PART

9

FEMALE REPRODUCTIVE SYSTEM DISORDERS

CASE STUDY

63 CANCER OF THE FEMALE BREAST

For the Patient Case for this case study, see the printed book.

DISEASE SUMMARY

Definitions

Breast cancer (BC) is a very common and aggressive growth of transformed cells that originates in the breast. It has the potential to invade surrounding tissues, spread to distant sites in the body, deprive healthy tissues of oxygen and nutrients, cause significant organ damage, and, ultimately, kill the patient. Furthermore, BC is not just one disease. Numerous subtypes of BC have been identified. Subtypes tend to vary in behavior and carry a different prognosis (i.e., probability for recovery).

Breast cancer generally arises from the epithelial lining cells of the large or intermediate-sized milk ducts of the breast (i.e., *ductal carcinomas*) or from epithelial cells of the terminal milk ducts of the lobules (i.e., *lobular carcinomas*). Most breast cancers (80–90%) arise from the intermediate-sized milk ducts of the breast and are invasive (i.e., *infiltrating ductal carcinoma,* IDC). Most subtypes of BC are merely types of IDC with different growth patterns. *Infiltrating lobular carcinomas* (ILC), the second most common type of BC, account for another 6–8% of all BC. The most aggressive form of breast cancer, *inflammatory carcinoma*, constitutes <3% of all cases.

Prevalence

The United States has the highest reported incidence of BC in the world. Furthermore, second only to non-melanoma skin cancer (which is rarely fatal), BC is currently the most frequently diagnosed cancer in American women. Breast cancer currently comprises 26% of all potentially fatal cancers diagnosed in American women. The American Cancer Society has estimated that there will be 182,460 new cases of invasive BC in females in the United States in 2008. In addition to invasive BC, 67,770 new cases of in situ BC are expected to be detected in women in 2008, principally by mammography screening. In situ *BC* means that the cancer is in its earliest stage and cancerous cells have not begun to spread from their site of origin. Among American women, 13.4% (1 of every 7–8 women) will be diagnosed with BC in their lifetime. In 1940, the lifetime risk of a woman developing BC was only 5% (1 in every 20 females).

Breast cancer can occur at any age. However, the probability for developing the disease begins to increase significantly between ages 25–30 years and most cases occur in women older than age 50 years. Mass screening programs consisting of physical and mammographic examinations of the breasts identify approximately 10 cases of BC per 1,000 women older than age 50 years (≈77% of all cases) and 2 cases/1,000 women younger than age 50 years.

Disease Summary Table 63.1 Approximate Frequencies of Breast Cancer in the United States by Race/Ethnic Group

Race/Ethnic Group	Cases of Breast Cancer Per 100,000 American Women
Whites	132–133
African-Americans	118
Hispanics/Latinos	89
Asian-Americans & Pacific Islanders	89
American Indians & Alaska Natives	70

Source: American Cancer Society website. 2008 Cancer Facts and Figures. Available at: www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf. Date accessed: February 2008, Table titled "Cancer Incidence and Mortality Rates by Site, Race and Ethnicity, US, 2000–2004," p. 44.

Breast cancer is extremely rare in women younger than age 25 years. The average age at time of diagnosis is 60–61 years.

There are racial/ethnic predispositions to BC in the United States. It has been estimated that one of every eight non-Hispanic white women will develop BC during her lifetime. For African-American women, the overall lifetime risk is 1 in 14. However, among women ages 40–50 years, African-American women have a higher incidence of BC than do Caucasian women. The lifetime risks for New Mexican Hispanics and New Mexican American Indians are 1 in 21 and 1 in 40, respectively. Approximate frequencies of BC in the United States by race/ethnic group are shown in descending order in Disease Summary Table 63.1.

Over the past 50 years, the number of women diagnosed with BC has increased every year. The overall frequency of the disease in the United States had been gradually increasing at the rate of 0.5% each year from 1987–2001, but now appears to be leveling off at approximately 11 cases per 10,000 women. There is some evidence that the incidence of BC among non-white populations (especially African-Americans) is still increasing, particularly among younger women. Although BC can also develop in males, it is 100 times more common in women. The predicted number of new breast cancers in men for 2008 is 1990.

Worldwide, the incidence of BC varies markedly among countries but appears to be increasing overall. Far Eastern countries (e.g., Japan), which historically have enjoyed low rates of BC in comparison with the United States, have seen as much as a two-fold increase in incidence in the past several decades.

Significance

Breast cancer elicits many fears, including those relating to surgery, loss of body image, loss of sexuality, and death. It is a potentially life-threatening illness and currently ranks second to lung cancer as a cause of cancer-related death in American women. Breast cancer now causes 15% of all cancer-related deaths among women in the United States. *Breast cancer is also the leading cause of death in the U.S. among women ages 40–44 years*. More than 3% of all women in the United States are now dying from BC. An estimated 40,480 deaths in women are expected in 2008. ***African-American women have the highest mortality rate from BC in the United States.*** Approximate mortality rates from breast cancer in the United States by race/ethnic group are shown in descending order in Disease Summary Table 63.2.

Breast cancer is much more difficult to treat after it spreads, and >30% of women in whom BC is diagnosed also learn that the disease is already far advanced.

Causes and Risk Factors

The exact cause of BC has not been established and, although research studies in this area are still preliminary, BC eventually may prove to have multiple causes. A significant number of research studies conducted during the past two decades have begun to establish risk factors. Some factors that may place a woman at risk for BC include hormonal influences, factors related to reproduction, environmental/lifestyle influences, family history, and increasing age. ***Increasing age is the single most significant factor that increases risk for developing BC in women today.***

Disease Summary Table 63.2 Approximate Mortality Rates for Breast Cancer in the United States by Race/Ethnic Group

Race/Ethnic Group	Deaths from Breast Cancer Per 100,000 American Women
African-Americans	34
Whites	25
Hispanics/Latinos	16
American Indians & Alaska Natives	16
Asian-Americans & Pacific Islanders	12–13

Source: American Cancer Society website. 2008 Cancer Facts and Figures. Available at: www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf. Date accessed: February 2008, Table titled "Cancer Incidence and Mortality Rates by Site, Race and Ethnicity, US, 2000–2004," p. 44.

Cancer-causing mutations in several BC susceptibility genes account for approximately 5–10% of all cases of breast cancer and up to 80% of all BC in women younger than 50 years of age. Two BC susceptibility genes—BRCA1 on chromosome 17 and BRCA2 on chromosome 13—account for most inherited forms of BC. Other gene mutations and genetic syndromes that have been linked to breast cancer include the following:

- PTEN mutation (Cowden disease)
- STKII/LKB1 mutation (Peutz-Jeghers syndrome)
- ATM mutation (ataxia telangiectasia)
- MSH2/MLH2 mutation (Muir-Torre syndrome)
- CHEK-2 mutation (cell-cycle checkpoint kinase 2 defect)

Although risk factors are commonly associated with BC, ***most women (3 of 4) who develop the disease have no identifiable risk factors.*** The medical literature is extensive, complicated, and somewhat confusing with regard to the risk factors of BC. The author has attempted to both simplify and clarify information relative to these risk factors with Disease Summary Table 63.3.

There has been some speculation and controversy over the years regarding the roles of hormone replacement therapy, smoking, use of oral contraceptives, alcohol consumption, and radiation exposure as risk factors of BC. Conflicting data continue to preclude the recommendation of guidelines for risk modification in these areas. Although the data is not as clear for these risk factors as those listed in Disease Summary Table 63.3, several large, well-controlled studies that were published in highly reputable medical journals are beginning to sort out these risks.

The best evidence for the benefits and risks of hormone replacement therapy is derived from the Women's Health Initiative (WHI). In July 2002, during a large study of 16,000 healthy women sponsored by the National Institutes of Health, researchers reported that hormone therapy, once considered standard treatment for menopausal symptoms, posed more health risks than benefits. Among these health risks was a *slightly higher risk* for BC among women taking a combination of estrogen and progesterone for several years. Combined hormone therapy also increased the probability that BC would be diagnosed at a more advanced stage. Risk seemed to normalize to that of the general population after discontinuation of hormone replacement therapy for at least 5 years. In March 2004, it was concluded from the WHI that those women taking estrogen alone had no increased risk for BC. Furthermore, data from the Breast Cancer Detection Demonstration Project indicated that long-term (>15 years) postmenopausal estrogen therapy alone did not increase the risk for BC.

A Mayo Clinic study published in April 2001 found that smoking significantly increases the risk for breast cancer in women with a family history of BC. Furthermore, a 2005 study published in the *International Journal of Cancer* revealed that exposure to secondhand smoke also increases the risk for BC in premenopausal women. The California Environmental Protection Agency had made a similar observation 1 year earlier.

A large study of women ages 35–64 years and published in the June 2002 edition of the *New England Journal of Medicine* concluded that current or former use of oral contraceptives did not significantly increase the risk for BC. Although there are conflicting data, most research studies—including the highly reputable Women's Contraceptive and Reproductive Experience conducted 1994–1998—have not revealed an increased risk for BC from the use of oral contraceptives.

Disease Summary Table 63.3 Factors That Increase Risk for Breast Cancer and Degrees of Risk

Factors That Increase Risk for Breast Cancer	Degree of Risk
Family History	
First-degree relative with breast cancer that developed before menopause	3
First-degree relative with bilateral breast cancer	3
Two first-degree relatives with breast cancer	3
Inherited mutation of BRCA1	3*
Inherited mutation of BRCA2	3**
Inherited mutation of p53 tumor suppressor gene (Li-Fraumeni syndrome)	3
First-degree relative with breast cancer before age 60	2
First-degree relative with breast cancer that developed after menopause	1
Previous Breast Disorders	
Ductal carcinoma in situ	3
Lobular carcinoma in situ	3
Fibrocystic change characterized microscopically by "atypical hyperplasia"	3#
Breast mass characterized microscopically by "moderate hyperplasia"	1
Breast mass characterized microscopically by "papillomatous changes"	1
Menstrual History	
Early onset of menses (before age 12)	1
Late natural menopause (after age 55)	1
Pregnancy	
No term pregnancies (*nulliparity*)	1
First full-term pregnancy after 30 years of age	1
Miscellaneous	
Postmenopausal obesity (especially excess fat around the waist)	1
High socioeconomic status	1
Physical inactivity	1

Adapted with permission from Morgan K, McCance KL. Disorders of the female breast: Cancer. In: McCance KL, Huether SE, eds. Pathophysiology: The Biologic Basis for Disease in Adults and Children. 5th Ed. St. Louis: Elsevier Mosby, 2006;Table 23-14:831. Original source: Lester SC. The breast. In: Kumar V, Abbas AK, Fausto N, eds. Robbins and Cotran Pathologic Basis of Disease. 7th Ed. Philadelphia: Saunders, 2005.
3, extremely high risk, >4-fold increase; 2, major risk, 2- to 4-fold increase; 1, slight-modest increase in risk, <2-fold increase
*Lifetime risk for breast cancer in females with this mutation is 36–87%.
**Lifetime risk for breast cancer in females with this mutation is 45–84%.
#Atypical hyperplasia may be observed in as many as 10% of tissue samples from women with suspected fibrocystic changes.

Females treated with ionizing radiation to the upper body before 30 years of age—and especially as a child or young adult—have a significantly higher incidence of BC than do females not exposed to radiation. Furthermore, women who consume more than one alcoholic drink per day have a *slightly greater risk* for developing BC. Finally, high breast tissue density (a mammographic measure that is defined by "significantly more glandular than fatty tissue in the breast") is also a risk factor. Cancer nearly always develops in glandular—not fatty—tissues of the breast.

Although there has been speculation by the public media, the following factors are *not considered risk factors for BC:* multiple pregnancies, abortion, miscarriage, excessive caffeine intake, and the use of antiperspirants, underwire bras, and breast implants. Furthermore, no dietary pattern or specific food has been definitively identified as a cause of breast cancer. Prospective studies do not support the concept that excessive consumption of fat in middle life or low fiber intake is related to increased BC risk.

Disease Summary Question 1. Suggest at least *two* reasonable explanations for the relationship between increasing age and increasing risk for breast cancer.

Pathophysiology

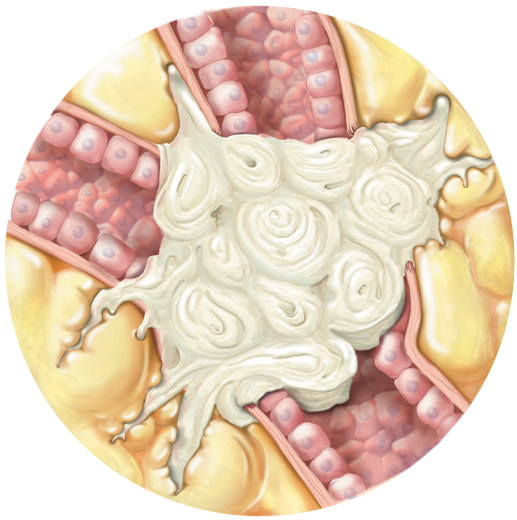
Cancer of the breast, like all cancers, results from a stepwise accumulation of genetic errors in the body's basic unit of life—the cell. Normally, the body maintains a system of checks and balances on cell growth so that cells divide to produce new cells only when needed (e.g., when cells get old or are injured and die). Disruption of this system of checks and balances on cell growth by repeated exposures to cancer-promoting agents results in uncontrolled division and proliferation of cells that eventually forms a mass known as a *tumor*. As cells continue to divide, they undergo a genetic transformation that both alters their appearance and permits them to spread to nearby lymph nodes or through the bloodstream and lymphatic vessels to other organs. As cancer cells spread and continue to divide, they deprive normal healthy cells of oxygen and vital nutrients and cause widespread tissue damage.

At the molecular level, permanent transformation of a normal cell into a cancerous one involves several pathophysiologic processes:

1. activation of multiple *oncogenes* (i.e., genes that encode proteins that promote uncontrolled cell division)
2. inactivation of several *tumor suppressor genes* (i.e., genes that regulate oncogenes and, in so doing, indirectly inhibit the proliferation of cells)
3. inactivation of genes that render transformed cells susceptible to genetically programmed cell death—a process known as *apoptosis*
4. inactivation of genes that encode enzymes that play a role in the repair of gene mutations—so-called *DNA repair enzymes*

Inherited mutations facilitate the transformation process. Once the development of breast cancer has been initiated by both acquired and inherited mutations, tumor development is sustained by a variety of mutation-encoded growth factors (e.g., epidermal growth factor [EGF]). As abnormal cells divide and cancer progresses, random mutations occur and new generations of cells become further removed from the original genotype and phenotype. Cells acquire the property of *locomotion* and secrete proteolytic enzymes that "dissolve" adjacent tissues, thus reducing resistance to movement. Transforming cells also acquire a capacity to synthesize and discharge so-called *angiogenic factors* (e.g., vascular endothelial growth factor) that induce new blood vessel formation (i.e., *angiogenesis*). Cancer cells ultimately gain access to the circulation and spread to remote sites in the body. Because abnormalities occur at various molecular target sites over time with repeated exposures to cancer-causing agents, cancer is considered both a *multi-hit* and *multistage disease*.

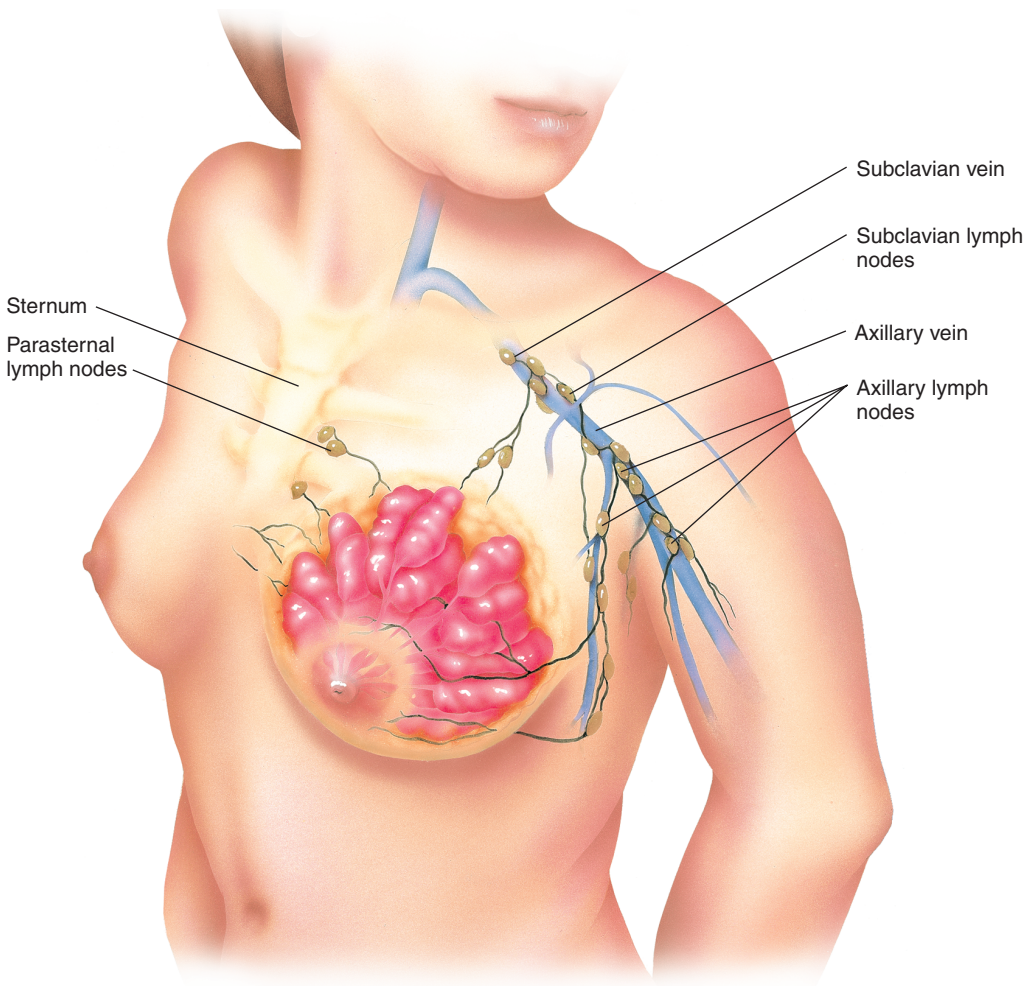
Most breast cancers originate in the lining cells of the glandular milk ducts. Tumors develop irregular borders, suggesting that cancer cells have begun to radiate outward and invade normal breast tissue. The process of breast cancer invasion is illustrated in Disease Summary Figure 63.1. After local invasion is complete, cancer cells begin to disseminate into



Disease Summary Figure 63.1
Illustration of breast cancer growing, radiating outward, and invading tissues adjacent to the glandular milk ducts. (Image provided by the Anatomical Chart Company.)

the lymph system of the axilla. The outer quadrants of the breast (in which 3 of every 4 breast cancers occur) reside in close proximity to a large system of axillary lymph nodes, which makes rapid dissemination of cancer cells possible. Less common inner-quadrant tumors may spread to mediastinal nodes or Rotter nodes (which are located between the pectoral muscles). Potential routes of dissemination by breast cancer cells to nearby lymph nodes are illustrated in Disease Summary Figure 63.2. Spread through the vertebral veins can cause new growth of cancer cells in the vertebrae, pelvic bones, ribs, and skull. The primary mechanism by which BC causes complications and death is by dissemination of cancer cells to more distant body sites—most commonly, the lungs, liver, and bone. *Metastasis* (i.e., spread and growth of cancer cells at a site distant from their origin) is associated with an extremely poor outcome.

As described above, a woman's age when her first child is born affects her risk for developing BC—the younger she is, the lower the risk. The most widely accepted explanation for this phenomenon is that differentiation (i.e., maturation) of the breast is completed at the end of the first term pregnancy or, if a term pregnancy has not occurred, at menopause. This is an important concept in view of the fact that cancer generally originates within an undifferentiated or embryonic-like cell. A critical factor with respect to the protective effect of pregnancy at a young age is the period of time between the onset of menses and the first pregnancy. Increased risk for BC is established with a time interval of more than 14 years. Protection established by an early pregnancy persists even in women older than age 75. The protective effect may be the result of the induction of lasting genetic changes brought about by the differentiation of cells in the breast. A more specific result of this process is that early pregnancy



Disease Summary Figure 63.2
Illustration showing potential routes of dissemination by breast cancer cells to nearby lymph nodes. (Image provided by the Anatomical Chart Company.)

may render critical BC susceptibility genes resistant to new mutations from external causes. Other explanations are that pregnancy induces a loss of cells that are prone to BC or that, after pregnancy, previously susceptible cells within the breast have an enhanced ability to repair mutations.

Pregnancy also has been found to cause a subsequent reduction of hormones within breast tissue and a decrease in cell receptors for epidermal growth factor and estrogen, both of which are known to promote breast cancer. The majority of breast cancers are initially hormone dependent (i.e., estrogen-positive and/or progesterone-positive), with estrogens playing a crucial role in the pathophysiology of the disease. The rationale for the importance of hormones is that concentrations of 17β-estradiol in breast cancer tissues, the most biologically active estrogen, are 10–40 times higher than serum levels.

Most of our current understanding of the carcinogenic (i.e., cancer-causing) role of estrogens is based on animal research, epidemiologic data, and observational studies. Two primary pathophysiologic mechanisms for the promotion of BC by estrogens involve:

1. a cell receptor-mediated effect that stimulates cell division, resulting in increased opportunities for random mutations
2. oxidative metabolism of estrogens mediated by various cytochrome P450 enzymes that generate reactive oxygen species (which are known to directly cause gene mutations)

A third potential pathophysiologic mechanism is that estrogens function as inducers of aneuploidy (i.e., abnormal number of chromosomes resulting from a gain or loss of chromosomes), which may be a critical determinant in the development of cancer. Still not clear, however, is whether aneuploidy is a cause or a byproduct of cancer development.

Depending on the tissue involved, progesterone induces either cell division or cell differentiation. Its effects also vary depending on the presence or absence of estrogen. Investigators have reported that, in cell culture, progesterone in the absence of estrogen facilitates cells through the cell cycle, but cells stop cycling at the G_1 phase. Cells remain in the G_1 phase unless estrogen or another growth factor prompts cells to divide and proliferate. The conclusion from these studies is that progesterone does not inherently stimulate cell division but is capable of doing so in the presence of estrogen or other growth factors.

BC can be divided into 3 distinct groups based on its link to a genetic cause:

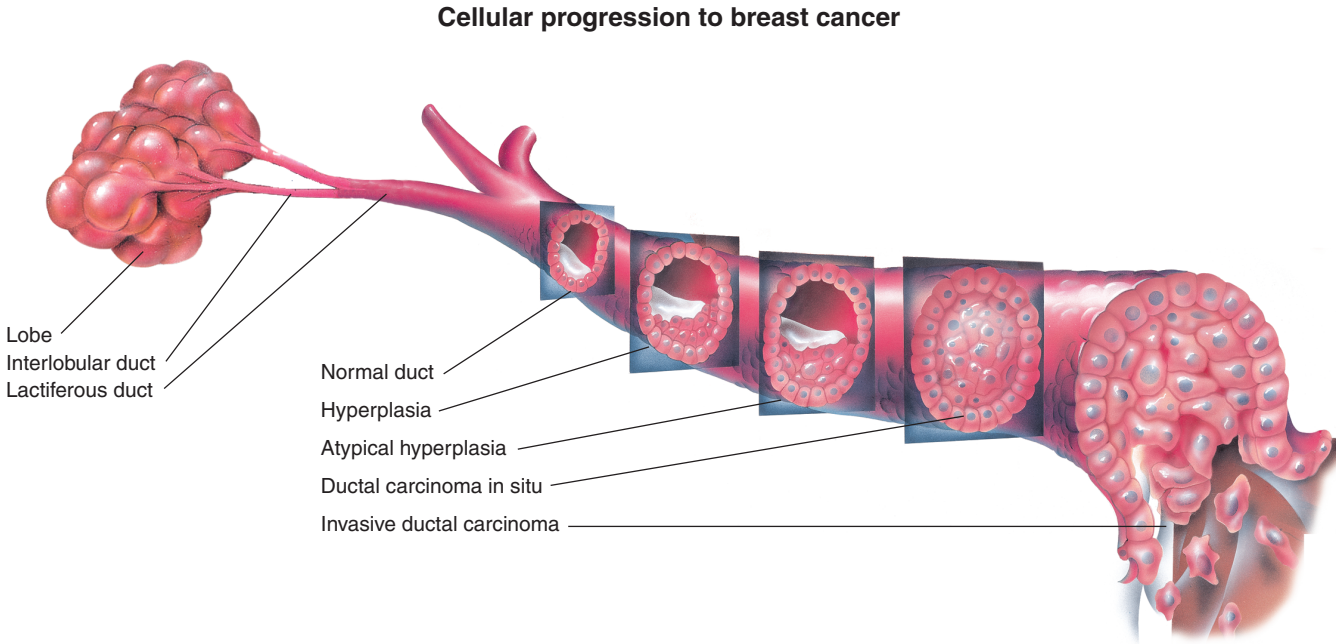
1. *sporadic BC* in which women with the disease have no family history of BC
2. *inherited cancer gene syndromes* in which the mutated gene is passed to future generations by autosomal dominant transmission
3. *polygenic BC* in which there is a positive family history but the cancer is not passed on to future generations with a high rate of transmission by a dominant gene

The total number of genes in the polygenic model, the nature of interactions among these genes, and the nature of gene interactions with environmental influences has not been determined. Genes important to the development of cancer regulate diverse cellular pathways, including progression of cells through the cell cycle, induction of apoptosis, and response to signals that direct a cell toward differentiation.

In summary, the development of BC involves several well-defined steps. Initially, abnormal changes in the deoxyribonucleic acid (DNA) of epithelial lining cells in the glandular milk ducts result from inherited mutations, new environmentally induced mutations, and new random and spontaneous mutations from accelerated cell cycling. Critical new mutations probably occur often in a woman's life before differentiation of breast tissue is complete, that is, before the first full-term pregnancy or before menopause, if the woman has never been pregnant. Secondly, mutation-induced synthesis of a variety of growth factors facilitates the passage of cells through the cell cycle to cell division. Estrogen is one of the most important growth factors in BC, as also is, possibly, progesterone. Finally, specific oncogenes are activated or specific tumor suppressor genes are inactivated, leading to progression of cancer to an advanced state—one characterized by the invasion and metastasis of cells.

Infiltrating ductal carcinoma is the single most commonly diagnosed BC in women. Although the theory remains controversial, IDC is considered to be the result of a multistep process that begins with ductal hyperplasia and progresses, in sequence, to ductal atypical hyperplasia, ductal carcinoma in situ, IDC, and metastatic ductal carcinoma. This multistep process is illustrated in Disease Summary Figure 63.3. There is also evidence that supports lobular carcinoma in situ as a precursor to infiltrating lobular carcinoma. The precise genetic abnormalities that correlate with these stages of cancer progression are currently unknown.

Unlike many human tissues that become fully differentiated by the end of fetal life, terminal differentiation of the breast occurs either with the first-term pregnancy or at menopause



Disease Summary Figure 63.3
Illustration showing the development of infiltrating ductal carcinoma of the breast from a normal milk duct. (Image provided by the Anatomical Chart Company.)

when no term pregnancies have occurred. Factors that impair full differentiation of ductal cells are likely to be crucial in the development of BC. Furthermore, DNA of epithelial cells within glandular milk ducts seems to be most susceptible to mutations from environmental agents like cigarette smoke, alcohol, and ionizing radiation when cells are in a relatively undifferentiated state. These cells can be rapidly restored by cell division of immortal stem cells. The period of greatest cell division by these stem cells occurs during the ovulatory cycle—especially during the luteal phase of the cycle (i.e., between ovulation and the end of menses) when progesterone is secreted. Since the number of potential mutations is directly related to both the rate and number of stem cell divisions, ***any factor that impairs differentiation and accelerates cell division in the breast may play a major role in the development of BC.***

Diagnosis: Clinical Manifestations and Laboratory Tests

Evaluation for BC begins with a thorough inquiry of the patient regarding symptoms, general history, and risk factors, and is followed by physical examination, imaging studies, and, ultimately, biopsy. This approach naturally lends itself to a gradually increasing degree of invasiveness so that, when a diagnosis is established, the evaluation process can be terminated with minimal discomfort to the patient. Since more invasive investigations also tend to be the most expensive, this approach is usually also the most economical.

Technical procedures most commonly used in the diagnosis of BC include mammography, ultrasonography, fine-needle aspiration, computerized stereotactic guided core needle biopsy, and excisional biopsy.

The aims of evaluation of a breast mass are to judge whether surgery is required and, if so, to determine the most appropriate type of surgery. The ultimate goal is to achieve the most appropriate degree of breast conservation while minimizing the need for further surgery.

The presenting complaint in approximately 70% of patients with BC is a solitary, painless, firm, non-mobile lump in the breast. The lump may be as small as 1 cm in diameter. Approximately 90% of all breast masses are discovered by the patient through breast self-examination (BSE) or accidentally. By the time BC can be palpated, however, it has already spread to the axillary lymph nodes in approximately half of all cases. The relative frequency of BC in various anatomic regions within the breast is shown in Disease Summary Table 63.4.

Disease Summary Table 63.4 Table Showing the Relative Frequency of Breast Cancer in Various Anatomic Regions Within the Female Breast

Origin of Breast Cancer	Frequency
Upper outer quadrant	60%
Upper inner quadrant	15%
Lower outer quadrant	15%
Lower inner quadrant	5%
Nipple	5%

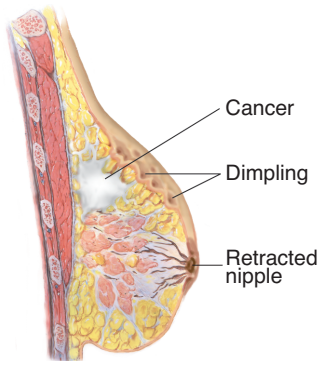
Adapted from Giuliano AE. Carcinoma of the female breast. In: McPhee SJ, Papadakis MA, Tierney LM Jr., eds. 2007 Current Medical Diagnosis and Treatment. 46th Ed. New York: McGraw-Hill, 2007;Figure 16-1:727.

Less frequent clinical manifestations include:

- breast pain/discomfort
- puckering/dimpling of the skin (as shown in Disease Summary Figure 63.4)
- nipple discharge
- erosion, retraction (see Disease Summary Figure 63.4), enlargement, or itching of the nipple
- redness, generalized hardness, enlargement, or shrinking of the breast

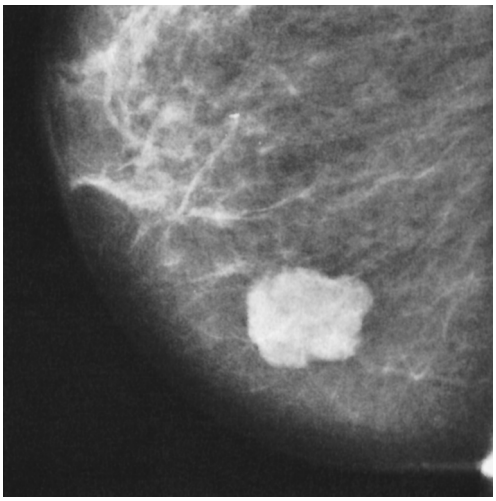
Rarely, an axillary mass (i.e., palpable lymph node) or swelling of the arm may be the initial manifestation. Back or bone pain, jaundice, and weight loss may be the result of metastasis, but these clinical manifestations are rarely seen with initial presentation.

Inspection of the breast is the first procedure in the clinical examination of the breast and is best conducted with the patient sitting—initially with her arms at her sides and then extended overhead. Abnormal variations in breast size and contour, nipple retraction, and swelling, redness, or retraction of the skin can be identified. Asymmetry of the breast and retraction or dimpling of the skin can often be accentuated when the patient raises her arms overhead or presses her hands on her hips to contract the pectoralis muscles. With the patient sitting, axillary and supraclavicular areas are thoroughly palpated for enlarged nodes. Firm or hard nodes larger than 1 cm are typical of metastasis. Axillary nodes that are non-mobile and swelling of the ipsilateral arm indicate advanced disease. Firm or hard nodes of any size just above or below the clavicle also suggest metastatic disease. Palpation of the breast for lumps is best performed with the patient both seated and supine with the arm abducted. Palpation with a rotary motion of the fingers by the examiner as well as a horizontal stripping motion has been recommended. A thorough physical examination also focuses on sites of skeletal pain and an abdominal and neurologic assessment.



Disease Summary Figure 63.4

Illustration showing dimpling and retraction of the breast with breast cancer. As breast cancer progresses, it causes fibrosis (scar-tissue formation). Shortening of the fibrotic tissue produces dimpling, changes in contour, and retraction or deviation of the nipple. (Reprinted with permission from Bickley LS, Szilagyi P. Bates' Guide to Physical Examination and History Taking. 8th Ed. Philadelphia: Lippincott Williams & Wilkins, 2003.)



DISEASE SUMMARY FIGURE 63.5
Mammogram of breast cancer. Note the irregular shape and border of the tumor. (Reprinted with permission from Mitchell GW. The Female Breast and Its Disorders. 1st Ed. Baltimore: Williams & Wilkins, 1990:140.)

The diagnostic use of mammography enables definition of the suspicious region. ***Mammography is one of the most reliable techniques available for early detection of BC.*** Two-view mammography (i.e., craniocaudal and oblique) is the imaging method of choice. Although research data have brought into question the value of mammography, the United States Preventive Services Task Force issued guidelines in 2002 concluding that there was sufficient evidence to justify recommending a mammogram every 1–2 years in women older than 40 years of age. A cancerous breast tumor is shown in the mammogram provided in Disease Summary Figure 63.5.

A generally slow-growing form of cancer, BC may have been present for as many as 9 years before it reaches a diameter of 1 cm—the smallest mass normally detectable with palpation. Mammography can disclose structural abnormalities as small as 1 mm and reveal areas of calcification that warrant a biopsy to exclude cancer. ***Small regions of calcification are the most easily recognized mammographic abnormalities and the most common findings associated with BC.*** Such calcifications are usually 5–8 in number, located in one part of the breast, differ from one another in size and shape, and often include V- or Y-shaped configurations.

Mammography has a maximum sensitivity of 90% for the detection of BC, even when performed by the most experienced personnel. In young women with more glandular than fatty tissue in the breasts, mammography is less sensitive than in older women with primarily fatty breasts. Approximately 40% of all BC is initially detected by palpation and another 40% with mammography. ***The most comprehensive and reliable approach for detecting BC is a combination of BSE, clinical examination by a health professional, and mammography.***

According to a 2007 American Cancer Society guideline, carefully selected women with an especially high risk for developing BC should now be tested with *magnetic resonance imaging* (MRI) along with a yearly mammogram as early as age 30 years. The two tests together give healthcare providers a better chance for detecting BC early in these women. MRI scans are more sensitive than mammograms. However, MRI scans are also more likely to show spots in the breast that are not cancerous, can lead to a high number of avoidable biopsies, and may cause unnecessary fear and anxiety in patients. That is why MRI is not recommended for women with an average risk for BC. The new guideline recommends MRI screening in addition to mammograms for women who meet at least one of the following criteria:

1. they have a BRCA1 or BRCA2 mutation
2. they have a first-degree relative (i.e., parent, sibling, or child) with a BRCA1 or BRCA2 mutation
3. their lifetime risk for BC is 20% or greater, based on one of several accepted risk assessment tools
4. they had radiation to the chest between 10 and 30 years of age
5. they have been diagnosed with a genetic syndrome that carries a high risk for BC (e.g., Cowden syndrome)

When a suspicious abnormality is identified with mammography and cannot be palpated, the mass is often biopsied with a *computerized stereotactic guided core needle* technique. These units have been added to mammography suites to localize abnormalities and perform a needle biopsy without surgery. Under mammographic guidance, a large-bore biopsy needle is mechanically inserted into the breast mass and a core of tissue is removed for microscopic examination. Use of a vacuum device to harvest the abnormal tissue increases the amount of sample that is obtained and improves diagnosis. Discomfort is minimal and, even when multiple samples are obtained, healing occurs rapidly. Cancer is detected with 96% accuracy.

Ultrasonography is only used as a supplement to physical examination and mammography and is performed primarily to distinguish cystic from solid masses. Breast cancer usually presents as a solid mass. Though not diagnostic, ultrasound may reveal features highly suggestive of cancer, such as an irregular border around a solid mass. Ultrasonography may also show an irregularly shaped mass within a cyst in rare cases of intracystic BC.

A definitive diagnosis of BC depends ultimately on examination of tissue removed by biopsy. Treatment is never undertaken without an unequivocal diagnosis of cancer. The safest course is a biopsy examination of all suspicious masses found during physical examination and of all suspicious lumps demonstrated with mammography or MRI. *Fine-needle aspiration*, the least invasive method of biopsy, is a simple outpatient procedure that can be performed repeatedly in multiple sites with minimal discomfort. The procedure is accomplished by stabilizing a palpable lump between two fingers or in conjunction with a handheld ultrasound device to define the periphery of the mass. Fine-needle aspiration can identify the presence of cancerous cells, but it cannot make the distinction between in situ and infiltrating carcinomas.

Excisional biopsy with local anesthesia provides the only definitive diagnosis of BC and often is curative without additional treatment. A surgical incision is made in the skin with the intent to remove the entire mass for microscopic examination. Approximately one third of abnormalities detected with a mammogram are found to be cancerous when a biopsy is performed. Mammography is never a substitute for biopsy.

Laboratory blood tests may suggest spread of BC. A consistently elevated erythrocyte sedimentation rate may result from metastatic cancer. Liver or bone metastases may be associated with an elevation in serum alkaline phosphatase concentrations. Hypercalcemia is an occasional but important finding in advanced BC. Serum markers for recurrent BC include carcinoembryonic antigen (CEA), cancer antigen 15-3 (i.e., CA15-3), CA72-4, and CA27-29 but are not helpful in diagnosing the initial lesion of BC.

Chest x-rays may show metastatic lesions in the lungs. *Computed tomographic (CT) scanning* of the liver and brain is of value only when metastases are suspected in these areas (e.g., when the patient is jaundiced or suffering from headaches). *Bone scans* with ^{99m}Tc-labeled phosphates or phosphonates are more sensitive than conventional x-rays for detecting metastatic BC in bone. However, bone scanning has not proved to be of clinical value in the absence of pain, physical findings, or abnormal serum alkaline phosphatase or calcium concentrations.

Positron emission tomography (PET) scans may prove to be an effective single scan for bone, soft tissue, and visceral metastases in patients with clinical manifestations of metastatic disease. PET is the most sensitive and specific of all imaging methods for breast disease, but it is also one of the most expensive and least widely available. With the use of a variety of labeled metabolites, abnormalities in metabolic activity, vascularization, oxygen consumption by tissues, and tumor receptor status can be detected.

Following a diagnosis of BC, the cancerous mass is graded. ***Establishing the grade of BC is the most reliable index for determining disease prognosis of carcinoma in situ.*** However, grading of infiltrating carcinomas is also important as a prognostic indicator, with high-grade tumors carrying the worse prognosis. Disease Summary Table 63.5 shows a typical grading system for BC. Cancer is assigned a *grade I* when A + B + C = 3–5, *grade II* when A + B + C = 6–7, and *grade III* when A + B + C = 8–9. Grade I tumors are associated with a 10-year survival rate of 85%, whereas survival rate decreases to 45% for grade III tumors.

Establishing the stage (i.e. extent of BC) is critical for determining the most appropriate treatment for the patient and also provides a strong index of prognosis. The American Joint Committee on Cancer and the International Union Against Cancer have agreed on a staging system for BC that is based on tumor size, the extent of spread of cancerous cells to lymph nodes, and the absence/presence of metastasis. High-stage tumors carry the worse prognosis. Disease Summary Table 63.6 shows a common staging system for BC and approximate survival rates for patients with each stage of BC.

Disease Summary Table 63.5 Table Showing a Typical Grading System for Breast Cancer

Microscopic Feature of Tumor Sample	Score = 1	Score = 2	Score = 3
A) Formation of small tubules within the sample	In more than 75% of the sample	In 10–75% of the sample	In less than 10% of the sample
B) Number of cell divisions in a high-power field (e.g., microscope magnification × 40)	Less than 7 cell divisions	7–12 cell divisions	More than 12 cell divisions
C) Pleomorphism	Near-normal nuclear size + little variation in cell size	Slightly enlarged nuclear size + moderate variation in cell size	Markedly enlarged nuclear size + marked variation in cell size

Adapted with permission from Singhal H, Kaur K, Thomson S. Breast cancer evaluation. eMedicine website. Available at: www.emedicine.com/med/topic3287.htm. Date accessed: August 2006. Table 3.

Disease Summary Table 63.6 Table Showing a Common Staging System for Breast Cancer and Approximate Survival Rates for Patients with Each Stage of Breast Cancer

Tumor Size	Lymph Node Involvement	Metastasis	Stage	5-Year Survival Rate	10-Year Survival Rate
T_{is}	N0	M0	0	95%	90%
T1	N0	M0	I	85%	70%
T0	N1	M0	IIA	70%	50%
T1	N1	M0	IIA		
T2	N0	M0	IIA		
T2	N1	M0	IIB	60%	40%
T3	N0	M0	IIB		
T0	N2	M0	IIIA	55%	30%
T1	N2	M0	IIIA		
T2	N2	M0	IIIA		
T3	N1	M0	IIIA		
T3	N2	M0	IIIA		
T4	N0	M0	IIIB	30%	20%
T4	N1	M0	IIIB		
T4	N2	M0	IIIB		
Any T	N3	M0	IIIC		
Any T	Any N	M1	IV	5–10%	2%

Adapted with permission from Giuliano AE. Carcinoma of the female breast. In: McPhee SJ, Papadakis MA, Tierney LM Jr., eds. 2007 Current Medical Diagnosis and Treatment. 46th Ed. New York: McGraw-Hill, 2007;Table 16-2: 732–733 and Table 16-6 (p. 743). Original source: American Joint Committee on Cancer (AJCC) Staging Manual. 6th Ed. Springer, 2002.
T_{is}, carcinoma in situ
T0, no evidence of primary tumor
T1, tumor <2 cm in size
T2, tumor 2–5 cm in size
T3, tumor >5 cm in size
T4, tumor of any size with extension into chest wall or skin
N0, no regional lymph node metastasis
N1, metastasis to movable ipsilateral axillary lymph node(s)
N2, metastasis in fixed ipsilateral axillary lymph nodes *or* ipsilateral internal mammary nodes
N3, metastasis in ipsilateral infraclavicular lymph nodes *or* ipsilateral internal mammary lymph nodes + axillary lymph node metastasis *or* metastasis in ipsilateral supraclavicular lymph nodes
M0, no distant metastasis
M1, distant metastasis

Estrogen- and progesterone-receptor assays are also performed on surgical specimens. Information about the presence or absence of receptors can be used in predicting the response of BC to various anticancer drugs. High levels of both estrogen and progesterone receptors (ER-positive and PR-positive) improve prognosis and increase the likelihood of remission.

Disease Summary Question 2. Provide a reasonable explanation for breast cancer described as T0N1M0; that is, there is no evidence of a primary tumor in the breast but the ipsilateral lymph nodes are positive for breast cancer cells.

Disease Summary Question 3. Briefly describe the pathophysiology of *edema of the ipsilateral arm* in a patient with breast cancer.

Disease Summary Question 4. Briefly describe the pathophysiology of *hemorrhage within the breast* in a patient with breast cancer.

Disease Summary Question 5. Briefly describe the pathophysiology of *reddened skin and local tenderness of the breast* in a patient with breast cancer.

Disease Summary Question 6. *True* or *false*? Routine breast self-examinations have definitively been shown to increase survival time in patients with breast cancer.

Disease Summary Question 7. Briefly describe the proper procedure for breast self-examination.

Disease Summary Question 8. Is a watery or bloody discharge from the nipple more commonly associated with *breast cancer* or *non-cancerous breast disease*?

Disease Summary Question 9. Briefly distinguish between a *false-positive* and a *false-negative* mammogram.

Disease Summary Question 10. *True or false*? Most breast lumps are cancerous.

Appropriate Therapy

Treatment for BC is considered *curative* (i.e., an attempt to cure the disease) or *palliative* (i.e., an attempt to minimize symptoms and make the patient comfortable). Curative treatment is routinely conducted for clinical stages I, II, and III disease and most patients can be cured. Patients with large tumors (e.g., T3) that have not spread to the lymph nodes (i.e., N0) may be cured, but in most of these patients, effective palliation is the best result that can be expected. Palliative treatment is appropriate for all patients with stage IV disease, for previously treated patients who develop advanced disease, and for those who have localized BC that cannot be surgically removed.

The extent of disease and its biologic aggressiveness are the principal determinants of the outcome of therapy. Although staging of BC helps to assess the extent of the disease, the process is—to some extent—imprecise. Other factors, such as tumor grade and hormone receptor assays, may have prognostic value but are not important in determining the type of primary therapy. Controversy surrounds the choice of primary therapy for stages I, II, and III BC. ***Currently, the standard treatment for stage I, stage II, and most stage III BC is surgical resection of the tumor followed by post-surgical radiation or systemic therapy when indicated.***

Modified radical mastectomy (i.e., total mastectomy + axillary lymph node removal) has been the standard therapy for most patients with BC. Approximately 75% of patients in the United States with stage I or stage II BC are currently treated with this approach. During this operation, the entire breast, overlying skin, nipple, areolar complex, underlying pectoralis fascia, and axillary lymph nodes are removed. The major advantage of this type of surgery is that radiation therapy may not be necessary afterward. The major disadvantage of modified radical mastectomy (MRM) is the psychological impact on the patient from losing the breast. *Radical mastectomy*, in which the underlying pectoralis muscle is also removed, has no additional merits and is now rarely performed. *Skin-sparing mastectomy* is currently gaining favor but is appropriate in only a small fraction of patients. Current studies suggest that the use of radiation therapy after mastectomy may improve survival.

Axillary node removal is not indicated for BC in situ. Furthermore, removal of axillary nodes increases the risk for numbness, recurrent infections, and significant swelling in the arm. Research studies suggest that removal of only biopsy-positive sentinel lymph nodes can safely replace the excision of axillary nodes when performed by an experienced surgeon. *Sentinel lymph nodes* are the first lymph nodes to receive lymphatic drainage from breast tumors and, therefore, the first to develop cancer. Successful identification of sentinel lymph nodes may be as high as 97%. If a sentinel lymph node is positive, more nodes are removed; if it is negative, further lymph node evaluation may be unnecessary.

A large, randomized trial conducted in the United States by the National Surgical Adjuvant Breast and Bowel Project showed that ***lumpectomy* (i.e., removal of the tumor with confirmed tumor-free margins) *plus axillary lymph node removal and postoperative radiation therapy of the entire breast*** was as effective as MRM for the management of patients with stage I and stage II BC. The results of this trial (and other trials) have shown that much less-aggressive surgical treatment for the primary tumor than was previously thought necessary provides an equivalent therapeutic result and preserves an acceptable cosmetic appearance. Currently, only 25% of patients in the United States with stage I or stage II BC are treated with lumpectomy and postoperative radiation. With 20 years of follow-up, the local recurrence rate among patients treated with lumpectomy and postoperative radiation is approximately 14%.

Tumor size is a major consideration when determining the feasibility of breast-conserving surgery through lumpectomy. To achieve an acceptable cosmetic result, the patient must have a breast of sufficient size to enable removal of the tumor without considerable deformity. Therefore, a large tumor is a contraindication for lumpectomy in some, but not all, patients. Other conditions that may cause both difficulty with complete surgical excision and deformity of the breast—and of which the patient should be informed—are:

- tumors located beneath the areola
- tumors that are fixed to the chest wall or skin
- tumors that have invaded the nipple or overlying skin

The combined approach of breast-conserving surgery and radiation therapy is offered whenever possible. Radiation treatment is typically given 5 days a week for 5–6 consecutive weeks. Furthermore, breast reconstruction is also discussed with patients who choose or require a mastectomy. Breast reconstruction is usually feasible after MRM, and most plastic surgeons currently implant a saline-filled prosthesis in the subpectoral plane between the pectoralis minor and pectoralis major muscles.

Following surgery and radiation therapy, *chemotherapy* or *hormonal therapy* is advocated for most patients with potentially curable BC. The objective of this type of systemic therapy is to eliminate any undetectable metastatic tumors while they are microscopic and most vulnerable to the effect of anticancer drugs. In addition, chemotherapy may decrease the probability of recurrence in patients treated with lumpectomy and radiation. Hormonal therapy also decreases the probability that BC will occur in the contralateral breast. Systemic therapy is not generally used in patients with small tumors and in those with negative lymph nodes who have favorable serum tumor marker concentrations.

Treatment with three potent anticancer drugs—cyclophosphamide, methotrexate, and fluorouracil (CMF)—modestly improves survival for 20 years and ***has become the standard regimen for all BC patients with node-positive disease.*** Improvement in survival for patients appears to be approximately 30% of the patient's risk for recurrence and death; that is, a woman with a 30% probability for recurrence and death derives a 10% overall improvement in survival.

Clinical studies that have compared the effects of doxorubicin + cyclophosphamide (DC) or epirubicin + cyclophosphamide (EC) with CMF therapy have shown that these drug regimens are at least as effective as treatment with CMF. Four cycles of DC (i.e., every month for 4 months) were as effective as six cycles of CMF in node-negative, estrogen receptor (ER)-negative patients. As a result, most oncologists today offer four cycles of DC or six cycles of CMF to patients with node-negative BC.

Paclitaxel, which belongs to a group of drugs known as taxanes, has been approved for and has been increasingly employed to treat patients with node-positive BC. However, a consensus panel at the National Institutes of Health recently reported that conclusions about the effectiveness and toxicity of taxanes could not yet be drawn and recommended that patients receive taxanes only in the context of a clinical trial.

The overall duration of chemotherapy for BC remains uncertain. However, the current recommendation is 3–6 months of the commonly used regimens. In general, current chemotherapy regimens decrease the probability of recurrence of BC by approximately 30%.

Hormonal therapy is highly effective in decreasing both the probability of recurrence and mortality and should be used in all women with ER-positive tumors. The standard regimen has been treatment with tamoxifen for 5 years. Hormonal therapy decreases the risk of mortality by approximately 25%.

More recently, a group of drugs that prevent the synthesis of estrogens and are known as aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane) has shown improved disease-free survival and fewer side effects than tamoxifen in postmenopausal women with ER-positive BC. However, the American Society of Clinical Oncology is still recommending tamoxifen as a first-line drug and anastrozole to patients who are at significant risk for developing serious complications from taking tamoxifen.

Palliative radiation therapy may be performed for BC patients with stage IV disease. Palliative irradiation is especially useful in the treatment of metastatic BC to bone (to control pain and prevent fractures), recurrences of BC in the chest wall, metastatic tumors to the brain, and spinal cord compression.

Disseminated BC may also shrink—or grow less rapidly—after:

- sex hormone administration (e.g., estrogens, androgens, or progestins)
- surgical removal of the ovaries (i.e., *bilateral oophorectomy*)
- administration of drugs that block ER sites (e.g., tamoxifen)
- administration of drugs that inhibit the synthesis of estrogens (e.g., anastrozole)

Palliative hormone therapy is usually more effective in postmenopausal women even if they have received estrogen replacement therapy. Treatment is based on the presence of ER proteins in the primary tumor or tumor metastases. Of those patients whose tumors contain ER-positive cells, a favorable response is seen in approximately three in five cases—four of five cases if tumors also contain cells with progesterone receptors.

Choice of hormone therapy depends primarily on the menopausal state of the patient. *Tamoxifen is the hormone treatment of choice in the premenopausal patient*. The average remission is approximately 12 months. Bilateral oophorectomy is less desirable than hormone therapy in premenopausal women, but can be achieved rapidly and safely. If the patient is a poor surgical candidate, ovarian function can also be eliminated by irradiation of the ovaries or treatment with certain drugs known as gonadotropin-releasing hormone analogs. All of these procedures decrease the production of sex hormones and inhibit tumor growth. Patients who do not respond to hormone therapy or oophorectomy are treated with chemotherapy.

Tamoxifen or anastrozole is the initial therapy of choice for postmenopausal women with stage IV disease that is amenable to hormone therapy. Anastrozole has fewer side effects and is equally effective. Postmenopausal women who do not respond to hormone therapy generally are treated with CMF or DC chemotherapy.

Palliative chemotherapy is considered for the treatment of stage IV BC if:

- metastatic lesions are present in the brain or pulmonary lymph nodes
- hormone treatment is unsuccessful, or
- BC is ER-negative

The single most useful chemotherapeutic agent currently in use for palliative chemotherapy is doxorubicin, with a positive response in 40–50% of patients. Combination chemotherapy has proved to be more effective with favorable responses in 60–80% of stage IV patients treated with DC.

Taxanes (e.g., paclitaxel and docetaxel) are given after failure of combination chemotherapy. These drugs have shown a favorable response in 30–40% of patients. Trastuzumab is a monoclonal antibody that binds with certain receptors on BC cells that have been designated *HER2/neu*. These receptors bind epidermal growth factor (EGF), which contributes to the proliferation of cancer cells. Trastuzumab competes for *HER2/neu* receptors with EGF and inhibits cell division of BC cells. For stage IV patients with overexpression of the *HER2/neu* gene, trastuzumab in combination with AC and paclitaxel has been shown to increase the patient's survival time.

Bevacizumab is a newly approved biological therapy for advanced BC that uses monoclonal antibody technology to prevent cancerous growths from producing new blood vessels. Tumors produce blood vessels not only to aid with nutrition but also to provide routes for metastasis.

In March 2007, the U.S. Food and Drug Administration (FDA) approved a new breast cancer drug known as lapatinib for use with another cancer drug—capecitabine—in selected patients with advanced breast cancer. The lapatinib-capecitabine combination has been

approved only for stage IV patients whose tumors contain significant amounts of *HER2*-encoded protein and who have already failed other treatments, including chemotherapy and treatments of trastuzumab.

Finally, *bisphosphonate therapy* (e.g., pamidronate, zoledronic acid, and clodronate) has shown excellent results in both delaying and reducing pain and fractures associated with tumor metastasis to bone. Growth factors, such as *erythropoietin* (which stimulates red blood cell production), *filgrastim*, *sargramostim,* and *pegfilgrastim* (which stimulate production of various types of white blood cells), prevent life-threatening anemia and infections, common complications of cancer chemotherapy. Nausea and vomiting associated with chemotherapy are often controlled with ondansetron or granisetron.

Disease Summary Question 11. Why have silicone gel implants not been as widely used for breast reconstruction in recent years as they once were?

Disease Summary Question 12. *True or false*? Women who are considered genetically "high risk" for developing breast cancer can be protected from the disease by taking tamoxifen.

Disease Summary Question 13. Why are multiple anticancer drugs often more effective in treating cancer than use of a single drug?

Disease Summary Question 14. What is the brand name of the FDA-approved biological therapy for treating breast cancer known as trastuzumab?

Serious Complications and Prognosis

The most common potentially serious complications of BC are those associated with metastasis of the primary tumor—to bone, resulting in severe pain and fractures; to the brain, resulting in headaches, seizures, and coma; to liver, resulting in hepatic failure; and to the lungs, resulting in respiratory failure. Malnutrition is also a potential serious complication of advanced BC.

Stage of BC is the single most reliable indicator of prognosis. Patients with disease localized to the breast and no evidence of regional spread to the lymph nodes have the most favorable prognosis (currently, 98% 5-year survival rate). Axillary lymph node status is the single most analyzed prognostic factor and correlates well with survival for any tumor size. An increasing number of positive axillary nodes correlate directly with lower survival rates (overall 83% 5-year survival rate). Patients with hormone-receptor negative BC and no evidence of dissemination to the axillary lymph nodes have a much higher recurrence rate than do patients with hormone receptor-positive BC and no regional spread. Most BC (70–80%) is ER-positive. The microscopically determined subtype of BC (e.g., ductal or lobular) seems to have little effect on prognosis once these tumors have progressed from the in situ to infiltrating state. Breast cancer with marked aneuploidy of cells (as determined with DNA flow cytometry) has a poorer prognosis than those tumors that are primarily diploid. Furthermore, tumors with >5% of the cell population within the S phase of the cell cycle have a more unfavorable prognosis than tumors with <5% of cells in the S phase.

Mortality rates of BC patients have exceeded those of age-matched controls for nearly 20 years. When cancer cells are localized to the breast with no evidence of regional spread, the clinical cure rate with accepted methods of therapy is >90%. Patients with small tumors that are both ER- and progesterone receptor-positive and show no evidence of axillary spread have a 5-year survival rate >95%. When axillary nodes are positive for cancer cells, survival rates decrease to 50–70% at 5 years and 25–40% at 10 years. The current overall 5-year survival rate for metastatic BC is 26%. In general, BC appears to be more aggressive in younger women and this may be related to the fact that fewer young women develop ER-positive tumors. The survival rate at 10 years for local, regional, and metastatic stages combined is currently 80%.

After primary therapy, patients with BC are followed for life to detect recurrences and BC in the opposite breast. Local and distant recurrences occur most frequently within the first 5 years. However, in some cases, metastatic lesions are dormant for long periods and

may appear 10–15 years or longer after treatment. When axillary nodes are negative, local recurrence rate is <5%; when nodes are strongly positive, a recurrence rate as high as 25% is possible. Approximately 20–25% of patients subsequently develop a second BC in the opposite breast. Approximately 8% of patients develop local recurrence in the chest wall after MRM and axillary node removal.

Breast cancer is characterized by a wide variation in clinical course. However, many patients who undergo therapy are able to achieve a satisfactory quality of life.

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