvant! Online model, which was developed using data from the Surveillance Epidemiology and End Results (SEER) database and from large meta-analyses of the benefits of systemic therapies (Ravdin et al. 2001). Adjuvant! has been validated in an independent population-based database (Olivotto et al. 2005). An example of the clinical user interface from Adjuvant! Online is presented in Fig. 17.2. With the development of trastuzumab, a targeted monoclonal antibody against the product of the HER-2/neu oncogene, amplification or overexpression of HER-2/neu further guides treatment choices.

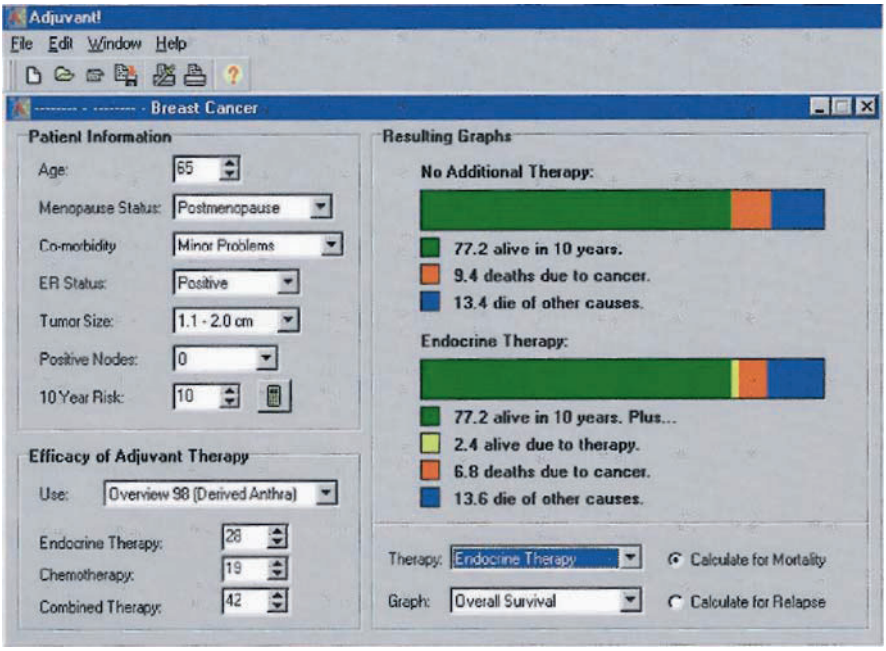

Fig. 17.2 Example of a computer-based tool (Adjuvant! Online, www.adjuvantonline.com) to guide selection of adjuvant therapy (Source: Ravdin et al. 2001)

Adjuvant Endocrine Therapy

The majority of breast cancers express either estrogen receptor (ER) or progesterone receptor (PR) and are, therefore, sensitive to a wide variety of endocrine therapies. If chemotherapy is also given, endocrine therapy generally commences following chemotherapy, and, when radiotherapy is used, endocrine therapy generally commences either concurrently with or after radiotherapy. The best-studied endocrine therapy is tamoxifen, an orally administered selective estrogen response modulator (SERM) with anti-estrogenic effects on breast tissue, but pro-estrogenic effects on some other tissues including endometrium and bone. A comprehensive meta-analysis by the Early Breast Cancer Trialists' Collaborative Group reported a 31% reduction in the annual odds of death for women with ER-positive breast cancer who used tamoxifen for a planned 5 years (in addition to reductions in risks of both recurrences and second primary breast cancers); this reduction persisted after 15 years of follow-up, regardless of age, axillary lymph node status, or chemotherapy use (EBCTCG 2005). No significant benefit results from tamoxifen use in women with hormone receptor-negative breast cancer. Durations of tamoxifen of 1–10 years have been evaluated, and a 5-year duration of tamoxifen therapy appears to be optimally effective. Although most women tolerate tamoxifen well, uncommon serious side effects include endometrial

carcinoma in post-menopausal women, deep vein thrombosis, stroke, and cataracts (Fisher et al. 1994). Five years of adjuvant tamoxifen therapy remains the standard endocrine regimen in pre-menopausal women with ER- and/or PR-positive breast cancers.

In post-menopausal women, the aromatase inhibitors play an increasing role, either in sequence with or in place of tamoxifen. Aromatase inhibitors (AIs) block the conversion of adrenally produced androgens to estrogens by inhibiting the aromatase enzyme. AIs have efficacy only in post-menopausal women, and if used inadvertently in pre-menopausal women, may stimulate ovarian function and cause benign ovarian pathology (Burstein et al. 2006). Although they lack the endometrial toxicity of tamoxifen, AIs may decrease bone density, increase fracture risk, and cause an arthralgia syndrome. Multiple randomized trials have assessed the efficacy of the third-generation AIs anastrozole, letrozole, and exemestane as adjuvant treatment for post-menopausal breast cancer. The earliest of these trials compared tamoxifen to anastrazole; 5 years of anastrozole yielded a significant reduction in the hazard of breast cancer recurrence (hazard ratio (HR) 0.86, 0.76–0.99) with no impact on overall survival (Baum et al. 2002). A subsequent study found a similar advantage to letrozole over tamoxifen (Thurlimann et al. 2005). Anastrozole and exemestane have been studied in sequence with tamoxifen, with tamoxifen given for 2–3 years and the AI for the remainder of 5 years of endocrine therapy (Jakesz et al. 2005, Coombes et al. 2004, Boccardo et al. 2006); switching from tamoxifen to an AI showed a survival advantage over 5 years of tamoxifen alone (Coombes et al. 2007). Extended therapy with letrozole after 5 years of tamoxifen also reduces breast cancer recurrences (Goss et al. 2005). The optimal schedule of AI therapy and the potential of AIs to replace rather than to follow tamoxifen remain important research questions. Adjuvant AIs should not be used in pre-menopausal women outside the investigational setting.

For pre-menopausal women with ER- and/or PR-positive breast cancers, suppression of ovarian function is an effective adjuvant therapy. One component of the benefit of cytotoxic chemotherapy to pre-menopausal women is its likelihood of inducing premature ovarian failure. Methods of ovarian function inhibition include permanent ablation by means of surgery, radiation, or cytotoxic chemotherapy or temporary suppression through treatment with gonadotropin-releasing hormone agonists. A meta-analysis of randomized trials found a survival benefit for pre-menopausal women treated with inhibition of ovarian function in the absence of chemotherapy; when combined with cytotoxic chemotherapy, the benefit was less significant (Early Breast Cancer Trialists' Collaborative Group 2000). Recent studies have found ovarian function suppression equivalent to treatment with an older, less efficacious chemotherapy regimen (Kaufmann et al. 2003), but the question remains as to whether ovarian function suppression adds to the combination of more effective modern chemotherapy regimens plus tamoxifen (Davidson et al. 2005). Several ongoing clinical trials aim to answer the question of whether ovarian suppression adds to endocrine therapy with tamoxifen or an AI in the presence or absence of chemotherapy.

Adjuvant Chemotherapy

Adjuvant cytotoxic chemotherapy is standard therapy for women with invasive cancers larger than 1 cm. Regimens for breast cancer usually contain two or three different cytotoxic drugs, given in combination or in sequence every 3–4 weeks for four to six repeated cycles. Toxicities common to most cytotoxic chemotherapies include damage to rapidly dividing normal cells: this affects hair follicles and the hematopoietic and the gastrointestinal systems, causing alopecia, bone marrow suppression, nausea, and vomiting. Recent developments in supportive care, including the serotonin and NK-1 receptor antagonist anti-emetics and the myeloid growth factors for management of neutropenia and anemia, have vastly improved the safety and tolerability of chemotherapy.

Over decades of clinical trials, the anthracyclines, which work by inhibiting the topoisomerase II enzyme involved in DNA replication, have emerged as a highly effective drug class. The anthracycline doxorubicin in combination with the DNA alkylating agent cyclophosphamide (AC chemotherapy) has been a widely used regimen. A meta-analysis with 15-year follow-up found that 6 months of an anthracycline-based combination chemotherapy regimen reduced the annual breast cancer death rate by 38% in women under age 50 and by 20% in women aged 50–69; such regimens were significantly more effective than a non-anthracycline chemotherapy regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF chemotherapy) (EBCTCG 2005) and are the current standard. An important side effect specific to the anthracyclines is cardiomyopathy, which may cause clinically significant systolic dysfunction and irreversible heart failure. The cardiac toxicity increases with cumulative anthracycline dose, and clinically significant damage is uncommon at the doses used in modern breast cancer treatment regimens (Shan et al. 1996). However, anthracycline-based chemotherapy regimens are contraindicated in patients with pre-existing cardiac dysfunction; non-anthracycline-based regimens are under study, with docetaxel and cyclophosphamide appearing superior to AC chemotherapy (Jones et al. 2006).

Clinical trials of breast cancer chemotherapy have focused on the addition of new agents, changes in dose, and changes in schedule of standard anthracycline-based regimens. Incorporation of the taxanes, which disrupt microtubules of the mitotic spindle required for cell division, has proved a significant advance. Adding four cycles of paclitaxel after four cycles of AC chemotherapy reduces cancer recurrence (Henderson et al. 2003, Mamounas et al. 2005) and likely improves overall survival (Henderson et al. 2003), as does giving docetaxel concurrently with adriamycin and cyclophosphamide (TAC chemotherapy) (Martin et al. 2005). Increases in bone marrow suppression with added taxanes, especially docetaxel, have prompted routine use of myeloid growth factors to reduce the risk of life-threatening febrile neutropenia (Martin et al. 2006). Multiple studies have evaluated increasing the doses of chemotherapy, from moderate dose escalation of anthracyclines (Henderson et al. 2003, Piccart et al. 2001) to bone marrow-ablative chemotherapy regimens requiring autologous stem cell rescue (Farquhar et al. 2005).

Although some increased efficacy was seen with modest dose increases of the anthracycline epirubicin (Piccart et al. 2001), high-dose chemotherapy with or without stem cell transplantation is highly toxic without yielding benefit and consequently is no longer in routine use (Farquhar et al. 2005). By contrast, dosing standard agents more frequently, defined as an increase in "dose density," appears more effective. The Norton–Simon hypothesis predicted that an increase in chemotherapy dose density would improve survival, based on a Gompertzian model of cancer cell growth and asymptotic cell kill with successive chemotherapy cycles (Simon and Norton 2006). In a randomized clinical trial, standard anthracycline- and taxane-based chemotherapy regimens improved survival when dosed every 2 weeks rather than every 3 weeks and proved more tolerable than the every 3-week regimen because of mandatory bone marrow support with myeloid growth factors (Citron et al. 2003). Although not all trials of dose density have demonstrated superiority (Venturini et al. 2005), a dose-dense anthracycline- and taxane-based combination is currently a standard regimen.

The subtypes of breast cancer differ in their response to chemotherapy. A retrospective analysis of clinical trials by the Cancer and Leukemia Group B found a significantly greater benefit from chemotherapy in women with ER-negative as opposed to ER-positive tumors: relative reductions in risk of death were 55 and 23%, with absolute improvements in 5-year survival of 17 and 4%, respectively (Berry et al. 2006). Subset analyses of taxane-based adjuvant chemotherapy trials demonstrate a variable impact on recurrence risk with stratification by ER and/or PR status (Henderson et al. 2003, Martin et al. 2005, Citron et al. 2003). However, such retrospective subset evaluations were unplanned and under-powered and should serve only to generate hypotheses for future study. There is evidence that the ER/PR/HER-2/neu-negative ("triple-negative") or basal breast cancer subtype may be particularly responsive to chemotherapy, albeit more prone to early recurrence (Carey et al. 2007). Amplification or overexpression of the HER-2/neu oncogene has been associated with benefit from anthracycline-based chemotherapy (Pritchard et al. 2006) and from escalation of anthracycline dose (Dressler et al. 2005). Some investigators have suggested that HER-2/neu amplification predicts benefit from anthracyclines because of the proximity of HER-2/neu to the topoisomerase IIα gene, which may serve as an anthracycline target; recent studies have reported that topoisomerase IIα gene amplification may independently predict anthracycline responsiveness (Tanner et al. 2006). The use of molecular markers for individualized selection of adjuvant chemotherapy remains a major research priority, with randomized trials and prospective studies needed to generate high-level evidence for clinical decision making.

Adjuvant Biologic Therapy

Molecularly targeted therapies contribute increasingly to the treatment of breast cancer. The guiding principle of molecularly targeted therapies has been to identify the phenotypic or genetic abnormality in the tumor which

drives its growth and then design a drug that targets this abnormality specifically, thus theoretically minimizing side effects to normal tissue. Trastuzumab, a monoclonal antibody against the HER-2/neu oncogene product, is a highly effective new targeted therapy. HER-2/neu is amplified or overexpressed in 15–20% of breast cancers and associated with poor prognosis and early systemic recurrence. Trastuzumab in addition to paclitaxel or AC chemotherapy was initially shown to provide a survival benefit compared to chemotherapy alone in metastatic, HER-2/neu-positive breast cancer (Slamon et al. 2001). This result prompted multiple trials of trastuzumab added to adjuvant chemotherapy, all of which demonstrated an approximate 50% relative reduction in the risk of breast cancer recurrence (Romond et al. 2005, Piccart-Gebhart et al. 2005, Joensuu et al. 2006, Slamon et al. 2005). A pooled analysis of two large trials of adjuvant trastuzumab given for 1 year concurrently and after adjuvant chemotherapy also demonstrated a 33% relative reduction in the risk of death (Romond et al. 2005). Adjuvant trastuzumab is now standard therapy for women with HER-2/neu-positive breast cancers greater than 1 cm. However, questions remain as to the best adjuvant trastuzumab regimen. The major toxicity of trastuzumab is cardiac dysfunction, with symptomatic congestive heart failure occurring in up to 4% of participants in the adjuvant clinical trials (Telli et al. 2007). Approximately 20% of trial participants had a measurable decline in cardiac systolic function; older women and those with pre-existing cardiac disease appear most likely to experience cardiac toxicity (Tan-Chiu et al. 2005). Substantial uncertainty remains about the degree to which this side effect is reversible after discontinuation of the drug, and many patients remain on cardiac medications. Results from a randomized trial of anthracycline- and non-anthracycline-based adjuvant trastuzumab regimens suggest comparable efficacy and lower cardiac toxicity from the non-anthracycline regimen, but longer follow-up is required (Slamon et al. 2005). The appropriate duration of trastuzumab therapy is also uncertain. A single randomized trial used only 9 weeks of adjuvant trastuzumab and found comparable reduction in risk of recurrence and death as in other trials in which trastuzumab was used for a full year, without associated cardiac toxicity (Joensuu et al. 2006). Despite uncertainty about the optimal regimen and schedule of trastuzumab, the substantial benefits in the adjuvant setting provide proof of principle for the concept of molecularly targeted breast cancer therapies.

Principles of Treating Metastatic Breast Cancer

In most developed countries a minority of patients with breast cancer present with distant spread of disease and are designated as having Stage IV or metastatic breast cancer. More commonly, women initially diagnosed with early-stage breast cancer experience recurrence at distant sites. In this circumstance, biopsy documentation of the recurrent disease and re-evaluation of the tumor for ER, PR, and HER-2/neu expression is performed.

The principles of treating metastatic breast cancer differ qualitatively from those for early-stage disease. In early breast cancer the goal is cure, and consequently relatively toxic short-term therapies are often considered acceptable. With metastatic breast cancer, cure is very uncommon and the goals are symptom palliation and prolongation of survival. Since cure is not normally possible and therapy is often lifelong, maximizing quality of life during therapy assumes greater importance (Chung and Carlson 2003). Diagnosis of asymptomatic recurrent metastatic breast cancer through screening tests has not been shown to improve survival and may worsen quality of life (Rosselli Del Turco et al. 1994). The median survival of metastatic breast cancer is 2–4 years; this estimate has been relatively stable over decades, although some studies suggest improvement due to recent therapeutic advances (Chia et al. 2007). There are prognostic differences in subsets of patients with metastatic breast cancer: those with ER-positive or PR-positive disease presenting with metastases only to the bones have a longer median survival, whereas patients with ER-negative/PR-negative disease involving liver, lung, or brain have a shorter median survival (Chung and Carlson 2003).

Some clinical presentations of metastatic breast cancer, such as pleural effusion, brain, or bone metastases, are best palliated with local surgical or radiation therapies. However, systemic therapy with endocrine, chemotherapeutic, biologic, and other systemic agents is the mainstay of treating metastatic breast cancer. Systemic agents are generally initiated at the time metastatic cancer is diagnosed, and treatment then occurs continuously, usually with a single agent at a time. Patients receiving treatment for metastatic breast cancer are regularly monitored by history, physical examination, and radiologic imaging for evidence of progressive cancer growth despite treatment, which constitutes evidence that the cancer has developed resistance to the agent in question; at that time, the agent is changed. Rates of tumor shrinkage, or response, are highest with initial therapies and decrease over time with increasing numbers of treatments. Once a patient has had no response to three successive chemotherapy regimens, the chance of response to a new agent is low and transfer to hospice care often advised (Carlson et al. 2007).

Endocrine Therapy for Metastatic Breast Cancer

Endocrine therapy is the initial treatment choice for ER-positive and/or PR-positive metastatic breast cancer, because of its favorable toxicity profile and substantial efficacy. Tumor shrinkage in response to endocrine agents is often slower to commence than with chemotherapy, although the duration of response to hormones may be prolonged; therefore, chemotherapy may be preferred in patients with symptomatic metastases involving visceral organs. Selection of endocrine therapy for metastatic breast cancer requires consideration of treatments the patient received for early breast cancer, with agents

different than received previously preferred due to a lower likelihood of resistance. In addition, menopausal status must be considered. For pre-menopausal women, the initial therapy is tamoxifen and/or ovarian function suppression, whether surgically or medically with gonadotropin-releasing hormone agonists (Taylor et al. 1998). If a woman is rendered functionally post-menopausal, then the endocrine agents active in post-menopausal women, such as the AIs, may be used.

Studies demonstrate that initial therapy in post-menopausal women with an AI may provide slightly greater disease response than tamoxifen (Thurlimann et al. 2003). After disease progression on first-line tamoxifen therapy, anastrozole, letrozole, or exemestane are superior to megestrol acetate (Buzdar et al. 1998), and the estrogen receptor antagonist fulvestrant is equivalent to anastrozole or exemestane (Robertson et al. 2003, Gradishar and Piccart 2006). There is little definitive evidence for a specified order of endocrine agent use: tamoxifen, the AIs, and fulvestrant are widely used in varying sequence, whereas the older endocrine agents megestrol acetate, ethinyl estradiol, and fluoxymestrone are used less often. Usual criteria for changing from endocrine agents to chemotherapy include absence of any cancer response or stabilization on three successive endocrine regimens or the development of symptomatic visceral metastases requiring the more rapid response which chemotherapy may provide (Carlson et al. 2007).

Chemotherapy for Metastatic Breast Cancer

Chemotherapy is the initial therapy for ER-negative/PR-negative metastatic breast cancer, of metastatic breast cancer with widespread, symptomatic visceral disease, and for ER-positive or PR-positive breast cancer that is endocrine therapy-refractory. Multiple chemotherapy agents have activity in metastatic breast cancer, with higher response rates in first (30–60%) than in subsequent (10–40%) lines of treatment (Gelmon et al. 2006, Jones et al. 2005). As in the adjuvant setting, the anthracyclines and taxanes are active, but an agent, which the patient has not previously received in the adjuvant setting, is preferred because of potential acquired drug resistance. Given the palliative nature of chemotherapy for metastatic disease, a favorable side effect profile is desirable. Other frequently used agents include capecitabine, a nucleoside analogue with relatively little hematologic or gastrointestinal toxicity and a convenient oral route of administration, the anti-mitotic vinca alkaloid vinorelbine, and the nucleoside analogue gemcitabine. Studies have reported higher tumor response rates and longer time to disease progression with combination versus single-agent chemotherapy regimens (O'Shaughnessy et al. 2002); however, trials that compared combination regimens to the same single agents given sequentially demonstrate no difference in overall survival (Carrick et al. 2005). Single-agent chemotherapy is consequently preferred over a combination regimen for most

patients, although those with immediately life-threatening visceral metastases for whom rapid shrinkage of tumor burden is a priority may benefit from immediate combination chemotherapy. There is no definitive sequence of specific chemotherapy drugs; the most active agents, such as taxanes, are often used early with the aim of inducing a long-term disease response. Trials have evaluated intermittent versus continuous chemotherapy and found a longer interval until disease progression, though no survival difference, in patients receiving continuous treatment (Muss et al. 1991); therefore, a chemotherapy agent is generally continued until there is evidence of disease progression, at which point a new agent is substituted. Cumulative toxicities such as low blood counts and fatigue often occur with prolonged chemotherapy duration, prompting consideration of a hiatus in treatment according to patient tolerance.

Biologic and Other Systemic Therapies for Metastatic Breast Cancer

Trastuzumab, a monoclonal antibody against HER-2/neu, was initially evaluated together with chemotherapy for metastatic disease and found to prolong survival (Slamon et al. 2001). Trastuzumab plus taxane-based chemotherapy is a standard treatment for HER-2/neu-positive metastatic breast cancer. Drugs commonly combined with trastuzumab include taxanes, vinorelbine, capecitabine, or platinum agents. In general, trastuzumab plus an anthracycline is avoided as a randomized trial showed a 27% incidence of congestive heart failure when anthracyclines were combined with trastuzumab (Slamon et al. 2001).

Lapatinib, an orally administered dual tyrosine kinase inhibitor active against the epidermal growth factor receptor (EGFR) and HER-2/neu, has recently been shown to prolong the time to disease progression when administered with capecitabine in patients whose disease has progressed despite trastuzumab and prior treatment with an anthracycline and taxane (Geyer et al. 2006); it represents a further option for patients with metastatic HER-2/neu-positive disease.

Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, is believed to work by inhibiting new blood vessel formation in tumors and/or by normalizing disordered tumor vasculature so as to enhance delivery of chemotherapy. Bevacizumab delays the time to disease progression when combined with paclitaxel in first-line metastatic therapy; it has also been shown to improve response rates to second-line capecitabine chemotherapy, but without a significant impact on survival or time to progression (Miller et al. 2007, 2005). Multiple ongoing clinical trials are designed to determine the optimal use of targeted therapies in metastatic breast cancer.

For women with metastatic breast cancer involving bone, bisphosphonates are an additional component of their systemic therapy. The bisphosphonates inhibit osteoclast function, thus inhibiting bone loss at sites of metastasis and reducing the risks of pathologic fracture, pain, and functional impairment. The

potent intravenous bisphosphonates pamidronate and zoledronic acid are the most effective, with some trials reporting superior outcomes with zoledronic acid compared to pamidronate (Coleman 2002). A side effect of bisphosphonates is osteonecrosis of the jaw, a failure of bone healing sometimes associated with dental work which may cause recurrent infections and pain (Wilkinson et al. 2007). The occurrence of osteonecrosis of the jaw appears related to the potency, frequency of administration, and duration of use of the bisphosphonates.

Summary

A combination of early detection and effective loco-regional and systemic therapies has reduced US breast cancer mortality over recent decades. The heterogeneity of breast cancer subtypes is increasingly recognized, and chemotherapy and therapies targeted against ER, PR, and the HER-2/neu oncogene are widely used with curative intent in early breast cancer. Major research priorities include refinement of molecular cancer profiling to guide therapeutic decisions and improvement upon the limited efficacy of current treatment options for advanced disease.

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Chapter 18
Breast Cancer Outcomes

Graham A. Colditz and Courtney Beers

Introduction

Although breast cancer incidence and mortality in the United States have declined in recent years, the number of survivors continues to grow and identifying factors that may modify survival is thus increasingly important (Espey et al. 2007). The twenty-first century has brought a continued decrease in breast cancer mortality in developed countries. Specifically, in the United States the death rate is now 25.5 per 100,000 women and survival rates at 5 years (86%), 10 years (78%), 15 years (71%), and 20 years (65%) have all improved (SEER; Espey et al. 2007) (Brenner 2002). Improved survival presents new questions and considerations for patients, clinicians, and researchers. Namely, better methods for screening and prevention of recurrence, second primary tumors, and metastases; improved management of long-term side effects of treatment including quality of life; and more complicated decisions when considering treatment options. In this chapter we address issues of breast cancer survival, recurrence, second primary breast cancer, and lifestyle changes to improve survival and quality of life.

Survival

The overall 5-year breast cancer survival rate in the United States was 87% between 1992 and 1999. Five-year survival varies substantially according to stage, with the highest survival rates for localized disease (97%) and the lowest for distant disease (23%). Age at diagnosis is also related to breast cancer survival, with slightly lower 5-year survival rates among women diagnosed at young ages (Ries et al. 2003).

Dr. Graham Colditz is supported in part by an American Cancer Society Cissy Hornung Clinical Research Professorship.

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C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4_18,

International survival rates vary widely by country with rates as low as 30–40% in Algeria, Brazil, and eastern Europe and as high as 70–80% in North America, Japan, and parts of north, west, and southern Europe with differences in survival attributed to health insurance, accessibility of diagnostic and treatment facilities, financial commitment to health technology and variation in national health expenditures (Coleman et al. 2008). Australia reports some of the highest 5-year survival in the world with 97% survival for women with node-negative tumors and 80% for those with node-positive tumors (Australian Institute of Health and Welfare & National Breast Cancer Centre 2007). Clearly the presence or absence of national screening programs and access to care contribute to the international variation in survival (Fig. 18.1).

Several studies have attributed differences in survival to level of education and other socioeconomic factors as determinants of adherence to screening recommendations, treatment options, stage at diagnosis, and access to care in general (Thomson et al. 2001; Kaffashian et al. 2003; Woods et al. 2006; Strand et al. 2007; Dalton et al. 2008). Associations between mortality/survival and socioeconomic factors have been demonstrated in the United States and in Europe; for example, studies have reported increased mortality in women determined to live in lower socioeconomic neighborhoods (Byers et al. 2008), worse survival in women with lower levels of education and disposable income (Dalton et al. 2008), and an association between lower social class and survival (Kaffashian et al. 2003). However, while socioeconomic status clearly impacts prognostic factors such as stage at diagnosis and treatment options, these characteristics do not entirely account for survival differences. Thomas et al. reports that only 20% of an identified survival difference between affluent and disadvantaged Scottish women can be accounted for by breast conservation versus mastectomy, uptake of endocrine therapy, and other treatment-related differences between the groups (Thomson et al. 2001) (Fig. 18.2).

Differences in survival rates by socioeconomic status and race/ethnicity have been most comprehensively evaluated in the United States. African-American women have poorer breast cancer survival rates at all ages of diagnosis compared to white women; between 1992 and 1999, the 5-year survival rate was 88% for white women and 74% for African-American women (Ries et al. 2003). This poorer survival can be attributed, in part, to the tendency of black women to be diagnosed at later stages of disease. However, whites also have higher survival rates than blacks at each stage of disease, suggesting that there may be racial differences in prognosis or treatment (Campbell 2002). Some studies indicate that black women diagnosed with breast cancer between the ages of 25 and 40 are more likely than white women to have tumors with biologically aggressive characteristics (Stanford and Greenberg 1989; Eley et al. 1994). According to data from the Florida State tumor registry, racial differences in survival remain apparent even after socioeconomic status, insurance payer, and stage at diagnosis are taken into account (Roetzheim et al. 2000). A more recent analysis among postmenopausal women, however, showed no difference in stage-specific survival rates for blacks and whites with access to care through

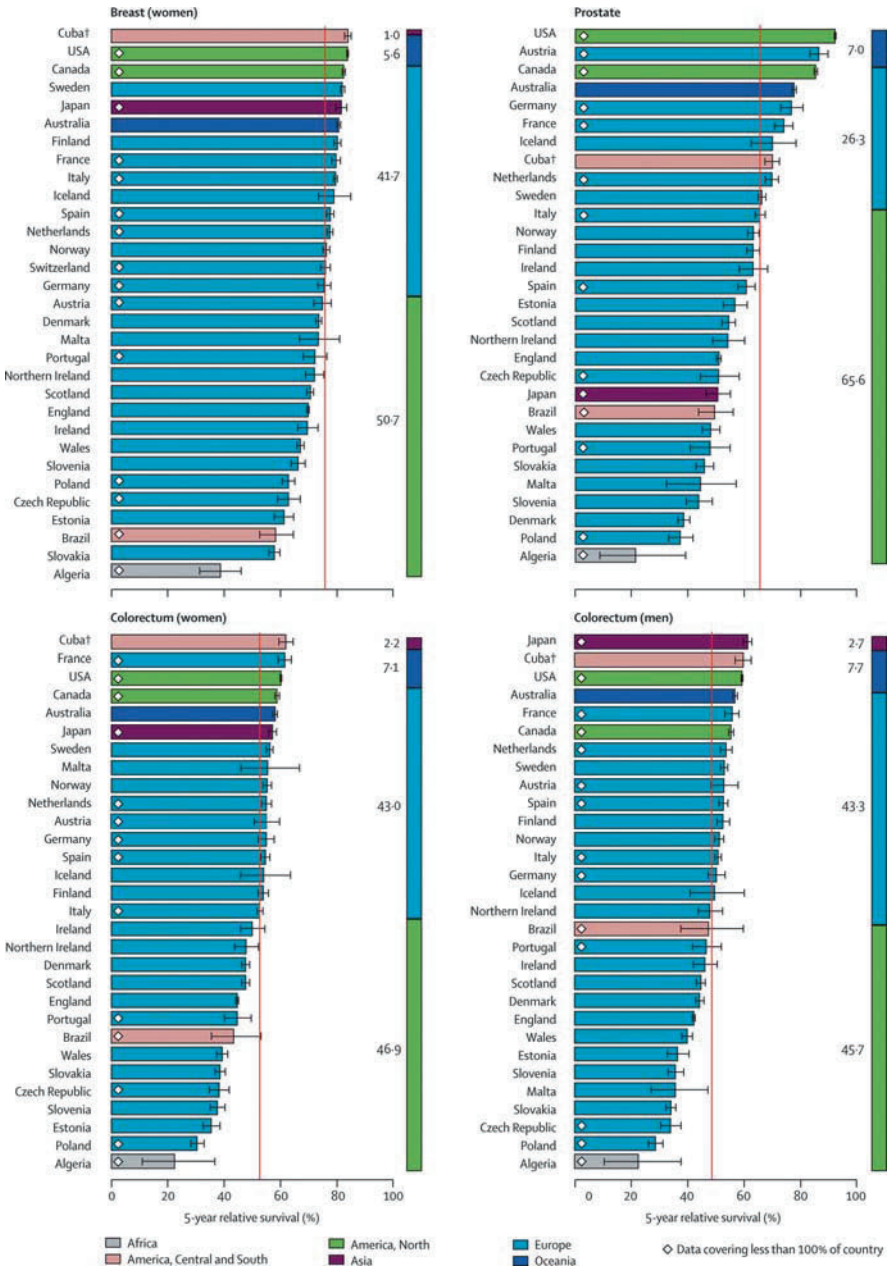

Fig. 18.1 5 year relative survival (%) age-standardized for adults ages 15–99 diagnosed with cancer of the breast, colorectum, or prostate during 1990–94 followed through December 31, 1999

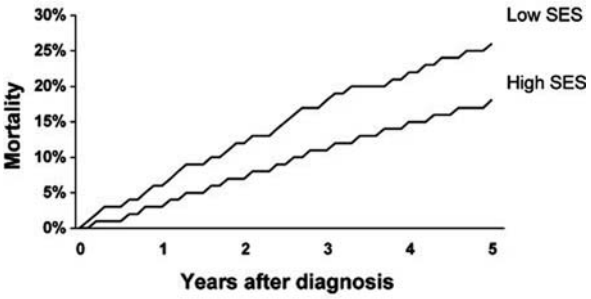

Fig. 18.2 The relation between socioeconomic status (SES) of area of residence and breast cancer mortality within 5 years after cancer diagnosis in the Patterns of Care Study

Medicare (Chu et al. 2003). Hence, the evidence remains inconclusive as to the extent of this difference being biologic versus socioeconomic.

Rates of Recurrence

Breast cancer outcomes and survival are significantly impacted by local recurrence, metastases, and second primary tumors. Tumor type, grade, lymphatic or vascular involvement, and hormone receptor status have been identified as the primary predictors of recurrence (Hayes et al. 2001). Based on a review of recurrence in seven clinical trials involving post-operative adjuvant treatment, of the 45% of women who recurred there was a peak risk for recurrence between 1 and 2 years post-diagnosis and a decrease in risk in subsequent years (Saphner et al. 1996). Risk factors for recurrence are often difficult to separate from prognostic factors and treatment strategies used for primary cancers. Young age has consistently been associated with increased risk of local recurrence. At the same time, young age is associated with a worse set of characteristics of the primary tumor such as absence of estrogen receptor expression. Even after controlling for tumor characteristics, young age is associated with increased recurrence. Inherited susceptibility, including *BRCA1* and *BRCA2*, has been evaluated but data are inconsistent relating family history and genetic markers to increased recurrence. Tumor characteristics, including an extensive intraductal component, and close margins at the primary resection also increase risk of recurrence.

Women who have had breast cancer have an estimated two- to sixfold increased risk of developing a second primary breast cancer and a 25% increased risk of developing a second non-breast primary when compared to the general population (Mellemkjaer et al. 2006). These second primary tumors more commonly occur as cancers of the contralateral breast, colon/rectum, bone, endometrium, ovary, kidney, connective tissue, lung, soft tissue sarcomas, leukemias, and melanomas (Chen et al. 1999; Mellemkjaer et al. 2006; Raymond and Hogue 2006; Trentham-Dietz et al. 2007). Time to second

primary has been reported in a study of over 10,000 breast cancer survivors where Trentham-Dietz et al. 2008 observed that 11% of survivors were diagnosed with a second primary tumor within 7 years of their initial diagnosis (Trentham-Dietz et al. 2007). Similarly, analysis of the US National Surveillance Epidemiology and End Results data system (SEER) shows that 12% of women with breast cancer developed a second primary tumor within a mean time period of 6 years from initial diagnosis (Raymond and Hogue 2006). Breast cancer survivors are at a particularly high risk of developing a second primary tumor in the contralateral breast when compared to the general population; an estimated 2–11% of survivors will develop a second primary tumor in the contralateral breast (Chen et al. 1999). A central methodological challenge in studying second primary tumors is the degree of workup required to confirm a second primary tumor versus metastatic spread.

Identified risk factors for second primary tumors include low parity, older age at menopause, greater body mass index, adult weight gain, family history, and genetic mutations. Additionally, women who are younger when diagnosed with initial breast cancer are at increased risk of developing a second primary tumor (Chen et al. 2001; Mellemkjaer et al. 2006; Raymond and Hogue 2006). It has been suggested that an additional risk factor for second primary tumors – particularly for tumors located in the region of the breast – may be radiotherapy and chemotherapy administered as treatment for the initial breast cancer (Chen et al. 1999; Mellemkjaer et al. 2006; Raymond and Hogue 2006).

Modifiers of Risk of Mortality, Recurrence, and Second Primary Breast Cancer

Existence of modifiable risk factors provides breast cancer survivors the opportunity to alter their lifestyle and thus reduce the likelihood of mortality, recurrence, and second primary tumors. Rock et al. reviewed 26 studies evaluating the effect of weight and weight gain on disease progression and found a 30–540% increased risk of death when comparing women with a higher body mass index to women with a lower body mass index (Rock and Demark-Wahnefried 2002). Rock concluded that being overweight or obese was associated with poorer prognosis and recommended strategies for survivors to achieve healthy weight control through diet and exercise (Rock and Demark-Wahnefried 2002). In the following sections we summarize the evidence for diet, weight control, and physical activity to modify outcomes.

Diet

Modifications to diet after diagnosis offer a unique opportunity for interventions that may improve breast cancer outcomes. Few studies have, however, focused on diet after diagnosis, a time when women with breast cancer may be

motivated to change their diet. As diet before diagnosis cannot be changed, we do not consider this growing literature as relevant to modifications that can improve breast cancer outcomes.

The hypothesis that fat intake may modify breast cancer outcomes draws support from several areas. Human evidence comes from studies of diet before diagnosis, such as an evaluation of dietary fat intake in the Iowa Women's Health Study, showing that higher fat intake prior to diagnosis may decrease survival (Zhang et al. 1995). The underlying assumption here is that the dietary pattern and fat intake is not modified by the diagnosis of breast cancer. While this is not well substantiated, studies that specifically addressed diet after diagnosis are far more pertinent. In a detailed analysis of diet after diagnosis recorded by women in the Nurses' Health Study, Holmes et al. observed that decreased fat intake after diagnosis was not associated with mortality from breast cancer. The only clear component of diet emerging from the rigorous evaluation was the observation that higher intakes of protein and poultry were associated with decreased mortality (Holmes et al. 1999). Randomized controlled trial evidence also shows no overall benefit from diet modification after diagnosis: the Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Living (WHEL) study have been unable to demonstrate a difference in overall survival when decreasing fat intake (Chlebowski et al. 2006; Pierce et al. 2007). The WINS study had substantial loss to follow-up and greater weight loss in the intervention arm of the trial, in addition to reported changes in diet, making interpretation of findings difficult. The WHEL study, on the other hand, showed substantial changes in diet by using biomarkers that reflected the increased intake of fruits and vegetables. Despite substantial modifications in dietary patterns, high compliance, and high follow-up rates, there was no detectable difference in breast cancer mortality.

Season of diagnosis has also been related to survival with lowest survival for women diagnosed in winter when circulating vitamin D levels are low (Robsahm et al. 2004; Lim et al. 2006). While the mechanism for this relation is proposed to be through vitamin D(3), the vitamin can be replaced through supplements and hence is potentially modifiable. A 25(OH)D level of 52 ng/ml has been found in observational studies to be sufficient to reduce breast cancer incidence by 50%. This level could be maintained by intake of 2,000 IU/day and, when appropriate, about 12 min/day in the Sun which is equivalent to an oral intake of 3,000 IU of Vitamin D(3) (Garland et al. 2007). However, confirming this potential benefit for change in vitamin D levels after diagnosis remains to be evaluated in clinical trials.

Weight Control

Weight has been identified in the "Nutrition and Physical Activity During and After Cancer Treatment: An American Cancer Society Guide for Informed

Choices" as the most important modifiable factor impacting breast cancer survival (Brown et al. 2003). Unfortunately, post-diagnosis weight gain is common in breast cancer survivors and possibly related to or exacerbated by adjuvant chemotherapy, hormonal therapy, age and menopausal status, and nodal status (Demark-Wahnefried et al. 1997; Chlebowski et al. 2002). An extensive literature review indicates that women who are overweight or gain weight after breast cancer diagnosis are at greater risk of recurrence, death, and decreased quality of life (Demark-Wahnefried et al. 1997; Chlebowski et al. 2002). These conclusions are consistent with a recent study conducted by Kroenke et al. that reported that increasing risk of recurrence or death is commensurate with increasing weight gain in breast cancer survivors (Kroenke et al. 2005). This study showed the clearest results among non-smokers, a group of women who do not have weight fluctuation history interrupted by cessation from smoking, and for whom hormone levels most directly reflect their weight history (Kroenke et al. 2005). Chlebowski et al. recommends that overweight or obese women be advised not to gain additional weight, to adhere to a healthy diet (high in vegetables and fruits and low in fat and refined sugars), and be encouraged to increase physical activity in an effort to decrease risk of recurrence and improve quality of life (Chlebowski et al. 2002). As there are extensive evidence-based guidelines for weight loss and sustained weight loss, these treatment guidelines should inform and be implemented routinely for women diagnosed with breast cancer (NHLBI Obesity Initiative Expert Panel 1998). Specifically, weight loss and weight maintenance therapy should employ the combination of low-calorie diets, increased physical activity, and behavior therapy (Evidence category A). The initial goal for weight loss therapy should be to reduce body weight by approximately 10% from baseline (Evidence category A).

Physical Activity

Despite the known benefits that physical activity has on survival in cancer patients and the awareness that cancer survivors may experience decreased physical activity attributable to treatment-related fatigue or inability to exercise (Brown et al. 2003), there has been some reluctance on the part of clinicians to recommend exercise regimens for women who are currently undergoing or who have recently completed treatment for breast cancer. Concern about lymphedema, the potential for injuries, and the impact of treatment-related fatigue on adherence to exercise regimens have been investigated and determined not to present additional risks or barriers for breast cancer survivors as described below.

In a meta-analysis of physical activity interventions in cancer survivors before and after treatment, Schmitz et al. determined that physical activity interventions initiated after treatment were generally well tolerated, had a positive effect on cardiorespiratory function, and improved vigor and vitality (Schmitz et al. 2005). A pilot study evaluating the safety and feasibility of group

exercise training in 40 breast cancer survivors demonstrated similar results in terms of fitness benefits (increased strength, flexibility, aerobic capacity) as well as improvement in quality of life (Kolden et al. 2002).

In addition to accessing the safety, tolerability, and feasibility of initiating exercise programs for breast cancer survivors, studies have demonstrated a survival advantage for women who exercise moderately or more vigorously. Holmes et al. using Nurses' Health Study data evaluated repeated measures of leisure time physical activity assessed after diagnosis and observed that any exercise greater than 3 MET-hours per week was associated with a decreased risk of death from breast cancer and that the equivalent of walking 3–5 hours per week presented the greatest benefit to survivors with a relative risk of 0.80 for 38.9 MET-hours per week and between 0.50 and 0.60 for greater than 9 MET-hours per week (Fig. 18.3) (Holmes et al. 2005). When comparing breast cancer survivors exercising less than 3 MET-hours per week to those exercising 9 or more MET-hours per week, analysis revealed an unadjusted mortality risk reduction of 6% at 10 years (Holmes et al. 2005).

The benefits of physical activity for cancer survivors are also recognized by the American Cancer Society (ACS) in its recommendation that cancer

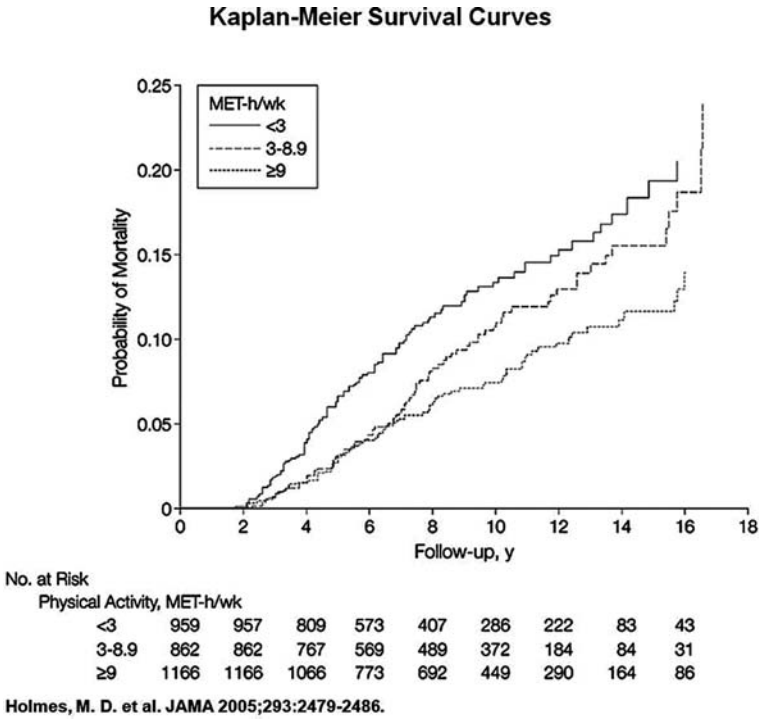

Fig. 18.3 Kaplan–Meier survival curves reflecting decreased mortality in women exercising >3 MET-hours per week

survivors exercise to improve physical functioning and quality of life. ACS encourages survivors to discuss exercise regimens with a treating physician prior to implementation and that type, frequency, duration, and intensity of exercise be based on the individual survivor's current medical status, physical capability and limitations, and energy level (American Cancer Society 2007).

Quality of Life

Modifying diet, weight, and physical activity are proactive measures survivors can take that may also have a positive impact on quality of life after breast cancer diagnosis and treatment. Extended survival has stimulated research on survivors' quality of life which allows patients and clinicians to make more informed treatment decisions and improve management of symptoms. Poorer health-related quality of life has been consistently found in breast cancer survivors (Ganz et al. 1998, 2004; Trentham-Dietz et al. 2007). We next address emotional well-being, fatigue, and physical functioning as primary predictors of post-diagnosis quality of life.

Emotional Well-Being

Using validated tools to assess mental health following breast cancer diagnosis, studies have demonstrated that breast cancer survivors have comparable emotional health/well-being when compared to women without breast cancer after treatment (Ganz et al. 2004), at greater than 2 years post-diagnosis (Trentham-Dietz et al. 2007), between 1 and 5 years post-diagnosis (Ganz et al. 1998), and when assessing quality of life at 6-month intervals through 72 months post-diagnosis (Land et al. 2006). Despite these findings, breast cancer survivors report feelings of anxiety, depression, difficulty sleeping, and worry or problems associated with sexual interest/activity prior to or, when applicable, following breast cancer recurrence (Kenne Sarenmalm et al. 2007; Lidgren et al. 2007; Meeske et al. 2007). Considering the potential for decreased quality of life among breast cancer survivors, Parker et al. compared survivors who had different surgical procedures and observed no difference in quality of life between women who had a mastectomy with reconstruction, a mastectomy without reconstruction, and breast conservation surgery.

Fatigue

The impact of emotional well-being on health-related quality of life is confounded by the effect of fatigue on emotional and psychosocial functioning. Fatigue was cited as a predominant predictor of quality of life in multiple

studies (Arndt et al. 2006; Bower et al. 2006; Kenne Sarenmalm et al. 2007; Lee et al. 2007; Meeske et al. 2007) and a symptom that was reported by 34% or survivors even 5–10 years post-diagnosis (Bower et al. 2006). The impact of physical activity on fatigue has been documented in the literature and is well represented by a study conducted by Meeske et al. of breast cancer survivors (41% of whom were fatigued) that demonstrated a nearly 50% reduction in fatigue in women who exercised 4 or more hours per week (Meeske et al. 2007).

Physical Health

Fatigue, pain, and physical symptoms factor into the level of physical function reported by breast cancer survivors. While treatment-related symptoms (e.g., nausea, vomiting) typically decrease after completion of therapy, symptoms such as chronic pain, fatigue, arm symptoms and lymphedema, and menopausal symptoms are experienced and impact quality of life on a long-term basis (Arndt et al. 2006). Decreased physical health was reported in survivors 10 or more years after diagnosis (Trentham-Dietz et al. 2007).

Management of physical symptoms can be difficult among breast cancer survivors. For example, Ganz et al. reported an association between adjuvant therapy and an increased risk of premature menopause with accompanying or related symptoms such as infertility, vasomotor symptoms, vaginal dryness, dyspareunia, weight gain, and osteoporosis (Ganz 2005). The consistent finding that menopausal symptoms significantly impact quality of life presents difficulty in terms of symptom management as hormone therapy is typically not recommended for breast cancer survivors.

Studies have been conducted to compare physical functioning in women with different treatment approaches. Although results have been inconsistent in determining whether there is an increased risk of physical or mental symptoms associated with singular or combination treatments for breast cancer, patients and clinicians should take physical and mental health symptoms and their potential impact on quality of life into consideration when weighing treatment options.

Summary

While diet after diagnosis has little direct relation to survival after breast cancer, increases in weight are directly related to poorer outcomes. Higher levels of physical activity and weight loss reduce mortality in observational studies and randomized trials show improved quality of life with increasing physical activity. This demonstrated improvement in survival and quality of life substantiates the need for future research focused on developing and/or identifying strategies to implement and sustain long-term changes in physical activity among breast cancer survivors, as well as routine use of evidence-based weight control and weight loss guidelines.

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Index

C.I. Li (ed.), *Breast Cancer Epidemiology*, DOI 10.1007/978-1-4419-0685-4,