Breast Cancer Genetics and Indications for Prophylactic Mastectomy

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KEYWORDS

• Risk-reducing mastectomy • Contralateral prophylactic mastectomy
• Multigene panel testing • BRCA • Genetic counseling

KEY POINTS

- The initial evaluation of patients who may be at risk for hereditary breast cancer begins with a risk assessment.
- There are 3 possible results from genetic testing: positive, negative, or uninformative.
- There are many strategies for breast cancer risk reduction, which include surveillance, risk reducing or prophylactic surgery, and chemoprevention.
- Management decisions should be individualized and may be based on genetic factors as well as personal and family history of breast and other cancers.

Since the first molecular diagnostic test for hereditary breast and ovarian cancer was introduced in 1996, there has been an explosion in the understanding and availability of genetic testing. Multigene panel testing, which uses next-generation sequencing technology to analyze several cancer predisposition genes simultaneously, has become commonplace for individuals suspected to have or be at risk for hereditary breast cancer.

As more genetic information becomes available to inform breast cancer treatment, screening, and risk-reduction approaches, clinicians must become more knowledgeable about possible genetic testing and prevention strategies, including outcomes, benefits, risks, and limitations. The aim of this article is to define and distinguish high- and moderate-risk breast cancer predisposition genes, summarize the clinical recommendations that may be considered based on the identification of pathogenic

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variants (mutations) in these genes, and indications for risk-reducing and contralateral prophylactic mastectomy.

DEFINING HIGH RISK

Initial evaluation of patients who may be at risk for hereditary breast cancer begins with a risk assessment. This assessment includes obtaining detailed information about cancer in the individual and in the family. Specifically, the types of cancer and age of onset are important to determine the potential for inherited breast cancer. Both maternal and paternal sides of the family are relevant and should be considered independently. Various guidelines establish criteria for genetic testing. The National Comprehensive Cancer Network's (NCCN) guidelines[1] are updated annually and provide evidence-based guidance for clinicians to decide which patients should undergo genetic testing (**Box 1**). Ideally, women with or at risk for hereditary breast cancer should be cared for by multidisciplinary teams including both breast and genetics specialists.

If patients meet criteria, it is recommended that they undergo pretest counseling with a complete pedigree evaluation and computational assessment of risk using available statistical models and tables. Using this information as well as the qualitative criteria from the NCCN, the clinician can provide patients with the probability of testing positive in addition to the risk of developing breast cancer. Reflecting on these data as well as the expectations and motivations for testing, patients can then make an informed decision about whether to pursue testing.

The next decision is which test to order and which family member should be tested first. Testing an affected relative is preferable and will yield the most useful information. With the widespread availability and the rapidly decreasing cost of DNA sequencing, the provider has multiple commercial tests to choose from, each with varying turnaround time, insurance coverage, and number of genes analyzed. For patients who have a personal or family history clearly suggestive of a specific hereditary breast cancer syndrome, genetic testing for genes associated with that syndrome makes sense. However, in many circumstances this is not the case. Multigene testing gives the provider the opportunity to analyze multiple genes associated with breast cancer all at one time in an efficient and cost-effective manner. This testing can be particularly helpful when there are other types of cancers in the family in addition to breast and ovarian cancer. These multigene panels often include high-risk genes or high-penetrance genes, meaning pathogenic variants in these genes cause a relatively high risk for female breast cancer, and moderate-risk genes or moderate-penetrance genes, meaning pathogenic variants in these genes cause a moderately increased risk for female breast cancer. Genes considered high risk are generally ones associated with a 50% or greater lifetime risk of breast cancer, and moderate genes are ones generally associated with a 20% to 49% lifetime risk of breast cancer. Pathogenic variants in BRCA1 and BRCA2 (50%–85% lifetime risk of breast cancer), PALB2 (33%–58%), TP53 (Li-Fraumeni Syndrome (50%–90%),[2] PTEN (Cowden syndrome/PTEN hamartoma tumor syndrome) (25%–50%), STK11 (32%–54%), and CDH1 (30%–50%) cause a relatively high lifetime risk for breast cancer.[3] Pathogenic variants in CHEK2 (20%–40% [c.1100delC]), ATM (20%), and NBN (20%–30% [c.675del5]) cause a moderately increased risk for female breast cancer. Pathogenic variants in other genes, such as MRE11A and RAD50, may cause an increased risk for breast cancer; but the exact level of risk is undetermined at this time. **Table 1** lists the lifetime risk of high-penetrance and moderate-penetrance genes and associated cancers.[4]