CHAPTER 36

DISEASES OF THE BREAST

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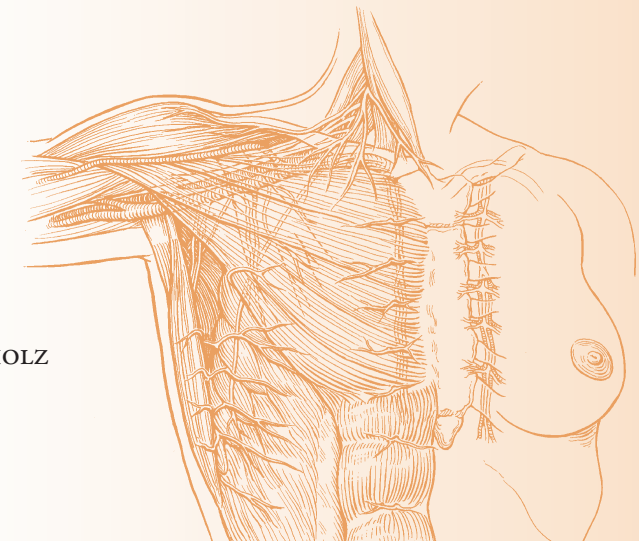

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ANATOMY

The breast lies between the subdermal layer of adipose tissue and the superficial pectoral fascia (Fig. 36-1). The breast parenchyma is composed of lobes that in turn are comprised of multiple lobules. There are fibrous bands that provide structural support and insert perpendicularly into the dermis, termed the *suspensory ligaments of Cooper.* Between the breast and pectoralis major muscle lies the retromammary space, a thin layer of loose areolar tissue that contains lymphatics and small vessels.

Located deep to the pectoralis major muscle, the pectoralis minor muscle is enclosed in the clavipectoral fascia, which extends laterally to fuse with the axillary fascia. The axillary lymph nodes, grouped as shown in Figure 36-2, are found within the loose areolar fat of the axilla; the number of lymph nodes is variable, depending on the size of the patient. The number of lymph nodes recovered from pathologic examination of Halsted-type radical mastectomy specimens is approximately 50 nodes.

The axillary nodes are typically described as three anatomic levels defined by their relationship to the pectoralis minor muscle. Level I nodes are located lateral to the lateral border of the pectoralis minor muscle. Level II nodes are located posterior to the pectoralis minor muscle. Level III nodes include the subclavicular nodes medial to the pectoralis minor muscle. The level III nodes are easier to visualize and remove when the pectoralis minor muscle is divided. The apex of the axilla is defined by the costoclavicular ligament (Halsted's ligament), at which point the axillary vein passes into the thorax and becomes the subclavian vein. Lymph nodes in the space between the pectoralis major and minor muscles are termed the *interpectoral group,* or *Rotter's nodes,* as described by Grossman and Rotter. Unless this group is specifically exposed, they are not encompassed in surgical procedures that preserve the pectoral muscles.

Lymphatic channels are abundant in the breast parenchyma and dermis. Specialized lymphatic channels collect under the nipple and areola and form Sappey's plexus, named for the anatomist who described them in 1885. Lymph flows from the skin to the subareolar plexus and then into the interlobular lymphatics of the breast parenchyma. Appreciation of lymphatic flow is important for performing successful sentinel lymph node surgery (see later). Of lymphatic flow from the breast, 75% is directed into the axillary lymph nodes. A minor amount goes through the pectoralis muscle and into more medial lymph node groups, as shown in Figure 36-2. Lymphatic drainage also occurs through the internal mammary lymph nodes as the predominant drainage in up to 5% of patients and as a secondary route in combination with axillary drainage in approximately 20%. A major route of breast cancer metastasis is through lymphatic channels; the regional spread of cancer is important to understand to provide optimal locoregional control of the disease.

Coursing close to the chest wall on the medial side of the axilla is the long thoracic nerve, or the external respiratory nerve of Bell, which innervates the serratus anterior muscle. This muscle is important for fixing the scapula to the chest wall during adduction of the shoulder and extension of the arm, and division of the nerve may result in the winged scapula deformity. For this reason, the long thoracic nerve is preserved during axillary surgery. The second major nerve encountered during axillary dissection is the thoracodorsal nerve, which innervates the latissimus dorsi muscle. This nerve arises from the posterior cord of the brachial plexus and enters the axillary space under the axillary vein, close to the entrance of the long thoracic nerve. It then crosses the axilla to the medial surface of the latissimus dorsi muscle. The thoracodorsal nerve and vessels are preserved during dissection of the axillary lymph nodes. The medial pectoral nerve innervates the pectoralis major muscle and lies within a neurovascular bundle that wraps around the lateral border of the pectoralis minor muscle. The pectoral neurovascular bundle is a good landmark in that it indicates the position of the axillary

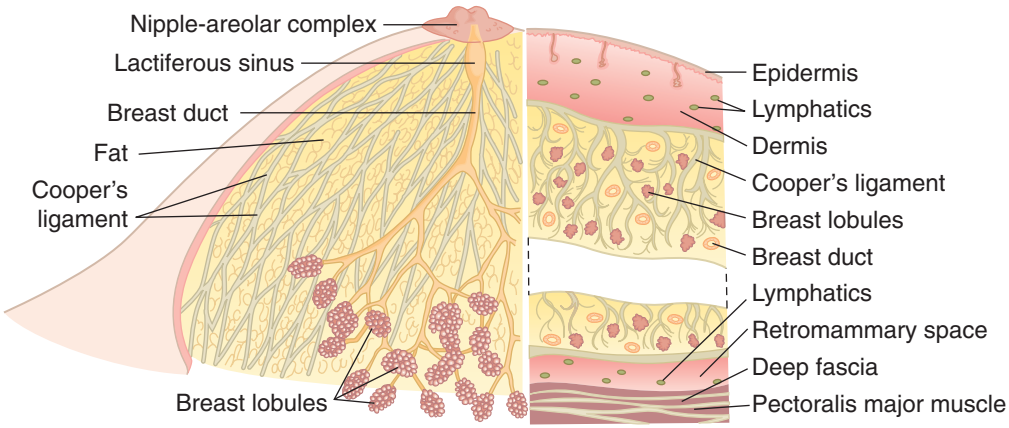

FIGURE 36-1 Cut-away diagram of a mature resting breast. The breast lies cushioned in fat between the overlying skin and pectoralis major muscle. Both the skin and retromammary space under the breast are rich with lymphatic channels. Cooper's ligaments, the suspensory ligaments of the breast, fuse with the overlying superficial fascia just under the dermis, coalesce as the interlobular fascia in the breast parenchyma, and then join with the deep fascia of breast over the pectoralis muscle. The system of ducts in the breast is configured like an inverted tree, with the largest ducts just under the nipple and successively smaller ducts in the periphery. After several branching generations, small ducts at the periphery enter the breast lobule, which is the milk-forming glandular unit of the breast.

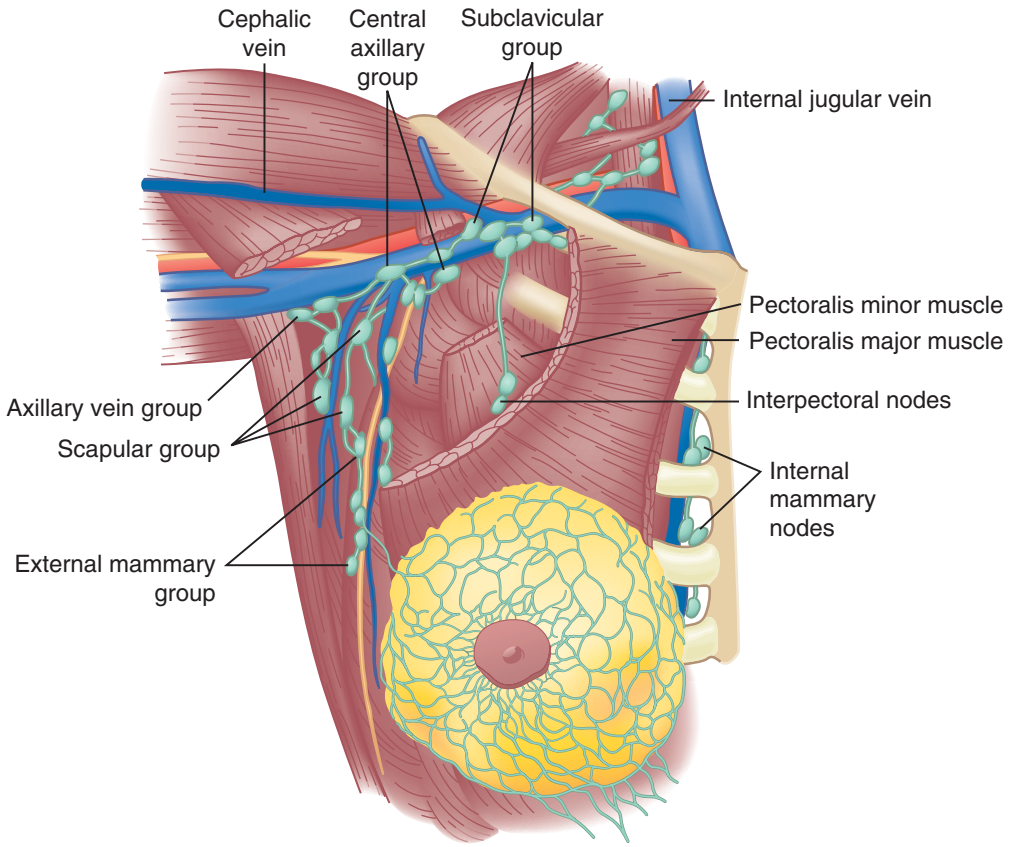

FIGURE 36-2 Contents of the axilla. In this diagram, there are five named and contiguous groupings of lymph nodes in the full axilla. Complete axillary dissection, as done in the historical radical mastectomy, removes all these nodes. However, note that the subclavicular nodes in the axilla are continuous with the supraclavicular nodes in the neck and nodes between the pectoralis major and minor muscles, called the *interpectoral nodes* in this diagram (also known as *Rotter's lymph nodes*). The sentinel lymph node is functionally the first node in the axillary chain and, anatomically, is usually found in the external mammary group. (From Donegan WL, Spratt JS: Cancer of the breast, ed 3, Philadelphia, 1988, WB Saunders, p 19.)

vein, which is just cephalad and deep (superior and posterior) to the bundle. This neurovascular bundle should be preserved during standard axillary dissection.

The large sensory intercostal brachial or brachial cutaneous nerves span the axillary space and supply sensation to the undersurface of the upper part of the arm and skin of the chest wall along the posterior margin of the axilla. Dividing these nerves results in cutaneous anesthesia in these areas and should be explained to patients before axillary dissection. Denervation of the areas supplied by these sensory nerves can cause chronic and uncomfortable pain syndromes in a small percentage of patients. Preservation of the superiormost nerve maintains sensation to the posterior aspect of the upper part of the arm intact without compromising the axillary dissection in most patients.

MICROSCOPIC ANATOMY

The mature breast is composed of three principal tissue types: (1) glandular epithelium; (2) fibrous stroma and supporting structures; and (3) adipose tissue. Lymphocytes and macrophages are also found within the breast. In adolescents, the predominant tissues are epithelium and stroma. In postmenopausal women, the glandular structures involute and are largely replaced by adipose tissue. Cooper's ligaments provide shape and structure to the breast as they course from the overlying skin to the underlying deep fascia. Because they are anchored into the skin, infiltration of these ligaments by carcinoma commonly produces tethering which can cause dimpling or subtle deformities on the otherwise smooth surface of the breast.

The glandular apparatus of the breast is composed of a branching system of ducts, roughly organized in a radial pattern spreading outward and downward from the nipple-areolar complex (see Fig. 36-1). It is possible to cannulate individual ducts and visualize the lactiferous ducts with contrast agents. Figure 36-3 demonstrates the arborization of branching ducts, which end in terminal lobules. The contrast dye opacifies only a single ductal system and does not enter adjacent and intertwined branches from functionally independent ductal branches. Each major duct has a dilated portion (lactiferous sinus) below the nipple-areolar complex. These ducts converge through a constricted orifice into the ampulla of the nipple.

Each of the major ducts has progressive generations of branching and ultimately ends in the terminal ductules or acini (Fig. 36-4). These acini are the milk-forming glands of the lactating breast and, together with their small efferent ducts or ductules, are known as *lobular units* or *lobules*. As shown in Figure 36-4, the terminal ductules are invested in a specialized loose connective tissue that contains capillaries, lymphocytes, and other migratory mononuclear cells. This intralobular stroma is clearly distinguished from the denser and less cellular interlobular stroma and from the adipose tissue within the breast.

The entire ductal system is lined by epithelial cells, which are surrounded by specialized myoepithelial cells that have contractile properties and serve to propel milk formed in the lobules toward the nipple. Outside the epithelial and myoepithelial layers, the ducts of the breast are surrounded by a continuous basement membrane containing laminin, type IV collagen, and proteoglycans. The basement membrane layer is an important boundary in differentiating in situ from invasive breast cancer. Continuity of this layer is maintained in ductal carcinoma in situ (DCIS), also termed *noninvasive breast cancer* (see later, "Pathology"). Invasive breast cancer is defined by penetration of the basement membrane by malignant cells invading the stroma.

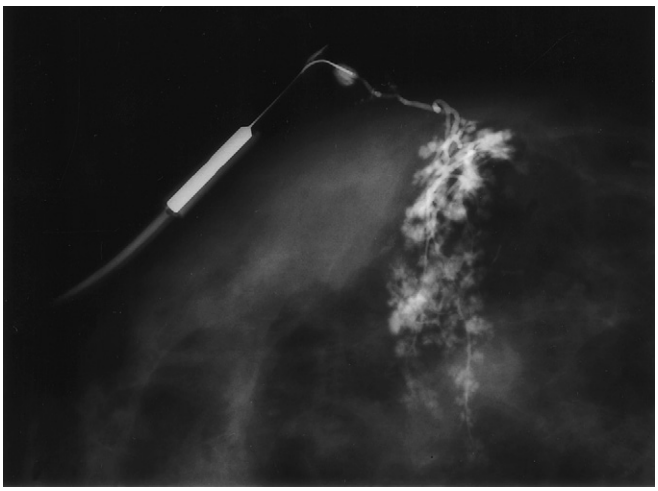

FIGURE 36-3 Injection of contrast into a single ductal system (ductogram). Occasionally used to evaluate surgically significant nipple discharge, ductography is performed by cannulation of an individual duct orifice and injection of contrast material. This ductogram opacifies the entire ductal tree, from the retroareolar duct to the lobules at the end of the tree. It also demonstrates the functional independence of each duct system; there is no cross-communication between independent systems.

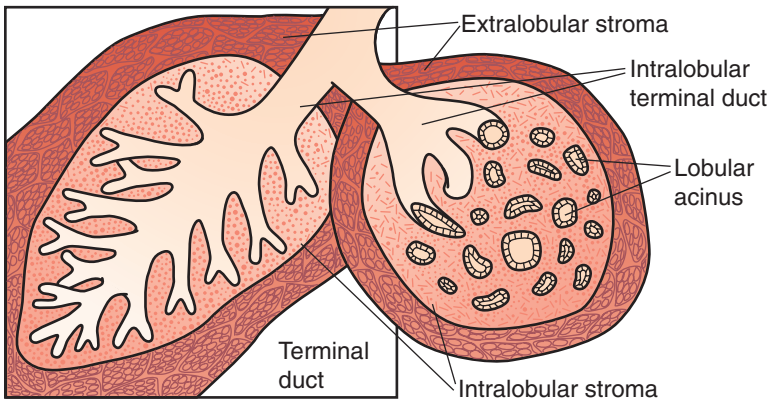

FIGURE 36-4 Mature resting lobular unit. At the distal end of the ductal system is the lobule, which is formed by multiple branching events at the end of terminal ducts, each ending in a blind sac or acini, and is invested with specialized stroma. The lobule is a three-dimensional structure but is seen in two dimensions in a histologic thin section, shown in the *lower right*. The intralobular terminal ductule and acini are invested in loose connective tissue containing a modest number of infiltrating lymphocytes and plasma cells. The lobule is distinct from the denser interlobular stroma, which contains larger breast ducts, blood vessels, and fat.

BREAST DEVELOPMENT AND PHYSIOLOGY

Normal Development and Physiology

Prior to puberty, the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. In the United States, puberty, as measured by breast development and the growth of pubic hair, begins between the ages of 9 and 12 years, and menarche (onset of menstrual cycles) begins at approximately 12 to 13 years of age. These events are initiated by low-amplitude pulses of pituitary gonadotropins, which raise serum estradiol concentrations. In the breast, this hormone-dependent maturation (thelarche) entails increased deposition of fat, the formation of new ducts by branching and elongation, and the first appearance of lobular units. This process of growth and cell division is under the control of estrogen, progesterone, adrenal hormones, pituitary hormones, and the trophic effects of insulin and thyroid hormone. There is evidence that local growth factor networks are also important. The exact timing of these events and the coordinated development of both breast buds may vary from the average in individual patients. The term *prepubertal gynecomastia* refers to symmetrical enlargement and projection of the breast bud in a young girl before the average age of 12 years, unaccompanied by the other changes of puberty. This process, which may be unilateral, should not be confused with neoplastic growth and is not an indication for biopsy.[1]

The postpubertal mature or resting breast contains fat, stroma, lactiferous ducts, and lobular units. During phases of the menstrual cycle or in response to exogenous hormones, the breast epithelium and lobular stroma undergo cyclic stimulation. It appears that the dominant process is hypertrophy and alteration of morphology rather than hyperplasia. In the late luteal (premenstrual) phase, there is an accumulation of fluid and intralobular edema. This accumulation of edema can produce pain and breast engorgement.

These physiologic changes can lead to increased nodularity and may be mistaken for a malignant tumor. Ill-defined masses in premenopausal women are generally observed through the course of the menstrual cycle prior to intervention. With pregnancy, there is diminution of the fibrous stroma and the formation of new acini or lobules, termed the *adenosis of pregnancy.* After birth, there is a sudden loss of placental hormones, which, combined with continued high levels of prolactin, is the principal trigger for lactation. The actual expulsion of milk is under hormonal control and is caused by contraction of the myoepithelial cells that surround the breast ducts and terminal ductules. There is no evidence for innervation of these myoepithelial cells; their contraction appears to occur in response to the pituitary-derived peptide oxytocin. Stimulation of the nipple appears to be the physiologic signal for continued pituitary secretion of prolactin and acute release of oxytocin. When breastfeeding ceases, there is a fall in the prolactin level and no stimulus for release of oxytocin. The breast then returns to a resting state and to the cyclic changes induced when menstruation resumes.

Menopause is defined by cessation in menstrual flow for at least 1 year; in the United States, it usually occurs between the ages of 40 and 55 years, with a median age of 51 years. Menopause may be accompanied by symptoms such as vasomotor disturbances (hot flashes), vaginal dryness, urinary tract infections, and cognitive impairment (possibly secondary to interruption of sleep by hot flashes). Menopause results in involution and a general decrease in the epithelial elements of the resting breast. These changes include increased fat deposition, diminished connective tissue, and the disappearance of lobular units. The persistence of lobules, hyperplasia of the ductal epithelium, and even cyst formation can all occur under the influence of exogenous ovarian hormones, usually in the form of postmenopausal hormone replacement therapy (HRT). Physicians should inquire about the menstrual history, onset of menses, and cessation of menses in postmenopausal women and record the use of HRT. HRT can lead to increased breast density, which may lower the sensitivity of mammography.

Fibrocystic Changes and Breast Pain

The condition previously referred to as *fibrocystic disease* represents a spectrum of clinical, mammographic, and histologic findings and is common during the fourth and fifth decades of life, generally lasting until menopause. An exaggerated response of breast stroma and epithelium to a variety of circulating and locally produced hormones and growth factors is frequently characterized by the constellation of breast pain, tenderness, and nodularity. Symptomatically, the condition is manifested as premenstrual cyclic mastalgia, with pain and tenderness to touch. This can be worrisome to many women; however, breast pain is not usually a symptom of breast cancer. Haagensen[1] has recorded the symptoms of women with breast carcinoma and found pain as an unprompted symptom in 5.4% of patients. In women with breast pain and an associated palpable mass, the presence of the mass is the focus of evaluation and treatment. Normal ovarian hormonal influences on breast glandular elements frequently produce cyclic mastalgia, generally pain in phase with the menstrual cycle. Noncyclic mastalgia is more likely idiopathic and difficult to treat. Women 30 years and older with noncyclic mastalgia should undergo breast imaging with mammography in addition to a physical examination. If examination reveals a mass, this should become the focus of subsequent evaluation. Occasionally, a simple cyst may cause noncyclic breast pain, and aspiration of the cyst will usually resolve the pain. Most patients with simple cysts do not require any further evaluation unless it is a complex cyst with solid intracystic components.

Patients with fibrocystic changes have clinical breast findings that range from mild alterations in texture to dense, firm breast tissue with palpable masses. The appearance of large palpable cysts completes the picture. Mammographically, fibrocystic changes are usually seen as diffuse or focal radiologically dense tissue. By ultrasound, cysts exist in up to one third of all women 35 to 50 years of age, with most of them being nonpalpable. However, palpable cysts or multiple small cysts are typical of fibrocystic disease. Cysts, with or without fibrocystic disease, are uncommon in women older than 60 and younger than 30 years.

Histologically, in addition to macrocysts and microcysts, identified solid elements include adenosis, sclerosis, apocrine metaplasia, stromal fibrosis, and epithelial metaplasia and hyperplasia. Depending on the presence of epithelial hyperplasia, fibrocystic change is classified as nonproliferative, proliferative without atypia, or proliferative with atypia. All three alterations can occur alone or in combination and to a variable degree and, in the absence of epithelial atypia, represent the histologic spectrum of normal breast tissue. However, atypical epithelial hyperplasia (atypical ductal hyperplasia [ADH]) is a risk factor for the development of breast cancer. Atypical proliferations of ductal epithelial cells confer increased risk for breast cancer; however,

fibrocystic change is not itself a risk factor for the development of breast malignancy.

Abnormal Development and Physiology

Absent or Accessory Breast Tissue

Absence of breast tissue (amastia) and absence of the nipple (athelia) are rare anomalies. Unilateral rudimentary breast development is more common, as is adolescent hypertrophy of one breast with lesser development of the other. In contrast, accessory breast tissue (polymastia) and accessory nipples (supernumerary nipples) are both common. Supernumerary nipples are usually rudimentary and occur along the milk line from the axilla to the pubis in males and females. They may be mistaken for a small mole; however, accessory nipples are usually only removed for cosmetic reasons. True polythelia refers to more than one nipple serving a single breast, which is rare. Accessory breast tissue is commonly located above the breast in the axilla. Rudimentary nipple development may be present, and lactation is possible with more complete development. Accessory breast tissue may be seen as an enlarging mass in the axilla during pregnancy and persists as excess tissue in the axilla after lactation is complete. The accessory mammary tissue may be removed surgically if it is large or cosmetically deforming or to prevent enlargement during future pregnancy.

Gynecomastia

Hypertrophy of breast tissue in men is a clinical entity for which there is frequently no identifiable cause. Pubertal hypertrophy occurs in boys between the ages of 13 years and early adulthood and senescent hypertrophy is diagnosed in men older than 50 years. Gynecomastia in teenage boys is common and may be bilateral or unilateral. Unless it is unilateral or painful, it may pass unnoticed and regress with adulthood. Pubertal hypertrophy is generally treated by observation without surgery. Surgical excision may be discussed if the enlargement is unilateral, fails to regress, or is cosmetically unacceptable. Hypertrophy in older men is also relatively common. The enlargement is frequently unilateral, although the contralateral breast may enlarge with time. A number of commonly used medications, such as digoxin, thiazides, estrogens, phenothiazines, and theophylline, may exacerbate senescent gynecomastia. In addition, gynecomastia may be a systemic manifestation of hepatic cirrhosis, renal failure, and malnutrition. In both age groups, the mass is smooth, firm, and symmetrically distributed beneath the areola. It is frequently tender, which is often the reason for seeking medical attention. Both pubertal and senescent gynecomastia may be managed nonoperatively and can be fully characterized with ultrasonography. There is little confusion with carcinoma occurring in the male breast. Carcinoma is not usually tender, is asymmetrically located beneath or beside the areola, and may be fixed to the overlying dermis or to the deep fascia. A dominant mass suspected of being carcinoma should be examined with core needle biopsy. Mammography and ultrasound can also be useful tools to discriminate between gynecomastia and a suspected malignancy of the breast in older men.

Nipple Discharge

The appearance of discharge from the nipple of a nonlactating woman is a relatively common condition and is rarely associated with an underlying carcinoma. In one review of 270 subareolar biopsies for discharge coming from one identifiable duct and without an associated breast mass, carcinoma was found in only 16 patients (5.9%). In these cases, the fluid was bloody or tested strongly positive for occult hemoglobin. In another series of 249 patients, breast carcinoma was found in 10 (4%). In 8 of these patients, a mass lesion was identified in addition to the discharge. In the absence of a palpable mass or a suspicious mammogram, discharge is rarely associated with cancer.

It is important to establish whether the discharge comes from one breast or from both breasts, whether it comes from multiple duct orifices or from just one, and whether the discharge is grossly bloody or contains blood. A milky discharge from both breasts is termed *galactorrhea.* In the absence of lactation or a history of recent lactation, galactorrhea may be associated with increased production of prolactin. Radioimmunoassay for serum prolactin is diagnostic. However, true galactorrhea is rare and is diagnosed only when the discharge is milky (contains lactose, fat, and milk-specific proteins). Unilateral discharge coming from one duct orifice is often treated surgically when there is a significant amount of discharge (Fig. 36-5). However, the underlying cause is rarely a breast malignancy.

The most common cause of spontaneous nipple discharge from a single duct is a solitary intraductal papilloma in one of the large subareolar ducts under the nipple. Subareolar duct ectasia producing inflammation and dilation of large collecting ducts under the nipple is common and usually involves discharge from multiple ducts. Cancer is a very unusual cause of discharge in the absence of other signs. In summary, nipple discharge that is bilateral and comes from multiple ducts is not usually a surgical problem. Bloody discharge from a single duct often requires surgical excision to establish a diagnosis and control the discharge. A diagnosis of intraductal papilloma is found in most of these cases.

Galactocele

A galactocele is a milk-filled cyst that is round, well circumscribed, and easily movable within the breast. It generally occurs after the cessation of lactation or when feeding frequency has curtailed significantly. Haagensen[1] has reported that galactoceles may occur up to 6 to 10 months after breastfeeding has ceased. The pathogenesis of galactocele is unknown, but it is thought that inspissated milk within ducts is responsible. The tumor is usually located in the central portion of the breast or under the nipple. Needle aspiration produces thick creamy material that may be tinged dark green or brown. Although it appears purulent, the fluid is sterile. Treatment is needle aspiration, and withdrawal of thick milky secretion confirms the diagnosis; surgery is reserved for cysts that cannot be aspirated or those that become infected.

DIAGNOSIS OF BREAST DISEASE

Patient History

It is important for the examiner to determine the patient's age and obtain a reproductive history, including age at menarche, age at menopause, and history of pregnancies, including age at first full-term pregnancy. A previous history of breast biopsies should be obtained, including the pathologic findings, especially proliferative breast disease. If the patient has had a hysterectomy, it is important to determine whether the ovaries were removed. In premenopausal women, a recent history of pregnancy and

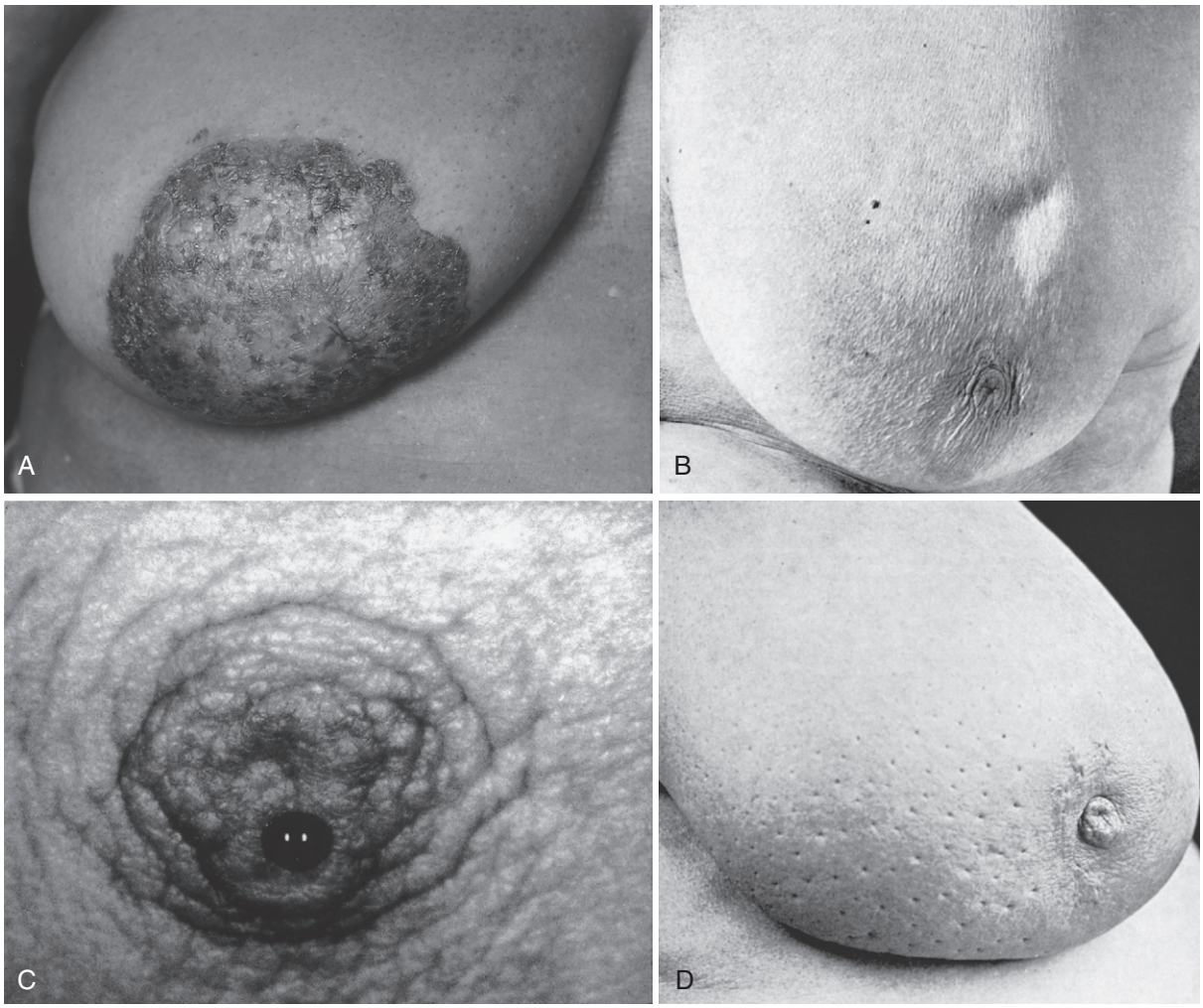

FIGURE 36-5 Common physical findings during breast examination. **A,** Paget's disease of the nipple. Malignant ductal cells invade the epidermis without traversing the basement membrane of the subareolar duct or epidermis. The disease appears as a psoriatic rash that begins on the nipple and spreads off onto the areola and into the skin of the breast. **B,** Skin dimpling. Traction on Cooper's ligaments by a scirrhous tumor is distorting the surface of the breast and producing a dimple best seen with angled indirect lighting during abduction of the arms upward. **C,** Nipple discharge. Discharge from multiple ducts or bilateral discharge is a common finding in healthy breasts. In this case, the discharge is from a single duct orifice and may signify underlying disease in the discharging duct. In this patient, a papilloma was the source of her symptoms. **D,** Peau d'orange (skin of the orange) or edema of the skin of the breast. This finding may be caused by dependency of the breast, lymphatic blockage (from surgery or radiation), or mastitis. The most feared cause is inflammatory carcinoma, in which malignant cells plug the dermal lymphatics—the pathologic hallmark of the disease.

lactation should be noted. The history should include any use of HRT or hormones used for contraception. The family history should detail any cancer of the breast and ovaries and the menopausal status of any affected relatives.

With respect to the specific breast complaint, questioning should include history of a mass, breast pain, nipple discharge, and any skin changes. If a mass is present, one should inquire as to how long it has been present and whether it changes with the menstrual cycle. If a cancer diagnosis is suspected, inquiry about constitutional symptoms, bone pain, weight loss, respiratory changes, and similar clinical indications can direct investigations that could reveal evidence of metastatic disease.

Physical Examination

The examination begins with the patient in the upright sitting position with careful visual inspection for obvious masses, asymmetries, and skin changes. The nipples are inspected and compared for the presence of retraction, nipple inversion, or excoriation of the superficial epidermis such as that seen with Paget's disease (see Fig. 36-5*A*). The use of indirect lighting can unmask subtle dimpling of the skin or nipple caused by a carcinoma that places Cooper's ligaments under tension (see Fig. 36-5*B*). Simple maneuvers such as stretching the arms high above the head or tensing the pectoralis muscles may accentuate asymmetries and dimpling. If carefully sought, dimpling of the skin or nipple retraction is a sensitive and specific sign of underlying cancer.

Edema of the skin produces a clinical sign known as *peau d'orange* (see Fig. 36-5*D*). When combined with tenderness, warmth and swelling of the breast, these signs and symptoms are the hallmark of inflammatory carcinoma and may be mistaken for acute mastitis. The inflammatory changes and edema

are caused by obstruction of dermal lymphatic channels with emboli of carcinoma cells. Occasionally, a bulky tumor may produce obstruction of lymph channels that results in overlying skin edema. This is not typically the case with inflammatory carcinoma, where there is usually no discrete palpable mass but diffuse changes throughout the breast parenchyma. In 40 patients with inflammatory carcinoma described by Haagensen,[1] erythema and edema of the skin were present in all cases, a palpable mass or localized induration was noted in 19 patients, and no localized tumor was present in 21 patients.

Involvement of the nipple and areola can occur with carcinoma of the breast, especially when the primary tumor is located in the subareolar position. Direct involvement may result in retraction of the nipple. Flattening or inversion of the nipple can be caused by fibrosis in certain benign conditions, especially subareolar duct ectasia. In these cases, the finding is frequently bilateral and the history confirms that the condition has been present for many years. Unilateral retraction or retraction that develops over a period of weeks or months is more suggestive of carcinoma. Centrally located tumors that go undetected for a long period of time may directly invade and ulcerate the skin of the areola or nipple. Peripheral tumors may distort the normal symmetry of the nipples by traction on Cooper's ligaments.

A condition of the nipple that is commonly associated with an underlying breast cancer is Paget's disease. First described by Sir James Paget in 1874, Paget's disease has histologically distinct changes within the dermis of the nipple. There is often an underlying intraductal carcinoma in the large sinuses just under the nipple (see Fig. 36-5*A*). Carcinoma cells invade across the junction of epidermal and ductal epithelial cells and enter the epidermal layer of the skin of the nipple. Clinically, this produces a dermatitis that may appear eczematoid and moist or dry and psoriatic. It begins in the nipple, although it can spread to the skin of the areola. Many benign skin conditions such as eczema frequently begin on the areola, whereas Paget's disease originates on the nipple and secondarily involves the areola.

Palpation of the breast tissue and regional lymph nodes follows visual inspection. While the patient is still in the sitting position, the examiner supports the patient's arm and palpates each axilla to detect the presence of enlarged axillary lymph nodes. The supraclavicular and infraclavicular spaces are similarly palpated for enlarged nodes. Palpation of the breast is always done with the patient lying supine on a solid examining surface, with the arm stretched above the head. Palpation of the breast while the patient is sitting is often inaccurate because the overlapping breast tissue may feel like a mass or a mass may go undetected within the breast tissue. The breast is best examined with compression of the tissue toward the chest wall, with palpation of each quadrant and the tissue under the nipple-areolar complex. Palpable masses are characterized according to their size, shape, consistency, and location and whether they are fixed to the skin or underlying musculature. Benign tumors, such as fibroadenomas and cysts, can be as firm as carcinoma; usually, these benign entities are distinct, well circumscribed, and movable. Carcinoma is typically firm but less circumscribed, and moving it produces a drag of adjacent tissue. Cysts and fibrocystic changes can be tender with palpation of the breast; however, tenderness is rarely a helpful diagnostic sign. Most palpable masses are self-discovered by patients during casual or intentional self-examination.

Biopsy

Fine-Needle Aspiration Biopsy

Fine-needle aspiration (FNA) biopsy is a common tool used in the diagnosis of breast masses. It can be done with a 22-gauge needle, an appropriate-sized syringe, and an alcohol preparation pad. The aspirate must be properly prepared on a slide for cytologic examination to be clinically useful. The main usefulness of FNA biopsy is differentiation of solid from cystic masses, but it may be performed whenever a new, dominant, unexplained mass is found in the breast. The routine performance of FNA to distinguish solid from cystic breast masses has largely been replaced by ultrasonography. With a mammographically identified mass or a palpable mass, ultrasonography can quickly discriminate solid from cystic masses, which this may often obviate the need for aspiration. Cyst fluid is usually turbid and dark green or amber and can be discarded if the mass totally disappears and the fluid is not bloody. If the FNA of a suspected cyst does not reveal cyst fluid, the next step to consider is a core needle biopsy, usually with mammographic or ultrasonographic guidance. If the cyst aspiration reveals blood-tinged fluid or fluid is produced but the mass fails to resolve completely, consideration should be given to pneumocystography or image-guided core needle biopsy. It is not uncommon for cysts to reaccumulate fluid after initial aspiration. If the cyst is demonstrated to be a simple cyst on breast imaging, no further intervention is required. If the cyst is classified as a complex cyst, further imaging and evaluation should be considered to rule out an underlying carcinoma.

If the mass is solid and the clinical situation is consistent with carcinoma, cytologic examination of the aspirated material is performed. The needle is repeatedly inserted into the mass while constant negative pressure is applied to the syringe. Suction is released and the needle is withdrawn. The scanty fluid and cellular material within the needle are submitted in physiologically buffered saline (Normosol) or fixed immediately on slides in 95% ethyl alcohol. Because the cytologic evaluation will not discriminate between noninvasive and invasive breast cancers, most clinicians recommend core needle biopsy for definitive histologic diagnosis prior to surgical intervention. A positive result on FNA biopsy allows the surgeon to begin informed discussions with the patient; however, definite plans for treatment should be based on the histologic diagnosis from a core needle biopsy.

Core Needle Biopsy

Core needle biopsy is the method of choice to sample nonpalpable, image-detected breast abnormalities. This technique is also preferred for the diagnosis of palpable lesions. Core needle biopsy can be performed under mammographic (stereotactic), ultrasonographic, or magnetic resonance imaging (MRI) guidance. Mass lesions that are visualized on ultrasonography can be sampled under ultrasonographic guidance; calcifications and densities that are best seen on mammography are sampled under stereotactic guidance. During stereotactic core needle biopsy, the breast is compressed, most often with the patient lying prone on the stereotactic core biopsy table. A robotic arm and biopsy device are positioned by computed analysis of triangulated mammographic images. After local anesthetic is injected, a small skin incision is made and an 11-gauge core biopsy needle is inserted into the lesion to obtain the tissue sample with vacuum

assistance. There are standards for the appropriate number of core samples to be obtained based on the type of abnormality being sampled and a clip should be placed to mark the site of the lesion, particularly for small lesions that may be difficult to find after extensive sampling. The specimens should be placed in a Petri dish and imaged to confirm that the targeted lesion has been adequately sampled. A similar approach is used for ultrasonographic and MRI-guided biopsy of lesions.

Specimen radiography of excised cores is performed to confirm that the targeted lesion has been sampled and to direct pathologic assessment of the tissue. A postbiopsy mammogram confirms that a defect has been created within the target lesion and that the marking clip is in the correct position. Wire localization and surgical excision are required if the lesion cannot be adequately sampled by core biopsy approaches, or if there is discordance between the imaging abnormality and pathologic findings.

Interpretation of Core Needle Biopsy Results The limited sample size obtained by core biopsy techniques requires proper interpretation of the pathology results. Most patients undergoing core biopsy will have benign findings and may return to routine screening, with no other intervention required. If a malignancy is detected, histologic subtype, grade, and receptor status should be determined from the core biopsy sample. The patient may proceed to definitive treatment of the cancer if it is an early-stage breast cancer. Patients with locally advanced or inflammatory breast cancer should be treated with systemic chemotherapy prior to surgical intervention. Depending on the size of the imaging abnormality, approximately 10% to 20% of patients with a diagnosis of DCIS on core biopsy will be found to have some invasive carcinoma at definitive surgery.

The diagnosis of breast lesions using a minimally invasive procedure, such as core needle biopsy, is the preferred approach. The use of excisional breast biopsy as a diagnostic procedure increases costs and results in delays to definitive surgery for patients with cancer.[2] Fewer than 10% of patients who undergo core biopsy will have inconclusive results and require wire-localized surgical biopsy for definitive diagnosis. Biopsy results that are not concordant with the targeted lesion (e.g., a spiculated mass on imaging and normal breast tissue on core biopsy) also require surgical excision. When ADH is found on core biopsy, surgical excision will reveal DCIS or invasive carcinoma in up to 20% of cases because of difficulty distinguishing ADH and DCIS in a limited tissue sample. A finding of a cellular fibroadenoma on core biopsy requires excision to rule out a phyllodes tumor.

BREAST IMAGING

Breast imaging techniques are used to detect small, nonpalpable breast abnormalities, evaluate clinical findings, and guide diagnostic procedures. Mammography is the primary imaging modality for screening asymptomatic women. During mammography, the breast is compressed between Plexiglas plates to reduce the thickness of the tissue through which the radiation must pass, separate adjacent structures, and improve resolution. Two views of each breast are obtained on a screening mammogram, mediolateral oblique and craniocaudal. A diagnostic mammogram is indicated for further evaluation of abnormalities identified on a screening mammogram or of clinical findings or symptoms. Magnification views are obtained to evaluate calcifications and compression views are used to provide additional detail when a mass lesion is suspected. Mammographic sensitivity is limited by breast density, with as many as 10% to 15% of clinically evident breast cancers having no associated mammographic abnormality. Digital mammography acquires digital images and stores them electronically, thereby allowing manipulation and enhancement of images to facilitate interpretation. Digital mammography appears to be superior to traditional film-screen mammography for detecting cancer in younger women and those with dense breasts. Mammography in women younger than 30 years, whose breast tissue is dense with stroma and epithelium, may produce an image without much definition. As women age, the breast tissue involutes and is replaced by fatty tissue. On mammography, fat absorbs relatively little radiation and provides a contrasting background that favors detection of small lesions. Computer-assisted diagnosis (CAD) has been shown to increase the sensitivity and specificity of mammography and ultrasound over review by the radiologist alone.

Screening Mammography

Screening mammography is performed in asymptomatic women with the goal of detecting breast cancer that is not yet clinically evident. This approach assumes that breast cancers identified through screening will be smaller, have a better prognosis, and require less aggressive treatment than cancers identified by palpation. The potential benefits of screening are weighed against the cost of screening and the number of false-positive studies that prompt additional workup, biopsies, and patient anxiety.

Eight prospective randomized trials of screening mammography have been performed, with almost 500,000 women participating. The impact of mammographic screening on breast cancer mortality has been assessed by age group at specific intervals by the U.S. Preventive Services Task Force and the most recent report resulted in a change in recommendations for breast cancer screening. Based on the review of eight trials in women aged 39 to 49 years, screening mammography reduced the risk for breast cancer death by 15% (relative risk [RR], 0.85; credible interval [CrI], 0.75 to 0.96). In the six trials that included women aged 50 to 59, there was a reduction in risk of 14% (RR, 0.86; CrI, 0.75 to 0.99). There were two trials that included women aged 60 to 69 and, in this age group, there was a reduction in risk of 32% (RR, 0.68; CrI, 0.54 to 0.87). There was only one trial that included women older than 70 years, and it was concluded that there were insufficient data to recommend routine screening in this age group. Based on these results, the most recent U.S. Preventive Services Task Force report recommended biennial screening mammography for women aged 50 to 74 years and recommended against screening for those aged 40 to 49 and women older than 75 years of age.[2] The recommendations were based on the risk reduction, number of women needed to invite for screening to prevent one breast cancer death, and potential for harm from additional testing and biopsies (Table 36-1).

At present, the American Cancer Society continues to recommend annual screening mammography for women older than 40 years and suggests that this practice should continue as long as the woman is in good health. Younger women with a significant family history, histologic risk factors, or history of previous breast cancer may also benefit from screening with MRI. Although the randomized trials did not enroll women

Table 36-1 Effect on Breast Cancer Mortality and False-Positive Mammograms by Age Group in Breast Cancer Screening Trials

AGE GROUP (YR)	NO. OF TRIALS	BREAST CANCER MORTALITY, RR (95% CRI)	NO. NEEDED TO INVITE FOR SCREENING TO PREVENT ONE BREAST CANCER DEATH (95% CRI)	FALSE-POSITIVE MAMMOGRAMS/ SCREENING ROUND*
39-49	8	0.85 (0.75-0.96)	1904 (929-6378)	97.8
50-59	6	0.86 (0.75-0.99)	1339 (322-7455)	86.6
60-69	2	0.68 (0.54-0.87)	377 (230-1050)	79.0
70-74	1	1.12 (0.73-1.72)	Not available	68.8

Adapted from Nelson HD, Tyne K, Naik A, et al; U.S. Preventive Services Task Force: Screening for breast cancer: Systematic evidence review update for the U.S. Preventive Services Task Force. Ann Intern Med 151:727, 2009.

*Per 1000 screened.

older than 74 years, breast cancer risk increases with advancing age, and the sensitivity and specificity of mammography are highest in older women, whose breast tissue has usually been replaced by fat. It is reasonable to continue mammographic screening in older women who are in good general health who would otherwise be considered appropriate surgical candidates.

Ultrasonography

Ultrasonography is useful in determining whether a lesion detected by mammography is solid or cystic. Ultrasonography can be useful for discriminating lesions in the patient with dense breasts. However, it has not been found to be a useful screening tool because it is highly dependent on the operator performing the freehand screening and there is a lack of standardized screening protocols. The American College of Radiology Imaging Network (ACRIN) has performed a trial (ACRIN 6666) in high-risk women in whom mammography and ultrasonography were performed in randomized order to compare the sensitivity, specificity, and diagnostic yield of ultrasonography plus mammography compared with mammography alone.[3] The investigators found that the combination of ultrasonography and mammography allowed for an increased diagnostic yield of 4.2 cancers/1000 women. However, the use of ultrasonography resulted in more false-positive events and required more callbacks and biopsies. There are no data available showing that the use of screening ultrasonography can reduce mortality caused by breast cancer.

Magnetic Resonance Imaging

MRI is increasingly being used for the evaluation of breast abnormalities. It is useful for identifying the primary tumor in the breast in patients who present with axillary lymph node metastases without mammographic evidence of a primary breast tumor (unknown primary). MRI may also be useful for assessing the extent of the primary tumor, particularly in young women with dense breast tissue, and for evaluating invasive lobular cancers. Some surgeons will use MRI preoperatively to determine eligibility for breast conservation; however, there is no level 1 evidence to support its routine use for this purpose. MRI has shown usefulness as a screening tool in patients with known *BRCA* gene mutations and for detecting contralateral breast cancers in women diagnosed with a unilateral cancer on mammography. The sensitivity of MRI for invasive cancer is higher than 90%, but is only 60% or less for DCIS. The specificity of MRI is only moderate, with significant overlap in the appearance of benign and malignant lesions. A meta-analysis of 22 studies reporting the detection of contralateral breast cancer by MRI has revealed a mean incremental cancer detection rate of 4.1% and a positive predictive value (PPV) of 47.9%. This high rate of detection may be partially the result of selection bias; however, it is of significant concern that more than 50% of the abnormalities detected on MRI are false- positives, resulting in the need for additional imaging studies and biopsies. The comparative effectiveness of MRI in breast cancer (COMICE) trial was a multicenter trial that recruited 1623 women aged 18 years or older with newly diagnosed breast cancer to assess the clinical efficacy of contrast-enhanced MRI.[4] Patients had standard clinical and radiological examination and then were randomized to undergo MRI or no further imaging. The primary end point was reexcision rates or need for mastectomy within 6 months. There was no statistically significant difference in reoperative rates between patients who did or did not undergo MRI. Of note, the contralateral breast cancer detection rate in the COMICE trial was 1.6%, significantly lower than that reported in other trials. This trial has been criticized because MRI-guided biopsy was not available at all centers to assess suspicious findings identified on MRI. This led to a number of mastectomies without pathologic verification of additional disease, which would have precluded breast-conserving therapy.

Nonpalpable Mammographic Abnormalities

Mammographic abnormalities that cannot be detected by physical examination include clustered microcalcifications and areas of abnormal density (e.g., masses, architectural distortions, asymmetries) that have not produced a palpable finding (Fig. 36-6). The Breast Imaging Reporting and Data System (BI-RADS) is used to categorize the degree of suspicion of malignancy for a mammographic abnormality (Table 36-2). To avoid unnecessary biopsies for low-suspicion mammographic findings, probably benign lesions are designated BI-RADS 3 and are monitored with a schedule of short-interval mammograms over a 2-year period. Biopsy is performed only for lesions that progress during follow-up.

Diagnostic biopsy of a nonpalpable mammographic lesion should be performed by image-guided core needle biopsy. Because 75% to 80% of patients for whom biopsy is recommended will have benign findings, the less invasive and less

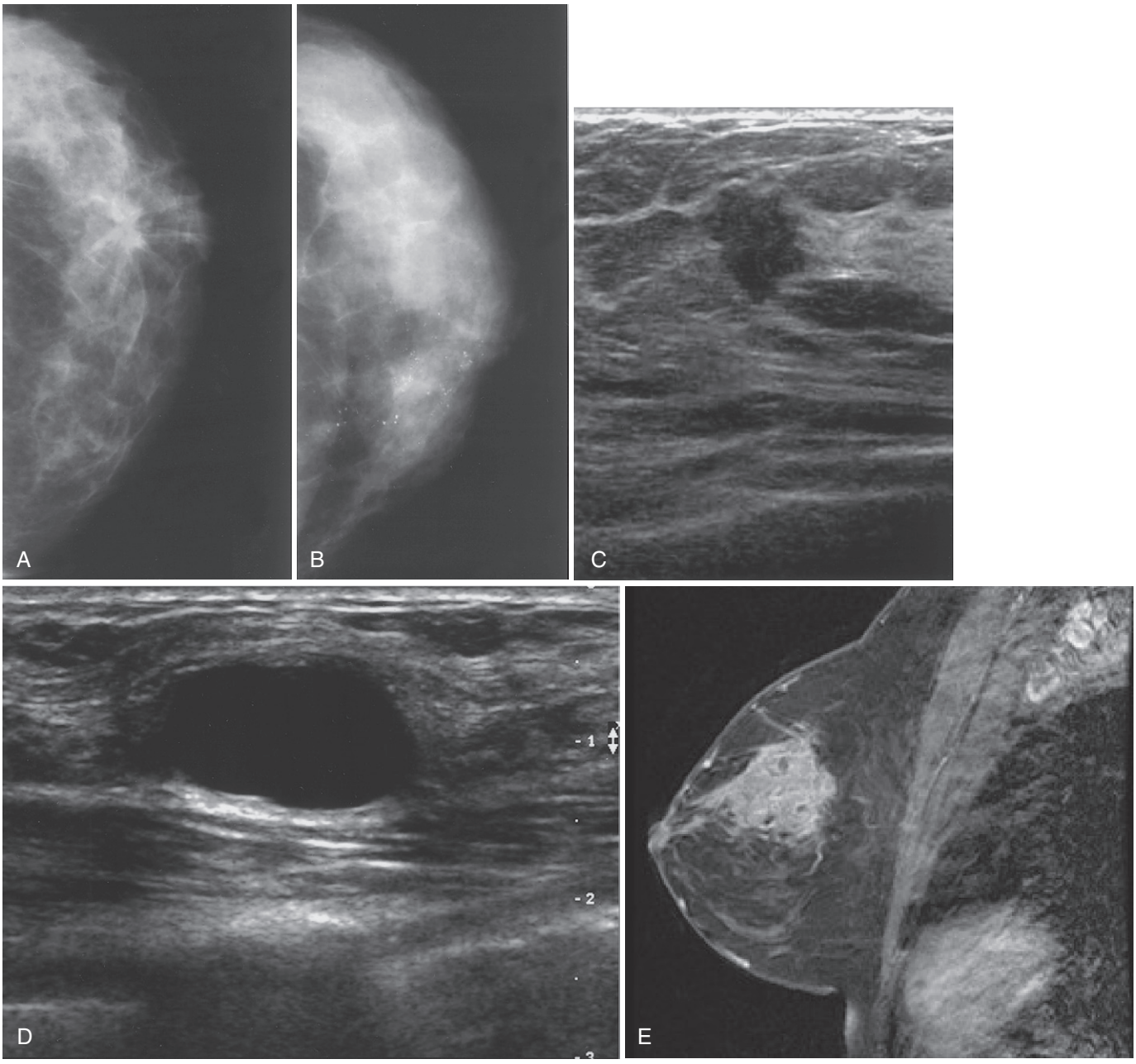

FIGURE 36-6 Mammographic, ultrasonographic, and MRI findings in breast disease. **A,** Stellate mass in the breast. The combination of a density with spiculated borders and distortion of surrounding breast architecture suggests a malignancy. **B,** Clustered microcalcifications. Fine, pleomorphic, and linear calcifications that cluster together suggest the diagnosis of ductal carcinoma in situ. **C,** Ultrasound image of breast cancer. The mass is solid, contains internal echoes, and displays an irregular border. Most malignant lesions are taller than they are wide. **D,** Ultrasound image of a simple cyst. By ultrasound, the cyst is round with smooth borders, there is a paucity of internal sound echoes, and there is increased through-transmission of sound, with enhanced posterior echoes. **E,** Breast MRI showing gadolinium enhancement of a breast cancer. Rapid and intense gadolinium enhancement reflects increased tumor vascularity. Lesion contour and size may also be assessed by MRI.

costly image-guided core needle biopsy approach is preferred whenever feasible.

Wire-Localized Surgical Excision

Nonpalpable breast lesions should be assessed with image-guided core biopsy, as appropriate, based on the type of abnormality. If the diagnosis is not concordant with imaging findings or there is ADH in a field of microcalcifications that may represent DCIS, most patients should proceed to excisional biopsy for definitive diagnosis. To ensure that the abnormality is completely excised, a localizing wire is placed adjacent to the lesion under mammographic or ultrasonographic guidance. The wire is placed though an introducer needle and has a hook that engages within the breast parenchyma at or near the abnormality to hold it in position after the introducer is withdrawn. Images with the wire in place are made available in the operating room

Table 36-2 Breast Imaging Reporting and Data System (BI-RADS): Final Assessment Category

CATEGORY	DEFINITION
0	Incomplete assessment—need additional imaging evaluation or prior mammograms for comparison
1	Negative—nothing to comment on; usually recommend annual screening
2	Benign finding—usually recommend annual screening
3	Probably benign finding (<2% malignant)—initial short-interval follow-up suggested
4	Suspicious abnormality (2%-95% malignant)—biopsy should be considered
5	Highly suggestive of malignancy (>95% malignant)—appropriate action should be taken
6	Known biopsy—proven malignancy

Adapted from Liberman L, Abramson AF, Squires FB, et al: The breast imaging reporting and data system: Positive predictive values of mammographic feature and final assessment categories. AJR Am J Roentgenol 171:35, 1998; and Liberman L, Menell JH: Breast imaging reporting and data systems (BI-RADS). Radiol Clin North Am 40:409, 2002.

to guide the surgeon. It is generally recommended that the surgical incision be placed directly over the lesion that is marked by the hook of the localizing wire, and not where the wire enters the skin. Depending on the size of the breast and length of the localization wire, the hook may be a long distance from the skin entry site. Placing the surgical incision over the site of the hook wire will minimize the amount of normal breast tissue excised during the biopsy procedure. Depending on the size of the lesion and the suspicion of malignancy, it is generally wise to excise a border of normal tissue around the lesion to ensure complete removal, with a negative margin. After excision, the specimen is sent for specimen radiography to confirm that the targeted lesion has been excised. Patients who have a diagnosis of benign findings on excision should undergo a new baseline mammography 4 to 6 months following the surgical procedure.

IDENTIFICATION AND MANAGEMENT OF HIGH-RISK PATIENTS

Identification of High-Risk Patients

Risk Factors for Breast Cancer

Identification of factors associated with an increased incidence of breast cancer development is important in general health screening for women (Box 36-1). Risk factors for breast cancer can be divided into seven broad categories—age, family history of breast cancer, hormonal factors, proliferative breast disease, irradiation of the breast or chest wall at an early age, personal history of malignancy, and lifestyle factors.

Age and Gender Age is probably the most important risk factor for breast cancer development. The age-adjusted incidence of breast cancer continues to increase with advancing age of the female population. Breast cancer is rare in persons younger than 20 years, and cases in these women constitute less than 2% of the total cases. Thereafter, the incidence increases to 1 in 233 from ages 30 to 39 years, 1 in 69 from ages 40 to 49, 1 in 42 from ages 50 to 59, 1 in 29 from ages 60 to 69, and 1 in 8 by age 80 years. Alternatively stated, women now have an average risk of 12.2% of being diagnosed with breast cancer at some time during their lives. Gender is also an important risk factor because the vast majority of breast cancers occur in women. Breast cancer does occur in men, however, although it is less than 1% of the incidence in females, with 1970 cases of invasive breast cancer having been anticipated in 2010 (out of a total burden of 209,060 estimated cases). Lumps in the male breast are more likely to be benign and the result of gynecomastia (see earlier) or other noncancerous tumors.

BOX 36-1 Risk Factors for Breast Cancer

Risk Factors That Cannot be Modified
Increasing age
Female gender
Menstrual factors
Early age at menarche (onset of menses prior to age 12 yr)
Older age at menopause (onset beyond age 55 yr)
Nulliparity
Family history of breast cancer
Genetic predisposition (*BRCA1* and *BRCA2* mutation carriers)
Personal history of breast cancer
Race, ethnicity (white women have increased risk compared with others)
History of radiation exposure

Risk Factors That Could be Modified
Reproductive factors
Age at first live birth (full-term pregnancy after age 30 yr)
Parity
Lack of breast-feeding
Obesity
Alcohol consumption
Tobacco smoking
Use of hormone replacement therapy
Decreased physical activity
Shift work (night shifts)

Histologic Risk Factors
Proliferative breast disease
ADH
ALH
LCIS

Personal History of Breast Cancer A history of mammary cancer in one breast increases the likelihood of a second primary cancer in the contralateral breast. The magnitude of risk depends on the age at diagnosis of the first primary cancer, estrogen receptor status of the initial breast cancer, and use of adjuvant systemic chemotherapy and hormonal therapy. In absolute terms, the actual risk varies from 0.5% to 1%/year in younger patients to 0.2% in older patients.[1,5]

Histologic Risk Factors Histologic abnormalities diagnosed by breast biopsy represent an important category of breast cancer risk factors. Lobular carcinoma in situ (LCIS) is a relatively uncommon condition that is observed predominantly in younger premenopausal women. It is typically an incidental finding at

biopsy for another condition and does not present as a palpable mass or suspicious microcalcifications on mammography. Haagensen[1] reported that LCIS was found in 3.6% of more than 5000 biopsies performed for benign disease. In a review of 297 patients with LCIS treated by biopsy and careful observation, it was determined that the actuarial probability of carcinoma developing at the end of 35 years was 21.4%. When compared with the Connecticut Tumor Registry data, a risk ratio (ratio of observed to expected cases) of 7 : 1 was calculated. Significantly, 40% of the carcinomas that subsequently developed were purely in situ lesions, the invasive cancers that developed were predominantly ductal and not lobular in histology, and 50% of the carcinomas occurred in the contralateral breast. Thus, LCIS is not considered a breast cancer but rather a histologic marker for increased breast cancer susceptibility, which is estimated at slightly less than 1%/year longitudinally.

A conservative approach is favored for most patients with a diagnosis of LCIS. The three options that can be discussed with the patient are close observation, chemoprevention with tamoxifen or raloxifene, and bilateral mastectomy. LCIS predisposes to subsequent carcinoma and the risk is lifelong and equal for both breasts. A 5-year course of tamoxifen provides a 56% reduction in breast cancer risk.[6] For those who elect surgery in preference to observation, bilateral total mastectomy remains the procedure of choice.

Benign breast disease produces a spectrum of histologic changes and is broadly divided into histologic lesions that display proliferative epithelial alterations and those that display nonproliferative epithelial alterations. Nonproliferative changes include mild to moderate hyperplasia of luminal cells within breast ducts; these changes do not significantly increase a woman's lifetime risk for development of breast cancer. Proliferative changes within the breast ductal system are associated with an increased risk of developing breast cancer. Dupont and Page have divided proliferative lesions into those with epithelial hyperplasia with atypia and those without atypia; proliferative lesions without atypia sometimes are termed *severe hyperplasia.*

Subsequent studies have adhered to this classification scheme—nonproliferative lesions, proliferative breast epithelium without atypia (severe hyperplasia), and proliferative changes with atypia. ADH and atypical lobular hyperplasia (ALH) are both categorized as proliferative changes with atypia. The risk ratio for breast cancer in women with ADH or ALH is approximately four to five times the risk for development of breast cancer in the general population. A family history of breast cancer and atypical hyperplasia increases the risk to almost nine times that of the general population. Thus, the annual risk for development of breast cancer in a woman with LCIS is slightly less than 1%/year and, with ADH or ALH, it is between 0.5% and 1%/year. These estimates are influenced by age at diagnosis, menopausal status, and family history. An overview of histologic risk factors is presented in Table 36-3.[7]

Table 36-3 Histologic Risk Factors for Development of Breast Cancer

HISTOLOGIC DIAGNOSIS	ESTIMATES, RR*
Nonproliferative disease†	1.0
Proliferative disease without atypia‡	1.3-1.9
Proliferative disease with atypia§	3.7-4.2
and a strong family history	4-9
Lobular carcinoma in situ	>7

Data from Hartmann LC, Sellers TA, Frost MH, et al: Benign breast disease and the risk of breast cancer. N Engl J Med 353:229, 2005; London SJ, Connolly JL, Schnitt SJ, Colditz GA: A prospective study of benign breast disease and the risk of breast cancer. JAMA 267:1780, 1992; and Dupont WD, Parl FF, Hartmann WH, et al: Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 71:1258, 1993.

*Ratio of observed incidence over the incidence in women without proliferative disease.

†Fibrocystic change with no, usual, or mild hyperplasia.

‡Fibrocystic change with hyperplasia greater than mild or usual, papilloma, papillomatosis, sclerosing adenosis, radial scar, and other findings.

§Any diagnosis of atypical ductal or lobular hyperplasia, or both.

Family History and Genetic Risk Factors Many studies have examined the relationship of family history and the risk for breast cancer. First-degree relatives (mothers, sisters, and daughters) of patients with breast cancer have a twofold to threefold excess risk for development of the disease. Risk is much higher if affected first-degree relatives had premenopausal onset and bilateral breast cancer. Risk is not significantly increased in women with distant relatives affected with breast cancer (cousins, aunts, grandmothers), although breast cancer in paternal aunts may be associated with a genetic predisposition. In families with multiple affected members, particularly with bilateral and early-onset cancer, the absolute risk in first-degree relatives approaches 50%, consistent with an autosomal dominant mode of inheritance in these families.

Genetic factors are estimated to be responsible for 5% to 10% of all breast cancer cases, but they may account for 25% of cases in women younger than 30 years. In 1990, King and colleagues identified a region on the long arm of chromosome 17 (17q21) that contained a cancer susceptibility gene. The *BRCA1* gene was discovered in 1994; it is now known that mutations in *BRCA1* account for up to 40% of familial breast cancers. One year later, a second susceptibility gene, *BRCA2,* was discovered. In addition to increased breast cancer risk, women with mutations in *BRCA1* or *BRCA2* are at increased risk for ovarian cancer (45% lifetime risk for *BRCA1* carriers).

Deleterious mutations in *BRCA1* or *BRCA2* are rare in the general population. The frequency of mutations is approximately 1 in 1000 (0.1%) in the American population. Certain relatively closed populations may have higher prevalence rates and show preference for certain mutations, termed *founder mutations,* including the 185delAG and 5382insC mutations in *BRCA1,* which are found in up to 1.0% of the Ashkenazi Jewish population (Jews of Eastern European descent), and the C4446T mutation in French Canadian families. *BRCA1* is a large gene with 22 coding exons and more than 500 mutations; many of these are unique and limited to a given family, which makes genetic testing technically difficult. *BRCA1* is a tumor suppressor gene with disease susceptibility inherited in an autosomal dominant fashion. Germline mutations inactivate a single inherited allele of *BRCA1* in every cell and this precedes a somatic event in breast epithelial cells, which eliminates the remaining allele and causes the cancer. The gene product may provide negative regulation of cell growth and is also involved in recognition and repair of genetic damage.

The *BRCA2* gene is located on chromosome 13 and accounts for up to 30% of familial breast cancers; unlike *BRCA1,* it is associated with increased breast cancer risk in males. Women with a mutation in *BRCA2* also have a 20% to 30% lifelong risk for ovarian cancer. Founder mutations of *BRCA2* include the 617delT mutation present in 1.4% of the Ashkenazi population, 8765delAG mutation in the French Canadian population, and 999del15 mutation in the Icelandic population. In Iceland, 7% of unselected female breast cancer patients and 0.6% of the general population carry the 999del15 mutation.

The penetrance of *BRCA1* and *BRCA2* refers to the chance that carriers of mutations in these genes will actually develop breast cancer. The initial estimates of this chance were high, but a more recent estimate has placed the penetrance of *BRCA1* and *BRCA2* mutations at 56% (95% confidence interval [CI], 40% to 73%). It is reasonable to quote lifelong rates of breast cancer between 50% and 70% for carriers of *BRCA1* or *BRCA2* mutations.

The histopathology of *BRCA1*-associated breast cancer is unfavorable when compared with *BRCA2*-associated cancer and includes tumors that are high grade, hormone receptor–negative, and aneuploid, with an increased S phase fraction. There is a strong association between the basal-like breast cancer subtype and *BRCA1* mutations. Women who carry a *BRCA1* mutation and contract breast cancer are highly likely to have a basal-like breast cancer; up to 10% of basal-like tumors arise in women found to have a mutation. The same is not true for *BRCA2*-associated cancers, which are more commonly hormone receptor–positive. Overall mortality rates in patients with *BRCA1*- or *BRCA2*-associated breast cancer are similar to those in women with sporadic breast cancer. Because the risk for development of breast cancer is high in carriers of a *BRCA* gene mutation, the use of prophylactic surgery is considered to be the most rational approach. The use of MRI is encouraged for women who prefer to undergo an intensive screening program. The efficacy of chemoprevention in *BRCA* mutation carriers is unclear, especially in those with *BRCA1* mutations who tend to develop estrogen receptor–negative breast cancers.

Reproductive Risk Factors Reproductive milestones that increase a woman's lifetime estrogen exposure are thought to increase her breast cancer risk. These include onset of menarche before 12 years of age, first live childbirth after age 30, nulliparity, and menopause after age 55 years. There is a 10% reduction in breast cancer risk for each 2-year delay in menarche; the risk doubles with menopause after age 55. Those having a full-term first pregnancy before age 18 have half the risk for development of breast cancer than women whose first pregnancy is after age 30. There is no increased risk associated with induced abortion. Breastfeeding has been reported to reduce breast cancer risk and this may be secondary to a decrease in the number of lifetime menstrual cycles. When compared with gender, age, histologic risk factors, and genetics, reproductive risk factors are relatively mild in terms of their contribution to risk (RR, 0.5 to 2.0). However, these factors, unlike family history or histologic factors, have a large influence on breast cancer prevalence in populations.[7]

Exogenous Hormone Use Therapeutic or supplemental estrogen and progesterone are taken for a variety of conditions, with the two most common scenarios being contraception in premenopausal women and HRT in postmenopausal women. Other indications for use include menstrual irregularities, polycystic ovaries, fertility treatment, and hormone insufficiency states. Studies have suggested that breast cancer risk is increased in current or past users of oral contraceptives, a risk that decreases as the interval after cessation of use increases.[8,9]

The use of HRT was studied by the Women's Health Initiative,[8] a prospective, randomized controlled trial in which healthy postmenopausal women 50 to 79 years of age received various dietary and vitamin supplements and postmenopausal HRT. The study assessed the benefits and risks associated with HRT, a low-fat diet, and calcium and vitamin D supplementation and their effects on rates of cancer, cardiovascular disease, and osteoporosis-related fractures. A total of 16,608 women were randomized to receive combined conjugated equine estrogens (e.g., Premarin, 0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) or placebo from 1993 to 1998 at 40 centers in the United States. Screening mammography and clinical breast examinations were performed at baseline and yearly thereafter. The study reached a stopping rule at 5.2 years of follow-up, at which time there were 245 cases of breast cancer (invasive and noninvasive) in the combined HRT group versus 185 cases in the placebo group. When compared with placebo, the combination of estrogen and progesterone, specifically PremPro, increased the risk of developing breast cancer in postmenopausal women with an intact uterus. Of greater concern was that women on estrogen plus progesterone were more likely to be diagnosed with a breast cancer at a more advanced stage, and there was a substantial increase in the number of women with abnormal mammograms. Women who had a hysterectomy were randomized to estrogen only versus placebo and, after 7 years of follow-up, 10,739 women receiving conjugated equine estrogens (e.g., Premarin) at a dose of 0.625 mg daily or a placebo had equivalent rates of breast cancer (RR, 0.80; 95% CI, 0.62 to 1.04).[9] There was a statistically significant difference between the treatment and control groups in the need for short-interval mammographic follow-up examinations, which was higher in the group that received Premarin (36.2% versus 28.1%). These data show that women receiving combination HRT with estrogen and progesterone for 5 years have approximately a 20% increased risk for the development of breast cancer. Women who take estrogen-only formulations (because of previous hysterectomy) do not appear to suffer an increased incidence of breast cancer.

Risk Assessment Tools

A model for assessing breast cancer risk was developed from case-control data in the Breast Cancer Detection Demonstration Project (available for clinical use at http://cancer.gov/bc risktool; also known as the *Gail model*). It was determined that age, race, age at menarche, age at first live birth, number of previous breast biopsies, presence of proliferative disease with atypia, and number of first-degree female relatives with breast cancer influenced the risk for breast cancer. The model does not include detailed information about genetic factors and may underestimate the risk for a *BRCA1* or *BRCA2* mutation carrier and overestimate the risk in a noncarrier. It should not be used in women with a diagnosis of LCIS or DCIS. The Gail model for breast cancer risk was used in the design of the Breast Cancer Prevention Trial, which randomly assigned women at high risk (>1.67%) to receive tamoxifen or a placebo, and in the Study

of Tamoxifen and Raloxifene (STAR),[10] which randomly assigned women at high risk to receive tamoxifen or raloxifene. The Gail model assesses population risk using nongenetic factors, whereas the hereditary and familial models assess genetic and familial risk of breast cancer. The Claus model is another risk assessment model, which is based on assumptions about the prevalence of high-penetrance breast cancer susceptibility genes. The Claus model incorporates more information about family history and provides individual estimates of breast cancer risk according to decade of life based on knowledge of first- and second-degree relatives with breast cancer and their age at diagnosis.

There have been several models designed to assess the risk for an individual harboring a mutation in *BRCA1* or *BRCA2.* This can be useful in determining the need for genetic testing. The Couch model predicts risk for a mutation in the *BRCA1* gene. The BRCAPro model was developed by Myriad Genetics Laboratories and provides estimates for the risk of *BRCA1* and *BRCA2* mutations. The Tyrer model incorporates personal risk factors and genetic analysis to give a more comprehensive and individual risk assessment. Such models have estimated that the incidence of clinically significant *BRCA1* or *BRCA2* mutations in the general population is approximately 1 in 300 to 500. Indications for consideration of genetic testing include a personal history of young age at diagnosis (<50 years), bilateral breast cancer, breast and ovarian cancer in the same individual, and male breast cancer. Other factors that may be an indication for testing are a family history (maternal or paternal) of two or more individuals with breast and ovarian cancer, close male relative with breast cancer, close relative with early-onset breast or ovarian cancer (<50 years), and known *BRCA1* or *BRCA2* mutation.

Management of High-Risk Patients

In practice, clinicians assess risk factors and consider those that are important to individual patients in making recommendations about screening and intervention. Increased risk for breast cancer is defined as a 5-year calculated risk of 1.7% or higher using the National Cancer Institute (NCI) risk calculator. This is the average risk for a woman who is 60 years old; it has been used in the design of the U.S. prevention trials. This risk calculator is not applicable to women with a history of invasive breast cancer, DCIS, or LCIS. The model does not make adjustments for a first-degree relative with premenopausal or bilateral breast cancer and genetic mutations are not considered in the calculation. The clinician must understand that risk may be significantly underestimated if these factors are present and, therefore, the risk calculation should be made within the context of the patient's overall personal and family history. However, even with these limitations, the Gail model provides a valuable starting point for the evaluation of breast cancer risk assessment. This risk assessment can provide a context for recommendations for primary prevention strategies and screening appropriate to the individual's risk level. For women found to be at high risk for the development of breast cancer, options include close surveillance with clinical breast examination, mammography, and breast MRI (depending on the lifetime risk), or interventions to reduce risk, such as chemoprevention with tamoxifen or raloxifene or a bilateral prophylactic mastectomy or oophorectomy.

Close Surveillance

Surveillance guidelines for individuals at high risk for breast cancer were established in 2002 by the National Comprehensive Cancer Network and the Cancer Genetics Studies Consortium. These guidelines are based primarily on expert opinion; screening guidelines for high-risk individuals are not established by prospective trials.

Recommendations for women in a family with a breast and ovarian cancer syndrome include monthly breast self-examination beginning at 18 to 20 years of age, semiannual clinical breast examination beginning at age 25, and annual mammography beginning at age 25, or 10 years before the earliest age at onset of breast cancer in a family member. Nonetheless, studies of women with known *BRCA1* or *BRCA2* mutations have found that 50% of the detected breast cancers were diagnosed as interval cancers; that is, they occurred between screening episodes and not during the course of routine screening. This observation has prompted many groups to add annual screening MRI to mammography, with some doing both simultaneously and others staggering the two examinations. If not done previously, genetic counseling is offered to those with a strong family history of early-onset breast and ovarian cancer, including a discussion of genetic testing for *BRCA1* and *BRCA2* mutations.

Chemoprevention for Breast Cancer

The drugs currently approved for reducing breast cancer risk are tamoxifen and raloxifene. Tamoxifen is an estrogen antagonist with proven benefit for the treatment of estrogen receptor (ER)–positive breast cancer. Raloxifene is a selective ER modulator (SERM). Tamoxifen has been used in the adjuvant setting for breast cancer for several decades and is known to reduce the incidence of a second primary breast cancer in the contralateral breast of women who received the drug as adjuvant therapy for a first breast cancer. Findings from the overview analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have demonstrated that adjuvant tamoxifen reduces the risk for a second breast cancer in the unaffected breast by 47%. Four prospective randomized trials have been completed evaluating tamoxifen as chemoprevention in healthy women known to be at increased risk for breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) recently reported findings of the STAR trial, which compared tamoxifen versus raloxifene.[10] Trials are ongoing assessing the role of aromatase inhibitors (AIs) as chemoprevention in postmenopausal women.

The NSABP P-1 trial randomized 13,388 women aged 35 to 59 years with a diagnosis of LCIS, women whose risk for breast cancer was moderately increased (RR, 1.66 over a 5-year period), and women 60 years or older to tamoxifen or placebo. The risk estimates were based on the Gail model of risk (see earlier). In this study, tamoxifen reduced the risk for invasive breast cancer by 49% through 69 months of follow-up, with a risk reduction of 59% in the subgroup with LCIS and 86% in those with ADH or ALH. The reduction in risk was noted only for ER-positive cancers. Tamoxifen treatment for 5 years was not without side effects and complications. In the tamoxifen treatment arm, endometrial cancers resulting from estrogen-like effects of the drug on the endometrium were increased by a factor of approximately 2.5. Pulmonary embolism (RR, 3) and deep venous thrombosis (RR, 1.7) were also more common in women who received tamoxifen. Data on the efficacy of tamoxifen for reduction of breast cancer risk in *BRCA1* and *BRCA2*

mutation carriers are limited because mutation testing was not routinely performed on P-1 study participants. Tamoxifen is most effective at reducing the incidence of ER-positive breast cancers, so its role in *BRCA1* mutation carriers (who more often develop ER-negative breast cancers) is questionable. Several other tamoxifen prevention trials were conducted at around the same time as the NSABP P-1 trial, including the Italian Tamoxifen Prevention Study, Royal Marsden Hospital Tamoxifen Prevention Pilot Trial, and International Breast Cancer Intervention Study (IBIS-1). The Italian and Royal Marsden studies did not show any benefit of tamoxifen over placebo in terms of reduced incidence of breast cancer. There were some differences in the study population and trial designs, which may explain the negative results as compared with the P-1 trial. The IBIS-1 trial showed a 33% reduction in the incidence of breast cancer, slightly lower than that in P-1 but confirming the risk reduction benefit of tamoxifen. Subsequently, a meta-analysis of all the tamoxifen prevention trials found that tamoxifen reduced the risk of breast cancer by 38%. This analysis also confirmed the increased risks of endometrial cancer and venous thromboembolic events seen with tamoxifen use.

The NSABP P-2 trial (STAR trial)[10] compared tamoxifen with raloxifene in postmenopausal women. This comparison was based on the findings from the MORE trial, which included more than 10,000 women who received placebo versus raloxifene for the prevention and treatment of osteoporosis. At an average 3 years of follow-up, there was a 54% reduction in the incidence of breast cancer and no increase in uterine cancer. The STAR trial enrolled 19,747 women at increased risk for breast cancer and demonstrated that tamoxifen and raloxifene reduced the risk for invasive breast cancer by approximately 50%. Raloxifene had a more favorable toxicity profile, the number of uterine cancers was reduced by 36% compared with tamoxifen, and women taking raloxifene had 29% fewer episodes of venous thrombosis and a reduced incidence of pulmonary embolism.

Prophylactic Mastectomy

Prophylactic mastectomy has been shown to reduce the chance of developing breast cancer in high-risk women by 90%. Hartmann and coworkers[11] have reported on a retrospective review of 639 women with a family history of breast cancer who underwent prophylactic mastectomy. The women were divided into high-risk (n = 214) and moderate-risk (n = 425) groups, with high-risk patients defined as those with a family history suggestive of an autosomal dominant predisposition to breast cancer. For women of moderate risk, the number of expected breast cancers was calculated according to the Gail model. Based on this model, 37.4 breast cancers were expected to have developed and 4 cancers actually did, for an incidence risk reduction of 89%. For women in the high-risk cohort, the Gail model would underestimate the risk for the development of breast cancer. Thus, the expected number of breast cancers was calculated by using three different statistical models from a control study of the high-risk probands (sisters). Three breast cancers developed after prophylactic mastectomy, for an incident risk reduction of at least 90%.

Several groups have reported on prospective studies in *BRCA1* and *BRCA2* mutation carriers treated with prophylactic mastectomy versus surveillance and have shown that mastectomy is highly effective in preventing breast cancers compared with a significant number of events in women not choosing preventive mastectomy. More recently, results of risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) were reported in *BRCA1* and *BRCA2* mutation carriers followed in 22 centers as part of the PROSE consortium.[12] None of the participants who underwent RRM developed a subsequent breast cancer compared with 7% of the women who did not undergo RRM. The use of RRSO reduced the incidence of ovarian cancers from 5.8% to 1.1% and the incidence of breast cancers from 19.2% to 11.4%. RRSO was associated with a significant reduction in breast cancer–specific mortality, ovarian cancer– specific mortality, and all-cause mortality. The available data suggest that *BRCA* mutation carriers should be counseled to consider risk-reducing surgeries as a strategy to reduce cancer incidence and improve survival.

Women who undergo annual mammographic screening have an overall 80% chance of surviving the breast cancer once it has been detected. Coupled with penetrance figures in the range of 50% to 60% for mutation carriers, the chance of *BRCA1* or *BRCA2* mutation carriers dying from breast cancer is approximately 10% if they choose not to undergo risk-reducing surgery.[11]

The use of risk-reducing surgery in women who are not known to have deleterious mutations in *BRCA1* or *BRCA2* remains controversial. Recent trends have suggested that more women with newly diagnosed breast cancer are choosing to undergo contralateral prophylactic mastectomy as a risk reduction strategy for contralateral breast cancer. Determining which patients may benefit from this approach has been challenging. Bedrosian and colleagues[13] used the Surveillance, Epidemiology, and End Results (SEER) database to study this and found that there was an improvement in breast cancer–specific mortality of 4.8% at 5 years in women with stage I or II breast cancer with ER-negative disease who underwent contralateral prophylactic mastectomy. There was a lower incidence of contralateral breast cancers in women with ER-positive disease who did not undergo prophylactic mastectomy compared with their ER-negative counterparts.

Summary: Risk Assessment and Management

Understanding risk factors for the development of disease provide clues to pathogenesis and identifies patients likely to benefit from risk-reducing strategies. Although breast cancer can develop in both genders, women are at greatly increased risk and breast cancer in men is uncommon. Age is a strong determinant of risk and is part of the NCI risk assessment tool. Family history is most significant when breast cancer affects young first-degree relatives (mothers, sisters, and daughters) and when cases of ovarian cancer are found in the same side of the family, and may preclude the use of the NCI tool for accurate risk assessment. The most significant histologic risk factors for the development of breast cancer are ADH, ALH, and LCIS. A personal history of breast cancer predisposes to contralateral breast cancer.

BENIGN BREAST TUMORS AND RELATED DISEASES

Breast Cysts

Cysts within the breast parenchyma are fluid-filled, epithelial-lined cavities that may vary in size from microscopic to large palpable masses containing as much as 20 to 30 mL of fluid. A palpable cyst develops in at least 1 in every 14 women, and 50%

of cysts are multiple or recurrent. The pathogenesis of cyst formation is not well understood; however, cysts appear to arise from destruction and dilation of lobules and terminal ductules. Microscopic studies have shown that fibrosis at or near the lobule, combined with continued secretion, results in unfolding of the lobule and expansion of an epithelial-lined cavity containing fluid.[1,5]

Cysts are influenced by ovarian hormones, a fact that explains their variation with the menstrual cycle. Most cysts occur in women older than 35 years; the incidence steadily increases until menopause and sharply declines thereafter. New cyst formation in older women is generally associated with exogenous hormone replacement.

Intracystic carcinoma is exceedingly rare. Rosemond has reported that only three cancers were identified in more than 3000 cyst aspirations (0.1%). Other investigators have confirmed this low incidence. There is no evidence of increased risk for breast cancer associated with cyst formation.

A palpable mass can be confirmed to be a cyst by direct aspiration or ultrasonography. Cyst fluid can be straw-colored, opaque, or dark green and may contain debris. Given the low risk for malignancy within a cyst, if the mass resolves following aspiration and the cyst contents are not grossly bloody, the fluid does not need to be sent for cytologic analysis. If the cyst recurs multiple times (more than twice is a reasonable rule), pneumocystography should be performed to evaluate for a sold component and core or FNA biopsy should be performed to evaluate the solid elements. Surgical removal of a cyst is usually not indicated but may be required if the cyst recurs multiple times, or based on the needle biopsy results.

Fibroadenoma and Other Benign Tumors

Fibroadenomas are benign solid tumors composed of stromal and epithelial elements. Fibroadenoma is the second most common tumor in the breast (after carcinoma) and is the most common tumor in women younger than 30 years. In contrast to cysts, fibroadenomas most often arise in the late teens and in women during their early reproductive years. Fibroadenomas are rarely seen as new masses in women after the age of 40 or 45 years. Clinically, they present as firm masses that are easily movable and may increase in size over a period of several months. They slide easily under the examining fingers and may be lobulated or smooth. On excision, fibroadenomas are well-encapsulated masses that may detach easily from surrounding breast tissue. Mammography is of little help in discriminating between cysts and fibroadenomas; however, ultrasonography can readily distinguish between them because each has specific characteristics. FNA biopsy can also be used to confirm the imaging findings.

Fibroadenomas are benign tumors, although neoplasia may develop in the epithelial elements within them. Cancer in a newly discovered fibroadenoma is exceedingly rare; 50% of neoplasias that involve fibroadenomas are LCIS, 35% are infiltrating carcinomas, and 15% are intraductal carcinoma.

Once a tissue diagnosis confirms that the breast mass is a fibroadenoma, the patient can be reassured without the need for surgical excision. If the patient is bothered by the mass or it continues to increase in size, the mass can be excised or treated with cryoablation under ultrasonographic guidance. The mass may remain palpable following cryoablation or, in other cases, the mass may calcify, causing it to feel more firm on palpation.

Two subtypes of fibroadenoma are recognized. *Giant fibroadenoma* is a descriptive term applied to a fibroadenoma that attains an unusually large size, typically greater than 5 cm. The term *juvenile fibroadenoma* refers to the occasional large fibroadenoma that occurs in adolescents and young adults and histologically is more cellular than the usual fibroadenoma. Although these lesions may display remarkably rapid growth, surgical removal is curative.

Hamartoma and Adenoma

These lesions are benign proliferations of variable amounts of epithelium and stromal supporting tissue. A hamartoma is a discrete nodule that contains closely packed lobules and prominent, ectatic extralobular ducts. On physical examination, mammography, and gross inspection, a hamartoma is indistinguishable from fibroadenoma. Page and Anderson have described an adenoma or tubular adenoma as a benign cellular neoplasm of ductules packed closely together so that they form a sheet of tiny glands without supporting stroma. During pregnancy and lactation, these tumors may increase in size, and histologic examination shows secretory differentiation. Biopsy is required to establish the diagnosis.

Breast Abscess and Infections

Infections of the breast fall into two general categories, lactational infections and chronic subareolar infections associated with duct ectasia. Lactational infections are thought to arise from entry of bacteria through the nipple into the duct system and are characterized by fever, leukocytosis, erythema, and tenderness. Infections are most often caused by *Staphylococcus aureus* and may be manifested as cellulitis with breast parenchymal inflammation and swelling, termed *mastitis,* or as abscesses. Treatment requires antibiotics and frequent emptying of the breast. True abscesses require surgical drainage because they are generally multiloculated.

In women who are not lactating, a chronic relapsing form of infection may develop in the subareolar ducts of the breast that is variously known as *periductal mastitis* or *duct ectasia*. This condition appears to be associated with smoking and diabetes. The infections that arise are most often mixed infections that include aerobic and anaerobic skin flora. A series of infections with resulting inflammatory changes and scarring may lead to retraction or inversion of the nipple, masses in the subareolar area and, occasionally, a chronic fistula from the subareolar ducts to the periareolar skin. Palpable masses and mammographic changes may result from the infection and scarring; these can make surveillance for breast cancer more challenging.

Subareolar infections may initially be manifested as subareolar pain and mild erythema. If treated at this stage, warm soaks and oral antibiotics may be effective. Antibiotic treatment generally requires coverage for aerobic and anaerobic organisms. If an abscess has developed, incision and drainage are required, in addition to antibiotics. Repeated infections are treated by excision of the entire subareolar duct complex after the acute infection has resolved completely, together with IV antibiotic coverage. Rarely, patients will have recurrent infections requiring excision of the nipple and areola.

A presumed infection of the breast generally clears promptly and completely with antibiotic therapy. If erythema or edema

persists, a diagnosis of inflammatory carcinoma should be considered.

Papillomas and Papillomatosis

Solitary intraductal papillomas are true polyps of epithelial-lined breast ducts. Solitary papillomas are most often located close to the areola but may be present in peripheral locations. Most papillomas are smaller than 1 cm but can grow to as large as 4 or 5 cm in size. Larger papillomas may appear to arise within a cystic structure, probably representing a greatly expanded duct. Papillomas are not associated with an increased risk for breast cancer.

Papillomas located close to the nipple are often accompanied by bloody nipple discharge. Less frequently, they are discovered as a palpable mass under the areola or as a density seen on a mammogram. Treatment is excision through a circumareolar incision. For peripheral papillomas, the differential diagnosis is between papilloma and invasive papillary carcinoma.

It is important to distinguish papillomatosis from solitary or multiple papillomas. Papillomatosis refers to epithelial hyperplasia, which commonly occurs in younger women or is associated with fibrocystic change. Papillomatosis is not composed of true papillomas but has hyperplastic epithelium that may fill individual ducts like a true polyp but has no stalk of fibrovascular tissue.

Sclerosing Adenosis

Adenosis refers to an increased number of small terminal ductules or acini. It is frequently associated with a proliferation of stromal tissue producing a histologic lesion, sclerosing adenosis, which can be confused with carcinoma both grossly and histologically. These lesions can be associated with deposition of calcium, which can be seen on a mammogram in a pattern indistinguishable from the microcalcifications of intraductal carcinoma. Sclerosing adenosis is the most common pathologic diagnosis in patients undergoing needle-directed biopsy of microcalcifications in many series. Sclerosing adenosis is frequently listed as one of the component lesions of fibrocystic disease; it is common and has no significant malignant potential.

Radial Scar

Radial scars belong to a group of abnormalities known as *complex sclerosing lesions*. They can appear similar to carcinomas mammographically because they create irregular spiculations in the surrounding stroma. These lesions contain microcysts, epithelial hyperplasia, adenosis, and a prominent display of central sclerosis. The gross abnormality is rarely more than 1 cm in diameter. Larger lesions may form palpable tumors and appear as a spiculated mass with prominent architectural distortion on a mammogram. These tumors can even result in skin dimpling by producing traction on surrounding tissues. They generally require excision to rule out an underlying carcinoma. Radial scars are associated with a modestly increased risk for breast cancer.

Fat Necrosis

Fat necrosis can mimic cancer by producing a palpable mass or density on a mammogram that may contain calcifications. Fat necrosis may follow an episode of trauma to the breast or be related to a prior surgical procedure or radiation treatment. The calcifications are characteristic of fat necrosis and can often be imaged on ultrasonography as well. Histologically, the lesion is composed of lipid-laden macrophages, scar tissue, and chronic inflammatory cells. This lesion has no malignant potential.

EPIDEMIOLOGY AND PATHOLOGY OF BREAST CANCER

Epidemiology

In 2010, a total of 209,060 cases of invasive breast cancer and almost 54,010 cases of in situ breast cancer were diagnosed in the United States. Breast cancer continues to be the second leading cause of cancer-related deaths. second to lung cancer, with approximately 40,000 deaths caused by breast cancer annually. Breast cancer is also a global health problem, with more than 1 million cases of breast cancer diagnosed worldwide each year. The overall incidence of breast cancer was rising until approximately 1999 because of increases in the average life span, lifestyle changes that increase the risk for breast cancer, and improved survival from other diseases. The rates began to decrease from 1999 to 2006 by approximately 2%/year. This decrease has been attributed to a reduction in the use of HRT after the initial results of the Women's Health Initiative were published but may also be the result of a reduction in the use of screening mammography (70.1% of women 40 years and older were screened in 2000 versus 66.4% in 2005). Survival rates in women with breast cancer have steadily improved over the last several decades, with 5-year survival rates of 63% in the early 1960s, 75% from 1975 to 1977, 79% from 1984 to 1986 and 90% from 1995 to 2005. The largest decrease in death rates caused by breast cancer have been in women younger than 50 years (3.2%/year), although they have also decreased in women older than 50 (2%/year). The decreased mortality from breast cancer is thought to be the result of earlier detection via mammographic screening, improvements in therapy, and a decreased incidence of breast cancer. The current treatment of breast cancer is guided by pathology, staging, and recent insights into breast cancer biology. There is an increased emphasis on defining disease biology and status in individual patients, with the subsequent tailoring of therapies toward that individual.

Pathology

Noninvasive Breast Cancer

Noninvasive neoplasms are broadly divided into two major types, LCIS and DCIS (Box 36-2). LCIS was initially believed to be a malignant lesion, but is now regarded more as a risk factor for the development of breast cancer. LCIS is recognized by its conformity to the outline of the normal lobule, with expanded and filled acini (Fig. 36-7). DCIS is a more heterogeneous lesion morphologically, and pathologists recognize four broad categories—papillary, cribriform, solid, and comedo types; the latter three types are shown in Figure 36-7. DCIS is recognized as discrete spaces filled with malignant cells, usually with a recognizable basal cell layer made up of presumably normal myoepithelial cells. The four morphologic categories of DCIS are rarely seen as pure lesions, but in reality are often mixed. The papillary and cribriform types of DCIS are generally of lower grade and may take a longer period of time to transform to invasive cancer. The solid and comedo types of DCIS are generally higher grade lesions.

BOX 36-2 Classification of Primary Breast Cancer

Noninvasive Epithelial Cancers
LCIS
DCIS or intraductal carcinoma
- Papillary, cribriform, solid, and comedo types

Invasive Epithelial Cancers (percentage of total)
Invasive lobular carcinoma (10%)
Invasive ductal carcinoma
- Invasive ductal carcinoma, NOS (50%-70%)
- Tubular carcinoma (2%-3%)
- Mucinous or colloid carcinoma (2%-3%)
- Medullary carcinoma (5%)
- Invasive cribriform carcinoma (1%-3%)
- Invasive papillary carcinoma (1%-2%)
- Adenoid cystic carcinoma (1%)
- Metaplastic carcinoma (1%)

Mixed Connective and Epithelial Tumors
Phyllodes tumors, benign and malignant
Carcinosarcoma
Angiosarcoma
Adenocarcinoma

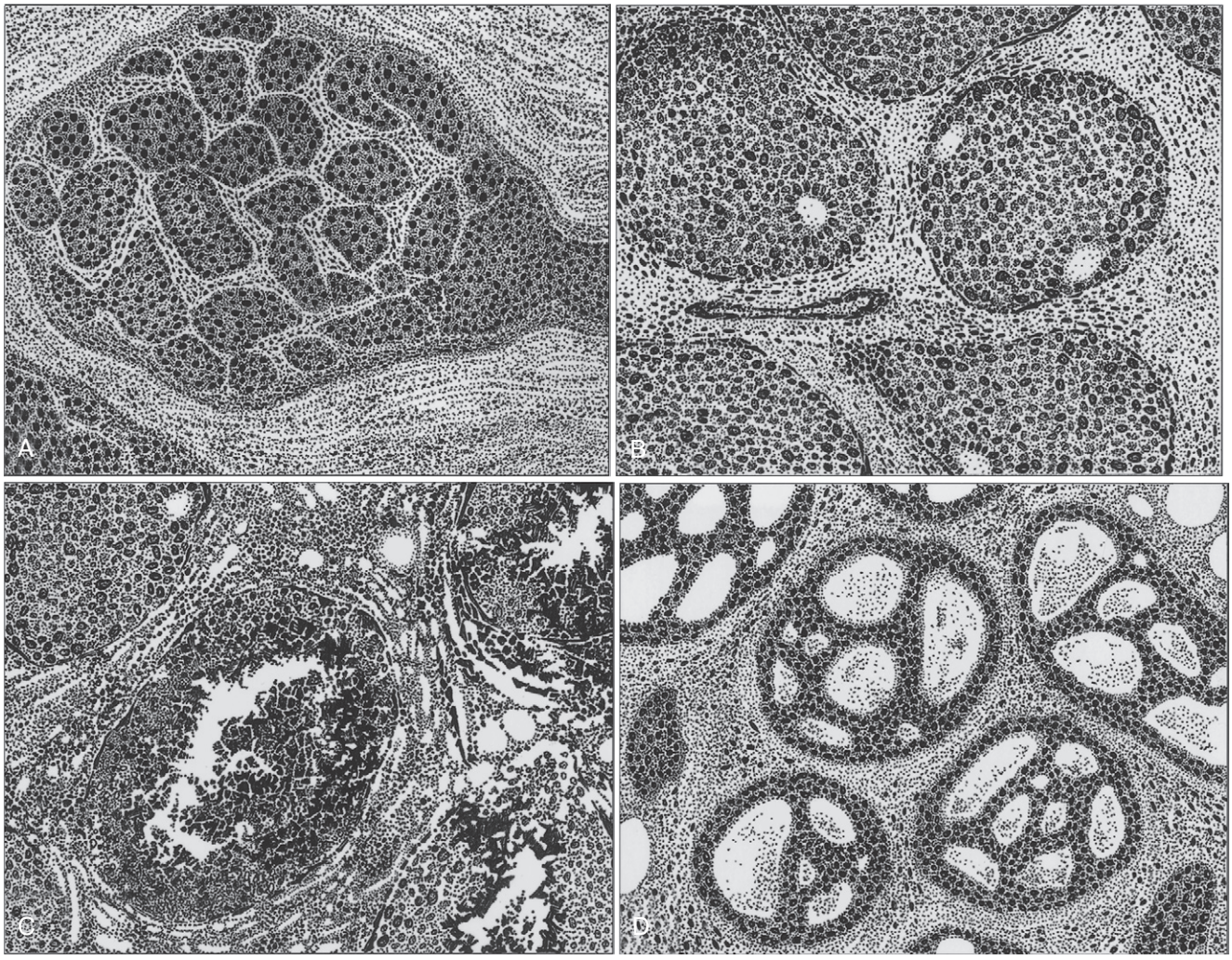

FIGURE 36-7 Noninvasive breast cancer. **A,** LCIS. The neoplastic cells are small with compact, bland nuclei and are distending the acini but preserving the cross-sectional architecture of the lobular unit. **B,** DCIS, solid type. The cells are larger than in LCIS and are filling the ductal rather than the lobular spaces. However, the cells are contained within the basement membrane of the duct and do not invade the breast stroma. **C,** DCIS, comedo type. In comedo DCIS, the malignant cells in the center undergo necrosis, coagulation, and calcification. **D,** DCIS, cribriform type. In this type, bridges of tumor cells span the ductal space and leave round, punched-out spaces.

As the cells inside the ductal membrane grow, they have a tendency to undergo central necrosis, perhaps because the blood supply to these cells is located outside the basement membrane. The necrotic debris in the center of the duct undergoes coagulation and finally calcifies, thereby leading to the tiny, pleomorphic, and frequently linear forms of microcalcifications seen on mammograms. In some patients, an entire ductal tree may be involved in the malignancy, and the mammogram shows typical calcifications from the nipple extending posteriorly into the interior of the breast (termed *segmental calcifications*). For reasons that are not completely understood, DCIS transforms into an invasive cancer, usually recapitulating the morphology of the cells inside the duct. In other words, low-grade cribriform DCIS tends to be associated with a low-grade invasive lesion that retains some cribriform features. There is no tendency for the grade to advance with invasion. DCIS frequently coexists with otherwise invasive cancers and, again, the two phases of the malignancy are in step with each other morphologically.

Invasive Breast Cancer

Invasive cancers are recognized by their lack of overall architecture, infiltration of cells haphazardly into a variable amount of stroma, or formation of sheets of continuous and monotonous cells without respect for form and function of a glandular organ. Pathologists broadly divide invasive breast cancer into lobular and ductal histologic types, which probably does not reflect histogenesis and only imperfectly predicts clinical behavior. Invasive lobular cancer tends to permeate the breast in a single-file nature, which explains why it remains clinically occult and often escapes detection on mammography or physical examination until the extent of the disease is large. Ductal cancers tend to grow as a more cohesive mass; they form discrete abnormalities on mammograms and are often palpable as a discrete lump in the breast at a smaller size compared with lobular cancers. The growth pattern of these lesions is shown in Figure 36-8, invasive ductal cancer in Figure 36-8*A* and invasive lobular cancer in Figure 36-8*B*.

Invasive ductal cancer, also known as *infiltrating ductal carcinoma*, is the most common form of breast cancer; it accounts for 50% to 70% of invasive breast cancers. When this cancer does not take on special features, it is called *infiltrating ductal carcinoma*. Invasive lobular carcinoma accounts for up to 10% of breast cancers, and mixed ductal and lobular cancers have been increasingly recognized and described in pathology reports. When infiltrating ductal carcinomas take on differentiated features, they are named according to the features that they display. If the infiltrating cells form small glands lined by a single row of bland epithelium, they are called i*nfiltrating tubular carcinoma* (see Fig. 36-8*D*). The infiltrating cells may secrete copious amounts of mucin and appear to float in this material. These lesions are called *mucinous* or *colloid tumors* (see Fig. 36-8*C*). Both tubular and mucinous tumors are usually low grade (grade I) lesions and represent about 2% or 3% each of invasive breast carcinomas.

In contrast, bizarre invasive cells with high-grade nuclear features, many mitoses, and lack of an in situ component characterize medullary cancer. The malignancy forms sheets of cells in an almost syncytial fashion, surrounded by an infiltrate of small mononuclear lymphocytes. The borders of the tumor push into the surrounding breast rather than infiltrate or permeate the stroma. This tumor is shown in Figure 36-8*E*, which demonstrates the bizarre and pleomorphic nuclear features of the cells. In its pure form, it accounts for only approximately 5% of breast cancers; however, some pathologists have described a so-called *medullary variant* that has some features of the pure form of the cancer. These tumors are uniformly high grade, ER- and progesterone receptor (PR)–negative, and negative for the human epidermal growth factor receptor 2 (HER-2/neu; HER-2) cell surface receptor. Tumors that lack expression of ER, PR and HER-2 are often called *triple-negative breast cancers*. Gene expression profiling and microarray analysis of breast cancers have revealed that triple-negative breast cancers are distinctly different from other ductal breast cancers and may also express molecular markers found in basal or myoepithelial cells. The term *basal-like breast cancer* describes a specific subtype of breast cancer as defined by microarray analysis, whereas triple-negative breast cancer is a definition determined by the lack of immunohistochemical detection of ER, PR and HER-2. Although there may be some overlap between triple-negative and basal-like breast cancers, the categories were developed using differing technologies and they are not always the same entity.

The different histologic subtypes of breast cancer have some relationship with prognosis, although this is influenced by tumor size, histologic grade, hormone receptor status, HER-2 status, lymph node status, and other prognostic variables. Infiltrating ductal carcinoma, not otherwise specified (NOS), is the most common form of breast cancer. Its prognosis is variable, modified by histologic grade and expression of molecular markers. Basal-like cancer, or medullary cancer in older classifications, is commonly an aggressive form of breast cancer and, because it is triple receptor–negative, there are no targeted treatments for this form of cancer. Infiltrating lobular breast cancers carry an intermediate prognosis, whereas tubular and mucinous cancers have the best overall prognosis. These generalizations, based on histologic subtype, are useful only in the context of tumor size, grade, and receptor status. Modern classification schemes are replacing these older morphologic descriptions with the determination of molecular markers and breast cancer subtype by microarray analysis.

Molecular Markers and Breast Cancer Subtypes There are numerous pathways and molecular markers that have been reported to affect breast cancer outcomes, including steroid hormone receptor pathway (ER and PR), human epidermal growth factor receptor pathway (HER family), angiogenesis, cell cycle (e.g., cyclin-dependent kinases [CDKs]), apoptosis modulators, proteasome, cyclooxygenase-2 (COX-2), peroxisome proliferator-activated receptor-γ (PPAR-γ), insulin-like growth factors (IGF family), transforming growth factor-γ (TGF- γ), platelet-derived growth factor (PDGF), and p53. Most these markers are not routinely tested on breast cancer specimens at the time of diagnosis nor would it be feasible to do so.

Incorporating predictive markers into the routine testing of breast cancers could help predict which patients would be most likely to benefit from therapies directed at that marker. The best example of this is the ER. Before the discovery of the ER, all breast cancers were considered potentially sensitive to endocrine therapy. Now, pathologic assessment of ER is performed on all primary tumors and predicts which patients should receive therapy directed at ER with endocrine therapy. Patients whose tumors are ER negative can be spared 5 years of endocrine

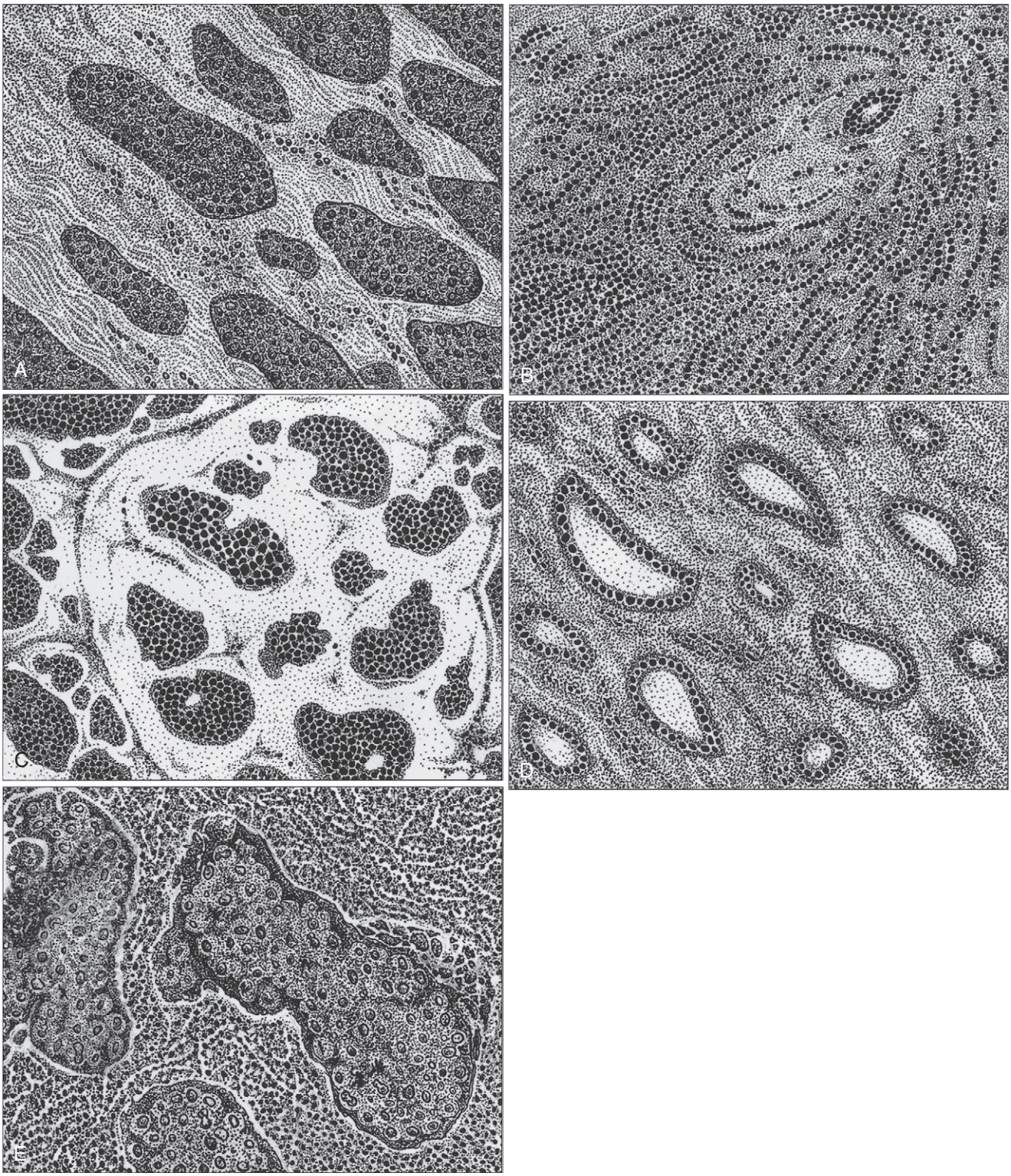

FIGURE 36-8 Invasive breast cancer. **A,** Invasive ductal carcinoma, NOS. The malignant cells invade in haphazard groups and singly into the stroma. **B,** Invasive lobular carcinoma. The malignant cells invade the stroma in a characteristic single-file pattern and may form concentric circles of single-file cells around normal ducts (targetoid pattern). **C,** Mucinous or colloid carcinoma. The bland tumor cells float like islands in lakes of mucin. **D,** Invasive tubular carcinoma. The cancer invades as small tubules, lined by a single layer of well-differentiated cells. **E,** Medullary carcinoma. The tumor cells are large and very undifferentiated, with pleomorphic nuclei. The distinctive features of this tumor are the infiltrate of lymphocytes and the syncytium-appearing sheets of tumor cells.

therapy. A second important predictive factor in breast cancer, discovered in 1985, is HER-2 or erb-B2/neu protein. This protein is the product of the *erb-B2* gene and is amplified in approximately 20% of human breast cancers. The extracellular domain of the receptor is present on the surface of breast cancer cells and an intracellular tyrosine kinase enzyme links the receptor to the internal machinery of the cell. The tyrosine kinase of HER-2 is activated by growth factors binding to partners and cross-stimulating the HER-2 kinase. Amplification leads to protein overexpression, generally measured clinically by immunohistochemistry and scored on a scale from 0 to 3+. Alternatively, fluorescent in situ hybridization (FISH) directly detects the quantity of HER-2 gene copies; there are normally two copy numbers. Research has shown that inhibition of the function of the HER-2 receptor–like protein slows the growth of HER-2–amplified tumors in laboratory models and in clinical trials. Trastuzumab is a humanized antibody directed against the extracellular domain of the surface receptor and is effective treatment for HER-2–positive breast cancer (see later). HER-2 testing is now a standard part of pathologic reporting on the primary tumor and is a predictive marker for HER-2–directed therapies.

A logical classification scheme for invasive breast cancer is based on the expression of ER status and HER-2 proteins. It has the advantage of directing treatment choices. ER-positive tumors receive endocrine therapies and HER-2–positive cancers are treated with HER-2 inhibitors. However, breast cancer is a heterogeneous disease, and different breast cancers behave in different ways. For example, some ER-positive tumors are indolent and not life-threatening, whereas other ER-positive tumors are very aggressive. In an attempt to subclassify the disease further, investigators are turning to global assessment of gene expression by using microarrays; these are composed of oligonucleotide probes to almost every known expressed sequence of DNA in the human genome. Similar technologies based on single-nucleotide polymorphisms (SNPs) in the cancer DNA and profiles of expressed proteins are being developed to subclassify cancers and direct treatment.

A typical microarray experiment is shown in Figure 36-9, commonly known as a *heat map*; the colors indicate levels of gene expression. Such a portrayal of the disease shows how different ER-positive tumors are from ER-negative tumors and underscores the modern concept that subclassification needs not only to define different groups of breast cancer but also to guide treatment.[14] In Figure 36-9, HER-2–positive tumors form two clusters (in green at the top), although these clusters are fused together in many depictions. HER-2–positive tumors cluster similarly and are responsive to inhibitors of the HER-2 tyrosine kinase–linked surface receptor (e.g., trastuzumab). An unexpected finding, emphasized recently, is the uniqueness of tumors that are both ER-negative and HER-2–negative. These cancers, also negative for PR, are called *triple-negative cancers*. They express proteins in common with myoepithelial cells at the base of mammary ducts and are also called *basal-like cancers* (see earlier). Because they do not express ER or HER-2, new treatments are required. Women who carry a deleterious mutation in *BRCA1* (but not *BRCA2*) are much more likely to contract a basal-like cancer than another subtype. In summary, categorizing breast cancer according to the expression of molecular targets of treatments is practical and appears to agree with nonbiased classifications based on gene expression. Classification schemes reflect biology and predict treatment efficacy.

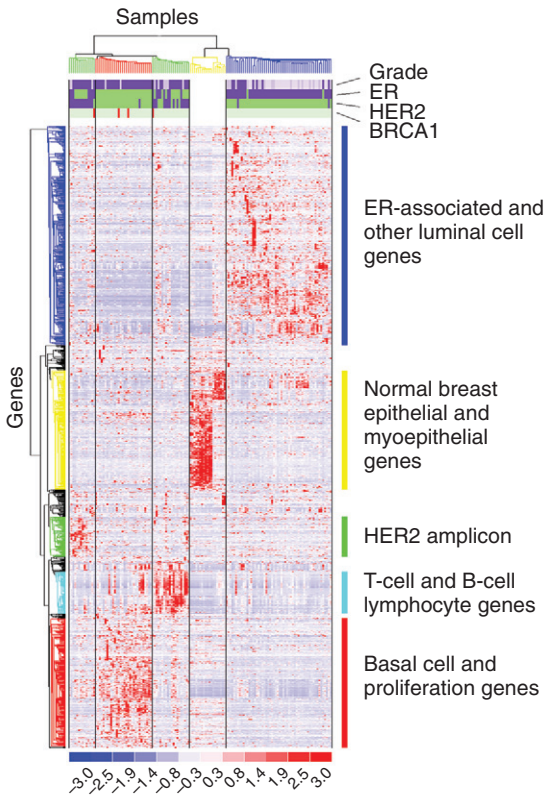

FIGURE 36-9 Microarray representation of human breast cancer. This portrayal of global gene expression is called a *heat map*, with shades of red indicating high gene expression and shades of blue indicating low gene expression relative to a mean across tissue samples. Tissue samples are present across the top in columns and individual genes are in rows down the side; the intersection is an individual gene in a particular sample. A computer-clustering algorithm aligns samples with similar gene expression and genes with similar expression patterns in the samples (two-way clustering). This illustration provides an unbiased look at breast cancer according to gene expression. The dendrogram at the top depicts the degree of similarity of the tissue samples: yellow, normal breast epithelium; blue, predominantly ER-positive cancers; red, basal-like or triple-negative cancers; and green, HER-2–positive cancers (in two clusters defined by the degree of lymphocytic infiltrate). The *stripes* at the top indicate grade (shades of darker purple are higher grades), ER expression (purple is positive; green is negative), and HER-2 (purple is positive; green is negative). *BRCA1* mutation was determined for other reasons in this experiment. (Courtesy Dr. Andrea Richardson, Department of Pathology, Brigham and Women's Hospital, Boston.)

In addition to classification, molecular markers are used to select patients for systemic treatment (e.g., chemotherapy, endocrine therapy) and to predict the response of patients to these pharmacologic treatments. The simplest example is the use of ER or HER-2 status to predict the response to endocrine treatment or trastuzumab. Multiple gene products may be used in combination for these determinations. Microarray experiments use thousands of gene transcripts (mRNAs) to provide a snapshot of an individual cancer's molecular phenotype. To adapt this technology for clinical application, investigators have

selected critical assemblies of gene products that provide the same predictive ability as a nonbiased, genome-wide analysis. The most advanced is a 21-gene test that can be used on paraffin-embedded tumor material from breast surgical specimens (Oncotype DX assay, a 21-gene recurrence score assay).[15] Originally designed to predict the recurrence of ER-positive, node-negative breast cancer treated with adjuvant endocrine therapy, the 21-gene recurrence score assay provides a recurrence score for ER-positive breast cancer that is used clinically to determine whether women with high-risk ER-positive breast cancer should receive adjuvant chemotherapy in addition to tamoxifen (an endocrine therapy; see later). Another multigene assay for determining prognosis is the MammaPrint assay. The MammaPrint assay uses fresh tissue prior to formalin fixation and analyzes data from 70 genes to develop a risk profile. The test provides a simple readout of low-risk or high-risk disease. This tool can be used for risk assessment in patients with ER-positive and ER-negative tumors. It is likely that tests based on critical combinations of genes will increasingly be used to assist clinical decision making when treating breast cancer.

Other Tumors of the Breast

Phyllodes Tumors Tumors of mixed connective tissue and epithelium constitute an important group of unusual primary breast tumors. On one end of the spectrum is the benign fibroadenoma, which is characterized by a proliferation of connective tissue and a variable component of ductal elements that may appear compressed by the swirls of fibroblastic growth. Clinically more challenging are the phyllodes tumors, which contain a biphasic proliferation of stroma and mammary epithelium. First called *cystosarcoma phyllodes*, the name has been changed to phyllodes tumor in recognition of its usually benign course. However, with increasing cellularity, an invasive margin, and sarcomatous appearance, these tumors may be classified as malignant phyllodes tumors. Benign phyllodes tumors are recognized as firm lobulated masses that can range in size, with an average size of approximately 5 cm (larger than average fibroadenomas). Histologically, these tumors are similar to fibroadenomas, but the whorled stroma forms larger clefts lined by epithelium that resemble clusters of leaflike structures. The stroma is more cellular than a fibroadenoma, but the fibroblastic cells are bland and mitoses are infrequent.

Mammographically, these lesions are seen as round densities with smooth borders and are indistinguishable from fibroadenomas. Ultrasonography may reveal a discrete structure with cystic spaces. The diagnosis is suggested by the larger size, history of rapid growth, and occurrence in older patients. Cytologic analysis is unreliable in differentiating a low-grade phyllodes tumor from a fibroadenoma. Core needle biopsy is preferred, although it is difficult to classify phyllodes tumors with benign or intermediate malignant potential based on a limited sampling. Thus, the final diagnosis is best made by excisional biopsy, followed by careful pathologic review.

Local excision of a benign phyllodes tumor is curative, similar to that for a fibroadenoma. The intermediate tumors, also called *borderline phyllodes tumors*, are those in which it is difficult to assign a benign label. These tumors are treated by excision, with margins of at least 1 cm to prevent local recurrence. Affected patients are at some risk for local recurrence, most often within the first 2 years after excision, and close follow-up with examination and imaging allows early detection of recurrence. Finally, frankly malignant stromal sarcomas are at the other end of the spectrum. Malignant phyllodes tumors are treated similar to soft tissue sarcomas that occur on the trunk or extremities. Complete surgical excision of the entire tumor with a margin of normal tissue is advised. When the tumor is large with respect to the size of the breast, this may require total mastectomy. Similar to other soft tissue sarcomas, regional lymph node dissection is not required for staging or locoregional control.

Metastases from malignant phyllodes tumors occur via hematogenous spread; common sites include lung, bone, abdominal viscera, and mediastinum. The optimal palliative treatment of patients with metastatic phyllodes tumors has not been determined. The systemic therapeutic agents used for sarcomas have resulted in minimal success.

Angiosarcoma This vascular tumor may occur de novo in the breast or within the dermis of the breast after irradiation for breast cancer. Angiosarcoma has also been seen to develop in the upper extremity of patients with lymphedema, historically after radical mastectomy. Angiosarcoma arising in the absence of previous radiation therapy or surgery generally forms an ill-defined mass within the parenchyma of the breast. In contrast, angiosarcomas caused by prior radiation therapy arise in the irradiated skin as purplish vascular proliferations that may go unrecognized for a period of time. The differential diagnosis is frequently between malignant angiosarcoma and atypical vascular proliferations in irradiated skin. Histologically, the tumor is composed of an anastomosing tangle of blood vessels in the dermis and superficial subcutaneous fat. The atypical and crowded vessels invade through the dermis and into subcutaneous fat. These tumors are graded by the appearance and behavior of the associated endothelial cells. Pleomorphic nuclei, frequent mitoses, and stacking of the endothelial cells lining neoplastic vessels are features seen in higher grade lesions. Rarely seen in hemangiomas, necrosis is common in high-grade angiosarcomas. Clinically, radiation-induced angiosarcoma is identified as a reddish brown to purple raised rash within the radiation portals and on the skin of the breast. As the disease progresses, tumors protruding from the surface of the skin may predominate.

Mammography is unrevealing in most cases of angiosarcoma. In the absence of metastatic disease at initial evaluation, surgery is performed to secure negative skin margins and usually involves a total mastectomy. A split-thickness skin graft or myocutaneous flap may be needed to replace a large skin defect created by the resection. Metastasis to regional nodes is extraordinarily rare and axillary dissection is not required.

Patients remain at high risk for local recurrence after resection of angiosarcoma. For patients who present with primary angiosarcoma of the breast, radiation therapy is of benefit in the locoregional treatment. Patients with radiation-related angiosarcoma are not candidates for further radiotherapy. Metastatic spread occurs hematogenously, most commonly to the lungs and bone and less frequently to abdominal viscera, brain, and even the contralateral breast. Chemotherapy is generally recommended in the adjuvant setting and may improve outcomes of patients with angiosarcoma. For those free of metastatic disease at initial evaluation, the median time to recurrence after mastectomy is 8 months and the median survival is 2 years.

STAGING OF BREAST CANCER

Breast cancer stage is determined prior to any treatment with physical examination and imaging studies (clinical staging) and on definitive surgical treatment by pathologic examination of the primary tumor and regional lymph nodes (pathologic staging). Staging is performed to group patients into risk categories that define prognosis and guide treatment recommendations for patients with a similar prognosis. Breast cancer is classified with the TNM classification system, which groups patients into four stage groupings based on the size of the primary tumor (T), status of the regional lymph nodes (N), and presence or absence of distant metastasis (M). The most widely used system is that of the American Joint Committee on Cancer (AJCC). This system is updated every 6 to 8 years to reflect current understanding of tumor behavior. Some of the most significant changes in the most recent update (seventh edition) include a more stringent classification of isolated tumor cells based on the number of cells and whether the cells are almost confluent or nonconfluent; stage I breast cancers have been subdivided to IA and IB, with IB classifying T1 tumors associated with micrometastasis (N1mi) in the lymph nodes, and a new category of M0(i+) for patients with circulating tumor cells, disseminated tumor cells (bone marrow micrometastases), or cells found incidentally in other tissues that do not exceed 0.2 mm. Table 36-4 presents the TNM working guide; stage groupings are shown in Table 36-5.

Metastasis to ipsilateral axillary nodes predicts outcome after surgical treatment more powerfully than tumor size. Prior to the incorporation of systemic therapies in the management of breast cancer patients, treatment with surgery alone revealed an almost linear decrement in survival rate with increasing nodal involvement. Although staging is an important part of the initial assessment of breast cancer patients, it is largely based on anatomic variables and does not incorporate other important prognostic factors. The new staging form has a place to record other variables, including tumor grade, ER status, PR status, HER-2/neu status, circulating tumor cells, disseminated tumor cells (bone marrow), multigene recurrence score, and response to chemotherapy. These variables are not currently part of the staging system but it is hoped that future versions will incorporate the most important biologic variables in order for the stage groupings to reflect expected outcomes more accurately. Some prefixes and suffixes are used with the cTNM (clinical) and pTNM (pathologic) staging systems to designate special cases. These do not affect the stage group but indicate that they must be analyzed separately. They include the "m" suffix, which signifies multiple primary tumors, pT(m) NM, the "y" prefix, which denotes patients who have received systemic therapy, ypTNM, and the "r" prefix, which indicates a recurrent tumor, rTNM. In clinical practice, physicians use the anatomic stage grouping in addition to important biologic factors to determine risk and guide treatment recommendations.

SURGICAL TREATMENT OF BREAST CANCER

Historical Perspective

Through the mid-20th century, breast cancer was thought to arise in the breast and progress to other sites largely via centrifugal spread. In this model, more extensive surgical procedures were expected to reduce mortality by resecting locoregional disease before it could spread to distant sites. This model was supported, in part, by the results of the Halsted radical mastectomy, which was the first procedure that demonstrated improvements in breast cancer survival relative to the local excision of tumors. Introduced in the 1890s, the radical mastectomy included removal of the breast, overlying skin, and underlying pectoralis muscles in continuity with the regional lymph nodes along the axillary vein to the costoclavicular ligament. The procedure often required a skin graft to cover the large skin defect that was created. This approach was well suited to breast cancer biology of the time, when most tumors were locally advanced, frequently with chest wall or skin involvement and extensive axillary nodal disease. Radical mastectomy provided improved local control and led to an increasing population of long-term survivors. Radical mastectomy continued as the mainstay of surgical therapy into the 1970s.

A large number of women continued to die of metastatic breast cancer after radical mastectomy and even more extensive surgical procedures, including en bloc resection of the internal mammary and supraclavicular nodes, were used but failed to improve survival. This eventually led to a shift in the theory of primary centrifugal spread to the more modern theory that breast cancer spreads both centrifugally to adjacent structures and embolically via lymphatics and blood vessels to distant sites.

In the modern era, breast cancer treatment includes local and regional approaches (surgery and radiation therapy) in addition to medical therapies designed to treat systemic disease. Multimodality treatment approaches were the first to show significant improvements in both locoregional control and survival. As breast cancer was being recognized at earlier stages, the radical mastectomy was abandoned for more conservative approaches in combination with radiation therapy. This has allowed for dramatic reductions in the extent of surgery required for local control of breast cancer, with decreases in treatment-related morbidity. It is recognized that breast cancer is a heterogeneous disease and current treatment strategies take into account properties of the individual patient's tumor, as well as the size and location of tumor, to guide treatment.

Initial Surgical Trials of Local Therapy for Operable Breast Cancer

For further information about clinical trials and their significance, see later section, "Interpreting Results of Clinical Trials."

Radical Mastectomy Versus Total Mastectomy, With or Without Radiation Therapy

The NSABP B-04 trial randomized patients with clinically negative nodes to radical mastectomy, total mastectomy with irradiation of the chest wall and regional nodes, or total mastectomy alone with delayed axillary dissection if nodes became clinically enlarged. Patients with clinically positive nodes were randomized to radical mastectomy or total mastectomy with irradiation of the chest wall and regional lymphatics. At 25 years of follow-up, overall survival and disease-free survival were equivalent in all treatment arms between the node-positive and node-negative groups.[16] In the clinically node-negative patients who underwent radical mastectomy, 38% were found to have nodal metastases at surgery, yet only 18% of patients undergoing total mastectomy without dissection or radiation therapy developed axillary recurrence requiring delayed dissection. Despite the differences in the timing of their treatment, these patients had

Table 36-4 TNM Classification for Breast Cancer (Pathologic Staging)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple not associated with invasive carcinoma or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin
T4a	Extension to the chest wall, not including only pectoralis muscle adherence or invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema of the skin
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional Lymph Nodes (N)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN0(i–)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (IHC)
pN0(mol+)	Positive molecular findings (RT-PCR), but no metastasis detected by histology or IHC
pN1	Micrometastases; or metastases in one to three axillary nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm)
pN1a	Metastases in one to three axillary nodes; at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastasis or macrometastases detected by sentinel lymph node biopsy (not clinically detected)
pN1c	Metastases in one to three axillary nodes and in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in four to nine axillary nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in four to nine axillary nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ten or more axillary nodes; or in infraclavicular (level III axillary nodes); or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary nodes; or in more than three axillary lymph nodes and internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

From Edge SB, Byrd DR, Compton CC, et al (eds): AJCC cancer staging manual, ed 7, New York, 2010, Springer-Verlag.

equivalent survival with delayed axillary dissection. The results of this trial led to the conclusion that the mode and time of treatment of axillary nodes does not alter disease-free survival or overall survival. Immediate removal, delayed removal, or irradiation produced equivalent clinical results.

Table 36-5 Stage Groupings for Breast Cancer

ANATOMIC STAGE	PROGNOSTIC GROUP		
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Clinical Trials Comparing Breast-Conserving Therapy With Mastectomy

Six prospective clinical trials have randomized more than 4500 patients to mastectomy versus breast-conserving therapy (Table 36-6). In all these trials, there was no survival advantage for the use of mastectomy over breast preservation. Ipsilateral breast recurrence rates were higher in patients undergoing breast-conserving surgery, but local recurrences could be salvaged by mastectomy at the time of recurrence, with no significant detriment in survival rates. Data from these trials have served to define predictors of local recurrence after lumpectomy and have led to modifications in surgical and radiation techniques to reduce local recurrence.

NSABP B-06: Mastectomy Versus Lumpectomy With Irradiation Versus Lumpectomy Alone A total of 1851 patients with tumors up to 4 cm in diameter and clinically negative lymph nodes were randomized in B-06 to receive modified radical mastectomy, lumpectomy alone, or lumpectomy with postoperative irradiation of the breast without an extra boost to the lumpectomy site.[17] All patients with histologically positive axillary nodes received chemotherapy. At 20 years of follow-up, overall survival and disease-free survival were the same in all three treatment arms (Fig. 36-10).

NSABP B-06 provided valuable information about rates of ipsilateral breast cancer recurrence after lumpectomy, with or without breast irradiation. At 20 years of follow-up, local recurrence rates were 14.3% in women treated with lumpectomy and radiation therapy and 39.2% in women treated with

Table 36-6 Randomized Trials Comparing Breast Conservation vs Mastectomy

TRIAL	NO. OF PATIENTS	MAX TUMOR SIZE (CM)	SYSTEMIC THERAPY	FOLLOW-UP (YR)	% SURVIVAL LUMPECTOMY + XRT	% SURVIVAL MASTECTOMY	LOCAL RECURRENCE (BCT) (%)
NSABP B-06[a]	1851	4	Yes	20	47	46	14*
Milan Cancer Institute[b]	701	2	Yes	20	44	43	8.8*
Institute Gustave-Roussy[c]	179	2	No		73	65	13
National Cancer Institute[d]	237	5	Yes	10	77	75	16
EORTC[e]	868	5	Yes	10	65	66	17.6
Danish Breast Cancer Group[f]	905	None	Yes	6	79	82	3

BCT, Breast-conserving therapy; *EORTC,* European Organization for Research and Treatment of Cancer; *NSABP,* National Surgical Adjuvant Breast and Bowel Project; *XRT,* radiation therapy.

*Includes only women whose excision margins were negative.

Data from the following sources:

[a]Fisher B, Anderson S, Bryant J, et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233, 2002.

[b]Veronesi U, Cascinelli N, Mariani L, et al: Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347:1227, 2002.

[c]Arriagada R, Le M, Rochard F, et al: Conservative treatment versus mastectomy in early breast cancer: Patterns of failure with 15 years of follow-up data. J Clin Oncol 14:1558, 1996.

[d]Jacobson J, Danforth D, Cowan K, et al: Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. N Engl J Med 332:907, 1995.

[e]van Dongen J, Voogd A, Fentiman I, et al: Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. J Natl Cancer Inst 92:1143, 2000.

[f]Blichert-Toft M, Rose C, Andersen J, et al: Danish randomized trial comparing breast conservation therapy with mastectomy: Six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr 11:19, 1992.

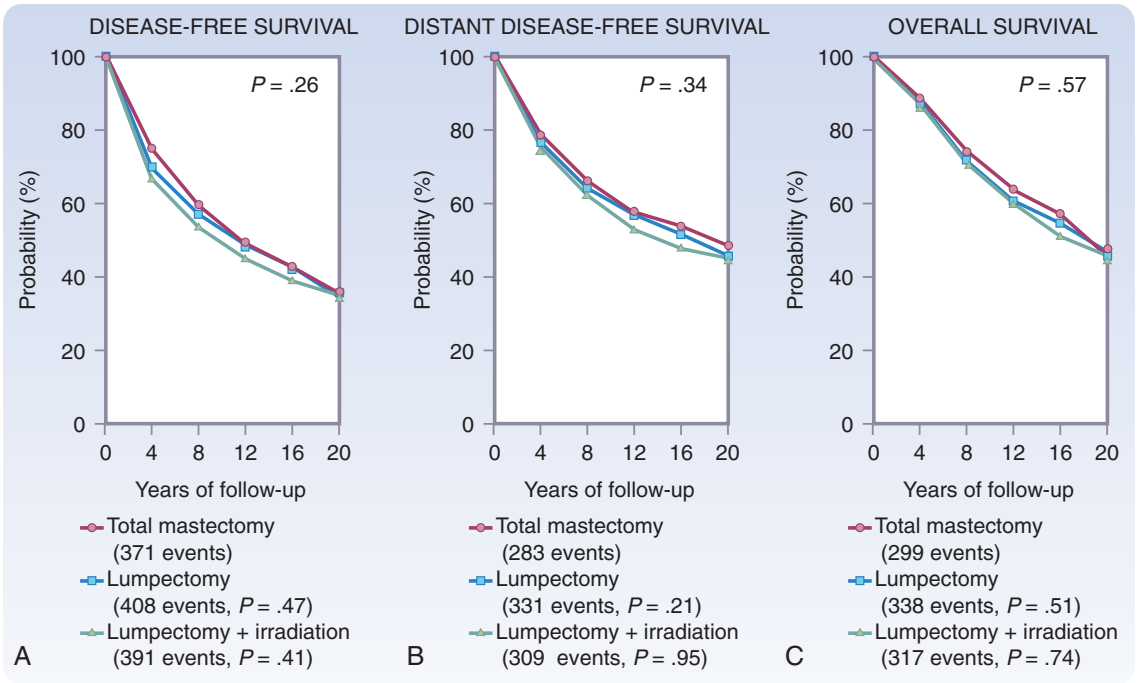

FIGURE 36-10 Disease-free survival **(A),** distant disease-free survival **(B),** and overall survival **(C)** after 20 years of follow-up in the NSABP protocol B-06. There were no significant differences in the three randomized arms of this trial. (From Fisher B, Anderson S, Bryant J, et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233–1241, 2002.)

lumpectomy alone ($P < .001$; Fig. 36-11). For patients with positive nodes who received chemotherapy, the local recurrence rate was 44.2% for lumpectomy alone as opposed to 8.8% for lumpectomy plus radiation therapy.

Milan I Trial The Milan I trial enrolled patients with smaller tumors and used more extensive surgery and radiation therapy than the NSABP B-06 trial. The Milan trial randomized 701 women with tumors up to 2 cm in size and clinically negative nodes to receive radical mastectomy versus quadrantectomy with axillary dissection and postoperative irradiation. Patients with pathologically positive nodes received chemotherapy. Overall survival at 20 years was not different in the two groups. Locoregional failures were different between groups with chest wall recurrence after radical mastectomy in 2.3% of women and ipsilateral breast tumor recurrence after quadrantectomy and radiation therapy in 8.8% of women (20-year follow-up). Contralateral breast cancer rates were identical, approximately 0.66%/year for all women, refuting the hypothesis that irradiation increases the incidence of contralateral breast cancers. Local failure rates were higher in younger women after quadrantectomy, with rates of 1%/year in women younger than 45 years and only 0.5%/year in older women.

Other Trials of Breast Conservation Three other randomized trials in patients with operable breast cancer found no survival benefit of mastectomy over breast-conserving therapy. The European Organization for Research and Treatment of Cancer (EORTC) Trial 10801 randomized 868 women to modified radical mastectomy or lumpectomy and irradiation and found no difference in survival at 10 years. Importantly, this trial included tumors up to 5 cm, and 80% of women enrolled had tumors larger than 2.0 cm. Positive margins were allowed, and the results showed lower rates of local recurrence with clear versus involved margins.

The Institut Gustave-Roussy trial randomized 179 women with tumors smaller than 2 cm to modified radical mastectomy versus lumpectomy with a 2-cm margin of normal tissue around the cancer. No differences were observed between the two surgical groups in risk for death, metastases, contralateral breast cancer, or locoregional recurrence at 15 years of follow-up.

The NCI (United States) trial randomized 237 women with tumors 5 cm or smaller to compare lumpectomy with axillary dissection and radiation therapy versus modified radical mastectomy. There were no differences seen in overall survival or disease-free survival rates at 10 years.

Planning Surgical Treatments

It is critical to establish the diagnosis of breast cancer firmly prior to initiating definitive surgical treatment. Biopsy of a palpable or image-detected lesion with core needle biopsy is the approach of choice for diagnosis. Open surgical biopsy is reserved for lesions not amenable to core biopsy or when core biopsy has proved nondiagnostic. FNA biopsy can be useful for diagnosing breast lesions, although its high false-negative rate means that a negative result requires additional workup. FNA biopsy is also unable to distinguish invasive from in situ lesions reliably. Examination of biopsy material should provide information about tumor histologic type and grade, ER and PR status, HER-2 status, and presence of lymphovascular invasion.

A history and physical examination, in addition to appropriate imaging studies, are important to establish the extent of disease and assign a clinical stage. The most common sites of

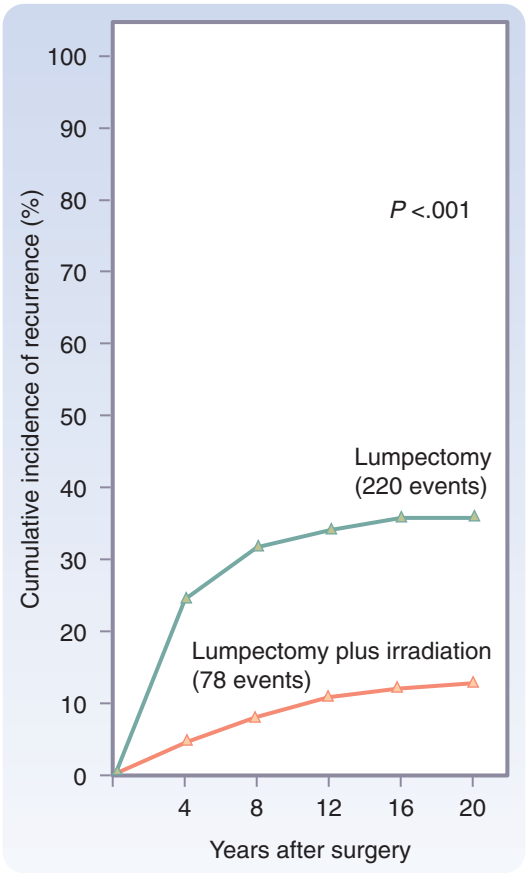

FIGURE 36-11 Cumulative incidence of a first recurrence of cancer in the treated conserved breast during 20 years of follow-up in the NSABP protocol B-06. The data presented here are for patients achieving a pathologically tumor-free margin after lumpectomy. There were 570 women treated by lumpectomy alone and 567 treated by lumpectomy and ipsilateral breast irradiation. (From Fisher B, Anderson S, Bryant J, et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233–1241, 2002.)

distant metastases from breast cancer are the liver, lungs, and bones. The National Comprehensive Cancer Network provides guidelines for the use of laboratory and radiologic testing in patients at initial diagnosis based on clinical stage. Computed tomography (CT) scans, bone scans, and other imaging studies are generally reserved for patients with abnormalities on blood chemistry tests or chest radiographs and for patients with locally advanced or inflammatory breast cancer. Thorough imaging of the ipsilateral and contralateral breast is performed to look for additional areas of concern other than the index lesion. Breast MRI may be used in select cases to define the extent of tumor and look for additional breast lesions.

In the absence of metastatic disease, the first intervention for patients with early-stage breast cancer is surgery to excise the tumor and surgically stage the regional lymph nodes, when appropriate. Assessment of the primary tumor size and regional lymph nodes defines the pathologic stage and provides an estimate of the prognosis to inform systemic therapy decisions. Patients with locally advanced and inflammatory breast cancers should receive systemic therapy before surgery (see later, "Neoadjuvant Systemic Therapy for Operable Breast Cancer").

The selection of surgical procedures takes into account patient characteristics and other clinical and pathologic variables. Patient characteristics, including age, family history, menopausal status, and overall health, are assessed. Some patients may undergo genetic testing for *BRCA* gene mutations at the time of diagnosis. Patients with a known mutation are generally counseled toward bilateral mastectomy for treatment of the index breast and risk reduction of the contralateral breast. The location of the tumor within the breast and tumor size relative to breast size are evaluated. Patient preferences for breast preservation versus mastectomy are determined. For patients considering mastectomy, options for immediate reconstruction are discussed.

Selection of Surgical Therapy

Mastectomy and breast conservation therapy have been shown to be equivalent in terms of patient survival; therefore, the choice of surgical treatment for patients with stage I or II disease is individualized. Patients who desire breast-conserving surgery must be willing to attend postoperative radiation treatment sessions and to undergo postoperative surveillance of the treated breast. Consideration should be made for consultation with a radiation oncologist before the planned surgery. Patients are advised about the risks and long-term sequelae of radiation therapy. A mastectomy is generally recommended for patients who have contraindications to radiation therapy.

A significant factor in determining whether breast conservation therapy is feasible is the relationship between tumor size and breast size. In general, the tumor must be small enough in relation to the breast size so that the tumor can be resected with adequate margins and acceptable cosmesis. In patients with large tumors for whom systemic chemotherapy will likely be recommended in the postoperative (adjuvant) setting, the use of preoperative chemotherapy may be considered because it can significantly reduce the size of the tumor, allowing more patients to undergo breast-conserving surgery. If chemotherapy is administered prior to surgery, it may decrease the tumor size sufficiently to permit breast-conserving surgery in patients who would not otherwise appear to be good candidates. Another strategy is to consider local tissue rearrangement or pedicled myocutaneous flaps (latissimus dorsi) to fill the defect resulting from breast-conserving surgery. Patients with multicentric tumors are usually served best by mastectomy because it is difficult to perform more than one breast-conserving surgery in the same breast with acceptable cosmesis. Although high nuclear grade, presence of lymphovascular invasion, and negative steroid hormone receptor status have all been linked to increased local recurrence rates, none of these factors are considered absolute contraindications to breast conservation.

Eligibility for Breast Conservation

Randomized trials have demonstrated the efficacy of breast-conserving surgery for a wide variety of breast cancers and have defined eligibility for breast conservation. With these criteria and current surgical and radiation approaches, local recurrence rates after lumpectomy and radiation therapy are now less than 5% at 10 years in many large centers.

Tumor Size Tumors up to 5 cm in size, tumors with clinically positive nodes, and tumors with both lobular and ductal histology were included in the randomized trials. In current practice, lumpectomy is considered in cases in which the tumor can be excised to clear margins and leave an acceptable cosmetic result.

Margins Local recurrence rates are reduced when 2- to 3-mm microscopically clear margins are obtained on all aspects of the lumpectomy specimen. Margins should be clear for invasive cancer and DCIS.

Histology Invasive lobular cancers and cancers with an extensive intraductal component are eligible for lumpectomy if clear margins are achieved. Atypical hyperplasia and LCIS at resection margins do not increase local recurrence rates.

Patient Age Local recurrence rates are somewhat higher for younger versus older women. Local recurrence rates are reduced in patients of all ages with the use of radiation therapy. A radiation boost to the tumor bed has been shown to reduce local failures after lumpectomy, particularly in younger women.

Surgical Procedures for Breast Cancer

Breast-Conserving Surgery

Technical Aspects Excision of the primary tumor with preservation of the breast has been referred to by many terms, including *lumpectomy, partial mastectomy, segmental mastectomy, segmentectomy, tylectomy,* and *wide local excision.* Breast-conserving surgery removes the malignancy with a surrounding rim of grossly normal breast parenchyma. This procedure is depicted in Figure 36-12, which shows the completed lumpectomy and skin incision for the axillary component of the procedure. A more extensive local procedure, quadrantectomy, used in some European trials of breast conservation, removes 2 to 3 cm of adjacent breast and skin over the tumor. These more extensive margins and skin excision have not been shown to improve survival and are not used in current approaches to breast conservation.

The breast conservation specimen that is removed is oriented and its edges inked prior to sectioning. Specimen radiography should be performed for all nonpalpable lesions or if there are microcalcifications associated with the palpable tumor. If a margin appears to be close or is positive histologically on intraoperative assessment, reexcision to remove more tissue will frequently achieve a clear margin and allow conservation of the breast. Orientation of the surgical specimen allows focal reexcision of involved margins rather than global reexcision and improves the cosmetic result by reducing the amount of normal breast parenchyma that is excised.

The surgical defect created after lumpectomy is closed in cosmetic fashion. There is increasing interest in the use of advancement flap closure and other oncoplastic surgical techniques to maximize the cosmetic result.

Surgical staging of the axilla is usually performed through a separate incision in most patients undergoing breast conservation. Sentinel lymph node dissection (see Fig. 36-12*B*) has largely replaced anatomic axillary node dissection in patients with clinically negative axillary nodes. For patients who require axillary dissection, the extent of the dissection is identical to the

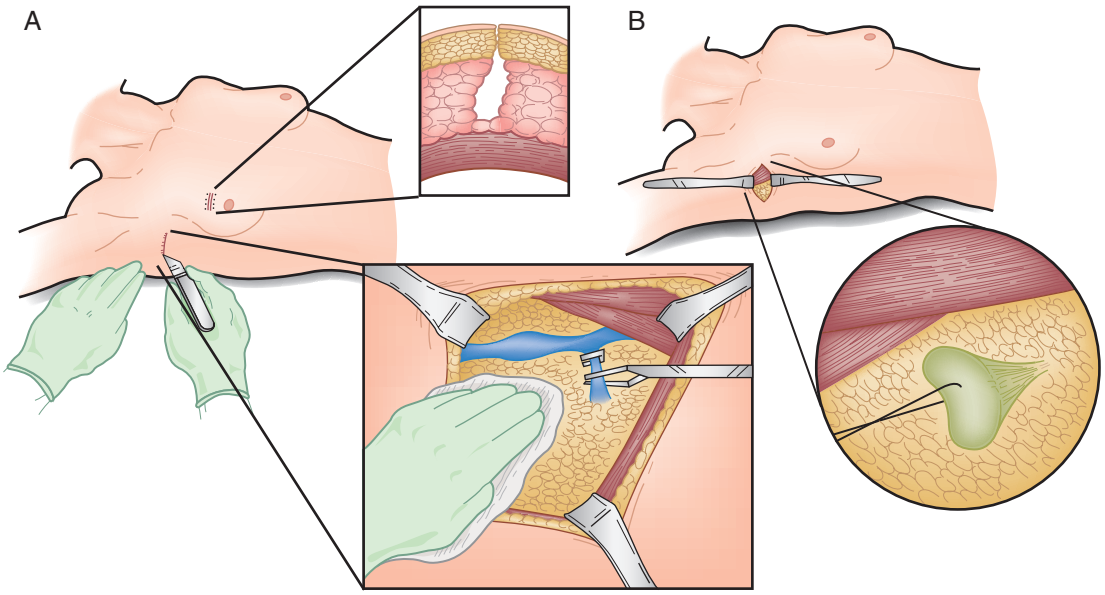

FIGURE 36-12 Breast-conserving surgery. **A,** Incisions to remove malignant tumors are placed directly over the tumor, without tunneling. A transverse incision in the low axillary region is used for sentinel node biopsy or axillary dissection. The axillary dissection is identical to the procedure for a modified radical mastectomy. The boundaries of the operation are the axillary vein superiorly, the latissimus dorsi muscle laterally, and the chest wall medially. The inferior dissection enters the tail of Spence (the axillary tail of the breast). *Inset,* Excision cavity of the lumpectomy. **B,** In sentinel node biopsy, a similar transverse incision is made, which may be located by percutaneous mapping with the gamma probe if radiolabeled colloid is used. It is extended through the clavipectoral fascia and the true axilla is entered. The sentinel node is located by its staining with dye, radioactivity, or both, and dissected free as a single specimen.

axillary component of the modified radical mastectomy (see Fig. 36-12*A*).

Cosmetic Challenges The term *oncoplastic surgery* has been popularized in recent years to stress the importance of achieving the best possible aesthetic result in the context of resecting the tumor with adequate oncologic margins. The goal is to retain as much of the natural breast size and contour as possible to provide optimal cosmesis and symmetry with the opposite breast. When the primary tumor is resected using an incision directly over the tumor and then closing the skin without reapproximating any breast tissue, several deformities can occur. These include volumetric deformity from a large parenchymal resection, retraction deformity when the seroma resorbs at the operative site, skin–pectoral muscle adherence deformity, in which the skin adheres to the underlying pectoral muscle, and lower pole deformity with downward turning of the nipple caused by excision of a tumor in the lower hemisphere of the breast. These deformities can make it difficult for patients to wear athletic clothing or bathing suits because significant asymmetry may be evident. It is important to correct these deformities prior to radiation therapy because the irradiation may further accentuate any asymmetry and make it more challenging to correct the defect in the future.

The surgeon should consider oncoplastic techniques when the following situations occur: (1) a significant area of skin will be resected with the tumor; (2) a large-volume resection is expected; (3) the tumor is in an area associated with poor cosmetic outcomes (e.g., lower hemisphere below the nipple); or (4) resection may lead to nipple malposition.

Extent of Breast Resection It is not the absolute breast volume that will be resected but rather the ratio of the anticipated defect to the volume of the remaining breast parenchyma that is important when considering oncoplastic surgery techniques. In general, oncoplastic surgery should be considered when the surgical defect is likely to be greater than 20% to 30% of the breast volume and for any tumor resection in the lower breast.

Breast Size and Body Habitus Patients with large breasts are often good candidates for tumor resection and bilateral reduction mammaplasty. Breast reduction strategies can allow for improved aesthetic outcomes after resection of large volumes of breast tissue at any location. Obese patients should be considered for this approach because they are often poor candidates for autologous tissue reconstruction after mastectomy and implants are often not large enough to recreate a proportional breast size. Breast reduction surgery is a good option because this can relieve the symptoms of macromastia and allow for improved outcomes after breast irradiation.

Tumor Location Tumors lying directly under the nipple-areolar complex and those located between the nipple-areolar complex and inframammary fold require special attention to avoid nipple-areolar complex distortion and contour deformity. In general, there must be an adjustment of skin and well-vascularized breast parenchyma to correct for the removal of breast tissue in these areas. As noted, deformities in the contour will be exacerbated by radiation and may be more challenging to correct at a later date.

Timing of Oncoplastic Surgery Immediate reconstruction of the partial mastectomy defect is almost always preferred to a delayed approach. Oncoplastic techniques such as tissue advancement and local tissue rearrangement at the initial surgical procedure tend to provide the optimal solution. This approach has not been associated with delay in delivery of adjuvant systemic therapy or radiation delivery. In general, local tissue transfer and breast reduction surgery cannot be performed on the irradiated breast; thus, it is preferable to perform the procedure prior to radiation. Tissue expanders and implants are not recommended to fill partial mastectomy defects because radiation may lead to capsular contracture, distortion, and infection.

If a cosmetic defect occurs following breast-conserving surgery and radiation, reconstruction of the treated breast is generally not recommended for up to 1 to 2 years after radiation therapy has been completed. In irradiated tissue, there is a higher rate of tissue necrosis, seroma formation, and infection. The use of vascularized tissue from outside the radiation field is the favored approach. If the main deformity is caused by asymmetry with the contralateral breast, a mastopexy of the contralateral breast can be considered. In general, surgical procedures on the irradiated breast should be minimized because healing and recovery are impaired, even when the skin appears healthy.

Mastectomy

Indications Certain tumors still require mastectomy, including those that are large relative to breast size, those with extensive calcifications on mammography, tumors for which clear margins cannot be obtained on wide local excision, and patients with contraindications to breast irradiation. Contraindications to the use of radiation therapy include previous breast or chest wall irradiation, active lupus or scleroderma, and pregnancy, although many patients pregnant at diagnosis can complete their pregnancy and receive radiation therapy after delivery. Patient preference for mastectomy or a desire to avoid radiation is also a valid indication for mastectomy.

Breast Reconstruction Breast reconstruction may be performed as immediate reconstruction—that is, the same day as mastectomy—or as delayed reconstruction, months or years later. Immediate reconstruction has the advantages of preserving the maximum amount of breast skin for use in reconstruction, combining the recovery period for both procedures, and avoiding a period of time without a breast mound. Immediate reconstruction does not have a detrimental effect on long-term survival, local recurrence rates, or detection of local recurrence. Reconstruction may be delayed in patients who might require postmastectomy radiation therapy and is usually delayed in patients with locally advanced cancer. Reconstruction options include tissue expander and implant and autologous tissue reconstructions, most often with transverse rectus abdominis muscle (TRAM) flaps, latissimus dorsi flaps and, more recently, muscle-preserving perforator abdominal flaps.

Technical Details

Simple and Modified Radical Mastectomy Simple or total mastectomy refers to complete removal of the mammary gland, including the nipple and areola. Sentinel lymph node surgery for axillary staging may be performed through the mastectomy incision or through a separate axillary incision. Modified radical mastectomy refers to removal of the mammary gland, nipple,

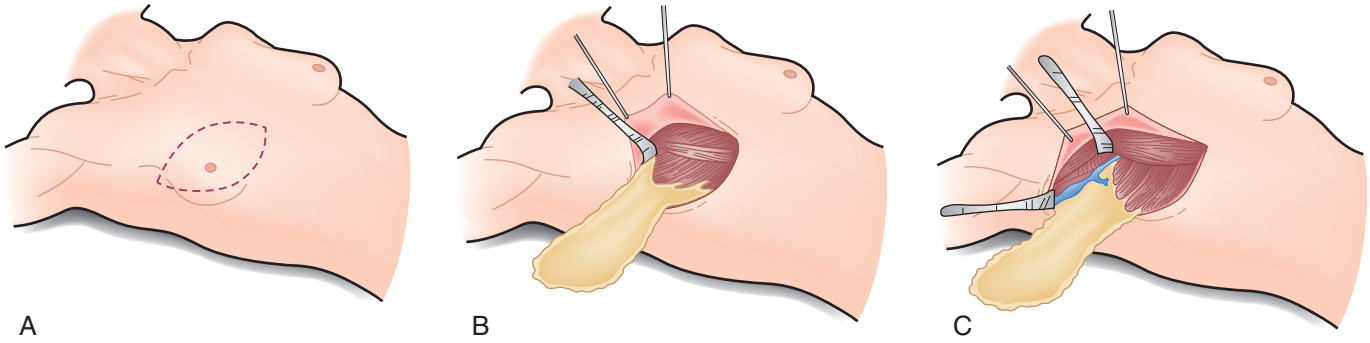

FIGURE 36-13 Total mastectomy with and without axillary dissection. **A,** Skin incisions are generally transverse and surround the central breast and nipple-areolar complex. **B,** Skin flaps are raised sharply to separate the gland from the overlying skin and then the gland from the underlying muscle. Simple mastectomy divides the breast from the axillary contents and stops at the clavipectoral fascia. **C,** In modified radical mastectomy, dissection continues into the axilla and generally extends up to the axillary vein, with removal of level I and II nodes. Division of a branch of the axillary vein is shown, with separation of the node-bearing axillary fat from the axillary vein at the superior aspect of the dissection.

and areola, with the addition of a complete axillary lymph node dissection (Fig. 36-13).

An elliptical skin incision is planned to include the nipple and areola and usually any previous excisional biopsy scars (see Fig. 36-13A). Skin flaps are raised to separate the underlying gland from the overlying skin along the subdermal plexus (see Figs. 36-13*B* and *C*). If immediate reconstruction is not planned, sufficient skin is taken to allow smooth closure of skin flaps without redundant skin folds. This will facilitate comfortable use of a breast prosthesis in the future. If immediate reconstruction is planned, a skin-sparing mastectomy may be performed in which only the nipple-areola complex is removed and the maximum amount of skin is left for use in the reconstruction. Nipple-areola–sparing mastectomy has been used with increasing frequency for patients undergoing prophylactic mastectomy for risk reduction. There are also some early reports suggesting that it may be appropriate for some select patients with a diagnosis of breast cancer.

Breast tissue is separated from the underlying pectoralis muscle and the pectoral fascia is generally taken with the breast specimen. In a total mastectomy (see Fig. 36-13*B*), breast tissue is separated from the axillary contents and all breast tissue superficial to the fascia of the axilla is removed. In a modified radical mastectomy, the levels I and II axillary lymph nodes are taken with the axillary breast tissue (see Fig. 36-13*C*). Level I nodes are those inferior to the axillary vein and lateral to the pectoralis minor muscle and level II nodes are those posterior to the pectoralis minor.

Lymph Node Staging

The pathologic status of the axillary lymph nodes is one of the most important prognostic factors in patients with breast cancer. Identification of metastatic tumor deposits in the axillary nodes indicates a poorer prognosis and often prompts a recommendation for more aggressive systemic and locoregional therapies.

Axillary lymph node dissection has long been a routine component of the surgical management of breast cancer patients. It provides prognostic information about axillary nodal status and also plays a therapeutic role in removing axillary disease in patients with positive nodes. The surgical procedure includes clearance of node-bearing tissue between the pectoralis major and latissimus dorsi muscles from the edge of the breast tissue in the low axillary region to the axillary vein and removal of the nodes posterior to the pectoralis minor muscle. Unfortunately, axillary dissection is often the main source of morbidity in patients with early-stage breast cancer. The immediate problems include acute pain and paresthesias, need for hospitalization, reduced range of motion at the shoulder joint, and need for a drain in the surgical bed for a period of 2 weeks or more. Long-term problems resulting from axillary dissection include lymphedema of the ipsilateral arm, numbness, chronic pain, and reduced range of motion at the shoulder joint.

The technique of sentinel lymph node dissection was developed to reduce the morbidity associated with axillary surgery while still providing accurate staging information. Because many patients now present with clinically node-negative disease, sentinel lymph node dissection can identify those with proven node-positive disease who may benefit from completion axillary dissection. Those patients with a negative sentinel lymph node can avoid the morbidity of axillary dissection. Identification of the first, or sentinel, node(s) draining the area of the primary tumor in the breast allows for this more selective approach to the axilla. The sentinel node(s) is the most likely node to contain metastatic disease, if present, and therefore the pathologist can focus the examination on the sentinel node(s) without the added cost and time required to examine the full axillary contents. In sentinel lymph node surgery, radiolabeled colloid and/or blue dye is injected into breast tissue at the site of the primary tumor; this then passes through the lymphatics to the first draining node, where the material accumulates. The procedure can also be performed with injection of the mapping agents at the subareolar position or in a subdermal location overlying the site of the primary tumor. The sentinel node is identified as a blue node, radioactive node or both. If the pathologic analysis of the sentinel node is negative for evidence of metastasis, the likelihood that other nodes are involved is sufficiently low that axillary lymph node dissection is not required. Published studies have confirmed the proof of concept and numerous subsequent studies have shown that the technique is accurate.

Identification of the sentinel node(s) allows for a more detailed analysis of the lymph node most likely to have a positive yield. In general, pathologists will section the sentinel node

along its short axis and submit all the sections for paraffin embedding of the tissues. The paraffin blocks can then be sectioned and examined with hematoxylin and eosin staining of sections from each block. Some pathologists will perform more detailed analysis of the sentinel nodes with step-sectioning of the paraffin blocks and immunohistochemical staining for cytokeratin, which enhances sensitivity by allowing detection of micrometastases. However, the clinical relevance of these micrometastases and small tumor deposits detected by immunohistochemical techniques has been questioned.[18]

Sentinel Node Technique

Lymphatic mapping can be performed with a combination of technetium-labeled sulfur colloid and a vital blue dye (isosulfan blue [Lymphazurin]) or with a single agent for localization of the sentinel lymph node. A number of studies have shown that using the combination technique results in the lowest possible false-negative rate. Preoperative lymphoscintigraphy can provide information on the specific nodal basins draining the primary tumor and can also demonstrate the number of sentinel nodes in each nodal basin. Using a peritumoral injection technique, approximately 70% of patients will have drainage to the axilla, 20% will have drainage to both the axilla and internal mammary nodal basin, 2% to 3% will have drainage to the internal mammary nodal basin alone, and approximately 8% will not show any drainage to the regional nodal basins. If a subareolar or subdermal injection technique is used, drainage is seen only to the axillary nodal basins. If preoperative lymphoscintigraphy demonstrates drainage to the internal mammary lymph nodes, an internal mammary sentinel node biopsy can be considered. The inability to demonstrate a sentinel lymph node on preoperative lymphoscintigraphy does not preclude the success of identifying a sentinel node intraoperatively but may indicate a higher chance of identifying positive lymph nodes. A dose of 2.5 mCi of technetium-labeled sulfur colloid can be injected on the day prior to surgery for the preoperative lymphoscintigraphy. This allows for adequate activity to remain in the sentinel nodes for the intraoperative lymphatic mapping procedure the following day, without the need for reinjection.

In the operating suite, 3 to 5 mL of blue dye is injected peritumorally and the injection site is massaged to facilitate passage of the dye through the lymphatics. A handheld gamma probe is used to transcutaneously localize the area of increased radioactivity and this helps to guide placement of the incision for the sentinel node procedure. After the incision is made, localization of an area of increased radioactivity is made with the hand-held gamma probe and the surgeon visualizes blue lymphatic channels leading to the sentinel node. Dissection is performed to avoid prematurely disrupting the afferent lymphatics. If a blue-stained lymphatic channel or a specific area of radioactivity ("hot spot") cannot be identified, resection of the primary tumor can be performed to remove the site of injection, decreasing the background shine-through radioactivity. The sentinel node may then be identified and removed and the nodal basin is checked again to confirm that the level of radioactivity has decreased. If the level of radioactivity remains high, additional sentinel nodes may remain in the nodal basin and additional dissection should be completed to remove all sentinel nodes. Published studies have demonstrated an average of two or three sentinel nodes per patient.

Surgeons experienced in sentinel lymph node surgery can identify a sentinel node in more than 95% of patients. The false-negative rate for sentinel lymph node surgery ranges from 0% to up to 10%, as reported in the NSABP B-32 trial.[19] Surgeons should be trained in the technique of sentinel lymph node surgery prior to using this procedure as a staging tool. Patients who present with clinically palpable lymph nodes should be evaluated with axillary ultrasonography and FNA biopsy of the nodes. If axillary metastasis is confirmed, patients can proceed directly to standard axillary node dissection or be considered for preoperative chemotherapy. If axillary metastasis is not confirmed by FNA biopsy, patients can proceed to sentinel lymph node surgery for staging.

Some studies have shown that patients who have undergone previous excisional biopsy of the primary tumor are more likely to have a false-negative sentinel lymph node.[19] The lymphatics may be disrupted by the biopsy, which can affect drainage patterns of the area surrounding the excisional biopsy site. To avoid this scenario, core needle biopsy is the preferred diagnostic approach in patients suspected of having breast cancer.

Sentinel lymph node surgery was reported in older studies to be less accurate in patients treated with preoperative chemotherapy. A meta-analysis of the published studies on sentinel node surgery after chemotherapy has suggested that this technique is accurate; a recent comparison has shown that false-negative rates after chemotherapy compare favorably with those observed in patients who undergo surgery first.[20] Patients with documented metastasis prior to the initiation of chemotherapy should undergo standard axillary node dissection on completion of chemotherapy.

Morbidity rates are substantially lower with sentinel node dissection compared with axillary dissection. Another advantage is that sentinel lymph node dissection can be performed as an outpatient procedure and does not require a drain. Patients have more rapid return to full mobility and are able to return to work and other activities weeks sooner than after axillary dissection. Long-term morbidity, including lymphedema, numbness, and chronic pain, is greatly reduced.

Sentinel node dissection has been shown to provide reliable pathologic staging of the axilla, with false-negative rates generally lower than 5% in experienced hands. Axillary recurrence rates have been shown to be extremely low after a negative sentinel node biopsy without axillary dissection. A negative sentinel node biopsy is now widely accepted as sufficient to establish a patient as node-negative, with no further axillary treatment required.[19]

When the sentinel node contains metastatic disease, the likelihood of additional involved nodes is directly proportional to the size of the breast primary, presence of lymphatic vascular invasion, and size of the lymph node metastasis. In approximately 50% of patients with positive sentinel nodes, the sentinel node is the only positive node. In the presence of a positive sentinel node, treatment guidelines have dictated completion axillary lymph node dissection (ALND) as the standard. This is most commonly achieved with a completion level I and II axillary dissection. Although ALND has been standard practice for patients with positive SLNs, the need for ALND in all patients with a positive SLN has come into question because many patients have small-volume metastases and the sentinel node is often the only positive node. A meta-analysis of studies evaluating patients with positive sentinel nodes has shown that 53% of patients have additional

positive nodes at ALND.[21] In the case of micrometastatic disease in the sentinel nodes, the rate of nonsentinel node involvement is as low as 20% and, for patients with isolated tumor cells, it is below 12%. This has led to a trend of omitting ALND in selected patients with positive sentinel nodes. An analysis of the SEER data from 1998 to 2004 revealed that up to 16% of sentinel node–positive patients did not undergo ALND. This was seen more commonly in older patients with low-grade, ER-positive tumors. During this time frame, the number of patients with micrometastasis in the sentinel node who did not undergo ALND increased from 21% to 38%. A review of the National Cancer Data Base (NCDB) data from 1998 to 2005 revealed similar findings, with 20.8% of sentinel–node positive patients avoiding ALND. There were no differences seen in axillary recurrence rates or survival for patients who had sentinel node surgery only versus those who underwent ALND.

One factor that may have contributed to the decrease in ALND for patients with positive sentinel nodes is the emergence of the use of nomograms, which can predict the probability of disease burden in the undissected nonsentinel nodes. For patients with micrometastasis in one of several sentinel nodes, or those with disease detected by immunohistochemistry only, the estimated risk of additional positive nodes remaining in the axilla is low. The first nomogram developed was published by researchers from the Memorial Sloan Kettering Cancer Center (MSKCC) and is available to clinicians on the Internet (http://nomograms.mskcc.org/Breast/index.aspx). A more recent tool, developed at the M.D. Anderson Cancer Center, includes the important variable of sentinel node metastasis size. This nomogram is also available on the Internet (http://www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln). Both these nomograms have been validated to estimate the degree of additional nodal involvement based on characteristics of the patient, primary tumor, number of sentinel nodes, and other factors. These and other nomograms can be used by the surgeon, in combination with clinical judgment and other available information, to estimate the risk of additional positive nonsentinel nodes in an individual patient.

The American College of Surgeons Oncology Group (ACOSOG) initiated a prospective randomized trial in 1999 designed specifically to evaluate the impact of ALND on locoregional recurrence and survival in patients with early-stage breast cancer.[22] The ACOSOG Z0011 trial enrolled patients with clinical T1 or T2 breast cancer with one or two positive sentinel nodes who were planned for breast-conserving surgery and whole-breast irradiation and then randomized them to undergo completion ALND or no further surgery (sentinel node surgery alone). The primary end point of Z0011 was overall survival with locoregional recurrence as a secondary end point. Patients who participated in Z0011 had relatively favorable disease characteristics; median age was 55 years, 70% had T1 tumors, 82% had ER-positive tumors, 71% had only one positive sentinel node, and 44% had micrometastases. At a median follow-up of 6.3 years, local recurrence was seen in 3.6% (n = 29) of the ALND group versus 1.8% (n = 8) of the sentinel node only group. Axillary recurrences were reported in 0.5% (n = 2) of patients in the ALND group versus 0.9% (n = 4) in the sentinel node only group. There were no differences in overall survival (91.9% after ALND versus 92.5% after sentinel node only; P = .24) or disease-free survival at 5 years (82.2% after ALND versus 83.8% after sentinel node only). The Z0011 study investigators concluded that the routine use of ALND was not justified in all patients with early-stage breast cancer found to have a positive sentinel node. The results of this study are practice-changing. It is now widely believed that ALND may be safely omitted in select patients with clinically node-negative disease who have a positive sentinel node and are similar to the participants in the Z0011 trial—women with T1 or T2, clinically node-negative breast cancer who undergo breast-conserving surgery and whole-breast irradiation who have one or two positive sentinel nodes and are planned for adjuvant systemic therapy. Patients with a positive sentinel node undergoing mastectomy and those undergoing breast-conserving surgery who are planned for accelerated partial-breast irradiation (APBI) should continue to undergo ALND as standard practice.

Axillary lymph node dissection remains the standard of care for patients with locally advanced breast cancer or inflammatory breast cancer, for those with a positive sentinel node who are planned for mastectomy, and for those with a positive sentinel node after neoadjuvant chemotherapy.

TREATMENT OF DUCTAL CARCINOMA IN SITU (INTRADUCTAL CARCINOMA)

DCIS, or intraductal cancer, currently accounts for approximately 25% of all newly diagnosed breast cancers, with more than 54,000 new cases diagnosed in 2010. Most DCIS is characterized by an area of clustered calcifications on a screening mammogram, without an associated palpable abnormality. Rarely, DCIS will be manifested as a palpable mass or as unilateral, single-duct nipple discharge.

Mammographic findings in patients with DCIS include clustered calcifications without an associated density in 75% of patients, calcifications coexisting with an associated density in 15%, and a density alone in 10%. The calcifications seen on a mammogram generally correspond to areas within the central involved duct in which there is often necrosis and debris. DCIS calcifications tend to cluster closely together, are pleomorphic, and may be linear or branching, thus suggesting their ductal origin.

DCIS is viewed as a precursor of invasive ductal cancer and treatment aims to remove the DCIS to prevent progression to invasive disease. Because the risk for metastatic disease in patients with DCIS without demonstrable invasion is rare (<1%), systemic chemotherapy is not required. Hormonal therapy may be used for prevention of new primary tumors and to improve local control after breast-conserving therapy but is generally only recommended when the DCIS is positive for ER on immunohistochemistry.

Treatment recommendations for an individual patient with DCIS are based on the extent of disease within the breast, histologic grade, ER status, and presence of microinvasion, as well as patient age and preference. Treatment options for DCIS include mastectomy, breast-conserving surgery with irradiation, and breast-conserving surgery alone. When the patient is treated with breast conservation or unilateral mastectomy, there is also the option of adjuvant hormonal therapy with tamoxifen as risk reduction for future breast cancers.[23]

Mastectomy

Breast cancer mortality after treatment of DCIS by total mastectomy is 1%, which is the standard against which breast-conserving approaches are compared (Table 36-7). Local

Table 36-7 Recurrence and Mortality Rates After Mastectomy for Ductal Carcinoma in Situ

STUDY (YEAR)	DATES OF STUDY	NO. OF PATIENTS	FOLLOW-UP (YR)	NONCLINICAL (%)	NO. OF RECURRENCES	NO. DEAD OF DISEASE
Farrow (1970)[a]	1949-1967	181	5-20	0	6	4
Brown et al (1976)[b]	1952-1975	39	1-15	10	0	0
Carter and Smith (1977)[c]	1960-1975	28	1-14		1	1
Sunshine et al (1985)[d]	1960-1980	73	10-year minimum	0	4	3
Von Rueden and Wilson (1984)[e]	1960-1981	45	Not reported	8	1	0
Ashikari et al (1971)[f]	1960-1969	92	11 year maximum	40	0	0
Schuh et al (1986)[g]	1965-1984	49	5.5 mean	33	1	1
Kinne et al (1989)[h]	1970-1976	101	11.5 median	58	1	1
Lagios et al (1982)[i]	1975-1980	42	Not reported		0	0
Fisher et al (1986)[j]	1976-1984	27	5		1	1
Arnesson et al (1989)[k]	1978-1984	28	6.4 median	100	0	0
Ward et al (1992)[l]	1979-1983	123	10	11	1	?
Silverstein (1997)[m]	1979-1990	98	4.9 median	62	1	0
Total		926			17 (2%)	11(1%)

Data from the following sources:

[a]Farrow JH: Current concepts in the detection and treatment of the earliest of the early breast cancers. Cancer 25:468, 1970.

[b]Brown PW, Silverman J, Owens E, et al: Intraductal "noninfiltrating" carcinoma of the breast. Arch Surg 111:1063, 1976.

[c]Carter D, Smith RL: Carcinoma in situ of the breast. Cancer 40:1189, 1977.

[d]Sunshine JA, Moseley MS, Fletcher WS, et al: Breast carcinoma in situ: A retrospective review of 112 cases with a minimum 10-year follow-up. Am J Surg 150:44, 1985.

[e]Von Rueden DG, Wilson RE: Intraductal carcinoma of the breast. Surg Gynecol Obstet 158:105, 1984.

[f]Ashikari R, Hajdu SI, Robbins GF: Intraductal carcinoma of the breast (1960-1969). Cancer 28:1182, 1971.

[g]Schuh ME, Nemoto T, Penetrante R, et al: Intraductal carcinoma: Analysis of presentation, pathologic findings, and outcome of disease. Arch Surg 121:1303, 1986.

[h]Kinne DW, Petrek JA, Osborne MP, et al: Breast carcinoma in situ. Arch Surg 124:33, 1989.

[i]Lagios MD, Westdahl PR, Margolin FR, et al: Duct carcinoma in situ: Relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. Cancer 50:1309, 1982.

[j]Fisher ER, Sass R, Fisher B, et al: Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 6). I: Intraductal carcinoma (DCIS). Cancer 57:197, 1986.

[k]Arnesson LG, Smeds S, Fagerberg G, et al: Follow-up of two treatment modalities for ductal cancer in situ of the breast. Br J Surg 76:672, 1989.

[l]Ward BA, McKhann CF, Ravikumar TS: Ten-year follow-up of breast carcinoma in situ in Connecticut. Arch Surg 127:1392, 1992.

[m]Silverstein MJ (ed): Ductal carcinoma in situ of the breast. Baltimore, 1997, Williams & Wilkins, p 443.

recurrences are rare and suggest malignant transformation of residual glandular tissue. Metastatic disease in patients with pure DCIS is suggestive of a histologically unrecognized invasive carcinoma in the mastectomy specimen or the development of a contralateral primary.

Reasons to select total mastectomy for treatment of DCIS include the following:

1. Diffuse suspicious mammographic calcifications suggestive of extensive disease
2. Inability to obtain clear margins with breast-conserving surgery
3. Likelihood of a poor cosmetic result after breast-conserving surgery
4. Patient not motivated to preserve her breast
5. Contraindications to radiation therapy

Contraindications to breast irradiation include the following:

1. Previous irradiation of the breast or chest wall
2. Collagen vascular disease (scleroderma or active lupus)
3. First- or second-trimester pregnancy

Breast Conservation Therapy

As in the case of invasive breast cancer, breast conservation for DCIS requires resection to microscopically clear margins. The use of adjuvant whole-breast radiation therapy has been demonstrated in prospective randomized trials to decrease the risk for local recurrence. The use of hormonal therapy in ER-positive DCIS can further decrease the risk for local recurrence and also reduces the risk for development of new contralateral and ipsilateral breast cancers.

The use of radiation after lumpectomy has been investigated in four prospective randomized trials and the results of these studies have been remarkably consistent. The NSABP B-17 trial randomized 818 women with DCIS to lumpectomy alone versus lumpectomy plus 50 Gy of postoperative whole-breast irradiation, and 12-year actuarial recurrence data showed that the addition of radiation decreased the ipsilateral recurrence rate from 30.8% in patients undergoing excision alone to 14.9% in patients undergoing excision with irradiation ($P < .000005$).[24] The use of radiation therapy resulted in a decrease in the incidence of invasive breast cancer (16.4% versus 7.1%; $P < .00001$), with a smaller decrease in the incidence of in situ recurrence

Table 36-8 Randomized Trials of Lumpectomy for Ductal Carcinoma in Situ: Impact of Radiation Therapy and Tamoxifen

			Local Recurrence Rates (%)			
TRIAL	NO. OF PATIENTS	FOLLOW-UP (YR)	LUMPECTOMY	LUMPECTOMY + XRT	LUMPECTOMY + XRT + TAMOXIFEN	*P* VALUE
NSABP B-17[a]	818	12	30.8	14.9		<.000005
EORTC 10853[b]	1010	4.25	16	9		<.005
UK ANZ	1701	5	20	8	6	<.0001
SweDCIS	1067	5	7	22		<.0001
NSABP B-24[c]	1804	7		9	6	0.04

EORTC, European Organization for Research and Treatment of Cancer; *NSABP,* National Surgical Adjuvant Breast and Bowel Project; *SweDCIS,* Swedish ductal carcinoma in situ trial; *UK ANZ,* United Kingdom, Australia and New Zealand; *XRT,* Radiation therapy.

Data from the following sources:

[a]Fisher B, Dignam J, Wolmark N, et al: Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 16:441, 1998.

[b]Julien JP, Bijker N, Fentiman IS, et al: Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: First results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 355:528, 2000.

[c]Fisher B, Land S, Mamounas E, et al: Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the National Surgical Adjuvant Breast and Bowel Project experience. Semin Oncol 28:400, 2001.

(14.1% versus 7.8%; $P < .001$; Table 36-8). The EORTC 10853 trial randomized 1010 women with DCIS to lumpectomy alone versus lumpectomy plus 50 Gy of radiation therapy.[25] Radiation use improved the 10-year rates of breast recurrence from 26% to 15% ($P < .0001$) and the rates of invasive recurrences from 13% to 8% ($P = .0011$). The UK ANZ (United Kingdom, Australia, and New Zealand) trial was a third large randomized trial that simultaneously evaluated the benefit of radiation therapy and tamoxifen after breast conservation surgery for patients with DCIS.[26] This trial, which enrolled 1701 patients, also demonstrated that radiation therapy reduced the risk of overall breast cancer recurrence (hazard ratio [HR], 0.38; $P < .0001$) and invasive breast cancer recurrence (HR, 0.45; $P = .01$). Finally, the SweDICS trial enrolled 1067 patients with DCIS; after a median follow-up of 5 years, a cumulative incidence of breast recurrence of 22% in the group that underwent surgery only versus 7% in the group that received surgery plus radiation ($P < .0001$) was reported.

Attempts have been made to identify subsets of DCIS for which wide excision without irradiation would provide sufficient local control. Silverstein[27] derived the Van Nuys criteria from a series of DCIS patients treated by wide excision, with and without radiation therapy. They proposed a system to identify patients who do not need radiation therapy based on low DCIS nuclear grade, small size of the lesion, age of the patient, and width of the surgical margin. They have reported low breast recurrence rates with surgery alone for patients with favorable Van Nuys scores. However, in a prospective trial testing this approach, investigators from Harvard enrolled 158 patients from the most favorable Van Nuys subset (low- or intermediate-grade DCIS <2.5 cm, with a minimum 1-cm margin on excision) and were not able to reproduce their results; they stopped the trial early because the rates of recurrence exceeded the predefined stopping rules. Most recently, the first result of a relatively large prospective single-arm study investigating surgery that achieved a 3 mm or greater negative margin without radiation for favorable subsets of patients with DCIS has been reported by Eastern Cooperative Oncology Group (ECOG) investigators.[28] Patients with low- or intermediate-grade DCIS measuring 2.5 cm or smaller had a 5-year rate of ipsilateral breast recurrence of only 6.1%. In contrast, patients with high-grade disease had a much higher 5-year rate of recurrence, 15.3%. In summary, these data suggest that most patients with DCIS should be recommended to receive whole-breast irradiation following lumpectomy. The one subgroup who appears to have favorable outcome are those patients with small-, low-, or intermediate-grade lesions.

Role of Tamoxifen

The use of tamoxifen has been shown to reduce the risk for development of new breast cancers in high-risk women, including those with previous breast cancer (see earlier, "Chemoprevention for Breast Cancer"). To evaluate the benefit of tamoxifen for DCIS, the NSABP B-24 protocol randomized 1804 women who underwent lumpectomy and radiation therapy for DCIS to 5 years of tamoxifen versus placebo.[23] Study criteria allowed enrollment of patients with positive margins, and ER measurements were not performed. At 7 years of follow-up, the addition of tamoxifen to lumpectomy and radiation therapy decreased the incidence of recurrent ipsilateral breast cancers from 9% to 6% and the risk for a new contralateral breast cancer was reduced by 47% (an absolute reduction of 2%; see Table 36-8).

Combining the results of NSABP B-17 and NSABP B-24 at 7 years of follow-up, the total ipsilateral and contralateral breast cancer recurrence rate was 30% for excision alone, 17% for excision with radiation therapy, and 10% for excision, irradiation, and tamoxifen. Subsequent analyses have demonstrated that the benefit from tamoxifen is seen only in women whose DCIS is ER-positive. Patients at highest risk for local recurrence, and therefore those most likely to benefit from tamoxifen, were patients with positive margins, comedo necrosis, a mass on physical examination, and age younger than 50 years. For individual patients, the benefits of tamoxifen are weighed against its side effects, including risk for endometrial carcinoma, thromboembolic events, hot flashes, and cataracts.

Sentinel Node Biopsy

DCIS, by definition, represents breast cancer contained within an intact basement membrane and without access to lymphatic or vascular channels. However, when axillary dissection is performed during mastectomy for intraductal disease, positive nodes can be seen in up to 3.6% of cases, as identified in a review of more than 10,000 patients in the National Cancer Database. These positive nodes probably result from the presence of microinvasion in the primary tumor that was not detected on routine pathologic analysis.

Patients with small, mammographically detected areas of DCIS have very low rates of occult invasion, so surgical staging of the axilla is not necessary. However, in women undergoing breast-conserving surgery for larger areas of DCIS, particularly those with high-grade histology or when the suspicion for microinvasion is high, sentinel node surgery to evaluate the lymph nodes may be considered.

Sentinel node surgery is currently recommended when mastectomy is performed for DCIS because up to 20% of patients with DCIS on a diagnostic core needle biopsy will be found to have invasive cancer on detailed evaluation of the mastectomy specimen. The addition of sentinel node surgery to mastectomy adds minimal morbidity and, because sentinel node mapping is no longer possible after mastectomy, avoids the need for axillary dissection if invasive cancer is identified.

RADIATION THERAPY FOR BREAST CANCER

After Breast-Conserving Surgery

For patients with invasive breast cancer treated with breast-conserving surgery, adjuvant radiation to the breast has been conclusively demonstrated to reduce the probability of a breast recurrence and improve outcome. The EBCTCG has published a meta-analysis of the data from 7300 women who participated in randomized trials of breast-conserving surgery, with or without radiation therapy.[29] In this analysis, radiation was found to reduce the 10-year rate of in-breast recurrence from 29% to 10% for patients with negative lymph nodes and from 47% to 13% for patients with positive lymph nodes. Importantly, this improvement in local control led to a reduction in the 15-year breast cancer mortality and overall death rate. On the basis of these data, radiation treatments should be considered as a standard. Most trials attempting to define subgroups who could potentially avoid radiation after lumpectomy have been unsuccessful, with the one potential exception of patients older than 70 years who undergo lumpectomy and adjuvant hormonal therapy for a stage I ER-positive breast cancer.[30]

Historically, radiation treatments after lumpectomy have consisted of a 6- to 8-week treatment course, which can be a hardship for patients. An important Canadian trial was successful in comparing a more abbreviated whole-breast irradiation treatment schedule. Based on long-term outcome results from this study, it is reasonable to treat a postmenopausal patient with a non– high-grade, estrogen receptor–positive, stage I breast cancer with a 16-fraction course of treatment, shortening the overall treatment time to approximately 3 weeks. In addition to this approach, there has been significant interest in shortening the treatment course to 1 week or less but focusing the radiation treatment exclusively to the area around the tumor bed. This approach, called *partial-breast irradiation*, may be performed with brachytherapy catheters, balloon catheters, or external beam radiation. Results from large phase III clinical trials comparing this approach with conventional whole breast treatment have yet to mature. Nonetheless, the approach has proven to be popular with physicians and patients. Recently, the American Society for Radiation Oncology (ASTRO) published a consensus statement highlighting appropriate selection criteria that should be considered if patients are to be treated with this approach outside the context of a clinical trial.[31]

Postmastectomy Radiation Therapy

For patients with T1N0 or T2N0 breast cancer, mastectomy and sentinel lymph node dissection provide effective local control and radiation therapy is not required.[32] In contrast, it is clear that patients with stage III breast cancer have high rates of locoregional recurrence after treatment with a modified radical mastectomy and adjuvant or neoadjuvant chemotherapy. Clinical trial data indicate that postmastectomy radiation can significantly improve the outcome of patients who have a 20% to 40% risk of locoregional recurrence.

Three prospective randomized trials have addressed the role of postmastectomy irradiation. In the Danish Trials, premenopausal women with stage II or III breast cancer were randomized to chemotherapy alone or chemotherapy plus chest wall and nodal irradiation (protocol 82b); postmenopausal women were randomized to tamoxifen alone or tamoxifen plus radiation therapy (protocol 82c).[33] In the British Columbia study, premenopausal women with node-positive breast cancer were randomized to chemotherapy alone or chemotherapy plus chest wall and nodal irradiation.[34] In addition to the expected benefit in reducing locoregional recurrences, postmastectomy irradiation also resulted in a significant improvement in overall survival in all three trials (Table 36-9). In 2005, the EBCTCG published the results of their meta-analysis of postmastectomy radiation trials, which included data from 9933 patients treated with mastectomy or axillary clearance, with or without postmastectomy radiation.[32] Postmastectomy radiation therapy decreased the 15-year isolated locoregional recurrence rate for patients with lymph node–positive disease from 29% to 8% and reduced the 15-year breast cancer mortality rate from 60% (no radiation) to 55% (radiation). The most recent analysis from this group has suggested that similar benefits are noted for patients with one to three positive lymph nodes as those with four or more positive lymph nodes.

There is consensus that patients with four or more positive lymph nodes, or other features that lead to stage III disease, should be recommended to receive radiation. However, the use of postmastectomy radiation for patients with stage II disease is controversial. This is because a number of U.S. series have indicated that locoregional recurrence rates after a standard modified radical mastectomy and adjuvant chemotherapy are only 12% to 15%, much lower than that reported in the clinical trials and the EBCTCG meta-analysis. Based on this disparity, it is reasonable to consider postmastectomy radiation only for selected patients with stage II disease, such as those with extracapsular extension, lymphovascular space invasion, age 40 years or younger, close surgical margins, a nodal positivity ratio of 20% or greater, and those patients who have undergone less than a standard axillary level I or II dissection.

Table 36-9 Trials of Systemic Therapy With or Without Irradiation After Mastectomy

	No. of Patients			Local Recurrence Rate (%)			Overall Survival (%)		
TRIAL	SYSTEMIC THERAPY + XRT	SYSTEMIC THERAPY ALONE	TOTAL	SYSTEMIC THERAPY + XRT	SYSTEMIC THERAPY ALONE	*P* VALUE	SYSTEMIC THERAPY + XRT	SYSTEMIC THERAPY ALONE	*P* VALUE
DBCG 82b (10 yr; chemo)[a]	852	856	1708	9	32	<0.001	54	45	<0.001
DBCG 82c (10 yr; tamoxifen)[b]	686	689	1375	8	35	<0.001	45	38	0.03
DBCG 82c (combined 18 yr)	1538	1545	3083	14	49	<0.001	37	27	
British Columbia Trial (20 yr)[c]	164	154	318	13	25	0.003*	64	54	0.003*

chemo, Chemotherapy; *DBCG,* Danish Breast Cancer Group; *XRT,* radiation therapy.

*Aggregate *P* value for comparisons at various follow-up intervals; this is the 10-year result.

Data from the following sources:

[a]Overgaard M, Hansen Per S, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 337:949, 1997.

[b]Overgaard M, Jensen M-B, Overgaard J, et al: Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial. Lancet 353:1641, 1999.

[c]Ragaz J, Jackson S, Le N, et al: Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337:956, 1997.

SYSTEMIC THERAPY FOR BREAST CANCER

Despite advances in locoregional therapy, a significant proportion of women with breast cancer will develop metastatic disease within 5 to 10 years after diagnosis. For most patients who develop metastatic breast cancer, this is a fatal condition. A systemic approach of treatment with medications is used to treat and prevent recurrence of possible microscopic metastatic disease. For women with advanced stage IV breast cancer, systemic therapy is given in efforts to palliate symptoms from cancer and potentially to prolong survival. Current thinking places the metastatic event early in the progression of breast cancer, probably before initial clinical evaluation in most patients. This concept argues for a systemic approach to breast cancer, administered in concert with local treatment. The missing link is the ability to detect occult metastatic disease accurately and select appropriate patients to receive systemic treatment.

Goals of Therapy and Determination of Risk of Harm

For stages I to III invasive breast cancer, the goals of treatment for patients are curative. Treatment is considered in the context of the potential benefits of therapy based on reduction of risk of recurrence, as well as the potential harm of treatment. In addition, patient preferences are strongly considered when determining adjuvant therapy use. For some patients, their personal belief is that the reduction in risk of recurrence with therapy is not worth the adverse effects of the treatment, in particular for chemotherapy. Often, several long discussions regarding therapy are essential when determining the treatment that best suits an individual patient.

With increasing stage of disease is an associated increased risk in the development of systemic recurrence. Not only does the volume (extent) of disease present at diagnosis affect the risk of cancer recurrence, the biologic characteristics of an individual tumor also influence the risk of recurrence. The most commonly used biomarkers—ER, PR, and HER-2—affect prognosis and are also predictive of response to different therapies. In very general terms, tumors that have low levels of expression of estrogen and PR, as well as tumors with high levels of HER-2, are associated with worse cancer outcomes when compared with tumors that are strongly estrogen- and PR-positive and HER-2–negative or normal. For most patients, risk of recurrence is estimated based on population-based statistics. Current federal and international guidelines use stage and biologic characteristics in the development of treatment recommendations (Table 36-10).

Recently, multigene assays (e.g., 21-gene recurrence score assay and MammaPrint assay) have been developed in an attempt to identify a specific molecular phenotype of an individual patient's tumor and then to use this phenotype in predicting the response to therapy or provide information regarding prognosis.[35] For example, the Oncotype DX assay was developed from a candidate pool of 250 genes and narrowed to a specific 21-gene panel based on three independent studies of the candidate genes.[15] This assay was validated first in a patient population with ER-positive, lymph node–negative breast cancer (NSABP B-14). It was found to be prognostic in terms of estimating overall survival and predictive for benefits from differing therapies, with higher recurrence scores estimating increased benefit from chemotherapy and lower scores estimating lesser benefit from chemotherapy and increased benefit from endocrine therapy. This assay was also validated in subsequent studies. The Oncotype DX (21-gene recurrence score) assay is a tool available to assist clinicians in estimating the benefits of therapy for patients with lymph node–negative, ER-positive breast cancer.

Table 36-10 Decision Making for Medical Therapy

STAGE	MEDICAL THERAPY	COMMENTS
I (<1cm)		
Hormone receptor–positive	Endocrine therapy ± chemotherapy	Consider genomic testing
Hormone receptor–negative	Consider chemotherapy	
HER-2–positive	Strongly consider trastuzumab based chemotherapy	
I (>1cm)		
Hormone receptor–positive	Endocrine therapy ± chemotherapy	Consider genomic testing
Hormone receptor–negative	Chemotherapy	
HER-2–positive	Trastuzumab based chemotherapy	
II (LN negative)		
Hormone receptor–positive	Endocrine therapy ± chemotherapy	Consider genomic testing
Hormone receptor–negative	Chemotherapy	
HER-2–positive	Trastuzumab-based chemotherapy	
II (LN positive), III		
Hormone receptor–positive	Chemotherapy* + endocrine therapy	*Consider tumor grade; extent of disease; % HR positive; markers of proliferation (Ki67); patient health
Hormone receptor–negative	Chemotherapy	
HER-2–positive	Trastuzumab based chemotherapy	

LN, Lymph node.

*The decision to use chemotherapy in patients with hormone receptor-positive disease is multifactorial. Consideration should be given to grade, percent of cells that are hormone receptor positive, proliferative rate and overall patient health and co-morbidities.

There are areas of uncertainty regarding its use that are still under investigation. For patients with low-risk recurrence scores, chemotherapy appears to add marginal benefit on reducing the risk of distant recurrence, whereas high-risk recurrence scores are associated with marked benefit from chemotherapy. The magnitude of benefit from chemotherapy is uncertain, however, for the group with intermediate- risk scores and was the subject of a recently completed cooperative group trial (TAILORx). These assays are used in the context of patient characteristics (e.g., general health, age) and extent of disease (e.g., tumor size) and are not the sole determinants of the type of medical therapy prescribed. It is expected that as assays (currently available or under development) are evaluated further in clinical studies, their ability to tailor medical therapy to an individual will improve.

Adjuvant! Online (www.adjuvantonline.com) is an online tool that has been designed to help physicians determine the 10-year risk of recurrence and death caused by breast cancer for an individual patient. This validated tool also informs the clinician about how specific interventions, such as chemotherapy, hormone therapy, or a combination of the two, are expected to affect survival.[36] These estimates of prognosis are based largely on the SEER registry estimates. The primary factors incorporated in this model include age, comorbidity, estrogen receptor status, grade, tumor size, and nodal status. HER-2 status is not currently in the model but is expected to be added in future updated versions. Once the clinician inputs patient and tumor-related information, this online tool provides graphics to depict 10-year recurrence-free and overall survival estimates for an individual patient, as well as estimates adjusted for the use of chemotherapy and/or endocrine therapy.

The Adjuvant! Online program does have limitations because it is based on registry information and relapse data, and cause of death may be inaccurate from these registries. Also, it does not incorporate information about HER-2 positivity or risk-stratify for breast cancer in women younger than 35 years. In some cases, estimating recurrence and breast cancer–related death information with estimates of survival may be distressing to patients. However, the design does allow the physician and patient to have an interactive discussion regarding the risks and benefits of therapies, and how these therapies may affect risk of recurrence and death caused by breast cancer. Some newer additions to the website include diagrams and patient education tools that may enhance this dialogue.

Chemotherapy

Metastatic disease is the principal cause of death from breast cancer. Patients who benefit from chemotherapy or hormonal therapy do so because metastasis is prevented, cured, or delayed. The first prospective trials of systemic treatment combined oophorectomy, to deprive patients of estrogens, with radical mastectomy. Since these early trials, hundreds of prospective studies have involved thousands of women.

Medications used to treat early breast cancer have their foundation as treatment of advanced disease. In general, treatments that are used effectively to improve outcome for patients with incurable breast cancer are estimated to have increased impact on outcomes for patients with earlier stages of breast cancer, in whom smaller volumes of disease, and potentially less resistance to therapy, will be present. When medications are identified that improve outcomes for patients with incurable stage IV breast cancer, they are often brought forward into

clinical studies for earlier stages of disease. Chemotherapy is generally used with combinations of medications in an effort to take advantage of nonoverlapping toxicities and maximize different mechanisms of action in targeting tumor cells. The concept of using non–cross-resistant therapies (i.e., drugs with different mechanisms of action to overcome cancer cell resistance to therapy) has dominated the development of adjuvant (after surgery) and neoadjuvant (before surgery) chemotherapy regimens. The duration of therapy is usually somewhere between four and eight cycles of treatment, depending on which regimen is used. Longer durations of chemotherapy with the same agents (>6 months) have not improved survival and are no longer used.

The largest comprehensive analysis of the benefits of chemotherapy is from the EBCTCG. This group meets every 5 years to review outcome data from breast cancer trials conducted worldwide. The most recently available data regarding adjuvant chemotherapy was published in 2005[37] and summarizes data from randomized trials that were initiated by 1995. The authors presented data from trials evaluating adjuvant chemotherapy versus no chemotherapy (60 trials) as well as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)–type chemotherapy versus anthracycline-based chemotherapy (17 trials). For younger women (<50 years), polychemotherapy reduces the risk of death by 30% and the risk of relapse by 37% compared with the use of no chemotherapy. For women older than 50 years, a reduction in the risk of death (12%) and relapse (19%) was also seen, even though the magnitude of benefit was less.

The main classes of chemotherapeutics used to treat early-stage breast include anthracyclines (e.g., doxorubicin, epirubicin) and taxanes (e.g., paclitaxel, docetaxel). The anthracyclines, whose activity is via action as both a topoisomerase II inhibitor and antimetabolite, have high levels of activity in the treatment of breast cancer. When used for the treatment of metastatic breast cancer as a single agent, responses to therapy are generally seen in from 45% to 80% of patients. The EBCTCG analysis[37] noted that anthracyclines add additional benefit when compared with nonanthracycline, CMF-type therapies, with a 16% reduction of death and 11% reduction in the risk of recurrence. Anthracyclines are associated with the potential long-term toxicity of cardiomyopathy, which may lead to congestive heart failure, often many years after treatment. The risk of cardiac dysfunction from anthracyclines is dose-dependent and current anthracycline-containing chemotherapy regimens have a risk of cardiac dysfunction from 1.5% to 3%. An additional dangerous risk from anthracycline-based chemotherapy is the risk of the development of leukemia (<1%).

Taxanes (microtubule inhibitors) have significant activity in the treatment of metastatic breast cancer and are active not only in tumors previously unexposed to chemotherapy, but also active in anthracycline-resistant tumors. A number of clinical trials have evaluated the use of taxanes as treatment of early-stage breast cancer. A meta-analysis regarding the use of taxanes in 13 different studies has described improvement in both DFS (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.79 to 0.87; $P <$ .0001) and OS (HR 0.85; 95% CI 0.79-0.91; $P <$ .0001).[38] The antitumor activity of paclitaxel is dependent on the timing of delivery of therapy—that is, more frequent administration of paclitaxel improves outcomes.[39] The activity of docetaxel is less dependent on timing of treatment and is generally used on an every 3-week schedule of administration. Both taxanes, when given at their optimal dose and schedule, have shown equivalence in outcome, as noted in the ECOG 1199 trial. This study randomized patients with lymph node–positive breast cancer to receive paclitaxel or docetaxel weekly or every 3 weeks after completion of an anthracycline based regimen. Weekly paclitaxel and every 3-week docetaxel were associated with the most favorable outcomes in terms of disease control and adverse effects when compared with every 3-week administration of paclitaxel. The taxanes are associated with the potential permanent toxicity of peripheral neuropathy but do not cause long-term increased risk of second cancers and/or cardiac dysfunction.

A variety of chemotherapy regimens are used in the United States in the systemic treatment of breast cancer patients (Box 36-3). Selection of a specific chemotherapy regimen is based on the potential risks of the regimen in context of the benefits of therapy. For example, the third-generation anthracycline- or taxane-containing chemotherapy regimens are associated with an approximately 50% to 60% reduction in the risk of relapse. Each of these regimens has variable toxicities and clinicians tailor the regimen prescribed in an attempt to maximize benefit and minimize harm. Most chemotherapy regimens used in routine practice were investigated for patients with lymph node–positive disease; however, the proportional reduction in risk of recurrence is thought to be similar for patients with high-risk, lymph node–negative breast cancer. Several studies have specifically targeted this population and found benefit from chemotherapy. Retrospective analyses of clinical studies have suggested that anthracyclines may have limited benefit when used as treatment in hormone-receptor positive, HER-2 normal breast cancers. A recent clinical trial evaluated a taxane-only–based chemotherapy regimen (docetaxel, cyclophosphamide) in comparison to an anthracycline-based regimen (doxorubicin, cyclophosphamide)

BOX 36-3 Commonly Used Chemotherapy Regimens

Non–Trastuzumab-Based Regimens

AC (doxorubicin, cyclophosphamide)
TC (docetaxel, cyclophosphamide)
TAC (docetaxel, doxorubicin, cyclophosphamide)
Dose-dense chemotherapy: AC followed by paclitaxel, administration every 2 wk
AC followed by paclitaxel administered weekly
AC followed by docetaxel
FAC (5-fluorouracil, doxorubicin, cyclophosphamide)
FEC (5-fluorouracil, epirubicin, cyclophosphamide)
CMF (cyclophosphamide, methotrexate, 5-fluorouracil)
FAC or FEC followed by paclitaxel weekly or docetaxel

Trastuzumab-Based Regimens

AC followed by paclitaxel weekly + trastuzumab → trastuzumab maintenance
AC followed by docetaxel + trastuzumab → trastuzumab maintenance
TCH (docetaxel, carboplatin, trastuzumab) → trastuzumab maintenance
Chemotherapy followed by trastuzumab maintenance ERA

Neoadjuvant Therapy

Paclitaxel weekly + trastuzumab followed by FEC + trastuzumab

Adapted from Carlson RW, Allred DC, Anderson BO, et al: Breast cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 7:122, 2009.

in efforts to lower long-term toxicity risks to patients while maintaining anticancer activity.[40] The taxane-based regimen, TC, improved DFS and OS when compared with an anthracycline-based regimen, AC (DFS 86% TC versus 80% AC; HR, 0.67; 95% CI, 0.50 to 0.94; $P = .015$). In an ongoing clinical trial, the NSABP (B-46-I/07132) is comparing taxane-only based regimens against an anthracycline-taxane regimen and may further clarify the role of anthracyclines in more modern systemic therapy for breast cancer.

Chemotherapy is most commonly administered in the adjuvant setting following completion of surgery. There are theoretical advantages regarding delivery of chemotherapy prior to surgery (neoadjuvant setting), including the potential for encountering lower volume of microscopic metastatic disease, potential decrease in drug resistance by treating tumors before resistance has developed, intact vascular system, improved rates of breast conservation, and ability to evaluate the in vivo response to treatment. In theory, the ability to evaluate response to therapy may help avoid administration of ineffective therapy and allow the clinician to tailor individual therapy. Neoadjuvant chemotherapy does have potential disadvantages in terms of loss of prechemotherapy prognostic information (e.g., axillary lymph node status, actual invasive tumor size) as well as potential impact for decision making with respect to postmastectomy radiation therapy. Overall, however, a number of clinical trials have shown equivalence in survival for administration of therapy in the neoadjuvant setting versus the adjuvant setting. A meta-analysis of nine randomized studies ($N = 3946$) has shown equivalence in survival as well as locoregional recurrence for neoadjuvant versus adjuvant therapy.[41] In routine practice, neoadjuvant chemotherapy is used outside of clinical trials for patients with locally advanced or inoperable breast cancer, patients with inflammatory breast cancer, or those who might benefit from reduction of tumor size in an effort to enhance the ability to perform breast conservation. In general, chemotherapy regimens that are routinely used in the adjuvant setting may also be used in the neoadjuvant setting.

Trastuzumab-Based Chemotherapy Regimens

Trastuzumab is a humanized monoclonal antibody developed to target the extracellular domain of the HER-2 receptor. HER-2 gene amplification or protein overexpression occurs in approximately 25% to 30% of breast cancers. Amplification leads to protein overexpression, measured clinically by immunohistochemistry and scored on a scale from 0 to 3+. Alternatively, FISH directly detects the quantity of HER-2 gene copies, with a normal copy number of two. Research has shown that inhibition of the function of the HER-2 receptor–like protein slows the growth of HER-2–amplified tumors in laboratory models and in clinical trials. When used as a single agent for treatment of metastatic breast cancer, response is seen in approximately 30% of patients.

Combined with chemotherapy, trastuzumab is even more powerful in the preclinical setting, with biologic synergy seen with multiple agents. Trastuzumab-based chemotherapy regimens improve disease-free and overall survival for patients with metastatic disease. Given the promising activity seen for metastatic disease, a number of adjuvant studies and neoadjuvant studies were conducted and have demonstrated improved outcomes for patients with stages I to III breast cancer. The HERceptin Adjuvant (HERA) trial ($N = 5090$) enrolled patients with HER-2–positive breast cancers and randomized patients to trastuzumab (for 1 or 2 years) versus observation after completion of chemotherapy.[42] Data regarding 2 years of therapy is not yet available; however, when comparing 1 year of trastuzumab versus observation, trastuzumab reduced the risk of a breast cancer–related event by 46% (HR, 0.54; 95% CI, 0.43 to 0.67; $P < .001$) and improved overall survival by 34% (HR, 0.66; 95% CI, 0.47 to 0.91; $P < .0115$).

The NSABP B-31 and NCCTG-N9831 adjuvant trials were similar in study design; the results from both studies were combined for initial analysis.[43] Patients in the control arm of these studies received AC followed by paclitaxel. Trastuzumab was added in the experimental groups, either concurrently with paclitaxel or sequentially after the paclitaxel. The patients who received trastuzumab had a reduction in breast cancer–related events by 52% (DFS HR, 0.48; 95% CI, 0.39 to 0.61; $P < .001$). There was toxicity noted with the addition of trastuzumab and patients receiving trastuzumab-based therapy in NSABP B-31(AC followed by paclitaxel-trastuzumab) had an increased risk of cardiac dysfunction, with a 3-year event rate of 4.1% versus a control arm rate of 0.8%. Patients who initiated therapy with lower ejection fractions, who were older and/or had hypertension, were at highest risk of cardiac dysfunction. The BCIRG 006 trial used a nonanthracycline-containing regimen as one of its treatment groups and showed equivalence in outcome between AC followed by docetaxel-trastuzumab (AC→TH) versus docetaxel combined with carboplatin and trastuzumab (TCH).[44] Both treatment groups were superior in terms of DFS to the control group treatment of AC followed by docetaxel, with a HR of 0.61 (95% CI, 0.48 to 0.76; $P < .001$) for the AC→TH arm and a HR of 0.67 for the TCH group (95% CI, 0.54 to 0.83). Patients receiving TCH had markedly reduced cardiac toxicity (0.37%) versus the AC→TH arm (1.87%). Current and ongoing studies for patients with HER-2– positive disease are evaluating the tyrosine kinase inhibitor lapatinib as well as the trastuzumab-drug conjugate TDM1. Trastuzumab-based therapy has significantly changed outcomes for patients with what is considered an aggressive biologic subtype of breast cancer, and ongoing efforts to identify other targets to enhance therapy are underway.

Endocrine Therapy

One of the original targeted therapy approaches was the use of oophorectomy to reduce systemic estrogen production as a treatment for breast cancer. Most breast cancers (>60%) have the presence of the ER and/or PR; interruption of the production of estrogen or the ability of estrogen to interact with the ER has been associated with improved disease-free and overall survival for women with metastatic breast cancer. This therapeutic approach is associated with a generally favorable side effect profile with each class of agents when contrasted with the adverse effects from chemotherapy.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator that has antagonistic and weak agonistic effects. Clinical trials using tamoxifen as treatment for early-stage breast cancer began in the 1970s. In 2005, the EBCTCG meta-analysis reported data of more than 80,000 women treated in clinical studies.[37] Tamoxifen administered for 5 years was found to improve outcomes by

reducing the risk of recurrence of breast cancer for patients with hormone receptor–positive disease by 41% (recurrence rate ratio, 0.59; standard error [SE], 0.03). The risk of death from breast cancer was reduced by approximately one third (death rate ratio, 0.66; SE, 0.04). Tamoxifen was shown to be of benefit for premenopausal and postmenopausal women and has a similar magnitude of benefit for patients with lymph node–positive versus lymph node–negative disease. The duration of therapy with tamoxifen was also evaluated; 5 years of therapy were found to be superior to only 1 to 2 years of therapy in terms of breast cancer recurrence (15.2% proportionate reduction; $P < .001$) and death from breast cancer (7.9% proportionate reduction; $P = .01$). There is uncertain benefit of longer durations of tamoxifen beyond 5 years because the agonistic effects of tamoxifen become more profound and there is an increasing risk of adverse events. Results from NSABP B-14 have shown no improvement in disease-free or overall survival for 10 years of therapy with tamoxifen versus 5 years of tamoxifen treatment.

Tamoxifen causes reduction of cell proliferation and has direct antagonistic effects when combined with chemotherapy. SWOG 8814 has found that patients who receive concurrent tamoxifen with anthracycline-based chemotherapy have numeric but nonsignificant reductions in disease-free and overall survival.[45] Tamoxifen is generally a well-tolerated medication, with the most common side effect being hot flashes or vasomotor symptoms, occurring in less than 50% of patients treated. In postmenopausal women, the estrogen-like agonist effect of tamoxifen will improve bone density, whereas in premenopausal women the agent is antagonistic to bone health. Potentially serious but rare effects include increased risk of thromboembolic disease and uterine cancer.

Ovarian Ablation

The EBCTCG meta-analysis evaluated premenopausal women who were treated with ovarian ablation or suppression and found that this treatment approach reduces the risk of relapse and death from breast cancer.[37] When compared with the use of CMF chemotherapy, the use of ovarian ablation with goserelin as treatment for lymph node–positive, premenopausal stage II breast cancer resulted in equivalent outcome in terms of DFS (HR, 1.01; $P = .94$) and OS (HR, 0.99; $P = .94$). Even with this high level of activity, the optimal role for the use of the addition of ovarian ablation in addition to modern chemotherapy and/or other antihormone therapies is controversial and is the subject of ongoing clinical trials.

Aromatase Inhibitors

AIs block the conversion of the hormone androstenedione into estrone by inhibition of the aromatase enzyme. This enzyme is present in adipose tissue, breast tissue, breast tumor cells, and other sites. Multiple generations of medications that block the aromatase enzyme have been evaluated; however, less specific agents such as aminoglutethimide also suppress production of other hormones, and this is associated with unacceptable side effects. Selective or third-generation AIs purely block the final step conversion of hormones into estrogen and are not associated with the broad hormone suppression seen with earlier AIs. These agents, which include anastrozole, exemestane, and letrozole, are not able to suppress ovarian function completely in a premenopausal or perimenopausal woman and are restricted for use in postmenopausal women.

Several different trial designs have been used to evaluate AIs in the adjuvant setting. Direct comparisons of 5 years of a selective AI versus 5 years of tamoxifen have demonstrated improvement in cancer outcomes for anastrozole and letrozole.[46] The ATAC (***a***rimidex, ***t***amoxifen, ***a***lone or in ***c***ombination) trial has demonstrated that 5 years of anastrozole significantly improve DFS by 17% when compared with 5 years of tamoxifen (HR, 0.83; 95% CI, 0.73 to 94; $P = .05$). In addition to reducing the risk of distant recurrence (distant DFS HR, 0.86; 95% CI, 0.74 to 0.99; $P = 0.04$), anastrozole reduced the risk of the development of contralateral breast cancers by 42%.[46]

The selective AIs have also been evaluated when given sequentially for 2 to 3 years after the use of tamoxifen for 2 to 3 years compared with 5 years of tamoxifen treatment.[47] The use of all three modern AIs after 2 to 3 years of tamoxifen has shown improved cancer outcomes when compared with the use of tamoxifen alone. In addition, extended adjuvant therapy with 5 years of the AI letrozole after 5 years of tamoxifen was shown to improve outcome when compared with placebo. The use of letrozole versus placebo reduced the risk of breast cancer events by 43% ($P < .008$).

The ideal use of AIs in the treatment of postmenopausal breast cancer patients with ER-positive disease is not known. The risk of recurrence of ER-positive breast cancer persists beyond 5 years after diagnosis and there is significant interest in evaluating the extended use of antiestrogen therapy to lower the risk of recurrence. Ongoing studies are evaluating the extended use of AIs beyond 5 years, and even beyond 10 years. In addition, it is not clear whether tamoxifen is an essential component in the adjuvant treatment for the postmenopausal patient population. Given the multiple studies demonstrating consistently improved outcomes with the selective AIs, the American Society of Clinical Oncology (ASCO) released a clinical practice guideline in 2010, which stated that postmenopausal women should receive a selective AI at some point during their cancer therapy.[48] Selective AIs as a group have similar adverse effects, including hot flashes, vasomotor symptoms, joint symptoms, myalgias, bone loss, and vaginal dryness.

Summary of Medical Therapy for Early-Stage Breast Cancer

Most patients diagnosed with early stage (I to III) invasive breast cancer will be offered medical therapy in an effort to improve disease-free and overall survival. In addition, the use of antiestrogen therapy as treatment of hormone receptor–positive breast cancer will also act to help lower the risk of new breast cancers. The use of medical therapy is guided by tumor characteristics (e.g., stage, molecular markers), patient characteristics (e.g., age, general health, personal preferences), and a careful balance of benefits of therapy versus potential risks of treatment. As advances in molecular analysis of tumors progress, it is likely that treatment recommendations and options will be refined toward a patient's tumor profile and more general guidelines, as are currently used, will not be implemented as often.

Neoadjuvant Systemic Therapy for Operable Breast Cancer

Administration of systemic chemotherapy or hormonal therapy before surgery can result in a significant reduction in tumor size in 50% to 80% of patients with locally advanced breast cancer. This preoperative, or neoadjuvant, therapy can convert

inoperable tumors to operable ones, convert tumors that would require mastectomy to eligibility for lumpectomy, and shrink larger tumors to allow an improved cosmetic outcome with breast-conserving surgery. This approach also allows for the study of tumor biology via serial analysis of tumor tissue before, during, and after treatment and has been used to study the efficacy and mechanism of action of systemic therapy agents.

Several prospective randomized trials have evaluated the efficacy of chemotherapy and hormonal therapy administered before (neoadjuvant) versus after (adjuvant) definitive surgery. These studies all demonstrated increased rates of breast conservation with the use of systemic therapy before surgery. The NSABP B-18 trial included 1523 patients and found no survival advantage (or detriment) in patients who received preoperative doxorubicin and cyclophosphamide chemotherapy versus the same regimen delivered postoperatively. The breast conservation rate was higher in women completing preoperative chemotherapy, and in-breast recurrence after preoperative therapy was not significantly different from that in women who underwent lumpectomy before adjuvant chemotherapy. Response to preoperative therapy was found to correlate with prognosis. At 9 years of follow-up, the disease-free survival rate in patients achieving a complete pathologic response in the preoperative arm (no evidence of tumor at surgery) was 75%, as opposed to 58% in patients who had any residual invasive disease left after chemotherapy.

The neoadjuvant approach is now commonly used for operable patients who would require mastectomy but could become candidates for breast conservation if their primary tumor size could be reduced before surgery. By the end of systemic therapy, 10% to 15% of such patients will have complete resolution of their tumors by clinical examination and imaging but might have microscopic residual disease. Consequently, a metallic clip is placed at the primary tumor site under image guidance before initiating chemotherapy to allow identification of the original tumor site for excision.

Management of the axilla in patients undergoing neoadjuvant therapy has evolved. Some centers perform sentinel node surgery before neoadjuvant therapy in patients with clinically negative nodes to inform systemic and radiation therapy decisions. Advocates of sentinel node surgery before neoadjuvant chemotherapy cite concerns about lower rates of successful mapping and higher false-negative rates after neoadjuvant therapy. Other centers now favor sentinel node surgery after neoadjuvant therapy for any patient whose axilla is clinically negative after therapy to obtain more information about the status of the nodes after neoadjuvant therapy. Studies have now shown the status of the axillary nodes after chemotherapy to be the strongest predictor of outcome. In addition, the chemotherapy can eradicate microscopic disease in the regional nodes in up to 40% of patients, reducing the need for complete axillary lymph node dissection at the time of surgical intervention. Complete axillary dissection remains the standard for all patients receiving neoadjuvant therapy who have biopsy-proven, node-positive disease at initial presentation.

In practice, the neoadjuvant approach is used routinely for patients with inoperable locally advanced breast cancer, including those with inflammatory breast cancer, those with large, fixed, or erosive lesions not amenable to mastectomy, and those with advanced nodal disease that is fixed, bulky, or causing arm edema. Most of these patients will then undergo mastectomy, radiation therapy, and possibly additional systemic therapy. In this setting, neoadjuvant chemotherapy serves as a remarkable research platform, in which it is possible to learn more about tumor biology and drug responses in an expedited time frame as compared with the adjuvant approach, in which long-term survival is the end point. More recently, there has been much interest in treating operable patients in the neoadjuvant setting because the response to systemic therapy can result in improvements in the clinical management of these patients. Patient selection is based on tumor characteristics beyond tumor size alone and therapies are targeted to specific subtypes with the greatest potential for affecting locoregional and systemic outcomes. Patients are monitored carefully during treatment and the pathologic assessment of the regional nodes can guide clinicians in determining how much additional therapy is warranted after a complete response or residual disease.

There are some key concepts that have been gleaned from the results of neoadjuvant therapy trials completed over the last few years. First, the use of neoadjuvant chemotherapy as a research platform has led to the identification of patient and tumor characteristics that can predict response to therapy. This allows clinicians to define better the population of patients who are most likely to benefit from the use of neoadjuvant chemotherapy. The use of targeted therapies, such as trastuzumab, in combination with chemotherapy can be safely administered in the neoadjuvant setting in HER-2–positive breast cancer patients, resulting in markedly increased rates of pathologic complete response. In the context of targeted therapy, patients with ER-positive disease can be treated with endocrine therapy in the neoadjuvant setting with significant response rates and increased rates of breast-conserving surgery. This approach is optimal in postmenopausal women with ER-positive tumors for whom endocrine therapy provides more protection against risk of recurrence and of death caused by breast cancer over standard chemotherapy. Finally, as new and more targeted regimens have led to an increasing population of patients with a clinical complete response to neoadjuvant therapy, accurately assessing the residual tumor burden in the breast and regional nodes will become increasingly important in terms of defining prognosis and determining further therapy that is needed.

TREATMENT OF LOCALLY ADVANCED AND INFLAMMATORY BREAST CANCER

Patients with locally advanced breast cancer include those with large primary tumors (>5 cm), tumors involving the chest wall, skin involvement, ulceration or satellite skin nodules, inflammatory carcinoma, bulky or fixed axillary nodes, and clinically apparent internal mammary or supraclavicular nodal involvement (stages IIB, IIIA, and IIIB disease). Central to treatment is the concept that the disease is advanced on the chest wall, in regional lymph nodes, or both, with no evidence of metastasis to distant sites. These patients are recognized to be at significant risk for the development of subsequent metastases, and treatment must address the risk for local and systemic relapse. Experience before the 1970s demonstrated that surgery alone provided poor local control, with local relapse rates in the range of 30% to 50% and mortality rates of 70%. Similar results were reported when radiation therapy was the sole modality of treatment. Current management includes surgery, radiation therapy, and systemic therapy, with the sequence and extent of treatment determined by specifics of the patient's circumstance.

Inflammatory breast cancer remains the most aggressive subtype of breast cancer but fortunately is rare, constituting approximately 5% of all breast tumors. The hallmark of inflammatory breast cancer is diffuse tumor involvement of the dermal lymphatic channels within the breast and overlying skin, often without an underlying tumor mass. Inflammatory breast cancer is clinically manifested as erythema, edema, and warmth of the breast as a result of lymphatic obstruction. There may be no mammographic abnormality beyond skin thickening, and a palpable mass is not required for the diagnosis. The term *peau d'orange* is used to describe the orange peel appearance of the skin resulting from edema and dimpling at sites of hair follicles (see Fig. 36-5*D*). The history should describe a rapid onset of the disease, with progression over a period of weeks to 3 months. Neglected breast cancer primaries that lead to secondary inflammatory changes within the breast should not be categorized as inflammatory breast cancer. Inflammatory cancer is a clinical diagnosis and can occur with tumors of ductal or lobular histology. The pathologic hallmark of inflammatory cancer is the presence of tumor cells within dermal lymphatics, but this can be often missed because of sampling error and therefore is not a prerequisite to diagnosis. Axillary nodal metastases are common, and there is a significant risk for distant metastases.

Current treatment approaches emphasize aggressive use of combined-modality treatment, including neoadjuvant chemotherapy, mastectomy, and radiation therapy, with hormonal therapy in ER-positive tumors and trastuzumab for HER-2–positive tumors. The results of this multimodality treatment now show relapse-free survival rates of 50% or higher at 5 years as compared with a single-institution historical series showing a 7% 5-year survival rate in patients receiving less aggressive treatment.[49]

TREATMENT OF SPECIAL CONDITIONS

Breast Cancer in Older Adults

Several studies have explored options that reduce the extent of surgery and radiation therapy for older women with breast cancer. Two recent trials randomized older women to lumpectomy with or without irradiation. In the Cancer and Leukemia Group B (CALGB) 9343 trial,[30] 647 women 70 years or older with ER-positive tumors 2 cm or smaller and clinically negative nodes received lumpectomy and tamoxifen and were randomized to irradiation or no irradiation. At 5 years' follow-up, survival was identical, and the in-breast recurrence rate was only 4% in the no-radiation arm versus 1% in the radiation arm. The death rate from breast cancer was 1% at 5 years in this population, with a 17% death rate from other causes.

Fyles and associates have reported the results of a Canadian trial with more inclusive eligibility criteria in which 769 women aged 50 years or older with tumors up to 5 cm and positive or negative ER status were enrolled. All patients underwent wide excision, received tamoxifen, and were randomized to irradiation or no irradiation. Recurrence rates were significantly higher overall in patients who did not receive radiation therapy. However, in an unplanned analysis of a subset of 193 women older than 60, the local recurrence rate was only 1.2% without radiation versus no recurrences with radiation therapy.

These low rates of local recurrence and the significant rates of death from other comorbid conditions have led to the acceptance of wide excision and hormonal therapy without irradiation for selected older patients with small ER-positive tumors and clinically negative axillary nodes. Axillary surgery has been omitted in such patients in the past; however, sentinel node surgery can easily be incorporated, with minimal morbidity.

Paget's Disease

Paget's disease accounts for 1% or less of breast malignancies. It is characterized clinically by nipple erythema and irritation with associated pruritus and may progress to crusting and ulceration. The condition may spread outward from the nipple and onto the areola and surrounding skin of the breast (see Fig. 36-5). The differential diagnosis of scaling skin and erythema of the nipple-areola complex includes eczema, contact dermatitis, postradiation dermatitis, and Paget's disease. A biopsy of the skin of the nipple should be performed; a specimen containing Paget cells secures the diagnosis.

Pathologically, a Paget cell is a large, pale-staining cell with round or oval nuclei and large nucleoli located between the normal keratinocytes of the nipple epidermis. Paget cells spread into the lactiferous sinuses under the nipple and upward to invade the overlying epidermis of the nipple. Paget cells do not invade through the dermal basement membrane and therefore are categorized as carcinoma in situ.

More than 95% of patients with Paget's disease have an underlying breast carcinoma. Paget's disease may be accompanied by a palpable mass in just over 50% of patients. Invasive breast cancer will be identified in patients with a palpable mass and Paget's disease in over 90% of patients.

Treatment of Paget's disease includes mastectomy with axillary staging or wide local excision of the nipple and areola to achieve clear margins, axillary staging, and radiation therapy. For many patients, lumpectomy and irradiation will provide an acceptable cosmetic appearance and avoid the more extensive surgery of mastectomy and reconstruction. Nipple-areolar reconstruction can be performed 4 to 6 months following radiation therapy. For patients considering lumpectomy, thorough preoperative evaluation is required to rule out occult multicentric disease.

Male Breast Cancer

Breast cancer occurring in the mammary gland of men is infrequent; it accounts for 0.8% of all breast cancers, less than 1% of all newly diagnosed male cancers, and 0.2% of male cancer deaths. Annually, in the United States, 1500 new cases and 400 deaths are reported. The median age at diagnosis is 68 years, 5 years older than in women.

Risk factors include increasing age, radiation exposure, and factors related to abnormalities in estrogen and androgen balance, including testicular disease, infertility, obesity, and cirrhosis. Risk factors related to a genetic predisposition include Klinefelter's syndrome (47,XXY karyotype), family history, and *BRCA* gene mutations, particularly *BRCA2* mutations. Gynecomastia is not a risk factor.

Histologically, 90% of male breast cancers are invasive ductal carcinomas. Approximately 80% are ER-positive, 75% are PR-positive, and 35% overexpress HER-2. The remaining 10% are DCIS. Given the absence of terminal lobules in the normal male breast, lobular carcinoma, both invasive and in situ, is rarely seen.

Most men with breast cancer have a breast mass. The differential diagnosis includes gynecomastia, primary breast

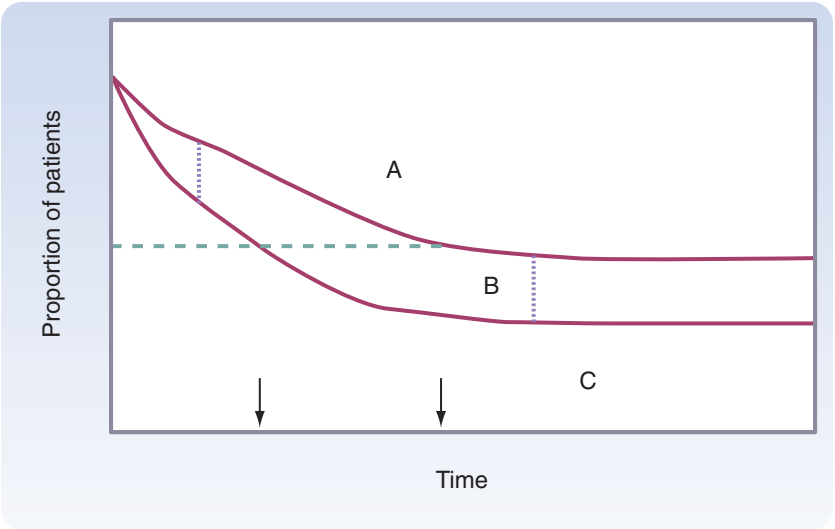

FIGURE 36-14 Interpretation of actuarial curves used in clinical trials comparing two groups of patients. See text for details.

carcinoma, metastatic carcinoma to the breast, sarcoma, and breast abscess. In addition to local pain and axillary adenopathy, other initial symptoms may include nipple retraction, ulceration, bleeding, and discharge. Evaluation includes breast imaging studies and diagnostic needle core biopsy.

Prognostic factors in male breast cancer are the same as in female breast cancer and include nodal involvement, tumor size, histologic grade, and hormone receptor status. When matched for age and stage, survival is similar to that in women.

Treatment of carcinoma in the male breast depends on the stage and local extent of the tumor, with treatment choices similar to those for women. Small tumors may be treated by local excision and irradiation or by mastectomy. Sentinel node biopsy has been shown to be effective for staging male breast cancer. Breast tumors in men more commonly involve the pectoralis major muscle, probably because breast tissue in men is scant. If the underlying pectoral muscle is involved, modified radical mastectomy with excision of the involved portion of muscle is adequate treatment and may be combined with postoperative radiation therapy.

Adjuvant systemic therapy for male breast cancer is used as for female breast cancer. Most male breast cancers are hormone receptor–positive. Adjuvant hormonal therapy with tamoxifen or AIs is indicated for node-positive and high-risk, node-negative patients. Adjuvant chemotherapy is used in men at substantial risk for metastatic disease.

INTERPRETING RESULTS OF CLINICAL TRIALS

Survival curves are the most familiar method of comparing groups of patients in randomized trials involving different therapies. To estimate the survival curve for any group of individuals, investigators use the life table method, also called the *actuarial method*. Kaplan and Meier proposed a popular modification of these general methods that suits clinical trials, and the resulting curves are often called *Kaplan-Meier curves*. This method tabulates the number of patients surviving as a proportion of the total number of patients reaching the interval of time in question after entering the trial. Survival or death is only one outcome that can be expressed in actuarial terms. Others include disease-free survival, event-free survival, and freedom from local failure, which can all be expressed in actuarial terms.

Comparisons between groups (e.g., treated versus control) can be described in several ways, each of which has limitations and ambiguities. As shown in Figure 36-14, the simplest way is to measure the absolute difference between the curves at any specified interval of time during follow-up, as demonstrated by the vertical dashed lines between the Kaplan-Meier curves. Alternatively, for any specific proportion of patients, there is a different time until relapse or death between the two curves, as shown by the horizontal dashed line in the figure. For example, the median survival time is the length of survival free of relapse or death for 50% of patients. Differences in median survival times between treated and control patients may be significant, even though absolute differences are small. For most treatment comparisons, there are three groups to consider. Some patients will remain free of recurrence or death with the control treatment, shown as the area under the lower curve (C). Other patients are destined to fail both the experimental and control treatments, shown as the area above the experimental curve (upper curve, A). It is only the patients falling between the two curves (B) who benefit (or are harmed) by the experimental treatment. The concept of proportional benefit is important when evaluating adjuvant chemotherapy or hormonal therapy for breast cancer; only a small proportion of treated patients benefit from receiving postoperative adjuvant treatments.

A popular way to express the difference between control and experimental groups is to cite the proportional reduction in treatment failures. For example, the proportional reduction in mortality is the difference in survival between the two groups at an interval divided by the percentage of patients who have died in the control group in the same interval. For the same proportional reduction in mortality, the absolute difference in survival varies greatly; it is generally larger for groups of patients with a higher risk of dying (e.g., node-positive versus node-negative patients). To calculate the proportional increase in survival, the absolute difference between the control and experimental curves in a specified interval is divided by the total surviving in the experimental group (assuming that it is larger). For groups with poor survival, small absolute differences lead to larger estimates of the percent increase in survival.

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