

Prophylactic Mastectomy: Who Needs It, When and Why

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Prophylactic mastectomy generally occurs in two different patient populations: (1) high-risk women without breast cancer who undergo bilateral prophylactic mastectomy (BPM) to reduce their risk of developing breast cancer and (2) women with unilateral breast cancer who choose contralateral prophylactic mastectomy (CPM) to prevent cancer in the contralateral breast. The purpose of this article is to review the indications, outcomes, and trends in the use of BPM and CPM.

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BILATERAL PROPHYLACTIC MASTECTOMY

Indications

The Society of Surgical Oncology issued a position statement in 2007 regarding indications for prophylactic mastectomy among healthy women without breast cancer [1]. In this statement, potential indications for BPM include BRCA mutation or other susceptibility genes, strong family history without genetic mutation, and histologic risk factors (atypical ductal hyperplasia (ADH), atypical lobular hyperplasia, or lobular carcinoma in situ (LCIS)) [2]. Although ADH and LCIS are associated with an increased risk of breast cancer, surgical risk reduction is usually not recommended for these indications alone. Current National Comprehensive Cancer Network guidelines state: “Although ...consideration of risk-reduction mastectomy is an option for a woman with LCIS without additional risk factors, it is not a recommended approach for most of these women” (www.nccn.org, v1.2013. Accessed 2/10/14). Bilateral prophylactic mastectomy (BPM) may also be indicated for other high-risk groups including women treated with mantle radiation (particularly at a young age) for Hodgkin’s lymphoma and those with non-BRCA hereditary breast cancer syndromes (Cowden, Li Fraumeni).

Importantly, many women without breast cancer substantially overestimate their risk. In one study of 200 women without breast cancer, respondents over-estimated their probability of dying from breast cancer within 10 years by more than 20-fold as compared to probabilities derived from the Gail model [3]. In another survey study of patients participating in chemoprevention trials, the mean lifetime calculated risk using the Gail model was 15%; however, the median risk perceived by patients was 50% [4]. After an educational intervention, the median perceived risk declined to 25%. Thus, physicians need to provide patients with accurate estimates of breast cancer risk in discussing management strategies so that patients have accurate information when making their decision.

Surgical Options

The three main options for surgical risk-reduction are bilateral simple mastectomy without reconstruction, bilateral skin-sparing mastectomy with immediate reconstruction, and bilateral nipple-sparing mastectomy with immediate reconstruction. Surgical complications from bilateral skin-sparing mastectomy occur in about 20% of patients [5]. The most common complications are infection, flap necrosis, and loss of reconstruction. In addition, Zion et al. [6] reported that unanticipated

operations occur in about half of patients within 14 years after BPM plus immediate reconstruction.

An increasing number of patients undergo surgical risk reduction with bilateral nipple-sparing mastectomies (NSM). Ideal candidates for NSM are younger patients, non-smokers, and non-obese patients. Generally, NSMs are performed with either a radial or inframammary incision. Ductal tissue beneath the nipple is excised and submitted to pathology separately. If DCIS or invasive cancer is identified in this tissue, then the nipple-areolar complex is excised. The cosmetic outcomes after nipple-sparing mastectomy and reconstruction are excellent. Nipple necrosis can occur in about 5% of patients. The occurrence of cancer in the nipple-areolar complex after NSM is extremely rare.

Results after BPM

As outlined in previous article by Tuttle et al. [2] a number of studies contribute information about expected results after BPM. First, several studies have demonstrated that BPM reduces the risk of breast cancer in moderate- to high-risk women, including those with BRCA mutations [7–9]. Hartmann et al. [7] conducted a retrospective review of all women with a family history of breast cancer who underwent BPM at the Mayo Clinic between 1963 and 1990. Using the Gail model and sisters of patients as controls, the authors determined the expected number of breast cancers in both moderate- and high-risk groups. In the moderate-risk group, 37.4 cancers were expected but only 4 occurred, a risk reduction of 89.5%. In the high-risk group, a risk reduction of 90% was observed. Other studies have demonstrated that the risk reduction is about 90% after BPM for patients with BRCA mutations [8]. A Cochrane review published in 2010 reported that BPM studies have demonstrated reductions in breast cancer incidence and mortality after BPM, particularly for those with BRCA 1/2 mutations [9]. Using Markov modeling, Schrag et al. estimated that an average 30-year old

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woman who carries a BRCA 1/2 mutation would gain an additional 2.9–5.3 years of life expectancy from prophylactic mastectomy [10].

Patient Satisfaction

Despite the potential complications and requirements for unanticipated surgery, most patients are satisfied with their decision to undergo BPM. In a survey study of high-risk patients who underwent BPM, Geiger et al. reported that 84% were satisfied with their decision [11]. In another study, Altschuler et al. evaluated the psychosocial response and satisfaction in women following prophylactic mastectomy [12]. The authors concluded that although most patients were satisfied with their decision to undergo risk-reducing surgery, some patients expressed more negative impressions of their procedures. Another study examined the impact of body image and sexual and partner relationship satisfaction in 48 healthy BRCA 1/2 mutation carriers after BPM with breast reconstruction [13]. The authors reported that sexual relationship satisfaction and body image tended to be lower compared to baseline. After a median follow-up of 21 months, 37% of women reported that their breasts felt unpleasant, 29% were unsatisfied with breast appearance, and 21% felt embarrassed of their naked body. The authors concluded that the psychosocial impact of BPM with reconstruction should not be underestimated.

Trends

Since most state and national cancer databases do not collect information on healthy women without breast cancer, precise determination of the national trends of BPM use is difficult [2]. A study from McLaughlin et al. utilized New York state cancer registry to study trends of prophylactic mastectomy from 1995 to 2005 [14]. This study included 1196 women who underwent BPM and had no history of breast cancer. McLaughlin et al. found that BPM was uncommonly performed, and the BPM rates increased only slightly during the study period. An analysis by Portschy et al. using the Surveillance Epidemiology and End Results (SEER) database evaluated the use of prophylactic mastectomy among women diagnosed with LCIS between 2000 and 2009 [15]. The overall mastectomy rate was 16%, but increased by 50% during the study period. We conjecture that BPM rates have likely increased in the United States secondary to increased awareness of genetic breast cancer, increased genetic testing, and improvements in mastectomy and reconstruction techniques [2].

Conclusions

Bilateral prophylactic mastectomy (BPM) reduces the incidence of breast cancer in moderate- and high-risk women and may reduce breast cancer mortality among carriers of BRCA mutations. Nevertheless, BPM is a major operation, is irreversible, and is not risk free. Many patients substantially overestimate their risk of developing breast cancer. Overall, patients are satisfied with their decision to undergo risk-reduction surgery, but physicians must provide accurate education and counseling to ensure that risk-reducing surgery is performed in the most appropriate setting with realistic expectations. Alternative strategies for managing high-risk patients include rigorous surveillance (clinical breast examinations, mammography, and potentially breast MRI), endocrine therapy, and life-style changes.

CONTRALATERAL PROPHYLACTIC MASTECTOMY

Trends

Contralateral prophylactic mastectomy (CPM) is the removal of the normal intact breast among women with unilateral breast cancer. The

SEER registry began coding CPM in 1998. At that time, the proportion of patients who underwent CPM in the United States was very low [16]. However, the CPM rate among all surgically treated patients with invasive breast cancer increased by 150% from 1998 to 2003 in the United States. Among patients who underwent mastectomy the CPM rate increased by 162% from 1998 to 2003. These trends were observed for all cancer stages and continued to increase at the end of the study period with no plateau. Although significant geographic variations were observed between different SEER registries, no general geographic trends were identified. Similar findings were observed in the SEER database among patients with ductal carcinoma in situ (DCIS) [17].

Other studies using different databases have confirmed these findings. Using the American College of Surgeons' National Cancer Data Base (NCDB), Yao et al. reported a similar increase in CPM rates from 1998 to 2007 with no plateau at the end of the study period [18]. In a study using the New York State Cancer Registry, McLaughlin et al. reported that CPM use more than doubled from 1995 to 2005 [14]. Single-institutional studies have also demonstrated marked increases in CPM rates [19–21].

In contrast, similar trends have not been observed in Europe. In a single-center study from Switzerland, Güth et al. reported that CPM rates at an academic surgery center did not increase from 1995 to 2009 [22]. The authors concluded that the increased use of CPM was a "trend made in the USA." Another study supports this viewpoint. In an international registry of women with unilateral breast cancer and BRCA mutation, Metcalfe et al. reported that 49% of women in the United States underwent CPM [23]. In contrast, the CPM rates from Europe and Israel were only about 10% or less.

Various patient, tumor, and treatment factors are significantly associated with CPM rates. Younger women are much more likely to receive CPM [16,18]. White race, higher education level, private health insurance, and family history of breast cancer have also been associated with higher CPM rates [16,18,19,21]. In a SEER database study, the presence of infiltrating lobular histology was one of the strongest predictors of CPM [16]. Yet, population-based studies indicate that the risk of contralateral breast cancer is not significantly increased for infiltrating lobular histology as compared with infiltrating ductal histology [24]. Multicentric breast cancer has also been associated with higher CPM rates [25]. BRCA testing is significantly associated with CPM, even among patients who do not have BRCA mutations. In one single center study, the CPM rate was 40% among those patients who tested negative for mutations [26]. Several studies have reported that preoperative MRI is associated with CPM [19,21,25]. Patients treated at comprehensive cancer programs or teaching facilities are more likely to receive CPM [18].

Reasons for Increased CPM Rates

This trend towards more aggressive breast cancer surgery is curious and counterintuitive in the modern era of minimally invasive surgery. However, many factors probably contribute to increased CPM use. Public awareness of genetic breast cancer and increased BRCA testing may partially explain these observations. Improvements in mastectomy techniques (including skin-sparing and nipple-sparing mastectomy), reconstruction techniques, and access to breast reconstruction probably contribute to increased CPM rates. Moreover, symmetric reconstruction is often easier to achieve after bilateral mastectomy as compared to unilateral mastectomy. Additionally, the native and reconstructed breast age differently, so symmetric outcomes may diminish over time if unilateral mastectomy is performed.

Several studies have reported that preoperative breast MRI is associated with higher CPM rates [19,21]. The proposed explanation is that MRI findings introduce concern and anxiety about the opposite breast. Preoperative breast MRI probably contributes to increased CPM

rates, but the initial observed CPM trends in the United States preceded the widespread use of breast MRI [16,18].

Obesity rates in the United States have markedly increased over the past 2 decades. It is not known whether increasing obesity rates are contributing to current CPM trends, but a plastic surgeon may have technical challenges in achieving a symmetric reconstruction after unilateral mastectomy for an obese woman with large breasts. For some women, bilateral mastectomy with or without reconstruction may provide better symmetry, effective local breast cancer treatment, avoidance of future radiographic surveillance, and may relieve symptoms from macromastia.

Another possible explanation for the increased CPM rates is that some patients may considerably overestimate their risk of developing contralateral breast cancer. Previous studies have reported that women with early stage breast cancer markedly overestimate their risk of recurrence [27]. In a survey of 350 mastectomy patients, Han et al. reported that the most common reason for CPM was worry about contralateral breast cancer [28]. The annual rates of metachronous contralateral breast cancer for women with unilateral breast cancer are fairly constant [24]. The Early Breast Cancer Trialists' Collaborative Group updated their meta-analyses and reported that the annual rate of contralateral breast cancer was about 0.4% for patients with estrogen receptor (ER)-positive breast cancer treated with tamoxifen [29]. The annual rate of contralateral breast cancer was about 0.5% for patients with ER-negative breast cancer. All age, tumor, and treatment subgroups had rates less than 0.7% per year. Thus, the 10-year cumulative risk of contralateral breast cancer is about 4–5%. Moreover, the rates of metachronous contralateral breast cancer have declined in the United States in recent decades [30], likely secondary to the increased use of adjuvant therapies.

Abbott et al. [31] published the results of a prospective single-center study designed to determine patients' perceived risk of contralateral breast cancer. Patients completed a standardized survey prior to surgical consultation and were asked to estimate their risk of developing contralateral breast cancer. Patients substantially overestimated their 10-year cumulative risk of contralateral breast cancer, with a mean perceived risk of 31.4%. In another survey study of young women (age \leq 40 years) who underwent CPM, Rosenberg et al. also concluded that many women overestimate their actual risk of developing contralateral breast cancer [32].

Moreover, some patients may overestimate the oncologic benefits of CPM. In a survey study by Rosenberg et al., 94% of women cited "desire to improve my survival/extend my life" as an extremely or very important reason for CPM [32]. Similarly, 85% of women cited "desire to prevent breast cancer from spreading to other places in my body" as another reason for CPM. In another survey study of women who underwent CPM, Altschuler et al. recorded comments such as "I do not worry about recurrence," and I am "free of worries about breast cancer." [12] Such comments suggest a lack of understanding of the benefits of CPM, since removal of the normal contralateral breast does not treat systemic metastases from the known ipsilateral breast cancer.

Outcomes after CPM

Several studies have demonstrated that CPM is effective in reducing the risk of contralateral breast cancer. In a study of 745 breast cancer patients with a family history of breast cancer, McDonnell et al. reported that CPM reduced the incidence of contralateral breast cancer by more than 90% [33]. In a retrospective study of 239 patients, Goldflam et al. reported that only 1 contralateral breast cancer (0.4%) developed after CPM [5]. Depending upon the statistical methods used, CPM reduces the risk of contralateral breast cancer by about 90%.

However, the effectiveness of CPM in reducing breast cancer mortality is not as clear. The only plausible way that CPM improves breast cancer survival is by reducing the risk of a potentially fatal contralateral breast cancer. Studies examining the potential survival

benefit with CPM report conflicting results. A published Cochrane analysis concluded, "There is insufficient evidence that CPM improves survival" [34]. Yet, several retrospective studies have reported a survival benefit after CPM for selected patients. Using the SEER database, Bedrosian et al. [35] reported that CPM was associated with a 4.8% absolute improvement in 5-year breast cancer-specific survival in young women with early-stage ER-negative breast cancer. In a retrospective single-center study, Boughey et al. [36] reported that CPM was associated with a 9% absolute improvement in 10-year overall survival. In another retrospective single-center study, Peralta et al. [37] reported a 15% absolute improvement in 15-year overall survival. In a study using the NCDB, Yao et al. reported that CPM was associated with a 2% absolute improvement in 5-year survival; the authors concluded, "After adjusting for confounding, the overall survival benefit for CPM was minimal at best" [38]. The absolute improvement in overall survival associated with CPM in these studies paradoxically exceeds the expected cumulative incidence of contralateral breast cancer in average risk breast cancer patients.

Selection bias markedly limits the ability to compare survival rates between CPM and no CPM patients in retrospective and cancer registry studies. Patient, tumor, and treatment characteristics differ significantly between those who undergo CPM and those who do not. Patients undergoing CPM are generally younger, more likely to be of white race, have higher education level, have private insurance, more likely to receive a breast MRI, and to be treated at a comprehensive cancer program [16–21]. Similarly, patients who undergo more aggressive surgery are probably healthier and more likely to receive adjuvant therapy. These differences likely explain the paradox of the CPM survival advantage exceeding the cumulative risk of contralateral breast cancer in retrospective studies.

Despite the results of retrospective or cancer registry studies, CPM is not likely to improve breast cancer survival rates for patients who do not have BRCA mutations. For these patients, the 10-year cumulative risk of contralateral breast cancer is about 4–5%; most metachronous contralateral breast cancers are stage I or IIA with a 10-year mortality rate of about 10–20%. Thus, the 20-year mortality rate from a contralateral breast cancer is about 1% or less. In addition, many patients die from systemic metastases from their known ipsilateral breast cancer or from other causes during 20-year follow-up. Finally, CPM does not prevent all contralateral breast cancers. Thus, CPM will not decrease breast cancer mortality rates for most breast cancer patients without BRCA mutations [39].

On the other hand, for patients with BRCA-associated unilateral breast cancer, the annual risk of contralateral breast cancer is about 4% per year with a cumulative 10-year risk of contralateral breast cancer of about 40% [40]. Thus, the possibility of developing a potentially fatal contralateral breast cancer is substantially higher among breast cancer patients with a BRCA mutation. The relative risk reduction of CPM is similar for patients with and without BRCA mutations. Using Markov modeling, Schrag et al. estimated that CPM would increase life expectancy by 0.6 to 2.1 years for a 30-year old breast cancer patient with a BRCA mutation [41]. Clearly, randomized trials comparing CPM with no CPM for either selected (BRCA mutations) or heterogenous patients are not feasible [39].

Contralateral prophylactic mastectomy (CPM) is an irreversible procedure and is not risk free. Severe complications after CPM may potentially delay recommended adjuvant therapy and may require additional surgical procedures and subsequent loss of reconstruction [39]. The overall complication rate after bilateral mastectomy and reconstruction is about 20% [9]. About half of the complications are secondary to the prophylactic mastectomy. Even without complications, these operations are long (often 5 to 6 hr) and require 2–3 days of inpatient hospital care, drainage catheters, and 3- to 4-week overall recovery [2].

Despite potential risks and complications, most patients are satisfied with their decision to undergo CPM. The greatest reported benefit

contributing to patient satisfaction is a reduction in breast cancer related concerns [2]. Frost et al. [42] reported that 83% of patients were either satisfied or very satisfied with their decision to undergo CPM at a mean of 10 years after surgery. Some women have negative psychosocial outcomes following CPM, most often related to high levels of psychological distress, sexual function, and body image or poor cosmetic outcome [12]. Montgomery et al. [43] reported that the most common reasons for regret after CPM were a poor cosmetic outcome and diminished sense of sexuality.

Alternatives to CPM

Patients with unilateral breast cancer have options that are less drastic than CPM. Surveillance with clinical breast examination, mammography, and potentially breast MRI may detect cancers at earlier stages [39]. Prospective randomized trials have demonstrated that tamoxifen, given as adjuvant therapy for ER-positive breast cancer, significantly reduces the rate of contralateral breast cancer [44,45]. Aromatase inhibitors may reduce the risk of contralateral breast cancer as much as, or even more than, tamoxifen [46]. The Arimidex, tamoxifen alone or in combination (ATAC) Trial demonstrated that anastrozole was superior to tamoxifen in preventing contralateral breast cancer in postmenopausal women. Ovarian ablation and cytotoxic chemotherapy also reduce the risk of contralateral breast cancer [45].

CONCLUSIONS

Increasingly more patients in the United States with invasive breast cancer and DCIS undergo CPM to prevent contralateral breast cancer. Patient, tumor, and treatment factors are associated with increased use of CPM. Indeed, CPM does reduce the risk of contralateral breast cancer, but likely does not impact breast cancer survival rates for patients without BRCA mutations. Controversy exists about whether the physician or patient should initiate the discussion of CPM. If a patient appropriately chooses breast-conserving surgery, then CPM is not a relevant treatment. For patients who undergo mastectomy, CPM may be a reasonable option, particularly if a patient has a BRCA mutation, strong family history, is obese, or if imaging of the contralateral breast is difficult [39]. However, immediate CPM is generally discouraged for patients with more advanced breast cancers; for these patients, prolonged recovery and surgical complications after CPM may delay receipt of recommended adjuvant therapy.

High-risk patients without breast cancer may take months or years to obtain accurate information on the risks and benefits of BPM. In contrast, women with newly diagnosed unilateral breast cancer often make the decision to undergo CPM within a few days or weeks. This decision may be compromised by the stress of being diagnosed with breast cancer. Recent studies have demonstrated that many patients are not well informed about the risk of contralateral breast cancer or the benefits of CPM. Physicians need to provide breast cancer patients with accurate information on the risk of contralateral breast cancer and on the risks and benefits of CPM. In addition, physicians should encourage appropriate patients to consider less drastic options (e.g., endocrine therapy) to reduce the risk of contralateral breast cancer.

Presently, no study has prospectively evaluated the complex decision-making processes that lead to CPM. Future research should include development of models and instruments to elucidate these processes [39]. Also, the surgeon's role and influence in choice of breast cancer surgery should be evaluated. Finally, decision aids should be developed for breast cancer patients and physicians.

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