Current Status of Prophylactic Mastectomy

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By Karthik Ghosh, MD [2] and Lynn C. Hartmann, MD [3]

The management of women at high risk for breast cancer presents a clinical dilemma to the health-care provider as well as to the woman herself. Current options include surveillance, prophylactic surgery (mastectomy and/or oophorectomy), and/or chemoprevention. An accurate assessment of the risk of breast cancer is the first step in planning future preventive strategies. Women at high risk of breast cancer are those with known BRCA mutations or a strong family history characterized by multiple relatives with breast cancer, early age at diagnosis, and in some cases, ovarian cancer. These women currently have three management options: cancer surveillance, prophylactic surgery (mastectomy and/or oophorectomy), and/or chemoprevention. Prophylactic mastectomy includes bilateral prophylactic mastectomy in a high-risk woman who has not had cancer and contralateral prophylactic mastectomy, defined as mastectomy of the opposite breast in a woman with a primary breast cancer. In this review, we discuss the currently available literature on prophylactic mastectomy, its indications, and role in breast cancer prevention.

Surgical Techniques

Surgical options for prophylactic mastectomy include subcutaneous mastectomy or total mastectomy, usually followed by breast reconstruction. Subcutaneous mastectomy is performed via an inframammary incision through which the breast tissue is resected, sparing the nipple-areolar complex.[1] Historically, subcutaneous mastectomy was performed more commonly than total mastectomy, which removes the majority of the breast tissue along with the nipple-areolar complex through an elliptical skin incision. Given current nipple reconstruction techniques, total mastectomy is the preferred prophylactic procedure today.[2] With both procedures, however, small amounts of remaining breast tissue which can develop into cancer may be left behind in the axilla, inframammary fold, and skin flaps.[3] This issue must be clearly explained to the patient, because the risk of breast cancer, therefore, cannot be completely eradicated with prophylactic mastectomy.

Historical Perspective

Prophylactic mastectomy has been performed for decades. Historically, contralateral prophylactic mastectomy was advocated to reduce the increased risk of a second primary breast cancer in women who had had a first breast cancer. Bloodgood was the first to report on this strategy, in his 1921 discussion of the management of the remaining breast after radical removal of the opposite breast for carcinoma.[4] With the availability of breast implants for reconstruction, and the increasing awareness of familial breast cancer risk, bilateral prophylactic mastectomy began to be more commonly performed in the 1960s and 1970s.

In 1989, Pennisi and Capozzi published data on 1,500 women who had undergone subcutaneous mastectomy.[5] Patients were identified through solicitations to the membership of the American Board of Plastic Surgery. A total of 165 plastic surgeons contributed cases. A family history of breast cancer (first-degree, second-degree, maternal, or paternal relatives) was noted in 41% of involved patients. Of the 1,500 patients, 139 underwent a contralateral subcutaneous prophylactic mastectomy after a modified radical mastectomy of the opposite breast for primary breast cancer. Subsequently, six women (0.4%) developed breast cancer, leading the authors to conclude that the procedure provided effective prophylaxis. However, some of the limitations regarding this study included a possible bias toward inclusion of patients with a favorable outcome, lack of definition of the patients’ risk of breast cancer, a high "lost-to-follow-up" rate of 30%, and inclusion of women with a history of cancer in the opposite breast.[5]

In 1997, the Cancer Genetics Studies Consortium, organized by the National Human Genome Research Institute, published a consensus statement on the optimal care of individuals carrying mutations in the BRCA1 and BRCA2 genes.[6] Regarding prophylactic mastectomy, their recommendation stated,
There is insufficient evidence to recommend for or against prophylactic mastectomy as a measure for reducing breast cancer risk. Individuals should be counseled that this is an option available to them. Those considering prophylactic mastectomy should be counseled that cancer has been documented to occur after the procedure; its efficacy in reducing risk is uncertain.[6] Indeed, case reports had detailed the recurrence of breast cancer in residual breast tissue following both total and subcutaneous prophylactic mastectomy.[7-9] Several studies of the efficacy of the procedure (see below) have been published since this consensus statement.

**Efficacy of Prophylactic Mastectomy**

**Bilateral Prophylactic Mastectomy**

**Mayo Clinic Study** In an effort to quantify the risk reduction associated with prophylactic mastectomy, Hartmann and colleagues at the Mayo Clinic performed a retrospective cohort analysis of 639 women with a family history of breast cancer who had undergone prophylactic mastectomy between 1960 and 1993.[10] Women were assigned retrospectively to either a moderate-risk group (425 women) or high-risk group (214 women) based on the extent of their family history of breast cancer. Follow-up was available for 99% of the cohort for a minimum of 2 years; median follow-up was 14 years (9,095 person-years).

The investigators compared the total number of breast cancers observed among study participants with the total number predicted by the Gail model (for the moderate-risk group) and by a nested sister control study (for the high-risk group). The Gail model predicted that 37.4 women in the moderate-risk group would develop breast cancer by the median follow-up of 14 years. However, only four of these women developed the disease, representing an 89.5% reduction (P < .00001) in incidence following prophylactic mastectomy. The Gail model also predicted that 10.4 women in the moderate-risk group would die of breast cancer, but, in fact, no deaths from breast cancer occurred in these women.

With regard to the high-risk group, 3 of the 214 women developed breast cancer after prophylactic mastectomy. From their sisters’ experiences, 30 breast cancers were predicted in these high-risk women (see Table 1).[10] Thus, prophylactic mastectomy was associated with a 90% reduction in the risk of breast cancer in high-risk women. Similarly, compared with the expected number of breast cancer deaths in the probands, prophylactic mastectomy in the high-risk group resulted in an 81% to 94% reduction in breast cancer mortality.

**Dutch Study** A recent prospective Dutch study evaluated 139 BRCA1 or BRCA2 carriers followed at the Rotterdam Family Cancer Clinic; none had a history of breast cancer.[11] A total of 76 of these women elected to undergo prophylactic mastectomy, and 63 remained under careful surveillance. At a mean follow-up of 2.9 ± 1.4 years, no cases of breast cancer were observed in the prophylactic mastectomy group, compared to eight cases in the surveillance group (hazard ratio: 0; 95% confidence interval [CI]: 0-0.36).

Of the eight cases, four were interval cancers diagnosed between scheduled screening tests. Four of the cancers involved axillary lymph nodes, and seven were estrogen-receptor and progesterone-receptor negative. The interval from initiation of surveillance to diagnosis of cancer ranged from 2 to 42 months. These investigators concluded that in women with a BRCA1 or BRCA2 mutation, at 3 years of follow-up, prophylactic bilateral total mastectomy reduced the incidence of breast cancer (relative risk reduction: 100%, absolute risk reduction: 12.7%).

**Contralateral Prophylactic Mastectomy**

Contralateral breast cancers occur at a rate of approximately 0.5% to 1.0% per year of follow-up after a primary breast cancer in women at average risk.[12] In women with a family history of breast cancer, Harris et al described a 35% risk of contralateral breast cancer by 16 years after the first breast cancer diagnosis.[13] However, in carriers of a BRCA1 or BRCA2 mutation, the contralateral breast cancer rate is higher, ranging from 12% at 5 years in BRCA2 carriers, to 20% to 31% at 5 years in BRCA1 carriers[14] and Ashkenazi BRCA1 or BRCA2 carriers.[15]

Data on the efficacy of contralateral prophylactic mastectomy have been relatively sparse. However, two recent studies have addressed this issue.

**Peralta et al Study** Peralta et al studied the efficacy of contralateral prophylactic mastectomy in a retrospective analysis of 64 patients with a personal history of breast cancer who underwent this procedure, compared with 182 controls who did not.[16] The end points were contralateral breast cancer rate, disease-free survival, and overall survival. The groups were matched by age, stage,
surgery, chemotherapy, and hormonal therapy.

In the contralateral prophylactic mastectomy group, three incidental contralateral breast cancers (4.5%) were found at the time of prophylactic mastectomy, but none occurred subsequently; 36 contralateral breast cancers occurred in the control group (P = .005). The mean follow-up was 6.8 years (range: 0.3-23.6 years). Overall survival at 15 years was 64% (95% CI: 45%-78%) in the contralateral prophylactic mastectomy group vs 49% (95% CI: 39%-58%) in the control group (P = .26). The researchers concluded that contralateral prophylactic mastectomy prevented contralateral breast cancer and that the potential benefit was greatest when the risk of contralateral breast cancer was highest.[16]

**McDonnell et al Study**[17] McDonnell et al followed 745 women (388 premenopausal, 357 postmenopausal) with a first breast cancer and a family history of breast and/or ovarian cancer who underwent contralateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. Using life tables for contralateral breast cancers (referred to as the Anderson model), the investigators considered current age, age at first breast cancer, and type of family history (which is based only on breast cancer events in the family and requires one of three types of pedigree: parent-affected, sibling-affected, second-degree relative-affected). With these data, they predicted the number of contralateral breast cancers in this cohort had patients not undergone contralateral prophylactic mastectomy. The median length of follow-up was 10 years, with a minimum follow-up of 2 years for 98% of the cohort.

Eight women developed contralateral breast cancer. Six events were observed in the premenopausal group of 388 women compared with 106.2 predicted, representing a risk reduction of 94.4% (95% CI: 87.7%-97.9%). In the postmenopausal group of 357 subjects, two events were observed compared with 50.3 predicted, representing a 96% risk reduction (95% CI: 85.6%-99.5%). The incidence of contralateral breast cancer, therefore, appears significantly reduced after contralateral prophylactic mastectomy in women with a personal and family history of breast cancer.[17]

**Schrag et al Study**[20] Schrag et al performed a decision analysis using a Markov model to predict years of life gained through various prevention strategies in BRCA1 or BRCA2 carriers. They estimated the probabilities of developing contralateral breast cancer and ovarian cancer, dying from these cancers, and dying from primary breast cancer, based on published studies. They also calculated reductions in the incidence and mortality of cancer resulting from prophylactic surgeries and/or tamoxifen.

Using hypothetical breast cancer patients with BRCA1 or BRCA2 mutations who faced secondary cancer prevention strategies, they assessed the effect of contralateral prophylactic mastectomy, bilateral prophylactic oophorectomy, and 5 years of tamoxifen therapy on their life expectancy. Based on the assumed penetrance of BRCA mutations, compared to surveillance alone, 30-year-old, early-stage breast cancer patients with BRCA mutations gain 0.4 to 1.3 years of life expectancy with tamoxifen therapy, 0.2 to 1.8 years with prophylactic oophorectomy, and 0.6 to 2.1 years with contralateral prophylactic mastectomy. The magnitude of the gain was highest for women with high-penetrance mutations.[20]

Thus, contralateral prophylactic mastectomy provides a potential benefit for patients at high risk of contralateral breast cancer, with chemoprevention and close surveillance being important alternatives. It is essential to provide each patient with appropriate counseling regarding the risk of recurrence of her primary breast cancer, the risk of contralateral breast cancer, and the efficacy of contralateral prophylactic mastectomy (and its cosmetic outcomes), in order to optimize the ultimate outcome, including patient satisfaction.

**Optimal Communication Regarding Risk Reduction**

It is imperative that we communicate the long-term benefits, risks, and limitations of prophylactic mastectomy to patients in as clear-cut a manner as possible. In a recent review, Stefanek et al recommended the use of the term "risk-reduction mastectomy" instead of prophylactic mastectomy because the term "prophylactic" may suggest complete protection from breast cancer.[21]

We should also examine our traditional use of relative risk reduction to convey the impact of an intervention. Although this is the customary tool used to describe the results of cancer treatment and prevention strategies, it can overstate the impact of an intervention by not accounting for the baseline risk. In Table 2, we present both the relative risk and absolute risk figures for bilateral prophylactic mastectomy, contralateral prophylactic mastectomy, and tamoxifen—risk-reduction strategies that are frequently considered by high-risk women.[10,11,17,22]

In the Mayo Clinic retrospective cohort study,[10] prophylactic mastectomy reduced the risk of breast cancer in high-risk women by 90% over a 14-year period. The absolute incidence of breast cancer was 14% in the control group of sisters and 1.4% in the prophylactic mastectomy group,
representing an absolute risk reduction of 12.6%. In the Dutch prospective study of bilateral prophylactic mastectomy cited earlier,[11] the absolute incidence of breast cancer in the surveillance group was 12.7%, whereas the prophylactic mastectomy group had an incidence of 0%. The relative risk reduction was, therefore, 100% over the 2.9-year period.

In the Breast Cancer Prevention Trial, 13,388 women at increased risk for breast cancer (due to age over 60, age 35 to 59 with a 5-year predicted risk for breast cancer of at least 1.66% by the Gail model, or a history of lobular carcinoma in situ) were randomly assigned to receive placebo (n = 6,707) or tamoxifen at 20 mg/d (n = 6,681) for 5 years.[22] Tamoxifen reduced the risk of invasive breast cancer by 49% over 5.75 years. The absolute incidence of invasive breast cancer was 2.6% in the placebo group and 1.3% in the tamoxifen group.

Although all these studies report on “high-risk” women, it is clear that the absolute risk of breast cancer varies among these populations. Periods of follow-up in the studies cited in Table 2 also differ. It is beneficial to convey to patients both their underlying risk of an event—their baseline absolute risk—and the extent of risk reduction with a strategy, via both the change in the absolute risk or the relative risk.

Utilization of Prophylactic Mastectomy

What proportion of women at high risk of breast cancer contemplate and actually undergo prophylactic mastectomy? In one study by Stefanek et al, 65% (n = 106) of women at high risk initially expressed an interest in discussing prophylactic mastectomy as an option, but only 13% (14 of 106 women) actually underwent the procedure.[23] In the study, 164 women with at least one first-degree relative with breast cancer seen at Johns Hopkins between 1988 to 1992 were surveyed before their first evaluation in a high-risk clinic.[23] The investigators collected information relating to risk perception, screening practices, cancer worry, interest in prophylactic mastectomy, and depression.

A total of 58 women reported no interest in prophylactic mastectomy, 92 were interested but did not undergo prophylactic mastectomy, and 14 were interested and subsequently underwent bilateral prophylactic mastectomy. Women in the prophylactic mastectomy group reported more worry about breast cancer than women in either of the other two groups. The 10-year subjective risk estimate was significantly lower for women who expressed no interest in prophylactic mastectomy (risk estimate: 37%), compared with women who expressed interest in the procedure (49%) and those who underwent prophylactic mastectomy (59%). A prior history of breast biopsy was also more common in the prophylactic mastectomy and mastectomy interest-only groups than in the "mastectomy noninterest" group.[23]

Influence of Genetic Factors

In a recent Dutch study of unaffected women found to be BRCA carriers, 51% opted for prophylactic mastectomy.[24] When examining how frequently a procedure is chosen, it is important to consider how the study group was selected. In the Dutch work, investigators studied those who came forward to have genetic testing. These may well be individuals who sought testing because they planned to act upon the results, if positive.

In a prospective observational study of female members of hereditary breast/ovarian cancer families (84 BRCA1/2 mutation carriers, 83 noncarriers, and 49 test-decliners) from 1994 to 1997, Lerman et al[25] assessed prophylactic surgery and surveillance behavior during the year following BRCA1/2 gene testing. Mutation carriers aged 25 and older were informed of prophylactic mastectomy and/or oophorectomy as options and were also told that neither procedure had been proven to eliminate cancer risk in mutation carriers.

At 1-month follow-up, 36% of mutation carriers were considering prophylactic mastectomy. However, only one woman (3% of the unaffected carriers) underwent the procedure during the 1-year follow-up period. It is noteworthy that of the 216 women in this study, 13 had already undergone prophylactic mastectomy prior to the availability of genetic testing, based on their family risk status. In addition, 60 women had a prior history of breast cancer, and 96% of this group had undergone mastectomy for treatment. Of the 156 unaffected women in this study, 14 (9%) had prophylactic mastectomy, reflecting the actual proportion of high-risk women who opted for the procedure. A concern with this study, however, is a relatively high lost-to-follow-up rate of 22%.[25]

In summary, literature on the utilization of prophylactic mastectomy is sparse, and larger studies are needed to identify such trends, as well as factors that influence a high-risk woman’s choice of this option.
Complications of Prophylactic Mastectomy

**Surgical Complications**

Complications following prophylactic mastectomy may be immediate or delayed. Gabriel and colleagues reported a 5-year complication rate of 30% in 92 women undergoing prophylactic mastectomy and implant reconstruction. Immediate complications include necrosis of the skin, necrosis of the nipple-areolar complex (with subcutaneous mastectomy), infection, wound dehiscence, hematoma or seroma, and pain. Later complications include capsular contracture, implant rupture or leakage, asymmetry or unsatisfactory cosmetic outcome, and lack of sensitivity of the overlying skin.[26-28]

Zion et al reported the experience of women who underwent prophylactic mastectomy and reconstruction with implants at the Mayo Clinic and subsequently required reoperation.[29] Of 592 women who had bilateral prophylactic mastectomy and implant reconstruction, 52% required reoperation over a median follow-up of 14.2 years; 95% of these women had subcutaneous mastectomy.

They also studied 502 women with a personal and family history of breast cancer who had undergone contralateral prophylactic mastectomy and reconstruction with implants along with therapeutic mastectomy for the affected breast. In this group, 39% required reoperation over a median follow-up of 8.8 years; 62% had had subcutaneous mastectomy, and 38% received a total mastectomy. Indications for reoperation included postoperative complications (10% of all indications), implant-related concerns (50% to 60%)—eg, implant rupture or leakage or capsular contracture,—nodule excision (4% to 10%), and non-implant-related aesthetic concerns (15% to 23%)—eg, revision of the scar or nipple-areolar revision.[29]

**Psychosocial Issues**

Accumulating data by questionnaire, Frost et al assessed long-term satisfaction as well as psychological and social function in 572 of 609 women (94% participation) with a family history of breast cancer after bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993.[30] Family history of breast cancer was the most commonly cited reason for prophylactic mastectomy. The most frequent combination of reasons was family history, physician advice, and nodular breasts.

Of note, 74% of the women reported a diminished level of emotional concern regarding the development of breast cancer. The majority of women reported no change or favorable effects in level of emotional stability, stress, self-esteem, sexual relationships, and feelings of femininity. However, 36% reported reduced satisfaction with their body appearance after prophylactic mastectomy.

The variables associated with satisfaction after prophylactic mastectomy included satisfaction with body appearance (strongest association), lower level of stress, fewer implant-related problems, and no reconstruction after prophylactic mastectomy. On the other hand, physician’s advice as the primary reason for undergoing prophylactic mastectomy was associated with dissatisfaction.[30]

In the Stefanek study cited earlier, it was found that cancer-related worry, prior breast biopsies, and subjective risk estimates were the most significant variables in the group undergoing prophylactic mastectomy.[23] Women completing the procedure with strong support from family and friends (and those following formal risk counseling) were most satisfied with their decision.[23]

**British Study**

Hatcher and colleagues prospectively studied the psychosocial impact of bilateral prophylactic mastectomy through questionnaires and semistructured interviews in 143 women at increased risk of breast cancer who were offered bilateral prophylactic mastectomy and accepted (79 women) or declined (64 women), and 11 others who deferred making a decision.[31] Follow-up interviews were conducted at 6 and 18 months. Psychological morbidity and anxiety were high before surgery and declined significantly after surgery in the group that received a bilateral prophylactic mastectomy, but remained high in the group that opted for regular surveillance. The researchers noted that women who chose surgery were more likely to have undergone prior breast biopsies or genetic testing. After surgery, these women maintained a positive body image and reported few or no changes in sexual functioning. Notably, women who chose prophylactic mastectomy strongly believed that the procedure would significantly reduce their chances of developing breast cancer.[31] Overall, the acceptors tended to report higher lifetime risks of developing the disease than the decliners. Genetic counseling is, therefore, mandatory prior to making any decision about prophylactic mastectomy, to ensure accurate risk assessment and to educate the patient regarding this risk.
Follow-up After Prophylactic Mastectomy

As discussed, prophylactic mastectomy does not completely eliminate the risk of subsequent breast cancer. Hence, it is mandatory that women treated with this procedure undergo long-term follow-up, perform regular, monthly examination of the chest wall, and undergo annual clinical examination.[27]

Annual mammography should be strongly considered in women who have had subcutaneous mastectomy. This has been an area of controversy, with proponents maintaining that the residual breast tissue warrants a thorough clinical and radiologic assessment to enable early detection of malignancy. However, practitioners who do not recommend annual mammography in these women believe that the thin layer of residual breast tissue can be easily palpated on clinical examination of the chest wall and that annual mammography does not provide additional benefit. Clearly, this issue requires further research.

Conclusions

Bilateral prophylactic mastectomy is one risk-reducing measure for women at high risk of breast cancer. Accurate risk assessment by a trained genetic counselor is an obligatory first step, as many women overestimate their risk of breast cancer. It is a highly personal decision that must, therefore, be preceded by an in-depth discussion with the patient by a multidisciplinary team regarding the benefits of the procedure vs the potential surgical and psychological risks. In addition, it is imperative that these women be informed of alternative management options, including chemoprevention, increased surveillance, and prophylactic oophorectomy.

References:


30. Frost MH, Schaid DJ, Sellers TA, et al: Long-term satisfaction and psychological and social function following bilateral prophy-


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