breast cancer risk are being investigated intensively, but definitive associations have yet to be made.

Etiology and Pathogenesis

Like other cancers, breast cancers are clonal proliferations that arise from cells with multiple genetic aberrations, acquisition of which is influenced by hormonal exposures and inherited susceptibility genes. Breast cancers may be hereditary, arising in women with germline mutations in tumor suppressor genes, or sporadic. However, environmental factors clearly influence the penetrance of hereditary forms of breast cancer, and both genetic and environmental factors contribute to sporadic forms of breast cancer. The identification of breast cancer susceptibility genes has provided important insights into the pathogenesis of both familial and sporadic forms of breast cancer. We begin our discussion with hereditary breast cancer and the major susceptibility genes.

Familial Breast Cancer

Approximately 12% of breast cancers occur due to inheritance of an identifiable susceptibility gene or genes. The probability of a hereditary etiology increases when there are multiple affected first-degree relatives, early onset cancers, multiple cancers, or family members with other specific cancers. As with other familial forms of cancer (Chapter 7), in some instances cancer risk is an autosomal dominant trait that is conferred by inheritance of a defective copy of a tumor suppressor gene. In such instances, a single sporadic mutation in the remaining normal allele is all that is required to completely lose tumor suppressor function, which is likely to be the initiating driver mutation in these forms of breast cancer. The major known susceptibility genes for familial breast cancer—*BRCA1*, *BRCA2*, *TP53*, and *CHEK2*—are all tumor suppressor genes that have normal roles in DNA repair and maintenance of genomic integrity (Chapter 7 and Table 23-2). It is likely that complete loss-of-function of these proteins creates a "mutator" phenotype, an increased propensity to accumulate genetic damage that speeds cancer development.

Mutations in *BRCA1* and *BRCA2* are responsible for 80% to 90% of "single gene" familial breast cancers and about 3% of all breast cancers. Penetrance (the percentage of carriers who develop breast cancer) varies from 30% to 90% depending on the specific mutation present. Mutations in *BRCA1* also markedly increase the risk of developing ovarian carcinoma, which occurs in as many as 20% to 40% of carriers. *BRCA2* confers a smaller risk for ovarian carcinoma (10% to 20%) but is associated more frequently with male breast cancer. *BRCA1* and *BRCA2* carriers are also at higher risk for other epithelial cancers, such as prostatic and pancreatic carcinomas.

BRCA1 (on chromosome 17q21) and *BRCA2* (on chromosome 13q12.3) are both large genes, and hundreds of different mutations distributed throughout their coding regions have been associated with familial breast cancers. The frequency of mutations that increase breast cancer risk is only about 1 in 400 persons in the general population,

Table 23-2 Most Common "Single Gene" Mutations Associated with Hereditary Susceptibility to Breast Cancer

Gene (Location) Syndrome (Incidence)*	% of "Single Gene" Hereditary Cancers†	Breast Cancer Risk by Age 70‡	Changes in Sporadic Breast Cancer	Other Associated Cancers	Functions	Comments
BRCA1 (17q21) Familial breast and ovarian cancer (1 in 860)	52% (~2% of all breast cancers)	40%- 90%	Mutations rare; inactivated in 50% of some subtypes (e.g., medullary and metaplastic) by methylation	Ovarian, male breast cancer (but lower than *BRCA2*), prostate, pancreas, fallopian tube	Tumor suppressor, transcriptional regulation, repair of double-stranded DNA breaks	Breast carcinomas are commonly poorly differentiated and triple negative (basal-like), and have *TP53* mutations
BRCA2 (13q12-13) Familial breast and ovarian cancer (1 in 740)	32% (~1% of all breast cancers)	30%-90%	Mutations and loss of expression rare	Ovarian, male breast cancer, prostate, pancreas, stomach, melanoma, gallbladder, bile duct, pharynx	Tumor suppressor, transcriptional regulation, repair of double-stranded DNA breaks	Biallelic germline mutations cause a rare form of Fanconi anemia
TP53 (17p13.1) Li-Fraumeni (1 in 20,000)	3% (~1% of all breast cancers)	>90%	Mutations in 20%, LOH in 30%-42%; most frequent in triple negative cancers	Sarcoma, leukemia, brain tumors, adrenocortical carcinoma, others	Tumor suppressor with critical roles in cell cycle control, DNA replication, DNA repair, and apoptosis	*TP53* is the most commonly mutated gene in sporadic breast cancers 53% ER- and HER2-positive
CHEK2 (22q12.1) (1 in 100)	5% (~1% of all breast cancers)	10%-20%	Mutations in 5%	Prostate, thyroid, kidney, colon	Cell cycle checkpoint kinase, recognition and repair of DNA damage, activates BRCA1 and p53 by phosphorylation	May increase risk for breast cancer after radiation exposure 70%-80% ER-positive

*Frequency of heterozygotes in the U.S. population; the incidence of gene mutations is higher in some ethnic populations (e.g., *BRCA1* and *BRCA2* mutations occur at high frequencies in Ashkenazi Jews).
†Defined as familial breast cancers showing a pattern of inheritance consistent with a major effect of a single gene.
‡Risk varies with specific mutations and is likely modified by other genes. *LOH,* loss of heterozygosity.