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Managing the Breast in Patients Who Test Positive for Hereditary Breast Cancer

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ABSTRACT

Purpose and Methods. The patient who tests positive for hereditary breast cancer has several important decisions to make regarding management of the breasts. Before making an informed decision, the physician must first review the screening assessment to make sure that the patient does not harbor an undiagnosed breast malignancy. In the absence of a malignancy, the management options for the breast range from nonoperative surveillance to prophylactic mastectomy to prevent cancer. In the event that a breast malignancy is diagnosed after a positive genetic test, implications for management of both the affected and the unaffected breast must be considered.

Results and Discussion. The clinical assessment of the patient who tests positive is discussed. If routine pretest mammograms were negative, should additional diagnostic studies be performed to exclude an undetected/occult malignancy, and if so, what are the roles of magnetic resonance imaging, ultrasonography, digital mammogram, and detection of breast cancer circulating tumor cells? Medical management may include increased surveillance and chemopreventative therapy, including tamoxifen and oral contraceptives. Surgical interventions may be undertaken to reduce risk in people with a genetic susceptibility gene for breast or ovarian cancer; risk-reducing surgical options include mastectomy with or without reconstruction and nipple-sparing techniques. Finally, we discuss management decisions for women who test positive and who are diagnosed with a primary breast cancer, compared to women who have no obvious primary tumor but test positive.

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MANAGING THE RISK OF PRIMARY BREAST CANCER

A major goal of systematic breast cancer risk assessment is the identification of *BRCA* gene mutation carriers before they developed breast cancer. The surgical oncologist is often called upon to manage breast cancer risk in these patients (Table 1). The initial clinical evaluation focuses on quantifying and clearly communicating the risk, discussing options for managing the risk, understanding the unique social and reproductive concerns of the patient, and then developing a long-term risk management strategy that is acceptable to the patient. All women seeking information about managing breast cancer risk should be assisted in adopting a healthy diet and establishing a consistent physical activity program. Physical activity, avoidance of weight gain, and weight loss, especially early in life, have all been associated with later age at breast cancer diagnosis in *BRCA* gene mutation carriers.[1,2] This effect is most pronounced for *BRCA1* mutation carriers, and may reflect one of the key roles of *BRCA1* in mimicking negative energy balance in the cell.[3] Beyond lifestyle, the primary options for managing breast cancer risk fall within three broad categories: (1) enhanced surveillance, (2) chemoprevention, and (3) prophylactic surgery. The astute clinician will listen to the patient and gauge her comfort level as each of these options is discussed. In this way, it is actually the patient who develops the management plan. This is essential for ensuring compliance and minimizing the potential for regret in what will likely be a long-term relationship.

TABLE 1 Key decisions and discussion points for *BRCA* gene mutation carriers

Key decisions	Key data and discussion points
Managing the risk of primary breast cancer	
Enhanced surveillance	Risk tolerance
Chemoprevention	Affected gene (*BRCA1* or *BRCA2*)
Bilateral prophylactic mastectomy	Ages at diagnosis in the family
Bilateral salpingo-oophorectomy	Intimate relationships (status and plans)
	Childbirth history and plans
Managing primary breast cancer	
Breast conservation	Risk tolerance
Mastectomy	Affected gene (*BRCA1* or *BRCA2*)
Contralateral prophylactic mastectomy	Age at diagnosis
Bilateral salpingo-oophorectomy	Hormone receptor status
	Proposed adjuvant chemotherapy
	Prognosis of the primary tumor

Quantifying the Risk

Lifetime breast cancer risk ranges 65–81% for *BRCA1* mutation carriers and 45–85% for *BRCA2* carriers.[4–6] The mean age at diagnosis of breast cancer is about 44 years for *BRCA1* mutation carriers and 47 years for *BRCA2* carriers but age at onset varies by family, particularly for *BRCA2* families.[7] Gene-gene and gene-environment interactions likely account for this variability in age-specific and cumulative breast cancer risk; consequently, attention to the specific cancer family history contributes to the development of a long-term individualized risk management strategy.

Enhanced Surveillance

BRCA gene mutation carriers are at significantly increased risk for breast cancer early in life when the breasts are often still quite dense by mammography. This significantly reduces the sensitivity of mammography. In addition, *BRCA* gene mutation-associated breast cancers tend to have pushing rather than spiculated margins making them more difficult to detect in a dense mammographic background.[8] Some have postulated that the ionizing radiation exposure from yearly mammography beginning early in life may promote tumor development in women with impaired DNA double-strand break repair.[9] To date, a carcinogenic effect at the radiation doses delivered by mammography has not been convincingly demonstrated. Contrast-enhanced screening magnetic resonance imaging (MRI) provides an additional modality that is particularly well suited to younger high risk women without increasing radiation exposure. The sensitivity of screening MRI for breast cancer detection in high risk women ranges 71–94% as compared to 33–59% for mammography.[10–15] Screening MRI is less specific than mammography so its use will increase the rate of benign breast biopsies (about 10% for the first MRI); but this rate decreases with successive rounds of screening. Screening sonography has a sensitivity of 17–65% and will occasionally identify a cancer missed by mammography and MRI.[12–14] Third-party payors nearly always cover the costs of screening mammography and MRI in *BRCA* gene mutation carriers, but reimbursement for screening sonography is more variable. Adding modalities to the screening algorithm will incrementally increase the cancer detection rate, but will also increase the benign biopsy rate. Currently, the primary role of sonography is in the further characterization of mammographic or MRI lesions, but the introduction and validation of automated screening sonography platforms may force a reassessment.[16] The combination of clinical breast examination, screening mammography and screening MRI has a sensitivity of 86–94% for breast cancer detection among *BRCA* gene mutation carrriers.[11,12] The National Comprehensive Cancer Network has recommended that *BRCA* gene mutation carriers begin practicing breast self-examination at the age of 18 years and twice yearly clinical breast examination with yearly screening mammography and MRI beginning at the age of 25 years.[17] The age when screening begins may be adjusted according to the earliest age at breast cancer diagnosis in the family. A common practice is to stagger the mammography and MRI by 6 months to reduce the screening interval.

Chemoprevention

Tamoxifen reduces the risk of breast cancer by nearly 50% and this effect is observed even for women with up to three first degree relatives with breast cancer.[18] Tamoxifen has not been prospectively studied in women with deleterious *BRCA* gene mutations but an analysis of 19 mutation carriers included in the National Surgical Adjuvant Breast and Bowel Project P1 Breast Cancer Prevention Trial suggested a 50% reduction in risk for *BRCA2* mutation

carriers but no effect for *BRCA1* carriers.[19] This is not unexpected as tamoxifen only reduces the risk for estrogen receptor (ER)-positive breast cancer; and, while 75% of *BRCA2*-associated breast cancers are ER positive, 80% of *BRCA1*-associated breast cancers are ER negative. Tamoxifen is approved by the U.S. Food and Drug Administration for breast cancer prevention in women age 35 years or older. Given the early age at onset of breast cancer in *BRCA* gene mutation carriers, the modern trend for delayed childbirth, and uncertainty concerning the impact of tamoxifen on lifetime risk, tamoxifen is used only infrequently (6%) among *BRCA* mutation carriers.[20] Raloxifene, which is approved by the U.S. Food and Drug Administration for postmenopausal women only, is used even less frequently (3%).

Prophylactic Surgery

Premenopausal bilateral salpingo-oophorectomy (BSO) reduces breast cancer risk in *BRCA* gene mutation carriers by about 50% even when hormone replacement therapy is used.[21–23] An initial report from the Memorial Sloan Kettering Cancer Center that included data from the Prevention and Observation Surgical Endpoints (PROSE) Study Group suggested that BSO reduced breast cancer incidence by 72% among *BRCA2* mutation carriers but only 49% for *BRCA1* carriers.[24] Breast cancer risk reduction was not statistically significant for *BRCA1* mutation carriers. Of note, oophorectomy appeared to reduce the risk of ER-positive but not ER-negative breast cancer in this data set. A more recent publication from the PROSE Study Group that included 1,370 *BRCA* gene mutation carriers not previously diagnosed with breast cancer reported a 64% reduction in breast cancer risk for *BRCA2* mutation carriers and a 37% reduction for *BRCA1* mutation carriers.[25] Both results were statistically significant. There were no breast cancer deaths reported among the 120 *BRCA2* carriers undergoing BSO compared to 6 deaths among the 392 women not undergoing BSO. BSO appeared to reduce breast cancer-specific mortality among *BRCA1* mutation carriers as well, but this result was not statistically significant (hazard ratio 0.3, 95% confidence interval 0.06–1.53). The National Comprehensive Cancer Network guidelines recommend risk reducing BSO for *BRCA* gene mutation carriers between the ages of 35 and 40.[17] Though most women adjust well to the abrupt onset of menopause it can pose serious quality of life issues for others necessitating hormone replacement therapy which should not be withheld. We favor hysterectomy at the time of BSO so that estrogen replacement therapy can be used without progestins, but a report from the PROSE Study Group showed similar breast cancer risk reduction after BSO irrespective of the use of estrogen or progestins.[23] Most *BRCA* gene mutation carriers (45–58%) accept BSO.[20,26,27]

Bilateral prophylactic mastectomy (BPM) reduces breast cancer risk by more than 90%.[28–30] An initial report from the PROSE Study Group that included 102 *BRCA* gene mutation carriers recorded 2 breast cancers after a mean follow-up of 5.5 years.[31] One patient was diagnosed with an axillary node metastasis two years after BPM and one developed a primary breast cancer in residual breast tissue 9 years after BPM. A more recent report from the PROSE Study Group that included 959 *BRCA* mutation carriers with prior or concurrent BSO and 660 patients with no BSO recorded no primary breast cancers during 3 years of follow-up after BPM. Nipple preserving mastectomy is still controversial for *BRCA* gene mutation carriers as some believe that it leaves more residual breast tissue behind than traditional skin-sparing BPM.[31] This belief is not supported by other published series.[30,32–37]

Nipple-preserving mastectomy is more technically demanding than other types of mastectomy, but when performed correctly it does not leave detectible breast tissue either behind the nipple or in the axillary tail. Use of a lateral inframammary incision minimizes interference with the dominant vascular patterns for the nipple while permitting reconstruction with no visible scars (Fig. 1). A tumescent technique that uses sharp dissection allows the operator to elevate flaps of the appropriate thickness to the anatomic

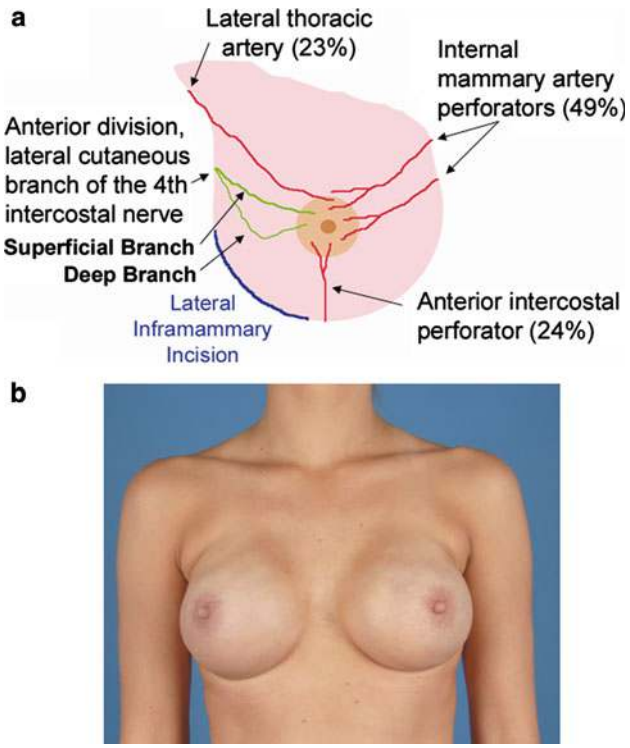

FIG. 1 Nipple-preserving mastectomy. **a** Dominant blood and nerve supply for the nipple. **b** The lateral inframammary incision permits reconstruction with no visible scars. (Expander/implant reconstruction by Sumeet Teotia, MD; used with permission.)

boundaries of the breast with minimal trauma. The retroareolar dissection is performed sharply under direct vision just deep to the vascular plane of the areolar dermis and the nipple ducts are sharply cored out for frozen section.

It is currently not clear whether women who have undergone BPM benefit from breast cancer screening.[38] When subpectoral implant reconstruction has been performed, all of the excision margins are pushed anteriorly and surveillance with clinical examination alone should be sufficient. In the case of autologous tissue reconstructions, primary breast cancers can develop in the skin, along the peripheral margins of excision, or on the chest wall deep to the autologous tissue flap. Some have advocated screening mammography or MRI in these patients, but the yield is exceedingly low. Until more data are accumulated, it would seem reasonable to continue with yearly clinical examination after BPM.

The decision to proceed with BPM (18–40%) is less than for BSO, but technical advances in BPM and better reconstruction options appear to be increasing acceptance.[20,26,27] Women who have undergone BPM experience less anxiety when assessed one year after the procedure, but 48% report feeling self-conscious and less sexually attractive primarily because of visible scars.[39] Health-related quality of life is not adversely impacted. There are currently no well-justified recommendations concerning timing of BPM and the decision is often based on family experiences with breast cancer and childbearing plans. For instance, we recently performed bilateral nipple sparing prophylactic mastectomy for a 27 year old *BRCA1* mutation carrier whose sister died of breast cancer at age 29 (Fig. 2). Because pregnancy in *BRCA* gene mutation carriers, especially later in life and especially for *BRCA2* carriers, is associated with increased breast cancer risk it is not uncommon for *BRCA2* carriers to seek BPM in their 30 s before childbirth.[40–44] Most commonly, however, BPM is either combined with BSO around the age of 40, is delayed until later in life, or avoided all together.

MANAGING BREAST CANCER IN *BRCA* GENE MUTATION CARRIERS

Despite the aggressive features of *BRCA1* mutation-associated breast cancer, disease-specific and overall survival are similar to that of sporadic breast cancer.[45]

Breast-Conserving Surgery

Partial mastectomy followed by adjuvant whole-breast radiotherapy in *BRCA* gene mutation carriers is associated with the same regional and distant recurrence rates and the same breast cancer-specific and overall survival as

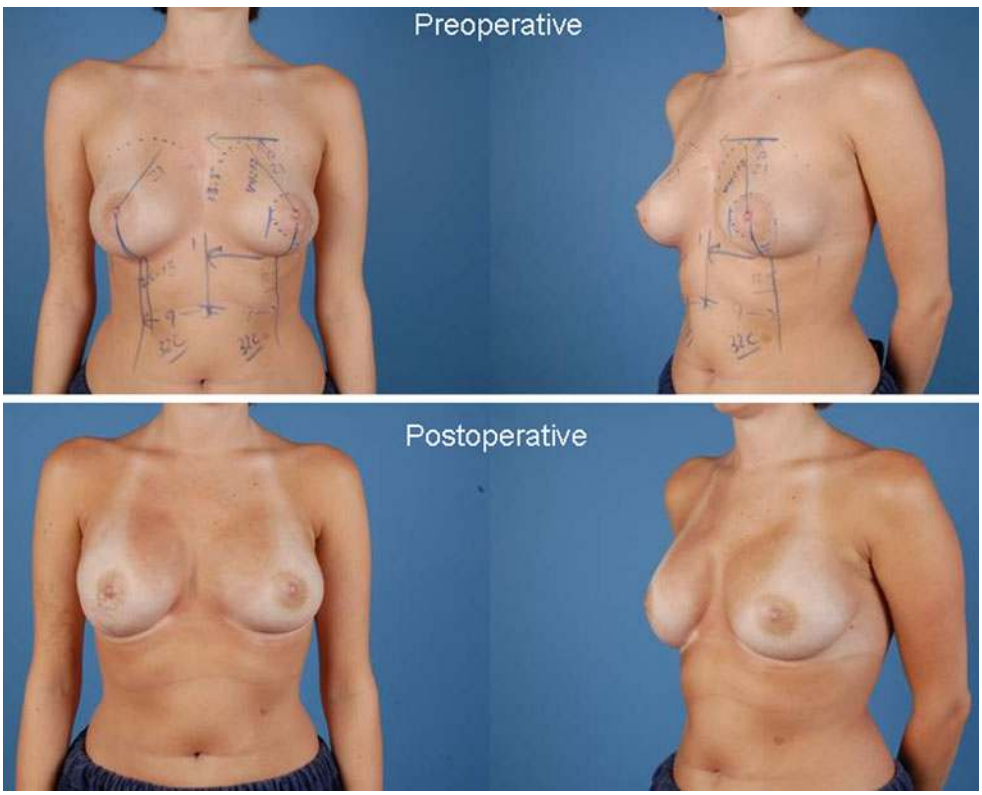

FIG. 2 Prophylactic bilateral nipple-preserving mastectomy in a young *BRCA1* gene mutation carrier. (Expander/implant reconstruction and photos by Michel Saint-Cyr, MD; used with permission.)

mastectomy.[45,46] However, breast conservation is associated with a greater risk of local failure in *BRCA* gene mutation carriers than noncarriers. These rates are highest for younger patients, approaching 4% per year in *BRCA1* mutation carriers diagnosed before the age of 43.[47] Other studies have reported local recurrence rates ranging from 1.7–2.7% per year.[46,48] Most local recurrences are second primary breast cancers rather than true recurrences of the primary cancer. A recent study that combined data from 9 centers reported that, among the 302 patients treated by breast conserving surgery, ipsilateral breast events, as the first recurrence event, were more frequent in *BRCA2* mutation carriers. Systemic adjuvant chemotherapy significantly reduced the ipsilateral breast tumor recurrence rate (15 year actuarial rate 44% without chemotherapy vs. 11% with chemotherapy). There was a trend for reduced local failure when tamoxifen was used, but no effects for BSO. Data from the PROSE Study Group also suggest that BSO does not reduce subsequent breast events in *BRCA* gene mutation carriers with a prior breast cancer diagnosis but it did significantly reduce breast cancer-specific mortality for *BRCA1* carriers (hazard ratio 0.27, 95% confidence interval 0.12–0.58).[25] Of note, contralateral breast cancer rates are the same in women treated with breast conservation or mastectomy, suggesting that side scatter radiation is not carcinogenic for the contralateral breast.[46] Breast conservation remains a reasonable option for the well-informed *BRCA* gene mutation carrier diagnosed with a primary breast cancer. Disease-specific and overall survival is the same whether the patient opts for breast conservation or mastectomy so the discussion should focus primarily on the risk for ipsilateral breast tumor recurrence. The primary factors to consider in this regard are the patient's risk tolerance, the patient's age, the histology of the primary tumor, and whether adjuvant chemotherapy will be recommended and accepted.

Contralateral Breast Cancer Risk

It is clear that *BRCA* gene mutation carriers diagnosed with primary breast cancer are at significantly increased risk for contralateral breast cancer.[45] This risk is greater in *BRCA1* than *BRCA2* families and is also related to the age when the primary breast cancer was diagnosed.[49] For instance, 63% of *BRCA1* mutation carriers diagnosed with primary breast cancer before the age of 40 will develop a contralateral breast cancer within 25 years as compared to 17% for *BRCA2* mutation carriers diagnosed after age 50. Tamoxifen has been shown to reduce the risk of contralateral breast cancer in *BRCA* gene mutation carriers by 50–69% and would be recommended in women with ER-positive cancer.[50–53] It is not clear whether premenopausal BSO reduces the risk of contralateral breast cancer as results from published studies are mixed.[25,50–52] Similarly, one study has suggested that adjuvant chemotherapy reduces the risk of contralateral breast cancer.[50] However, other studies have not observed this.[46,51] The most important factors to consider when developing a plan for managing the contralateral breast in a *BRCA* gene mutation carrier newly diagnosed with breast cancer are the patient's risk tolerance, the patient's age, the mutated gene (*BRCA1* or *BRCA2*), the hormone receptor status of the tumor, and the prognosis of the primary breast cancer. Options for managing contralateral breast cancer risk include enhanced surveillance, tamoxifen (for ER-positive primary breast cancer) and contralateral prophylactic mastectomy. Use of contralateral mastectomy ranges from 0% in Norway to 49% in the United States.[54] Contralateral prophylactic mastectomy is not associated with diminished quality of life or elevated distress.[55]

New Advances in Chemotherapy

Because *BRCA* gene mutations are associated with deficiencies in a form of double strand DNA break repair called homologous recombination, breast cancers arising in mutation carriers appear to be particularly sensitive to the DNA damaging agent cisplatin and to a new class of drugs called PARP inhibitors.[56] PARP inhibitors interfere with DNA single strand break repair.[57] Early clinical trial results are extremely promising and there are a number of new trials available for these patients.[58,59]

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