and inconsequential polymorphisms are common. As a result, genetic testing is difficult and generally restricted to individuals with a strong family history or those belonging to certain ethnic groups. For example, in Ashkenazi Jewish populations, about 1 in 40 individuals carry one of three specific mutations, two in *BRCA1* and one in *BRCA2*. Identification of carriers is important, since increased surveillance, prophylactic mastectomy, and salpingo-oophorectomy can reduce cancer-related morbidity and mortality.

BRCA1-associated breast cancers are commonly poorly differentiated, have "medullary features" (a syncytial growth pattern with pushing margins and a lymphocytic response, described later), and are biologically very similar to ER-negative/HER2-negative breast cancers identified as "basal-like" by gene expression profiling (described later), as well as to serous ovarian carcinomas (Chapter 22). *BRCA2*-associated breast carcinomas also tend to be relatively poorly differentiated, but are more often ER-positive than *BRCA1* cancers.

The remaining known susceptibility genes accounts for fewer than 10% of hereditary breast carcinomas (Table 23-2). Germline mutations in *TP53* (Li-Fraumeni syndrome) and mutations in *CHEK2* together account for about 8% of breast cancers caused by single genes. Three other tumor suppressor genes—*PTEN* (Cowden syndrome), *STK11* (Peutz-Jeghers syndrome), and *ATM* (ataxia telangiectasia)—are mutated in less than 1% of all familial breast cancers.

Most of these genes play complex and interrelated roles in maintaining genomic integrity. After a cell sustains DNA damage, it must undergo cell cycle arrest and either repair its DNA or die by apoptosis. ATM senses DNA damage and with p53 and CHEK2 induces cell cycle arrest. BRCA1, BRCA2, and CHEK2 all have important functions in repair of double stranded DNA breaks. If any of these functions are impaired, the likelihood that cells with permanent DNA damage will survive is increased and the mutation will be propagated.

Yet it must be admitted that it is unknown why malfunction of these genes, particularly *BRCA1* and *BRCA2*, is more highly associated with breast cancer than other cancers. BRCA1 and BRCA2 are part of a large complex of proteins that are required to repair double stranded DNA breaks through a process called homologous recombination, in which a normal sister chromatid is used as a template for repairing the broken stretch of DNA. BRCA1 and BRCA2 are expressed ubiquitously, so the link to breast cancer is not obviously explained by tissue-specific patterns of gene expression. An alternative possibility is that breast (and ovarian) epithelial cells may be particularly prone to suffer the type of DNA damage that BRCA1 and BRCA2 are required to repair. BRCA1 also interacts with protein complexes that regulate chromatin structure, and it remains possible that its tumor suppressive role involves functions that are independent of DNA repair.

Sporadic Breast Cancer

The major risk factors for sporadic breast cancer are related to hormone exposure: gender, age at menarche and menopause, reproductive history, breastfeeding, and exogenous estrogens. Other environmental risk factors, proven or suspected, include radiation exposure (discussed under risk factors) and exposure to chemicals with estrogen-like effects (Chapter 9).

Estrogen clearly functions as a promoter of breast cancers (Chapter 7), probably through several different effects on the breast. Hormonal exposure stimulates breast growth during puberty, menstrual cycles, and pregnancy, thereby increasing the number of cells that can potentially give rise to a cancer. The proliferation of breast epithelium during the menstrual cycle is also conducive to the accumulation of DNA damage, and the temporary lull in cell division that occurs during the latter part of the menstrual cycle may allow time for defective DNA repair to occur and for mutations to become "fixed" in the genome. Repeated rounds of this process during each cycle may underlie the association between the cumulative number of menstrual cycles a woman experiences and her risk of developing breast cancer. Once premalignant or malignant cells are present, hormones can stimulate their growth as well as the growth of normal stromal cells that may aid and abet tumor development.

Molecular Mechanisms of Carcinogenesis and Tumor Progression

The diverse histologic appearances of breast carcinomas and putative precursor lesions are the outward manifestations of the complex genetic and epigenetic changes that drive carcinogenesis. As with other cancers, resident breast tissue stem cells have been hypothesized to be the cell of origin for all breast cancers. Once the process is initiated in such cells by a driver mutation, there appear to be three major genetic pathways of carcinogenesis (Fig. 23-16).

- **ER-positive, HER2-negative cancers arise via the dominant pathway of breast cancer development, constituting 50% to 65% of cases.** This is the most common subtype of breast cancer in individuals who inherit germline mutations in *BRCA2*. They are often associated with gains of chromosome 1q, losses of chromosome 16q, and activating mutations in *PIK3CA*, a gene that encodes phosphoinositide-3 kinase (PI3K), which is an important component of signaling pathways downstream of growth factor receptors (Chapter 7). These same genetic lesions are often found in flat epithelial atypia and atypical ductal hyperplasia, which are hypothesized to be precursor lesions for this subtype of breast cancer. ER-positive cancers are termed "luminal," as these cancers most closely resemble normal breast luminal cells in terms of their mRNA expression pattern, which is dominated by genes that are regulated by estrogen. As discussed later, tumors arising through this pathway include at least two major molecular subtypes that differ in their proliferation rate and response to therapy.
- **HER2-positive cancers arise through a pathway that is strongly associated with amplifications of the HER2 gene on chromosome 17q.** They constitute approximately 20% of all breast cancers and may be either ER-positive or ER-negative. This is the most common subtype of breast cancer in patients with germline mutations in *TP53* (Li-Fraumeni syndrome). A putative precursor lesion termed atypical apocrine adenosis has