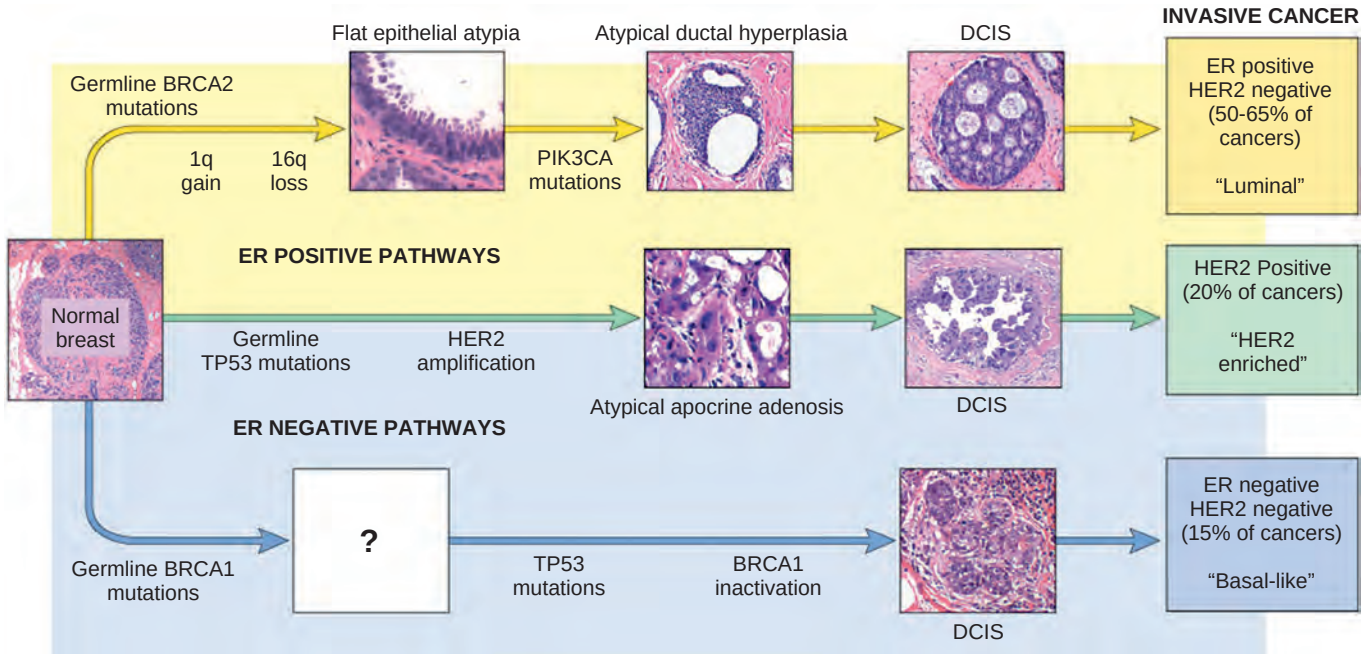

Figure 23-16 Major pathways of breast cancer development. Three main pathways have been identified. The most common pathway *(yellow arrow)* leads to ER-positive carcinomas. Recognizable precursor lesions include flat epithelial atypia and atypical hyperplasia. A less common pathway *(blue arrow)* leads to carcinomas that are negative for ER and HER2. The box with the question mark indicates that no precursor lesions have been identified—perhaps because lesions progress quickly to carcinoma. The third pathway *(green arrow)* consists of HER2-positive cancers, which may be ER-positive or ER-negative. Amplification of the *HER2* gene is also present in a subset of atypical apocrine lesions, which may represent a precursor lesion. Each molecular subtype has a characteristic gene expression profile termed luminal, HER2 enriched, and basal-like, respectively. See text for other details.

been described. These cancers have a distinct gene expression pattern that is dominated by genes related to proliferation that are regulated by signaling pathways lying downstream of the HER2 receptor tyrosine kinase.

- **ER-negative, HER2-negative cancers arise through a distinct pathway that is independent of ER-mediated changes in gene expression and HER2 gene amplifications.** Precursor lesions have yet to be described and as a result this is the least understood of the pathways. These tumors comprise about 15% of breast cancers overall, but are the most common tumor type observed in patients with germline *BRCA1* mutations; they also occur with increased frequency in African American women. Sporadic tumors of this type often have loss-of-function mutations in *TP53*; mutations in *BRCA1* are uncommon, but *BRCA1* may be silenced in sporadic tumors through epigenetic mechanisms. These tumors have a "basal-like" pattern of mRNA expression that includes many genes that are expressed in normal myoepithelial cells.

Deep sequencing of breast cancer genomes has been used to reconstruct the genetic events that occur during tumor development and progression. The most common driver mutations involve the proto-oncogenes *PIK3CA*, *HER2*, *MYC*, and *CCND1* (which encodes cyclin D1), and the tumor suppressor genes *TP53* and (in familial cancers) *BRCA1* and *BRCA2*. Once a founding tumor clone is established, subclonal heterogeneity arising by chance due to genomic instability undoubtedly contributes to both tumor progression and resistance to therapy. As with many solid tumors, the profound genetic heterogeneity of breast cancer is a major challenge to the success of therapy, as it increases the likelihood of emergence of more aggressive, therapy-resistant subclones.

Neoplastic epithelial cells do not develop in isolation, but are dependent on interactions with stromal cells in the local microenvironment. Cancers occur in the areas of greatest mammographic density, suggesting that increased amounts of fibrous stroma is both a marker of risk and biologically important for tumorigenesis. The role of stroma is not yet completely understood. The stroma is a complex mixture of fibroblasts, blood vessels, lymphatics, inflammatory cells, and extracellular matrix. Focal alterations in the stroma may play a direct role by creating a microenvironment conducive to tumor development and growth. Angiogenesis and tumor-associated inflammation are commonly associated with carcinoma, starting at the in situ stage. With better understanding of the role played by stroma, it may be possible to develop therapies that target stromal components.

The final step of carcinogenesis, the transition of carcinoma in situ to invasive carcinoma, is both the most important and the least understood. The majority of genetic changes observed in invasive carcinomas are already present in the associated carcinoma in situ (Fig. 23-16). It is possible that the same molecular events that allow for the normal formation of new ductal branch points and lobules during pregnancy—abrogation of the basement membrane, increased proliferation, escape from growth inhibition, angiogenesis, and invasion of stroma—may be replicated during invasion. Remodeling of the breast during post-pregnancy involution, which involves inflammatory and "wound healing-like" tissue reactions and is known to increase the risk of tumor invasion, may also facilitate the transition of carcinoma in situ to invasive carcinoma.