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

Disclosure Statement: The authors have nothing to disclose.

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Surg Clin N Am 98 (2018) 677–685
https://doi.org/10.1016/j.suc.2018.03.004 **surgical.theclinics.com**

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]

Box 1
Criteria for genetic risk evaluation

- Patients without a personal history of cancer
  - A close relative with any of the following:
    - A known mutation in a cancer susceptibility gene within the family
    - A first- or second-degree relative with breast cancer at or before 45 years of age
    - Two or more individuals with breast cancer on the same side of the family and at least one diagnosed at or before 50 years of age
    - Two or more breast cancer primaries in a single individual
    - An individual with ovarian cancer, fallopian cancer, or primary peritoneal cancer
    - Male breast cancer
    - Family history of 3 or more of the following (especially if diagnosed at or before 50 years of age): breast cancer, pancreatic cancer, prostate cancer (Gleason score ≥7 or metastatic), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, di use gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, or hamartomatous polyps of gastrointestinal tract
- An individual with a breast cancer diagnosis with any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Breast cancer diagnosed at or before 50 years of age
  - Triple negative (ER−, PR−, HER2−) breast cancer diagnosed at or before 60 years of age
  - Two breast cancer primaries
  - Breast cancer at any age and more than 1 close blood relative with breast cancer diagnosed at or before 50 years of age or 1 or more close blood relatives with invasive ovarian cancer at any age
  - Two or more close blood relatives with breast cancer, prostate cancer (Gleason score ≥7 or metastatic), and/or pancreatic cancer at any age
  - Personal history of pancreatic cancer at any age
  - An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
  - Male breast cancer
  - An individual with a personal and/or family history of 3 or more of the following (especially if diagnosed at or before 50 years of age): breast cancer, pancreatic cancer, prostate cancer (Gleason score ≥7 or metastatic), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, di use gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, or hamartomatous polyps of gastrointestinal tract

Abbreviations: ER−, estrogen receptor negative; HER−, human epidermal growth factor receptor 2; PR−, progesterone receptor negative.

Data from Daly MB, Pilarski R, Berry M, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. J Natl Compr Canc Netw 2017;15(1):9–20; and American Society of Breast Surgeons. Consensus guideline on hereditary genetic testing for patients with and without breast cancer. 2017. Available at: https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/BRCA_Testing.pdf. Accessed December 30, 2017.

INTERPRETATION OF RESULTS

Interpretation of genetic testing results is a critical part of the process. There are 3 possible results from genetic testing: positive, negative, or uninformative. A positive result indicates that a harmful (deleterious or pathogenic) mutation was identified. Negative results are somewhat more complicated, as the results have to be interpreted in the context of the family pedigree. A true negative is when there is a known pathogenic or deleterious mutation in the family and the patients presenting for testing are negative. These individuals have a substantially lower risk of developing breast cancer than a member of the family who does carry the mutation.[5–7] Negative results

Table 1
Genes associated with hereditary breast cancer

Gene	Genes Associated with Hereditary Breast Cancer	Associated Cancers	Lifetime Breast Cancer Risk in Women with Mutation (%)
BRCA1	Hereditary breast and ovarian cancer (HBOC)	Breast cancer, ovarian/fallopian tube cancers, primary peritoneal malignancies	50–85
BRCA2	Hereditary breast and ovarian cancer (HBOC)	Breast cancer, ovarian/fallopian tube cancers, pancreatic cancers, melanomas, prostate cancer	50–85
PALB2	Familial breast cancer	Spectrum of associated cancers may be similar to those in BRCA2	40–60
TP53	Li-Fraumeni syndrome (LFS)	Multiple primary cancers, sarcomas, brain tumors, premenopausal breast cancers, leukemias, adrenocorticocarcinomas	50–90
PTEN	Cowden syndrome (CS)	Breast cancer, thyroid cancers, endometrial cancer, renal cell carcinoma, melanoma, colorectal cancer, endometrial cancers	25–50 (may be up to 85)
STK11	Peutz-Jeghers syndrome (PJS)	Breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, lung cancer, ovarian and testicular cancers	45–50
CGH1	Hereditary diffuse gastric cancer (HDGC)	Diffuse gastric cancer, lobular breast cancer	39–52
CHEK2	Familial breast cancer	Breast cancer, possibly colorectal cancer	20–40 (c.1100delC)
ATM	Familial breast cancer	Breast cancer	20
NBN	Familial breast cancer	Breast cancer	20–30 (c.675del5)
MRE11A	Familial breast cancer	Breast cancer	Undetermined
RAD50	Familial breast cancer	Breast cancer	Undetermined
BRIP1	Familial breast cancer	Breast cancer	20

Data from Rainville IR, Rana HQ. Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. Curr Oncol Rep 2014;16(3):371.

in an unaffected individual when there is not a known deleterious mutation in the family should be interpreted with caution, and every attempt should be made to test an affected relative if possible. Ideally, the youngest and closest in relation to the patients should be tested to clarify the pedigree. When no other relatives are available for testing, a negative result does not eliminate the risk in those patients. Another example of an uninformative result is a variant of unknown significance (VUS). A VUS is a mutation in a gene that is not yet defined to be associated with an increased risk of developing cancer or a normal change in the gene. Over time as more information is gained about the particular mutation, these may be reclassified as deleterious or benign. It is recommended that patients with VUS be managed based on their personal and family history of breast cancer.

MANAGEMENT OF INCREASED RISK

There are many strategies for breast cancer risk reduction. These strategies 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. In the individual with a known breast cancer, the risk of subsequent cancer should also be taken into consideration.

A systematic review of studies comparing prophylactic bilateral total mastectomy with observation yielded 2 contemporary studies.[8] Neither study demonstrated a survival benefit for prophylactic bilateral mastectomy. Although there has not been a randomized controlled trial to determine the efficacy of prophylactic mastectomy for women at increased risk of breast cancer, retrospective and prospective observational studies demonstrate that prophylactic bilateral mastectomy is effective and decreases the incidence of breast cancer by as much as 90% (and up to 100%) in women with genetic predisposition to breast cancer.[9–12]

Women opting for bilateral prophylactic mastectomy with either skin-sparing or nipple and skin sparing approaches can have synchronous reconstruction without impacting the preventive effects.[13–15] Subcutaneous mastectomy, however, is not recommended for prevention, as it leaves too much glandular breast tissue behind.

Contralateral prophylactic mastectomy (CPM) is a mastectomy of the other breast in the setting of unilateral breast cancer to reduce the risk of a second breast cancer. The use of contralateral mastectomy in the United States is increasing.[16] Characteristics associated with the increasing use of CPM are Caucasian race, higher socioeconomic status, private insurance, high-volume centers, younger age, increasing use of MR imaging, genetic testing, and reconstructive surgery.[17,18] Most patients undergoing CPM do so for "peace of mind."[19] Anxiety and fear of cancer or recurrence of cancer can be a contributing factor in the perception of risk. Many patients often overestimate the cancer outcome benefits of CPM. CPM does reduce the risk of contralateral breast cancer (CBC), but for most patients that risk is quite small. In fact, there has been a declining incidence of CBC in the United States among most women diagnosed with breast cancer.[20] In a study using data from the US Surveillance, Epidemiology, and End Results database, the estimated risk of CBC at 10 years for patients whose first breast cancers were estrogen receptor (ER) positive and who were diagnosed between 2001 and 2005 was less than 5% for all age groups. For women 40 years of age or older with ER-negative first cancers, the estimated 10-year risk of CBC was between 4.7% and 6.3%. For women younger than 40 years with ER-negative first cancers, it was between 6.4% and 12.6%. In a population-based case-control study,[21] the 10-year cumulative risk of CBC in noncarriers of BRCA mutations with unilateral breast cancer and no known family history of breast cancer ranged from 5% to 7% in women diagnosed with their first cancer in their 20s and 30s to approximately 4% in women diagnosed in their 50s. As expected the 10-year cumulative risk of CBC in BRCA 1 and 2 mutation carriers diagnosed with first cancer in their 20s and 30s was much higher at 24% to 31%. Interestingly, in noncarriers with a family history of bilateral breast cancer the 10-year cumulative risk of CBC for the same age group was similar to that of BRCA mutation carriers (18%–24%). Additionally, a large retrospective study from the German Consortium for Hereditary Breast and Ovarian Cancer of more than 2000 women with BRCA1 or 2 deleterious mutations demonstrated that the cumulative risk for CBC after 25 years after first breast cancer diagnosis was 47.4% and was even higher in younger women with BRCA1 mutations specifically.[22] There is a paucity of data regarding CBC risk in other hereditary breast cancer

syndromes; however, one study found that the risk of a CBC primary within 5 years in women with a pathogenic PALB2 variant was estimated to be 10%.[23]

Although CPM does reduce the risk of a CBC, CPM does not change the risk of recurrence associated with the index cancer. Compared with less favorable index cancers, the CBCs that do develop are often stage I, T1, node negative, and ER positive.[24] Thus, for most patients, CBCs have very little, if any, impact on survival. However, for a small subset of patients there may be a potential survival benefit. In a retrospective analysis of 181 patients with breast cancer with deleterious BRCA mutations, CPM was associated with a 48% reduction in death from breast cancer.[25] Furthermore, the 20-year survival rate for BRCA1 and 2 carriers undergoing a CPM was 88% compared with a 66% survival rate for carriers treated with a unilateral mastectomy even after controlling for factors, such as age and treatment. In a smaller study of 105 BRCA mutation carriers with case-matched controls, the 10-year overall survival was 89% for the CPM group and 71% for the non-CPM group.[26] As these are retrospective studies, selection bias may confound the results.

When counseling patients considering risk-reducing mastectomy or CPM, it is important to inform patients about the risks, benefits, and alternatives of the operation. In addition, the patients should understand the various options for reconstruction, and a formal consultation with a plastic surgeon is encouraged. Overall health and comorbidities should also be taken into account when considering prophylactic surgery. The decision-making process for patients considering mastectomy is based on many factors, including personal choice as well as influences from clinicians, family, and friends. The NCCN's guidelines for genetic/familial high-risk assessment for breast and ovarian cancer offer recommendations for the management of risk based on genetic test results.[1] For instance, in the case that a pathogenic variant has been identified in BRCA1, BRCA2, TP53, or PTEN, the option of risk-reducing mastectomy should be discussed. However, in the case of other genes associated with breast and ovarian cancer, there is insufficient evidence regarding the benefit of risk-reducing surgery to recommend consideration of prophylactic mastectomy and management should be tailored based on family history.

As with any operation there are risks related to bleeding, infection, and anesthesia. But there are potential side effects and complications unique to mastectomy, such as seroma, skin flap necrosis, nipple necrosis, pain, phantom breast syndrome, arm mobility issues, and lymphedema. The frequency of surgical complications following a bilateral mastectomy is greater than with a unilateral mastectomy, with rates ranging from 5% to 35%.[27–29] Data from the National Surgical Quality Improvement Program confirm these findings.[30,31] Patients who had a bilateral mastectomy were 1.9 times more likely to have postoperative complications than those patients who had unilateral mastectomy. More specifically, bilateral mastectomy was also associated with longer hospital stays and increased transfusion rates. When implant reconstruction was used, there was also an increase in reoperation rates for bilateral mastectomy compared with unilateral mastectomy. However, the rate of surgical site infection and prosthesis or flap failure was less than 5%; there was no statistical difference between the two groups. In addition to potential surgical complications, patients who undergo mastectomy, whether bilateral prophylactic or CPM, may experience changes in body image, self-esteem, perception of femininity, libido, and sexual function.[32–34] Still, most patients report satisfaction with the decision to have CPM and would choose CPM again.[35]

For women who desire to delay or not pursue risk-reducing surgery, breast cancer surveillance is an acceptable option. Based on current the NCCN's guidelines, recommendations for surveillance for those at high risk for breast cancer include annual mammogram and annual breast MRI. At the authors' institution, they stagger each

of these by 6 months.[36] Because of the concern for the development of interval cancers, a clinical breast examination every 6 to 12 months is also recommended.[1] Although there are some data about the efficacy of screening breast ultrasound in women who are at an increased risk or with dense breasts,[37] breast ultrasound is not recommended for routine screening but may be used in adjunct to clinical breast examinations, MRI, and mammogram.

Chemoprevention is the use of medications or drugs to reduce the risk of developing cancer. Chemoprevention is less effective than prophylactic mastectomy in the reduction of breast cancer risk. Chemoprevention for the prevention of breast cancer includes selective ER modulators (SERMs) and aromatase inhibitors. Tamoxifen is a SERM that can be considered for high-risk women who opt against or to delay mastectomy, especially if they have a pathogenic BRCA2 variant. There are limited data in the preventive benefit of tamoxifen use in women with pathogenic BRCA variants.[38] The NSABP P-1 trial demonstrated a 62% reduction in breast cancer risk with pathogenic BRCA2 variants versus no risk reduction in women with pathogenic BRCA1 variants.[38] This finding makes sense given the fact that breast cancers that arises in patients with BRCA2 mutations are often ER positive. However, this study was limited in the number of patients with deleterious mutations in BRCA 1 or 2 who developed breast cancer. There are no data regarding raloxifene (another SERM) or aromatase inhibitors and patients with BRCA mutations specifically, but there is evidence of significant reduction in breast cancer risk in women at an increased risk for breast cancer.[39,40]

SUMMARY

Genetic testing for breast cancer has become more complex in the era of next generation sequencing. Physicians charged with the management of patients at increased risk for hereditary breast cancer should individualize recommendations based on genetic factors and personal and family history of breast and other cancers while at the same time listening to and respecting the patient's motivations and desires.

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