Management Options After Prophylactic Surgeries in Women With BRCA Mutations: A Review

Dawn C. Allain, MS, CGC, Kevin Sweet, MS, CGC, and Doreen M. Agnese, MD, FACS

Background: Although breast cancer is relatively common, only about 5% of cases are due to inheritance of highly penetrant cancer susceptibility genes. The majority of these are caused by mutations in the BRCA1 and BRCA2 genes, which are also associated with an increased risk of ovarian cancer. Increased surveillance, chemoprevention, and prophylactic surgeries are standard options for the effective medical management of mutation carriers. However, optimal management of female carriers who choose to undergo prophylactic surgeries is still poorly understood.

Methods: The authors provide an overview of the current literature regarding medical management options for women carriers of BRCA1 and BRCA2 gene mutations and the implications for those individuals who have chosen to undergo prophylactic surgeries.

Results: BRCA mutation carriers who opt for prophylactic surgeries are still at risk for development of malignancy, and appropriate monitoring is warranted.

Conclusions: There are limited data on the appropriate medical management for BRCA mutation carriers after prophylactic surgeries. However, a management plan can be extrapolated from the general management recommendations for surveillance and other risk-reducing strategies in BRCA-positive individuals.
Introduction

In families where a strong history of breast and/or ovarian cancer exists, individuals who have not developed cancer may want to ascertain their risk for developing cancer and identify ways to manage this risk. This concern often appropriately leads to genetic counseling and testing, which can identify individuals at increased risk. Mutations in the BRCA1 and BRCA2 genes are responsible for the hereditary breast and ovarian cancer (HBOC) syndrome. The cumulative lifetime risk of breast cancer in women who carry BRCA1 or BRCA2 gene mutations is approximately 60% to 80%, and these cancers often occur at a younger age. The lifetime risk for ovarian cancer in women with BRCA1 mutations is estimated to be 40% to 50% and is slightly lower, 10% to 20%, in women who carry BRCA2 gene mutations. Although women with BRCA mutations might also be at higher risk for additional malignancies, the absolute risk is small compared to breast and ovarian cancer risk. Original studies suggested a relative risk of two- to fourfold for colon carcinoma in BRCA1 carriers, although this remains debatable. Malignant melanoma was originally reported as at excess relative risk (RR = 2.58, 95% confidence interval [CI] = 1.28–5.17; \( P = .01 \)) in the BRCA2 Linkage Consortium study but not confirmed in a smaller Dutch study; thus, the risk may be higher in specific BRCA2 families. Pancreatic cancer risks for female carriers was also shown to be elevated. In the BRCA2 Linkage Consortium study, estimated cumulative risk for pancreatic cancer by 70 years of age was 1.5% (95% CI = 0.9-2.1). A smaller BRCA2 carrier study in the Dutch population noted a four-fold lifetime risk for pancreatic cancer. For female BRCA1 carriers, the cumulative risk for pancreatic cancer by age 70 was significant (1.26%, 95% CI = 0.92-1.72). Since the identification of the BRCA genes, a number of advisory bodies and clinicians have published guidelines and review articles delineating clinical management options for individuals with BRCA mutations. Much of the early literature called for consideration of increased cancer surveillance, chemoprevention, and prophylactic surgeries despite the fact that, initially, efficacy of these modalities was unknown. Emerging literature demonstrates the efficacy of many but not all of these primary and secondary prevention and management strategies. 

Surveillance

Current recommendations for breast cancer surveillance in BRCA1 mutation carriers consist of breast self-examination, clinical breast examination, and breast imaging. Monthly breast self-examination should begin at age 18, although research studies have failed to show that this technique reduces breast cancer mortality. Clinical breast examinations should be performed by an experienced health care provider every 6 months beginning at 25 years of age or at 5 to 10 years before the earliest breast cancer diagnosis in the family. Annual mammography beginning at age 25 (or 5 to 10 years prior to the earliest breast cancer diagnosis in the family) is also recommended for surveillance in BRCA mutation carriers. A number of studies have demonstrated that annual breast MRI is more sensitive than mammography in detecting tumors in BRCA mutation carriers, and the most successful screening is one in which clinical breast examination, mammography, sonography, and MRI are utilized. Based on these recent studies, annual breast MRI has been incorporated into the surveillance recommendations.

The role of ovarian cancer screening remains controversial because it has not been shown to lead to earlier diagnosis or reduce mortality. Several studies that have attempted to determine whether ovarian cancer surveillance is beneficial in BRCA mutation carriers have failed to demonstrate a clear advantage, thereby supporting the concern that screening women with BRCA4 mutations is no more effective at reducing mortality than screening the general population. Despite the lack of literature to document decreased mortality, BRCA mutation carriers who have not yet had their ovaries removed are advised to undergo annual or semiannual screening using transvaginal ultrasound with color flow Doppler and serum CA-125 levels, beginning at age 25 to 35 years.

Chemoprevention

A number of investigators have attempted to assess the benefit of chemoprevention in BRCA1 mutation carriers. A case-control study by Narod et al found a 50% reduction in contralateral breast cancer risk in affected BRCA1 and BRCA2 mutation carriers when treated with tamoxifen. King et al performed BRCA mutation analysis for 288 women enrolled in the initial NSABP P-1 trial for whom DNA was available. Nineteen of the women who developed cancer (6.6%) were found to have either a BRCA1 or BRCA2 mutation. Individuals with BRCA2 mutations who used tamoxifen for 5 years were found to have a 62% reduction in primary breast cancer risk. There was no risk reduction in those with BRCA1 mutations. This study, although limited by a small sample size, suggests that tamoxifen may reduce breast cancer risk in BRCA2 mutation carriers but not BRCA1 carriers. More recently, Gronwald et al in a matched case-control study, analyzed data from 285 BRCA mutation-positive women with bilateral breast cancer and 751 BRCA mutation-positive controls with unilateral breast cancer. They found a 50% contralater-
al breast cancer risk reduction in carriers of \textit{BRCA} mutations when tamoxifen was given as treatment for the initial breast cancer. This suggests that tamoxifen may be effective in preventing breast cancers regardless of \textit{BRCA} mutation status.

Chemoprevention is also effective in lowering ovarian cancer risk. The long-term use of oral contraceptives has been shown to reduce the risk for ovarian cancer, even in women with \textit{BRCA} mutations. Bosetti et al\textsuperscript{50} showed a protective effect with oral contraceptive use for more than 5 years, regardless of age, parity, menopausal status, or family history of breast or ovarian cancer. In an initial case-control study of 168 matched \textit{BRCA} pairs, Narod et al\textsuperscript{31} found a significant reduction in ovarian cancer risk with any past use of oral contraceptives. The risk decreased with increasing duration of use (20% reduction for up to 3 years of use, 60% for 6 or more years). More recently, McLaughlin et al\textsuperscript{32} published a case-control study (3,223 women with \textit{BRCA} mutations from 10 countries) in which oral contraceptive use showed a highly significant reduction in ovarian cancer risk (\textit{BRCA1} odds ratio = 0.56, \textit{BRCA2} odds ratio = 0.39) in both univariate and multivariate analyses. The maximum protective effect was seen with 3 to 5 years of oral contraceptive use. Although other studies have confirmed this protective effect,\textsuperscript{33-35} the use of oral contraceptives has remained controversial,\textsuperscript{36} in large part because of the concern of a modest increase in the risk of breast cancer with long-term use (more than 5 years), especially among young \textit{BRCA1} mutation carriers.\textsuperscript{37}

\section*{Prophylactic Surgeries}

Several studies have shown conclusive evidence that prophylactic mastectomy is an effective risk-reducing strategy available to \textit{BRCA} mutation carriers.\textsuperscript{38-40} However, since good breast cancer screening is available and effective breast cancer treatment options exist, this is considered optional. In 2001, an early prospective study of 139 women with germline mutations in the \textit{BRCA} genes demonstrated a significant reduction in the incidence of breast cancer after 3 years of follow-up in women who underwent bilateral prophylactic mastectomy (BPM).\textsuperscript{38} A retrospective study by Hartmann et al\textsuperscript{39} published the same year, also found a substantial reduction in breast cancer risk in \textit{BRCA} mutation carriers who underwent BPM. Notably, in 2004, Rebbeck et al\textsuperscript{40} prospectively studied 483 women with \textit{BRCA} mutations who underwent BPM. Controls were \textit{BRCA} mutation carriers with no history of prophylactic surgery matched to \textit{BRCA} gene, center of care, and year of birth. These data confirmed findings from earlier studies showing a 90% reduction in breast cancer risk in women with \textit{BRCA1/2} mutations with BPM. Interestingly, women who had previously undergone prophylactic oophorectomy were afforded an even greater protective effect (95% risk reduction). Of note, 2 women who were diagnosed with breast cancer after BPM had both undergone subcutaneous mastectomy, which is discouraged as a prophylactic measure because significant breast tissue remains after this procedure (thicker skin flaps are made, leaving residual breast tissue behind, and often the nipple and areola are preserved). In 1 of these women, metastatic adenocarcinoma was detected in axillary lymph nodes with no evidence or primary tumor. In the other, cancer was detected in residual breast tissue.

Methods of surgical prophylaxis include total mastectomy, skin-sparing mastectomy (SSM), nipple-sparing mastectomy (NSM), and areola-sparing mastectomy (ASM).\textsuperscript{41} All of these techniques involve the removal of all breast tissue and vary with respect to the tissue retained. Total mastectomy involves removal of an ellipse of skin including the nipple and areolar complex. SSM preserves the majority of the breast skin but removes the nipple-areolar complex. NSM and ASM, as the names imply, preserve the nipple and areola, respectively.

SSM appears to be oncologically safe,\textsuperscript{42,43} and although no specific data for prophylaxis with SSM exist, it appears based on the treatment data that it is equivalent to traditional total mastectomy. While preserving the breast skin and all or part of the nipple-areolar complex has a cosmetic advantage, allowing a more natural-appearing reconstruction, the oncologic safety of SSM and ASM has not been fully established. Previous studies of mastectomy specimens for breast cancer treatment have shown that involvement of the nipple-areolar complex occurs in 6% to 50% of cases.\textsuperscript{44-52} This risk of occult nipple involvement has resulted in fear that salvaging the nipple and areola may lead to an increased incidence of breast cancer after prophylactic mastectomy. There are emerging data suggesting that in selected individuals with breast cancer, salvaging the nipple and/or areola may be oncologically safe.\textsuperscript{53,54} Only one study addressed the safety of NSM as a risk-reduction strategy.\textsuperscript{55} In this multi-institutional study, 55 unaffected women underwent NSM with immediate reconstruction. With a median follow-up of 24 months, 2 women developed breast cancer, but neither occurred at the nipple-areolar complex. The investigators concluded that NSM is a safe alternative; however, the limited number of patients studied and the short follow-up suggest that more data are necessary before this is considered the standard of care for high-risk women. It is believed that the prophylactic mastectomy in an unaffected \textit{BRCA} gene carrier calls for complete removal of all breast tissue, making subcutaneous mastectomy a suboptimal choice.\textsuperscript{56,57}

\textit{BRCA} mutation carriers are strongly advised to consider prophylactic bilateral salpingo-oophorectomy (PBSO) after age 35 years or after childbearing is com-
plete. Early studies demonstrated the efficacy of bilateral prophylactic oophorectomy in this high-risk group. However, most were retrospective studies that did not take into account genetic status or provide standardized pathologic examination of removed tissue. In a few of these studies, a significant percentage of women developed peritoneal carcinoma after surgery. Reports of a high incidence of occult carcinoma (2.5% to 12.8%) with more rigorous pathologic examination led to the realization that many of these purported primary peritoneal carcinomas might in fact represent manifestations of occult ovarian or tubal carcinomas. Thus, a standardized surgical and pathological protocol should be followed that includes serial sectioning and microscopic examination of the ovaries and Fallopian tubes as well as peritoneal lavage cytology at the time of PBSO. Recent work by Finch et al, which prospectively assessed the incidence of ovarian, fallopian tube, and peritoneal cancer in 1,045 BRCA mutation carriers who underwent PBSO compared with 783 BRCA carriers who did not have surgery, provided evidence for an 80% overall reduction in cancer risk (multivariate hazard ratio = 0.20, 95% CI 0.07–0.58; \( P = 0.003 \)). The estimated cumulative incidence of peritoneal carcinoma in this high-risk group, 20 years after surgery, was 4.3%. Domchek et al also examined the effect of oophorectomy on mortality in BRCA mutation carriers to show significant reduction in ovarian cancer-specific mortality (hazard ratio = 0.05, 95% CI 0.01–0.46) and overall mortality (hazard ratio = 0.24, 95% CI 0.08–0.71).

PBSO also provides a protective effect against breast cancer. An analysis of 1,439 women with breast cancer and 1,866 matched controls from a registry of BRCA mutation carriers was performed to estimate the odds ratio of breast cancer after having a PBSO. This study found a history of PBSO was associated with an overall 56% breast cancer risk reduction in BRCA1 mutation carriers and a 46% breast cancer risk reduction in BRCA2 carriers. Interestingly, this protective effect was sustained 15 years after surgery. In addition, data suggest that breast cancer risk reduction was greater if PBSO was performed before 40 years of age, presumably due to the decrease in circulating estrogens. Several other studies have confirmed the effect of PBSO on breast cancer risk reduction, with Rebbeck et al further showing that short-term use of hormone replacement therapy (HRT) does not offset this protective effect on breast cancer risk. Additional studies should provide more direct comparisons regarding the timing of surgery relative to the individual age and induction of natural menopause as well as use of estrogen only vs the use of combined HRT supplements and the longer-term impact on cancer risk.

Based on the accumulation of data demonstrating the combined ovarian and breast cancer risk reduction, PBSO may be the most important intervention available for these high-risk women. Drawbacks include the induction of surgical menopause and the residual but small (3% to 4%) risk for peritoneal cancer. In fact, fear of surgically induced menopausal symptoms causes some women to decline or delay surgery.

One of the most common questions that women with a BRCA mutation ask in genetic counseling sessions is how to best manage their risk after prophylactic surgery. In this context, there are several scenarios to consider. First, a BRCA mutation carrier could choose to undergo only a prophylactic mastectomy or only a BPSO. Second, she could elect to have both BPM and BPSO. Finally, she could choose prophylactic surgeries after having already been treated for a cancer, such as a contralateral prophylactic mastectomy or a BPSO after having had a breast cancer diagnosis. The remainder of this article reviews the current literature regarding medical management of BRCA mutation carriers after prophylactic surgeries, specifically focusing on unaffected carriers.

**Medical Management of BRCA Mutation Carriers Following Prophylactic Surgeries**

**Management of Risk After Prophylactic Mastectomy**

Given the high risk of breast cancer as well as the significantly increased risk for a contralateral breast cancer in BRCA mutation carriers, some women elect to undergo prophylactic mastectomy. To date there have been no studies that demonstrate how to manage residual breast cancer risk in BRCA mutation carriers who have undergone prophylactic mastectomy. Recommendations can be extrapolated from studies of women affected with breast cancer who were treated with therapeutic mastectomy and/or contralateral prophylactic mastectomy. Unfortunately, although there are many observational studies of breast cancer patient follow-up, there are no published consensus statements or guidelines regarding appropriate medical follow-up after mastectomy.

In all BRCA mutation carriers who undergo prophylactic mastectomies, regardless of whether or not breast reconstruction has been performed, a physical examination should be done at least annually. The obvious goal of this approach is to detect any masses in the residual breast skin, chest wall, or axilla that could represent breast cancer. Routine imaging is available regarding the use of mammography, ultrasonography, or MRI in BRCA mutation-positive women after prophylactic mastectomy with reconstruction, and there is controversy among clinicians regarding the role of breast imaging in
this setting. After an extensive search of the literature, only one study that discussed the use of ultrasonography in this situation was identified. This report suggested that in this setting, ultrasound was useful only to clarify findings identified on clinical examination. There is no evidence to support that tamoxifen, raloxifene, or aromatase inhibitors would be of additional benefit in lowering breast cancer risk in BRCA mutation carriers who have undergone prophylactic mastectomy.

Management of ovarian cancer risk in BRCA mutation carriers who have undergone prophylactic mastectomy would not differ from the current recommendations previously discussed. PBSO is recommended in these women. Semiannual screening with transvaginal ultrasonography with color Doppler, pelvic examination, and CA-125 analysis should occur until PBSO is performed, although the effectiveness of this screening is questionable. In addition, a discussion regarding the use of oral contraceptives as a risk-reducing strategy is warranted.

**Management of Risk After Prophylactic Bilateral Salpingo-Oophorectomy**

Due to the reduction in breast and ovarian cancer risk associated with the removal of the ovaries, women with BRCA gene mutations can elect to undergo PBSO without undergoing prophylactic mastectomy. To date, there is scant research regarding the management of BRCA mutation carriers after risk-reducing salpingo-oophorectomy. The residual cancer risks for both peritoneal and breast cancers warrant attention.

There are no studies that support screening for the residual risk of primary peritoneal cancer (3% to 4%). Questions remain as to whether serial measurements of serum CA-125 would be useful for detection, but this seems unlikely as this has not shown benefit in screening women with intact ovaries. The role of oral contraceptive use in reducing the risk of primary peritoneal carcinoma in women with BRCA mutations who undergo PBSO has not been evaluated. Although a theoretical benefit may be extrapolated from the data on ovarian cancer risk reduction, a study assessing the benefit on primary peritoneal cancer risk reduction in BRCA mutation carriers would be difficult to conduct due to the rarity of this condition.

Although PBSO is associated with a 46% to 56% breast cancer risk reduction, if BRCA mutation carriers start with a 60% to 80% lifetime risk, their residual risk for breast cancer is still significantly higher than the general population risk. This risk requires continued surveillance, as well as consideration of additional risk-reducing strategies such as chemopreventive agents (e.g., tamoxifen) or prophylactic mastectomy.

Another issue that arises in this group is whether the uterus should be preserved. Because women with BRCA mutations may eventually take tamoxifen, which is associated with an increased risk for endometrial carcinoma, some experts advocate the removal of the uterus at the time of PBSO. Another potential benefit of hysterectomy addresses the concern that HRT, used to ameliorate symptoms of surgical menopause, might increase breast cancer risk. Several studies have indicated that unopposed estrogen is associated with an increased risk for endometrial cancer, so if the uterus is left in place, combination estrogen/progesterone HRT would be preferred. However, the Women’s Health Initiative trial reports that extended use of combination estrogen-progesterone compounds is associated with an increased risk of breast cancer compared with estrogen alone. Thus, if hysterectomy is done at the time of PBSO, unopposed estrogen could be used as HRT with negligible breast cancer risk. Limited data exist regarding HRT after PBSO in BRCA mutation carriers, but most experts agree that the beneficial effects of PBSO far outweigh the theoretical increased risks associated with HRT. Several papers (decision analysis and indirect comparison) suggest that short-term use of HRT after PBSO does not significantly impact breast cancer risk.

Based on these early data, it is currently considered acceptable to treat premenopausal BRCA mutation carriers who undergo PBSO with short-term HRT to improve their menopausal symptoms. However, further studies are needed to determine the optimal duration of HRT use in BRCA mutation carriers after PBSO.

No data currently exist to assess the role of aromatase inhibitors after PBSO.

**Management of Risk Following Prophylactic Mastectomy and Oophorectomy**

BRCA mutation carriers who have undergone both BPM and prophylactic oophorectomy have significantly lowered but not completely eliminated their cancer risk. No data exist regarding the management of this group. However, routine follow-up should continue on an annual or semiannual basis. This follow-up should center on the detection of any skin, chest wall, or axillary masses that might represent primary breast cancers in retained breast tissue or nodal tissue. In addition, any abdominal complaints should be investigated to rule out the possibility of a primary peritoneal carcinoma. HRT should not be a significant issue since minimal breast tissue remains.

**Other Cancer Risk Management**

As women elect to undergo prophylactic surgeries to reduce their risk of dying of breast and ovarian cancer, medical management for other cancer risks associated with BRCA mutations is warranted. While studies have documented that BRCA mutations are associated with an increased risk for other cancers, such as pancreatic cancer and melanoma, there is a paucity of literature...
Discussing the appropriate management for these cancer risks. In regard to the cutaneous and ocular melanoma risk, a review by Liede et al suggests that discussion of annual skin and eye examinations be included in cancer surveillance recommendations for all individuals who carry \( BRCA2 \) mutations. Currently, screening \( BRCA \) carriers for pancreatic cancer is not recommended by the National Comprehensive Cancer Network (NCCN). However, a recent study suggests that screening for pancreatic cancer in \( BRCA2 \) mutation carriers with endoscopic ultrasonography and computed tomography may be beneficial. In addition, according to Habbe et al, a consensus conference of experts stated that screening for pancreatic cancer should be performed in \( BRCA2 \) carriers with at least one pancreatic cancer case in a first- or second-degree relative. The recommendation states that screening should start 10 years before the youngest age of onset in the family or by the age of 40 years. Currently, most experts agree that this screening should be performed in expert centers and, if possible, within a research setting.

**Psychosocial Management**

In addition to managing residual cancer risks after prophylactic surgeries, follow-up for \( BRCA \) mutation carriers who undergo prophylactic surgeries should include psychosocial assessment and support. The majority of studies exploring the psychologic impact of BPM have shown that women who choose surgery are satisfied with their decision, have diminished anxiety about cancer risk, and experience few psychologic difficulties. A study of 14 women who underwent BPM found a high level of satisfaction regarding their decision, their physical and emotional recovery, the side effects of surgery and reconstruction, and support of family and friends. However, 4 out of 11 of the women who underwent breast reconstruction were dissatisfied with the surgery. This dissatisfaction was primarily due to the impact of postoperative complications. Still, other studies have reported that women regret their decision and are dissatisfied with their cosmetic outcome. In addition, a subset of women who underwent BPM report adverse effects on emotional stability, self-esteem, sexual relationships, and feelings of femininity. Indicators predicting adverse negative psychologic reaction to BPM are lacking, thus until these factors are delineated, long-term follow-up of all women who undergo BPM might be warranted to monitor the postoperative, psychologic, sexual, and relationship outcomes.

Similarly, the majority of studies on BPSO found high levels of satisfaction with surgical prophylaxis and quality of life. Yet, studies have also found that some women who had BPSO experienced dissatisfaction with their decision. Dissatisfaction was associated with postoperative recovery, menopausal symptoms, and compromised sexual functioning. In addition, one study found that approximately 20% of the women who underwent BPSO still had elevated ovarian cancer risk concerns, which can affect psychologic well-being.

Since preventive surgeries are irreversible, it is important to identify women who might be dissatisfied with their decision so they may benefit from follow-up medical management, including psychologic support. A follow-up genetic counseling consultation after prophylactic surgeries have been performed can be useful in identifying women who require additional support services.

**Conclusions**

Much progress in our understanding has occurred since the description of the \( BRCA1 \) genes as a cause of hereditary breast cancer in the mid 1990s. \( BRCA \) mutation carriers undergoing BPM and/or BPSO dramatically reduce their risk for breast and ovarian cancer. Nonetheless, follow-up medical care is necessary to enhance detection of cancer that may occur because of residual risk. Screening modalities and risk-reducing strategies are dependent on the surgeries elected and should also include psychologic follow-up. Research regarding long-term follow-up of \( BRCA1 \) mutation carriers is warranted to better address the management of residual cancer risk and the psychologic impact of surgeries. Key to the continued growth in our understanding of risk reduction strategies in these high-risk individuals is the identification of at-risk families and the referral to genetic specialists. Soliciting individual participation in research studies that identify additional factors predictive of subsequent cancer development is imperative to refine our risk reduction strategies. Much has been learned; much more will follow.

**References**

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