Management of Women Who Have a Genetic Predisposition for Breast Cancer

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Breast cancer is a major public health problem, affecting 12.3% or one in eight of all women in the United States (123/1000 women) during their lifetime [1]. The three most important risk factors for breast cancer, in decreasing order of importance, are gender, aging, and family history [2]. Although many women have no immediate family members who have had breast cancer, some clearly do. Since the nineteenth century, there have been numerous reports of families suffering from multiple cases of breast cancer. In 1866, Paul Broca, a French surgeon, published the first such description, reporting that 10 of 24 women through five successive generations of his wife’s family had died of breast cancer [3].

Approximately 5% to 10% of all breast cancers in the United States occur in women who have a genetic predisposition, and most of these are attributable to mutations in the breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) [4,5]. Other genes also are associated with breast cancer, including p53, PTEN, STK11/LKB1, CDH 1, ATM, and CHEK 2 [6]. The lifetime risk of breast cancer...
(penetrance) varies considerably among women who carry these mutations. The high-penetrance mutations (eg, *BRCA1*, *BRCA2*, *p53*, *PTEN*, *STK11/LKB1*, *CDH1*) are associated with a high lifetime risk of breast cancer (40%–85%), whereas the low-to-moderate penetrance mutations (eg, *ATM*, *CHEK 2*) are associated with a lower risk [6]. These mutations are associated with an increased risk for other cancers and diseases as well as breast cancer. Thus, these mutations are linked with a diverse spectrum of syndromes that includes the hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*), Li-Fraumeni syndrome (*p53*), Cowden’s disease (*PTEN*), Peutz-Jeghers syndrome (*STK11/LKB1*), hereditary diffuse gastric carcinoma syndrome (*CDH 1*), ataxia-telangiectasia (*ATM*), and a Li-Fraumeni syndrome variant (*CHEK 2*) [6,7]. Many of these syndromes are discussed in other articles in this issue. This article focuses on the hereditary breast and ovarian cancer syndromes, which are responsible for more than half of the known cases of hereditary breast cancer. Much of the discussion focuses on the management of breast cancer risk, but *BRCA* mutation carriers also are at increased risk for ovarian cancer [8]. Therefore, issues pertinent to the management of ovarian cancer risk in *BRCA* mutation carriers are discussed briefly. Finally, issues relevant to breast cancer treatment in mutation carriers are discussed.

**Hereditary breast and ovarian cancer syndrome**

*BRCA1* and *BRCA2* are tumor-suppressor genes, identified in chromosomes 17 and 13, respectively, coding for proteins intimately involved in cellular growth and differentiation [9,10]. In the United States approximately 1 woman in 250 carries a mutation in these genes, predisposing these women to an increased risk for breast and ovarian cancer [11]. The *BRCA1* and *BRCA2* gene mutations are transmitted in an autosomal dominant manner and therefore may originate from either the maternal or paternal side [12]. Each offspring of a *BRCA1* or *BRCA2* mutation carrier has a 50% chance of inheriting that mutation, and a carefully documented family history is essential for the initial assessment of any woman concerned about a hereditary predisposition to breast cancer. If a woman has multiple close relatives (mother, sisters, daughters, grandmothers, aunts) who have had breast and ovarian cancer diagnosed at an early age (before age 50 years), close relatives who have had bilateral breast cancer, close male relatives (father, brothers, uncles, grandfathers, sons) who have had breast cancer, and/or if the woman is of Ashkenazi Jewish ancestry, a hereditary predisposition to breast cancer might be suspected [13]. Even in women who have one or more of these risk factors, however, the likelihood of a *BRCA1* or *BRCA2* mutation is quite low [14].

The *BRCA1* and *BRCA2* genes were cloned in 1994 and 1995, respectively, and genetic testing for breast cancer susceptibility was adopted widely
soon afterwards [15,16]. Numerous mutations now have been identified in each of these genes, and different mutations within the same gene are associated with different risks for breast and ovarian cancer [12]. Among women who have \textit{BRCA1} and \textit{BRCA2} mutations, the lifetime risk of breast cancer is 36\% to 85\%, and the lifetime risk of ovarian cancer is 16\% to 60\% [17,18]. These risk estimates, however, were derived from large families with many affected members. Although family members share mutations in the \textit{BRCA} genes, they share other genes as well and often live in a similar environment. Thus, these risk estimates partly reflect the impact of other genetic or environmental factors and may not indicate the risk of breast and ovarian cancer among mutation carriers in the general population. Also, risk estimates often were derived from families outside the United States. Chen and colleagues [19] recently have estimated that, in the United States population, the cumulative breast cancer risk by age 70 years for \textit{BRCA1} and \textit{BRCA2} mutation carriers is 46\% and 43\%, respectively, and the cumulative risk for ovarian cancer is 39\% and 22\% [19]. These estimates point out that many women who have \textit{BRCA} mutations never develop breast or ovarian cancer.

Alterations in the \textit{BRCA1} or \textit{BRCA2} genes are more common in certain ethnic and geographic populations (eg, Ashkenazi Jewish, Norwegian, Dutch, Icelandic), and specific mutations (founder mutations) often are clustered in particular ethnic groups [20]. For example, alterations in the \textit{BRCA1} or \textit{BRCA2} gene occur in approximately 2.5\% of individuals of Ashkenazi Jewish decent, and three specific mutations (two in the \textit{BRCA1} gene and one in the \textit{BRCA2} gene) are ubiquitous in these individuals [21]. The three founder mutations frequently observed in persons of Ashkenazi Jewish heritage are 185delAG (\textit{BRCA1}), 5383insC (\textit{BRCA1}), and 617delT (\textit{BRCA2}). The risk of breast cancer is similar in carriers of the two founder \textit{BRCA1} gene mutations (approximately 65\%) but is lower in carriers of the founder \textit{BRCA2} mutation (43\%) [22]. Individuals of Ashkenazi Jewish heritage should be tested for all three founder mutations, because two or more may coexist in the same family.

Clearly, women who have \textit{BRCA} mutations have a markedly increased risk of developing breast and ovarian cancer at an early age. Men who have \textit{BRCA1} or \textit{BRCA2} mutations (particularly \textit{BRCA2}) also are at increased risk for breast cancer, although that risk is considerably lower than it is in women. Recently, it was estimated that the cumulative risk, by age 70 years, of breast cancer is about 1.2\% for male \textit{BRCA1} mutation carriers and about 6.8\% for male \textit{BRCA2} mutation carriers [23]. Carriers of the \textit{BRCA1} and \textit{BRCA2} mutations also are at increased risk for other cancers, notably cancers of the prostate and pancreas [24]. Women who have a strong family history for breast cancer may consider genetic testing, particularly if they wish to pursue strategies to lower their risk.
Genetic testing

Many organizations, including the US Preventive Services Task Force (USPTF) and the American Society of Clinical Oncology, recommend against genetic testing in women who have a low risk for the \textit{BRCA} mutation \cite{25,26}. In low-risk individuals, the potential risks of genetic testing outweigh the benefits. For instance, in a woman without a family history of breast cancer, how might one interpret an alteration in the \textit{BRCA} gene that never has been strongly linked to cancer? Such an alteration might be less pathogenic than other mutations or even phenotypically silent. Thus, indiscriminate genetic testing may produce needless anxiety and lead to unnecessary prophylactic surgery or other treatments. Women might be labeled falsely as having a genetic predisposition to breast cancer, with adverse ethical, legal, financial, and social consequences.

Over the years, a number of empiric models were developed to estimate a woman’s risk of developing breast cancer (eg, the Gail, Claus, Tyrer-Cuzick, and BRCAPRO models) \cite{6}. There now are models that specifically estimate the likelihood for deleterious \textit{BRCA} mutations (eg, the Myriad Genetic Laboratories, Couch, BRCAPRO, and Tyrer models) \cite{6,13}. These models incorporate information about personal or family history of breast and ovarian cancer as well as Ashkenazi Jewish background \cite{27}. If a woman has a 10% or greater probability of carrying a \textit{BRCA1} or \textit{BRCA2} gene mutation, genetic testing should be considered \cite{28}. Informed consent should be obtained before genetic testing, and the potential risks and benefits should be discussed in detail. Women should understand that the \textit{BRCA} test is “predictive” rather than “diagnostic” \cite{29}. Diagnostic tests confirm the diagnosis of a particular condition (eg, an extra chromosome 21 in an infant confirms the diagnosis of Down’s syndrome), whereas predictive tests reveal the likelihood of developing a particular disease (in this case, breast cancer) but do not confirm that an individual will develop the disease.

The first person tested for the \textit{BRCA} mutation should be a family member most likely to test positive, generally an individual who has developed breast cancer at a young age or an individual who has ovarian cancer \cite{27}. If a mutation is found in that family member, other members of the family should be tested for the same mutation. In a family in which a \textit{BRCA1} or \textit{BRCA2} mutation has been identified, individuals who do not carry the mutation are not at increased risk for breast or ovarian cancer. At worst, their risk is similar to that of the overall population, but it might be even less, because risk estimates of the overall population include women who carry the \textit{BRCA1} and \textit{BRCA2} mutations.

If a \textit{BRCA} mutation is not found in a family member who has breast or ovarian cancer, the test is not informative and does not provide useful information to other family members. In such instances, the cluster of breast cancer cases within a family might be attributable to mutations other than those in the \textit{BRCA1} or \textit{BRCA2} genes or to environmental or lifestyle factors. If no
family members who have cancer are alive or available for testing, the options for testing should be weighed and considered on an individual basis.

**Management options for mutation carriers**

To reduce cancer-related mortality, women who have *BRCA1* or *BRCA2* mutations may wish to consider screening, chemoprevention, or prophylactic surgery (Fig. 1). The impact of these interventions on cancer-related mortality is not understood fully, however, because no randomized, prospective trials have addressed their impact specifically in mutation carriers. The results of clinical trials indicate that breast cancer screening is beneficial in the overall population and that chemoprevention is useful in high-risk populations. Additionally, the results of retrospective and nonrandomized prospective studies indicate that these risk-reducing strategies benefit mutation carriers.

**Screening**

There always has been a widespread belief that the early detection of cancer is beneficial. For individuals at high risk for developing cancer, intensive cancer screening often is recommended, even if proper evidence to support such a recommendation is lacking. For example, it long was assumed that screening with sputum cytology and/or chest radiographs would reduce lung cancer mortality among smokers. Eventually, the results of four randomized, controlled trials proved this assumption wrong [30]. This example

![Fig. 1. Management options for women who carry the *BRCA1* or *BRCA2* mutations.](image-url)
illustrates why the impact of screening on cancer-related mortality should be ascertained through large, randomized, prospective trials whenever feasible. Such trials, however, probably are not feasible in women who have a genetic predisposition for breast cancer, so screening recommendations in these women often are based on the results of randomized, controlled trials undertaken in the general population. Although other types of studies (eg, retrospective and case-control control) have been used to assess the efficacy of screening, those studies have limitations, particularly in lead time, length, and selection biases [30,31].

“Survival” refers to the interval of time from diagnosis of cancer to death, and “lead-time bias” refers to the interval between the diagnosis of cancer by screening and usual clinical detection [30,31]. As a result of “lead-time bias,” one might conclude that screening improves survival, when in fact it simply extends the period of time over which the cancer is observed. The only way to exclude the effect of lead-time bias is to test the efficacy of screening in a randomized, controlled trial, with mortality as the end point. Thus, even though screening may result in the early detection of cancer, early detection alone never should justify its use. It is necessary to conduct randomized, controlled trials to prove that a particular screening modality reduces mortality.

In addition to “lead-time bias,” retrospective studies are subject to length bias and selection biases [30,31]. “Length bias” refers to the fact that slower-growing cancers exist in the preclinical phase for a longer period of time and therefore are more likely to be detected by screening. In contrast, faster-growing tumors exist for a shorter period of time in the preclinical phase and are more likely to be detected clinically in the intervals between screening sessions. Retrospective comparisons of screen-detected and clinically detected cancers might reveal that screen-detected cancers have better outcomes, but this finding could reflect, in part, the more indolent biology of the screen-detected cancers. Thus, length bias reflects the differences in tumor biology between the screen-detected and clinically detected cancers. There also are differences in the characteristics of women who volunteer for screening and those who do not; these differences result in selection bias. Women who volunteer for cancer screening generally are more health conscious (eg, eat nutritional foods, exercise regularly) than those who decline screening. As a result, women who volunteer for screening may have better outcomes after a cancer diagnosis, and these outcomes might be attributable in part to their lifestyle.

The only way to exclude lead-time, length, and selection biases is to conduct randomized, prospective trials with mortality as the end point. For breast cancer, five screening modalities commonly are considered: mammography, ultrasound, MRI, clinical breast examination (CBE), and breast self-examination (BSE) (screening CBE differs from screening BSE in that it requires the use of trained personnel) [30–32]. Nine randomized, prospective trials have assessed the impact of mammography screening (with or without
CBE) on breast cancer mortality in the general population: the Health Insurance Plan (HIP) of New York, Malmo, Two-County, Stockholm, Gothenburg, Edinburgh, Canadian National Breast Screening Study I (CNBSS I), Canadian National Breast Screening Study II (CNBSS II), and Age Trials [30,31,33]. Currently, a trial is underway in India to assess the impact of screening CBE alone in the general population [31]. Additionally, two trials, conducted in St. Petersburg, Russia, and in Shanghai, China, have assessed the impact of screening BSE on breast cancer mortality in the general population [34,35]. To date, no randomized, prospective trials have assessed the impact of ultrasound or MRI screening on breast cancer mortality. At least six nonrandomized prospective studies have shown that in high-risk patients MRI is more sensitive than mammography [36], but no randomized, prospective trials have assessed the impact of any of these screening modalities specifically in mutation carriers.

Several overviews (meta-analyses) of the mammography screening trials have been published [37,38]. These meta-analyses indicate that, in the general population, the impact of screening differs in younger and older women. For women who are over the age of 50 years at the start of these trials, a significant 20% to 25% reduction in breast cancer mortality is attributable to screening, evident after 7 to 9 years of follow-up. In contrast, for women below age 50 years at the start of these trials, the benefit of mammography screening emerges gradually, with a significant reduction in mortality (about 18%) appearing after 12 or more years of follow-up. These meta-analyses did not include the results of the Age trial, the most recent randomized clinical trial to examine the efficacy of screening mammography in women aged 40 to 49 years [33]. This trial showed that breast cancer deaths in the screened group were decreased, but that decrease did not reach statistical significance (relative risk, 0.83; 95% confidence interval [CI], 0.66–1.04).

Although mammography screening seems to be efficacious in the general population, its impact on mutation carriers is not known. Some investigators have suggested that, because the \textit{BRCA1} and \textit{BRCA2} genes code for proteins involved in DNA repair, low-dose radiation from mammography might be particularly detrimental in mutation carriers, potentially increasing their risk for breast cancer [39]. Additional data are needed to determine if this concern is valid, but recent studies seem to indicate that it is not [40,41].

To date, no randomized, controlled trials have compared CBE screening alone with no screening, although four of the nine mammography screening trials (HIP, Edinburgh, CNBSS I, CNBSS II) also included CBE as a screening modality [31]. The results of these four trials suggest that screening CBE can detect cancers effectively, and Barton and colleagues [42] estimate that screening CBE has a sensitivity of approximately 54% and a specificity of about 94%. Additionally, two randomized, controlled trials have examined the effect of screening BSE alone on breast cancer mortality in the general population [34,35]. The first of these trials conducted by the World Health Organization recruited women between the years 1985 and 1989 in
St. Petersburg, Russia. The other was initiated between the years 1989 and 1991 in Shanghai, China. In the control and study arms of these trials, breast cancer detection and mortality rates were nearly identical, but the number of breast biopsies performed was nearly twofold higher in the screened group. Thus, false-positive results are common with BSE screening and may lead to unnecessary biopsies.

At least six prospective, nonrandomized studies have evaluated annual MRI screening (in conjunction with mammography) in women at increased risk for developing breast cancer (Fig. 2) [36]. These studies were conducted in the United States, the Netherlands, Canada, the United Kingdom, Germany, and Italy, and participants either were documented BRCA1 or BRCA2 mutation carriers or had a very strong family history of breast cancer. In some of these studies, ultrasound and/or CBE also were used as screening modalities. The sensitivity of MRI ranged from 77% to 100%, whereas the sensitivity of mammography or ultrasound was only 16% to 40%. There are, however, no data from randomized prospective trials to indicate whether the improved detection rates associated with MRI screening translate to a reduction in breast cancer mortality. Although MRI is more sensitive than mammography, its specificity is lower. Kriege and colleagues [43] found that the specificity of MRI was 88%, compared with 95% for mammography. The lower specificity of MRI leads to higher recall and false-positive rates. The danger of false-positive screening results is unnecessary biopsies.

As mentioned earlier, evidence concerning the efficacy of breast cancer screening is derived from trials undertaken in the general population. To date, no randomized clinical trials have been designed to assess the benefit

Fig. 2. Breast cancer (arrow) detected on screening MRI.
of these screening modalities in mutation carriers. Nonetheless, several organizations have published screening guidelines for women who have a hereditary predisposition for breast cancer. The National Comprehensive Cancer Network recommends monthly BSE starting at age 18 years, CBE every 6 months starting at age 25 years, annual mammography starting at age 25 years, and annual breast MRI starting at age 25 years [6]. The American Cancer Society recommends annual BSE and annual breast MRI [44], beginning at age 30 years and continuing for as long as a woman is in good health. The USPTF, however, maintains that there is insufficient evidence at the present time to recommend for or against breast cancer screening in mutation carriers [26]. Given the uncertainty surrounding the efficacy of breast cancer screening among mutation carriers, it seems prudent to discuss its potential for benefit and harm with each patient.

*BRCA* mutation carriers also are at considerable risk for developing ovarian cancer. As yet, no data from randomized clinical trials (either in the general population or in high-risk women) indicate whether ovarian cancer screening reduces cancer-related mortality. Furthermore, there are no reliable methods for detecting ovarian cancer early. Nonetheless, a number of screening tests have been investigated for potential use, particularly the serum marker CA-125 and transvaginal ultrasound [45]. CA-125 is a protein produced by more than 90% of advanced epithelial ovarian cancers. Transvaginal ultrasound is the most promising imaging method for the early detection of ovarian cancer. Combining transvaginal ultrasound and CA-125 results in a higher sensitivity for ovarian cancer detection than either method alone but increases false-positive rates. Although *BRCA* mutation carriers generally have been urged to undergo screening with transvaginal ultrasound and CA-125, a recent study suggests that this screening may not detect tumors at a sufficiently early stage to influence prognosis [46].

**Prophylactic surgery**

To reduce cancer risk, *BRCA1* and *BRCA2* mutation carriers may wish to consider prophylactic surgery. These patients are at increased risk both for breast and ovarian tumors and for tumors arising from the fallopian tubes [47]. Thus, *BRCA* mutation carriers should consider prophylactic mastectomy and prophylactic salpingo-oophorectomy (rather than oophorectomy alone). Patients concerned about the potential impact of prophylactic mastectomy on body image may elect to undergo salpingo-oophorectomy alone because it is a “hidden” procedure and may reduce the risk of both ovarian and breast cancer risk. These patients generally opt for continued surveillance of the breasts. Alternatively, nulliparous women may consider prophylactic mastectomy initially and delay salpingo-oophorectomy until after childbearing. Again, no randomized, prospective trials have assessed the impact of these procedures, although the results of several retrospective studies indicate that they dramatically reduce
cancer risk. Patients should be made aware that these procedures do not eliminate cancer risk entirely.

Hartmann and colleagues [48] conducted a retrospective analysis of women who had a family history of breast cancer and who underwent prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. To estimate the number of breast cancers expected in the absence of prophylactic mastectomy, the authors applied the Gail model for women at moderate risk. For women at high risk, the authors compared those who underwent prophylactic mastectomy with their sisters who did not. In this study, prophylactic mastectomy reduced the incidence of breast cancer by 90%, and other studies have shown similar results [49–51].

Three procedures are used commonly for prophylactic mastectomy: total, skin-sparing, and subcutaneous (nipple-sparing) mastectomy (Table 1) [47]. Total mastectomy involves removal of the breast tissue, nipple, areola, and much of the skin overlying the breast. In contrast, skin-sparing mastectomy involves removal of the breast tissue, nipple, and areola, but preserves skin overlying the breast. Skin-sparing mastectomy facilitates breast reconstruction and results in a better cosmetic outcome than total mastectomy [52]. The reduction in breast cancer risk seems to be similar for total mastectomy and skin-sparing mastectomy. Subcutaneous mastectomy, which involves removal of the breast tissue but leaves the nipple and areola intact, seems to be less effective [47].

Breast reconstruction usually is undertaken at the time of prophylactic mastectomy. Reconstruction is feasible with either prostheses alone or autogenous tissue (with or without prostheses) [53]. If a patient opts for prosthesis alone, the prosthesis generally is placed below the pectoralis major muscle at the time of mastectomy. Alternatively, an expander can be placed and inflated gradually over a period of several weeks by injecting solution through a port. This process creates a ptosis, and the injectable port and expander subsequently are removed and replaced with a permanent prosthesis. In some instances, the expander is left in place as the permanent prosthesis. If the patient chooses reconstruction with autogenous tissue, then either a latissimus dorsi flap or the transverse rectus abdominis muscle (TRAM) flap might be considered [54]. The latissimus dorsi flap does not provide sufficient tissue bulk, and a prosthesis usually is placed beneath the flap.

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<td>Procedure</td>
<td>Description of procedure</td>
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<tr>
<td>Skin-sparing mastectomy</td>
<td>Removal of breast, nipple, areola</td>
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<tr>
<td>Total mastectomy</td>
<td>Removal of breast, nipple, areola, and skin overlying breast</td>
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<tr>
<td>Subcutaneous mastectomy</td>
<td>Removal of breast; preserves nipple and areola</td>
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TRAM flap provides considerable tissue bulk, and a prosthesis usually is not required. Although it might result in an aesthetically more appealing outcome, the TRAM procedure is technically more challenging and carries a greater risk of complications.

Among *BRCA* mutation carriers, the risk of ovarian cancer is considerably less than that of breast cancer. There are, however, no reliable means of detecting ovarian cancer early, and it is more lethal than breast cancer. Thus, mutation carriers often are urged to undergo bilateral salpingo-oophorectomy after completion of childbearing. Kauff and colleagues [55] and Rebbeck and colleagues [28] reported that prophylactic surgery (either salpingo-oophorectomy or oophorectomy) reduces the risk of ovarian cancer by about 90% in mutation carriers. Additionally, premenopausal oophorectomy in mutation carriers was associated with about a 50% reduction in breast cancer risk [28,55]. After removal of the ovaries, *BRCA* mutation carriers still are at small risk for developing papillary serous carcinoma of the peritoneum, so continued surveillance is warranted.

**Chemoprevention**

Tamoxifen is a selective estrogen-receptor modulator widely used in the treatment of estrogen receptor–positive breast cancers [56]. More than 20 years ago, Cuzick and Baum [57] reviewed the results of women who received tamoxifen following surgery for breast cancer and found that it reduced the risk of contralateral breast cancer. This observation led to the hypothesis that tamoxifen could prevent breast cancer, and four randomized, prospective trials were initiated to test this hypothesis. These trials were the Royal Marsden trial [58], the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial [59], the Italian trial [60], and the International Breast Intervention Study-1 trial [61], all of which assigned women randomly to receive either tamoxifen (20 mg daily) or placebo for at least 5 years. An overview of these trials showed that the administration of tamoxifen reduced the risk of invasive breast cancer by about 38% (95% CI, 28%–46%; *P* < .0001) [62]. Tamoxifen now is approved as a chemopreventive agent for women at high risk for breast cancer.

No randomized, prospective trial has tested the impact of tamoxifen specifically in *BRCA* mutation carriers, although each of the four trials mentioned earlier undoubtedly included women who had *BRCA* mutations. A subgroup analysis of the NSABP P-1 trial failed to show a significant benefit of tamoxifen in preventing breast cancers in *BRCA* mutation carriers, but such a benefit could not be excluded completely [63]. A case-control study, however, did find that tamoxifen was effective in preventing breast cancer in *BRCA* mutation carriers. In that study, Narod and colleagues [64] compared *BRCA* mutation carriers who had bilateral breast cancer with those who had unilateral disease. Women were interviewed or given a self-administered questionnaire to ascertain whether they had been treated with tamoxifen
after surgery for their first breast cancer. In these mutation carriers the multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0.50 (95% CI, 0.28–0.89). Tamoxifen was associated with a lower risk of contralateral breast cancer in *BRCA1* mutation carriers (odds ratio, 0.38; 95% CI, 0.19–0.74) than in *BRCA2* mutation carriers (odds ratio, 0.63; 95% CI, 0.20–1.50), even though *BRCA1* mutation carriers are more likely to develop estrogen receptor–negative tumors (83% of the breast cancers developing in *BRCA1* mutation carriers and 14% of those in *BRCA2* mutation carriers are estrogen receptor–negative).

The differential response rates among *BRCA* mutation carriers in the NSABP P-1 trial [59] and in the case-control study of Narod and colleagues [64] might be related to the timing of chemoprevention. Sixty percent of the P-1 participants were 50 years old or older, whereas nearly 90% of the case-control participants were younger than 50 years. Given that premenopausal oophorectomy is effective in preventing *BRCA1* tumors [65], tamoxifen also possibly should be administered before menopause.

Tamoxifen increases the risk of endometrial cancer and thromboembolism by twofold or more [66]. Raloxifene is a selective estrogen modulator that seems to have a better safety profile (lower risk of uterine cancer and thromboembolism) than tamoxifen [67]. A large, randomized, prospective trial compared the impact of tamoxifen and raloxifene in lowering the risk of breast cancer in postmenopausal women and found that the two were equally efficacious [67]. Much less is known about the potential impact of raloxifene in reducing breast cancer risk in *BRCA* mutation carriers, however.

Thus, women who carry the *BRCA* mutations have three major options to consider, with significant trade-offs. Screening is the most commonly used option but frequently is associated with false-positive results that produce needless anxiety. Additionally, cancers missed on screening (false-negative results) might affect outcome adversely. Although prophylactic surgery may reduce the risk of breast and ovarian cancer by 90%, mastectomy may affect a woman’s perception of her body image, and oophorectomy prevents childbearing. Even though chemoprevention may reduce the risk of breast cancer by as much as 50%, it increases the risk of endometrial cancer and venous thromboembolism by more than twofold. Clinicians should discuss the potential risks and benefits of these options with *BRCA* mutation carriers. Finally, the timing of intervention may be important, but this issue is not well defined and could differ for *BRCA1* and *BRCA2* carriers [68]. Ultimately, the best choice is the one made by a fully informed patient.

**Breast cancer treatment**

If a *BRCA* mutation carrier develops breast cancer, options for local therapy should be weighed carefully. Radiotherapy can be administered safely after breast-conserving surgery in *BRCA* mutation carriers, although
these patients are at increased risk for developing second primary cancers (particularly contralateral breast cancers) [69]. Pierce and colleagues [70] followed 160 mutation carriers and 445 matched controls diagnosed with breast cancer following breast-conserving surgery. Mutation carriers who had not undergone oophorectomy had an increased risk of ipsilateral breast tumor recurrence; those who had undergone oophorectomy did not. Many women who have BRCA mutations opt for bilateral mastectomy, however. A recent study of women who had BRCA1 or BRCA2 mutations who had been diagnosed with unilateral breast cancer found that bilateral mastectomy was accepted more widely in North America than in Europe [71]. In the United States, nearly half of all BRCA mutation carriers opted for bilateral mastectomy. At the time of mastectomy, a sentinel biopsy generally should be performed in the axilla on the side affected by breast cancer. If the sentinel node contains metastatic disease, a complete axillary dissection is indicated. Patients who have significant involvement of the axillary lymph nodes (generally with four or more lymph nodes containing metastatic disease) should consider postmastectomy radiotherapy [72].

For BRCA mutation carriers who are diagnosed with breast cancer, the choice of systemic therapy is determined by standard prognostic and predictive factors [69]. There are no treatments specifically tailored for patients who have BRCA mutations. Decisions concerning systemic therapy are based both on nodal status and tumor size and, more importantly, on estrogen receptor status and HER-2 status of the tumor. Thus, BRCA mutation carriers who are diagnosed with breast cancer should receive the same systemic treatments as patients who have sporadic breast cancer, based on standard prognostic and predictive factors.

Summary

Genetic testing now makes it possible to identify women who have a greatly increased risk for developing breast cancer. Not all women who have a family history of breast cancer are appropriate candidates for genetic testing, however. Women must be informed about the potential risks and benefits of genetic testing, and those who are found to carry mutations in the BRCA1 or BRCA2 genes should be advised of all management options. Three strategies commonly are employed to manage BRCA mutation carriers: screening, prophylactic surgery, and chemoprevention. No randomized prospective trials have addressed the impact of these interventions in mutation carriers, however, and their potential risks and benefits should be discussed with each patient. Ultimately, many patients may elect more than one option (eg, screening initially and then prophylactic surgery after completing childbearing). Thus, physicians who manage patients who have BRCA mutations should be prepared to follow these patients over a span of many years.
References


