The Genetics of Breast Cancer
What the Surgical Oncologist Needs to Know

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KEYWORDS
- BRCA1 • Genetics • TP53 • Breast cancer • Ovarian cancer

KEY POINTS
- Surgeons need to understand the implications of germline predisposition to breast cancer, as revealed by increasingly more complicated next-generation sequencing–based tests.
- The rapid pace of change will continue to challenge paradigms for genetic cancer risk assessment (GCRA).
- Germline predisposition to breast cancer and GCRA can influence the medical and surgical management of breast cancer risk as well as strategies for screening and for risk reduction.

INTRODUCTION

Genetic cancer risk assessment (GCRA) is an established multidisciplinary practice that can be applied to the recognition/detection of hereditary forms of breast and ovarian cancer, to enable enhanced surveillance, risk-appropriate surgical management, and targeted therapy for metastatic disease.1,2 Most breast cancer is hormone receptor positive, diagnosed after the age of 50 years old, and multifactorial in cause.3

Distinguishing features that suggest the subset of breast cancers associated with inherited predisposition include:

- Early age at onset
- Increased prevalence of bilateral breast cancer
- Association with ovarian cancer
- Family history of breast or ovarian cancer

Inheritance plays a role in the development of all human cancers to varying degrees. Hereditary forms of breast cancer constitute only 5% to 7% of breast cancer cases.
overall. However, the magnitude of the risk that a woman will develop cancer if she inherits a highly penetrant cancer gene mutation (up to 85% lifetime risk for \textit{BRCA1}) justifies the intense interest in predictive testing. There is a growing roster of identified breast cancer susceptibility genes, and next-generation sequencing (NGS) technologies have enabled diagnostic testing for an ever broader spectrum of relatively rare and incompletely understood causal variants.\textsuperscript{4} Although less common than breast cancer, ovarian cancer is relatively more lethal, and several breast cancer associated genes are also associated with elevated ovarian cancer risk.\textsuperscript{5} In addition, breast cancer can be a minor component of other genetic syndromes such as diffuse hereditary gastric cancer.\textsuperscript{6,7} This article summarizes germline predisposition to breast cancer and how GCRA can influence the medical and surgical management of breast cancer risk as well as strategies for screening and for risk reduction.

\textbf{THE PRIME EXEMPLAR: HEREDITARY BREAST AND OVARIAN CANCER ASSOCIATED WITH \textit{BRCA1} AND \textit{BRCA2} MUTATIONS}

Consider the following clinical scenario illustrated in Fig. 1. The consultand (indicated by an arrow) was 45 years old and unaffected at the time of consultation, although she was certain she would develop cancer. She was contemplating both prophylactic mastectomy and oophorectomy because her mother and 2 of her sisters died of breast or ovarian cancer. She was also concerned about her own daughter’s risk. A mutation in \textit{BRCA1} (4184del4) had been found in her sister just before her death from breast cancer at age 50. After extensive counseling, the consultand decided to pursue genetic testing for the familial mutation. Fortunately, testing revealed that she did not carry the mutation. She canceled the surgical procedures after being told that her risk for breast or ovarian cancer was no more than that of the general population (11% and 1.6%, respectively). Moreover, she was relieved to learn that her daughter was not at increased risk either, because she had not inherited the familial mutation and thus could not pass it on to her. Other family members also came forward for testing. Her 47-year-old sister was found to carry the familial mutation (indicated by + in the Fig. 1). Before counseling and testing, she was so anxious about her cancer risk that she was unable to examine her own breasts. However, despite the bad news about her carrier status, she was empowered to pursue appropriate interventions from the surveillance and preventive surgery options presented. Genetic testing had a real impact on health care decisions in this carefully counseled high-risk family and presumably reassured some individuals and spared them from unnecessary procedures.

Fig. 1. Pedigree for family with hereditary breast and ovarian cancer.
BACKGROUND

The extent of the hereditary breast and ovarian cancer phenotype associated with BRCA1 started to emerge from initial linkage studies in 1990. The cumulative risk for developing breast cancer in hereditary breast ovarian cancer (HBOC) families exceeds 50% by age 50 years and is up to 85% by age 70 years. The cloning of the BRCA1 gene on chromosome 17 in 1994, and of a second high-risk locus on chromosome 13 (BRCA2) in 1995, ushered in an era with increasing appreciation of the potential for oncogenetics to influence breast cancer screening, treatment, and prevention. The subsequent decades have been marked by an ever higher resolution understanding of gene-specific pathology, overall and age-specific risk for BRCA-associated breast cancers, as well as a growing understanding of hormonal and genetic modifiers of risk.

GENETIC TESTING AND BRCA MUTATIONS

Commercial testing in a CLIA (Clinical Laboratory Improvement Amendments)-approved laboratory became available for BRCA1 and BRCA2 in 1996 in the United States, and professional society policy statements affirmed the value of their use in GCRA. BRCA testing has long been offered (through regional or national laboratories) in most of Europe, Australia, Israel, and Iceland (for specific founder mutations). The National Comprehensive Cancer Network (NCCN) publishes testing guidelines that are updated annually and largely adopted by most insurers. Notable exceptions include Medicare (which does not cover testing for unaffected patients, even if a BRCA mutation is known in the family) and Medicaid, wherein coverage varies among different states. Box 1 includes the top-level NCCN indicators for genetic testing, most of which should be well known by surgeons involved in the care of women with breast cancer. A deeper appreciation of the more complicated combinations of family history indications for GCRA is helpful.

Specialized training is often warranted to achieve practitioner level competence in the application of GCRA and knowledgeable interpretation of molecular genetic test results, including variants of uncertain significance (VUS). (Please see the article in this issue by Marc S. Greenblatt.) If a patient with a strong personal or family history of breast cancer is tested and no deleterious or pathogenic (pathogenic is another term increasingly used on genetic test reports) mutation is identified, they are grouped as “negative” test results as well as all VUS in the same clinical category, described as uninformative, because they are essentially uninformative and ambiguous findings in most cases.

Box 1

Key single case indicators* for genetic susceptibility testing

- Breast cancer diagnosis ≤ age 45 years
- Triple-negative breast cancer < age 60 years
- Bilateral breast cancer (with 1st diagnosis ≤ age 50 years)
- Male breast cancer
- Epithelial ovarian cancer

*Most apply to individual or close relative; see NCCN guidelines for additional family history–dependent indications.
There are reasonable concerns that VUS results can be confusing to patients and providers alike. However, a longitudinal study of patients receiving a VUS result at an academic health center employing an experienced multidisciplinary team that includes certified genetic counselors as well as medical doctors suggested there was no evidence of patients choosing risk-inappropriate follow-up care. Although a challenge, especially for a consultative practice, it is important that reclassifications of VUS results by genetic testing vendors, which may occur years later, be shared with patients and incorporated into their record. (Please see articles in this issue by Vickie L. Venne and Maren T. Scheuner as well as by Amanda Gammon and Deborah W. Neklason.) The same concepts apply to VUS results from multigene panel tests, albeit with much less supportive evidence for the clinical implications of even pathogenic changes in the respective genes (see later discussion). 

A separate important issue is that testing is most informative when it is initiated with the youngest affected individual in a given family. Even if one is convinced that a family has hereditary cancers based on clinical criteria, there is only a 50% chance that an offspring or sibling of an affected patient will have inherited the familial mutation. Therefore, only a positive test result (detection of a known or likely deleterious mutation) is truly informative. Until the familial mutation is known, a negative test result could mean: (1) that the unaffected person being tested did not inherit the cancer susceptibility mutation; (2) that the person inherited the disease-associated gene, but the mutation was not detectable by the methods used; or (3) that the familial mutation is in an entirely different gene that has not yet been tested. Thus, there is a limit to how much reassurance (negative predictive value) is clinically appropriate and can be offered in the context of negative/uninformative testing for one or even for a comprehensive panel of multiple cancer predisposition genes. Low- to moderate-risk genes on such gene panels are even more problematic, because there seems to be a significant residual risk even after informative negative test results. The residual risk is likely multifactorial, reflecting shared environmental factors as well as minor genetic determinants (such as single-nucleotide polymorphism [SNP] risk variants) that are not assessed in any panels and individually may convey minuscule (1%–2%) risk.

Despite the discovery of large genomic rearrangements (LGR) in the BRCA genes in 1999, the approach to variant analysis remained limited to Sanger sequencing of translated exons and adjacent intronic regions for many subsequent years. This discovery was followed by the addition of targeted assays for the 5 most frequently identified recurrent LGRs (associated with apparent European origin). More comprehensive screening for LGRs was offered by the commercial vendor in 2006, shortly after a publication from Dr Mary-Claire King’s laboratory documented a 12% rate of LGRs among 300 multicase families with negative (uninformative) Sanger sequencing. A clinic-based series suggested that LGRs represented greater than 10% of BRCA1 mutations detected among women meeting NCCN criteria for testing. The author reported the discovery of a frequent LGR (BRCA1 ex9-12del) among Hispanic patients of Mexican ancestry in 2007. In a study of 746 US Hispanic patients, 21 of 189 detected mutations were LGRs, and 13 of 21 (62%) LGRs were the BRCA1 ex9-12del. A recent study of the prevalence of BRCA LGRs among 48,456 patients tested by a commercial laboratory confirmed that approximately 10% of carriers had an LGR, and a 21% rate was reported for Latin American/Caribbean Islanders. Notably, one-third of LGRs were the BRCA1 ex9-12del mutation in this latter group. Thus, BRCA1 ex9-12del is clinically significant and one of the most frequent population-specific large rearrangement mutations in the world as well as the first reported Mexican founder mutation. The bottom line for clinicians is that testing is not
complete for given susceptibility genes unless complete sequencing and rearrangement screening are performed.

**BRCA MUTATIONS AND FOUNDER POPULATIONS**

Although thousands of different BRCA mutations have been documented, the spectrum of mutations among certain populations that are geographically or culturally isolated may be limited and characterized by the presence of specific founder mutations. Perhaps the most extensively studied founder effects are the 3 BRCA mutations associated with Jewish ancestry, which are thought to account for up to 95% of BRCA-associated breast or ovarian cancers among Jews. The Ashkenazi Jewish population frequency of the BRCA1 185delAG (187delAG) is ~1%, and BRCA2 6174delT variants is about 1.5%. The BRCA1 5382insC (5385insC) variant is thought to be of Baltic origin and is detected in both Jewish (0.3%) and non-Jewish populations from that region. BRCA1 185delAG is present in Sephardic and Middle Eastern Jewish populations, although at a lower frequency, and has been reported among populations from Latin America as well, presumably from colonial Hispanic influences and the flight from the Spanish Inquisition in the fifteenth century.

There are founder mutations in most world populations, although few (eg, BRCA2 999del5 in Iceland) that account for most observed BRCA mutations in a given population as observed in the specific populations described above.

**TESTING STRATEGIES AND LIMITATIONS FOR PATIENTS WITHOUT CANCER**

In some cases, no affected family members are available for testing. In that case, one may proceed with genetic testing of an unaffected person, but only after that individual has been thoroughly counseled regarding its risks, benefits, and limitations. Similarly and most important for this volume, unless there is a suggestive family history, cancer susceptibility testing is not considered appropriate for screening unaffected individuals in the general population. However, a recent study of population-based genetic testing for Jewish founder mutations, using unaffected men in Israel as a less biased reference population and then testing female relatives, prompted Mary-Claire King in her 2014 Lasker Award address to call for population-based testing of women who are 30 years in age or older. Although generally sympathetic to aspects of such an approach, careful consideration highlights unresolved issues: “There are some difficult questions that come up, centered around who is the right target, what is the right test, to whom should it be delivered, should it be full sequencing or should it just be looking for mutations in target populations, and what information do people need to be able to decide whether or not they want to participate?” Nonetheless, it may be reasonable to test unaffected persons who are members of an ethnic group in which specific ancestral mutations are prevalent and whose family structure is limited (ie, the family is small, with few female relatives or no information due to premature death from noncancerous causes).

**BRCA-ASSOCIATED RISK, VARIABLE PENETRANCE, AND THE INDICATIONS FOR PROPHYLACTIC SURGERY**

Among high-risk clinic populations, a woman with a BRCA1 mutation faces a breast cancer risk of nearly 6% by the age of 30 years, 20% by the age of 40 years, and up to 85% lifetime. Although BRCA2 is often associated with a later age at onset than for BRCA1, the cumulative lifetime risk is similar. In contrast to high-risk clinic studies, population-based studies suggest a lower breast cancer penetrance (as low as 36% for
carriers of BRCA2 999del5 in Iceland).\textsuperscript{17,73–76} However, most patients are identified via clinic-based services, so adjustment of risk estimation is rarely necessary in that setting. A large study of cancer risk by mutation site/type, by the Consortium of Investigators of Modifiers of BRCA, confirmed previous observations of positional effects, such as a relatively greater risk for ovarian cancer with BRCA2 mutations in the middle third (ovarian cancer cluster region) of the gene.\textsuperscript{77–79} In practice, even the lowest ovarian cancer risk associated with BRCA2 is still enough to warrant risk reduction salpingo-oophorectomy (RRSO), although one may consider it after age 40 years old if preferred by the patient, and in any event, as soon as practicable after menopause. There are a growing number of genetic modifiers of BRCA-associated breast and ovarian cancer risk.\textsuperscript{80,81} It is known that family history confers risk beyond the BRCA gene status. There is controversy as to the negative predictive value of an informative negative test result (a close relative wherein a known family BRCA mutation was not detected).\textsuperscript{82} However, most clinicians consider that almost all the familial risk tracks with a deleterious familial BRCA mutation. There is less negative predictive value of diagnostic testing for moderate risk genes (eg, CHEK2, ATM); that is, there is often still enough empiric risk to warrant enhanced surveillance for a CHEK2-negative daughter of a CHEK2-positive woman with breast cancer (see later discussion).

Expert opinion suggests it is important to calibrate risk estimation and management recommendations to be age and clinical scenario appropriate. That is, an unaffected 30-year-old woman with a BRCA1 mutation has the most to gain from risk reduction mastectomy (RRM) as measured by quality-adjusted years of life gained, compared with a 58-year-old woman with a recently diagnosed stage III BRCA-associated breast cancer, who may be better served by a unilateral therapeutic mastectomy alone.\textsuperscript{83,84} That is, the latter woman would not be expected to benefit significantly from contralateral RRM with regard to reduced mortality, and she may suffer pain and complications of surgery.

Nonetheless, it is the extraordinary risk of BRCA-associated new primary breast cancers\textsuperscript{85} that has driven the application of GCRA in the initial evaluation and management of young women with breast cancer. The author and others demonstrated that GCRA could be integrated into busy oncologic practices,\textsuperscript{86,87} wherein most women chose risk-appropriate surgery. That is, they were more likely to choose unilateral (therapeutic) breast surgery if they were determined to have sporadic breast cancer and counseled about the respective, modest new primary breast cancer risk, and those with high (genetic) risk were more likely to choose therapeutic ipsilateral and risk reduction contralateral mastectomies.

It has been suggested that the best timeframe for GCRA was during adjuvant therapy after definitive resection of the tumor, but before adjuvant radiation therapy necessary to complete breast-conserving treatment.\textsuperscript{86,88} This window of opportunity for GCRA has increasingly shifted to immediately after biopsy, especially with increasing use of neoadjuvant chemotherapy. This shift represents a time when the cancer risk counseling service can be engaged to support a risk-informed approach for the patient and surgeon to decide about surgery appropriate to the circumstance. Most younger (<age 50) women with limited stage (I–II) BRCA-associated breast cancer will choose bilateral mastectomy if they understand the elevated risks for new primary ipsilateral and contralateral breast cancer. There is no compulsory approach, because conservative therapy is as effective for breast cancer treatment. The 2 issues driving decision-making for women is a strong desire to “never face this circumstance again” and limitation of options for reconstruction if a previously irradiated breast requires a mastectomy for treatment of ipsilateral breast tumor recurrence (most would require a tissue-based approach).
There are numerous counseling and support challenges for these newly diagnosed women, who are often overwhelmed with fear and information overload as they contemplate options for adjuvant chemotherapy and primary surgical management of the breast, which could include RRM. Other potential intervention points for GCRA include survivors of early onset (<45 years old) breast cancer, often at the behest of at-risk relatives, or when considering revision of breast reconstruction. Although breast-conserving therapy is efficacious with respect to treatment of BRCA-associated breast cancer, there is an elevated risk for both ipsilateral and contralateral new primary breast cancers.

Nuances of cancer risk counseling for newly diagnosed patients with breast cancer contemplating breast-conserving therapy include how to secure accurate GCRA to determine risks for ipsilateral breast tumor recurrence (local recurrence and ipsilateral new primary breast cancer risk) and contralateral new primary breast cancer risk moving forward. When counseling about the risk of future ipsilateral or contralateral breast cancer following breast-conserving therapy for invasive breast cancer, one approach is to consider annualized rather than cumulative lifetime risk estimates. This depends on menopausal status, regardless of whether premature due to RRSO or due to natural menopause. The BRCA-associated annualized risk for breast cancer is about 3% to 5% per year while premenopausal, and 1% to 2% per year when postmenopausal. The risk of new primary cancers over 10 years after initial BRCA-associated breast cancer is listed as follows:

- **BRCA2**—34% for breast cancer; 6% for ovarian cancer
- **BRCA1**—43% for breast cancer; 12% for ovarian cancer

Modifiers of risk:

- **BRCA2** mutation is associated with less risk than **BRCA1**
- Less risk if first cancer diagnosis was age 50 years or older
- Tamoxifen reduced the risk of new primary breast cancers
- Oophorectomy reduced new primary breast cancer risk

Furthermore, premenopausal RRSO reduces ovarian cancer, breast cancer, and all-cause mortality (hazard ratio [HR] = 0.40 [0.26–0.61]), with the greatest breast cancer risk reduction (HR: 0.15 [95% confidence interval [CI] 0.04–0.63]) among **BRCA1** mutation carriers without a prior diagnosis of breast cancer.95

Elevated risk for new primary breast cancer drives surgeons’ opinions and patient preferences regarding both ipsilateral and contralateral mastectomy recommendations. The concept of considering options for the surgical approach as compared with recommendations may be a challenge for patients and surgeons alike, but shared decision-making is important for long-term satisfaction.

RRM is associated with greater than 95% reduction in new primary breast cancer risk among **BRCA** pathogenic mutation carriers, whether performed prophylactically bilaterally in an unaffected woman or as risk reduction for the contralateral breast in a woman treated for breast cancer. The uptake of RRM among unaffected women varies by age, parity, marital status, and country of residence. Quality-of-life issues associated with RRM include altered self-body image, and multiple studies suggest the potential for disruption in personal relationships following RRM. The most frequently reported changes were in sexual attractiveness (55%), feeling less physically attractive (53%), and self-consciousness about appearance (53%). A minority of women had more serious psychological or body image concerns, usually in relation to surgical complications, and required psychiatric intervention. Most concerns regarding RRM pertained to subsequent cosmetic options, including...
reconstruction. These concerns include the look and feel of implants, pain, numbness, scarring, and the details of some complex, multistep reconstruction options the technical aspects of which are well described in the literature, and beyond the scope of this article. Although skin-sparing approaches would be considered standard of care, one key controversy is whether preservation of the nipple and areolar complex is safe. Neoplastic involvement of the nipple was noted in 21% of 232 therapeutic mastectomies and none of 84 risk reduction procedures in one study.107 The authors concluded that nipple-sparing mastectomy may be suitable for selected cases of breast carcinoma with low probability of nipple involvement by carcinoma; a retroareolar en-face margin may be used to test for occult involvement. Where this practice has been systematically studied, the nipple may retain erectile function, and the rate of neoplasia in the nipple is quite low and usually considered salvageable. However, there is usually significant anesthesia of the reconstructed breast. So, on balance, the absolute safest procedure includes removal of the nipple and subareolar complex, although a well-informed patient (and surgeon) may choose a nipple-sparing procedure if they prioritize a possibly better cosmetic outcome over the very modest risk of locally recurrent disease. Clearly, careful attention should be paid to the information needs of women undergoing RRM. However, despite the concerns, limitations, and challenges described above, most studies suggest satisfaction with risk reduction surgery decisions, especially if the woman feels that the locus of control was hers, rather than driven mostly by physician recommendation.111

**BRCA-ASSOCIATED BREAST CANCER PATHOLOGY**

BRCA1-associated breast cancer has relatively distinct pathologic characteristics, including a prevalence of estrogen receptor negative (ER-), progesterone receptor negative (PR-) HER2/neu-negative breast cancer (triple-negative breast cancer; TNBC). There is usually a high histologic grade, and medullary histology is more common. TNBC tumors can be further subdivided into the basal subset, which is particularly associated with BRCA1 status. Somatic TP53 mutations are evident in greater than 80% of BRCA-associated breast cancers. There is a high level of pathology concordance between first and second primary BRCA-associated breast cancers; the 2 tumors are concordant more often than expected for ER status (P<.0001) and for grade (P<.0001), but not for histology (P = .55). The ER status of the first tumor was highly predictive of the ER status of the second tumor (odds ratio [OR], 8.7; 95% CI, 3.5–21.5; P<.0001). Neither age, menopausal status, oophorectomy, nor tamoxifen use was predictive of the ER status of the second tumor. Thus, there is strong concordance in ER status and tumor grade between independent primary breast tumors in women with a BRCA mutation. Interestingly, tamoxifen seems to reduce new primary breast cancer risk regardless of receptor status or which BRCA gene is associated with the disease.23,27,117

**THE ISSUE OF IONIZING RADIATION EXPOSURE: AGE-SPECIFIC WINDOW OF VULNERABILITY**

Similar to the effect noted in survivors of Hodgkin disease treated with mantle radiation during the pubertal years, there seems to be an increased breast cancer risk with medical radiation exposure, with important implications for the use of radiographic imaging in young BRCA carriers. A study of chest radiographic exposures before age 30 among patients with breast cancer in a Polish registry also suggested early radiation exposure may be a risk factor for breast cancer in BRCA1 carriers. On the other hand, a large case-control study did not lend support to the idea that
exposure to ionizing radiation through routine screening mammography contributes substantially to the burden of breast cancer in \textit{BRCA1} and \textit{BRCA2} mutation carriers.\textsuperscript{122} Although the latter study was reassuring regarding the safety of mammography, it is common practice among oncogenetic services to use annual MRI alone for surveillance up to the age of 30 years.\textsuperscript{12}

\textbf{BRCA-ASSOCIATED RISK FOR OVARIAN CANCER: THE CLEAREST MEDICAL NECESSITY}

Although virtually all breast surgery decisions based on genetic status are considered options for care (ultimately at the discretion of the patient, albeit with varying degrees of encouragement/support by the surgeon), RRSO is considered a recommendation for care and thus a medical necessity. Given the documented lack of efficacy of clinical screening surveillance for ovarian cancer,\textsuperscript{123,124} advanced stage at diagnosis, and associated morbidity and mortality, RRSO upon completion of childbearing is a recommendation for women with a \textit{BRCA} mutation (NCCN guidelines; Society of Gynecologic Oncology, and others).\textsuperscript{42,125,126} Studies suggest that although women who choose to have RRSO have a good overall quality of life and significant decrease in risk perception as a result of surgery, they do experience menopausal symptoms and in some cases compromised sexual function.\textsuperscript{127–129}

Observations from careful pathologic examination of RRSO specimens have revealed a 2\% to 6\% incidence of occult cancer, often in the fimbriated end of the fallopian tube at the time of risk reduction surgery.\textsuperscript{130–133} There is an age trend, with the finding rare in women less than the age of 40 years and increasing frequency thereafter. Thus, recommendations for high-risk populations are that the fallopian tubes and ovaries should be submitted entirely, along with peritoneal washing for cytologic evaluation, and be evaluated by a pathologist with expertise in gynecologic malignancies in serial sections, and that the laparoscopic surgeon should examine the peritoneal surfaces thoroughly at the time of prophylactic salpingo-oophorectomy.\textsuperscript{134,135} Based on the high frequency of the tubal origin, some investigators have suggested salpingectomy alone as a risk reduction procedure among premenopausal \textit{BRCA} carriers.\textsuperscript{136} However, the residual possibility of ovarian cancer (at least 20\% of the occult cancers are ovarian in origin) necessitates oophorectomy in any event. The author thinks the number of women, properly advised, who would choose salpingectomy alone, preserving the ovaries to preserve childbearing options in their 40s, would be very low. With recent technical advances, egg preservation is an increasingly viable (and preferable) solution (fertility preservation is an important issue in the management of young patients with breast cancer, but beyond the scope of this article). Thus, although possibly imperfect in terms of hormonal balance, RRSO coupled with hormone therapy at the lowest dose that preserves quality of life (eg, freedom from vasomotor symptoms, preservation of libido, and healthy vaginal mucosa) is preferable as it obviates a second surgical procedure. Despite evidence from the Women’s Health Initiative trial suggesting modestly increased breast cancer risk associated with postmenopausal combination hormone (estrogen plus progestosterone) therapy, monotherapy with conjugated estrogens appeared safe.\textsuperscript{137} Furthermore, monotherapy with estrogen, possible if the uterus is absent (obviating the risk of uterine cancer in the face of either tamoxifen or estrogen monotherapy), is likely neutral with respect to breast cancer risk among \textit{BRCA} carriers. Thus, salpingectomy alone as a risk reduction procedure should be considered an investigational risk management option of unproven usefulness, and questionable safety given that delay in oophorectomy could result in the development of lethal ovarian cancer as well as reduce the protective effect against breast cancer risk that has been documented in women who have undergone RRSO.\textsuperscript{136} The increased proportion of the papillary serous uterine cancer subtype
among BRCA carriers, albeit without measurable increased risk of uterine cancer, has prompted discussion about whether to consider hysterectomy concomitant with RRSO.\textsuperscript{138,139} Although there is no consensus on this point, the other rationale for the latter approach is that it may enable post-RRSO monotherapy with estrogen for unaffected BRCA carriers, with associated enhanced quality of life.

Oral contraceptives seem to reduce the risk (adjusted OR, 0.5 [95% CI = 0.3–0.8]) for ovarian cancer among BRCA (both BRCA1 and BRCA2) carriers, with a trend for more decreased risk with increasing duration of use ($P$ for trend, <.001).\textsuperscript{140} Additional studies confirm that oral contraceptives, number of full-term pregnancies, and tubal ligation are associated with ovarian cancer risk in BRCA1 carriers, similar to that observed in the general population.\textsuperscript{141}

The NCCN guidelines (NCCN.com) are updated annually and describe referral and testing criteria as well as evidence-based management guidelines.\textsuperscript{42} Box 2 presents a summary of current options and recommendations for care of the BRCA carrier.

**MRI SCREENING FOR WOMEN AT HIGH RISK OF BREAST CANCER**

Given the limited efficacy of mammography among young high-risk patients with significant breast density, one of the biggest advances in breast cancer screening was the validation of high sensitivity for contrast-enhanced breast MRI.\textsuperscript{142} Table 1 summarizes several studies demonstrating the superiority of MRI compared with mammography and firmly establishes the use of breast MRI as the standard of high-risk care.\textsuperscript{142–145} The American Cancer Society guidelines suggest that women with high risk (eg, >20% empiric risk or carriers of genetic susceptibility mutations) would benefit from the addition of MRI to their surveillance regimen.\textsuperscript{146}

Importantly, a prospective study of annual surveillance with breast MRI demonstrated a significant reduction in the incidence of advanced-stage breast cancer in

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**Box 2**

**Risk management options for BRCA mutation carriers***

*Recommended for breast cancer detection:*

- Monthly self-examination of the breast beginning in late teen years
- Beginning at age 25 (or 5–10 years before the earliest onset cancer in the family): Clinician breast examination every 6 months, with alternating imaging procedures
- Annual mammography, and
- Annual breast MRI

*Discussed as options:*

- Bilateral risk reduction mastectomy
- Participation in clinical trials for chemoprevention

*Recommended for ovarian cancer prevention or BC risk reduction:*

- Risk reduction salpingo-oophorectomy recommended on completion of childbearing

*Considered from age 30 years to completion of childbearing:*

- Serum CA-125 every 6 months
- Transvaginal ultrasonography every 6 months

*Also offered to women at increased risk because of a positive family history of hereditary breast and ovarian cancers but for whom genotypic information is not available.*
Given the data and practice guidelines indicating the use of MRI as standard of care,42 a randomized trial with a mortality endpoint will not be forthcoming. Nonetheless, the evidence from these studies provides a measure of confidence for women who prefer not to pursue RRM.

OTHER GENETIC SYNDROMES ASSOCIATED WITH BREAST CANCER

Syndromes that have long been recognized as having a strong association with breast cancer susceptibility include Li-Fraumeni syndrome (LFS), associated with TP53 mutations, Cowden disease (CD), associated with PTEN mutations, and diffuse hereditary gastric cancer and lobular breast cancer, associated with CDH1 mutations. Each of these syndromes is quite rare. However, when faced with a young adult patient with breast cancer and no evidence of BRCA involvement, it is important to consider these other syndromes. Therefore, this article has included information regarding the clinical phenotypes for each. Efforts to define optimal clinical practice with regard to breast cancer screening, RRM, and optimal surgical management for first breast cancer diagnosis for these are hampered by relatively small numbers and the confounding effects of the other serious pathologies associated with each syndrome. However, recognition of the specific syndromic phenotypes described should serve as a prompt to secure focused diagnostic germline genetic testing because knowledge of carrier status greatly assists families and their providers in management decision-making. Importantly, the genes associated with predisposition to each of these syndromes are increasingly included on multigene testing panels. These genes include TP53, PTEN CDH1, PALB2, CHEK2, and ATM. Information regarding each of these genes as well as others increasingly included in breast cancer gene panel testing are summarized in later discussion (Table 2).140–142

Li-Fraumeni Syndrome (LFS)

LFS is one of the most severe breast cancer susceptibility phenotypes (50% cancer incidence in women with a TP53 mutation by age 30, 90% lifetime) seen among the additional rare syndromes associated with breast cancer risk.171 Associated with germline TP53 mutations, LFS family members are at significant risk for the development of several tumor types, particularly sarcomas, breast cancer, brain tumors, and adrenocortical carcinomas.172,173 The incidence of de novo TP53 mutations is approximately 10%,174 which means that providers may encounter patients carrying de novo TP53 mutations with no family history suggestive of the LFS. BRCA-negative women with breast cancer onset before age 36 years and association with other core Li-Fraumeni cancers in the family should prompt consideration of directed TP53 testing.42 The inclusion of TP53 in multigene testing panels is yielding an ever greater number of cases (see later discussion). The phenotype of breast cancer in LFS is unique beyond markedly early onset disease with median age at diagnosis of 32 years (range 22–46). In the largest study to date, 43 tumors from 39 women demonstrated exclusively ductal

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<td>PALB2</td>
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<td>CHEK2</td>
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histology. Of the invasive cancers, 84% were positive for ER or PR; 81% were high grade. Sixty-three percent of invasive and 73% of in situ carcinomas were positive for HER2/neu (IHC 3+ or fluorescence in situ hybridization amplified). These findings suggest that modern HER2-directed treatments may result in improved outcomes for women with LFS-associated breast cancer. In a landmark paper, David Malkin’s group documented decreased mortality for LFS patients participating in an intense multimodality surveillance protocol, albeit predominantly in a pediatric population. A pilot project with PET-computed tomography detected several asymptomatic neoplasms, although there are reasonable concerns about potential morbidity from cumulative exposure to ionizing radiation exposure. However, beyond a recommendation for annual contrast-enhanced breast MRI and colonoscopy, there is less uniformity in the regimens being offered to adults with LFS, and the efficacy of surveillance programs for the diverse malignancies seen in LFS is uncertain. Recommendations for management of the adult woman with LFS include monthly self-examination, clinical examination every 6 months, annual breast MRI from age 20 years of age on (or 5 years before earliest breast cancer in family, whichever is earlier). Concerns about ionizing radiation exposure prompt consideration of omission of mammograms until after 30 years old. The most common approach given the extraordinary risk for breast cancer is consideration of RRM.

**Cowden disease (CD)**

CD (multiple hamartoma syndrome) is a cancer-associated autosomal-dominant genodermatosis with characteristic mucocutaneous findings including multiple smooth facial papules (cutaneous tricholemmomas), acral keratosis, and multiple oral papillomas, associated with mutations in the PTEN gene. Central nervous system manifestations of CD may include macrocephaly, epilepsy, and dysplastic gangliocytomas of the cerebellum (Lhermitte Duclos disease). Other associated lesions include benign and malignant disease of the thyroid, intestinal polyps, and genitourinary abnormalities. Expression of the disease is variable and penetrance of the dermatologic lesions is thought to be complete by age 20. The incidence of breast cancer in affected women classically ranges from 22% to greater than 50%. The risk for new primary breast cancers among women with PTEN-associated breast cancer is increased, although there are significant limitations of the available data. In one study, 11 of 51 (22%) PTEN mutation-positive patients with breast cancer had a subsequent new primary breast cancer and 10-year second breast cancer cumulative risk of 29% (95% CI, 15.3–43.7). Although RRM may be considered, the risk of new primary breast cancers is more moderate than BRCA or TP53, and less well characterized. The major associated risks that prompt changes in care include thyroid cancer (10%–30%; annual thyroid ultrasound) and endometrium (10%–28%; annual transvaginal ultrasound and option for hysterectomy). CD is one of the few cancer-associated syndromes wherein physical examination (eg, head circumference >58 cm; multinodular goiter, mucocutaneous findings) may have as much or more clinical sensitivity than molecular testing. The NCCN guidelines would support high-risk breast cancer surveillance, following essentially the same approach as for BRCA.

**Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer (HDGC)**

HDGC and lobular breast cancer were first noted for autosomal-dominant high risk for diffuse, signet ring gastric cancer. Later, it became clear that there was also a relatively high risk (30%–60%) for lobular breast cancer, and that some families presented with lobular breast cancer alone. Thus, management of women with CDH1 mutations warrants MRI screening at the least.
Partner and localizer of BRCA2 (PALB2)

Biallelic mutations in PALB2 cause Fanconi anemia type N, characterized by growth retardation, developmental disabilities, and a high risk for pediatric solid tumors. Monoallelic (heterozygous) mutations in PALB2 cause an increased risk for breast cancer that seems to be modified by family history. The largest study of PALB2 mutation carriers to date indicated that the cumulative risk of breast cancer to age 70 was 35% regardless of family history, whereas those with 2 first-degree relatives diagnosed with breast cancer before age 50 had an absolute risk of 58% by age 70. Thus, most clinicians now group PALB2 with the other high-penetration genes with regard to actionability (eg, high-risk surveillance and consideration, albeit less compelling, for RRM).

PALB2 founder mutations exist in Polish, Danish, and Russian HBOC cohorts. Although there seems to be an increased ovarian cancer risk for PALB2 carriers, findings did not reach statistical significance in the most recent study. PALB2 mutations have also been identified in a small proportion of hereditary pancreatic cancer families. The magnitude of pancreatic cancer risk conferred by PALB2 mutations remains unclear (likely <5% absolute risk), but it may be near the level observed in BRCA2 mutation carriers.

Ataxia-Telangiectasia Mutated (ATM) gene

Modest increased risk (relative risk, RR = 3.9–6.4) may be seen in women who are heterozygous for a mutation in ataxia telangiectasia mutated (ATM), which is associated with the recessive disease ataxia-telangiectasia in the homozygous state. Carrier frequency is estimated at 1%. Although most studies suggest that female carriers have a moderately elevated risk of breast cancer (2–3 times), 2 ATM mutations found in families with multiple cases of breast cancer in Australia (T7271G, IVS10-6T > G) demonstrated 15.7-fold elevated risk of breast cancer in carriers. Unfortunately, despite the relative rarity of these specific high-risk variants and the fact that the vast majority of variants seem to confer a risk of ~25% lifetime, test reports from genetic testing vendors often cite the high risk in the range of risk, raising concern about inappropriate application of RRM as part of management.

Genomic studies linked ATM to modestly elevated risk for pancreatic cancer (<5% absolute lifetime risk). Given the frequency of ATM mutations on multigene panel test results, clarification of breast (and other) cancer risks will be important. There is no evidence to date suggesting a hazardous effect of screening mammography or therapeutic radiation.

Checkpoint kinase 2 (CHEK2)

CHEK2 is a moderate-risk tumor suppressor gene that encodes the checkpoint kinase 2 protein. Germline mutations in the CHEK2 gene have been associated with a moderate risk for breast cancer, with an OR of 2.7 for unselected breast cancer cases. Despite concerns about limited clinical utility that have limited application of single gene testing for CHEK2 mutations, emerging data on associated risk for bilateral breast cancer and breast cancer–related mortality, as well as inclusion on multigene panels, have increased the clinical relevance of CHEK2. Evidence suggests there is an approximately 2-fold risk for CRC in CHEK2 mutation carriers. Currently, the breast cancer risk for CHEK2 mutation carriers does not seem elevated enough to warrant consideration of risk-reducing bilateral mastectomy, but heightened surveillance with additional annual breast MRI is recommended. In breast
cancer families found to have a \textit{CHEK2} mutation, empiric risk estimates (eg, Tyrer-Cuzick empiric risk model) may match the genetic risk, so that the impact on management may be modest.

**MULTIGENE PANELS: THE “SHOTGUN” APPROACH**

The introduction of multigene panels represents an important new and rapidly evolving genomic technology. Traditional genetic counseling and testing driven by syndromic features, with testing focused on one or a few high penetrance cancer predisposition genes, has been the standard of care for decades. However, recent technical advances, including NGS, have upended these well-established paradigms. (See the article by John Burn in this issue.) National guidelines now include discussion of hereditary cancer panels inclusive of multiple genes as a potentially cost- and time-effective alternative to sequentially test more than 2 to 3 single genes associated with a given phenotype, or when atypical family presentations or limited family structure make it difficult to use family history alone to determine the most appropriate gene or genes to test.\(^{42}\) Moving beyond single-gene testing has unveiled new challenges to the clinician involved in providing GCRAs.\(^{206}\) Since the implementation of multi-gene panels, significant gaps in the gene-specific phenotypic knowledge base have been identified. The prevalence of VUS (see article by Marc S. Greenblatt in this issue) and unexpected findings, such as off-phenotypic-target (gene mutation does not match or account for any of the clinical picture) gene mutations, challenge the counseling repertoire.\(^{207}\)

Risk management guidelines, with varying degrees of supportive evidence, have been articulated for the high-penetrance genes and the associated syndromes.\(^{42}\) However, absolute cancer risk estimates and management guidelines are largely lacking for identified intermediate- and low-risk genes. A recent review summarized the state of knowledge about many of the genes on the panels (see \textit{Table 2}), limitations in absolute risk estimates, gaps and variations in management guidelines and outlined possible study designs for determining risks for the moderate-risk genes.\(^{1}\) The practicing surgical oncologist needs to know about these trends as she or he is increasingly likely to come under pressure from commercial interests and patients to use these technologies when traditional genetic testing approaches fail to meet genetic diagnostic expectations. The problem for the clinician and their patient is the interpretation, clinical implementation, and medicolegal implications of results that lack evidence-based validation. These challenging issues underscore the value and professional importance of consulting a certified genetic counselor or clinical genetics service when confronted by these situations. (See the article in this issue by Zohra Ali-Khan Catts and Heather Hampel).

**CANCER RISK AND MUTATION PROBABILITY MODELS**

There are several models available to estimate the probability of an individual carrying a \textit{BRCA} mutation, and these include Couch,\(^{208}\) Penn 2,\(^{209}\) and Myriad\(^{210}\) models. Both mutation probability and empiric risk can be estimated by \textit{BRCAPRO},\(^{211–213}\) Tyrer-Cuzick,\(^{214}\) and \textit{BOADICEA}.\(^{215,216}\) The interested reader is directed to literature wherein these models have been reviewed.\(^{217–220}\) For concerned patients with a low probability of a mutation, the numeric presentation may provide substantial reassurance supporting recommendations based on empiric cancer risks in lieu of or after uninformative genetic testing. Because most women who participate in GCRAs receive uninformative (negative) test results, the art of breast cancer risk management depends on accurate estimation of empiric risk, and each of the models incorporates
different factors, used selectively based on the characteristics of the patient’s personal and family history. Claus and colleagues determined useful age-specific risk estimates, based on the number and age of first- and second-degree relatives with breast cancer, from analysis of epidemiologic data from the Cancer and Steroid Hormone study. The author adapted the published tables to a free, easy-to-use application for the iPhone and iPad (BRisk; Breast Cancer Risk Assessment Application). All of these models may serve as a basis for determining applicability of breast MRI screening (see discussion above). Although less applicable to women wherein family history of early onset breast or ovarian cancer is present, the Gail model based on age at menarche, age at first live birth, number of previous breast biopsies (± atypical ductal hyperplasia), and number of first-degree relatives with breast cancer, has been validated in several ethnic populations and is the primary tool for determining eligibility for chemoprevention with tamoxifen or raloxifene. For additional information regarding breast cancer risk probability models, please see the article by Zohra Ali-Khan Catts and Heather Hampel in this issue.

SUMMARY

This article summarizes the surgical implications of germline predisposition to breast cancer as it pertains to the application of increasingly more complicated NGS-based tests. The rapid pace of change will continue to challenge paradigms for GCRA, including contemplation of the interface between somatic (tumor) and germline genomic profiles. This is a complex, rapidly changing field. Keep this issue with you at all times and please tell your colleagues to do the same.

REFERENCES


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