Breast Cancer Genetics for the Surgeon: An Update on Causes and Testing Options

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Breast cancer is the most commonly diagnosed cancer among women and is the second leading cause of cancer death after lung cancer.[1] Family history has long been recognized as a risk factor for the development of breast cancer, and in some of these families, a genetic mutation predisposing to a high risk of breast cancer may be responsible. Several highly penetrant genes, those associated with a very high risk of cancer in mutation carriers, have been described, including the *BRCA1* and *BRCA2* genes (Table 1). Familial clustering of breast cancers in families in whom no high penetrance gene mutation is found suggests there are other causes of breast cancer in these families, and currently it is thought that a number of lower penetrance genes may explain these cases. Any of these genes alone may have only a modest effect on risk, but a combination of these genes or combinations with certain environmental factors could explain the family history. Of course, the value of family history in determining hereditary risk is dependent on its accuracy and completeness, and it is important to realize that the cancer history of both the maternal and paternal lineage is important. It is important to note, however, that highly penetrant germline mutations only account for approximately 5% to 10% of breast cancer cases overall. Those of low penetrance account for approximately 5%. Recent advances in technology have made more extensive genetic testing possible for families with breast cancer. This has increased the complexity of decision making and prompted this review of the currently recognized causes of hereditary breast cancer and available options for genetic testing.

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HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOC)

The first study demonstrating evidence of an autosomal dominant pattern of inheritance for breast cancer was published in 1988.[2] Soon after, linkage to a gene on chromosome 17 was established and the *BRCA1* gene was identified.[3,4] Shortly after that, a second breast cancer susceptibility gene, *BRCA2*, was identified.[5] Both genes are tumor suppressor genes and are important in maintaining genomic stability and homologous DNA repair.[6]

Among the general population, the carrier frequency of mutations in *BRCA1* or *BRCA2* is about 1 in 400 (about 0.25%), but due to the founder effect, the frequency is much higher in Ashkenazi Jewish individuals, in whom the carrier frequency is 1 in 40 (2.5%).[7-9] Clinical criteria that predict an increased likelihood of carrying a mutation include individuals with early onset breast cancer (diagnosed under age 45 to 50), ovarian cancer at any age, bilateral breast cancer, a history of both breast and ovarian cancer, male breast cancer, and triple negative breast cancer under the age of 60.

The lifetime risk of developing breast cancer in women who carry a mutation in *BRCA1* or *BRCA2* is generally considered to be about 45% to 80%, and the risk of developing a second cancer in the contralateral breast is approximately 20% and increases as age of diagnosis decreases, with risks of up to 60% possible for those diagnosed at very early ages.[10] The lifetime risk of developing ovarian cancer (including Fallopian tube cancer and primary peritoneal carcinoma) is 18% to 54% in *BRCA1* carriers and 2.4% to 21% in *BRCA2* carriers.[11,12] An increased risk of cancers of the male breast, pancreas, prostate, and melanoma has also been described, particularly for *BRCA2* mutation carriers.[13-15]

Breast cancers in *BRCA1* carriers are more likely to be of medullary histology and triple negative; breast cancers in *BRCA2* carriers appear to be more heterogeneous, but are generally estrogen receptor/progesterone receptor (ER/PR) positive. Ovarian cancers in both *BRCA1* and *BRCA2* carriers are more likely to be high grade serous adenocarcinomas. Mucinous and borderline ovarian tumors are less likely to be seen.[16]

The options for management of risk include increased surveillance, chemoprevention, and risk-reducing

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Table 1. Hereditary Breast Cancer Syndromes, Associated Genetic Mutations, and Risk

Syndrome	Mutation	Lifetime risk of breast cancer, %
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*	45–80
Li-Fraumeni	*TP53*	~22
Cowden	*PTEN*	25–50
Hereditary diffuse gastric cancer syndrome	*CDH1*	30–50
Peutz-Jeghers	*STK11*	32–54
Lynch	*MLH1, MSH2, MSH6, PMS2*	Unknown
Fanconi anemia	*PALB2**	33–58

*Syndrome has other associated mutations of unclear significance at this time.

surgery. Breast cancer screening generally consists of clinical breast examination semiannually, annual MRI beginning at age 25, with alternating MRI and digital mammography (each test done annually, but staggered by 6 months) beginning at age 30.[17,18] Screening for ovarian cancer has not been shown to allow for detection at an early stage or be associated with improvement in survival and is not recommended. There are limited data on the use of tamoxifen for breast cancer risk reduction. In a subset analysis of the National Surgical Adjuvant Breast Project (NSABP) P1 trial participants in whom *BRCA* status was available, tamoxifen appeared to be as effective in *BRCA2* carriers as in nonmutation carriers, but no benefit was noted in *BRCA1* carriers.[19] The Royal Marsden Study on chemoprevention evaluated their *BRCA* population; no direct conclusion could be drawn because only 4 patients were found to have *BRCA* mutations. Interestingly, they did find a lower incidence of estrogen receptor positive vs estrogen receptor negative breast cancers in patients taking tamoxifen vs placebo.[20] Taken together with the fact that *BRCA1* carriers are more likely to develop triple-negative cancers, the benefit of chemoprevention may exist for *BRCA2* but not *BRCA1*. These data must be interpreted with caution, however, due to the extremely small numbers of mutation carriers evaluated in chemoprevention studies. Oral contraceptive use is associated with a lowered risk of ovarian cancer in *BRCA1/2* carriers, with longer durations of use associated with greater protection. In addition, current formulations have not been associated with increased risk for breast cancer.[21] Risk-reducing mastectomy has been shown to reduce breast cancer risk by 90% to 95% in *BRCA* carriers.[22] Risk-reducing salpingo-oophorectomy significantly lowers ovarian cancer risk, and when performed at early age may also reduce breast cancer risk.[23]

LI-FRAUMENI SYNDROME

Li-Fraumeni syndrome is a rare syndrome caused by germline mutation in the *TP53* gene. This syndrome is characterized by early onset breast cancer, sarcoma, brain tumors, leukemia, and adrenocortical carcinomas.[24,25] Of these cancers, breast is the most common. In affected women, breast cancer often occurs under age 35, and testing for this gene is generally recommended for women with breast cancer diagnosed under age 35 when *BRCA* testing is negative. Germline mutations in *TP53* are thought to account for less than 1% of breast cancers.[26] Although estimating risk has been difficult due to selection bias in studies, some have estimated it to be approximately 22%.[27] Because *TP53* is important in repair of radiation-induced DNA damage, there is at least theoretical concern that patients treated with chemotherapy and/or radiation therapy may be at increased risk for treatment-induced second primaries.[28] In affected carriers, screening for breast cancer with annual MRI is recommended.[18] The role of screening for detection of other cancers is still being determined, but whole body MRI is considered at some centers.

COWDEN SYNDROME

Cowden syndrome is an autosomal dominant condition caused by mutations in the *PTEN* gene. This syndrome is characterized by benign overgrowths and increased risk for several types of cancers, including breast cancer. It is characterized by multiple hamartomas, trichilemmomas, papillomatous papules, fibrocystic breast disease and breast cancer, benign and malignant thyroid disease, and uterine cancer. The lifetime risk of breast cancer is estimated to be between 25% and 50%, but some studies report risks as high as 85%.[29-31] Breast cancer typically occurs at an early age and may be bilateral. Screening recommendations include clinical breast examinations every 6 to 12 months beginning at age 25 (or 5 to 10 years before the earliest known breast cancer in the family) and annual mammography and breast MRI beginning at age 30 to 35 (individualized based on family history).[18]

DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME

Hereditary diffuse gastric cancer syndrome is an autosomal dominant condition caused by mutations in the *CDH1* gene. As the name implies, the syndrome is characterized by diffuse, poorly differentiated invasive adenocarcinoma of the stomach (linitis plastica). In affected individuals,