

## Breast

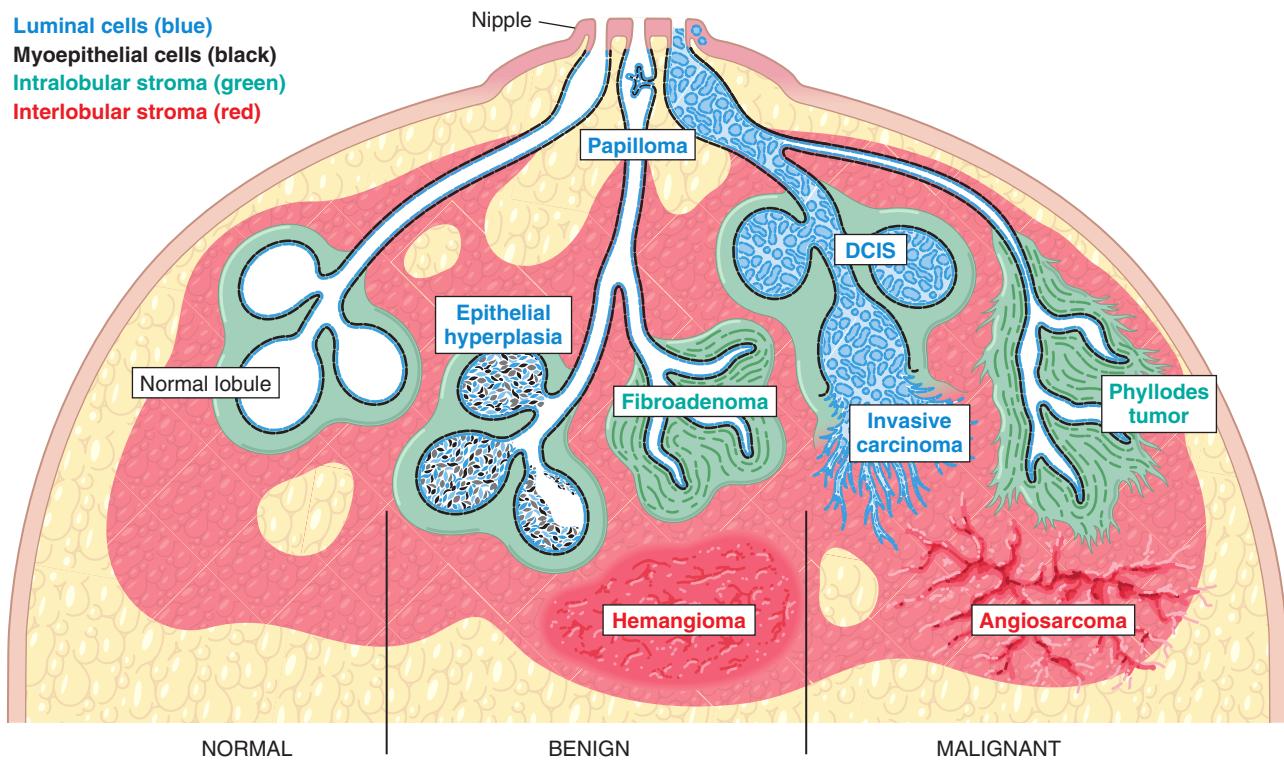
Three important features distinguish the breast from other organs. First, rather than being essential for survival, the major function is the nutritional support of another individual, the infant. Second, the structure of the organ undergoes marked changes throughout life: expansion of the lobular system after menarche, periodic remodeling during adulthood, especially during and after pregnancy, and ultimately involution and regression of lobules. Finally, breasts are visible and as a result have a social, cultural, and personal significance not shared by other organs. All of these features play a role when considering the origins, presentations, and treatment of breast disease.

The functional unit of the breast is the lobule, which is supported by a specialized intralobular stroma. The inner luminal epithelial cells produce milk during lactation. The basally located myoepithelial cells have contractile function to aid in milk ejection and also help support the basement membrane. The ducts are conduits for milk to reach the nipple. The size of the breast is determined primarily by interlobular stroma, which increases during puberty and involutes with age. Each normal constituent is a source of both benign and malignant lesions (Fig. 19.22).

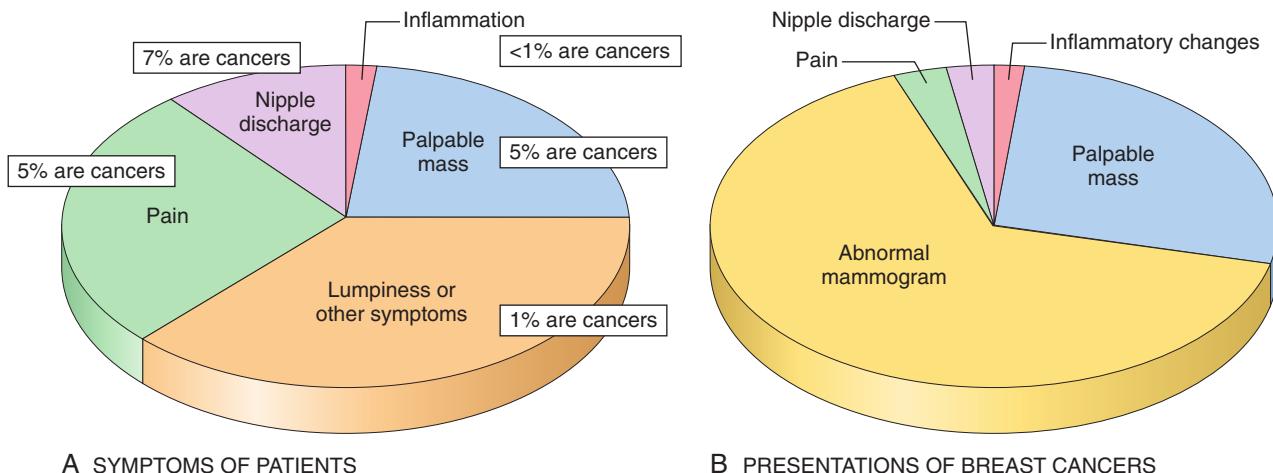
## CLINICAL PRESENTATIONS OF BREAST DISEASE

The predominant symptoms and signs of diseases of the breast are pain, inflammatory changes, nipple discharge, "lumpiness," or a palpable mass (Fig. 19.23A). However, few symptoms are so severe as to require treatment, and the primary reason for investigating their cause is to evaluate the possibility of malignancy. Most symptomatic breast lesions (>90%) are benign. Of women with cancer, about 45% have symptoms, whereas the remainder come to attention through screening tests (Fig. 19.23B).

- **Pain** (mastalgia or mastodynia) is a common symptom often related to menses, possibly due to cyclic edema and swelling. Pain localized in a specific area is usually caused by a ruptured cyst or trauma to adipose tissue (fat necrosis). Almost all painful masses are benign, but for unknown reasons a small fraction of cancers (about 10%) cause pain.
- **Inflammation** causes an edematous and erythematous breast. It is rare and is most often caused by infections, which only occur with any frequency during lactation and breastfeeding. An important mimic of



**Fig. 19.22** Origins of breast disorders. Benign epithelial lesions include intraductal papillomas that grow in sinuses below the nipple and epithelial hyperplasia that arises in lobules. Malignant epithelial lesions are mainly breast carcinomas, which may remain in situ or invade into the breast and spread by metastasis. Specialized intralobular stroma (green) cells may give rise to fibroadenomas and phyllodes tumors, whereas interlobular stroma (green) may give rise to a variety of rare benign and malignant tumors.



**Fig. 19.23** Presenting symptoms of breast disease. (A) Common breast-related symptoms that bring patients to clinical attention. (B) Presentations of breast cancer.

inflammation is “inflammatory” breast carcinoma (discussed later).

- *Nipple discharge* may be normal when small in quantity and bilateral. The most common benign lesion producing a nipple discharge is a papilloma arising in the large ducts below the nipple (Fig. 19.22). Discharges that are spontaneous, unilateral, and bloody are of greatest concern for malignancy.
- *Lumpiness*, or a diffuse nodularity throughout the breast, is usually a result of normal glandular tissue. When pronounced, imaging studies may help to determine whether a discrete mass is present.
- *Palpable masses* can arise from proliferations of stromal cells or epithelial cells and are generally detected when they are 2 to 3 cm in size (Fig. 19.22). Most (~95%) are benign; these tend to be round to oval and to have circumscribed borders. In contrast, malignant tumors usually invade across tissue planes and have irregular borders. However, because some cancers grow deceptively as circumscribed masses, all palpable masses require evaluation.
- *Gynecomastia* is the only common breast symptom in males. There is an increase in both stroma and epithelial cells resulting from an imbalance between estrogens, which stimulate breast tissue, and androgens, which counteract these effects.

Regardless of presenting symptom, the likelihood of malignancy increases with age. For example, the risk of nipple discharge being due to cancer increases from 7% in women younger than 60 years of age to 30% in women older than 60. Similarly, only 10% of palpable masses in women younger than 40 years of age are carcinomas, as compared to 60% in women older than 50.

Mammographic screening was introduced in the 1980s as a means to detect early, nonpalpable asymptomatic breast carcinomas before metastatic spread has occurred. Mammography has met this promise, as the average size of invasive carcinomas detected by mammography is about 1 cm (significantly smaller than cancers identified by palpation), and only 15% will have metastasized to regional

lymph nodes at the time of diagnosis. In the United States, most cancers in women more than 50 years of age are now detected by mammography (Fig. 19.23B). As with symptomatic breast lesions, the likelihood that an abnormal mammographic finding is caused by malignancy increases with age, from 10% at age 40 to more than 25% in women older than age 50.

## SUMMARY

### CLINICAL PRESENTATIONS OF BREAST DISEASE

- Symptoms affecting the breasts are evaluated primarily to determine if malignancy is present.
- Regardless of the symptom, the underlying cause is benign in the majority of cases.
- Breast cancer is most commonly detected by palpation of a mass in younger women and in unscreened populations and by mammographic screening in older women.

## INFLAMMATORY PROCESSES

Inflammatory diseases of the breast are rare and may be caused by infections, autoimmune disease, or foreign body-type reactions. Symptoms include erythema and edema, often accompanied by pain and focal tenderness. Because inflammatory diseases are rare, the possibility that the symptoms are caused by inflammatory carcinoma should always be considered (discussed later).

The only infectious agent to cause breast disease with any frequency is *Staphylococcus aureus*, which typically gains entry via fissures in nipple skin during the first weeks of breastfeeding. The invading organisms may lead to the formation of “lactational abscesses,” collections of neutrophils and associated bacteria in fibroadipose tissue. If untreated, tissue necrosis may lead to the appearance of fistula tracks opening onto the skin. Most cases are treated adequately with antibiotics and continued expression of milk. Rarely, surgical incision and drainage is required.

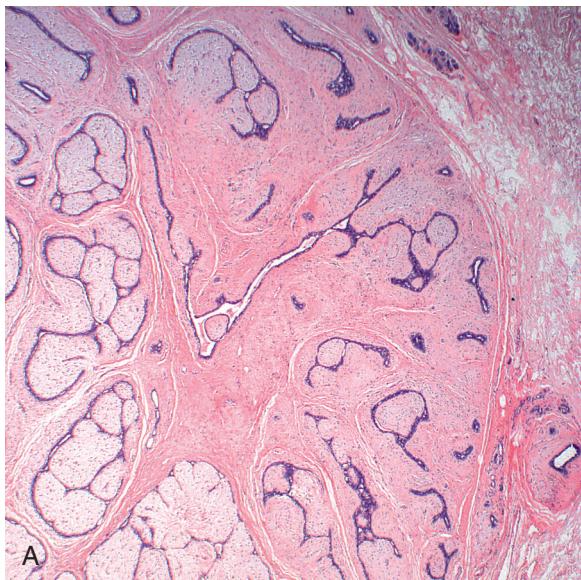
## STROMAL NEOPLASMS

The two types of stroma in the breast, intralobular and interlobular, give rise to different types of neoplasms (Fig. 19.22). Historically, tumors derived from intralobular stroma have been cleanly divided into benign fibroadenomas and more cellular phyllodes tumors, which sometimes recur following excision and rarely pursue a malignant course. It is now appreciated that these tumors share driver mutations in the same genes and appear to be part of a spectrum of related neoplasms. Nevertheless, the old classification is engrained in the medical lexicon and we will follow it here for simplicity's sake.

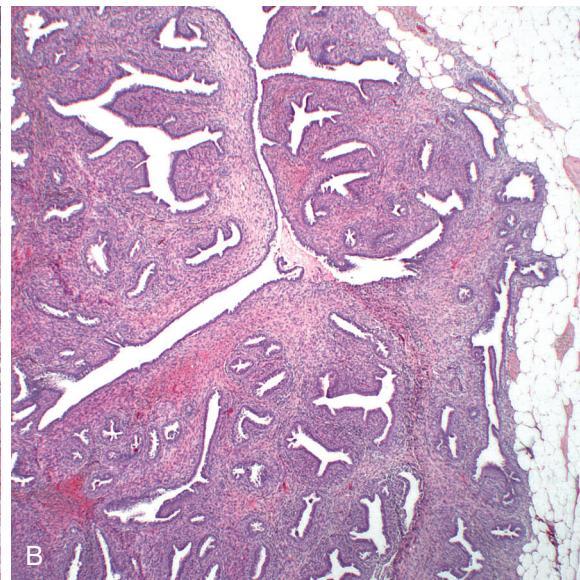
### MORPHOLOGY

Tumors derived from intralobular stroma are comprised of both stromal cells and epithelial cells (i.e., they are “biphasic”), as the neoplastic proliferation of specialized lobular fibroblasts also stimulates reactive proliferation of lobular epithelial cells. As the intralobular fibroblasts proliferate, they push and distort the epithelial cells so that they form elongated slitlike structures rather than round acini. In benign **fibroadenoma**, the tumor mass has circumscribed borders and low cellularity (Fig. 19.24A); mitoses are rare. By contrast, in **phyllodes tumors** the stromal cells tend to outgrow the epithelial cells, resulting in bulbous nodules of proliferating stromal cells that are covered by epithelium (Fig. 19.24B), the characteristic “phyllodes” (Greek for “leaflike”) growth pattern. In high-grade phyllodes tumors epithelium may be scant or absent, producing a sarcomatous appearance. Overall, about 2% of phyllodes tumors metastasize to distant sites.

Lesions of interlobular stroma are monophasic (only comprised of mesenchymal cells) and include benign soft tissue tumors found elsewhere in the body, such as hemangiomas (Chapter 10) and lipomas (Chapter 21). The only malignancy derived from interlobular stromal cells of note is angiosarcoma (Chapter 21), which may arise in the breast after local radiotherapy. The morphologies of these lesions are described elsewhere.



A



B

**Fig. 19.24** Intralobular stromal neoplasms. (A) Fibroadenoma. This benign tumor has an expansile growth pattern with pushing circumscribed borders. (B) Phyllodes tumors. Proliferating stromal cells distort the glandular tissue, forming cleftlike spaces, and bulge into surrounding stroma.

## BENIGN EPITHELIAL LESIONS

The majority of benign epithelial lesions are incidental findings detected by mammography. Their major clinical significance is their relationship to the subsequent risk of developing breast cancer. Benign changes are divided into three groups, *nonproliferative disease*, *proliferative disease without atypia*, and *proliferative disease with atypia*, each associated with a different degree of breast cancer risk (Table 19.6).

- Nonproliferative disease is not associated with an increased risk of breast cancer.
- Proliferative disease without atypia encompasses polyclonal hyperplasias that are associated with a slightly increased risk of breast cancer.
- Proliferative disease with atypia includes monoclonal “precancers” that are associated with a modest increase in the risk of breast cancer in both breasts; overall, 13% to 17% of women with these lesions develop breast cancer.

### MORPHOLOGY

**Nonproliferative disease** consists of three major morphologic changes: cysts, fibrosis, and adenosis. It is termed “nonproliferative” because the lesions contain single layers of epithelial cells. The most common nonproliferative breast lesions are simple cysts lined by a layer of luminal cells that often undergo apocrine metaplasia (Fig. 19.25A). The apocrine secretions may calcify and be detected by mammography. When cysts rupture, chronic inflammation and fibrosis in response to the spilled debris may produce palpable nodularity of the breast (so-called “fibrocystic changes”). **Proliferative disease without atypia** includes epithelial hyperplasia, sclerosing adenosis, complex sclerosing lesion, and papilloma. Each is associated with varying degrees of epithelial cell proliferation. For example, in epithelial

**Table 19.6 Factors Associated With Development of Invasive Carcinoma**

Factor	Relative Risk <sup>a</sup>	Absolute Lifetime Risk <sup>a</sup>
Women with no risk factors	1.0	3%
First-degree relative(s) with breast cancer <sup>b</sup>	1.2–9.0	4%–30%
Germline tumor suppressor gene mutation (e.g., <i>BRCA1</i> mutation)	2.0–45.0	6% to >90%
<b>Menstrual History</b>		
Age at menarche <12 years	1.3	4%
Age at menopause >55 years	1.5–2.0	5%–6%
<b>Pregnancy</b>		
First live birth <20 years (protective)	0.5	1.6%
First live birth 20–35 years	1.5–2.0	5%–6%
First live birth >35 years	2.0–3.0	6%–10%
Never pregnant (nulliparous)	3.0	10%
Breast-feeding (slightly protective)	0.8	2.6%
<b>Benign Breast Disease</b>		
Proliferative disease without atypia	1.5–2.0	5%–6%
Proliferative disease with atypia (ALH and ADH)	4.0–5.0	13%–17%
Carcinoma in situ (ductal or lobular)	8.0–10.0	25%–30%
Ionizing radiation	1.1–1.4	3.6%–4.6%
Mammographic density	3.0–7.0	10%–23%
Postmenopausal obesity and weight gain	1.1–3.0	3.6%–10%
Postmenopausal hormone replacement	1.1–3.0	3.6%–10%
Alcohol consumption	1.1–1.4	3.6%–4.6%
Alcohol consumption	1.1–1.4	3.6%–4.6%

<sup>a</sup>Relative risk is the likelihood of developing cancer compared to a woman with no risk factors—whose relative risk is 1.0. Absolute lifetime risk is the fraction of women expected to develop invasive carcinoma without a risk reducing intervention. For women with no risk factors, there is about a 3% chance of developing invasive breast cancer.

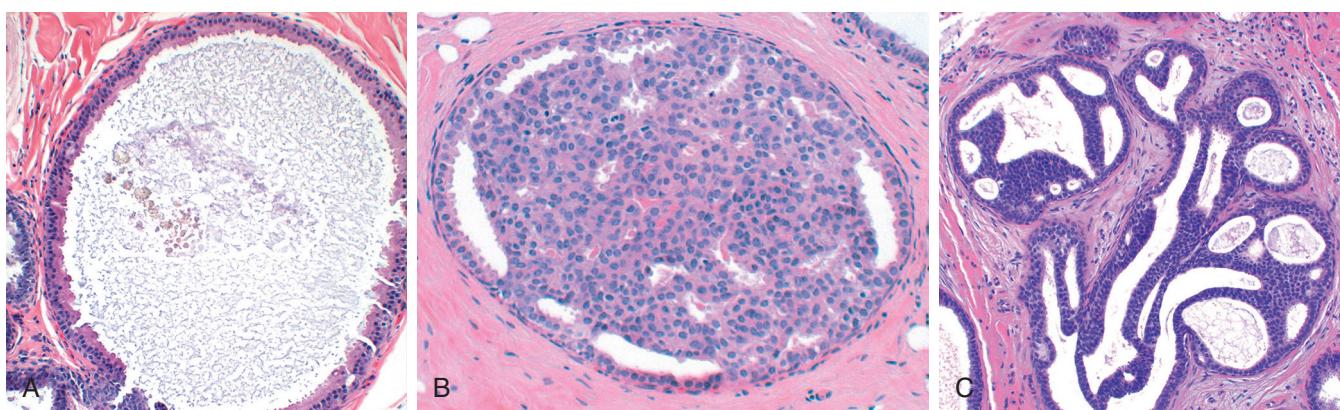
<sup>b</sup>The most common family history is a mother who developed cancer after menopause. This history does not increase the risk of her daughters.

hyperplasia, increased numbers of both spindled myoepithelial cells and epithelioid luminal cells expand ductal and lobular spaces (Fig. 19.25B).

**Proliferative disease with atypia** includes atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH). ALH closely resembles lobular carcinoma in situ (LCIS) and ADH closely resembles ductal carcinoma in situ (DCIS) (both described later), but are more limited in extent. The cells in ADH are uniform in appearance and form sharply marginated spaces or rigid bridges (Fig. 19.25C).

## CARCINOMA

Breast carcinoma is the most common malignancy of women globally (excluding nonmelanoma skin cancer) and causes the majority of cancer deaths in women. Although the incidence in the United States decreased slightly in 2002 and then stabilized (changes attributed to a decrease in the use of postmenopausal hormone therapy and a plateau in the number of women undergoing mammographic screening), the worldwide incidence



**Fig. 19.25** Benign epithelial breast disease. (A) Nonproliferative disease. An apocrine cyst is shown that is a common feature of nonproliferative breast disease. (B) Proliferative breast disease is characterized by increased numbers of epithelial cells, as in this example of epithelial hyperplasia. (C) Proliferative breast disease with atypia. The proliferating epithelial cells are monomorphic in appearance and pile up to form abnormal architectural structures.

and mortality is increasing at an alarming rate. The major factors underlying this trend in developing countries are thought to be social changes that increase breast cancer risk—specifically, delayed childbearing, fewer pregnancies, and reduced breastfeeding—combined with a lack of access to optimal health care.

The lifetime risk of breast cancer is 1 in 8 for women living to age 90 in the United States. It is predicted that about 250,000 breast cancers will be diagnosed in 2016 and about 40,000 women will die of the disease—a toll among cancers second only to lung cancer. Since the mid-1980s the mortality rate has dropped from 30% to less than 20%. The decrease is attributed to both improved screening, which detects some cancers before they have metastasized, and more effective systemic treatment.

Almost all breast malignancies are adenocarcinomas (>95%). In the most clinically useful classification system, breast cancers are divided based on the expression of hormone receptors—estrogen receptor (ER) and progesterone receptor (PR)—and the expression of the human epidermal growth factor receptor 2 (HER2, also known as ERBB2), into three major groups:

- ER positive (HER2 negative; 50%–65% of cancers)
- HER2 positive (ER positive or negative; 10%–20% of cancers)
- Triple negative (ER, PR, and HER2 negative; 10%–20% of cancers)

These three groups show striking differences in patient characteristics, pathologic features, treatment response, metastatic patterns, time to relapse, and outcome (Table 19.7 and Fig. 19.26). Within each group are additional histologic subtypes (discussed later), some of which also have clinical importance.

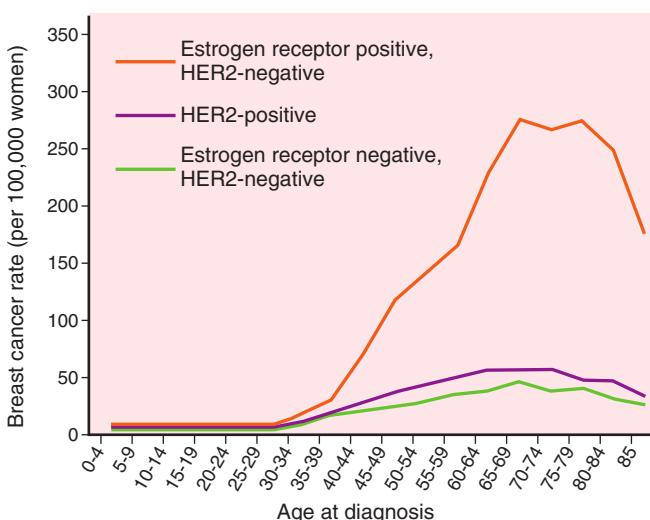


Fig. 19.26 Age and the incidence of breast cancer subtypes.

Table 19.7 Summary of the Major Biologic Types of Breast Cancer

Feature	ER Positive/HER2 Negative	HER2 Positive (ER Positive or Negative)	Triple Negative (ER, PR, and HER2 Negative)
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline BRCA2 mutation carriers	Young women; germline TP53 mutation carriers	Young women; germline BRCA1 mutation carriers
<b>Ethnicity</b>			
European/American	70%	18%	12%
African/American	52%	22%	26%
Hispanic	60%	24%	16%
Asian/Pacific Islander	63%	26%	11%
Grade	Mainly grade I and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	Low grade (<10%), higher grade (10%)	ER positive (15%), ER negative (>30%)	30%
Timing of relapse	May be late (>10 years after diagnosis)	Usually short (<10 years after diagnosis)	Usually short (<8 years after diagnosis)
Metastatic sites	Bone (70%), viscera (25%), brain (<10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Similar group defined by mRNA profiling	Luminal A (low grade), luminal B (high grade)	Luminal B (ER positive), HER2-enriched (ER negative)	Basal-like
Common special histologic types	Lobular, tubular, mucinous, papillary	Apocrine, micropapillary	Carcinoma with medullary features
Common somatic mutations	PIK3CA (40%), TP53 (26%)	TP53 (75%), PIK3CA (40%)	TP53 (85%)
PIK3CA encodes phosphoinositide 3-kinase (PI3K).			

## Epidemiology and Risk Factors

A large number of risk factors for breast cancer have been identified (Table 19.6). Some of the more important risk factors are summarized next.

**Age and Gender.** Breast cancer is rare in women younger than age 25, but increases in incidence rapidly after age 30 (Fig. 19.26); 75% of women with breast cancer are older than 50 years of age, and only 5% are younger than 40. The incidence in men is only 1% of that in women.

**Family History of Breast Cancer.** The greatest risk is for individuals with multiple affected first-degree relatives with early-onset breast cancer. In most families, it is thought that various combinations of low penetrance, "weak" cancer genes are responsible for increased risk. However, approximately 5% to 10% of breast cancers occur in persons who inherit highly penetrant germline mutations in tumor suppressor genes (discussed later). For these individuals, the lifetime risk of breast cancer may be greater than 90%.

**Geographic Factors.** Significant differences in the incidence and mortality rates of breast cancer have been reported in various countries. The risk is significantly higher in the Americas and Europe than in Asia and Africa. For example, the incidence and mortality rates are five times higher in the United States than in Japan. Some risk factors must be modifiable because migrants from low-incidence to high-incidence areas tend to acquire the rates of their new home countries. Diet, reproductive patterns, and breastfeeding practices are thought to be involved. In line with this, breast cancer rates appear to be rising in parts of the world that are adopting Western habits.

**Race/Ethnicity.** The highest rate of breast cancer is in women of European descent, largely because of a higher incidence of ER-positive cancers. Hispanic and African American women tend to develop cancer at a younger age and are more likely to develop aggressive tumors. Such disparities are thought to result from a combination of differences in genetics, social factors, and access to health care and are an area of intense study.

**Reproductive History.** Early age of menarche, nulliparity, absence of breastfeeding, and older age at first pregnancy are all associated with increased risk, probably because each increases the exposure of "at-risk" breast epithelial cells to estrogenic stimulation.

**Ionizing Radiation.** Radiation to the chest increases the risk of breast cancer if exposure occurs while the breast is still developing. For example, breast cancer develops in 25% to 30% of women who underwent irradiation for Hodgkin lymphoma in their teens and 20s, but the risk for women treated later in life is not elevated.

**Other Risk Factors.** Postmenopausal obesity, postmenopausal hormone replacement, mammographic density, and alcohol consumption also have been implicated as risk factors. The risk associated with obesity probably is due

to exposure of the breast to estrogen produced by adipose tissue. In keeping with this, obesity is only associated with an increased risk of tumors that express ER.

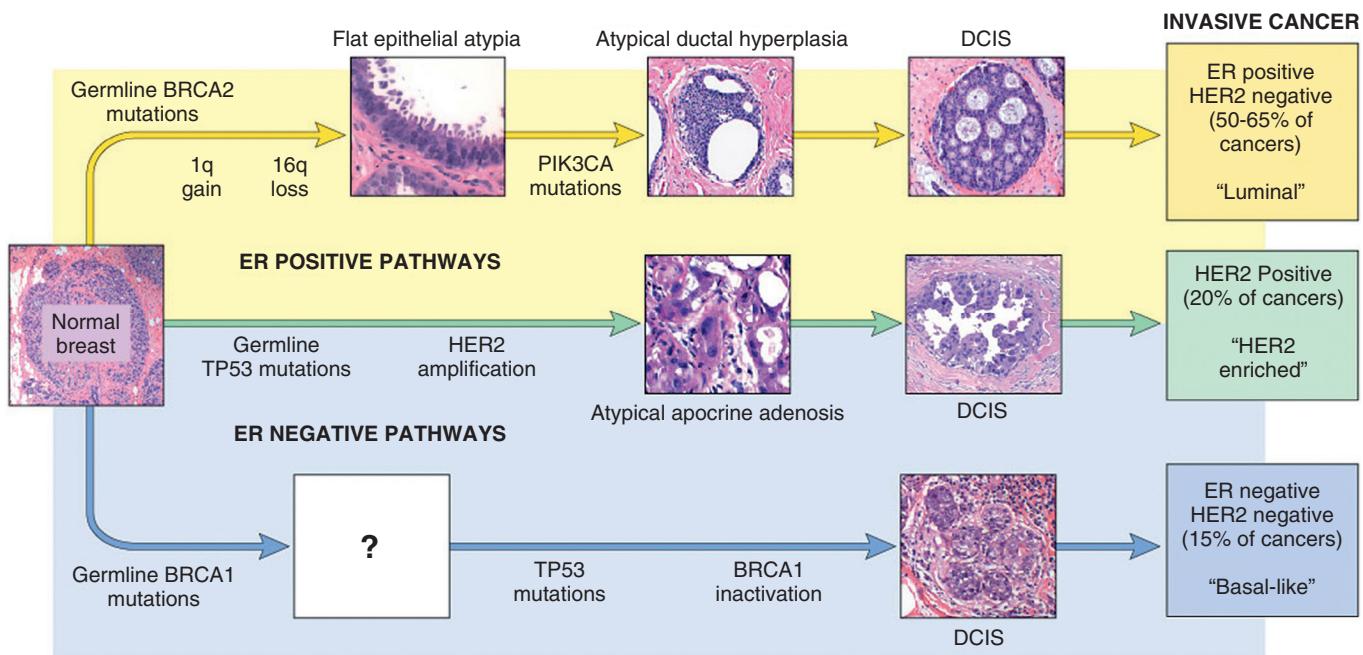
### Pathogenesis

The three major subtypes of breast cancer defined by differential expression of hormone receptors and HER2 arise through more-or-less distinct pathways that involve the stepwise acquisition of driver mutations in the epithelial cells of the duct/lobular system (Fig. 19.27). Factors that contribute directly to the development of breast cancer can be grouped into genetic, hormonal, and environmental categories.

**Genetic.** Driver mutations in cancer genes that contribute to breast carcinogenesis can be divided into those that are inherited and those that are acquired. The major germ-line mutations conferring susceptibility to breast cancer affect genes that regulate genomic stability or that are involved in pro-growth signaling pathways. *BRCA1* and *BRCA2* are classic tumor suppressor genes, in that cancer arises only when both alleles are inactivated or defective (Chapter 6). *BRCA1* and *BRCA2* encode proteins that are required for repair of certain kinds of DNA damage. They are normally expressed in many different cells and tissues, and why germline mutations in these genes lead mainly to an increased risk of breast and serous ovarian cancer (discussed earlier) remains mysterious. The degree of penetrance, age of onset, and susceptibility to other types of cancers differ among the many *BRCA1* and *BRCA2* germ-line mutations, but most carriers develop breast cancer by the age of 70 years, as compared to about 12% of women with an average risk of breast cancer. For unclear reasons, *BRCA2* mutations are primarily associated with ER-positive tumors, whereas *BRCA1* mutations show a strong association with triple-negative cancers (Fig. 19.27). Other mutated genes associated with familial breast cancer include *TP53* (the so-called "guardian of the genome", Chapter 6) and *PTEN* (an important negative regulator of the pro-growth PI3K-AKT pathway), already mentioned earlier as a risk factor for endometrial carcinoma as part of *Cowden syndrome*.

As might be expected, the pathways in which familial breast cancer genes function also are often disturbed in sporadic breast cancers. Somatic mutations in *BRCA1* and *BRCA2* are rare in sporadic cancers, but *BRCA1* is inactivated by methylation in up to 50% of triple-negative cancers. Somatic mutations in *TP53* are common in breast cancer, particularly triple-negative and HER2-positive tumors (Table 19.7), whereas mutations that activate PI3K-AKT signaling are frequently found in sporadic ER-positive and HER2-positive breast cancers (Fig. 19.27).

A common clinically important driver mutation in breast cancer is amplification of the HER2 gene. HER2 is a receptor tyrosine kinase that promotes cell proliferation and opposes apoptosis by stimulating the RAS- and PI3K-AKT signaling pathways. Cancers that overexpress HER2 are pathogenically distinct and highly proliferative. In the past they had a poor prognosis; however, the availability of therapeutic agents that specifically target HER2 has markedly improved the prognosis for patients with HER2-amplified tumors.



**Fig. 19.27** Major pathways of breast cancer development. The most common pathway (yellow arrow) leads to ER-positive cancers. Morphologically recognized precursor lesions include flat epithelial atypia, ADH, and DCIS, all of which share certain genomic events with invasive ER-positive carcinomas, such gains of chromosome 1, losses of chromosome 16, and mutations of *PIK3CA* (the gene encoding PI3K). By gene expression profiling, these cancers are classified as "luminal." This is the type of cancer that arises most commonly in individuals with germline *BRCA2* mutations. Less common are cancers that overexpress HER2 because of gene amplification (green arrow). These cancers may be positive or negative for ER and are usually associated with germline *TP53* mutations. A possible precursor lesion is atypical apocrine adenosis, which shares features with apocrine DCIS. The least common but molecularly most distinctive type of breast cancer is negative for ER and HER2 ("triple negative"; blue arrow). These cancers have loss of *BRCA1* and *TP53* function and are genetically unstable. The majority of triple-negative cancers are classified as "basal-like" by gene expression profiling.

**Hormonal Influences.** Estrogens stimulate the production of growth factors, such as transforming growth factor- $\alpha$ , platelet-derived growth factor, fibroblast growth factor, and others, which may promote tumor development through paracrine and autocrine mechanisms. In addition, ER regulates dozens of other genes in an estrogen-dependent fashion, some of which are important for tumor development or growth. Hormonal influences likely drive proliferation during the development of cancers from precursor lesions (which typically strongly express ER) to fully malignant and even metastatic carcinomas. The clearest measure of the importance of estrogen is found in the therapeutic benefits of estrogen antagonists, which reduce the development of ER-positive cancers in women at high risk and are mainstays in the treatment of established ER-positive tumors.

**Environmental Factors.** Environmental influences are suggested by the variable incidence of breast cancer in genetically homogeneous groups (e.g., Japanese women living in Japan and the United States) and the geographic differences in breast cancer incidence, as discussed earlier.

Breast cancers are classified morphologically according to whether they have penetrated the basement membrane. Those that remain within this boundary are termed *in situ carcinomas*, and those that have spread beyond it are designated *invasive carcinomas*. In this classification, the main forms of breast carcinoma are as follows:

- A. Noninvasive
  1. Ductal carcinoma *in situ*
  2. Lobular carcinoma *in situ*
- B. Invasive
  1. Invasive ductal carcinoma (includes all carcinomas that are not of a special type)—70% to 80%
  2. Invasive lobular carcinoma—~10% to 15%
  3. Carcinoma with medullary features—~5%
  4. Mucinous carcinoma (colloid carcinoma) — ~5%
  5. Tubular carcinoma—~5%
  6. Other types

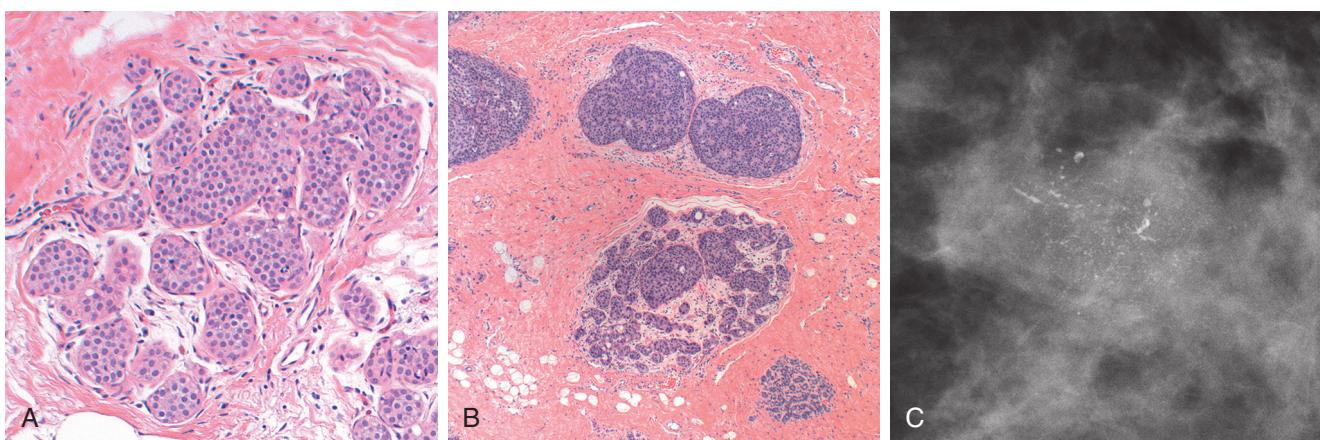
#### Noninvasive (*in Situ*) Carcinoma

There are two morphologic types of noninvasive breast carcinoma: ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS). The terms *ductal* and *lobular* are misleading, as both types of CIS are thought to arise from cells in the terminal duct that give rise to lobules. LCIS usually expands involved lobules (Fig. 19.28A), whereas DCIS distorts lobules into ductlike spaces (Fig. 19.28B). By definition, both "respect" the basement membrane and do not invade into stroma or lymphovascular channels.

**DCIS** has a wide variety of histologic appearances, including solid, comedo, cribriform, papillary, micropapillary, and "clinging"

#### MORPHOLOGY

The most common location of tumors within the breast is in the upper outer quadrant (50%), followed by the central portion (20%). About 4% of women with breast cancer have bilateral primary tumors or sequential lesions in the same breast.



**Fig. 19.28** Carcinoma in situ. (A) Lobular carcinoma in situ (LCIS). (B) Ductal carcinoma in situ (DCIS). DCIS partially involves the lobule in the lower half of this photo and has completely effaced the upper lobules, producing a ductlike appearance. (C) Mammographic detection of calcifications associated with DCIS.

types. Nuclear appearances range from bland and monotonous (low nuclear grade) to pleomorphic (high nuclear grade). The distinctive **comedo** subtype is characterized by extensive central necrosis, which produces toothpaste-like necrotic tissue that extrudes from transected ducts on application of gentle pressure. **Calcifications frequently are associated with DCIS** (Fig. 19.28C), resulting from calcification of necrotic debris or secretory material. DCIS constitutes only 5% of breast cancers in unscreened populations but up to 30% in screened populations, largely because of the ability of mammography to detect calcifications. Current treatment strategies for DCIS use surgery and irradiation to eradicate the lesion. Treatment with anti-estrogenic agents such as tamoxifen also is used to decrease the risk of recurrence of ER-positive DCIS. The prognosis is excellent, with greater than 97% long-term survival. If untreated, DCIS progresses to invasive cancer in roughly one-third of cases, usually in the same breast and quadrant as the earlier DCIS.

**Paget disease of the nipple** is caused by the extension of DCIS up the lactiferous ducts and into the contiguous skin of the nipple, producing a unilateral crusting exudate over the nipple and areolar skin. Unlike Paget disease of the vulva (described earlier), Paget disease of the nipple stems from *in situ* extension of an underlying carcinoma. The prognosis of the carcinoma of origin is affected by the presence of Paget disease and is determined by other factors (discussed under Clinical Features).

**LCIS** has a uniform appearance. The cells are monomorphic, have bland, round nuclei, and are found in loosely cohesive clusters within the lobules (Fig. 19.28A). LCIS is virtually always an incidental finding because, unlike DCIS, it is only rarely associated with calcifications. Therefore, the incidence of LCIS has remained unchanged in mammographically screened populations. Approximately one-third of women with LCIS eventually develop invasive carcinoma. Unlike DCIS, invasive carcinomas following a diagnosis of LCIS may arise in either breast— $\frac{2}{3}$  in the same breast and  $\frac{1}{3}$  in the contralateral breast. Thus, **LCIS is both a marker of an increased risk of carcinoma in both breasts and a direct precursor of some cancers**. Current treatment options include close clinical and radiologic follow-up, chemoprevention with tamoxifen or, less commonly, bilateral prophylactic mastectomy.

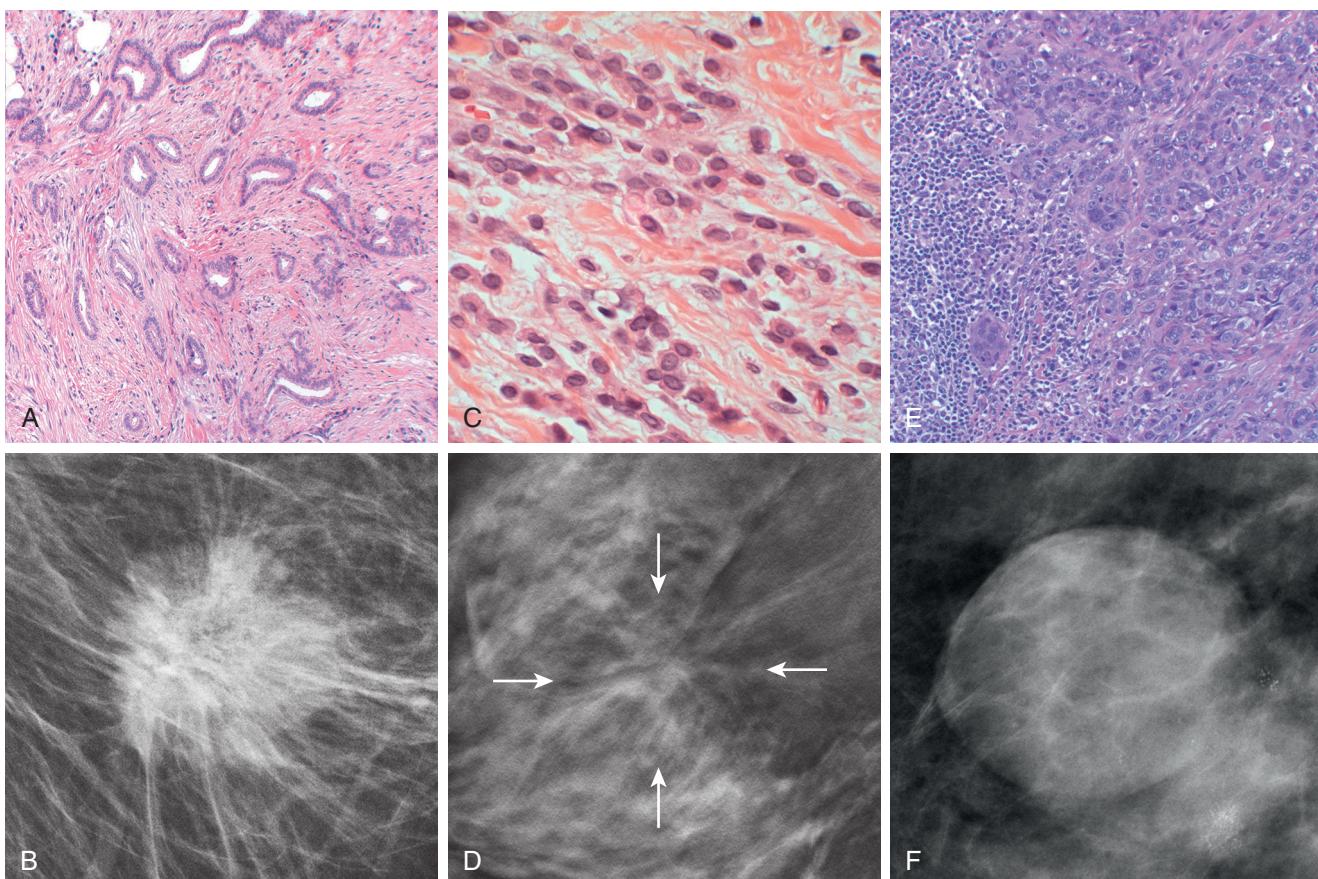
### Invasive (Infiltrating) Carcinoma

The distinctive histologic patterns of the subtypes of invasive carcinoma are described first, followed by grading, which is used for all.

**Invasive ductal carcinoma** is a term used for all carcinomas that cannot be subclassified into one of the specialized types described below. A majority (70%–80%) of cancers falls into this group. This type of cancer usually is associated with DCIS. The microscopic appearance varies, ranging from tumors with well-developed tubules and low-grade nuclei (Fig. 19.29A) to tumors consisting of sheets of anaplastic cells. Most invasive ductal carcinomas produce a desmoplastic response, which replaces normal breast fat (resulting in a mammographic density; Fig. 19.29B) and eventually leads to the appearance of a hard, palpable irregular mass. About 50% to 65% of ductal carcinomas are ER positive, 20% are HER2 positive, and 15% are negative for both ER and HER2 (Table 19.7).

**Invasive lobular carcinoma** consists of infiltrating cells that are morphologically similar to the tumor cells seen in LCIS; indeed, two-thirds of the cases are associated with LCIS. These tumors comprise 10% to 15% of all breast carcinomas. The cells invade stroma individually and often are aligned in “single-file” (Fig. 19.29C). Although most manifest as palpable masses or mammographic densities, a significant subgroup invade without producing a desmoplastic response; such tumors may be clinically occult and difficult to detect by imaging (Fig. 19.29D). The pattern of metastasis of lobular carcinoma is unique among breast cancers, as they frequently spread to cerebrospinal fluid, serosal surfaces, gastrointestinal tract, ovary, uterus, and bone marrow. Almost all lobular carcinomas express hormone receptors, whereas HER2 overexpression is rare.

**Carcinomas with medullary features** are a special type of triple-negative cancer comprising about 5% of all breast cancers. These carcinomas typically grow as rounded masses that can be difficult to distinguish from benign tumors on imaging (Fig. 19.29F). They consist of sheets of large anaplastic cells associated with pronounced lymphocytic infiltrates composed predominantly of T cells (Fig. 19.29E). The presence of lymphocytes is associated with a favorable prognosis, at least in part due to a better response to chemotherapy compared to poorly differentiated carcinomas without lymphoid infiltrates. This type



**Fig. 19.29** Growth patterns of invasive breast carcinomas. (A) Most grow as tubules (“ductal” carcinoma) and stimulate a reactive desmoplastic stromal proliferation. In mammograms (B), these carcinomas appear as dense masses with spicular margins resulting from invasion of adjacent radiolucent breast tissue. (C) Lobular carcinomas are composed of noncohesive tumor cells that invade as linear cords of cells and induce little stromal response. Accordingly, in mammograms (D) lobular carcinomas often appear as relatively subtle, irregular masses (arrows). (E) Uncommonly, carcinomas consist of tightly adhesive clusters of cells, as in this carcinoma with medullary features, or when there is abundant extracellular mucin production. (F) Such tumors may appear as well-circumscribed masses in mammograms, mimicking the appearance of a benign lesion.

of carcinoma is seen frequently in women with germline *BRCA1* mutations, but most women with these carcinomas are not carriers.

**Mucinous (colloid) carcinoma** is an ER-positive/HER2-negative tumor that produces abundant amounts of extracellular mucin. The tumors usually are soft and gelatinous because of the presence of mucin pools that create an expansile circumscribed mass.

**Tubular carcinoma** is another type of ER-positive/HER2-negative cancer and is almost always detected on mammography as a small irregular mass. The tumor cells are arranged in well-formed tubules and have low-grade nuclei. Lymph node metastases are rare, and the prognosis is excellent.

**Inflammatory carcinoma** is defined by its clinical presentation, rather than a specific morphology. Patients present with a swollen erythematous breast without a palpable mass. The underlying invasive carcinoma is generally poorly differentiated and diffusely infiltrates and obstructs dermal lymphatic spaces, causing the “inflamed” appearance; true inflammation is absent. Many of these tumors metastasize to distant sites; the overall 5-year survival is less than 50%, and understandably even lower in those with metastatic disease at diagnosis. About half express ER and 40% to 60% overexpress HER2.

All types of invasive breast carcinoma are assigned a grade from 1 (low-grade) to 3 (high-grade) based on nuclear pleomorphism, tubule formation, and proliferation. Low-grade nuclei are similar in appearance to the nuclei of normal cells. High-grade nuclei are enlarged and have irregular nuclear contours resulting from abnormal DNA content and structure. Most low-grade carcinomas form well-defined tubules and may be difficult to distinguish from benign lesions, whereas high-grade carcinomas lose this capacity and invade as solid sheets or single cells. Proliferation is evaluated by counting mitotic figures. The majority of HER2-positive and triple-negative carcinomas are highly proliferative, whereas ER-positive cancers show a wide range of proliferation.

### Clinical Features

As previously discussed, in unscreened populations (including young women, for whom screening is not indicated) most breast cancers are detected as a palpable mass by the affected patient. Such carcinomas are almost all invasive and are typically at least 2 to 3 cm in size. At least half of these cancers will already have spread to regional lymph nodes. In older screened populations,

approximately 60% of breast cancers are discovered before symptoms are present. About 20% are *in situ* carcinomas. Invasive carcinomas detected by screening in older women are 1 to 2 cm in size and only 15% will have metastasized to lymph nodes. Palpable cancers in the older age group are often “interval” cancers—cancers that appear suddenly between screening intervals. Understandably, interval cancers generally are highly proliferative and usually are high grade.

The clinical outcome for a woman with breast cancer can be predicted based on the molecular and morphologic features of the cancer and its stage at the time of diagnosis. Factors that influence outcome include the following:

- *Biologic type.* The biologic type of cancer is evaluated by a combination of histologic appearance, grade (including proliferative rate), expression of hormone receptors, and expression of HER2.

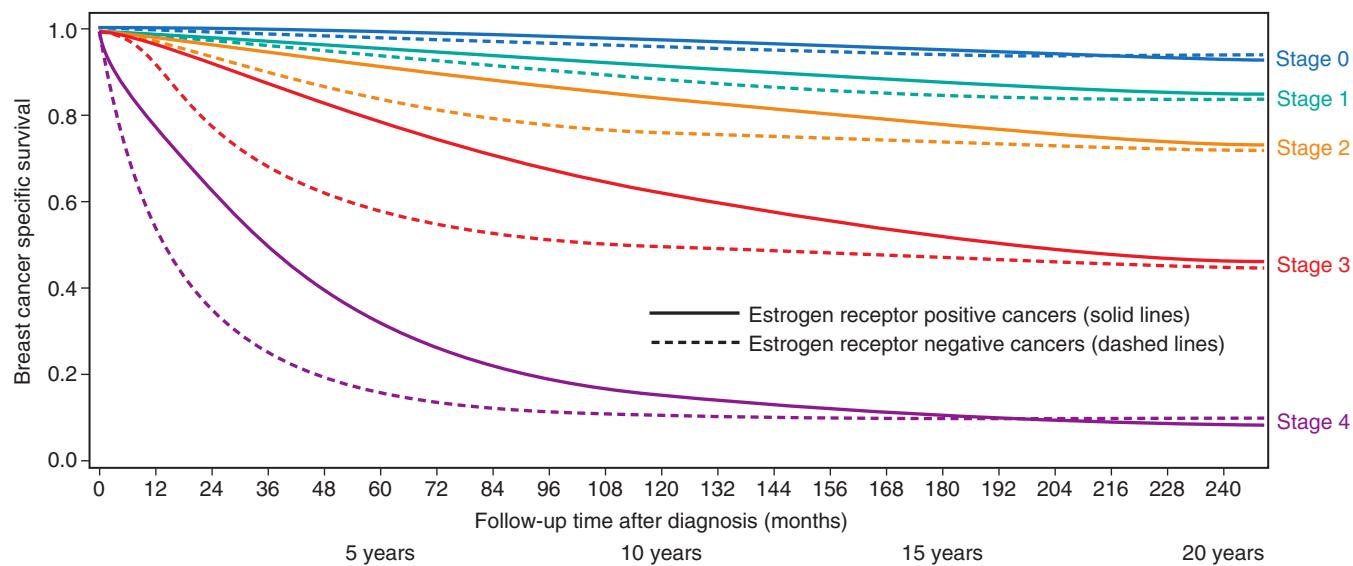
*Proliferation* is evaluated by mitotic count and is closely tied to responsiveness to cytotoxic chemotherapy. This is because rapidly growing cancer cells are more sensitive to agents that damage DNA or otherwise interfere with cell division.

*Expression of estrogen or progesterone receptors* predicts response to anti-estrogen therapy. The growth of hormone receptor-positive cancers can be inhibited for many years with therapy and it is possible for patients to survive for long periods with distant metastases. However, resistance often eventually develops—in some cancers because of mutations in the gene for ER. In contrast, there is no targeted therapy available for triple-negative cancers, which are treated with chemotherapy. Cancers that do not respond to initial therapy metastasize and usually cause the death of the patient.

*Overexpression of HER2* is seen in about 20% of breast cancers. HER2 remains one of the best-characterized examples of an effective therapy that is directed against a tumor-specific molecular lesion. Before targeted therapy, which may take the form of blocking antibodies or small

molecular inhibitors of HER2, outcomes were similar to patients with triple-negative carcinomas. However, complete response rates exceed 60% when targeted therapy is combined with chemotherapy, and the outlook for these patients has been markedly improved.

- *RNA expression profiling* is a newer method of subclassifying cancers. For breast cancers, many of the genes that predict prognosis are involved in proliferation. The greatest clinical value of these assays is their ability to identify patients with slow-growing, anti-estrogen-responsive cancers who can be spared the toxicity of chemotherapy.
- *Tumor stage.* “Stage” is a measure of the extent of tumor at the time of diagnosis and is important for all biologic types of carcinoma. It is based on features of the primary tumor (T), involvement of regional lymph nodes (N), and the presence of distant metastases (M) (Fig. 19.30). The AJCC/UICC staging system, used in the United States and Europe, classifies tumors as T1, T2, and T3 based on the tumor size, whereas T4 tumors have ulceration of the skin, involvement of the deep muscles of the chest wall, or are clinically diagnosed as inflammatory carcinoma. *The majority of cancers first metastasize to regional nodes*, and nodal involvement is a very strong prognostic factor. Lymphatic drainage goes to one or two sentinel lymph nodes in the axilla in most patients. If these nodes are not involved, the remaining axillary nodes are usually free of carcinoma. *Sentinel node biopsy* has become the standard for assessing nodal involvement, replacing more extensive lymph node dissections, which are associated with significant morbidity. *Distant metastases* (M) are only detected in 5% of newly diagnosed women. Stage 0 is CIS, which is associated with survival rates greater than 95%. Stage I includes women with smaller cancers and nodes either free of carcinoma or with only very small micrometastases. Survival is ~86% at 10 years. Carcinomas are classified as Stage II either because of larger tumor size or because of up to



**Fig. 19.30** Ten-year breast cancer specific survival according to AJCC stage for ER-positive and ER-negative cancers. Both stage and biologic type of cancer are important determinants of survival. ER-positive invasive cancers have improved survival over ER-negative cancers at all stages, but this advantage diminishes after 5 years because of late recurrences of ER-positive tumors. (Graph courtesy of Dr. Stephanie Wong; data from SEER-18, 1992–2012. <http://seer.cancer.gov>.)

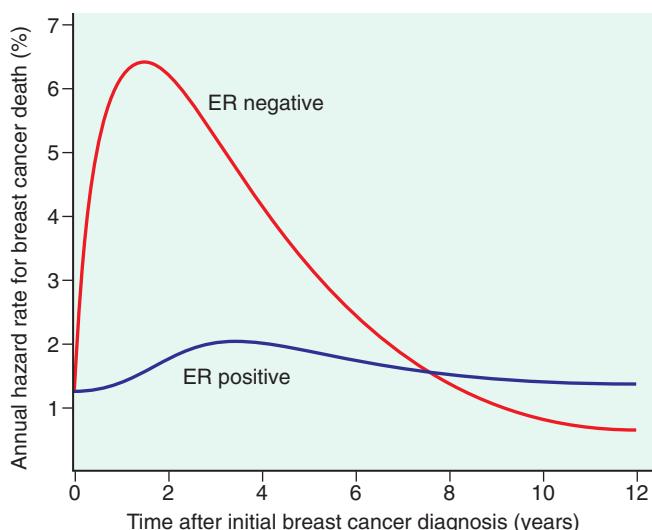
three positive nodes. Survival declines to ~71% at Stage II. Stage III is the group of locally advanced cancers defined by large size, involvement of skin or chest wall, or by four or more positive nodes. Only ~54% of patients survive 10 years. Stage IV is reserved for patients with distant metastases, and survival is very poor (~11%). The most likely site of a distant recurrence varies with the biologic type of cancer. Triple-negative cancers and HER2 cancers are more likely to metastasize to the brain and viscera, in contrast to ER-positive cancers, which most often metastasize to bones (Table 19.7).

Combining stage and biologic factors may provide a more accurate assessment of outcome. For example, for each cancer stage, the survival of patients with ER-positive cancers is higher than patients with ER-negative cancers 5 years postdiagnosis, especially for Stages III and IV (Fig. 19.30). It must be noted, however, this advantage diminishes with time, with progressively smaller differences being seen at 10 years post-diagnosis and beyond (Fig. 19.30). This narrowing of survival differences is explained by two factors. First, most deaths from ER-negative cancers happen within 5 years of diagnosis (Fig. 19.31). Women who live beyond this point are those whose tumors have had excellent responses to treatment, and many of these women may be cured. Second, although the growth of ER-positive cancers is held in check for years by anti-estrogen therapy, this therapy is not curative and these cancers may eventually become resistant to treatment.

Historically, virtually all women with untreated breast cancer died within 3 to 4 years. However, great strides have been made in treatment and now 80% of women with breast cancer who receive optimal therapy will survive.

Endocrine therapy with tamoxifen and aromatase inhibitors is very effective for ER-positive cancers, which may remain dormant for many years.

Targeted therapy has the promise of being more effective and less toxic than conventional chemotherapy (Table



**Fig. 19.31** Time to recurrence of breast cancers. The hazard ratio reflects the risk of recurrence of each molecular type of breast cancer at various points in time after diagnosis. ER-negative cancers usually recur within the first 8 years. Patients who survive beyond this interval are likely cured. In contrast, ER-positive cancers have a lower rate of recurrence, but remain at risk decades after the primary diagnosis.

**Table 19.8 Targeted Treatment of Breast Cancer**

Target	Treatment	Assay	Comments
ER	Estrogen deprivation (oophorectomy, aromatase inhibitors) Blockage of ER (tamoxifen)	IHC for nuclear ER	Effective cytostatic (but not cytotoxic) therapy for ER-positive cancer
HER2	Antibodies to HER2 Cytotoxic therapy linked to HER2 antibody Tyrosine kinase inhibitors	IHC for membrane HER2 ISH for HER2 gene amplification	Effective for HER2-positive cancers
Susceptibility to DNA damage resulting from BRCA 1 and BRCA2 mutations that cause defects in HRR	Chemotherapy with agents causing DNA damage that requires HRR (e.g., platinum agents) Inhibition of alternative DNA repair pathway (poly-ADP ribose polymerase or PARP inhibitors)	Sequencing of <i>BRCA1</i> and <i>BRCA2</i>	May be effective for carcinomas arising in patients with germline <i>BRCA1</i> or 2 mutations or cancers with somatic loss of BRCA function
PI3K/AKT pathway	Inhibition of proteins in the pathway	Activating mutations or pathway activation—not yet validated	>80% of breast cancers have alterations in this pathway Effectiveness of treatment not yet demonstrated
Immune checkpoint proteins	Blocking antibodies to PD-L1, PD-1, and other immune checkpoint proteins	IHC for immune checkpoint proteins—not yet validated	Under investigation in patients with triple-negative breast cancer

ER, Estrogen receptor; HRR, homologous recombination repair; IHC, immunohistochemistry; ISH, in situ hybridization.

## SUMMARY

### BREAST CARCINOMA

- The lifetime risk of developing breast cancer for an American woman is 1 in 8.
- A majority (75%) of breast cancers are diagnosed after the age of 50.
- The major risk factors for developing breast cancer are related to hormonal factors and inherited susceptibility.
- About 12% of all breast cancers are caused by identified germline mutations; *BRCA1* and *BRCA2* genes account for one-half of the cases associated with single-gene mutations.
- DCIS is a precursor to invasive ductal carcinoma and is most often found on mammographic screening as calcifications. When carcinoma develops in a woman with a previous diagnosis of untreated DCIS, it is usually is an invasive ductal carcinoma in the same breast.
- LCIS is both a marker of increased risk and a precursor lesion. When carcinoma develops in a woman with a previous diagnosis of LCIS, two-thirds are in the same breast and one-third is in the contralateral breast.
- Invasive carcinomas are classified according to histologic type and biologic type: ER-positive/HER2-negative, HER2-positive, and ER/PR/HER2-negative (triple-negative). The biologic types of cancer have important differences in patient characteristics, grade, mutation profile, metastatic pattern, response to therapy, time to recurrence, and prognosis.
- Prognosis is dependent on the biologic type of tumor, stage, and the availability of treatment modalities.

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