Rare variants of LCIS have high-grade nuclei and/or central necrosis. The cells may be ER negative and some overexpress HER2. The natural history of this type of LCIS is not well known and may well be different from typical LCIS.

Invasive (Infiltrating) Carcinoma

Invasive carcinomas can be divided based on molecular and morphologic characteristics into several clinically important subgroups. Breast carcinomas have a wide variety of morphologic appearances. One third can be classified morphologically into special histologic types, some of which are strongly associated with clinically relevant biologic characteristics (discussed later). The remainder are grouped together and called "ductal" or no special type (NST). Recent detailed description of genomic alterations and gene and protein expression in large cohorts of breast cancers has provided a framework for a molecular classification for this group of breast cancers (Fig. 23-20 and Table 23-3). These breast cancers fall into three major molecular subtypes, each with important associations with clinical features, response to treatment, and outcome (Table 23-3).

ER-positive, HER- negative (also termed "luminal," 50% to 65% of cancers) is the most common form of invasive breast cancer. Based on proliferation rates, it is further divided into two subgroups.

- **ER-positive, HER2-negative, low proliferation (40% to 55% of cancers): This group of breast cancers makes up the majority of cancers in older women and in men.** It is also the most common type detected by mammographic screening and in women treated with menopausal hormone therapy. The gene expression signature of this group of cancers is dominated by genes that are directly regulated by estrogen receptor. Many of these cancers are detected at an early stage. They have the lowest incidence of local recurrence and are often cured by surgery. When these carcinomas do metastasize, it is often after a long period of time (over 6 years) and typically to bone. They respond well to hormonal treatment and long survival with metastatic disease is possible, despite the fact that incomplete responses to chemotherapy are the rule. Indeed, in most patients chemotherapy appears to add little to hormone therapy, which is standard in this subtype of disease.
- **ER-positive, HER2-negative, high proliferation (approximately 10% of cancers):** Although these tumors are ER-positive, ER levels may be low and progesterone receptor expression may be low or absent. This is the most common type of carcinoma associated with *BRCA2* germline mutations. The mRNA expression pattern is similar to other ER-positive cancers, but there is higher expression of genes related to proliferation. These tumors tend to have a much higher burden of chromosomal aberrations than low-grade ER-positive tumors. However, unlike low-grade ER-positive cancers, about 10% of these carcinomas show a complete response to chemotherapy; such patients have a much better prognosis than patients with cancers that do not respond.

HER2-positive (approximately 20% of cancers) is the second most common molecular subtype of invasive breast cancer. About half of these cancers are ER-positive. When present, ER expression is usually low; progesterone receptor expression is often absent. These cancers are relatively more common in young women and in non-white women. More than half (53%) of familial breast cancers in patients with germline *TP53* mutations (Li-Fraumeni syndrome) develop carcinomas that are positive for both ER and HER2. The mRNA profile shows increased expression of *HER2* and flanking genes on the same amplicon, as well as genes related to proliferation. These cancers characteristically have complex interchromosomal translocations, high-level amplifications of *HER2*, and a high mutational load. Identification of cancers belonging to this subtype is achieved through assays of HER2 protein overexpression or *HER2* gene amplification (Fig. 23-21). Cancers in this

Table 23-3 Molecular Subtypes of Invasive Breast Cancer

Defining Features	ER-positive, HER2-negative		HER2-Positive (ER-Positive or Negative*)	ER-Negative† HER2-Negative
Frequency	~40-55% (Low proliferation)	~10% (High proliferation)	~20%	~15%
Included special histologic types	Well or moderately differentiated lobular, tubular, mucinous	Poorly differentiated lobular	Some apocrine	Medullary,‡ adenoid cystic,‡ secretory,‡ metaplastic
Typical patient groups	Older women, men, cancers detected by mammographic screening	*BRCA2* mutation carriers	Young women, non-white women, *TP53* mutation carriers (ER positive)	Young women, *BRCA1* mutation carriers, African American and Hispanic women
Metastatic pattern	Bone (70%), more common than visceral (25%) or brain (<10%)	Bone (80%) more common than visceral (30%) or brain (10%)	Bone (70%), visceral (45%),and brain (30%) are all common	Bone (40%), visceral (35%), brain (25%) are all common
Relapse pattern	Late, >10 years, long survival possible with metastases	Intermediate	Usually short, <10 years, survival with metastases rare	Usually short, <5 years, survival with metastases rare
Complete response to chemotherapy	<10%	~10%	ER positive—15% ER negative—>30%	~30%

*About half of HER2-positive cancers are ER positive and half ER negative. ER and PR levels tend to be low in this group.
†This group is also referred to as "triple negative" carcinoma.
‡Some special histologic types have a more favorable prognosis than this group as a whole.