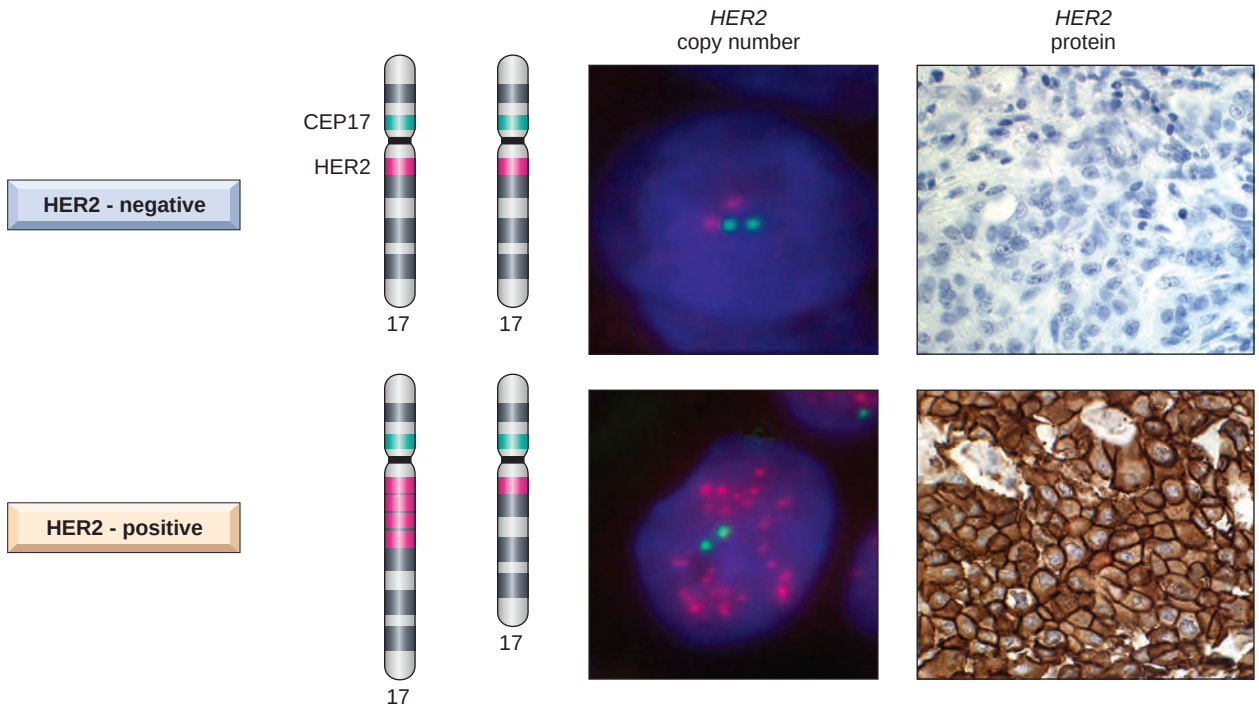

Figure 23-21 Identification of HER2-positive breast cancer. HER2 protein overexpression is virtually always caused by amplification of the region of chromosome 17q that contains the *HER2* gene. The increase in *HER2* gene copy number is detected by fluorescence in situ hybridization (FISH) using a *HER2*-specific probe (red signal), which is typically co-hybridized to tumor cell nuclei with a second probe specific for the centromeric region of chromosome 17 (green signal), allowing the chromosome 17 copy number to be determined. Alternatively, HER2 protein overexpression in tumor cells can be detected by immunohistochemical staining with antibodies specific for HER2.

group can metastasize when small in size and early in the course, often to viscera and brain.

Before the implementation of HER2-targeted therapy, HER2-positive cancers were associated with a poor clinical outcome. However, one third or more of these carcinomas respond completely to antibodies that bind and block HER2 activity, and such patients now have an excellent prognosis. The remarkable efficacy of this form of therapy proves the importance of HER2 as an oncogenic "driver."

While the introduction of trastuzumab (Herceptin), a humanized monoclonal antibody that specifically binds and inhibits HER2, markedly improved the outlook for patients with HER2 overexpressing cancers, not all HER2-positive carcinomas respond and some that do become resistant to treatment. Multiple mechanisms of primary or acquired resistance have been described. Some tumors express a truncated form of HER2 that lacks the trastuzumab-binding site but retains kinase activity, while others upregulate downstream pathways, such as the PI-3 kinase pathway. Numerous therapeutic agents are under investigation to improve response and overcome resistance to trastuzumab, including new antibodies that bind different HER2 epitopes; dual tyrosine kinase inhibitors that target both EGFR and HER2; antibody-toxin conjugates (one of which is now approved for use); and inhibitors of downstream signaling components, such as PI-3 kinase and AKT.

ER-negative, HER2-negative tumors ("basal-like" triple negative carcinoma; approximately 15% of cancers) are the third major molecular subtype. These cancers are more common in young premenopausal women as well as African American (20% to 25% of carcinomas in this group) and Hispanic women (17% of carcinomas in this group). The majority of carcinomas arising in women with *BRCA1* mutations are of this type. Due to high proliferation and rapid growth, this type of cancer is particularly likely to present as a palpable mass in the interval between mammographic screenings.

ER-negative, HER2-negative tumors are the most distinctive group of breast cancers. They share a number of genetic similarities with serous ovarian carcinomas, including the association of familial cancers of both types with germline *BRCA1* mutations. Nevertheless, in some cases features are present that overlap with other molecular subgroups. For example, about 10% of basal-like cancers (as defined by gene expression profiling) express ER and about 15% express HER2. Thus, assays for protein expression or gene amplification must be done to determine whether treatment targeting ER or HER2 is indicated. These cancers can metastasize when small in size, frequently to viscera and to the brain. However, approximately 30% completely respond to chemotherapy and cure may be possible in this chemosensitive subgroup. Recurrences are generally diagnosed within 5 years of treatment. Local recurrence is common, even after mastectomy. Prolonged survival after distant metastasis is rare.

MORPHOLOGY

Invasive carcinomas presenting on mammography as calcifications without an associated density are generally less than 1 cm in size. In the absence of mammographic screening, invasive carcinoma usually presents as a mass of at