Management of the asymptomatic BRCA mutation carrier

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Abstract: Current management of an asymptomatic BRCA mutation carrier includes early initiation and intensive cancer screening in combination with risk reduction strategies. The primary objectives of these interventions are earlier detection and cancer prevention to increase quality of life and prolonged survival. Existing recommendations are often based on the consensus of experts as there are few, supportive, randomized control trials. Management strategies for unaffected patients with BRCA mutations are continually redefined and customized as more evidence-based knowledge is acquired with regard to current intervention efficacy, mutation-related histology, and new treatment modalities. This review provides an outline of current, supported management principles, and interventions in the care of the asymptomatic BRCA mutation carrier. Topics covered include surveillance modalities and risk reduction achieved through behavioral modification, chemoprevention, and prophylactic surgery.

Keywords: high risk, screening, risk reduction, hereditary breast cancer syndrome

Introduction
BRCA prevalence and related cancer risk
Breast cancer susceptibility genes, BRCA1 and BRCA2, were discovered in the early 1990s.1–3 Inheritance of a mutation in these tumor suppressor genes accounts for approximately 7% of breast and 10% of ovarian cancer cases.4 The estimated BRCA1 and BRCA2 mutation carrier frequencies in the general population are 1 in 300 and 1 in 800, respectively.5 In the Ashkenazi Jewish population, the BRCA mutation carrier frequency is as high as 1 in 40.6–9 These frequencies estimate that between 400,000 and 1 million individuals in the United States are gene mutation carriers.10 Despite the availability of BRCA gene mutation testing for over a decade and increasing knowledge about related cancer risks, only 5% of the carrier population has been identified.11

Risk of breast cancer
The cumulative probability that a carrier of a mutation in BRCA1 or BRCA2 will develop breast cancer (penetrance) is uncertain and varies according to the population studied. The most comprehensive analysis of population-based studies reported a risk at age 70 of 65% for female BRCA1 carriers and 45% for female BRCA2 carriers.12 Risk for an individual female carrier is also influenced by family history. Women with relatives diagnosed with breast cancer at younger ages or bilateral breast cancer appear to be at higher risk.13 Location of the mutation on the gene may also impact cancer risk. Mutations located within the central region of the BRCA2 gene are associated with
a higher risk of ovarian cancer and a lower risk of breast cancer. This region of the BRCA2 has been designated the ovarian cluster region.13

The risk of contralateral breast cancer in a female BRCA mutation carrier with a prior history of breast cancer is also increased. In a nested, case-control study of women diagnosed with unilateral breast cancer before age 55, women with contralateral breast cancer diagnosed 1 year or greater from the primary breast cancer were identified.14 These cases were then tested for mutations in BRCA1 and BRCA2. Carrying a BRCA1 mutation was associated with a 4.5-fold increased risk of developing contralateral cancer.14 The risk for BRCA2 mutation carriers was increased by 3.4-fold.14 The relative risk for BRCA1 mutation carriers is inversely related to the age of first cancer diagnosis, with increased risk seen in those diagnosed with their first cancer at a younger age.14,15 The impact of age at first breast cancer diagnosis for contralateral cancer risk in BRCA2 carriers is less clear. While one study showed a lower risk for patients who were older at the time of diagnosis with their first cancer, this difference was not statistically significant.15

The risk of breast cancer for men who carry a mutation in BRCA2 is greater than that of the general population. The estimated cumulative risk by age 70 is 6.8%.16 The risk for male carriers of BRCA1 mutations is less well established but also appears to be increased at 1.2%.16

**Risk of ovarian cancer**
The cumulative risk of ovarian cancer in BRCA1 mutation carriers is estimated to be between 27% and 45%.11,17 There is also a significantly increased risk for fallopian tube cancer.17 Lifetime risk for the development of ovarian cancer in a BRCA2 mutation carrier ranges between 10% and 20%.12,18

**Risk of other cancers**
In addition to the increased risk of breast and ovarian cancer, carriers of mutations in BRCA1 are reported to have a 2-fold to 3-fold increased risk of pancreatic cancer.17,19 Prostate cancer risk does not appear to be increased, although the disease may occur at an earlier age.20 Additionally, BRCA1 mutation carriers have an increased lifetime risk of developing cancer in general than nonmutation carriers. A kin-cohort study revealed that by age 80, a female mutation carrier’s estimated risk of cancer was 98% as compared with a noncarrier whose risk was 32%.18 This risk was estimated to be 59% for a male BRCA1 mutation carrier as compared with 40% for a noncarrier.18

Carriers of BRCA2 germ line mutations are also at increased lifetime risk of developing pancreatic cancer.21 Male BRCA2 mutation carriers are at an increased risk of prostate cancer.21 These individuals have a 7-fold greater likelihood of being diagnosed with prostate cancer before the age of 65 years than noncarriers.22 As with BRCA1, the lifetime risk of any cancer in BRCA2 mutation carriers is increased as compared with noncarriers with a 73% risk for women and 58% for men.18

**Surveillance**
Current screening recommendations for the asymptomatic BRCA mutation carrier encompass examination, imaging, and laboratory evaluation. Surveillance for female carriers emphasizes screening techniques for breast and ovarian cancers. Recommendations for male carriers include breast and prostate cancer screening modalities. Screening does not reduce the risk of developing these cancers but may result in earlier detection. Early detection leads to earlier initiation of treatment when cancers may be more responsive and treatment may be more efficacious. The lack of scientific evidence to support some of these modalities requires providers to make informed decisions with their patients regarding the benefits, risks, and limitations of these screening options.

**Breast cancer screening**
Several national guidelines exist for breast cancer screening in women of average population risk.22,23 Amongst these guidelines, much debate exists regarding age at which screening should be initiated, frequency of screening, and modalities used to screen women in the general population for breast cancer. There is general agreement that women with a higher lifetime risk of breast cancer, such as that conferred by a BRCA4 mutation, should undergo earlier, more frequent screening with consideration of additional imaging modalities. A consolidated summary of current screening recommendations published by National Comprehensive Cancer Network (NCCN), American Cancer Society (ACS), American College of Radiology (ACR) and other national organizations for the asymptomatic, female, BRCA mutation carrier includes the following22,24–26 (Table 1):

- Monthly breast self-exam (BSE) beginning at the age of 18 years
- Semiannual clinical breast exam (CBE) beginning at the age of 25 years
- Annual mammograms beginning at the age of 25–30 years or individualized based on the earliest age of cancer onset in the family
- Annual breast magnetic resonance imaging (MRI) beginning at the age of 25–30 years or individualized based on the earliest age of cancer onset in the family
BSE and CBE

BSE and CBE played an important role in breast cancer detection prior to the advent of screening mammography practices. In recent years, some screening guidelines removed the recommendation for monthly BSE in women at average risk for breast cancer. A 2003 Cochrane Review of two, large clinical trials concluded that the routine practice of BSE does not improve breast cancer mortality rates and nearly doubles the negative breast biopsy rate.²⁷ Despite these data, the ACS continues to advocate for the practice of BSE in high-risk women.²²,²⁶ Two, recently published, single-institution studies demonstrated support for BSE as an important means of initial tumor detection.²⁸,²⁹ A retrospective study by Samphao et al²⁸ concluded that of 628 women aged <40 years diagnosed with breast cancer (10% were BRCA mutation carriers), 71% of tumors were initially detected by BSE. Similarly, a prospective study conducted by Wilke et al²⁹ looked at 147 women undergoing high-risk surveillance. BSE was the most common initial method for detection of a mass in this study, exceeding the detection rate achieved by MRI.²⁹ Of the 24 masses detected by BSE in this study, 6 (25%) were confirmed cancers.²⁹ BSE in the high-risk population may be beneficial in detecting interval cancers. It represents a cost-effective, empowering, noninvasive technique to increase awareness of breast composition in these high-risk women.

The current value of CBE in the average-risk population is also controversial. The highest reported sensitivity of CBE in the literature is 54% when utilized in women of average population risk.³⁰ As with BSE, there is limited evidence of a mortality benefit to CBE alone. With improvements in imaging technology, detection of occult disease by CBE may become less frequent amongst the general population. Conversely, BRCA mutation carriers are likely to be younger with denser breast tissue. Dense breast tissue is an independent risk factor for breast cancer with a reported 2- to 6-fold increase in relative risk.³¹-³³ Mammography sensitivity is known to diminish with increasing breast tissue density. The fast growth rate of BRCA-related cancers may lead to a higher interval detection rate by physical exam in the high-risk patient population.³⁴

Mammography and MRI

Most national guidelines support the initiation of annual screening mammograms for the general population at age 40.²²,³³ While expert opinion recommends early initiation of imaging in high-risk women, there is a paucity of evidence-based data to support this recommendation. The quality of mammography as a screening tool in women of younger ages remains uncertain. As previously discussed, the sensitivity and specificity of mammography are recognized to be inversely related to breast tissue density. In addition to efficacy, there

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**Table 1** Surveillance recommendations for the asymptomatic BRCA mutation carrier

| Screening modality | Age to initiate (y) | Frequency | Notes |
|--------------------|---------------------|-----------|-------|
| **Recommended screening** | | | |
| Breast (female) | | | |
| BSE | 18 | Monthly | Mammogram and MRI initiated at age 25–30 or individualized based on the earliest age of cancer onset in the family |
| CBE | 25 | Semiannual | |
| Mammogram | 25–30 | Annual | |
| MRI | 25–30 | Annual | |
| Breast (male) | | | |
| BSE | | Monthly | Annual mammogram with presence of gynecomastia/parenchymal tissue |
| CBE | | Semiannual | |
| Mammogram | | Baseline (annual) | |
| Ovarian | Pelvic exam | 35 | Semiannual | Studies performed concurrently. Initiation age 35 or 5–10 y earlier than youngest diagnosed family member |
| TVU | 35 | Semiannual | |
| CA-125 | 35 | Semiannual | |
| Prostate | DRE | 40–50 | Annual | |
| PSA | 40–50 | Annual | |
| **Additional screening (investigational)** | | | |
| Pancreatic | Endoscopic ultrasound | 50 | Annual | Initiation age 50 or 10 y earlier than youngest diagnosed family member |
| Melanoma | Skin exam | | Annual | |
| | Ocular exam | | Annual | |
| Colorectal | FOBT | 50 | Annual | Follow population screening guidelines |
| | Sigmoidoscopy | 50 | Every 5 y | |
| | or colonoscopy | | Every 10 y | |

**Abbreviations:** BSE, breast self-exam; CBE, clinical breast exam; MRI, magnetic resonance imaging; CA, cancer antigen; TVU, transvaginal ultrasound; DRE, digital rectal exam; PSA, prostate-screening antigen; FOBT, fecal occult blood testing.
are safety concerns with earlier initiation of mammography screening. While the risk of radiation-induced breast cancer is low in the general population, the risk associated with a younger age at initial exposure, greater cumulative lifetime exposure, and increased chromosomal radiosensitivity in BRCA mutation carriers may be clinically significant. The disadvantages of lower sensitivity and higher ionizing radiation risk with surveillance mammograms in young BRCA mutation carriers has led to the investigation and support of other imaging modalities such as ultrasound and MRI.

In 2003, the ACS issued their recommendation for annual MRI screening as an adjunct to mammography in the high-risk population. This recommendation received additional endorsement from the ACR. A number of prospective studies demonstrated an increased rate of breast cancer detection through MRI screening in women at high risk. However, current recommendations emphasize that MRI should be used as an adjunct not as a replacement for mammography in the screening setting. Arguments against the use of screening MRI have included cost, limited patient access, poorer detection of ductal carcinoma in situ, and lower specificity with resultant higher false-positive biopsy rates. The perceived weakness of MRI screening may be abating as experience, technology, availability, and universal reporting criteria improve. More recent investigations demonstrate higher sensitivities and positive predictive values for MRI in a high-risk screening population. A prospective, multicenter cohort study by Kuhl et al investigated the use of mammogram, ultrasound, and MRI, alone or in combination, for screening of familial breast cancer. In this study, 687 asymptomatic women at high genetic risk for breast cancer underwent screening imaging. The sensitivity of each individual or combination of modalities was assessed. The detection sensitivities of mammogram and MRI alone were 33% and 93% respectively. When used in combination, mammogram and MRI achieved a greater although not statistically significant sensitivity of 100%. The addition of ultrasound to MRI did not increase sensitivity compared to MRI alone. Results of a more contemporary, multicenter study, the EVA trial (EVAulation of imaging methods for the secondary prevention of familial breast cancer) were recently published by the same author. The EVA trial demonstrated further support for MRI over mammography. It also challenges the current recommendation for a combined screening technique, questioning whether screening mammography should still be utilized in the high-risk population.

When to start mammography and MRI screening
Current guidelines have not established a single age to initiate screening. Consensus is to start screening at an earlier age (25–30 years) than women of average risk (40 years). Given the younger age of disease onset seen in women at risk for hereditary breast cancer, a recent study by Litton et al investigated the age of cancer diagnosis for successive generations of BRCA mutation carriers. The study concluded that genetic anticipation does occur with successive generations of BRCA carriers developing cancer at an earlier age. This finding was more pronounced amongst BRCA2 mutation carriers. Cumulative risk amongst BRCA1 carriers is estimated to be 3% by the age of 30 years and 19% by 40 years.

Timing of mammography and MRI
There is no current consensus on the time interval between annual mammogram and MRI. Screening with these modalities is either done concurrently or done staggered by 6 months. The concurrent approach allows for correlation between the two imaging techniques. The perceived advantage to staggering modalities by 6 months is the shorter interval between imaging exams. Most of the studies investigating screening mammography and MRI published in the past decade performed these imaging techniques in a concurrent or short- interval (within 1 month) fashion. The interval cancer rate detected in many of these studies was <10%. This relatively low, interval cancer, detection rate might suggest lack of benefit with a staggered approach. However, there are notable differences in the protocol design of these studies. No current evidence-based data are available to demonstrate the superiority of one timing scheme vs the other.

When to stop screening
No published recommendations provide an age or age range to consider discontinuing screening exams. Discontinuation of screening in an asymptomatic BRCA carrier can most practically be considered when the comorbidities of the patient confer a life expectancy of <5–7 years. Alternatively, it is logical to stop screening when no intervention would be pursued for an abnormal finding secondary to age or physical condition.

Additional research is needed to determine if there is any benefit to adjusting imaging modalities for different age ranges. Should all modalities be initiated or discontinued at the same time? The literature already questions the added value and potential harm of combination screening (mammography plus MRI) vs MRI alone in the young mutation carrier. Is it feasible to limit early screening to
MRI and transition to mammogram as sensitivity improves with age and decreasing breast density? Additional research is needed to answer these questions.

Other imaging modalities

The most common imaging modality to be considered in addition to the screening mammogram and MRI in high-risk women is breast ultrasound. Breast ultrasound is typically employed as an adjunct to mammogram for targeted diagnostic evaluation of a focal, suspicious area. As a screening tool, whole breast ultrasound has the lowest sensitivity of the three imaging modalities. The sensitivity of screening breast ultrasound in the literature is 17%-33%.51 Support for breast ultrasound screening initially stemmed from earlier screening studies in women at high risk or with dense breast tissue.52–55 However, ultrasound in combination with current mammogram plus MRI surveillance has not shown additional benefit.25 Therefore, the utility of screening ultrasound as an adjunct to mammogram may be limited to high-risk patients with contraindications or poor access to MRI.

Numerous other imaging modalities are currently under investigation. Modalities achieving US Food and Drug Administration approval include tomography, computed tomography–positron emission tomography, thermography, and scintimammography. To date, none of these imaging techniques achieved evidence-based support or expert consensus for screening in the asymptomatic BRCA mutation carrier.

Ovarian cancer

Unlike breast cancer, there is no recommended ovarian cancer screening for the general population. Despite a low incidence of 1.4%, ovarian cancer remains the fourth leading cause of death in American women. Early stages of ovarian cancer are often asymptomatic. Consequently, the majority of women present with late-stage disease. Investigative efforts to establish effective screening strategies for earlier detection and mortality reduction have been unyielding. Most prior studies examined the use of annual transvaginal ultrasound (TVU) and CA-125 testing in both average and high-risk populations. Two studies by van Nagell et al56,57 reported a decrease in stage at detection and ovarian cancer mortality with TVU. These studies also reported superior sensitivity and specificity in the high-risk vs average-risk population with TVU and CA-125 levels.56,57 A specificity of 22.7% was demonstrated with a single abnormal result, but an increase in specificity to 90.9% with repeatedly abnormal test results.56,57 Those arguing against TVU and CA-125 testing cite low positive predictive values, the high cost of a false-positive, exploratory laparotomy, and failure of TVU to detect primary peritoneal cancers or ovarian malignancy with normal ovarian size.56–58 However, given the 10%-45% lifetime risk for ovarian cancer in BRCA mutation carriers,11,12,17,18 additional consideration is given to ovarian cancer screening by TVU and CA-125 testing. While the risk-reducing prophylactic oophorectomy is more effective in preventing ovarian cancer in these women, some may not opt to pursue this intervention until after their childbearing years. Without more effective screening methods available, TVU and CA-125 levels continue to be recommended and endorsed by national organizations for women at high risk for hereditary breast and ovarian syndromes.24 Current NCCN screening guidelines for BRCA mutation carriers not undergoing prophylactic oophorectomy include the following24 (Table 1):

- Semiannual concurrent pelvic exam, TVU, and CA-125 antigen determination beginning at the age of 35 years or 5–10 years earlier than the youngest family member diagnosed with ovarian cancer

Male breast cancer and prostate cancer

Cancer risk for male BRCA mutation carriers is less well defined. Fewer men have pursued BRCA testing. Consequently, there are fewer studies investigating cancer risk attributable to BRCA1 and BRCA2 in men. BRCA4 mutations in the male population are reported to increase risk for breast, prostate, pancreatic, colon, melanoma, stomach, and other cancers. Phenotypic expression is thought to be variable amongst the two genes and various patient subpopulations. However, these differences are not well defined. As a result, there are few established screening recommendations for male carriers. Recommendations are limited to breast and prostate screening and do not distinguish between BRCA1 vs BRCA2 gene mutations carriers. Current NCCN guidelines include the following24 (Table 1):

- Monthly BSE
- Semiannual CBE
- Baseline mammogram followed by annual mammogram in the presence of gynecomastia or noted parenchymal tissue
- Population screening guidelines for prostate cancer beginning at the age of 40–50 years
  - Digital rectal exam (DRE)
  - Prostate screening antigen (PSA) testing

The literature suggests that BRCA mutations account for at least 20% of male breast cancer cases, with a higher phenotypic expression in BRCA2 carriers.39 Stage per stage female and male breast cancer is equivalent in prognosis. The later stage of presentation for male breast cancer cases portends a worse overall prognosis.40 This may justify the
recommendation to follow male carriers with mammography in addition to exam, especially in the presence of appreciable breast volume.

Prostate cancer is the leading cancer diagnosis amongst the male population in the United States. Guidelines for screening in the general population were recently updated by the ACS in 2010.\textsuperscript{61} Earlier stages of detection and decreasing mortality in prostate cancer have been observed since the inception of PSA testing. Controversy and uncertainty remains as to whether PSA testing results in overdiagnosis and overtreatment of prostate cancers that would otherwise have low clinical impact. The benefit of DRE in addition to PSA testing is even less certain. At best, DRE increases cancer detection rates by 17%.\textsuperscript{62} Consequently, the updated ACS guidelines emphasize the need for shared and informed decision-making prior to the initiation and continuation of prostate screening in the general population.\textsuperscript{61} Given the risk of prostate cancer is increased 3-to 5-fold in male \textit{BRCA} mutation carriers,\textsuperscript{21,63} this population is encouraged to follow the ACS guidelines for men at high risk. The ACS recommends initiating annual DRE and PSA testing at the age of 40 years.\textsuperscript{61} Similar to the phenotypic expression of male breast cancer, the Breast Cancer Linkage Consortium reports a greater relative risk (RR) for prostate cancer amongst \textit{BRCA2} carrier (RR = 7.3).\textsuperscript{63} None of the current guidelines further delineate prostate screening by specific gene mutation or age. The recommended time to discontinue prostate screening is at life expectancy <10 years.\textsuperscript{60}

**Other associated cancer screening**

Mutations in the tumor suppressor genes \textit{BRCA1} and \textit{BRCA2} place male and female carriers at increased risk for a number of other cancers, notably pancreatic, melanoma, colorectal, and other gastrointestinal tumors. Further research is needed to define the association of specific \textit{BRCA} mutations with these cancers. No expert consensus or evidence-based guidelines exist regarding screening for these cancers. Some literature and investigational studies support considering the following additional surveillance modalities\textsuperscript{59,64–66} (Table 1):

- **Pancreatic:** annual endoscopic ultrasound, beginning at the age of 50 years or 10 years prior to earliest pancreatic cancer diagnosis in family\textsuperscript{64–65}
- **Melanoma:** annual full body skin and ocular exam\textsuperscript{69}
- **Colorectal:** population screening guidelines, beginning at the age of 50 years and continuing until 75 years old
  - Annual fecal occult blood testing
  - Sigmoidoscopy every 5 years or colonoscopy every 10 years\textsuperscript{66}

**Risk reduction**

**Behavioral modifications**

**Body mass index**

Obesity and postmenopausal weight gain have been associated with an increased risk of sporadic breast cancer. A single study of French–Canadian families with \textit{BRCA} mutations has addressed these risk factors for \textit{BRCA}-related breast cancer risk.\textsuperscript{67} This case-control study of 80 families examined dietary intake, physical activity, and weight gain.\textsuperscript{67} Findings demonstrated an increased risk of breast cancer associated with increased total energy intake and weight gain.\textsuperscript{67} Those in the highest total energy intake tertile had a breast cancer odds ratio (OR) of 2.76 (95% confidence interval [CI]: 1.10–7.02; \textit{P} = 0.026) as compared with those in the lowest tertile of intake.\textsuperscript{67} Weight gain after the age of 18 years and after the age of 30 years were associated with OR of 4.64 (95% CI: 1.52–14.12; \textit{P} = 0.011) and 4.11 (95% CI: 1.46–11.56; \textit{P} = 0.013), respectively.\textsuperscript{67} This study also concluded that women who consumed >2239 kcal/day were at greater risk of \textit{BRCA}-related breast cancer compared to women who consumed <1724 kcal/day.\textsuperscript{67} This finding was independent of age, BMI, and participation in sports or exercise, suggesting that caloric restriction may be related to a reduction in \textit{BRCA}-related breast cancer risk.\textsuperscript{67} Further investigations by the same author examined the impact of specific diets and foods on breast cancer risk.\textsuperscript{68} A diet rich in different types of vegetables and fruits was found to correlate with a decreased risk of breast cancer.\textsuperscript{69}

**Lifestyle**

Collaborative research conducted by the Breast Cancer Family Registry (a consortium of research groups in the United States, Australia, and Canada), the Kathleen Cunningham Consortium for Research into Familial Breast Cancer (Australia and New Zealand), and the Ontario Cancer Genetics Network (Ontario, Canada) have improved the understanding of how lifestyle may impact breast cancer risk among \textit{BRCA} mutation positive women.\textsuperscript{70} Data collected from case-control studies reported no evidence of increased breast cancer risk with alcohol consumption among carriers of \textit{BRCA1} and \textit{BRCA2} mutation who are aged <50 years.\textsuperscript{70} However, there was an increased risk of breast cancer before the age of 50 years in mutation carriers who smoke.\textsuperscript{70} Compared to nonsmokers, the OR for risk of breast cancer in
females with $\geq 5$ pack-years of smoking was 2.3 for $BRCA1$ carriers (95% CI: 1.6–3.6) and 2.6 (95% CI: 1.8–3.9) for $BRCA2$ carriers.\textsuperscript{71}

**Oral contraception**

Oral contraceptive use by $BRCA$ mutation carriers has been associated with a decrease in ovarian cancer risk.\textsuperscript{72–73} However, the impact of oral contraceptive use on the risk of breast cancer is less clear. A case-control study of $BRCA$ mutation carriers aged $<50$ years found no evidence of increased breast cancer risk amongst those who used oral contraceptives for at least one year.\textsuperscript{74} For $BRCA1$ mutation positive carriers, there was no association between longer duration of use and breast cancer risk.\textsuperscript{75} Conversely, an increased breast cancer risk was observed in $BRCA2$ mutation carriers who used oral contraceptives for at least 5 years (OR = 2.06; 95% CI: 1.08–3.94).\textsuperscript{74} Other investigators have not identified an association between oral contraceptive use and increased breast cancer risk.\textsuperscript{73} The use of current, low dose, contraceptive formulations in $BRCA$ mutation carriers can be supported by the lack of evidence for increased early-onset breast cancer risk and the known benefit of ovarian cancer risk reduction.

**Chemoprevention**

Two, large chemoprevention studies conducted by the National Surgical Adjuvant Breast and Bowel Project demonstrate that tamoxifen and raloxifene are effective in lowering the risk for developing an estrogen receptor (ER)-positive breast cancer in women at high risk by Gail model assessment.\textsuperscript{76} While there are no data on the impact of raloxifene on breast cancer risk for $BRCA$ mutation carriers, a subset analysis of the original prevention trial was performed to determine whether there is a benefit to tamoxifen over placebo in women with $BRCA$ mutations.\textsuperscript{77,78} Genetic testing was performed on the 288 women in the trial who developed breast cancer.\textsuperscript{77} Only 19 of the 288 patients were found to carry a $BRCA1$ or $BRCA2$ mutation.\textsuperscript{77} Of the 8 patients who carried a $BRCA1$ mutation, 5 received tamoxifen and 3 received placebo, yielding a risk ratio for tamoxifen of 1.67 (95% CI: 0.32–10.70).\textsuperscript{77} Of the 11 patients who carried a $BRCA2$ mutation, 3 received tamoxifen and 8 received placebo, yielding a risk ratio for tamoxifen of 0.38 (95% CI: 0.06–1.56).\textsuperscript{77} The differential effect of tamoxifen in reducing risk of breast cancer amongst $BRCA1$ and $BRCA2$ carriers has been hypothesized to relate to the increased frequency of ER-negative cancers arising in the setting of $BRCA1$ mutations and ER-positive cancers in the setting of $BRCA2$ mutations.\textsuperscript{20} Additional research has investigated the role of tamoxifen in risk reduction for contralateral breast cancer. Retrospective reviews of the impact of tamoxifen on contralateral breast cancer risk in patients with a personal history of unilateral, hormone receptor positive, breast cancer support its efficacy as a protective agent. A case-control study conducted by the Hereditary Breast Cancer Clinical Study Group found tamoxifen protective against contralateral breast cancer for both $BRCA1$ and $BRCA2$ mutation positive patients.\textsuperscript{79} The OR for contralateral breast cancer for $BRCA1$-positive patients on tamoxifen was 0.38 (95% CI: 0.19–0.74).\textsuperscript{79} For $BRCA2$-positive patients, the OR was 0.63 (95% CI: 0.20–1.50).\textsuperscript{79} In this study, the benefit of tamoxifen appeared to be independent of oophorectomy.\textsuperscript{79} A second case-control study confirmed the protective benefit of tamoxifen in preventing a contralateral breast cancer in women starting tamoxifen after diagnosis of their first breast cancer.\textsuperscript{80} The multivariant OR for contralateral breast cancer associated with tamoxifen use was 0.50 (95% CI: 0.30–0.85) in $BRCA1$ mutation carriers and 0.42 (95% CI: 0.17–1.02) in $BRCA2$ mutation carriers.\textsuperscript{81} However, in this study the benefit of tamoxifen was not seen in women who had undergone prior oophorectomy.\textsuperscript{81}

**Prophylactic surgery**

Risk reduction can also be achieved through removal of the “at risk” tissue by prophylactic bilateral mastectomy or bilateral salpingo-oophorectomy. While these procedures represent the most aggressive strategy, they are the most effective at reducing breast and ovarian cancer risk. Consideration of prophylactic surgery is appropriate for both $BRCA1$ and $BRCA2$ mutation carriers.

**Prophylactic bilateral mastectomy**

Prophylactic bilateral mastectomies (PBM) exhibit an 85%–100% reduction in breast cancer risk in retrospective and prospective studies.\textsuperscript{81,82} Similar findings were reported in studies conducted in known female $BRCA$ mutation carriers.\textsuperscript{81,83} The Prevention and Observation of Surgical Endpoints study is the largest, prospective cohort study to look at the risk reduction benefit of PBM in women with $BRCA$ mutations.\textsuperscript{84} Results of this trial supported a 90% reduction in risk with breast cancer being diagnosed in 2% of $BRCA$ carriers undergoing PBM compared to 49% of carrier who did not.\textsuperscript{84} Risk reduction was increased to 95% in women undergoing prior or concurrent prophylactic bilateral oophorectomy.\textsuperscript{84} To date, no randomized control trial has been conducted to examine the benefit of PBM. It is unlikely such a trial will be carried out...
given the probable disinterest of patients to be randomized to the procedure, the existing support for the efficacy of PBM, and the long follow-up time necessary for such a study.

Discussion of the risks and benefits of PBM requires open dialogue between patient and provider and must include type of surgery, reconstruction options, related risks, and potential psychological effects. Until recently, the majority of PBM were performed using a simple or skin-sparing mastectomy technique, removing the nipple areola complex with all the underlying breast parenchyma. More recently, a nipple-sparing approach has gained acceptance in the prophylactic mastectomy setting. Using a periareolar or inframammary incision, the breast parenchyma is removed with preservation of the nipple areolar complex. Breast tissue within the nipple is cored out to minimize the amount of breast tissue left behind. This technique is often best for women desiring reconstruction with smaller breast volume and minimal ptosis. Reconstruction options include immediate vs delayed and implant vs an array of autologous tissue flaps. Selection of the optimal reconstructive procedure must take into account patient choice, body habitus, and comorbidities. Risks associated with PBM can relate to the invasiveness of the procedures. Short-term complications include bleeding, seroma formation, and infection. It is not technically feasible to provide 100% risk reduction with this procedure. The risk of recurrence may be higher with nipple-sparing techniques that have the potential for greater amounts of residual breast tissue. The psychological impact of PBM must also be taken into consideration. Current data on the negative impact of PBM on body image are limited. Some data indicate that PBM improves quality of life by reducing emotional concern for developing breast cancer.85

Prophylactic bilateral salpingo-oophorectomy
Prophylactic bilateral salpingo-oophorectomy (PBSO) demonstrates a similar 80%–90% reduction in ovarian cancer risk for mutation carriers.86 An added benefit to PBSO is the 50% observed reduction in breast cancer when it is performed in premenopausal women.87,88 Breast cancer risk reduction is attributed to the beneficial effect of hormone deprivation.88,89 A recent meta-analysis conducted by Rebbeck et al86 pooled hazard ratio (HR) results from 10 studies investigating the reduction in risk associated with PBSO in BRCA1 and BRCA2 mutation carriers. Compiled results demonstrated a significant risk reduction with PBSO for both breast cancer (HR = 0.49) and ovarian cancer (HR = 0.21) in premenopausal BRCA4 mutation carriers.86 No difference was observed in breast cancer risk reduction between BRCA1 (HR = 0.47) and BRCA2 (HR = 0.47) carriers with PBSO.86 However, a recent prospective cohort study by Kauff et al90 concluded that the risk reduction associated with PBSO may be greater in the BRCA1 carrier. The equivalent or superior reduction achieved in BRCA1 carriers may be counterintuitive when considering the association of BRCA1 mutation to ER-negative breast cancers. Perhaps more intuitive is the inverse relationship suggested between breast cancer risk reduction with PBSO and age. Eisen et al91 investigated the difference in HR for carriers undergoing PBSO when aged <40 years, 41–50 years, and >50. Negligible risk reduction was found with PBSO in BRCA carriers aged >50 years compared to a 50% reduction in carriers aged 41–50 years, and a 64% reduction in carriers aged <40 years.91 Given these findings, the NCCN recommends consideration of PBSO in BRCA1 and BRCA2 carriers aged 35–40 years, at completion of child bearing, or based on the age of the earliest family member diagnosed with ovarian cancer.24

In addition to the increased risk for ovarian cancers, mutations in the BRCA genes increase the risk of fallopian and peritoneal cancers of common epithelial origin. For this reason, PBSO includes removal of both ovaries and fallopian tubes. The addition of a hysterectomy is advocated by some providers on the basis of residual epithelial fallopian tube tissue within the wall of the uterus.92,93 With the advent of minimally invasive surgery, the majority of PBSO are performed using a laparoscopic technique. NCCN guidelines additionally recommend that peritoneal washings be obtained at the time of surgery and fine sectioning be used in the pathologic examination of the ovaries and fallopian tubes.24

Patients should be appropriately informed about both the operative and long-term risks related to risk-reducing, bilateral salpingo-oophorectomy. As with mastectomy, it is not feasible to remove all of the cells at risk even with inclusion of a hysterectomy. The reported risk of BRCA1-associated, primary peritoneal carcinoma is up to 4.3%.86–88 PBSO limits reproduction and can precipitate early menopausal symptoms in younger women. Early menopause may increase the risks of osteopenia, osteoporosis, and cardiovascular disease. While data are limited, short-term administration of hormone replacement therapy does appear to be safe.94

Risk-reducing surgery: who, when, and what
The optimal timing of prophylactic surgery for an asymptomatic BRCA mutation carrier is highly personal. The earlier onset of disease seen in mutation carriers would support recommending these procedures at a younger age. However, efforts to optimize risk reduction in the younger age group may conflict with the negative impact of undergoing invasive procedures during or near childbearing years. It appears safe to delay PBSO until completion of parturition. Overall, PBSO
is pursued more often than PBM amongst BRCA mutation carriers.95–97 An increased acceptance of PBSO over PBM may relate to the “double” benefit effect of reducing breast and ovarian cancer risk, the less effective screening for ovarian cancer, the reduced invasiveness (shorter postoperative recovery, fewer operative wound complications) of the procedure, and the lesser impact it has on external body image.98

Two studies by Beattie et al98 in 2009 and Scheuer et al99 in 2002 investigated the adoption of prophylactic procedures, time from genetic testing to operative intervention, and predictors for undergoing risk reducing surgeries amongst BRCA carriers. Scheuer et al99 found that the 14.9% of carriers with at risk tissue chose to undergo PBM and 50.3% opted for PBSO. Median time to surgery from receipt of genetic test results was 5.3 months for PBM and 3.4 months for PBSO.99 Patients selecting PBM were younger and more likely to have first and second degree relatives affected by breast or ovarian cancer as compared with those opting for surveillance.89 Women choosing PBSO were 5 years older (47 vs 42 years) and more likely to have a history of breast cancer than those declining PBSO.99 A contemporary study by Beattie et al99 complements Scheuer’s findings. In this study, 23% of carriers pursued PBM and 51% underwent PBSO.98 Both procedures were performed at a median of 4 months from patient knowledge of positive BRCA test results.89 Predictors for utilization of risk reducing surgery included age <60 years, prior history of breast or ovarian cancer, and concurrent or prior acceptance of the alternative prophylactic procedure.98

Conclusion
The optimal management approach for early detection and cancer prevention in the asymptomatic BRCA carrier continues to evolve. This review presents the guidelines and data supporting the development of a personalized strategy for each asymptomatic BRCA mutation carrier. Many of the recommendations are based on expert opinion as it is difficult to conduct randomized control trials in this population. Optimizing management strategies requires knowledge of the benefits and limitations of the presented strategies, ongoing investigation with newer surveillance techniques and risk-reducing interventions, and informed decision-making between patient and provider.

Disclosure
The authors disclose no conflicts of interest.

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