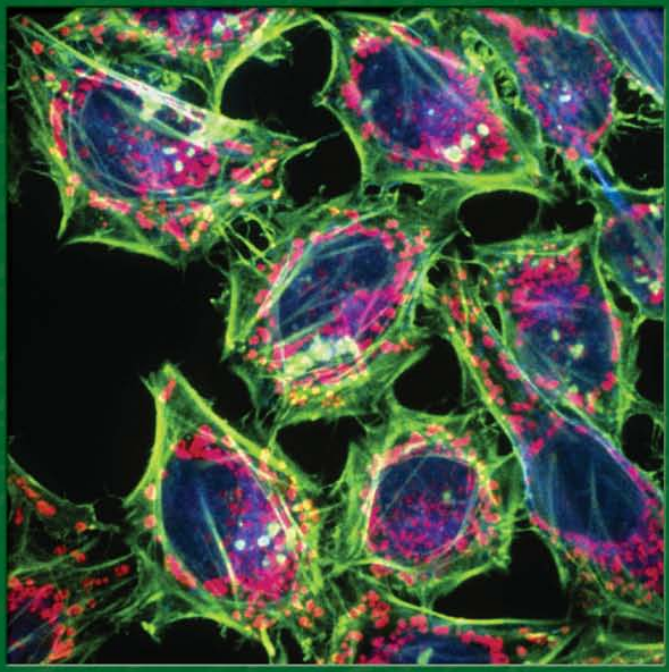
DEADLY DISEASES AND EPIDEMICS

CERVICAL CANCER



Juliet V. Spencer, Ph.D.

Foreword by David Heymann
World Health Organization

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CERVICAL CANCER

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Anthrax
Avian Flu
Botulism
Campylobacteriosis
Cervical Cancer
Cholera
Ebola
Encephalitis
Escherichia coli Infections
Gonorrhea
Hantavirus Pulmonary Syndrome
Hepatitis
Herpes
HIV/AIDS
Infectious Fungi
Influenza
Legionnaires' Disease
Lung Cancer
Lyme Disease
Mad Cow Disease (Bovine Spongiform Encephalopathy)
Malaria
Meningitis
Mononucleosis
Pelvic Inflammatory Disease
Plague
Polio
Prostate Cancer
SARS
Smallpox
Staphylococcus aureus Infections
Streptococcus (Group A)
Syphilis
Toxic Shock Syndrome
Tuberculosis
Tularemia
Typhoid Fever
West Nile Virus

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CERVICAL CANCER

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Foreword

In the 1960s, many of the infectious diseases that had terrorized generations were tamed. After a century of advances, the leading killers of Americans both young and old were being prevented with new vaccines or cured with new medicines. The risk of death from pneumonia, tuberculosis (TB), meningitis, influenza, whooping cough, and diphtheria declined dramatically. New vaccines lifted the fear that summer would bring polio, and a global campaign was on the verge of eradicating smallpox worldwide. New pesticides like DDT cleared mosquitoes from homes and fields, thus reducing the incidence of malaria, which was present in the southern United States and which remains a leading killer of children worldwide. New technologies produced safe drinking water and removed the risk of cholera and other waterborne diseases. Science seemed unstoppable. Disease seemed destined to all but disappear.

But the euphoria of the 1960s has evaporated.

The microbes fought back. Those causing diseases like TB and malaria evolved resistance to cheap and effective drugs. The mosquito developed the ability to defuse pesticides. New diseases emerged, including AIDS, Legionnaire's, and Lyme disease. And diseases which had not been seen in decades reemerged, as the hantavirus did in the Navajo Nation in 1993. Technology itself actually created new health risks. The global transportation network, for example, meant that diseases like West Nile virus could spread beyond isolated regions and quickly become global threats. Even modern public health protections sometimes failed, as they did in 1993 in Milwaukee, Wisconsin, resulting in 400,000 cases of the digestive system illness cryptosporidiosis. And, more recently, the threat from smallpox, a disease believed to be completely eradicated, has returned along with other potential bioterrorism weapons such as anthrax.

The lesson is that the fight against infectious diseases will never end.

In our constant struggle against disease, we as individuals have a weapon that does not require vaccines or drugs, and that is the warehouse of knowledge. We learn from the history of

science that "modern" beliefs can be wrong. In this series of books, for example, you will learn that diseases like syphilis were once thought to be caused by eating potatoes. The invention of the microscope set science on the right path. There are more positive lessons from history. For example, smallpox was eliminated by vaccinating everyone who had come in contact with an infected person. This "ring" approach to smallpox control is still the preferred method for confronting an outbreak, should the disease be intentionally reintroduced.

At the same time, we are constantly adding new drugs, new vaccines, and new information to the warehouse. Recently, the entire human genome was decoded. So too was the genome of the parasite that causes malaria. Perhaps by looking at the microbe and the victim through the lens of genetics we will be able to discover new ways to fight malaria, which remains the leading killer of children in many countries.

Because of advances in our understanding of such diseases as AIDS, entire new classes of antiretroviral drugs have been developed. But resistance to all these drugs has already been detected, so we know that AIDS drug development must continue.

Education, experimentation, and the discoveries that grow out of them are the best tools to protect health. Opening this book may put you on the path of discovery. I hope so, because new vaccines, new antibiotics, new technologies, and, most importantly, new scientists are needed now more than ever if we are to remain on the winning side of this struggle against microbes.

David Heymann
Executive Director
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Introduction

She came from humble beginnings—an illegitimate child born into poverty in a small town in Argentina. Years later, she became the wife of President Juan Perón and the First Lady of Argentina. María Eva Duarte de Perón, better known as Evita, was one of the most powerful and controversial women in the history of Latin America. She was beloved as a champion of the poor and a savior of the working class, and she was also hated by those who saw her as the vindictive wife of a ruthless dictator. She influenced many people during her short lifetime, which inspired the Tony Award–winning Broadway musical *Evita.* Had she lived, one can only imagine the impact she might have had on her country and the rest of the world, but her life ended tragically in 1952 at the age of 33.

Evita was a victim of cervical cancer. This cancer is still one of the leading killers of women today.

This book aims to educate readers about cervical cancer. Chapter 1 describes this silent killer in some detail. In Chapter 2, the basic anatomy and physiology of the cervix are described to help clarify the location of the cervix and the important functions it performs. An examination of when and where cervical cancer occurs is presented in Chapter 3, with some discussion of the sexual transmission of human papillomavirus (HPV) and strategies for avoiding infection. Chapter 4 focuses on HPV, with detailed information about the structure and infection cycle of this pathogen. In Chapter 5, we will look at the process by which HPV can transform a normal cell into a malignant one. Screening tests such as the Pap smear and other diagnostic procedures are described in detail in Chapter 6, and treatment options are discussed in Chapter 7. Chapter 8 provides an overview of the development of the cervical cancer vaccine, and Chapter 9 describes what the future may hold for those individuals with cervical cancer or HPV infection. Although cervical cancer is still a leading killer of women today, recent advances in the prevention, detection, and treatment of this disease may lead to a sharp decline in the future.

1

A Silent Killer

Cervical cancer is the second-most common cancer in the world. More than 500,000 women worldwide are diagnosed each year with this disease and nearly half of those will die from it. Before the invention of the **Pap smear** procedure in the 1940s, cervical cancer was the most deadly form of cancer for women in the United States. Since regular preventive **screenings** have become common, the incidence of cervical cancer has dropped in this country by over 75 percent. Still, between 10,000 and 13,000 American women are diagnosed with cervical cancer each year, and over one-third of those women will die from it.

Many of these deaths could be prevented if the Pap smear test were accessible to all women, but for those who lack resources, such as money, health insurance, or access to medical care, regular screenings are not possible. In developing nations, the lack of regular gynecological screenings is an even more serious problem that leads to a majority of the world's cases of cervical cancer.

The **cervix** is the lower, narrow end of the uterus that leads to the vagina. Cervical cancer occurs when cells of the cervix begin to divide uncontrollably. The abnormally dividing cells form a mass, or **tumor**. As the cells continue to divide, they may invade the surrounding normal tissue. Cells may also break off of the primary tumor and spread to distant sites in the body, a process known as **metastasis**.

Fortunately, cervical cancer usually develops slowly, over the course of months or even years, so with regular screenings it is possible to detect this cancer in its earliest stages when it is most easily treated. Before cancer appears in the cervix, there are typically **precancerous** changes,

known as **dysplasia**, which may occur. The Pap smear is a procedure specifically designed to identify these changes so that potentially cancerous cells can be monitored or removed before they progress to an advanced, and potentially life-threatening, stage of cancer.

Cancer of the cervix often has no symptoms, which is why it is so important for women to have regular gynecological examinations that include either a standard Pap smear test or the newer **HPV DNA test**. When they do appear, symptoms of cervical cancer may include pelvic pain, bleeding or pain during sexual intercourse, bleeding between menstrual cycles, and unusual discharge from the vagina. Having these symptoms does not necessarily mean that an individual has cervical cancer, but it does mean that a physician should be consulted immediately to determine the cause of the symptoms.

As with other forms of cancer, there are several risk factors associated with the development of cervical cancer. Among these are cigarette smoking, a poor diet that lacks specific vitamins and nutrients, a compromised immune system, or a family history of cervical cancer. In addition, there is one particular factor that correlates strongly with cervical cancer: infection with the human papillomavirus, or HPV. Cervical cancer almost never occurs in young girls or in women who have never engaged in sexual intercourse. Because HPV is transmitted through sexual intercourse any woman who is sexually active can become infected and develop cervical cancer. HPV is one of the most common sexually transmitted diseases in the world, with millions of new infections occurring each year in the United States. There is no specific drug for the treatment of HPV infection, although in many cases the immune system will respond vigorously and clear the **virus** on its own, with no long-term effects to the host. Most women who become infected with

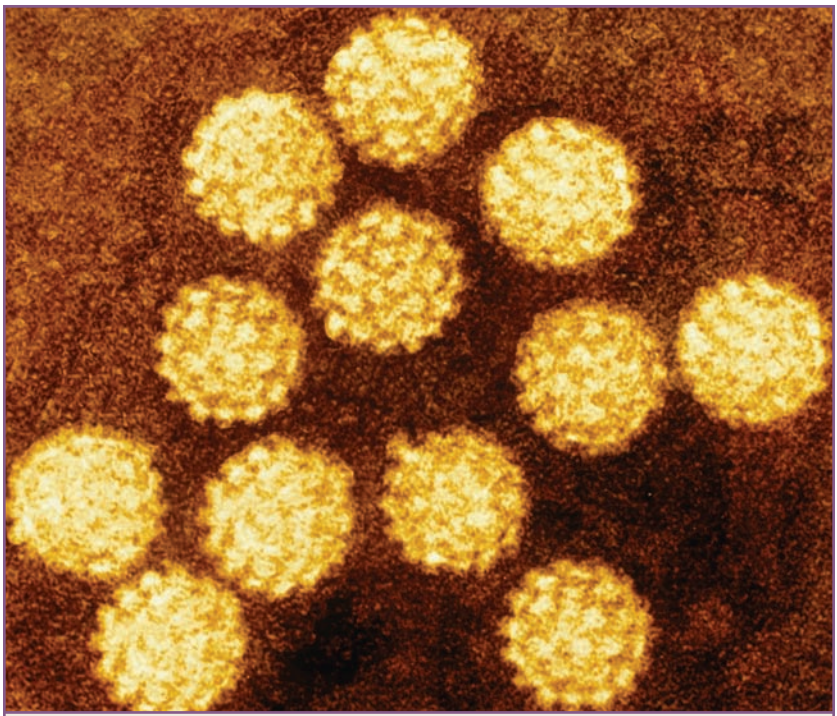


Figure 1.1 Colored transmission electron micrograph (TEM) of a group of papilloma viruses. These icosahedral-shaped DNA viruses have a coat containing 72 capsomers (or protein units). The human papilloma viruses causes warts and can contribute to cervical cancer. © Dr. Linda Stannard, UCT./Photo Researchers, Inc.

HPV will not develop cervical cancer; there are more than 100 different strains of HPV and only a small subset of these are associated with cervical cancer. For women who do become infected with the **oncogenic** (cancer-causing) strains of HPV, early detection of precancerous changes, by means of regular gynecologic examinations and Pap smear tests, is vital to ensure the greatest chance of successful treatment and recovery.

WHAT IS CANCER?

Cancer is a collection of diseases that result from the uncontrolled growth of cells. Melanoma, leukemia, and carcinoma are all different types of cancer caused by the abnormal growth of a particular type of cell. The body is made up of many different types of cells, but these cells grow and divide to produce more cells only when the body needs them. The tightly regulated control of cell growth is necessary to keep the body healthy. Occasionally, when normal growth control mechanisms fail, cells begin to divide inappropriately. A spontaneous growth of cells that forms an abnormal mass is known as a tumor, or neoplasm. A tumor serves no useful function and grows at the expense of the healthy organism.

Tumors may be classified as benign or malignant. Benign tumors pose less risk to the patient because they are typically slow-growing, small, localized masses. This means that they are well separated from the normal tissue and do not disrupt normal function. They are an easy target for a surgeon to remove. Benign tumors are generally denoted with the suffix *-oma*; for example, a fibroma is a benign tumor of the fibrous connective tissue and an adenoma is a benign tumor of a gland. Although benign tumors are usually not dangerous, a large benign tumor could block an important passageway, such as the colon or an artery, or could put pressure on a vital organ, disrupting its function. In general, however, benign tumors are considered much less serious than malignant tumors. The hallmark feature of malignant cells is that they can invade the surrounding normal tissue. This not only disrupts organ function, but also makes the tumor much more difficult for a surgeon to remove. Malignant tumors often contain very rapidly growing cells, and these cells can break off from the primary tumor and spread, or metastasize, throughout the body, forming secondary tumors.

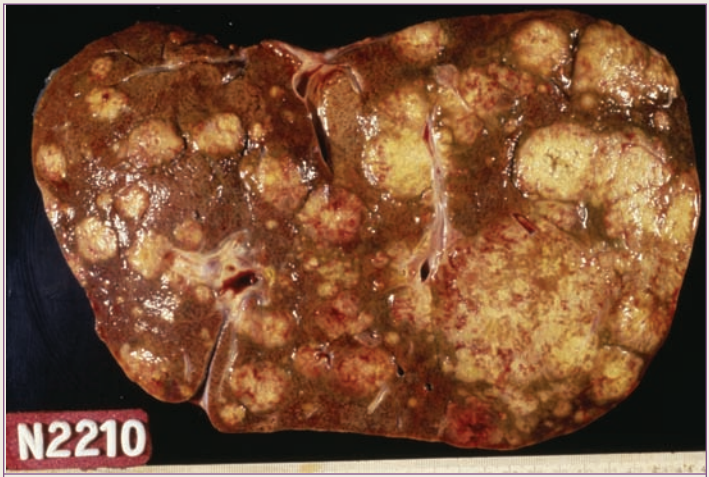


Figure 1.2 Widespread secondary cancers, seen here as numerous, pale lumps, spread from the colon to the liver as seen in this liver tissue sample. © CNRI/Photo Researchers, Inc.

Malignant tumors are generally designated by three suffixes: *-carcinoma*, *-sarcoma*, and *-blastoma*. Carcinoma is the name for a malignant tumor of cells of the epithelium, which is a layer of cells that line the body's internal or external surfaces. An example is cervical carcinoma, a cancer of the cervical epithelium. Sarcoma is the name for malignant tumors of the body's connective tissue, such as osteosarcoma, or cancer of bone-forming cells. Blastomas are usually aggressive malignant tumors that affect children, such as retinoblastoma, or cancer in the retina of the eye. Cancer that involves malignant cells is life threatening because it can result in organ failure, obstruction of passageways, or cachexia, which is a wasting syndrome that occurs when the tumor robs the body of important nutrients.

2

Female Anatomy 101

A gynecologist is a doctor who specializes in the treatment and care of the female **reproductive system**. Every woman over the age of 18 needs to have a gynecologist whom she trusts. Regular gynecological exams are essential for good health, and women may be reluctant to schedule appointments with doctors they don't like or with whom they aren't comfortable.

During the average yearly exam, the gynecologist will do three things. First, he or she will perform a visual examination for any obvious signs of infection or disease, such as redness, sores, or discharge. Next, a sample of cervical tissue will be taken for a Pap smear test, a process that is described in more detail in Chapter 6. Lastly, the physician will **palpate**, or feel for any signs of abnormal tissue growth. In this chapter, we discuss the basic structure and function of the female reproductive system. The goal is to demystify the female anatomy by clarifying the location and role of the various parts.

THE FEMALE REPRODUCTIVE SYSTEM

First consider the human body as a whole, and then think of the many body systems that keep it running. The respiratory system, the cardiovascular system, and the digestive system are all essential to the functioning of the human body because they provide it with necessary oxygen and nutrients to nourish and sustain the tissues and cells. In contrast, the reproductive system is actually nonessential. This means that the reproductive system is not required for the individual to survive. The sole function of the female reproductive system is to

produce offspring, ensuring the continued existence of the human race. For this reason, when part of the female reproductive system becomes diseased, surgical removal is frequently one of the first options discussed. In fact, the removal of the uterus, called a **hysterectomy**, is one of the most common surgical procedures performed in the United States today, second only to caesarean delivery. More than 700,000 hysterectomies were performed on American women in the year 2004. Although it can be devastating to lose the anatomical structures associated with the ability to reproduce, many women would still choose to have a hysterectomy if faced with a life-threatening disease of the reproductive tract.

Human reproduction requires the coordinated action of the principal structures of the female reproductive system, which are shown in Figure 2.1. Two **ovaries** contain **ova** (or eggs), which are the female reproductive cells. These eggs are also known as **gametes**, and reproduction occurs only when a male gamete (a sperm) fertilizes an egg. During **ovulation**, the female gametes leave the ovary and travel through the **fallopian tubes**, eventually reaching the **uterus**. The egg is generally fertilized by a sperm inside the fallopian tubes, and then the fertilized egg travels to the uterus and becomes embedded in the uterine wall. The uterus is a small, hollow, pear-shaped organ, and this is where the fetus develops throughout pregnancy. The uterus is lined with a layer called the **endometrium**, which is the part of the uterus where the fertilized egg first implants. The tall cells of the endometrium are richly supplied with blood vessels that provide for the **placenta** and pregnancy. If a woman does not become pregnant, the cells in the endometrial lining are shed during her menstrual period. The lowest portion of the uterus is the cervix, which connects the uterus to the vagina. The **vagina** is a muscular tube that opens to the external environment. During sexual intercourse, the male penis

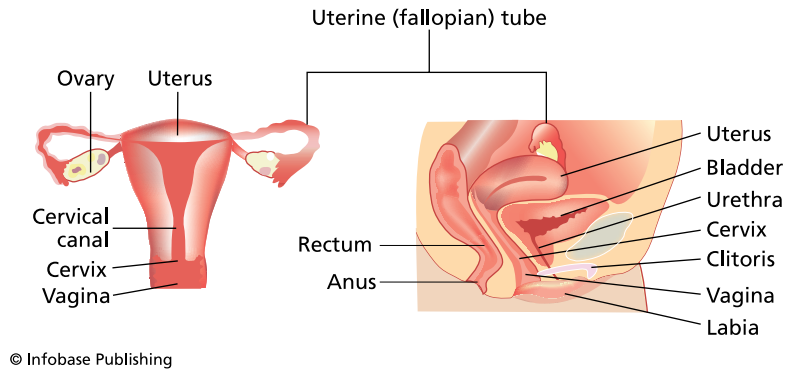


Figure 2.1 A front view of the organs of the female reproductive system (left). Side view of the position in the body (right).

enters the vagina. In order for fertilization to occur, the sperm must travel through the cervix and the uterus to reach an egg.

The exterior structures of the female anatomy are collectively known as the **vulva**. The vulva includes the vaginal opening, which is located between the urethral opening (urinary tract) and the anus. In children and young women, the vaginal opening is covered by a thin membrane called the **hymen**. The hymen can be disrupted in several ways, but tearing occurs during the first instance of sexual intercourse and is accompanied by some bleeding, which is normal. On either side of the vaginal and urethral openings are folds of skin known as the **labia minora** and the **labia majora**. The labia minora are smaller and are located closer to the vaginal opening, while the labia majora are larger and are found just outside of the labia minora. The **clitoris** is a small structure composed of a tissue similar to that of the penis. It is located at the front of the folds of the labia minora, and it can become swollen or erect during sexual arousal.

STRUCTURE OF THE CERVIX

The word *cervix* comes from the Latin word for "neck," and the cervix itself is a long, cylinder-shaped passageway. A gynecologist may view the opening of the cervix during a regular exam with the aid of a **speculum**, a device that opens the vagina slightly wider than usual.

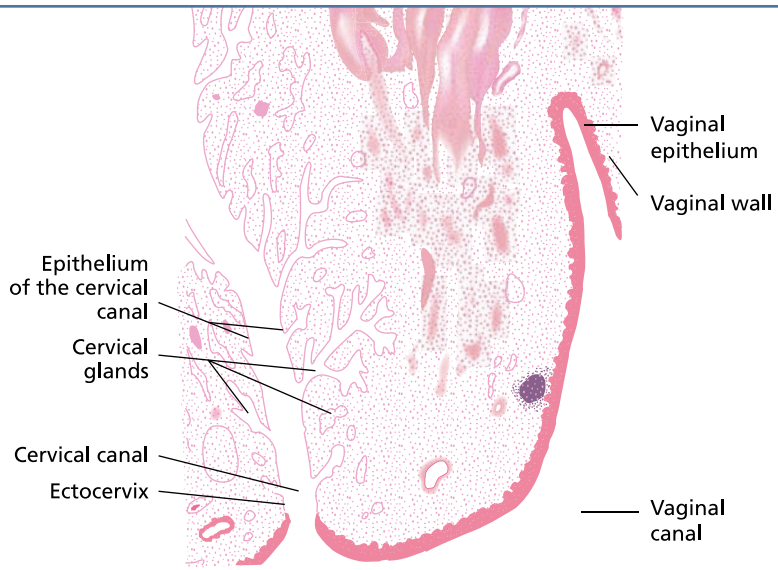
The cervix is much more than just a connector between the uterus and the vagina. If the entire cervix were taken and sliced in half lengthwise (this is known as a longitudinal tissue section), four defined regions would be seen: the ectocervix, the external os, the endocervical canal, and the internal os (Figure 2.2). *Os* is the Latin term for "mouth" or "orifice," and since the cervix is a channel, there are openings at each end. In a woman who has not had children, the cervix channel is often fairly narrow, with a small gap that allows for menstrual flow. The **ectocervix** (or exocervix, as it is sometimes called) is the section of tissue that protrudes

FEMALE REPRODUCTIVE CANCERS

Every tissue in the female reproductive tract has the potential to become malignant. The most commonly diagnosed gynecological cancers in the United States are listed below. The list is in order of the frequency of new cases reported in 2005, starting with the most commonly diagnosed.

Uterine/endometrial cancer	40,880
Ovarian cancer	22,220
Cervical cancer	10,370
Vulva	3,870
Vagina and other sites*	2,140

* Includes cancer of the fallopian tubes and a rare condition called gestational trophoblastic disease, which involves abnormal growth of cells in the tissue that surrounds the embryo immediately after conception.



Source: From Eroschenko, V. P. diFiore's Atlas of Histology with Functional Correlations, 10th ed.

Figure 2.2 **Longitudinal section showing the cervix and cervical canal.**

into the vagina. This region is on average about 3 centimeters (1.2 in) long and 2.5 centimeters (0.9 in) wide. The **external os** is the opening of the ectocervix into the vagina. The size and shape of the external os vary widely, depending on the age of the woman and her hormonal state (for example prepuberty, adolescence, or menopause). Another factor that affects os size is whether a woman has given birth, and whether the delivery took place through the vagina or by cesarean section. The **endocervical canal** is the passageway between the external os and the uterus. The length and width of this structure is highly variable from woman to woman. Finally, the **internal os** is the opening of the cervix inside the uterine cavity.

CELLS OF THE CERVIX

The cervix and the other structures of the female reproductive tract are **organs**. Each organ is made up of specific types of **tissues**, which are composed of groupings of individual **cells**. Cancer is a disease that begins at the cellular level—the uncontrolled growth of just a single cell is what generally leads to the formation of a tumor or cancerous tissue. This notion was described by Dr. Robert Weinberg in his

OUCH! ITCHING AND BURNING . . . WHAT DOES IT MEAN?

Periodically, many women may experience itching or burning sensations in the genital region. These symptoms may accompany urination or they may be more generalized in the area of the vagina, causing pain during intercourse. When the pain is associated with urination, this is commonly a sign of a urinary tract infection (UTI). Over 40 percent of women will experience at least one UTI in their lifetime, and some will experience recurrent infections. UTIs are most commonly caused by infection with *Escherichia coli* (*E. coli*) bacteria and can be easily treated with antibiotics.

When the itching or burning is localized in the vagina, it may also be accompanied by a white, yellow, or greenish discharge, as well as a foul or fishy odor. These symptoms are more likely signs of vaginitis. Vaginitis is an inflammation of the vagina, which generally occurs as a result of infection with bacteria, fungi, or parasites. *Candida albicans* (*C. albicans*) is a yeast that is part of the normal *biota*, the collection of harmless microorganisms found in the vagina, but occasionally conditions such as poor diet, stress, illness, or pregnancy can alter the environment of the vagina, making it

best-selling 1999 book *One Renegade Cell*. Since cervical cancer can develop from a single abnormal cell, it is important to examine the types of cells from which cancer can develop.

Cells that cover a body surface are known as **epithelial cells**. The surface of the cervix contains two distinct types of cells: columnar epithelial cells and squamous epithelial cells. Either type of cell can be infected with HPV and give rise to

more favorable for increased *C. albicans* growth. This can result in candidiasis, which is commonly referred to as a yeast infection, and it can be controlled with a topical antifungal medication.

Vaginitis can also be caused by bacteria. This is often associated with sexual intercourse; the penis may not be clean or it can push bacteria from the anus region into the vagina. Having vaginal intercourse immediately following anal intercourse can also cause bacterial vaginitis, so it is essential to wash the genitals thoroughly after engaging in anal sex. Another common cause of vaginitis is a protozoan parasite, *Trichomonas vaginalis*, which can also infect the urethra of males and is generally transmitted by sexual intercourse.

If you experience itching, burning, or vaginal discharge, it is important to contact your doctor right away. Sometimes, these symptoms may be associated with other conditions, especially sexually transmitted diseases such as chlamydia, gonorrhea, or herpes simplex virus. A physician can take a swab of the area to determine the specific cause and prescribe the appropriate medication.

cervical cancer, although the vast majority of cervical cancers are of squamous cell origin.

The columnar epithelial cells are tall and packed single file next to one another, whereas the squamous cells are flattened, elongated, and piled on top of one another. The endocervical canal is lined with the tall, mucus-secreting columnar epithelial cells, and they meet up with the flattened squamous cells at a location known as the **transformation zone**. The transformation zone, or transition zone, as it is sometimes called, is exactly that—an abrupt transition from one cell type to another. This is also the region where most HPV infections tend to occur, and the region from which the doctor will try to obtain a sample of cells for the Pap smear test.

As a woman gets older, the size and shape of the transformation zone may change. Before puberty, the columnar epithelial cells extend all the way past the cervical canal and out onto the ectocervix in the vagina. As the body matures and prepares for sexual activity, a single cell layer is not enough to protect the cervical tissue, so the squamous cell layers extend farther while the columnar epithelium retreats farther into the endocervical canal. This change occurs gradually as the woman develops, and the transformation zone may get smaller over time.

The columnar epithelial cell layer is continuous with the surface of the uterus, which is also known as the endometrium. However, the cervical epithelium differs from the uterine tissue in two ways. First, the endometrial lining is sloughed off during menstruation each month, whereas the lining of the cervix itself undergoes little change throughout the menstrual cycle. The second difference is that the lining of the cervix contains large, highly branched cervical glands. These glands produce a substance known as **cervical mucus** (Figure 2.3). Most of the time, the cervical mucus produced is quite thick and viscous, forming a plug that blocks the external os. Cervical mucus plays an essential role in pro-

tecting the uterus (and a developing fetus) from infection. The vagina is a warm, moist environment that is readily colonized by bacteria and fungi, and it is constantly exposed to the outside world through the action of wiping after urination, insertion of tampons, and sexual intercourse. A thick cervical mucus plug can prevent the passage of sperm and stop harmful microorganisms from the vagina from entering the endocervical canal.

The mucus secretions by the cervical glands do, however, go through changes during the menstrual cycle. Under the influence of ovarian hormones, the amount and consistency of cervical mucus can change. During the middle of the menstrual cycle, near the time of ovulation, cervical mucus secretions increase in volume, but the mucus itself becomes thinner and more watery. This type of mucus secretion allows sperm to pass through the endocervical canal and into the uterus. This thinner mucus, which is often described as having the consistency of a raw egg white, is produced only a short period of time prior to ovulation. After the egg has been released, the mucus secretions will become thick again to cover the os and protect the uterus.

FUNCTIONS OF THE CERVIX

The cervix is not just a passive thoroughfare; it actively performs several important functions. During menstruation, the cervix can stretch slightly to allow the shedding endometrial lining to be released. This stretching of the cervix is believed to be part of the menstrual cramping that some women experience. Also, when sexual activity results in orgasm, the walls of the endocervical canal convulse and the external os dilates, or opens more. This is thought to draw additional semen into the uterus, increasing the likelihood of fertilization. Finally, the cervix can dilate up to 10 centimeters (3.9 in) during childbirth to allow the passage of the child. During pregnancy, however, the narrow opening of the

Figure 2.3 Colored scanning electron micrograph of cervical secretory cells in the epithelium. The red and yellow particles are mucus secretions. © Prof. P. Motta/University "La Sapienza"/ Photo Researchers, Inc.

cervix helps hold the fetus in the uterus. If the cervix becomes too weak, a condition known as **cervical incompetence** may develop. When this occurs, the **amniotic sac** may enter the vagina and rupture prematurely. There are generally no early warning signs, and this usually occurs before the child has developed enough to survive outside the womb. It is estimated that around 20 percent of miscarriages that occur between 16 and 24 weeks of pregnancy may be due to cervical incompetence. For women who have experienced the loss of a pregnancy due to cervical incompetence, doctors can stabilize the cervix with a small stitch early in the next pregnancy.

The more women know about their own anatomy, including the cervix, the better they can take care of themselves. Far from being just a passageway, the cervix is an essential part of the female anatomy and performs many important functions. Unfortunately, the cervix also contains cells that are readily

PELVIC INFLAMMATORY DISEASE (PID)

PID is a chronic infection of the female reproductive tract, generally caused by an untreated sexually transmitted disease, such as chlamydia or gonorrhea. PID usually occurs in sexually active women between the ages of 15 and 25. Symptoms vary for each woman, but most women experience a "stomachache," or dull pain and tenderness in the abdomen. There may also be a yellow or green vaginal discharge. The consequences of ignoring the signs of a sexually transmitted disease can include chronic pelvic pain, ectopic pregnancy, and infertility. PID is one of the leading causes of infertility today. Infertility is defined as the inability to bear children, and a woman may be diagnosed as infertile if she has not become pregnant after more than one year of trying to conceive without using any form of birth control (women over 35 may be considered infertile if they have been trying for over six months without a pregnancy). Some women who have had PID will develop scarred fallopian tubes, which can hinder the passage of the eggs and prevent fertilization. For these women, the only way to become pregnant is through in vitro fertilization, a process in which the egg and sperm are combined in a culture dish in a laboratory, and then the fertilized egg is implanted into the woman's uterus.

infected by the sexually transmitted **pathogen** HPV. Because a woman cannot properly inspect her own cervix, it is essential to have regular gynecological exams to ensure that this organ is free of disease.

3

Epidemiology of Cervical Cancer

Most people associate epidemiology with outbreaks of deadly infectious diseases like Ebola virus or severe acute respiratory syndrome (SARS). In fact, **epidemiology** is the study of when and where diseases of any kind occur in the population. Epidemiologists track the number of cases of a disease and try to identify specific factors that contribute to its development so that they understand how the disease can be avoided. One of the first epidemiological studies involving cancer was done by Percival Pott in 1775. Pott was an English surgeon who noted that cancer of the scrotum was common among young boys who worked as chimney sweeps. The chimney sweep's job was not a pleasant one, and the smallest boys were needed to fit into the tiny spaces and clean the hot, sooty chimneys. Pott suspected that the coal soot became trapped in the folds of the scrotum, causing cancer, and he published an article describing his observations and theories. Pott's work drew attention to the plight of chimney sweeps and led to new laws that required bathing and the use of protective clothing, which virtually eliminated scrotal cancer as an occupational hazard for young chimney sweeps.

Today we have learned much more about the epidemiology and risk factors associated with cancer, yet more than 500,000 Americans still die from cancer each year. A **risk factor** is something that increases a person's chances of developing a particular disease or condition. For example, smoking is a major risk factor for lung cancer, and 87 percent of lung cancer deaths can be attributed to tobacco use. Another example of a risk factor is excessive exposure to sunlight, which has a strong link with skin

cancer. People who don't use sunscreen or clothing and hats to protect themselves from the sun's harmful ultraviolet (UV) rays have a higher chance of developing melanoma and other forms of skin cancer.

What are the risk factors for cervical cancer? The main risk factor is infection with human papillomavirus (HPV). HPV is a virus that infects epithelial cells in many parts of the body. There are believed to be more than 100 different strains of this virus, and most of these seem to prefer to infect specific regions of the body. One of the most frequent results of HPV infection is benign warts, which are also known as **papillomas**. These warts can be flat or raised lesions on the surface of the skin. Some of the most common strains of HPV cause palmar warts on the hands and plantar warts on the

MAJOR RISK FACTORS FOR CERVICAL CANCER

- **Infection with human papillomavirus (HPV)**
- **Smoking**
- **Infection with human immunodeficiency virus (HIV) and/or any type of immune suppression**
- **Extended use of oral contraceptives**
- **Giving birth to many children**
- **A diet low in fruits and vegetables**
- **Low socioeconomic status**
- **Age**
- **Diethylstilbestrol (DES), a hormone drug, administered to the woman's mother**
- **Family history of cervical cancer**

soles of the feet. A few strains of HPV can cause **genital warts**, which are raised bumps that may be found on the vulva or vagina in women and on the shaft of the penis or around the anus in men (Figure 3.1). Genital warts are known to the medical community as **condyloma accuminatum**, and they are most often caused by strains such as HPV 6 and HPV 11.

Although the vast majority of HPV strains do not seem to be related to cancer of the cervix, there are a few high-risk strains that are common in cervical cancer patients. About 70 percent of all cervical cancers are associated with infection with either HPV 16 or HPV 18. These two strains, along with a few others, are said to be oncogenic, meaning that they can cause malignant lesions, or cancer. HPV itself is described in greater detail in Chapter 4, and the process of malignant transformation by HPV is described in Chapter 5. In this chapter the emphasis is on how people get infected with HPV and the other risk factors that lead to cervical cancer.

TRANSMISSION OF HPV

HPV infects mainly skin cells, or epithelial cells. Humans have two types of skin—cutaneous and mucosal. **Cutaneous** surfaces are the usual skin covering that is found on the arms, legs, and trunk. This type of skin has a thick protective layer of a protein called keratin that makes it relatively smooth and tough. **Mucosal** skin surfaces, on the other hand, are the moist surfaces that line the mouth, vagina, and anus. These surfaces are much thinner and are more easily damaged. HPVs can infect both cutaneous and mucosal skin surfaces. In each case, the virus is transmitted from person to person by direct contact. That means that one person's skin cells come in contact with another person's skin cells that are producing the virus. Despite the prevalence of the popular myth, a person can't get warts from touching toads, because HPVs are species-specific. This means that human viruses

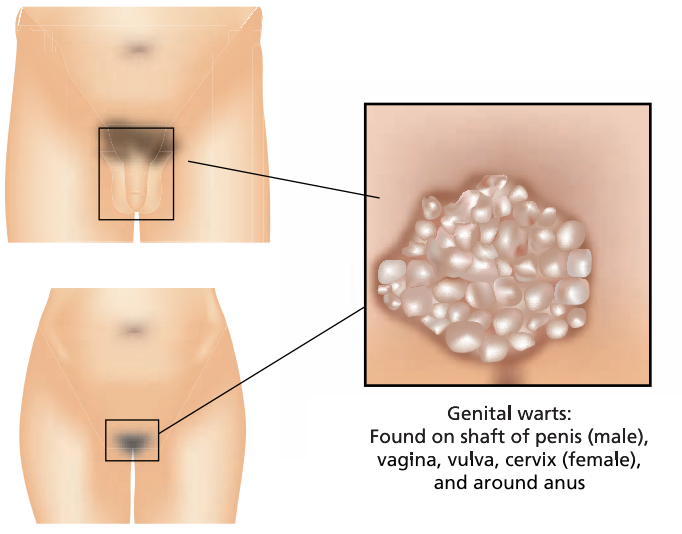


Figure 3.1 Appearance of genital warts that may be found on shaft of penis (male; top), and on vagina, vulva, cervix (female; bottom) and around anus in both sexes.

only infect humans, and toad viruses infect only toads. The most common way people get warts on their hands is by touching other people's warts.

The HPV strains that cause genital warts and cervical cancer infect the cells at the mucosal surfaces of the genital tract. The virus is still transmitted by direct contact, but since these strains live only in the genital skin, direct genital-to-genital skin contact is required. In other words, these strains are sexually transmitted.

HPV is one of the most common sexually transmitted diseases (STDs) today, with more than 5 million new cases diagnosed each year. STDs are sometimes also called venereal diseases (named after Venus, the Roman goddess of love), and they are infectious diseases that are spread through vaginal intercourse, anal intercourse, and oral-genital or oral-anal contact. Besides

HPV, the most common STDs include chlamydia, gonorrhea, syphilis, genital warts, and genital herpes (Table 3-1). Human immunodeficiency virus (HIV), the virus that causes AIDS, may also be classified as an STD, since it is transmitted through intimate sexual contact. There are about 15 million new STD cases each year, and half of all young adults will contract at least one STD before reaching the age of 25.

Any woman who is sexually active is at risk for HPV infection. The more sexual partners a woman has, the greater her chances of becoming infected and, thus, developing cervical cancer. Women who started to have intercourse at an early age appear to be at higher risk of contracting HPV. There may also be an increased risk of HPV infection by having intercourse with men who are not circumcised. Many women have never even heard of HPV, yet some studies suggest that the HPV infection rate among college-age women may be as high as 50–60 percent. This means that at least one out of every two college-age women is infected.

HPV infections that cause genital warts occur most frequently in the 15- to 30-year-old age group, with males and females affected equally. The absence of visible warts does not mean there is no risk, because HPV can still be found in the skin even when there are no warts present. Unfortunately, many people can be infected with HPV without showing any symptoms, which means that you can get it or pass it on to others without knowing it. The most oncogenic strains, HPV 16 and 18, almost never cause genital warts or any obvious symptoms, so what you can't see *can* hurt you! Experts estimate that 75 percent of sexually active adults have or will have transmitted some strain of HPV at some time in their lives.

Although condoms are always important for preventing unwanted pregnancies, HIV, and other sexually transmitted diseases, they are not 100 percent effective in protecting against HPV infection. Condoms will greatly reduce the chances of transmission, but there is still a possibility of infection even if

Table 3.1 Sexually Transmitted Diseases

Disease	Infectious agent	Incidence*	Curable	Treatment
Condyloma acuminata (genital warts)	Human papillomavirus	5.5 million	Sometimes	Cryotherapy
Chlamydia	*Chlamydia trachomatis* bacteria	3 million	Yes	Doxycycline, erythromycin
Genital herpes	Herpes simplex virus	1 million	No	Acyclovir, valcyclovir
Gonorrhea	*Neisseria gonorrhoeae* bacteria	650,000	Yes	Ciprofloxacin
AIDS	Human immodeficiency virus	40,000	No	Retrovir, indinavir (17 drugs available)
Syphilis	*Treponema pallidum* bacteria	34,000	Yes	Penicillin

*Incidence refers to the number of new cases reported per year in the United States. In each state, local health department officials require that physicians report certain diseases for public health records and epidemiological tracking purposes. Chlamydia, gonorrhea, syphilis, and AIDS are all reportable diseases by law. In contrast, diagnoses of genital herpes and genital warts are not required to be reported to public health officials.

they are used. This is because the virus may be present on areas of genital or anal skin that are not covered by the condom. Direct skin-to-skin contact with these areas can lead to infection.

Some people worry that they could get genital warts or cervical cancer if they have a wart on their hand and scratch or touch their genitals, but this is not true. Recall that most strains

of HPV prefer specific sites on the body, and strains that cause common warts on the hands never infect the genitals. There have been a few documented cases where transmission of HPV occurred by sharing a damp towel or through contact with a contaminated toilet seat, but such cases are extremely rare.

It is important to be aware that a person can be infected with more than one strain of HPV at the same time. In other words, a person who has genital warts, usually caused by HPV 6 or 11, is not necessarily free of the more oncogenic strains HPV 16 or 18. Infection with multiple strains can occur at once. In one Brazilian study, nearly 80 percent of HPV-positive women were found to be infected with more than one strain of the virus; the average was three but some women were infected with as many as ten different types of HPV.

Having a risk factor does not mean that an individual will develop HPV; it only means that he or she has an increased chance of contracting it. Although HPV infection is confirmed in almost every case of cervical cancer, not every woman who is infected with HPV will develop cervical cancer. In many of the women who become infected with HPV, there will be no long-term impact, and in many cases, the virus infection will be successfully cleared by the immune system. In cases where HPV infection does cause cells of the cervix to become malignant, other risk factors are likely to play a role in the development of the disease.

SMOKING

Smoking is considered an important risk factor for cervical cancer. Smoking is known to impair the immune system, making it less able to fight HPV infection. In addition, smoking allows nicotine to be absorbed through the lungs and transported throughout the body by the bloodstream. Nicotine can be broken down into cancer-causing chemicals, and some of these by-products have been found in the cervical mucus in women who smoke. The risk appears to increase with the

number of cigarettes smoked per day and the number of years a woman has smoked. For women who have smoked, the risk of developing cervical dysplasia (abnormal precancerous cells in the cervix) is three to four times greater than that for women who have never smoked. The risk of actually developing cervical cancer is about twice as high for smokers as for nonsmokers.

IMMUNE SUPPRESSION

Another risk factor for developing cervical cancer is having a weakened immune system due to infection with HIV or from taking immune-suppressing drugs after an organ transplant. When the immune system is not functioning normally, the body is susceptible to a host of infections, and may be more likely to become infected with HPV. In addition, in someone with a weakened immune system, cervical dysplasia may develop into an invasive cancer faster than it normally would in a woman whose immune system is not weakened.

LONG-TERM USE OF ORAL CONTRACEPTIVES

Some research has shown that women who have been using oral contraceptives (birth control pills) for extended periods of time are at greater risk of developing cervical cancer. The chance of developing cervical cancer was higher for women who had been taking the pill for more than five years compared to those who had not, and the risk may be as much as four times greater for women who have been using the pill for longer than ten years. A direct link between the pill and cervical cancer is difficult to prove, however, because the use of oral contraceptives may be more common in women who begin having intercourse at an early age or have multiple sexual partners, two major risk factors for HPV infection. Still, the labels on many oral contraceptives warn of the slightly increased risk of cervical cancer and advise women who use them to have yearly gynecological exams with Pap tests.

HAVING MANY CHILDREN

Women who have had many children tend to have a higher chance of developing cervical cancer. The specific reasons for this are not clear, although it may be related to the fact that during pregnancy the mother's immune system is suppressed and significant changes in hormone levels occur. Although these changes happen during the nine months of pregnancy, undergoing these changes many times, as occurs with multiple pregnancies, may make the body more susceptible to HPV infection or to a rapid progression of precancerous cells to malignant cancer. One study showed that Mexican women who had 7–9 children were 2.6 times more likely to develop cervical cancer than women who had 1–3 children. The study suggested that limiting the size of families in developing nations might help reduce the incidence of cervical cancer.

POOR NUTRITION AND/OR OBESITY

Diet and exercise are essential components of a healthy life. Studies show that cancer rates in general are lower among people who eat diets that are high in fruits and vegetables, while women who have diets low in fruits and vegetables have an increased risk of cervical cancer. Although specific cancer-fighting nutrients have not been positively identified, it is believed that vitamins—especially vitamins A, C, and E—can aid in the body's natural defenses against cancer and virus infection. Regular physical activity is also important for maintaining healthy bones, muscles, and joints. Physical exercise substantially reduces the risk of heart disease, stroke, and cancer. Exercise also helps control weight, and there is a strong connection between obesity and cancer. In one study, the cancer death rate was much higher among patients with a high **body mass index (BMI)** than patients with a BMI in the normal range. Specifically, the mortality rates for women with cancer of the breast, uterus, cervix, and ovary were significantly higher among those with higher BMI values.

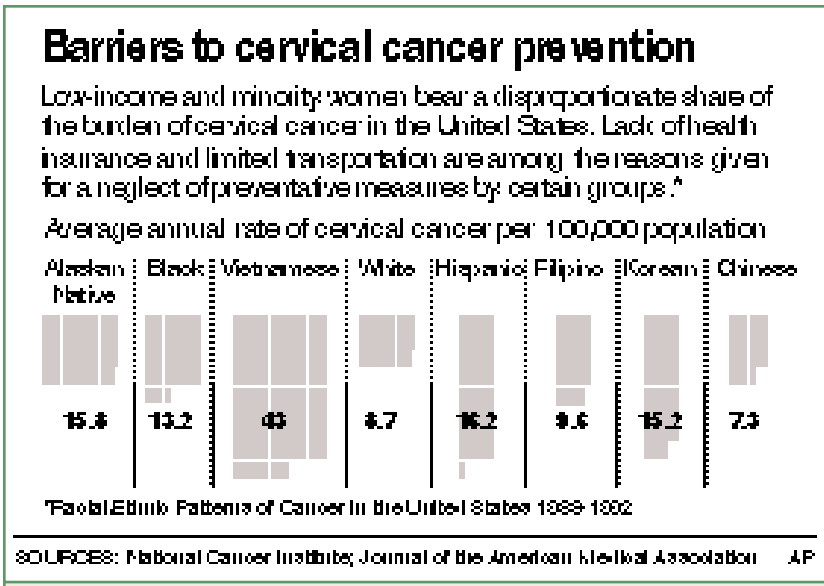


Figure 3.2 ©AP/Wide World Photos.

LOW SOCIOECONOMIC STATUS

One very important risk factor for cervical cancer is low socioeconomic status (Figure 3.2). Regular preventive screening tests such as the Pap smear are extremely effective in detecting the early signs of cervical cancer. The number of yearly cases of cervical cancer has decreased by nearly 75 percent in the past 30 years since the Pap smear technique has come into widespread use. Women who have lower incomes or who come from economically disadvantaged backgrounds tend to have limited access to medical care. This means that many of these women do not have the benefit of regular preventive screening tests. Unfortunately, there are generally no outward signs or symptoms of cervical cancer until the more advanced stages, when cancer cells have begun to invade surrounding tissue. This invasion can cause irregular or abnormal bleeding from the vagina, which is the most frequent symptom that women

notice. This means that poor women are more likely to progress to an advanced and potentially lethal stage before they even realize that there is a problem.

In the United States, about 10,000–13,000 women are diagnosed with cervical cancer each year, and about 3,700 die as a result of it. However, cervical cancer deaths vary widely by race and ethnicity. The mortality rate for African Americans is more than twice the rate for Caucasians. Hispanics and American Indians also have death rates from cervical cancer that are well above the average. The significantly increased death rates among these groups are believed to be related to limited access to adequate health care and a lack of preventive screening. Although the difference in cancer death rates among races in the United States is disturbing, it is even more shocking to learn that the death rate from cervical cancer in developing nations is nearly 60 times higher than that of the United States. More than 500,000 women are diagnosed with cervical cancer worldwide each year, and more than half of these women will die. Worldwide, the highest rates of cervical cancer occur in sub-Saharan Africa and South America (Figure 3.3), and are mainly due to lack of preventive screening tests.

OTHER FACTORS

Age may also play a role in determining a person's risk of developing cervical cancer. Although cervical cancer can be diagnosed in women in their early twenties and even in their teens, the risk of developing cervical cancer begins to increase after the age of 25. Once a woman reaches 40, however, the risk of developing cervical cancer stays about the same.

Women whose mothers were given the drug diethylstilbestrol (DES) are at a slightly increased risk of developing cervical cancer. Between the years 1940 and 1970, doctors prescribed DES to pregnant women who were thought to be at an increased risk for miscarriage. An unusual form of cervical and vaginal cancer has been found in about one out of

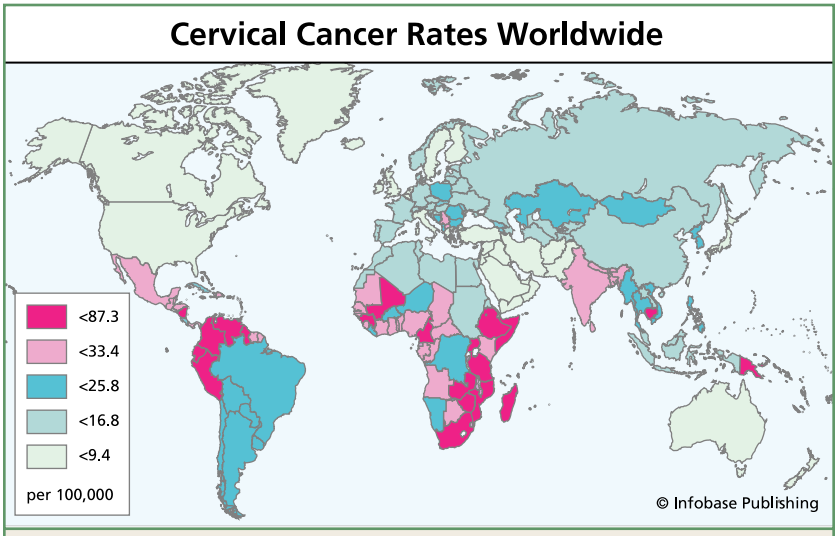


Figure 3.3 Geographic distribution of cervical cancer worldwide.

COUNTRIES WITH THE HIGHEST CERVICAL CANCER DEATH RATES IN 2002

1. Zimbabwe
2. Uganda
3. Mali
4. South African Republic
5. Colombia
6. Venezuela
7. Mexico
8. Romania
9. Chile
10. Mauritius

AN UNWELCOME INHERITANCE

Anita Mui, also known as the Madonna of Hong Kong, was a flamboyant and widely popular entertainer among Chinese communities worldwide. She skyrocketed to fame after winning a singing contest in Hong Kong in 1982, and released more than 40 albums during her career. In addition to singing talent, Mui excelled in acting and performed in dozens of films, frequently costarring with world-renowned actors such as Jackie Chan and Chow Yun-Fat. Mui won Taiwan's Golden Horse Award for best actress in 1987 for her role as a tormented ghost in the movie *Rouge*. In September 2003, Mui announced that she had been diagnosed with cervical cancer, and she passed away just three months later, on December 30, 2003. Hereditary factors may have been involved in the progression of Mui's cancer. Mui's sister, Ann, who was also a singer and actress (best known for her supporting roles in many movies, including Jackie Chan's *Police Story 2*), died of cervical cancer in 2000.

Figure 3.4 Hong Kong canto-pop diva Anita Mui performs at one of her last concerts on November 6, 2003. ©Reuters/Corbis

CANCER AND PUBLIC HEALTH

President Richard Nixon declared war on cancer in 1972, and the U.S. government has made a significant investment in oncology research during the past 30 years. Unfortunately, the overall death rate from all types of cancer combined in the United States has not changed much since 1972, although improvements have been made in some cancers. Cervical cancer is one of the most dramatic examples in which the death rate has decreased, mainly due to the availability of a reliable and inexpensive preventive screening test.

Even though the death rates for some types of cancer have been reduced, public health organizations are always trying to improve the health of the American people. The director of the National Cancer Institute (NCI) recently announced an initiative called NCI Challenge Goal 2015. The aim of the program is to eliminate suffering and death due to cancer by the year 2015. This does not mean that by 2015 cancer will no longer exist. Instead, it means that a greater effort will be made to eliminate many preventable cancers and to control the others, so that people can live with—and not die from—cancer.

The Centers for Disease Control and Prevention (CDC) has instituted a Healthy People 2010 Program. Its major goal is to reduce the overall cancer death rate. Other specific goals of the program include reducing the death rate from cervical cancer to fewer than 2 per 100,000 women, reducing the rate of HPV infection, and increasing to 97 percent the number of women aged 18 or older who have ever had a Pap smear test.

every 1,000 women whose mothers took DES when pregnant with them.

Family history may also be a risk factor. Women whose mothers or other family members have had cervical cancer are more likely to develop the disease themselves. Although no specific genes have yet been linked to cervical cancer, researchers believe that there may be hereditary factors that make some women more susceptible than others to HPV infection.

SUMMARY

Cervical cancer is a leading killer of women worldwide, with more than half a million cases diagnosed and more than 250,000 deaths each year. Despite advances in the use of preventive screening tests in the United States, cervical cancer is still diagnosed in more than 10,000 American women each year, and about one-third of these women will die from the disease. HPV infection and lack of regular Pap smear tests are the strongest risk factors associated with cervical cancer development, but smoking, immune suppression, multiple births, long-term use of oral contraceptives, and other factors may also influence the development of cervical cancer.

4

Public Enemy Number 1: Human Papillomavirus

The number-one risk factor for developing cervical cancer is infection with HPV. There are more than 100 different strains of this virus that infect humans. Although HPV infection is strongly linked to cervical cancer, many of its strains are relatively harmless. It is only a small group of HPV strains that can pose a major threat to female health.

WHAT IS A VIRUS?

The ancient Chinese philosopher and warrior Sun Tzu taught his men that in order to win a battle, one must know the enemy. When it comes to cervical cancer, the enemy is a virus. A **virus** is a nonliving particle that needs a host cell to carry out the basic functions of life. These functions include metabolism, growth, and reproduction. Cells contain specialized machinery such as enzymes and protein complexes that act like little factories for breaking down nutrients and producing cellular materials that allow the cell to grow and divide. A virus lacks most of these features, but it is designed to invade a cell and take over, using the cell's own machinery to produce more viruses. In fact, HPV is an incredibly small particle. It consists only of protein and genetic material (DNA, or deoxyribonucleic acid, in the case of HPV, although some viruses have RNA, or ribonucleic acid, as their genetic material). The HPV proteins form a coat that is on the outside and serves as the "suitcase" to protect and transport the genetic information needed to make more virus particles.

Because the virus is so small, it cannot be seen with the naked eye, or even with a regular light microscope. A speck of dust is about 10,000 times

larger than an HPV particle. Viruses, including HPV, can only be seen using a specialized device called the electron microscope. Instead of using light to illuminate the virus, an electron microscope uses a beam of electrons that bounce off the specimen, creating an image on a display screen. When viewed this way, the intricate shape of the HPV particle is truly amazing. The protein portion of the virus, which is known as the **capsid**, forms a perfectly symmetrical icosahedron. An **icosahedron** is a geometric figure with 20 triangular faces. This shape is actually common among viruses, because it is a stable structure that forms readily in nature, making it a good way to protect the viral DNA. Because viruses are so small, they have to travel light. Basically, they have only enough room inside the capsid for genetic material that directs production of the essentials, and they rely on the host cell for everything else. Since all the

DOES HPV CAUSE CANCER IN MEN?

Many strains of HPV infect men and women equally. Both sexes can develop palmar warts or plantar warts, and genital warts are known to occur with about the same frequency in both males and females. Men don't have a cervix, but can HPV infection still cause cancer in men? The answer is most definitely yes. Male cancers of the penis and anus are strongly associated with HPV infection. If small abrasions occur on the penis or around the anus during sexual intercourse, the virus may enter and infect the basal cell layers. Fortunately, these forms of cancer are relatively rare. There were fewer than 4,000 cases of anal cancer diagnosed in the United States in 2004 (more than half of these were in women) and fewer than 1,400 new cases of penile cancer. Penile cancer accounts for only 0.2 percent of cancers in men in North America and Europe, although in some parts of Africa and South America the rates are significantly higher. When diagnosed at early stages, both penile and anal cancers are highly curable.

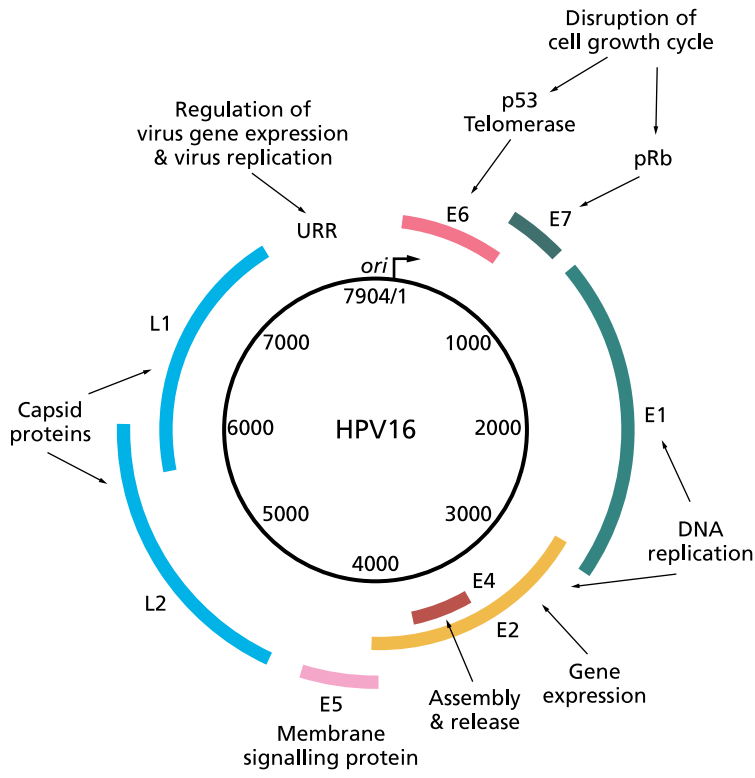
capsid proteins have to be encoded by the viral DNA, it is most efficient to have just one gene that encodes for a capsid protein, and then have the cell make enough copies of it to assemble new virus particles.

THE HPV PARTICLE

The HPV virus is an intricate little particle. It is shaped like an icosahedron, but on each of the triangular faces there are small structures that extend outward. These protrusions are called **capsomers**, or subunits of the capsid. The virus has a total of 72 capsomers, each with pentagonal, or five-sided symmetry. HPV actually has two capsid proteins—one major capsid protein encoded by the L1 gene and one minor capsid protein encoded by the L2 gene. Most of the capsid shell is formed by the L1 protein. In fact, even when there are no other components of the virus present, the L1 protein can assemble into capsid structures known as virus-like particles (VLPs).

An infectious HPV particle is made of the capsid plus the viral genome. The **genome** is all of the hereditary information for an organism that is encoded in its DNA. The DNA in the genome is organized into **genes**, and these genes contain all the information needed to reproduce. The DNA molecule is made up of **nucleotide bases** that are paired to form a stable double helix structure. The genome of HPV comprises one piece of circular DNA, as shown in Figure 4.1. Compared to the human genome, the HPV genome is extremely small. It consists of only about 8,000 base pairs and contains only 8 to 10 different genes (depending on the strain). In contrast, the human genome contains more than 3 billion base pairs and more than 30,000 different genes!

HPV genes are classified as either early (E) or late (L), depending on when they are expressed in the infection cycle. The early genes are the ones needed immediately after the virus infects a cell. The early genes E1 and E2 are absolutely essential



Source: From http://www-micro.msb.le.ac.uk/3035/Papillomaviruses.html

Figure 4.1 **A schematic diagram of the HPV genome showing the location and a brief description of each gene. This diagram represents the genome of HPV strain 16 which contains 7904 base pairs of DNA in a circular strand.**

for virus replication, so they direct production of proteins right away once the virus enters the cell. Other early genes like E6 and E7 are not necessary for virus replication, but the proteins made from them contribute to the development of cancer (see Chapter 5). The late genes, L1 and L2, are not necessary until

later in the replication cycle. These genes direct production of proteins that are used to make new capsid shells. The new capsid shells are the last step in making more virus particles that can go on to infect other nearby cells.

VIRUSES AND CANCER: ARE OTHER TYPES OF CANCER CAUSED BY VIRUSES?

In the 1950s, British physician Denis Burkitt was working in equatorial Africa. While there, he examined a five-year-old boy with tumors on the head and neck. The tumors grew rapidly, and the child died within a few weeks. As Burkitt began to see other children with the same types of tumors, he realized that this was a previously unrecognized form of cancer. He traveled to dozens of hospitals in eastern and southern Africa to find more patients and gather additional data. Because the distribution of this common tumor (now known as Burkitt's lymphoma) appeared to be influenced by climatic factors and occurred in regions where malaria was endemic, Burkitt speculated that the tumor might be caused by a virus transmitted by mosquitoes. Several years later, research scientists Tony Epstein and Yvonne Barr identified virus particles in cells from a Burkitt's lymphoma tumor biopsy. They subsequently established that this virus was a new type of herpesvirus, and that it was not transmitted by mosquitoes. Rather, like all herpesviruses, Epstein-Barr virus (EBV), as it came be known, is transmitted by direct contact, such as touching or kissing an infected person. Based on the discovery of virus particles in the tumor cells, it was then speculated that viruses that caused many other forms of cancer would soon be identified. In fact, after considerable research, viruses have been implicated in very few forms of cancer in humans. Even in those cases where there is an association between a particular virus and form of cancer, there are clearly additional factors that

VIRUS INFECTION

How does HPV actually infect a human cell? As discussed in Chapter 3, HPV is transmitted by direct skin-to-skin contact. The infection begins when the virus enters the skin. The skin is

lead to the development of the cancer, because not all individuals who have the virus go on to develop cancer. Epstein-Barr virus is an excellent example. This common herpesvirus is widespread in all parts of the world, infecting over 95 percent of adults in the general population. In most people, the infection is subclinical (lacking any obvious symptoms), although in some cases mononucleosis develops, and the patient experiences fatigue, muscle aches, and flu-like symptoms that can last for weeks or months. Development of Burkitt's lymphoma is extremely rare, and it is likely associated with virus infection along with other genetic or environmental factors. Similarly, HPV is strongly associated with cervical cancer, in that the virus can be detected in 99 percent of women who have cervical cancer. However, less than 0.2 percent of the 6.2 million annual cases of HPV infection progress to cancer.

Although there are many instances of viruses that cause cancer in animals, only a few other viruses have been linked to human cancers. For example, there is a higher incidence of liver cancer among individuals with chronic hepatitis B or hepatitis C infection. A new virus, called human herpesvirus 8, was identified from samples of lesions from AIDS patients with Kaposi's sarcoma in 1995. Finally, a virus related to HIV, called HTLV, or human T-cell lymphotrophic virus, has been associated with certain forms of adult lymphomas.

composed of several layers of epithelial cells that sit on top of a structure known as the **basement membrane.** The outermost layers of cells are called **keratinocytes**, because they contain lots of the protein keratin, which makes them durable and provides a protective coating on the surface. These keratinocytes from the surface, however, are continually dying and falling off. They are constantly being replaced by long-lived cells in the deeper layers of skin that are continuously dividing. These basal cells are essential for generating new skin. Each time these cells divide, their daughter cells are pushed up into the upper layers of the epithelium. As the cells move farther away from the basal layer and closer to the surface, they mature. As they mature, they change shape and begin to produce more keratin, eventually becoming keratinocytes. It takes about 30 days for a new cell to reach the top of the epithelium and fall off. This process continues over and over again throughout our lives.

Understanding the basic structure of the skin is important for understanding how HPV infection occurs. HPV likes to infect epithelial cells, but it specifically prefers the long-lived basal cells. In order for the virus to get to these basal cells at the bottom of the skin layer, there must be a small break or tear in the skin. During sexual intercourse, it is not uncommon for chafing or minor abrasions to occur in the genital region, especially on the thinner, less durable mucosal surfaces. These tiny breaches in the cell layers allow HPV to infect the basal cells (Figure 4.2). When many virus particles are present, infection can begin at many different sites. In the case of genital warts, each wart probably represents a site where a minor trauma occurred during intercourse, allowing HPV to gain entry and start an infection in the basal cells.

At the molecular level, the usual sequence of events in a virus infection are 1) attachment of the virus particle to the cell, 2) entry into the cell, 3) expression of viral genes, 4) replication of viral DNA, and 5) assembly and release of new infectious virus particles. For HPV, virtually nothing is known

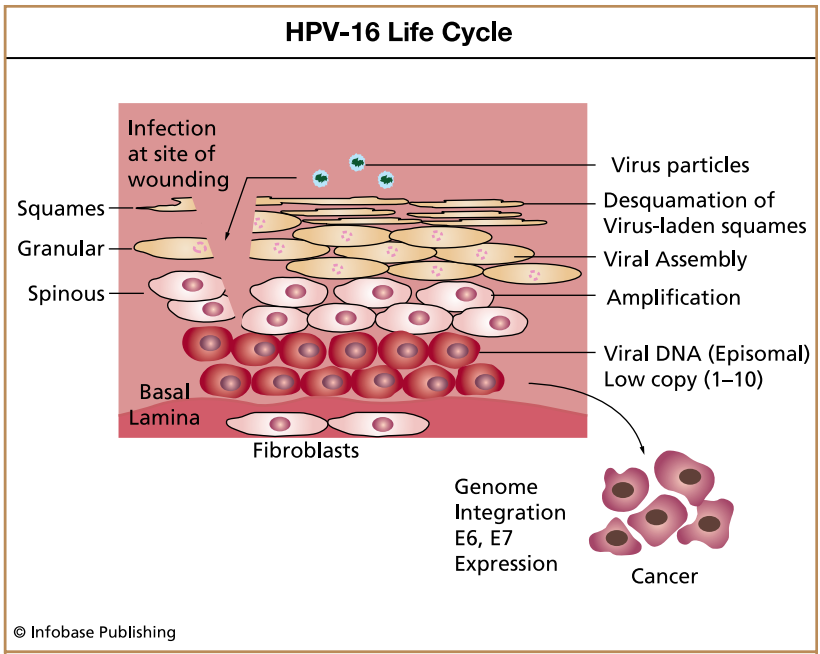


Figure 4.2 Diagram of the replication cycle of HPV. The virus accesses basal cells through breaks in the skin, and the genome is copied and amplified each time a basal cell replicates. The genome directs production of new virus particles only in the cells of the outermost skin layers, and the replicated viruses can then infect other people who come into contact with this skin.

about the initial attachment and entry steps. Viral gene expression and DNA replication have been studied, but there are differences depending on the epithelial cell's stage of maturation. Expression of the early genes and DNA replication occur in the basal cells, but the late genes are expressed only in more mature keratinocytes. Since the late genes are the viral capsid proteins, the keratinocytes are the only cells capable of producing new virus particles. Many viruses cause the infected cell to rupture when new virus particles are released, but this does not appear to happen with HPV. Little is known about the final stages of

HPV production. The life cycle of the virus is difficult for scientists to study because the virus does not grow well under laboratory conditions.

What scientists do know is that, like many viruses, HPV likes to infect cells that are actively dividing. This is important for the virus because it means that all the cellular machinery for copying DNA is already active. Also, as the infected basal cells divide, copies of the HPV genome end up in each of the daughter cells. This makes it even more difficult for the body to rid itself of the virus. There is some debate in the scientific community about whether HPV can ever truly be eradicated. Some experts believe that the immune system can fight the virus and completely eliminate it from the body, but the

Table 4.1 Sites of Infection for Specific HPV Strains

Clinical Syndrome	HPV Strain	Body Surface
Verruca plantaris (plantar warts)	1, 4	Feet
Verruca vulgaris (common wart)	2, 4, 7	Hands, arms, any body surface
Flat warts	3, 10	Hands, arms, any body surface
Juvenile laryngeal papillomata (laryngeal warts)	6, 11	Larynx
Oral papillomata	2, 6, 11, 16, 18, 57	Mouth, tongue
Heck's disease	13, 32	Mouth, tongue
Condyloma acuminata (genital warts)	6, 11	Vagina, vulva, anus (women) Penis, anus (men)
Cervical cancer	16, 18, 31, 33, 35, 52, 56, 58, 59, X	Cervix

process occurs slowly and may take months or even years. Others believe that the virus simply enters a dormant state in which it doesn't make any viral proteins or cause any obvious health problems.

The strains of HPV that cause cervical cancer infect mucosal epithelial surfaces in the genital region. Specifically, there is a type of basal cell found in the cervix that seems to be a preferred site of infection. These preferred basal cells are found in the transformation zone of the cervix. The transformation zone is the region where the endocervical columnar epithelial cells meet the exocervical squamous epithelial cells. Because oncogenic strains of HPV prefer to infect these cells, this is also where the majority of cervical cancers arise.

PAPILLOMAVIRUSES EVERYWHERE

Unfortunately, it's hard to avoid papillomaviruses because they are so widespread in nature. These viruses infect a wide variety of species, including rabbits, cows, dogs, monkeys, and humans. As early as 1907 it was recognized that warts were most likely of viral origin, a theory put forth by an Italian physician named G. Ciuffo, who developed warts after inoculating himself with material that he took from a human wart. He took the wart tissue, grinded it, and then passed it through a filter so small that the only thing that could have gone through and caused his warts was a virus. The very first papillomavirus was isolated from the warts on cottontail rabbits by American virologist Richard Shope in 1933. Despite their abundance in the environment, each particular papillomavirus is extremely species-specific, meaning that a rabbit virus can only infect rabbits, a cow virus can only infect cows, and humans can only get HPV infections from other humans.

5

The Transformation

Any student who takes a general biology course learns that the cell is the basic unit of life. All living things are composed of cells. From the smallest *E. coli* bacterium to the largest of mammals, *Balaenoptera musculus* (the blue whale), this concept holds true. Furthermore, cells can arise only from division of preexisting cells, which means that the only way to make more cells is by repeated rounds of cell growth and division. Normal cells divide in a way that leads to the balanced growth of the organism. Cancer cells, on the other hand, divide uncontrollably, resulting in the formation of an invasive tumor mass.

THE CELL DIVISION CYCLE

The process of cell reproduction occurs by a specific sequence of events known as the cell cycle. For an average human cell, the entire cycle generally takes about 24 hours. As shown in Figure 5.1, the **cell cycle** is frequently drawn as a circle with four distinct phases.

The first phase is known as **G1 phase,** and this stands for either "gap" or "growth" phase. It refers to the time when the cell is going about its normal cellular business. The cell's activities during this time may include acquiring and metabolizing nutrients, synthesizing new proteins or enzymes, or making other products required for basic cell maintenance.

Next, the cell enters S phase, the period of DNA synthesis, in which the cell focuses most of its energy on accurately replicating all of its chromosomes. The cell must carefully replicate its DNA so that each daughter cell receives a complete copy, then it must prepare to partition the other cellular contents so that they are equally divided when the cell splits in two, a process known as cytokinesis.

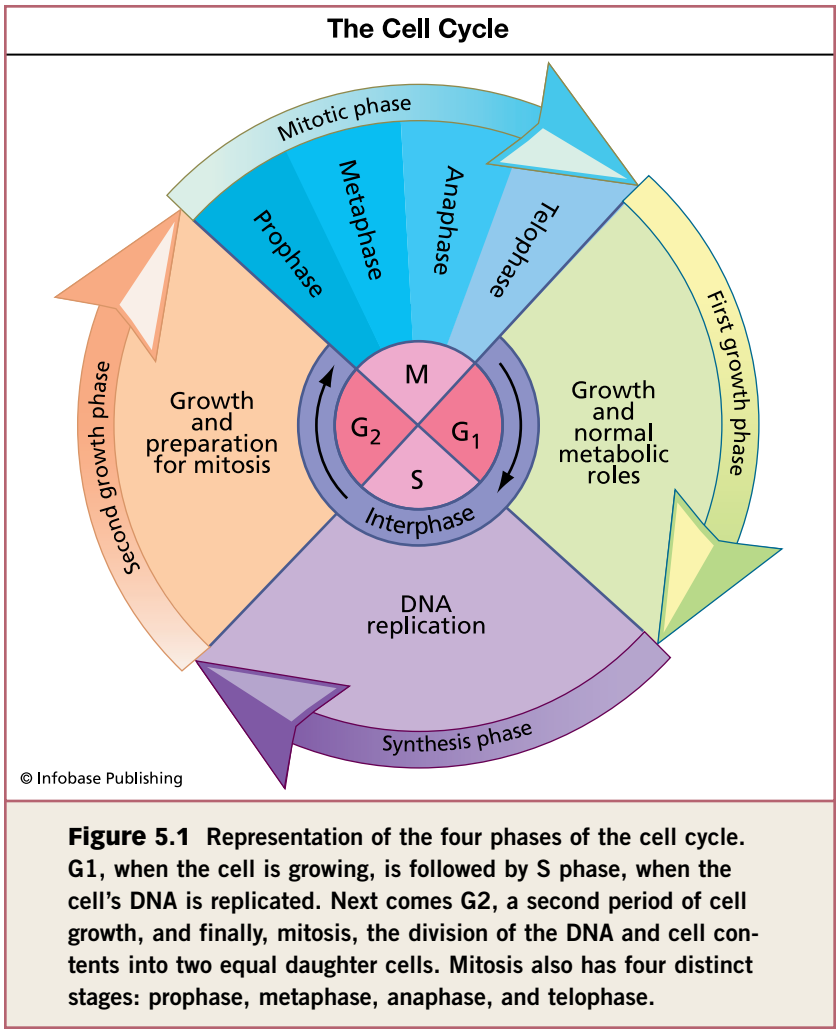


Figure 5.1 Representation of the four phases of the cell cycle. G1, when the cell is growing, is followed by S phase, when the cell's DNA is replicated. Next comes G2, a second period of cell growth, and finally, mitosis, the division of the DNA and cell contents into two equal daughter cells. Mitosis also has four distinct stages: prophase, metaphase, anaphase, and telophase.

After DNA replication has been completed, the cell enters a second "gap" period known as G2 phase. This is a time of preparation for the main event, **mitosis**. Together, the G1, S, and G2 periods are known as **interphase**. They last about 23 hours on average.

Mitosis, or **M phase,** is the last period of the cell cycle. It is a dramatic series of events during which the **nucleus** of

the cell divides and a full set of chromosomes is segregated to each of the two resulting daughter cells. The process of mitosis involves a series of specific changes in cell structure that occur rapidly in about 30–60 minutes, which is just a fraction of the total time it takes to complete an average cell cycle.

MITOSIS

Mitosis, the fourth phase of the cell cycle, actually occurs in four distinct stages. This process can easily be visualized under a microscope (Figure 5.2). Before the start of mitosis, the cell is in interphase, and during this time, the cell has a dark nucleus, the region where the chromosomes are housed separately from the rest of the cell's **cytoplasm**. Before mitosis begins, the chromosomes have already replicated into structures called **sister chromatids.**

The first change observed at the onset of mitosis is that these duplicated chromosomes condense and become visible as distinct thick, dark strands. This period, the first stage of mitosis, is known as **prophase**. The condensation of the chromosomes is followed by the breakdown of the nuclear membrane, so that the sister chromatids are no longer separated from the rest of the cell. This is important because, at this point, a structure called the **mitotic spindle** begins to form in the cytoplasm. The mitotic spindle is a network of fibers that attach to the sister chromatids and help them get organized for the separation. The genome of HPV has been found to attach to the mitotic spindle, which is how the virus ensures that each daughter cell receives a copy of the viral genome.

In **metaphase**, the second stage of mitosis, the spindle has arranged the duplicated chromosomes along a central "equator" so that the sister chromatids will separate from one another and each new cell will receive a single copy of each chromosome. The separation of sister chromatids occurs during

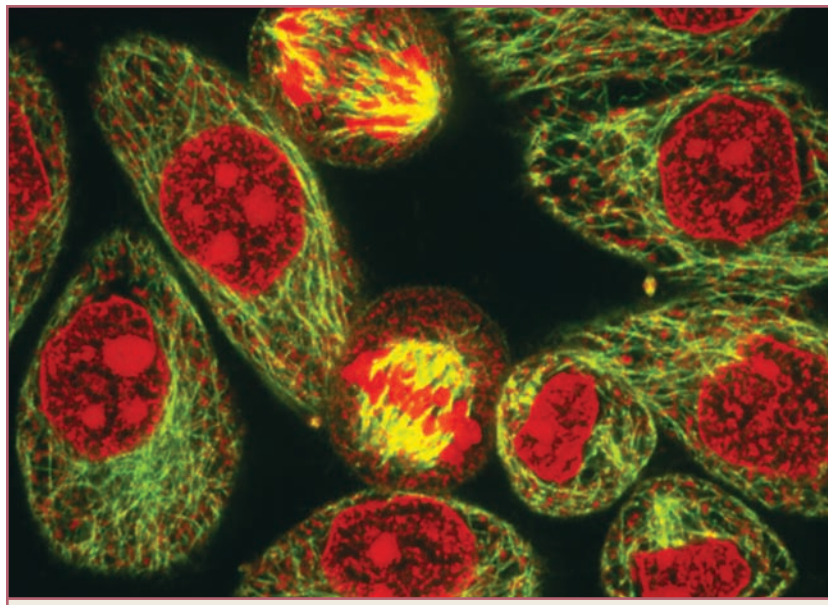


Figure 5.2 Immunofluorescent light micrograph of HeLa cancer culture cells. Their nuclei are red and the microtubules of their cytoskeletons are green. Two cells are undergoing mitotic cell division. The chromosomes (red) are aligned along the middle of the cell at lower center during the metaphase stage of mitosis. They are separating in the cell at upper left (late anaphase). © Dr. Gopal Murti/Photo Researchers, Inc.

anaphase, the third stage of mitosis. Anaphase is a critical time when the separated chromosomes are essentially reeled in toward opposite ends of the cell. Finally, during **telophase**, the fourth stage of mitosis, a nuclear membrane forms around each new set of chromosomes, and the cytoplasm divides by cytokinesis, resulting in two new cells that are perfect replicas of the original cell.

REGULATION OF THE CELL CYCLE

Given the complicated series of events required for cell division, each of the steps must be coordinated to ensure a smooth

process. In this sense, the cell cycle works sort of like the cycle of a dishwasher. It would be inefficient, for example, to dry and then rinse, or to rinse before the wash step was finished. The cell cycle is very much the same, in that each step occurs in a specific order and proceeds only if the previous step has been

RSV—THE ORIGINAL CANCER VIRUS

It was the early 1900s, and American pathologist Peyton Rous was becoming obsessed with chickens. More specifically, he was interested in a specific type of tumor that seemed to arise in chickens with some frequency. Rous took material from one chicken's fibrosarcoma tumor and injected it into another chicken. When the second chicken developed the same type of tumor, he set out to determine what had caused it. He took a sample from another chicken's tumor. This time he passed it through a porcelain filter that would remove whole cells and any bacteria from the material. When he injected the filtered sample into a chicken, the chicken still developed cancer. Rous's results suggested that the chicken tumors were caused by a virus—the only infectious particle small enough to pass through the filter.

Despite the importance of Rous's discovery, it was largely ignored until many years later when scientists studied the genome of the Rous sarcoma virus (RSV), as it came to be known. They found that it was a retrovirus that contained only four genes (Figure 5.3). Retroviruses are viruses that have an RNA genome but produce a DNA "provirus" that inserts itself into the genome of the host cell. Three of the RSV genes—*gag, pol*, and *env*—encoded essential viral proteins and were common to all retroviruses. The fourth gene—*src*—however, was different. Mutant viruses that lacked the *src* gene could still infect cells and produce more viruses. However, when the mutant viruses were introduced into chickens, no tumors developed. It turned out that *src*, named for the sarcoma tumor from which the virus was isolated, was an

completed. In a human being, **cell cycle checkpoints** ensure that the replication of cells is carefully regulated and responsive to the specific needs of the body. What scientists have learned is that cancer cells often divide uncontrollably because they are able to ignore these checkpoints.

oncogene, or a gene with the ability to cause cancer. The *src* gene actually promoted the unregulated cell growth that led to the chicken tumors. Later it was learned that *src* is actually a normal cellular protein (called *c-src*, short for "cellular-*src*") that had a role in regulating cell growth. The gene was captured by the retrovirus and changed into a form that was tumorigenic (*v-src*, short for "viral-*src*"). The normal cellular version of *src* is known as a proto-oncogene, because it is the precursor to the oncogenic form that promotes tumor growth.

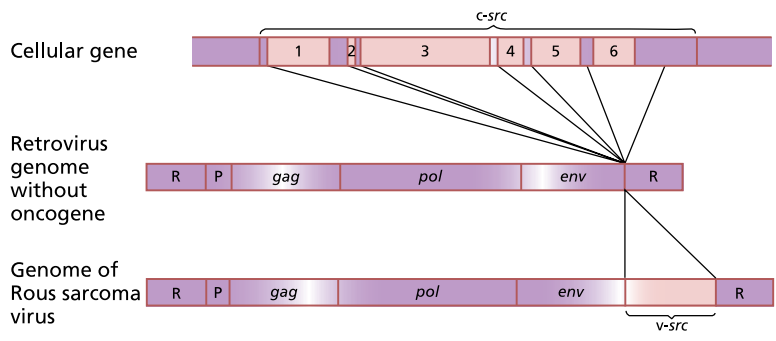


Figure 5.3 Diagram of the Rous Sarcoma Virus genome, showing the three main viral genes: gag, pol, and env. Cancer-causing strains of RSV have fourth gene, v-src, which is the viral version of a cellular gene captured from the genome of a host cell and modified to become an oncogene.

For example, imagine a skin cell that is exposed to massive amounts of ultraviolet (UV) radiation. Perhaps you have gone to the beach, forgotten to apply sunscreen, and experienced a painful sunburn. The UV light from the sun has caused serious damage to the DNA in your skin cells. As a result, if those damaged skin cells were to enter the cell cycle, they would be replicating damaged DNA. That damaged DNA would then be passed on to the daughter cells, and their daughter cells, and their daughter cells. To protect our genetic material and prevent this passage of mutations to future generations, cell cycle checkpoints kick in.

One important cell cycle checkpoint involves a protein called p53 that actually halts the cell cycle. The *p* stands for "protein" and the *53* refers to the molecular mass of the protein in kilodaltons (a unit of measure used by biologists). Normally, p53 acts to stop cell division whenever it senses that a cell's DNA is damaged, giving the cell a chance to repair the DNA before its errors are duplicated and passed on to daughter cells. Scientists call p53 the "guardian of the genome" because it plays such a crucial role in the body's fight to prevent cancer. Acting like an emergency brake on a car, p53 can halt cell growth, or, if the damage to the cell's DNA is too extensive, p53 can send a cell into a programmed spiral of death, known as **apoptosis**. Because of its important role in overseeing normal cell growth, p53 is known as a **tumor suppressor**. When the gene for p53 is mutated, tumors are more likely to form because the cells don't have a checkpoint to stop them from dividing. In addition, p53 mutations can promote abnormal cell growth because the cell cannot undergo apoptosis. To date, p53 has been found to be mutated to an inactive form in over 50 percent of all human cancers. This includes cancers of virtually all types, including skin cancer, breast cancer, prostate cancer, and colon cancer, among others. In cervical cancer, however, the p53 gene is not mutated, but the p53 protein is affected by HPV infection.

CELL TRANSFORMATION BY HPV

A German virologist named Harald zur Hausen first linked HPV with cervical cancer in 1975, but for many years his research was ignored. Although he found evidence of viral DNA in virtually every cervical biopsy sample he tested, it was not clear how the virus could have caused the abnormal cell division; after all, most viruses ultimately kill their host cell, not make it immortal. It was not until the 1990s that scientists discovered the **transforming** properties of two HPV proteins, and zur Hausen's work took on new significance. When a normal cell gains the ability to undergo unlimited rounds of replication, it is said to be transformed. A transformed cell is essentially immortal, or cancerous.

The immortalizing properties of the oncogenic strains HPV 16 and 18 appear to be caused by the expression of the E6 and E7 viral proteins. E7 binds to a cellular protein called Rb. *Rb* stands for "retinoblastoma," which is a rare tumor of the eye. The Rb protein is also considered a tumor suppressor, because it halts abnormal growth and thus prevents cancer, but when it is mutated, cancer can develop. The genetic defect that leads to retinoblastoma was identified in children with a hereditary form of the cancer. They had all inherited a defective copy of the Rb gene, usually due to a small deletion on chromosome 13.

The Rb protein functions as a tumor suppressor because its normal role is to inhibit cell replication. Rb binds to another protein called E2F, which is an important activator of DNA replication and gene expression. However, E2F can only activate these events when it is free and unattached to Rb. When Rb binds to E2F, it is prevented from stimulating cell division. In the basal epithelial cells, replication is constant because these cells must replenish the outer layers of skin. The outermost layers, the keratinocytes, however, are no longer actively dividing. They are supposed to exit the cell cycle and begin their special tasks—namely, the production of keratin and the protection of the inner epithelial cell layers. For this

to happen, Rb must bind to E2F and prevent additional cell replication cycles in the keratinocytes. When a cell is infected with HPV, the E7 protein grabs hold of the Rb protein, preventing it from interacting with E2F. Because E2F is now free and uninhibited by Rb, it promotes further rounds of cell division.

The interference with normal Rb function by the E7 protein is believed to be the major way that HPV transforms cells. However, the E6 protein interacts with another important tumor suppressor, p53. Recall that p53 can halt the cell cycle in the event of DNA damage, or it can trigger cell death if the damage is too extensive. The virus would prefer that neither of these two things occur, so E6 attaches to p53 and causes p53 to break down inside the cell. Without p53, the cell cycle can't be stopped. In cervical cancer, the p53 gene is not necessarily mutated, as it is in many other cancers. Instead, the protein is destroyed by E6 binding.

ONCOGENES AND TUMOR SUPPRESSORS

E6 and E7 are classified as viral **oncoproteins**, because they promote abnormal cell growth (Figure 5.4). The viral genes that encode these transforming proteins are known as oncogenes. Cervical cancer develops because these viral oncogenes are expressed, and the E6 and E7 proteins inhibit tumor suppressors and promote the cell division cycle. What's interesting is that most cancers are caused by oncogenes, but the oncogenes do not always come from viruses. Most oncogenes are actually normal cellular genes that have become overactive. These proto-oncogenes once provided normal regulation of cell growth, but when they get mutated to an "always on" state, there is too much growth, and cancer develops. One might compare oncogenes to the gas pedal in a car. It's impossible to drive anywhere without using the gas pedal, but we expect other drivers to use the gas pedal sensibly. They should observe speed limits and remove their foot

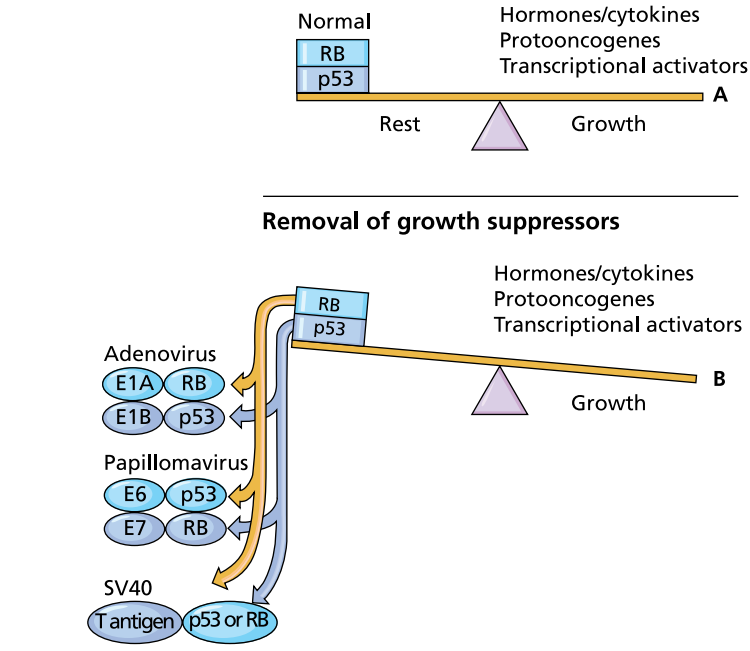


Figure 5.4 Depiction of the action of viral oncogenes. In normal cells, growth suppressors carefully balance growth signals to regulate cell division. In infected cells, viral oncogenes prevent growth suppressors from working properly, allowing accelerated growth and unchecked cell replication.

from the gas pedal at stop signs and red lights. When a reckless driver puts the pedal to the metal and disregards the rules of the road, people can get hurt and there may be serious consequences. Likewise, in the body, proto-oncogenes are needed for normal cell growth, but when a cell is told to divide and divide and divide, cancer develops.

A vehicle has both a gas pedal and a brake, however. Just taking one's foot off the gas may not always be enough to stop the car; applying the brake is often necessary, too. Tumor

THE IMMORTAL HENRIETTA LACKS

Henrietta Lacks was buried in an unmarked grave in Virginia, yet she is more alive now than ever. The thirty-one year-old Baltimore woman passed away in 1951 after succumbing to an especially aggressive form of cervical cancer. Henrietta Lacks was diagnosed and treated at Johns Hopkins, and during the course of her treatment, a biopsy sample of her tumor was given to Dr. George Gey, head of tissue culture research at Johns Hopkins. Dr. Gey had been trying to grow human cells *in vitro* (from the Latin for "within glass," basically meaning "outside of a human body") for quite some time without success. In each case, the cells would "crash,"—meaning all the cells would die off abruptly after a few weeks in culture dishes. Henrietta's cells, however, were something extraordinary.

The cells taken from Henrietta's cervix were multiplying like crazy in the laboratory. They used up every bit of nutrient available in the culture vessels and kept on growing with record speed. This was the first time human cells were able to be maintained *in vitro* for an extended period of time. This was a monumental breakthrough for scientists who were trying to cure cancer, study virus replication, and understand genetic control mechanisms. Within months, vials of the cells, designated HeLa cells for the first two letters of the patient's first and last name, were sent out to researchers at laboratories in New York, Minnesota, Chile, and Russia, among other places.

Meanwhile, the cells grew just as aggressively inside Henrietta Lacks as they did in the lab. Within months after undergoing radiation treatment at Johns Hopkins, tumors riddled almost every organ in her body. Lacks succumbed to cancer on October 4, 1951. Her cells, however, live on in research laboratories around the world, providing valuable clues to scientists studying the genetic changes that can convert a normal cell into a malignant one.

suppressors are the brakes that function at crucial cell cycle checkpoints. They stop the cycle if a previous step occurred incorrectly or if there was damage to the cellular DNA. Almost all human tumors form by the action of oncogenes and the inactivation of tumor suppressors. Not every strain of HPV is able to transform cells and promote tumor growth. A few strains have this ability because of their E6 and E7 oncoproteins, which attach to and inactivate cell growth regulators called tumor suppressors. When these tumor suppressors are inactivated, cervical cancer develops.

6

Screening Tests and Diagnostic Procedures

Since the 1950s, the number of women diagnosed with cervical cancer each year in the United States has continued to decrease, down nearly 75 percent from World War II levels. However, the number of HPV infections keeps going up. That means that there are more and more women who have the most important risk factor for developing cervical cancer. In other words, the number of cases of cervical cancer could increase exponentially, and the only reason it hasn't happened is that there is a reliable screening test available. In this chapter, this very successful test—the Pap smear—will be described, along with other procedures that can be used to detect and treat abnormal cells in the cervix before they become life-threatening.

THE PROCEDURE

Doctors generally recommend that all women should begin yearly Pap smear tests at the age of 18 or when they become sexually active—whichever happens first. The procedure is usually performed as part of a yearly gynecological exam, and it is relatively quick and painless. The patient lies back on an examination table with her knees bent and her heels in stirrups. The gynecologist will use a speculum to spread the walls of the vagina so that the cervix can be seen. A speculum is an instrument shaped like a duck's bill with a handle (Figure 6.1). The doctor performs a visual examination of the cervix to inspect for any obvious signs of abnormality and to identify the transformation zone. Using a small plastic or wooden spatula, the doctor scrapes the surface of the cervix, preferably an area that

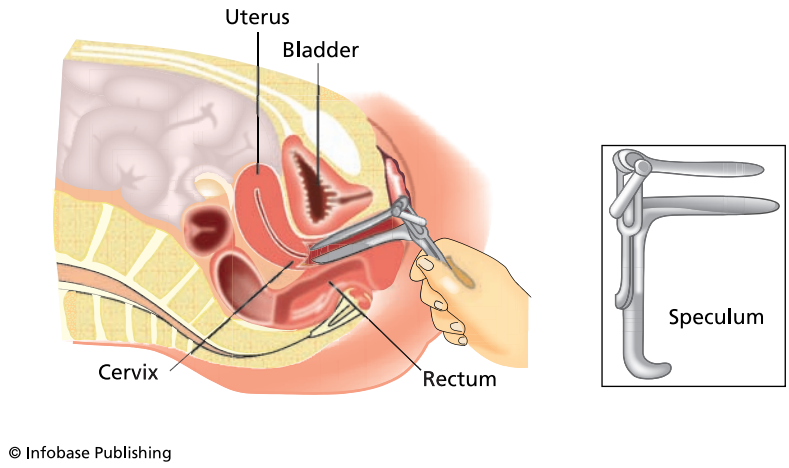


Figure 6.1 A drawing of a speculum and its use during a pelvic exam.

includes the transformation zone, to remove some of the surface epithelial cells. A small brush may also be rotated over the surface to obtain more cells. These cells are then placed onto a glass slide, sprayed with a preservative, and then examined by a **cytopathologist**. A cytopathologist is a technician who is trained to identify signs of disease at the cellular level. Cells have two main parts that can be seen clearly under a microscope: the nucleus and the cytoplasm. The nucleus contains all the genetic material, and it is usually a dark, dense structure found near the center of the cell. The cytoplasm is the rest of the cell, a more diffuse gel-like area where most of the cell's metabolic reactions occur. A normal cell will have a relatively small nucleus and a large amount of cytoplasm, whereas an abnormal cell has a large, irregular nucleus and a relatively small amount of cytoplasm (Figure 6.2).

A Pap smear is not the same thing as a pelvic exam. The Pap smear is generally performed before the pelvic exam. After the cells have been collected for the Pap smear, the doctor looks

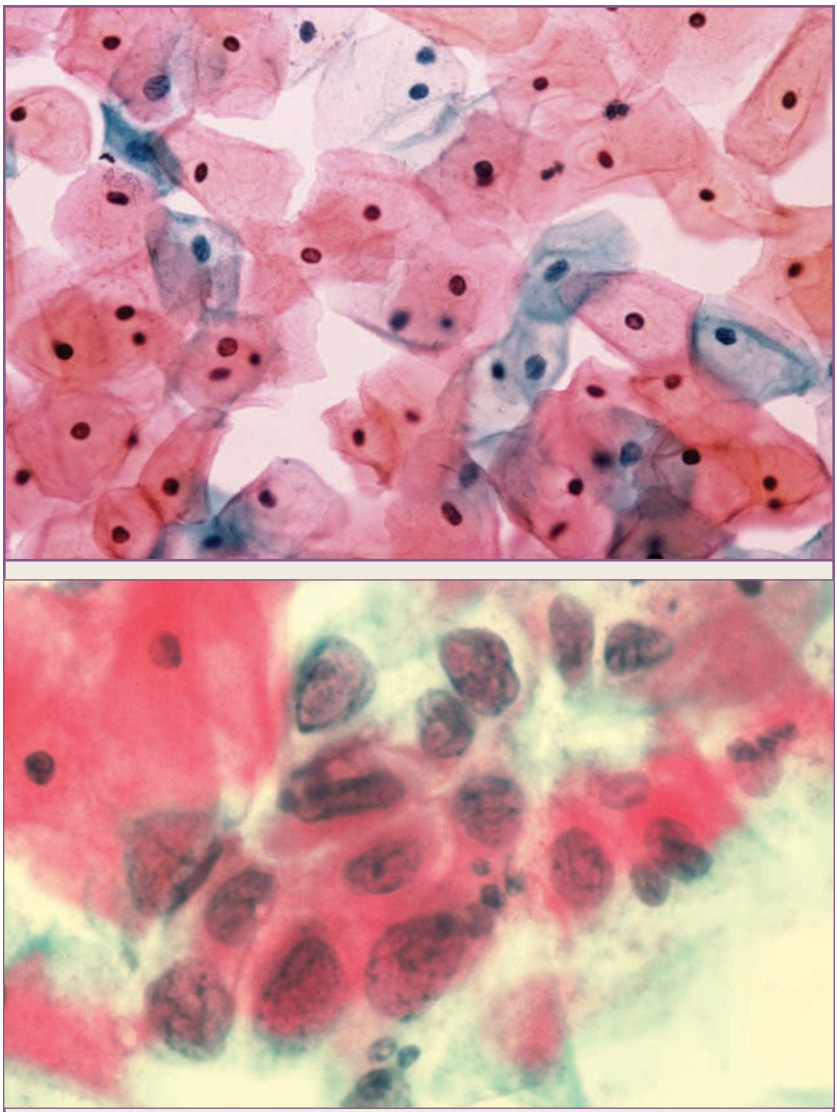


Figure 6.2 (Top) Light micrograph of normal squamous cells in a cervical smear. These cells make up the outer wall of the cervix. (Bottom) Light micrograph of cervical cells showing severe dysplasia in epithelial cells. Large dark-stained nuclei of dysplastic cells can be seen at center, indicating cell division. © Dr. E. Walker/ Photo Researchers, Inc. and SPL Photo Researchers, Inc.

at and feels the reproductive organs, including the uterus and the ovaries. With one hand the doctor pushes the cervix upward from the inside of the vagina. The other hand is placed on the abdomen, so that the size and shape of the uterus can be felt between the two hands. A larger than expected uterus might be due to the presence of **fibroids**, which are benign growths in the muscle that lines the uterus, and are generally not a cause for concern. The ovaries are about the size of a walnut, and they can be felt on either side of the uterus. Larger

DR. GEORGE PAPANICOLAOU, INVENTOR OF THE "PAP" SMEAR

George Papanicolaou is responsible for saving the lives of hundreds of thousands of women through his development of the Pap smear technique. Papanicolaou was born in Kymi, Greece, in 1883, where his father, Nicolas, was a respected physician, and his mother, Maria, had a passion for Greek music and literature. George's father encouraged him to attend medical school, but Nicolas was disappointed that his son preferred medical research to seeing patients. Eventually George Papanicolaou moved to the United States, where he conducted extensive cytology research at Cornell Medical School. During his studies of the menstrual cycle of guinea pigs, he observed specific cellular changes that appeared to correlate with the onset of cancer. He and his colleague Dr. Herbert Traut worked to develop a consistent and reliable procedure that could be used for diagnostic purposes. They published their findings in 1943, and there was rapid, widespread acceptance of the technique by the medical community. Over the next few years, the "Pap test" became widely used, enabling doctors to detect precancerous conditions before they developed into invasive cervical cancer. Today, millions of women have the Pap test done each year.

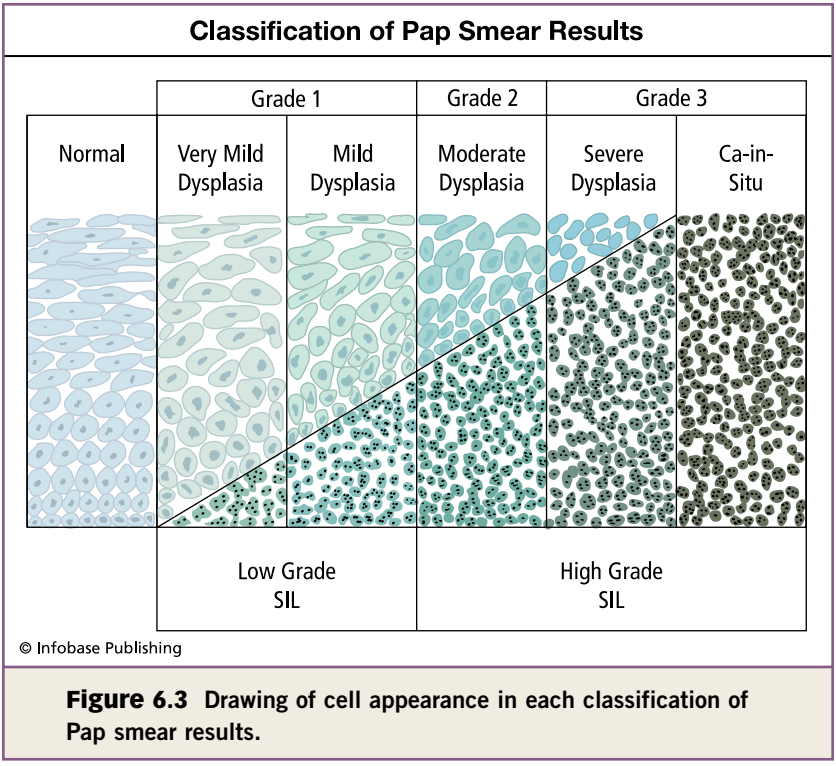


Figure 6.3 Drawing of cell appearance in each classification of Pap smear results.

than expected ovaries might indicate a cyst, which is a collection of fluid in the ovary. Alternatively, a large ovary might indicate a benign tumor, or more rarely, ovarian cancer.

THE RESULTS

The appearance of the cells on the Pap smear is graded by the cytopathologist according to the Bethesda System (Table 6-1), which was developed in 1988 to replace an older, and somewhat confusing, grading system. In the Bethesda System, the cells are considered normal if there are no obvious signs of abnormality. If the patient is engaging in risky behavior, such as having unprotected intercourse or having multiple sexual partners, it is even more important that she undergo a Pap smear and pelvic exam every year.

Table 6.1 The Bethesda System for Classification of Pap Smear Results

Bethesda System Rating	Cellular Observations	CIN[1] Rating (tissue biopsies)
Unsatisfactory	Poor sample quality, unable to make an accurate reading	Unsatisfactory
Normal	Normal	Negative
Reactive Changes	Reactive changes, benign cellular changes	Negative
ASCUS[2], AGUS[3]	Atypical cells, but not dysplasia	No term
Low grade SIL[4]	Koilocytosis	No term
Low grade SIL	Mild dysplasia	CIN 1
High grade SIL	Moderate dysplasia	CIN 2
High grade SIL	Severe dysplasia	CIN 3
Carcinoma in situ	Suspicious High Grade SIL	CIN 3
Invasive carcinoma	Microinvasion (<3mm) Frankly invasive (>3mm)	Carcinoma

[1]CIN = Cervical intraepithelial neoplasia
[2]ASCUS = atypical squamous cells of undetermined origin
[3]AGUS = abnormal glandular cells of undetermined significance
[4]SIL = squamous intraepithelial lesion

Some samples may also show what are called **reactive cellular changes**, meaning that the cervical cells are responding to some sort of infection or other irritation. These findings may be unrelated to cervical cancer, but they may indicate that the patient has a yeast infection or an STD such as herpes or chlamydia. It is important to note that a Pap smear cannot diagnose any of these conditions. If there is any reason—such as irritation, discharge, or odor—to suspect an STD or a

bacterial or yeast infection, these symptoms should be discussed with the doctor during the exam so that the appropriate diagnostic test can be performed.

One of the most common abnormalities reported in the lab is called **ASCUS**, which stands for "atypical squamous cells of undetermined significance." In other words, the cells don't really look like cancer, but they don't look entirely normal either. In most cases the doctor will recommend that another Pap test be performed in three to six months. About 70 percent of the time the follow-up Pap smear reveals that the cells have returned to normal. In some cases the lab might designate the cells as **ASC-H**, which refers to atypical squamous cells that cannot exclude high-grade intraepithelial lesions, or **HSIL**, which is moderate to severe dysplasia. This is a slightly more troubling finding, and the doctor would most likely perform **colposcopy**—a procedure where an illuminated, magnified view of the cervix is obtained by using an instrument called a colposcope. The colposcopy is performed in the doctor's office and takes about 10 to 15 minutes. During the procedure, the doctor may apply an acid solution to the cells of the cervical wall to reveal abnormalities, because areas of dysplasia will turn white when exposed to the acid. A biopsy sample may be taken from the suspicious area at this time, and the results will determine the best course of treatment. Tissue biopsies are graded differently from Pap smears, using the CIN Rating System. *CIN* stands for "cervical intraepithelial neoplasia." CIN 1 indicates mild dysplasia, CIN 2 stands for moderate dysplasia, and CIN 3 denotes the presence of severe dysplasia in the tissue sample.

Another possible Pap test finding is **AGUS**, meaning "atypical glandular cells of undetermined significance." Although atypical squamous cells are not very suspicious, atypical glandular cells (columnar epithelial cells) from the lining of the cervical canal are more of a concern. The vast majority of cervical cancers begin in the squamous cells, but a rare form called

adenocarcinoma originates in the glandular cells. This type of cancer generally progresses much more rapidly than the squamous cell type, so the doctor would most likely recommend colposcopy for further examination. About half of the women who have an AGUS rating will have some abnormality of the cells lining the cervical canal, and about 10 percent of these women have cancer.

Mildly abnormal cells or cells that appear to be infected with HPV are considered low-grade intraepithelial lesions, or **LSIL**. One sign that a cell may be infected with HPV is **koilocytosis**, a condition in which the cell has a little halo around its nucleus (Figure 6.4). Mild dysplasia is not generally considered to be precancerous, because in many cases, the cells will return to a normal state without any treatment.

Most women will experience an abnormal Pap smear result at some point in their lives. In many cases there is no clear reason for the abnormality, although the woman's general health, immune system function, smoking, and nutrition are presumed to play some role. Generally the doctor will not suggest any treatment for mild dysplasia, but a follow-up Pap smear would be done after a few months to see if the dysplasia has gone away or if it has progressed to a more moderate or severe form.

A finding of HSIL on the Pap test indicates moderate or severe dysplasia and is a cause for concern. In these cases, the normal, mature surface keratinocytes are being replaced by smaller, immature basal-like cells. They aren't true basal cells, because they are found much closer to the surface of the cervix tissue than a normal basal cell would be. In moderate dysplasia, about half of the normal top layer of the cervix is replaced by these abnormal cells. In severe dysplasia, abnormal cells have replaced almost the entire normal surface layer. This means that actively dividing cells are found at the surface, whereas they are normally found only deeper in the cell layer. Moderate and severe dysplasias are not cancer, but

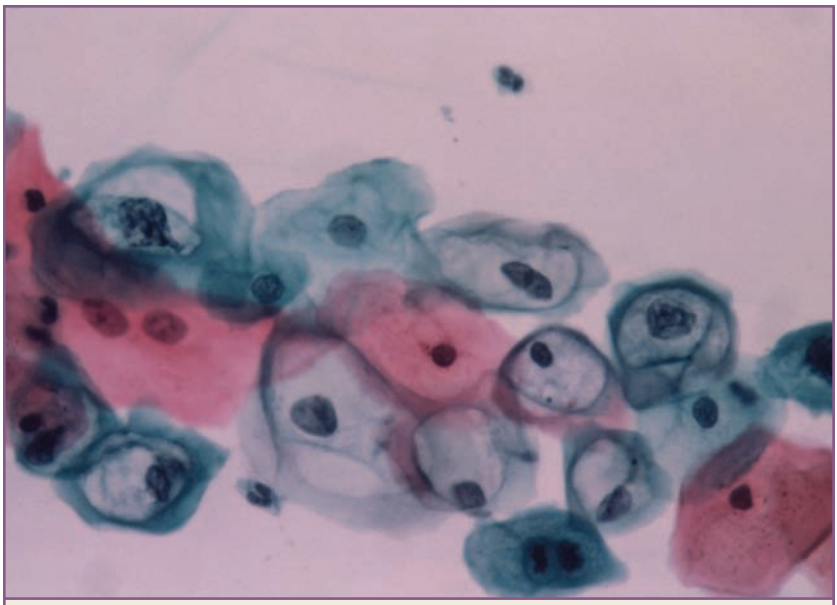


Figure 6.4 Light micrograph of cervical smear revealing epithelial cells infected with the human papilloma virus (HPV). Note the large haloes around the nuclei (koilocytosis). © Dr. E. Walker/ Photo Researchers, Inc.

they are potentially precancerous. Many women with dysplasia will not develop cancer. However, treatment of severe dysplasia can prevent the development of cancer, so many doctors will suggest treatment at this stage, rather than waiting to find out if true cancer, known as **carcinoma in situ**, will develop.

The factors that control the progression of mild to moderate to severe dysplasia to invasive cancer are not well understood. The amount of time it takes to progress through the stages, if there is a progression at all, varies significantly from patient to patient. In some cases it may take a few months; in other cases, it may take several years.

If a Pap smear test came back with a finding of carcinoma in situ or invasive carcinoma, a biopsy would be

scheduled immediately to determine the best course of action. Staging, or rating the severity of the cancer, as well as the various treatment options for cervical cancer, are discussed in Chapter 7.

ACCURACY

The Pap smear test is an easy, inexpensive screening procedure, but it is not infallible. More than 50 million Pap smear tests are performed on women in the United States. About 7 percent of the time, or among 3.5 million women each year, some type of abnormality is diagnosed that requires a follow-up investigation. The number of women diagnosed with cervical cancer each year is only around 10,000, so in most cases of abnormal Pap smears, either the precancerous cells go away on their own or they are removed by the doctor before they become malignant. The next Pap smear is then normal. But what about those cases in which the result is listed as normal, when in reality the findings should have been categorized as ASCUS or mild dysplasia? These are known as **false negatives**, and the rate of false negatives varies dramatically from institution to institution. After all, the results of the Pap smear are interpreted by a human being, and mistakes are sometimes made. Because progression from mild to moderate to severe dysplasia usually occurs over a period of years, even if an abnormality is not detected the first year, as long as the woman gets yearly Pap tests, there is a very high probability that the dysplasia will be detected before cancer develops.

TIPS FOR A SUCCESSFUL PAP TEST

There are several things a woman can do to help improve the accuracy of her Pap tests. The first is to schedule yearly gynecological exams. It's important to be tested annually, and the appointments should not be scheduled during the woman's menstrual period. The shedding of the uterine lining can

AMERICAN CANCER SOCIETY GUIDELINES FOR EARLY DETECTION OF CERVICAL CANCER

- All women should begin cervical cancer testing (screening) about 3 years after they begin to have vaginal intercourse, or when they are 21 years old, whichever comes first. Testing should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test (see page 75).
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get tested every 2 to 3 years with either the regular or liquid-based Pap test. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be tested yearly.
- Another reasonable option for women over 30 is to get tested every 3 years (but not more frequently) with the regular Pap test or the liquid-based Pap test, plus the HPV DNA test.
- Women who are 70 years of age or older and have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer testing. Women with a history of cervical cancer, DES exposure before birth, HIV infection, or a weakened immune system should continue to be tested as long as they are in good health.
- Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer testing, unless the surgery was done as a treatment for cervical cancer or precancer. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines above.

contaminate the cervical cell sample and result in an unsatisfactory Pap test. Second, the test will be more accurate if the woman has not had sexual intercourse in the previous 48 hours. The trauma of sexual intercourse can irritate the cervix and may lead to abnormal or unclear findings. Likewise, the use of tampons, birth control foams and jellies, or other vaginal creams or medications can impact the results and should be avoided for 48 hours before the test.

Lastly, some guidelines state that the patient should not **douche** for 48 hours before the test, but in reality, doctors and health-care workers are now telling women that they should not douche at all. Douching, or washing the vagina with water or a vinegar solution, is a relatively common practice by women who feel they need to clean the vagina after menstruation or after sexual intercourse to prevent STDs. Actually, douching removes the microbes that naturally live in the vagina, making it more likely to become infected by harmful yeast and bacteria. Douching can also spread existing infections up into the uterus or fallopian tubes. Women who douche regularly should at least avoid doing so before their yearly Pap test, and they may wish to consult their doctor about the pros and cons of the practice.

RECENT ADVANCES IN SCREENING

Researchers are always searching for ways to improve the accuracy of the Pap smear. A newer method called **liquid-based cytology**, or the liquid-based Pap test, can remove some of the contaminants commonly found in a sample, such as pus, cervical mucus, bacteria, and yeast cells. This method enables the cervical cells to be spread more evenly on the slide. Instead of placing the samples directly on the slide, the doctor places the sample into a small container of a preservative solution, which prevents cells from drying out and becoming distorted. At the laboratory, a machine spreads the cells onto the slide in a single layer. This technique has been found to make the Pap smear

results easier to interpret. It also reduces the rate of false negatives and reduces the number of unsatisfactory samples that have to be repeated. Unfortunately, this method is also significantly more expensive than a traditional Pap smear and may not be available everywhere, since special equipment is required.

As with many processes these days, technology and automation have been introduced in an effort to improve the efficiency and accuracy of the Pap test. The AutoPap is a computerized instrument approved by the U.S. Food and Drug Administration (FDA) to replace humans in reading Pap smear slides. However, a cytotechnologist is still required to examine any tests that the AutoPap identifies as abnormal. At some institutions AutoPaps are used to test slides that human technicians have identified as normal. In several cases the AutoPap has successfully identified early stage abnormal cells that were missed by humans, and in some cases, high-grade abnormalities that humans missed have been found by the computerized instrument. Automated testing is not available at every facility, however, and it increases the cost of the cervical cytology testing.

Another emerging technology is known as the Polarprobe. The Polarprobe is a portable device that is designed to detect the electrical and optical properties of cervical tissue. The method is based on the finding that there are detectable differences between normal, precancerous, and cancerous cells. The Polarprobe is a small wand that is about 17 centimeters (6.7 in) long with optical and electrical sensors located in the tip. The probe is inserted into the vagina and passed over the cervix for one to two minutes. The results are instantaneous, and the sensitivity appears to be about equal to that of the Pap smear, without the mess of cell sampling and slide preparation. However, the technology is still in the developmental stages, and it is likely to be more costly than the Pap test.

THE HPV DNA TEST

One important point about the Pap smear is that it doesn't test for HPV. The Pap smear test can only reveal signs of abnormal cells, which may or may not be due to virus infection. As discussed in Chapter 3, the most important risk factor for the development of cervical cancer is infection with HPV. Of the many strains of HPV, however, only a handful are associated with cervical cancer. Using the same type of sampling procedure as for the Pap test, doctors can now directly test cervical cells for the presence of DNA from the high-risk types of HPV that are most likely to cause cervical cancer. Instead of examining the cells on a slide, a molecular diagnostic kit is used to determine whether any HPV DNA is present in the sample. Since DNA cannot be seen with the naked eye, laboratory procedures rely on light signals or intensification techniques to find a specific type of DNA in a sample. In the commonly used Hybrid Capture II® (HCII) test, molecular probes bind to DNA sequences from high-risk strains of HPV. The binding of the probe to the viral DNA causes a light signal that is then compounded, or enhanced, and read as a positive result in the laboratory. The HCII test screens for the presence of DNA from twelve different oncogenic strains of HPV (16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, and 68). Other tests make use of target amplification, a process used to test for viral DNA, and if it is present in the sample, make a lot more copies of that DNA so that it can be detected by the laboratory scientists. This procedure is generally known as the polymerase chain reaction (PCR), and it is used to amplify and detect specific high-risk HPV DNA sequences in a sample. These DNA tests are especially useful for women who have had an abnormal Pap result. In many cases the same sample can be used to determine whether the cause of the abnormal Pap smear is infection with a high-risk strain of HPV. Because it requires some specialized equipment, the HPV DNA test is not available at every institution and is more expensive than the Pap test.

SUMMARY

Four out of five women who die of cervical cancer did not have a Pap smear in the past five years. The Pap test is the most successful screening test to date for cancer prevention, but it is not a perfect test. The best way to improve early detection of cervical cancer is to make certain that all women are tested either yearly or, after several normal tests in a row, every other year. Unfortunately, many of the women who are most at risk for cervical cancer are not being tested often enough, or at all.

A NOTE ABOUT FIBROIDS AND CYSTS

Fibroids are noncancerous growths that commonly occur in the female reproductive tract, especially in the muscle that lines the uterus. Using a very sensitive imaging technique, medical professionals have found small fibroids in more than 75 percent of women, but only a fraction of these growths are large enough to be detected during a routine pelvic exam. The majority of women who do have fibroids will never have symptoms and will never require any type of treatment. If the location of the fibroid does cause pain, pressure, irregular bleeding, or other symptoms, there are a variety of treatment options available. A hysterectomy, the removal of the uterus, is almost never warranted unless the fibroids are excessively large, numerous, or if the patient is older and wishes to eliminate the possibility of future fibroids.

Cysts can occur in various locations, but ovarian cysts are particularly common. A cyst is a collection of fluid within the normally solid ovary. The vast majority of ovarian cysts will go away on their own, and these are considered benign. In less than 5 percent of cases, cancerous cysts are found, and these require surgical removal.

7

Treatment for Cervical Cancer

Benjamin Franklin is credited with saying that an ounce of prevention is worth a pound of cure. When it comes to cervical cancer, he was absolutely right! If a woman has a Pap test done every year, precancerous conditions can be detected and treated before they become a major problem. In this chapter, the treatments for mild and severe dysplasia are discussed first, and then the options for treating cervical cancer, including surgery, radiation therapy, and chemotherapy, are described.

TREATMENT FOR DYSPLASIA

Moderate or severe dysplasias are the early warning signs that cancer is developing. This stage is not life-threatening. However, there is a high likelihood that dysplasia could become life-threatening if action is not taken to prevent the onset of cervical cancer. Moderate or severe dysplasia is usually indicated by a Pap smear with HSIL, and then confirmed by a cervical biopsy. The gynecologist examines the cervix with a colposcope and then removes a small area of the tissue for further evaluation by a pathologist. Because the biopsy sample is larger than just the cells scraped off during the Pap smear, the results are more accurate. Depending on how severe the dysplasia is, the doctor may recommend one of several possible treatments. **LEEP** (loop electrosurgical extension procedure), cryotherapy, and cone biopsy are the most common.

The most widely used procedure for the treatment of moderate or severe dysplasia is LEEP. The procedure generally takes place in the gynecologist's office, and it makes use of a small wire loop electrode to shave off

the abnormal tissue (Figure 7.1). An electric current is passed through the loop so that it becomes extremely hot, allowing it to slice through the cervix tissue quickly and easily. The patient lies back on the examination table with her heels in the stirrups, the vagina is widened with a speculum, and a local anesthetic is usually applied to the cervix. A gel-covered electrode is attached to the thigh to complete the electrical circuit, and the doctor uses a colposcope to view the area where tissue will be removed. More tissue can be removed with this procedure than with a standard cervical biopsy, although the LEEP is also more costly to perform. The entire process takes only about five minutes, although it will take three to six weeks for the cervix to heal fully. For most women, the LEEP is a relatively painless procedure, but it is not unusual to experience mild pain or cramps afterward.

The portion of cervical tissue that is removed with the wire loop is then sent to the pathologist, who will examine the **margins**, or the outer edges of the tissue, to determine whether it contains normal cells or abnormal ones. If there are signs of dysplasia right up to the edge of the tissue sample (positive margins), it is very likely that some dysplasia remains in the cervix, and additional treatment may be required. Even if it appears that all the dysplasia has been removed, it is still important to return for follow-up Pap tests every three months for the next year.

Cryotherapy involves freezing to kill the abnormal cells in the cervix. Liquid nitrogen is used to super-cool a metal probe, and the probe is held against the cervix tissue. This is typically done twice for two to three minutes at a time, during which time the woman may experience cramping sensations similar to menstrual cramps. The damaged cells will be shed from the cervix over the next few weeks in a clear fluid discharge. This procedure is also performed in the gynecologist's office, and it is fast and fairly inexpensive. Healing takes about three to six weeks, and follow-up Pap smears every three months for the next year are needed to confirm that there is

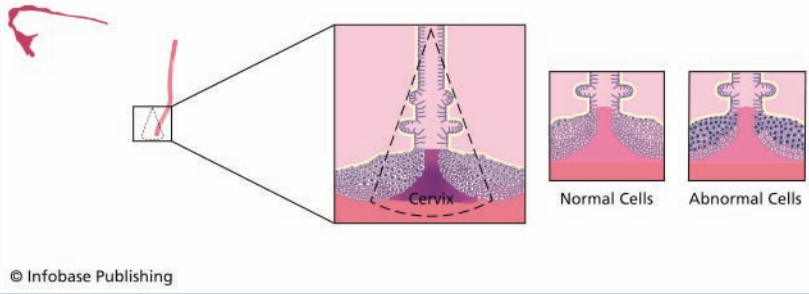


Figure 7.1 Drawing of the area of tissue removed from the cervix during a cone biopsy.

no more dysplasia. One problem with cryotherapy is that some women experience scarring where the cervix heals, making future Pap smears more difficult to interpret.

A cone biopsy, or **conization**, removes much more tissue than a standard cervical biopsy, and the tissue that is removed forms a cone-shaped region (Figure 7.1). The procedure is usually done in the hospital using general anesthesia on an outpatient basis, so the patient goes home the same day. A surgical scalpel is used to remove tissue from both sides of the cervical canal, and sutures are placed around the cervix. Vaginal bleeding for about a week after the procedure is normal; physical activity should be limited and sexual intercourse should be avoided for several weeks. Fever, excessive bleeding, or pelvic pain following the procedure should be reported to the physician immediately. Full healing after a cone biopsy takes four to six weeks. As with the other treatment methods, follow-up Pap tests should be done every three months for the next year.

Laser therapy is one other option for treating cervical dysplasia, but it is no longer widely used because it requires hospitalization, general anesthesia, and expensive equipment. The LEEP method has taken the place of laser surgery because it is faster and less expensive. LEEP can be performed in the

doctor's office with a local anesthetic, and it is just as effective as laser therapy. LEEP, cryotherapy, and conization all have success rates of about 95 percent for curing dysplasia, but LEEP is usually the first choice of treatment for precancerous conditions of the cervix.

CANCER STAGING

It is fairly unusual for Pap smear results to indicate cervical cancer directly, although it does happen at times. This is because cancer cells are generally invasive, so truly malignant cells are usually found deeper in the cervical tissue, and not on the surface where the cells for the Pap test are collected. More likely is that the Pap results show LSIL or HSIL, and then a colposcopy indicates that there is cancer. When the **diagnosis** is confirmed with a biopsy, it is important to determine how far the cancer has spread, a process known as **staging**. Staging describes the size of the tumor, how deeply the tumor has invaded tissues around the cervix, and whether or not the cancer has spread to lymph nodes or distant organs (metastasis). This is an important process because the stage of the cancer is the key factor in selecting the right treatment plan. The woman's age and general health must be considered, but the primary factors in determining the choice of treatment for cervical cancer are the size of the tumor, its location, and the stage of the disease. The FIGO (International Federation of Gynecology and Obstetrics) system of staging for cervical cancer is commonly used to characterize the extent of tumor invasion (see box on page 83). About 60 percent of patients are in Stage I when their cancer is first discovered, 25 percent are in Stage II, 10 percent are in Stage III, and 5 percent are in Stage IV. Treatment is most successful for patients who are diagnosed in Stages I and II.

GETTING A SECOND OPINION

Before beginning any treatment, it is wise to consider getting a second opinion from another medical specialist. Some insurance

FIGO STAGING OF CERVICAL CANCER

Stage I: The cancer is confined to the tissue of the cervix.

- **Stage IA:** The area of invasion is less than 5 mm (0.2 in) deep and less than 7 mm (0.28 in) wide.
- **Stage IB:** A larger amount of cancer is found in the tissues of the cervix, but it does not extend beyond the cervix.

Stage II: The cancer has spread beyond the cervix to nearby areas, but it is still inside the pelvic area.

- **Stage IIA:** The cancer has spread beyond the cervix to the upper part of the vagina. It is not found in the lower third of the vagina.
- **Stage IIB:** The cancer has spread to the tissue next to the cervix, called the parametrial tissue.

Stage III: The cancer has spread to the lower part of the vagina or the pelvic wall. The cancer may be blocking the ureters (tubes that carry urine from the kidneys to the bladder).

- **Stage IIIA:** The cancer has spread to the lower third of the vagina but not to the pelvic wall.
- **Stage IIIB:** The cancer extends to the pelvic wall and/or blocks urine flow to the bladder, or, as defined by the alternate staging system of the American Joint Committee on Cancer, the cancer has spread to lymph nodes in the pelvis.

Stage IV: This is the most advanced stage of cervical cancer. The cancer has spread to nearby organs or other parts of the body.

- **Stage IVA:** The cancer has spread to the bladder or rectum, which are organs close to the cervix.
- **Stage IVB:** The cancer has spread to distant organs beyond the pelvic area, such as the lungs.

companies may require a second opinion, while others will cover the costs of an appointment for consultation with a different physician. The short delay needed to arrange for a second opinion will not reduce the chance that the treatment will be successful, and it may ease the patient's mind to know that two separate physicians agree about the severity of the disease and the recommended course of treatment. To find a doctor who can give a second opinion, women might ask their own doctors for a referral, consult a local hospital or medical school, or search the phone book or Internet.

PREPARING FOR CANCER TREATMENT

One of the best things a patient can do is to be prepared for the treatment. Generally, this means being fully aware of the treatment plan and procedures and being comfortable with that plan. A positive, well-informed patient will likely handle the treatment better than a stressed, panicked patient. When a person first learns that she has cancer, shock and stress are normal reactions, and it may be difficult to ask the doctor questions right away. However, it is important for the patient to have time to digest the diagnosis and then prepare a written list of questions for the doctor. It may also be beneficial to either record the doctor's responses or have a family member or friend present to take notes. Once the patient is comfortable with the treatment plan, it's time to begin. Treatment for cervical cancer might involve surgery, radiation therapy, chemotherapy, or a combination of these.

SURGERY

Surgery is performed to remove abnormal tissue in or around the cervix. Depending on how deeply the cancerous cells have invaded the normal surrounding tissues, the surgeon may have to remove more tissue. In some cases a hysterectomy—the removal of the uterus and cervix—may be necessary. Because the cervix is the lower portion of the uterus, one of

the first places that cervical cancer spreads is to the uterus. For women under the age of 40, the ovaries are left in place. If the patient is over 40, it is more likely that the ovaries will be removed as well. Since the ovaries are an important source of female hormones such as estrogen and progesterone, this surgery will cause early menopause. Women who have their ovaries removed will need hormone replacement therapy to reduce these effects. If the tumor has invaded surrounding tissue more deeply, a **radical hysterectomy** may be performed. This surgery removes not only the cervix and uterus, but also

QUESTIONS TO ASK THE DOCTOR

- **What is my diagnosis? What type of cancer do I have?**
- **Has my cancer spread to lymph nodes or internal organs?**
- **What is the stage of my disease and what does that mean in my case?**
- **What are my treatment options?**
- **Which do you recommend for me and why?**
- **What is the goal of this treatment?**
- **What are the risks or side effects of the treatment?**
- **What should I do to be ready for treatment?**
- **Will I have to change my normal activities?**
- **What are the risks and possible side effects?**
- **Would a clinical trial be appropriate for me?**
- **What is the chance that the cancer will come back after this treatment?**
- **What are my chances of survival, based on my cancer, as you see it?**

parts of the tissue from the vagina and lymph nodes in the pelvic area.

A hysterectomy is major surgery that is performed in the hospital using general anesthesia. The most common form is an **abdominal hysterectomy**, in which the uterus is removed through an incision in the abdomen. The patient generally remains in the hospital for several days, and total recovery takes four to six weeks. Another method is the **vaginal hysterectomy**, where the uterus is removed though the vagina. The recovery time is shorter with this procedure, but it cannot be used if the cancer has spread beyond the uterus. **Laparoscopic surgery** may be used in conjunction with the vaginal hysterectomy for patients who have pelvic scar tissue or **endometriosis**. Laparoscopic surgery is a minimally invasive procedure in which the surgeon inserts a tube that allows for a video projection of the inside of the abdomen. The video tube is generally inserted through the navel, and other small insertions are made in the abdomen so that specialized microsurgical tools can be manipulated to remove the necessary tissue. This type of surgery is used whenever possible because it results in fewer complications, less scarring, and faster recovery times for the patient.

Because the reproductive organs are not necessary for the survival of the patient, a hysterectomy is a reasonable option for treating a potentially life-threatening disease. However, having a hysterectomy means that the woman loses her ability to bear children. If the patient is an older woman who does not plan to have any more children, this may not be an issue. For younger women who might still have been considering children, however, this can be devastating. Women who had plans for children should discuss the reproductive options with their doctor *before* surgery. Although a hysterectomy will render them unable to carry a pregnancy, it is still possible that eggs could be harvested from the ovaries for later fertilization and implantation into a surrogate mother. Beyond the reproductive

issues, many women experience feelings of loss after having a hysterectomy. There are many support groups available to help women deal with their anxieties and recover fully, both physically and mentally.

RADIATION THERAPY

Radiation therapy involves the use of high-energy radiation waves to kill the cancer cells. The radiation causes severe DNA damage that leads to cell death. Because cancer cells divide more rapidly than normal cells, they are more likely to be affected by radiation treatment, although it is expected that some normal cells will also be killed. The doctor will try to protect the normal cells by limiting the radiation dose, spreading the treatments out over time, and covering other parts of the body with a lead shield. Radiation treatment may be used instead of surgery, or it may be used after surgery has been performed. For cervical cancer, radiation may be applied either externally or internally.

External radiation is generally performed on an outpatient basis. A large machine aims a radiation beam at the pelvis for short periods of time, several days in a row. A typical course of external radiation treatment might involve 20-minute exposures, 5 days a week, for 6 weeks. With **internal radiation** therapy, a capsule of radioactive material is implanted directly into the cervix. This procedure is performed in a hospital, using either general or local anesthesia. The patient generally remains in the hospital for several days. The implant is removed before the patient leaves the hospital. Fatigue is the most common side effect of radiation treatment and, because the radiation is concentrated in the pelvis, nausea and loss of appetite are also common.

CHEMOTHERAPY

Chemotherapy uses chemicals, or drugs, to kill cancer cells. Unlike surgery and radiation, which are localized treatments,

chemotherapy is **systemic**, meaning that it reaches the entire body. Chemotherapy is used mainly if the cancer has spread to other parts of the body. Most chemotherapeutic drugs are administered intravenously (IV). A needle is inserted into the arm and a solution containing the chemicals drips slowly into the bloodstream. The treatment can be given at the doctor's

LAUGHTER IS THE BEST MEDICINE

In 1994, Julia Sweeney was on top of the world. She had been a regular on *Saturday Night Live* for several years, and one of her characters, the androgynous Pat, was a huge hit. All across the country, audiences were doubling over in laughter at the antics of this chubby goofball as they tried to figure out if Pat was a man or a woman. Sweeney was riding high on the success of Pat, who would soon be featured in the film *It's Pat.* On that high note, Sweeney left *Saturday Night Live* to settle into her dream home, a chic little bungalow in Hollywood, where she planned to entertain friends, write screenplays, and enjoy life. According to her book by the same name, this is when *God said "Ha!"* Just as Sweeney settled into her new life, a series of unexpected twists changed everything.

Sweeney's younger brother Mike was diagnosed with advanced lymphoma. She wanted to be close to him and help take care of him, so he came to live with her. What followed was a very stressful nine-month period during which her brother's health continued to decline, her parents moved into her bungalow, and then Sweeney herself was diagnosed with cervical cancer. According to her gynecologist, the cancer had spread to the uterus and fallopian tubes, making a hysterectomy the only option. Three days before her surgery was scheduled, her brother Mike passed away. Numb from the loss of her brother, Sweeney underwent the surgery and then tried to deal with the fact that she would never be able to have children of her own.

office or in a clinic. The dose and duration of the treatment vary, but it is always given in cycles with a treatment period followed by a recovery period, and then the treatment begins again.

Two of the drugs that are often used to treat cervical cancer are called cisplatin and 5-fluorouracil. Both of these agents

Years later, Julia Sweeney is alive and well. She survived cancer by remaining positive and keeping her sense of humor.

Figure 7.2 Comedienne Julia Sweeney, star of *Saturday Night Live* and survivor of cervical cancer. ©AP/Wide World Photos

interfere with cell division. Since cancer cells are dividing rapidly, they are the most affected by the drugs. However, normal cells that divide rapidly are affected, too. Hair follicles, the cells that line the digestive tract, and the cells of the reproductive system are also affected by chemotherapy, which is why hair thinning or loss, nausea and vomiting, and reduced **fertility** are the most common side effects.

CURE RATES

The earlier the stage of the cancer when it is detected, the higher the rate of success of the treatment. The cure rate for early-stage cervical cancers is well over 85 percent. For cancers diagnosed at Stage III, the cure rate decreases to about 35 percent. For Stage IV cancers, the cure rate is around 10 percent. However, scientists are continually performing more research and testing new drugs and treatments, so more effective therapies for late stage cervical cancer may one day be available.

8

Cancer Vaccines

There was a time when getting sick with the measles and chicken pox were rites of passage for schoolchildren in the United States. With the introduction of successful **vaccines** to protect against these illnesses, those days are over. A vaccine is a substance that stimulates the body's immune system to recognize and eliminate the agents, such as bacteria or viruses, that cause a particular disease. If a person is later exposed to the disease or infectious agent that causes it, he or she is usually protected from infection. Because cancer is a condition in which the patient's own body cells are growing out of control, it can be difficult to develop vaccines that stimulate the immune system to eliminate cancer cells. However, there has been some success in this area. Cancer vaccines are generally designed either to treat an existing cancer (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines). To date, prophylactic cancer vaccines have been useful for cancers that are associated with an infectious agent, such as a virus, like HPV. Recent scientific research has led to the development of an HPV vaccine that offers hope for future protection from cervical cancer. This chapter will look at vaccines, cancer vaccines, and specific vaccines for cervical cancer.

PROPHYLACTIC VACCINES

Ideally, a vaccine is administered to produce immunity, or protection from some later instance of a particular disease. Most vaccines are produced to prevent infectious diseases, like influenza, but prophylactic vaccines can also protect people against cancers that develop as a result of an infection, such as liver cancer, which is strongly linked to chronic hepatitis B infection.

Prophylactic vaccines can be produced in several ways. They may contain live microorganisms that are **attenuated**, or weakened, so that they don't cause disease. The vaccinations for measles and mumps, for example, contain live, attenuated measles or mumps virus. Attenuated vaccines tend to produce long-lasting immunity, because the microorganism replicates inside the body and stimulates a very strong immune response. **Inactivated vaccines** contain microorganisms that have been killed by heat or chemical treatment. They are still effective in stimulating immunity, but several doses may be required to generate a protective immune response. Generally there will be an initial immunization, followed by one or more **boosters** at specified time intervals (weeks, months, or years later). This type of immunization is used for bacterial illnesses such as whooping cough and typhoid fever.

Some vaccines don't contain the entire microorganism. Instead they contain a specific part of it. These are called **acellular** vaccines, because they don't include whole cells, just certain components. **Toxoids**, purified bacterial toxins inactivated by heat or chemicals, were the first acellular vaccines. These are effective against diseases like tetanus and diphtheria, which are caused by toxins, or proteins that are released by the bacteria that cause tissue damage, and not by the bacteria itself. Subunit vaccines are another type of acellular vaccine that contain purified protein components of the infectious agent. The hepatitis B vaccine (HBV) is composed of a single virus protein produced by **recombinant DNA technology**. This means that another organism, such as a harmless laboratory strain of *E. coli* bacteria or *S. cerevesiae* yeast, is genetically altered to produce large quantities of the desired viral protein. This is much safer and more efficient than producing millions of infectious virus particles from which to purify the protein. Like inactivated vaccines, acellular vaccines generally require several boosters to provide lasting immunity.

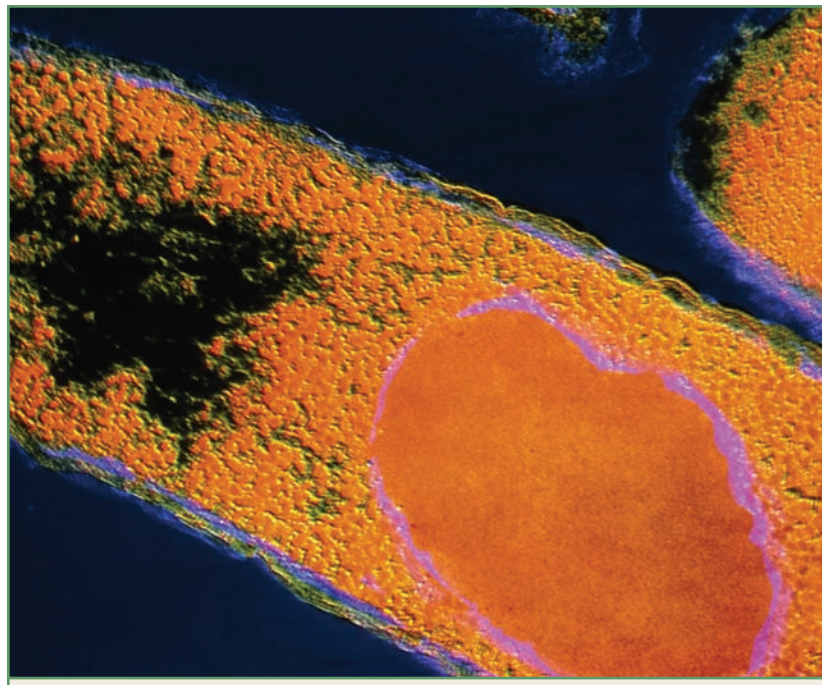


Figure 8.1 False-color transmission electron micrograph (TEM) of the bacterium *Escherichia coli*, genetically engineered to produce quantities of human gamma interferon, appearing as the orange mass ringed in mauve. © CNRI/Photo Researchers, Inc.

The hepatitis B vaccine has greatly contributed to the decline of liver cancer in recent years. Hepatitis is an inflammation of the liver. Symptoms can include abdominal pain, loss of appetite, fatigue, and jaundice. Infection with hepatitis B virus is one of the most common causes of chronic hepatitis, which can cause cirrhosis (scarring) of the liver, liver damage, and liver cancer, and is estimated to be responsible for more than one million deaths each year worldwide. Hepatitis B virus is transmitted in blood and blood products, so a person may be infected though sexual intercourse or IV drug use. In developing countries, many children are infected during childbirth. Although initially recommended only for health-care professionals, the hepatitis B vaccine is now given

to all schoolchildren as part of their routine immunizations in an effort to reduce the incidence of liver disease and liver cancer.

THERAPEUTIC VACCINES

One of the biggest challenges in creating a cancer vaccine is that cancer is a disease in which the person's own body cells are dividing uncontrollably. In some cases the cancer is strongly

THE FIRST VACCINE

Smallpox was a disfiguring and often fatal disease that affected many thousands of people in Europe, Asia, and Africa during the 1700s. Today, smallpox has been eradicated through a worldwide vaccination effort. It now exists only in a few tightly restricted laboratories. The smallpox vaccines used for the eradication effort were based on the work of Edward Jenner, who developed the world's first vaccine back in 1796. Jenner was an English physician who had survived a severe case of smallpox as a child. He was intrigued by an old wives' tale that said milkmaids who had recovered from mild cases of cowpox were protected for life from smallpox infection. Eager to find out whether the story was true, Jenner took some material from the blisters of a cowpox-infected milkmaid and introduced it into the skin of a young boy named James Phipps who had never had smallpox. James was mildly ill for a day, but recovered quickly. Jenner then introduced some material from a smallpox lesion into James's skin, but James did not get sick. Jenner tried inoculating James again with the smallpox material, but still James remained healthy and was protected from even a mild case of smallpox. The cowpox had made James immune to smallpox. The term *vaccine*, from the Latin word *vacca*, for "cow," was introduced some years later by French scientist Louis Pasteur to honor Jenner's original work with cowpox.

linked to an infectious agent, as with HPV and cervical cancer or HBV and liver cancer, and so vaccine development is possible. However, the vast majority of human cancers are not caused by a particular infectious agent. So how can people be vaccinated against themselves?

Ongoing research is aimed at training the body's immune system to recognize and eliminate cancer cells. The strategy

Figure 8.2 Edward Jenner injects James Phipps with the first smallpox vaccine. ©Hierophant Collection.

makes use of **dendritic cells**, which are a type of white blood cell that has the ability to stimulate potent immune responses. Another important ingredient for this procedure is a protein marker that is specific to the type of cancer. Since tumor cells started out as normal cells, but then became transformed, the tumor will often express different proteins that distinguish them from their normal cell counterparts. **Tumor antigens**, as these proteins are called, have been identified for melanoma, prostate cancer, and several other forms of cancer. Currently in clinical trials, these vaccines are administered to patients who already have cancer to encourage their immune systems to fight it. The vaccine treatment is highly personalized because the patient's own dendritic cells are removed and exposed to the tumor antigen. The process is similar to the way a search and rescue dog works to find a missing person. The dog is "primed" by sniffing an article of the missing person's clothing, and then the dog goes off in search of the same scent. Similarly, dendritic cells that have engulfed the tumor antigens have the ability to "prime" the patient's immune system, essentially training it to seek out and destroy cancer cells. Preliminary evidence suggests that this strategy is effective, but more research still needs to be done.

THE CERVICAL CANCER VACCINE

A new vaccine that produces lasting immunity to HPV is currently in clinical trials and will likely become available to the public very soon. The vaccine is an acellular vaccine that is produced by recombinant DNA technology, just like the hepatitis B vaccine. The vaccine consists of viruslike particles, or VLPs, that are formed from the L1 major capsid protein of HPV. Scientists learned several years ago that when this protein was produced separately from other HPV proteins, it would still assemble into icosahedral capsids. These capsids have no viral DNA inside and are not infectious. These VLPs look just like the real virus to the human immune system, but they can't

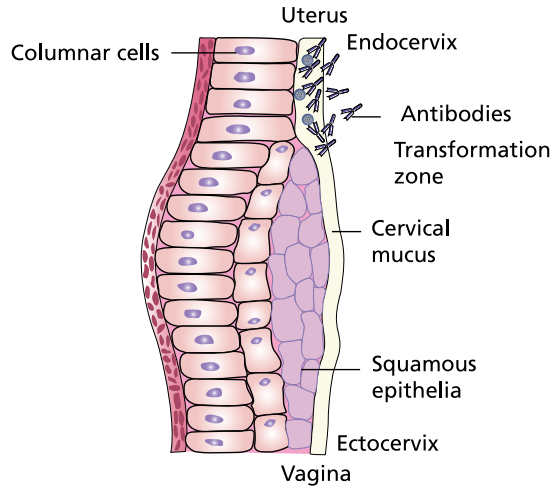


Figure 8.3 Schematic illustration of how antibodies produced by vaccination would help prevent infection in the cervix.

actually infect cells or cause disease (Figure 8.3). The discovery of VLPs was a crucial step in the development of a vaccine for HPV because the virus itself grows so poorly under laboratory conditions.

Two different pharmaceutical companies have developed HPV vaccines. The Belgium-based company GlaxoSmithKline (GSK) has produced what is called a bivalent vaccine, meaning that it protects against infection by two viral strains. This vaccine, called Cervarix®, contains VLPs from the L1 protein of HPV strains 16 and 18, which are implicated in more than 70 percent of all cervical cancers. Meanwhile, the New Jersey–based company Merck has developed a "tetravalent" vaccine, which means that it protects against infections by four strains. The Merck vaccine, called Gardasil®, contains VLPs from the oncogenic HPV strains 16 and 18, as well as the genital

wart–causing strains 6 and 11. Including protection from HPV strains 6 and 11 may provide a stronger incentive for men to get the vaccine, since males and females are equally affected by genital warts.

The HPV vaccine works by stimulating an immune response to the virus, so that in the event of exposure, the body is ready to fight before it can be infected. One of the immune responses that have been measured in clinical trials

THE ABCS OF CLINICAL TRIALS

Clinical trials are research studies that involve human beings. They are carefully conducted in order to find the fastest and safest way to improve human health or find new treatments. There are four types of clinical trials, and all are strictly regulated by the Food and Drug Administration (FDA).

Phase I: The goal is to develop a safety profile of the new treatment. Researchers test an experimental drug or treatment in a small group of healthy volunteers for the first time to study the metabolism of the drug, determine a safe dosage range, and identify any side effects. In some cases, terminally ill patients with no other treatment options may also take part in Phase I trials. The number of human subjects in these studies is generally fewer than 100, and the duration of testing may range from one to three years.

Phase II: A larger number of human subjects is given the drug to further evaluate its safety. In these trials the volunteers are generally patients who have the disease or condition being targeted by the drug. During these studies the optimal dosage of the drug is established. In addition, Phase II tests whether the new drug is as effective or more effective than the currently used treatments.

for both vaccines is the production of protective antibodies. **Antibodies** are proteins that are secreted by immune cells. They bind to and neutralize virus particles, preventing them from infecting the body's cells. Nearly 100 percent of women in Phase II clinical trials for both vaccines were protected from any signs of HPV infection or cervical dysplasia. The first cervical cancer vaccine was approved by the FDA in June 2006.

Phase III: In these trials, the experimental drug or treatment is given to larger groups of people (1,000–3,000) to verify its effectiveness and to monitor side effects or adverse reactions. The new drug is compared to commonly used treatments in a tightly controlled, double-blind manner, meaning that neither the patient nor the people administering the drug know which patients are receiving the drug that is being studied. The aim is to collect information that will allow the experimental drug or treatment to be used safely. Phase III testing generally takes three to four years. If the results indicate that the new drug is effective in treating the condition, a New Drug Application is filed. Upon approval, which may take anywhere from a few months to several years, the company can begin to market the drug.

Phase IV: These are post-marketing studies performed to obtain additional information about the drug's risks, benefits, and optimal use. At this time the company may begin to investigate whether the drug may be useful for treating other conditions, although it is not permitted to advertise such alternative uses. Post-marketing trials can also reveal dangerous side effects of long-term use of the medication. The pain reliever Vioxx® was removed from the market after post-marketing studies showed that users had a greatly increased risk of cardiovascular disease.

UNANSWERED QUESTIONS

Although the evidence shows that the HPV vaccine induces a protective immune response, some questions still remain. To determine how long the protective immunity will last, it will be important to track the early vaccine recipients and clinical trial participants for years to come. By monitoring the levels of protective antibodies that remain in the blood, as well as testing for signs of HPV infection, scientists will be able to determine when a booster might be required.

Another unknown factor is how effective the vaccine will be in men. Merck has begun testing Gardisil in men, but the results have not yet been reported. There have been cases in which vaccines protect men and women differently, a hard lesson learned from earlier herpes vaccine trials. In those studies, a vaccine failed to protect men at all, although a specific subset of women—those who had not previously been infected with either herpes simplex virus type 1 or type 2—were efficiently protected. If the HPV vaccine is effective at protecting men from infection, it could reduce the incidence of genital warts, decrease the risk of penile and anal cancers, and prevent men from spreading HPV to their female partners.

What about the other strains of HPV that can cause cervical cancer? Although HPV 16 and 18 are responsible for 70 percent of the total cases of cervical cancer, that still leaves 30 percent of cervical cases that are caused by other strains of the virus. Vaccinated women would still be at risk for developing cervical cancer due to these viruses. A large international study has shown that by adding VLPs made from the L1 proteins of HPV strains 45 and 31 to the vaccine, another 10 percent of cervical cancers could be prevented. Adding two more strains—HPV X and HPV 33—would reduce about another 5 percent of the cases of cervical cancer, but each strain after that only adds about 1 percent protection. However, the more VLPs that are included in the vaccine, the higher the production costs are likely to be. This may be counterproductive, since it is

women in lower socioeconomic classes and developing countries who would benefit most from the vaccine, and they would not be able to afford a more expensive vaccine.

In addition a host of social issues have been raised by the approval of a vaccine for a virus that is transmitted primarily through sexual intercourse. Some of these social issues are examined in Chapter 9. Regardless of how the vaccine is ultimately used, it is important for women to know that a preventive vaccine for HPV is now available. The vaccine has the potential to save thousands of lives and reduce the incidence of cervical cancer worldwide.

9

The Future of Cervical Cancer

Between the HPV vaccine and the fast and reliable Pap test for screening, cervical cancer could one day be eliminated. All of the tools needed to make that happen are currently available, yet more than 500,000 women worldwide are still diagnosed with cervical cancer each year.

SOCIAL ISSUES AND THE HPV VACCINE

Now that the HPV vaccine has been approved by the FDA for use in the United States, a number of important issues will need to be addressed. A primary concern is who will be vaccinated and at what age. Should all children be immunized, or only females, or only those females who are sexually active? Since there are currently no data showing how long the protective immunity will last, it is hard to recommend the best age for a person to be vaccinated. Some people think the vaccine should be administered as part of the standard childhood immunizations. If the immunity lasts for 40 years, that seems reasonable, but if it lasts for only three or four years, it might make more sense to wait until the children are closer to puberty. Since there are already several booster shots that are given to children in the 11- and 12-year-old age group, there has been some discussion about this being an ideal time to vaccinate for HPV.

Other people oppose any form of mass-vaccination strategy and prefer that teens be educated about abstinence as a way to avoid STDs. Some people feel that the vaccine could encourage teens to engage in casual sex. Unprotected sex can lead to pregnancy and a host of STDs, including HIV and genital herpes, which would not be prevented by the HPV vaccination.

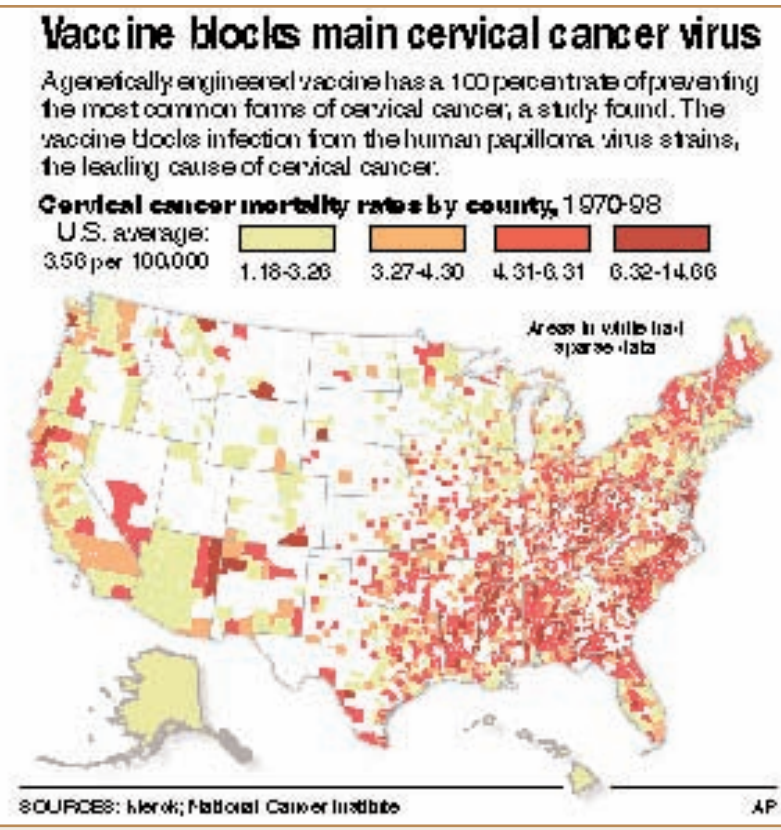


Figure 9.1 ©AP/Wide World Photos

The ultimate decision regarding who should receive the vaccine will be made by a government committee called the Advisory Committee on Immunization Practices, or ACIP. ACIP is a part of the Centers for Disease Control and Prevention (CDC). It is a 15-member panel composed mainly of public health physicians who make up the national list of recommended immunizations. Doctors and clinics follow ACIP guidelines for administering vaccinations, and insurance companies use the guidelines to decide which immunizations they will cover. A recommendation that the HPV

vaccine be placed on the national list would virtually guarantee that the vaccine reaches as many people as possible. Deliberations on the HPV vaccine are already shaping up to be a major battle, with lobbyists for social conservative groups on one side and public health organizations on the other. At the time this book went to press, ACIP had not announced a recommendation for the administration of the cervical cancer vaccine.

The controversy stems largely from the fact that the virus is transmitted sexually. In this sense, the HPV debate echoes the discussion that took place regarding the hepatitis B virus vaccine more than 20 years ago. Hepatitis B virus is also transmitted through sexual intercourse, as well as from mother to child during childbirth. Chronic hepatitis B infection is one of the major risk factors for the development of liver cancer, a disease that kills more than 400,000 people worldwide each year, mostly in developing countries. When the hepatitis B vaccine was first approved by the FDA in 1982, ACIP recommended immunization only for high-risk groups such as health-care workers and intravenous drug users. As a result, there was virtually no change in the levels of hepatitis B infections or the rate of liver cancer in the United States. Meanwhile, because hepatitis B is so prevalent in children born to chronically infected mothers in developing nations, the World Health Organization (WHO) began to support its use as a routine childhood vaccine. Universal hepatitis B vaccination in Taiwan was shown to significantly decrease the incidence of chronic infection and reduce liver cancer rates. In 1991, ACIP revised its original guidelines and recommended that doctors immunize newborns against hepatitis B. Only then did the incidence of hepatitis B infections begin to decline in the United States. The similarities between the current HPV vaccine debate and the hepatitis B situation are remarkable. We can only hope that the outcome regarding HPV is as positive as that for HBV.

A HEAVY PRICE

Whether ACIP recommends the HPV vaccine for national immunizations or not, the vaccine will most likely become available to people in the United States who want it and are able to pay for it. An even bigger social concern is whether the people who need the vaccine most will be able to afford it, both in the United States and in other countries. More than 80 percent of cervical cancer cases occur in developing nations, and almost 30 percent occur in India alone. Both Merck and GSK have indicated that they will make the vaccines available to poorer countries at a discount, but the WHO and other philanthropic agencies will have to help cover the costs and administer the vaccines. The Bill and Melinda Gates Foundation has already granted $7 million to the WHO to help introduce vaccines to the developing nations that need them.

GLOBAL MEDICINE: THE WORLD HEALTH ORGANIZATION

The World Health Organization (WHO) was established in 1948 as the health agency for the United Nations (UN). The WHO's objective is to help all people attain the highest possible level of health. Health is defined in the WHO's constitution as a state of complete physical, mental, and social well-being, not merely the absence of disease.

The WHO was the driving force behind the successful eradication of smallpox, and it is currently poised to eradicate polio by the end of the decade. Other WHO efforts are aimed at immunizing children in developing nations against preventable childhood illnesses such as measles and tetanus. The WHO will likely play a pivotal role in ensuring that women in developing nations have access to the new HPV vaccine in order to reduce the incidence of cervical cancer worldwide.

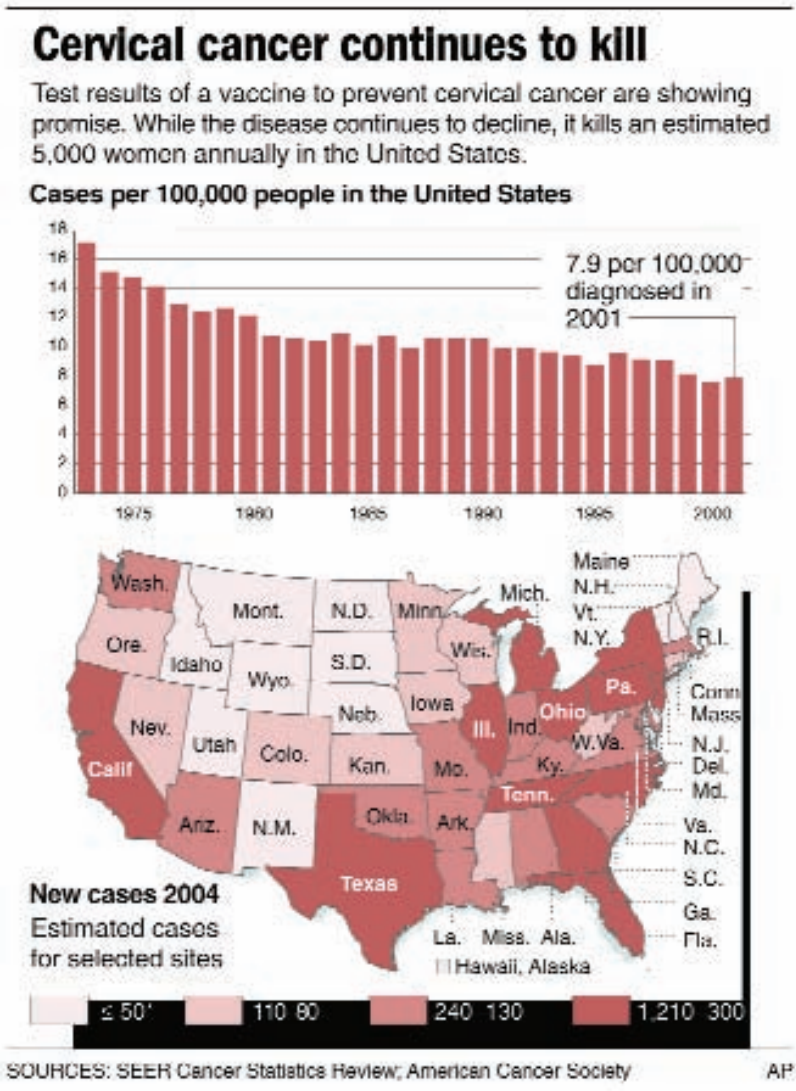


Figure 9.2 ©AP/Wide World Photos

FILLING THE CRACKS

Even with the advent of vaccines, will the cervical cancer rate really go down in United States? Although the vaccines that are

currently in development have the potential to make an impact on the incidence of cervical cancer worldwide, HPV infection is still widespread and cervical cancer will never be eliminated without vaccines to cover all oncogenic strains. The current vaccines offer protection only against HPV 16 and HPV 18, and these strains cause only about 70 percent of cervical cancers. As a result, it is essential that women continue to undergo yearly Pap smears. Even in the United States, where many women are routinely screened, there is a concern that women will think they no longer need Pap testing once they have been vaccinated against HPV. For women of low socioeconomic status who already have limited access to health care, getting vaccinated will not make Pap testing more accessible. The same is true in developing nations, where women not only need to be vaccinated, but strategies for making basic health care more accessible to all people must be developed.

The future of cervical cancer is now. We currently have all the tools needed to eliminate this health problem: education about risk factors; an effective vaccine; and a simple, reliable screening procedure. If cervical cancer continues to kill women 50 years from now, it will be because not enough attention was paid and insufficient energy expended to stop the pain and suffering.

Glossary

abdominal hysterectomy—The surgical removal of the uterus through an incision in the abdomen.

acellular—Not composed of cells.

adenocarcinoma—A maliganant adenoma, or tumor arising from epithelial gland cells.

adenoma—A type of growth that originates from epithelial cells, typically from the lining of glands or digestive organs.

AGUS—A pap smear result in which there are some abnormal glandular cells present, but it is not certain whether this indicates cancer.

amniotic sac—A thin membrane that contains the developing fetus and the amniotic fluid that surrounds and cushions the fetus.

anaphase—A stage of mitosis in which sister chromatids separate from each other and move toward opposite ends of the cell.

antibodies—A protein produced by the immune system to bind to and clear foreign particles or organisms.

apoptosis—An orderly program of cell death.

ASC-H—A qualification of the ASCUS pap smear result; a more serious finding that can not rule out abnormal changes due to cancer.

ASCUS—A pap smear result with atypical squamous cell changes of undetermined significance; suspicious results that do not appear cancerous but do not appear normal either.

attenuated—Refers to a weakened, nonpathogenic, live microorganism, typically used for vaccines.

basal cells—A single layer of tall, simple columnar epithelial cells that undergo rapid cell division to replenish the skin layers that are regularly lost by shedding from the surface.

basement membrane—A matrix of materials such as collagen and other fibrous proteins located beneath a cell or tissue layer.

benign—A growth that is not malignant or does not invade nearby tissue.

biopsy—A procedure to remove a small sample of tissue that will be examined under a microscope for signs of disease.

biota—Normal, harmless bacteria and other organisms present in parts of the body.

blastoma—A type of cancer that is caused by malignancies in precursor cells, which are often called "blasts."

Body Mass Index (BMI)—A measurement of a person's weight scaled according to height; used as a means of classifying people as underweight or overweight.

booster—A follow-up vaccination given after a previous vaccination to help maintain or increase the protective immune response.

cachexia—The weight loss and wasting that can occur in terminal cancer patients, resulting from starvation and debilitation of the patient by the cancer.

candidiasis—Commonly called a yeast infection, this is a fungal infection by any species of the organism *Candida.*

capsid—The outer protein coat of a virus that serves to transport and protect the genetic material.

capsomers—Smaller subunits that stick out from the outer capsid of a virus; these may serve as a point of attachment to a host cell.

carcinoma—A type of cancer that begins in the lining or covering of an organ.

carcinoma in situ—Cells or tissue that is not truly cancerous, but likely to become cancerous; sometimes referred to as Stage 0 cancer or "cancer in waiting."

cell cycle—The period of time it takes a cell to complete all the steps required for cell division.

cell cycle checkpoints—Spots where the cell cycle may be paused or even aborted if there is cellular damage, particularly to DNA.

cells—The individual units that makes up all tissues of the body. All living things are made up or one or more cells.

cervical incompetence—Condition where a weakened cervix may be unable to support a fetus during pregnancy; a common cause of miscarriage.

cervical mucus—Liquid secretions from the glandular cells lining the cervix.

cervix—The narrow end of the uterus that forms a canal between the uterus and the vagina.

clitoris—A region of the vulva that protrudes slightly and is sometimes compared to the male penis because it is a source of sexual stimulation.

Glossary

colposcope—A medical instrument used for gynecological exams.

colposcopy—Examination of the vagina and cervix using a lighted magnifying instrument called a colposcope.

condylomata acuminata—Genital warts caused by infection with specific strains of HPV.

conization—Surgery to remove a cone-shaped piece of tissue from the cervix and cervical canal; also called a cone biopsy.

cryotherapy—The procedure of freezing tissue to kill and remove abnormal growths.

cutaneous—Relating to the surface, as in the outer surface of the skin.

cyst—A closed sac that has a distinct membrane and develops abnormally in a cavity or structure of the body. Cysts may be filled with air, fluid, or other semisolid materials.

cytology—The study of abnormal cellular changes that can be used as markers of disease.

cytopathologist—A technician trained to identify abnormal cellular characteristics associated with disease states.

cytoplasm—The semisolid material located between the nucleus and the plasma membrane of a eukaryotic cell.

dendritic cells—Specialized white blood cells that engulf foreign particles or organisms and use them to stimulate an immune response.

diagnosis—The process of identifying a disease by the signs and symptoms.

douche—A procedure in which water or a medicated solution is used to clean the vagina and cervix.

dysplasia—Cells that appear abnormal under a microscope but are not cancerous.

ectocervix—The portion of the cervix that extends into the vagina and is lined with stratified squamous epithelial cells.

ectopic pregnancy—Occurs when the fertilized egg implants at a site other than the uterus, most commonly the fallopian tubes.

endemic—Refers to a disease or infection that is always present in the population.

endocervical canal—The narrow channel of the cervix that connects the uterus to the vagina.

endometriosis—A common medical condition in which cells from the tissue lining the uterus (the endometrium) are found outside of the uterus and can affect other organs in the pelvic region.

endometrium—The layer of tissue that lines the cervix and is shed monthly during the menstrual cycle.

epidemiology—The study of where and when diseases occur and how they are transmitted in human populations.

epithelial cells—The individual cells found in the epithelium.

epithelium—A tissue composed of a layer of cells. Epithelium lines both the outside (skin) and the inside (such as the intestine) of many living organisms.

external os—The place where the cervix opens to the vagina.

external radiation—The therapeutic application of radioactivity to the outside of the body in a localized region, generally for cancer treatment.

fallopian tubes—A part of the female reproductive tract; long slender tubes through which the eggs pass from the ovaries to the uterus.

false negatives—When laboratory test results appear negative even though the condition actually exists in the patient.

fertility—The ability to produce children.

fibroids—A common term for fibromas, especially those that occur in the uterus.

fibroma—Benign tumors that are composed of fibrous or connective tissue.

gametes—Specialized cells (either the sperm or the egg) that are combined in sexual reproduction to initiate development of a new individual.

genes—Units of heredity.

genital warts—The common term for condyloma acuminata—raised bumps in the groin region that are generally caused by HPV infection.

genome—The total genetic information carried by a cell or an organism.

G1 phase—A period of the cell cycle in which the cell is producing proteins and growing; sometimes called Gap1 or Growth1 phase.

Glossary

gynecologist—A doctor who specializes in the care and treatment of women's reproductive systems.

HPV DNA test—A diagnostic test used to detect the presence of genetic material from oncogenic strains of HPV in a cervical tissue sample.

HSIL—High-grade squamous intraepithelial lesions; a diagnosis of abnormal cells on a Pap smear.

hymen—A ring of tissue around the vaginal opening.

hysterectomy—A surgical procedure in which the uterus is removed.

icosahedron—A 20-sided geometric shape commonly observed in virus capsids.

inactivated vaccines—Material used to elicit an immune response that does not contain any living microorganisms.

infertility—The inability to produce children.

internal os—The opening of the cervix into the uterus.

internal radiation—The therapeutic application of radioactivity to the inside of the body in a localized region, such as the vagina, generally for cancer treatment.

interphase—Includes all phases of the cell cycle except mitosis.

in vitro fertilization—A process in which female eggs and male sperm are combined in a laboratory and allowed to develop into an embryo that is then implanted into a female uterus.

keratinocytes—Specialized cells in the outermost layers of human skin, they contain large quantities of a tough, fibrous protein called keratin.

koilocytosis—A distinctive abnormality in the appearance of cervical cells, in which some of the nuclei are surrounded by space, or vacuoles.

labia majora—The outer two lips that protect the inner vulva.

labia minora—The inner two lips of the vulva that protect the clitoris.

laparoscopic surgery—A surgical technique designed to minimize blood loss and risk to the patient by inserting a lens cabled to a video camera through the navel to direct the surgeon to organs requiring treatment in the abdomen or pelvis.

LEEP—Loop eletrocautery excision procedure; the removal of abnormal tissue using an electrical loop.

liquid-based cytology—A newer technique for improving the spreading of cells for the Pap smear test.

LSIL—Low-grade squamous intraepithelial lesions; diagnosis of mildly abnormal cells on a Pap smear.

malignant—A growth that is truly cancerous—capable of invading, spreading, and destroying tissue.

margins—The distances between the tumor and the edge of the tissue sample, as in a biopsy.

metaphase—The stage of mitosis in which sister chromatids are aligned in the center of the cell.

metastasis—The spread of cancer from one part of the body to another site. These sites are often called secondary tumors.

mitosis—The period during the cell cycle when replicated chromosomes in one cell separate and segregate to form the nuclei for two daughter cells; also called M phase.

mitotic spindle—A network of proteins that attach to and arrange the replicated chromosomes for separation in a dividing cell.

M phase—The period during the cell cycle when replicated chromosomes in one cell separate and segregate to form the nuclei for two daughter cells; also called mitosis.

mucosal—Thin, fragile layers of skin found covering moist surfaces, as in the mouth, vagina, and anus.

neoplasm—A tumor or mass of cells resulting from abnormal growth.

nucleotide bases—The chemical subunits that make up genetic material; the building blocks of DNA.

nucleus—The control center of a cell, it contains the genetic material and is separated from the rest of the cell by a double membrane.

oncogene—A gene that is capable of promoting abnormal growth.

oncogenic—Causing cancer or promoting tumor growth.

oncology—A medical specialty dealing with the study and treatment of cancer.

oncoproteins—Proteins that have the ability to transform a normal cell into a cancerous one.

Glossary

organs—Groupings of cells and tissues into a distinct structure that performs a specialized task.

ova—Gametes, or eggs, produced by the female ovaries.

ovaries—A pair of female reproductive organs that produce eggs and hormones.

ovulation—The release of an egg from an ovary during the menstrual cycle.

palpate—To examine by pressing on the surface of the body to feel the organs or tissues underneath.

papillomas—Benign tumors growing from the epithelium of skin and mucous membranes, usually associated with HPV infection.

Pap smear—Collection of cells from the cervix for examination under a microscope, used to observe changes that may lead to cancer.

pathogen—A microorganism that causes disease.

placenta—A temporary organ that develops in pregnant females to help provide nutrients to the developing fetus and filter harmful materials away from it.

precancerous—A term used to describe a condition that may (or is likely to) become cancer.

prophase—The stage of mitosis during which chromosomes condense and the mitotic spindle forms.

proto-oncogene—A normal gene that controls cell growth but has the potential to be altered, giving rise to an oncogene.

radical hysterectomy—The surgical removal of the uterus, cervix, and additional parts of the female reproductive tract, such as fallopian tubes, local lymph nodes, and portions of the vagina.

reactive cellular changes—A Pap smear finding that indicates that cells may be showing signs of or responding to a recent infection.

recombinant DNA technology—Procedures for combining DNA from different sources.

reproductive system—All of the organs used in the creation of offspring.

retrovirus—A virus that has an RNA genome that is converted to DNA and inserted into the host cell's genome.

risk factor—A variable associated with an increased risk of disease or infection.

sarcoma—Cancer that originates from connective or supportive tissues, such as bone, cartilage, muscle, or fat.

screening—Checking for disease when there are no symptoms.

side effects—Unintended adverse effects of treatment with a drug.

sister chromatids—The two DNA strands of a duplicated chromosome.

speculum—A medical tool used to examine body cavities.

S Phase—A period of the cell cycle in which the cell's DNA is replicated.

staging—The process used to determine how advanced a cancer is.

systemic—Something that affects the entire body and is usually carried in the bloodstream.

telophase—The final stage of mitosis during which the nuclear envelopes reform around each of the two sets of chromosomes and the cell is split in two.

tissues—Groups of like cells that are arranged together and perform similar functions. Cells are organized into tissues, and tissues are organized into organs.

total hysterectomy—Surgical removal of the body of the uterus and the cervix.

toxoids—Inactivated forms of toxins that are used for immunizations.

transformation zone—The abrupt transition from simple columnar epithelium cells to stratified squamous cells in the cervix; location where most cervical cancers originate.

transforming—Having the ability to convert normal cells into cancerous ones.

tumor—An abnormal growth or mass of cells; also called a neoplasm.

tumor antigens—Substances derived from the cancer that elicit an immune response.

tumorigenic—Having the ability to cause tumor growth.

tumor suppressors—Genes that prevent tumor formation. When they are mutated or inactivated, tumors are more likely to form.

urinary tract infection (UTI)—An infection of the urinary system that may be caused by bacteria, viruses, or fungi.

Glossary

uterus—The small, hollow, pear-shaped organ in a woman's pelvis; the place where the fetus develops.

vaccines—Substances that are administered to generate a protective immunity to disease.

vagina—The muscular canal extending from the end of the uterus to the exterior of the body; also called the birth canal.

vaginal hysterectomy—The surgical removal of the uterus through an incision made at the top of the vagina.

vaginitis—Inflammation of the vagina, usually due to infection.

virus—An intracellular parasite that is not a living entity, but an agent that uses living cells to reproduce.

vulva—Female genitalia; the exterior structures of the female anatomy.

Bibliography

"Alliance for Cervical Cancer Prevention Receives $50 Million Gift From Bill and Melinda Gates." Available online. URL: http://www.gatesfoundation.org/globalhealth/pri_diseases/otherinfectiousdiseases/announcements/announce-98.htm. Accessed May 30, 2006.

American Cancer Society. "Cancer Facts & Figures 2005." Available online. URL: http://www.cancer.org/docroot/STT/stt_0.asp. Accessed May 11, 2006.

———. "Cancer Prevention and Early Detection Facts and Figures 2005." Available online. URL: http://www.cancer.org/docroot/STT/stt_0.asp. Accessed May 11, 2006.

———. "Cervical Cancer: Detailed Guide." Available online. URL: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_is_cervical_cancer_8.asp. Revised October 31, 2005.

Anne, Enright. "What's Left of Henrietta Lacks?" *London Review of Books.* Available online. URL: http://www.lrb.co.uk/v22/n08/enri01_.html. Updated May 11, 2006.

Bellenir, K., ed. *Cancer Sourcebook for Women*, 2nd ed. Detroit: Omnigraphics, 2002.

Burkitt, D. "A Lymphoma Syndrome in Tropical Africa." *International Review of Experiment Pathology* 2 (1963): 67–138.

Calle, E. E., C. Rodriguez, K. Walker-Thurmond, and M. J. Thun. "Overweight, Obesity, and Mortality From Cancer in a Prospectively Studied Cohort of U.S. Adults." *New England Journal of Medicine* 348(17) (2003): 1625–1638.

Canavan, T. P., and N. R. Doshi. "Cervical Cancer." *American Family Physician* 61(5) (2000): 1369–1376.

CBS Broadcasting Inc. "Merck: Cervical Cancer Vaccine Effective." Available online. URL: http://cbs5.com/health/health_story_280231349.html. Accessed May 11, 2006.

Chang, M. H., W. Y. Shau, C. J. Chen, T. C. Wu, M. S. Kong, D. C. Liang, H. M. Hsu, H. L. Chen, H. Y. Hsu, and D. S. Chen. "Hepatitis B Vaccination and Hepatocellular Carcinoma Rates in Boys and Girls." *The Medical Journal of Malaysia* 60 Suppl B (2005): 63–66.

China Internet Information Center. "Fans Mourn Hong Kong Pop Star Anita Mui." Available online. URL: http://big5.china.com.cn/english/culture/83803.htm. Accessed January 2, 2004.

Bibliography

Christensen, N. D., N. M. Cladel, C. A. Reed, L. R. Budgeon, M. E. Embers, D. M. Skulsky, W. L. McClements, S. W. Ludmerer, and K. U. Jansen. "Hybrid Papillomavirus L1 Molecules Assemble into Virus-like Particles That Reconstitute Conformational Epitopes and Induce Neutralizing Antibodies to Distinct HPV Types." *Virology* 291(2) (2001): 324–334.

Cohen, J. "High Hopes and Dilemmas for Cervical Cancer Vaccine." *Science* 308 (2005): 618–-621.

Epstein, M. A, B. G. Anchong, and Y. M. Barr. "Morphological and Biological Studies on a Virus in Cultured Lymphoblasts from Burkitt's Lymphoma." *Journal of Experimental Medicine* 121 (1965): 761–770.

Eroschenko, V. P. *DiFiore's Atlas of Histology with Functional Correlations*, 10th ed. Philadelphia: Lippincott William Wilkins, 2005.

Fields, B. N., D. M. Knipe, and P. M. Howley, eds. *Fields Virology*, 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1996.

Gold, M. *A Conspiracy of Cells: One Woman's Immortal Legacy and the Medical Scandal It Caused*. Albany: State University of New York Press, 1986.

Greenwood, D., R.C.B. Slack, and J. F. Peutherer, eds. *Medical Microbiology: A Guide to Microbial Infections: Pathogenesis, Immunity, Laboratory Diagnosis, and Control*, 16th ed. London: Churchill Livingston, 2002.

Guyon, J. "The Coming Storm Over a Cancer Vaccine: Christian Conservatives Fear That New, Amazingly Effective Cervical-cancer Vaccines Will Spur Promiscuity and Undermine Abstinence. Let the Lobbying Wars Begin." *Fortune* 152(9) (2005): 123.

Ingraham, J. L., and C. A. Ingraham. *Introduction to Microbiology*, 3rd ed. Pacific Grove, CA: Brooks/Cole-Thomson Learning, Inc., 2004.

Jiménez-Pérez, M., and D. B. Thomas. *Reproductive Factors and Risk of Cervical Cancer in Guadalajara, Mexico*. 128th Annual Meeting of APHA.

Kerr, J. *Atlas of Functional Histology*. London: Mosby, 2000.

Laberge, M. "Colpotomy." In *Gale Encyclopedia of Surgery: A Guide for Patients and Caregivers*, edited by Anthony J. Senagore, M.D., 331–334. Detroit: Gale, 2004.

Lenz, P., P. M. Day, Y. Y. Pang, S. A. Frye, P. N. Jensen, D. R. Lowy, and J. T. Schiller. "Papillomavirus-like Particles Induce Acute Activation of Dendritic Cells." *Journal of Immunology* 166(9) (2001): 5346–5355.

Levi, J. E., B. Kleter, W. G. Quint, M. C. Fink, C. L. Canto, R. Matsubara, I. Linhares, A. Segurado, B. Vanderborght, J. E. Neto, and L. J. Van Doorn. "High Prevalence of Human Papillomavirus (HPV) Infections and High Frequency of Multiple HPV Genotypes in Human Immunodeficiency Virus-infected Women in Brazil." *Journal of Clinical Microbiology* 40(9) (2002): 3341–3345.

Lodish, H., et al. *Molecular Biology of the Cell*, 5th ed. New York: W. H. Freeman and Co., 2004.

Mahon, C. R., and G. Manuselis, eds. *Textbook of Diagnostic Microbiology*. Philadelphia: W. B. Saunders Company, 2000.

Murray, P., K. S. Rosenthal, G. S. Kobayashi, and M. A. Phaller. *Medical Microbiology*. St. Louis, MO: Mosby, Inc., 2002.

National Cancer Institute. "Cervical Cancer." Available online. URL: http://www.cancer.gov/cancertopics/types/cervical/. Accessed May 11, 2006.

———. "Clinical Trials: Questions and Answers." Available online. URL: http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials. Accessed May 11, 2006.

———. "NCI Challenge Goals 2015: Eliminating the Death and Suffering Due to Cancer." Available online. URL: http://www.cancer.gov/about-nci/2015. Accessed May 11, 2006.

National Cervical Cancer Public Education Campaign. Available online. URL: http://www.cervicalcancercampaign.org/. Updated January 13, 2006.

Palefsky, J. *What Your Doctor May Not Tell You about HPV and Abnormal Pap Smears*. New York: Warner Books, Inc., 2002.

Papanicolaou, G. N. *New Cancer Diagnosis*. Proceedings of the Third Race Betterment Conference, January 1928. Battle Creek, MI: Race Betterment Foundation, 1928, pp. 528–534.

Papanicolaou, G. N., and H. F. Traut. "The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus." *American Journal of Obstetrics and Gynecology* 42 (1941): 193–206.

Parker, William H., with Rachel L. Parker. *A Gynecologist's Second Opinion*, 2nd ed. New York: The Penguin Group, 2003.

Quak, S. C., T. Mould, K. Canfell, A. Singer, V. Skladnev, and M. Coppelson. "The Polarprobe—Emerging Technology for Cervical Cancer Screening." *Annals of the Academy of Medicine*, Singapore 27 (1998): 717–721.

Bibliography

R. Skloot. "Henrietta's Dance." *Johns Hopkins Magazine*. April 2000. Available online. URL: http://www.jhu.edu/~jhumag/0400web/01.html. Accessed May 11, 2006.

Ross, M. H., G. I. Kaye, and P. Wojciech. *Histology*: *A Text and an Atlas*. Baltimore: Lippincott Williams & Wilkins, 2003.

Srivatanakul, P., H. Sriplung, and S. Deerasamee. "Epidemiology of Liver Cancer: An Overview." *Asian Pacific Journal of Cancer Prevention* 5 (2004): 118–125.

Stein, R. "Cervical Cancer Vaccine Gets Injected with a Social Issue". *The Washington Post*, October 31, 2005.

Sweeney, Julia. *God Said "Ha!"* New York: Bantam Books, 1997.

Van Tine, B. A., L. D. Dao, S. Y. Wu, T. M. Sonbuchner, B. Y. Lin, N. Zou , C. M. Chiang, T. R. Broker, and L. T. Chow. "Human Papillomavirus (HPV) Origin-binding Protein Associates with Mitotic Spindles to Enable Viral DNA Partitioning." *Proceedings of the National Academy of Sciences United States of America* 101(12) (2004): 4030–4035.

Wagner, E. K., and M. J. Hewlett. *Basic Virology*, 2nd ed. Malden, Mass.: Blackwell Science, Inc., 2004.

World Health Organization. "About WHO." Available online. URL: http://www.who.int/about/en/. Accessed May 11, 2006.

Wright, T. C., J. T. Cox, L. S. Massad, L. B. Twiggs, and E. J. Wilkinson. "2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities." *Journal of the American Medical Association* 287 (2002): 2120–2129.

Young, B., and J. W. Heath. *Wheater's Functional Histology: A Text and Colour Atlas*, 4th ed. London: Churchill Livingston, 2000.

Zur Hausen, H. "Papillomaviruses Causing Cancer: Evasion from Host-cell Control in Early Events in Carcinogenesis." *Journal of the National Cancer Institute* 92(9) (2000): 690–698.

Further Reading

Bellenir, Karen, ed.. *Cancer Sourcebook for Women.* Detroit: Omnigraphics, 2002.

Gold, Michael. *A Conspiracy of Cells: One Woman's Immortal Legacy and the Medical Scandal It Caused.* Albany: State University of New York Press, 1986.

Palefsky, Joel. *What Your Doctor May Not Tell You about HPV and Abnormal Pap Smears.* New York: Warner Books, 2002.

Parker, James N., and Philip M. Parker, eds. *The Official Patient's Sourcebook on Cervical Cancer: A Revised and Updated Directory for the Internet Age.* San Diego: Icon Health Publications, 2002.

Parker, William H. *A Gynecologist's Second Opinion: The Questions and Answers You Need to Take Charge of Your Health.* New York: The Penguin Group, 2003.

Plourde, Elizabeth. *Hysterectomy: The Best or Worst Thing that Ever Happened to Me?* Irvine, CA: New Voice Publications, 2003.

Weinberg, Robert. *One Renegade Cell.* New York: Basic Books, 1998.

Web Sites

American Cancer Society
http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=8

CDC HPV Fact Sheet
http://www.cdc.gov/std/HPV/STDFact-HPV.htm#common

Oncology Channel: Cervical Cancer
http://oncologychannel.com/cervicalcancer/

National Cancer Institute
http://www.cancer.gov/cancertopics/types/cervical/

National Cervical Cancer Coalition
http://www.nccc-online.org/

Women's Cancer Network
http://www.wcn.org/index.cfm

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About the Author

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