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CONTINUING EDUCATION– BREAST ONCOLOGY

Society of Surgical Oncology Breast Disease Working Group Statement on Prophylactic (Risk-Reducing) Mastectomy

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ABSTRACT Over the past several years, there has been an increasing rate of bilateral prophylactic mastectomy (BPM) and contralateral prophylactic mastectomy (CPM) surgeries. Since publication of the 2007 SSO position statement on the use of risk-reducing mastectomy, there have been significant advances in the understanding of breast cancer biology and treatment. The purpose of this manuscript is to review the current literature as a resource to facilitate a shared and informed decision-making process regarding the use of risk-reducing mastectomy.

Over the past 10 years, there has been an increase in the proportion of breast cancers diagnosed at an early stage,[1] but many groups have reported that the rates of bilateral prophylactic mastectomy (BPM) and contralateral prophylactic mastectomy (CPM) have been increasing.[2] The Society of Surgical Oncology (SSO) published position statements on the use of prophylactic (risk-reducing) mastectomy in 1993, 2001, and 2007 to help patients and providers understand the indications for risk-reducing mastectomy and to guide insurance coverage and reimbursement for this surgery. SSO Past-President, Monica Morrow, asked the SSO Breast Disease Working Group to review the current literature and produce an updated position statement.

Here, we present the results of our review. Topics covered include determinants of breast cancer risk; risk assessment tools; the impact of BPM and CPM on breast cancer risk and overall survival; the technical details of risk-reducing mastectomy; reported surgical complications; alternatives to surgery, including chemoprevention and surveillance imaging; and issues related to quality of life and patient satisfaction. This review is meant to be a resource to help physicians with patient counseling and decision making in relation to risk-reducing mastectomy.

FACTORS DETERMINING AN INDIVIDUAL'S FUTURE BREAST CANCER RISK

The decision to undergo risk-reducing mastectomy is intensely personal and often influenced by a variety of factors, including perceived breast cancer risk, anxiety over screening and diagnostic procedures, and the anticipated physical, emotional, cosmetic, and financial outcomes of the surgery.[3–6] A breast surgeon can facilitate this decision-making process by providing an accurate estimate of an individual's future breast cancer risk.

Predicting future breast cancer risk requires consideration of both genetic factors and non-genetic factors, including gene mutations, pathologic changes in breast tissue, prior chest wall irradiation, breast density, and other factors. Table 1 lists genetic and non-genetic risk factors and their risk ratios.

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Gene Mutations

Individuals who have inherited mutations in highly penetrant breast cancer susceptibility genes have the greatest breast cancer risk. For example, lifetime breast cancer risk ranges from 65 to 81% for *BRCA1* mutation carriers and 45 to 85% for *BRCA2* mutation carriers.[7–9] It is worth noting here that there is an increasing body of evidence that age at onset of first cancer influences the risk of second primary cancer development.

Less common mutations in highly penetrant breast cancer-associated genes include mutations in *TP53*[10] and *PTEN*,[11] which are associated with a lifetime breast cancer risk of 50–85%; mutations in the high-penetrance genes *PALB2*[12,13] and *RAD51C*[14] may also be associated with increased breast cancer risk. With the introduction of multigene panels and whole-genome sequencing, breast surgeons are likely to occasionally encounter patients with mutations in moderate-penetrance genes, such as *CDH1*[15] and *STK11*,[16] which are associated with a lifetime breast cancer risk of 35–50%, or even low-penetrance genes, such as *CHEK2*,[17] *p16*,[18] or others, which are associated with a 15–35% lifetime breast cancer risk. However, use of multigene panels to guide surgical treatment should be done so with caution due to the likelihood of misinformation to the consumer and the possibility of unnecessary harm to the individual.[19] Direct-to-consumer marketing of single-nucleotide polymorphism tests may prompt some individuals to seek the advice of a breast surgeon because of a result suggesting that they are at increased risk for breast cancer, despite limited data regarding the efficacy of these tests. The vast majority of such patients will have a lifetime risk in the 15–20% range, but rare individuals will have a lifetime risk as high as 35%.[20] Research continually

TABLE 1 Common risk factors and their risk ratios

Risk factor	Risk ratio
Genetic risk factors	
Being a woman	114[206]
Age	4–158[206]
Mutation in high-penetrance gene (*BRCA1*, *BRCA2*, *p53*, *STK11*)	26–36[207,208]
Mutation in moderate-penetrance gene (*PTEN*, *p16*, *PALB2*, *CDH1*, *NF1*, *CHEK2*, *ATM*, *BRIP1*)	2.0–2.7[209]
Family history of breast cancer in mother, daughter, or sister	1.55–1.8[210,211]
Family history of breast cancer in aunt, niece, or grandmother	1.15[37,212]
Genetic polymorphisms (e.g. FGFR2, TNRC9, MAP3K1, LSP1, MRPS30)	1.07–1.26[213]
Non-genetic factors	
Mantle radiation (lymphoma treatment)	5.6[214]
Acini/lobule in benign breast tissue	
11–20	2.8[215]
21–40	3.23
≥41	11.85
Mammographic density	
>25–50% (scattered densities)	2.4[216]
>50–75% (heterogeneously dense)	3.4
>75% (dense)	5.3
Lobular carcinoma in situ on a breast biopsy	5.4[217]
Atypical hyperplasia on a breast biopsy	5[218]
Increased bone mineral density	2.0–2.5[219]
Age at first birth > 35 years	1.31–1.93[38,220]
Obesity (body mass index > 30 kg/m^2)	1.2–1.8[211,220]
Any benign breast disease	1.47[220]
High circulating insulin level	1.46[221]
Five years of combined hormone replacement therapy (e.g. estrogen and progestin)	1.26–1.76[222–224]
High circulating estrogen level	1.1–1.7[221,225]
Nulliparity (no live births)	1.26–1.55[38,220]
Alcohol consumption more than approximately 1 drink/day	1.31[220]
Menstrual periods starting before age 12 years	1.21[38]

uncovers new genetic associations with breast cancer and until more is understood about the penetrance and role of these genes in developing breast cancers, the risk associated with them are best estimates and are likely to change.

Many women with extended family histories of breast malignancies test negative for a known genetic mutation; however, even with negative results, such women are considered to be at high risk for the development of breast cancer, in part because of a presumed undiscovered genetic abnormality. The 10-year risk of contralateral breast cancer for a 30- to 34-year-old breast cancer patient without *BRCA1/2* mutations and no family history is 7%. Patients without a mutation but with an affected second-degree relative have a 9% risk, and those with an affected first-degree relative have a 14.7% risk of contralateral breast cancer. A bilaterally affected family member increases the risk of a non-mutation carrier for contralateral breast cancer to 23.7%.[21] Women with extensive family histories but negative results on genetic testing are best counseled according to their lifetime risk, as predicted by the mathematical models described below.

Pathologic Changes in Breast Tissue

If a breast biopsy or tissue sampling has been performed, the proliferative pathologic changes within the breast are also used to estimate the future risk of an invasive breast malignancy.

In 1985, Dupont and Page published their analysis of the relationship between pathologic changes in 10,000 benign breast biopsy specimens and future risk of breast cancer. The authors found that patients could be divided into three categories with different future risks of breast malignancy: (i) non-proliferative changes; (ii) proliferative changes without atypia, associated with 1.9 times the breast cancer risk in patients with non-proliferative changes; and (iii) proliferative changes with atypia, associated with 4–5 times the breast cancer risk in patients with non-proliferative changes.[22] The cumulative absolute risk of invasive breast cancer in the patients with proliferative changes and atypia was 13% at 20 years.

A Mayo Clinic study showed a higher absolute 20-year risk of malignancy (21%) in women with proliferative changes and atypia, but included ductal carcinoma in situ in addition to invasive events. In this cohort of women with atypia, which included 331 patients, the cumulative lifetime risk rose to 50% if the woman had a history of multiple sites of atypia (three sites) and calcifications on breast imaging.[23] The group of women with three sites of atypia with calcifications was small ($n = 38$) and therefore the risk estimates may not be too secure. Similarly, in a larger (2938 patients) retrospectively analyzed cohort from Boston, patients with atypia in a breast biopsy specimen had a 5–11% 5-year risk of a breast malignancy; the estimated 10-year risk of a breast malignancy was 17.3% for patients with atypical ductal hyperplasia, 20.7% for patients with atypical lobular hyperplasia, 23.7% for patients with lobular carcinoma in situ, and 26% for patients with atypical ductal hyperplasia bordering on ductal carcinoma in situ.[24]

Prior Chest Wall Irradiation

Women who have been treated during adolescence or young adulthood with chest wall irradiation for malignancies (most frequently Hodgkin lymphoma) have a cumulative incidence of breast cancer of 30% by the age of 50 years, which is similar to the risk of breast cancer by the same age for *BRCA* mutation carriers.[25] Certain factors may reduce the risk associated with prior chest wall irradiation, including concurrent treatment with alkylating agents, ovarian irradiation or early ovarian failure, and modern radiation dosing.[26,27] Current national guidelines recommend initiating a breast cancer screening program for individuals with prior chest wall irradiation 8 years after that irradiation is completed or at age 25 years.[27]

Breast Density

Breast density or the ratio of fibroglandular to fatty breast tissue is the next most significant risk factor for the development of breast cancer. However, this risk factor has not been reported in a standard way and its assessment by radiologists has changed over time with the advent of digital mammography screening, which makes it difficult to estimate absolute risks associated with high breast density and may cause underestimation of the importance of this risk factor.[28,29] In a version of the Gail model (a breast cancer risk assessment tool; see the next section) that has been modified to include mammographic density, a 40-year-old woman with $> 75\%$ breast density and no other risk factors would have a lifetime breast cancer risk of 25–30%, but for a 40-year old woman with a breast density of $< 75\%$, the absolute lifetime risk likely never exceeds 20%.[28] The addition of breast density to the Gail model results in a greater improvement in predictive accuracy, as measured by area under the receiver operating characteristics curve, than the addition of the status of seven single-nucleotide polymorphisms.[29] In a meta-analysis of more than 14,000 cases, women with a $> 75\%$ breast density had 4.64 times the lifetime breast cancer risk of women with a 5% breast density.[30]

Hormonal treatments have been shown to induce changes in breast density.[31,32] In a study of 211 women with unilateral breast cancer, Sandberg et al. showed that women who experience $\geq 10\%$ decrease in density from the time of diagnosis until the first follow-up mammogram

decrease their risk of contralateral breast cancer by 55%. The association between decreasing mammographic density and the risk of contralateral cancer was independent of therapy administered for the first cancer. Importantly, there was no association between baseline density and occurrence of contralateral breast cancer.[33]

Other Factors

There are multiple additional non-modifiable and modifiable risk factors for the development of breast cancer (Table 1). Each of these risk factors contributes a small increase in relative risk (1.5–2.0), but the risk factors are best considered in association with one another to determine an absolute risk of breast cancer.[34] The Gail model optimally describes this absolute risk for the factors of age at menarche and age at first birth, but does not include the risk factors of body mass index and alcohol or tobacco use. These latter modifiable risk factors are unlikely to influence decision making regarding risk-reducing surgery in the absence of the more influential genetic or pathologic risk factors.

TOOLS AVAILABLE FOR BREAST CANCER RISK ASSESSMENT

Several mathematical models are available for calculating breast cancer risk on the basis of genetic and/or non-genetic factors. Widely used genetic models include BRCAPRO,[35] BOADICEA,[36] and the Claus model.[37] These models are most appropriate for women with a family history of early-onset breast cancer, ovarian cancer, or male breast cancer. The Gail model[38] is the most widely used and most thoroughly validated general risk assessment model but is not appropriate for women with a suspected inherited predisposition to breast cancer. The Tyrer-Cuzick model[39] is another very popular model and includes genetic factors as well as a wide range of non-genetic factors. However, the non-genetic factors were not combined with the same rigor demonstrated by Gail in the construction of his model, and the Tyrer-Cuzick model has not been thoroughly validated.

These models can be implemented in the clinic using the software program CancerGene[40] or Hughes Risk Apps.[41] The National Cancer Institute's Division of Cancer Control and Population Sciences has collated these models and references for review on a website (http://epi.grants.cancer.gov/cancer_risk_prediction/breast.html).[42] For women with a tissue diagnosis of atypical hyperplasia, both the Gail model[43] and the Tyrer-Cuzick model[44] have limitations in risk assessment. There are no tools currently available for predicting breast cancer risk for women with no family history or atypical hyperplasia.

LIFETIME VERSUS NEAR-TERM BREAST CANCER RISK ESTIMATES

Determining the optimal timing of risk-reducing mastectomy requires an understanding of both lifetime risk and near-term risk. For instance, the mean age at diagnosis of breast cancer is approximately 44 years for *BRCA1* mutation carriers and 47 years for *BRCA2* mutation carriers, but age at onset varies by family, particularly for families with *BRCA2* mutations.[45] Some genes, such as *TP53* and *STK11*, are associated with very early-onset breast cancer, while genes such as *CHEK2* and *PALB2* are associated with later-onset breast cancer.[46–48] Recently, a Monte Carlo modeling program was developed by Kurian et al. to help *BRCA1* and *BRCA2* mutation carriers make decisions about continued screening versus surgery.[49] The model offers surgeons and patients another tool for evaluating the impact of risk-reducing surgery on future breast cancer risk and breast cancer-specific survival.

Although the Gail model may calculate a high lifetime risk for a woman with a family history of breast cancer and a personal history of proliferative breast disease, many such women are relieved to learn that their 5-year risk is much lower. There is no single risk threshold above which risk-reducing mastectomy is clearly indicated. The role of the physician/surgeon is to help provide the best lifetime and near-term breast cancer risk estimate for the patient, understanding that quantitative assessments are just one piece of the discussion. The Gail model, while good for predicting how many women in a group will develop cancer, cannot predict which ones.

Younger women,[50] women with children,[51,52] and women who have experienced a particularly difficult breast cancer event in their families[53] are more likely to opt for bilateral risk-reducing mastectomy, even at lower risk levels. Additional decision support may be found in consultation with a health psychologist. The shared process of deciding whether the patient should undergo a risk-reducing mastectomy should involve several interactive discussions to ensure that the patient understands her real versus perceived risk and the physician understands the patient's risk tolerance.

IMPACT OF BILATERAL PROPHYLACTIC MASTECTOMY (BPM) ON BREAST CANCER RISK AND OVERALL SURVIVAL

What is the Level of Breast Cancer Risk Reduction with BPM?

There are no prospective, randomized clinical trials evaluating the effect of BPM on breast cancer risk, but

TABLE 2 Bilateral prophylactic mastectomy and breast cancer risk

Study	BPM		No BPM		Follow-up (years)	HR	*p* value
	N	BCD (%)	*N*	BCD (%)			
Meijers-Heijboer et al.[51,55]	76	0 (0)	63	8 (12.7)	3	NA[a]	0.003
Rebbeck et al.[56]	105	2 (1.9)	378	184 (48.7)	6.4	0.09	<0.0001
Skytte et al.[57]	96	3 (3.1)	211	16 (7.6)	7.7	0.394	0.14
Domcheck et al.[58]	247	0 (0)	1372	98 (7.1)	3	NA[a]	ND

BCD breast cancer diagnosis, *BPM* bilateral prophylactic mastectomy, *HR* hazard ratio, *ND* not determined

[a] There were no cancer events in those with risk-reducing mastectomy, therefore HRs cannot be estimated

several prospective and retrospective studies have demonstrated a significant reduction in the expected incidence of new breast cancers after BPM.[54] From the published data, it is clear that BPM confers a reduction in the risk of developing a primary breast cancer approaching 100% when meticulous surgical technique is used to remove the vast majority of breast tissue. The breast cancer risk reduction from BPM is greatest in healthy, unaffected women with a known genetic predisposition or a strong family history of breast and ovarian cancer. Almost all new breast cancers after BPM occur in patients who had significant breast tissue remaining, such as those who underwent subcutaneous mastectomy and those who had residual breast tissue in the axillary tail after surgery. Often, BPM is combined with risk-reducing bilateral salpingo-oophorectomy, which can further decrease breast cancer risk.

Four prospective studies have evaluated the breast cancer risk reduction after BPM, and two of these also reported on deaths from breast cancer. The earliest study, from the Rotterdam Family Clinic, identified 139 unaffected women with a mutation in *BRCA1/2*; 76 of these women underwent BPM, and 63 opted for surveillance. After 3 years of follow-up, no breast cancers had been identified in the BPM group, and eight breast cancers had been diagnosed in the surveillance group. One woman in the surveillance group died of breast cancer.[55] In a multicenter case–control study, Rebbeck et al. enrolled 105 unaffected women with a *BRCA1/2* gene mutation who underwent BPM and compared them with 378 women with a *BRCA1/2* mutation who had not undergone BPM. At a mean follow-up of 6.4 years, BPM reduced breast cancer by 90%, and BPM in conjunction with bilateral salpingo-oophorectomy reduced breast cancer risk by 95%. One-third of patients in this study had a subcutaneous mastectomy, which is known to leave some breast tissue underneath the nipple-areola complex. Both women who developed breast cancer after BPM had undergone subcutaneous mastectomies.[56] More recently, in a multicenter study from Denmark, 96 unaffected *BRCA1/2* mutation carriers who chose to undergo BPM were compared with 211 who did not. In the surgical group, three primary breast cancers were diagnosed over 379 person-years, and, in the no-surgery group, 16 breast cancers were diagnosed over 935 person-years. The authors attributed the development of the cancers to inadequate surgical technique.[57] The largest prospective study of breast cancer risk reduction after BPM was from the PROSE consortium and included 2484 women with *BRCA1/2* mutations from 22 centers in the US and Europe. No breast cancers were diagnosed in the 247 unaffected women who underwent BPM, whereas 98 breast cancers (7%) were diagnosed in the surveillance group during the follow-up period of 3 years.[58] The results of these studies are summarized in Table 2.

Two large retrospective studies with long-term follow-up have shown breast cancer risk reduction and a survival advantage in women undergoing BPM. In the earlier study, from the Mayo Clinic, 214 women classified as high risk and 425 classified as moderate risk underwent BPM. During a follow-up period of 14 years, seven breast cancers were diagnosed, which represented a 90% risk reduction compared with the expected number of breast cancers. All women who developed breast cancer after BPM had subcutaneous mastectomies.[59] There were no breast cancer deaths in the moderate-risk group and two breast cancer deaths in the high-risk group compared with 90 breast cancer deaths among the women's sisters during the follow-up period. The authors concluded that BPM reduces breast cancer-specific mortality by 81–94%. The second large retrospective study was conducted among six health plans of the National Cancer Institute–funded Cancer Research Network, and compared 297 women at increased risk who underwent BPM with a stratified sample of 666,800 women at increased risk who did not undergo BPM.[60] After a median follow-up of 10 years, none of the women who underwent BPM had died of breast cancer, while it was estimated that 0.2% of the controls had died of breast cancer.

Five recent studies from Europe have shown superior risk reduction with the use of improved surgical technique for BPM. Three Dutch studies identified women who were either known carriers of *BRCA1/2* mutations or had a strong family history of breast and ovarian cancer and underwent simple mastectomy or skin-sparing mastectomy with removal of the nipple-areolar complex, axillary tail, and pectoralis fascia. During the follow-up period after BPM, which ranged from 2.5 to 6.1 years, no new cancers were identified.[61–63] Arver et al. identified 223 high-risk women who underwent BPM at eight hospitals in Sweden, 129 (58%) of whom were BRCA1/2 mutation carriers. No primary breast cancers were observed after a mean follow-up of 6.6 years. This study is notable for the large proportion of women who underwent BPM with newer surgical techniques such as nipple retransplantation (45%) and nipple-sparing mastectomy (31%).[64] Lastly, Evans et al. collected data from 550 women at high risk for breast cancer from 10 European centers; 202 of these women (37%) were *BRCA1/2* mutation carriers, and 314 (57%) underwent BPM. Follow-up data were available for 98% of the women, and no breast cancers were identified after a median follow-up of 7.5 years.[65]

Does BPM Confer a Survival Benefit?

A Cochrane review published in 2010 acknowledges that observation studies show that BPM is effective in reducing the incidence of breast cancer and death due to breast cancer. The authors suggest that more rigorous studies are needed to understand the impact on breast cancer-specific survival or overall survival in women at high risk for breast cancer.[54]

Because breast cancer-specific mortality is generally low and life spans are generally long in the modern era, large studies with long follow-up times will be required to convincingly demonstrate a survival advantage for BPM. As an alternative, some investigators have modeled outcome for *BRCA1/2* gene mutation carriers on the basis of the uptake of risk-reducing interventions. One such study suggested a 7% survival gain for BPM performed at age 40 years,[66] while another study estimated that BPM would be associated with 2.0–5.8 years of life gained depending on the age when it is performed.[67]

On the basis of all available evidence, it is likely that BPM confers a survival advantage when it is performed at a relatively early age in women at very high risk for breast cancer. However, it is clear that among *BRCA1/2* mutation carriers, risk-reducing bilateral salpingo-oophorectomy has a greater impact on survival. In the average-risk woman or women with a small increase in risk there is no evidence it improves survival.

IMPACT OF CONTRALATERAL PROPHYLACTIC MASTECTOMY (CPM) ON BREAST CANCER RISK AND OVERALL SURVIVAL

What is the Level of Breast Cancer Risk Reduction with CPM?

Although there are no prospective randomized studies addressing the impact of CPM in women with breast cancer on the risk of subsequent breast cancer in the contralateral breast, several retrospective studies have addressed this question. Most of these studies are limited by biases, most frequently selection bias.[54]

Retrospective cohort studies have compared the incidence of contralateral breast cancer among women undergoing CPM to either (i) the observed incidence of contralateral breast cancer in a concurrently treated population that did not undergo CPM,[68–70] or (ii) the expected incidence of contralateral breast cancer as estimated by life tables or surveillance, epidemiology, and end results (SEER) data.[71,72] Case–control studies have matched women who underwent CPM with those who did not by various clinical and pathologic variables.[73–76] Some studies included only women with *BRCA1* or *BRCA2* mutations.[53,70]

Regardless of the population and method of analysis, all studies that have calculated the risk reduction have shown a statistically significant reduction in contralateral breast cancer risk ranging from 91 to 100%.

A Cochrane review published in 2010 examined the efficacy of CPM and concluded, in spite of methodologic limitations of the available retrospective data, that CPM markedly reduces the incidence of breast cancer in the contralateral breast.[54]

Does CPM Confer a Survival Benefit?

There are no prospective randomized studies addressing the potential survival benefit of CPM for women with breast cancer. All studies addressing this question are retrospective and used either SEER data[77] or institutional cohorts. Case–control studies have matched women undergoing CPM with those who did not by various clinical and pathologic variables.[73,74,76] Other studies have adjusted for confounders, such as age, stage, adjuvant treatment, and hormonal status.[69,70,77–79] Some studies included only women with *BRCA1* or *BRCA2* mutations.[53,70,79,80] Studies have reported breast cancer-specific survival or mortality,[69,70,73,74,77–81] disease-free survival[73,74,76] and overall survival.[69,70,73,74,76] Because disease-free survival includes contralateral breast cancer as an event, only breast cancer-specific survival and overall survival will be discussed below. With one exception,[74]

median follow-up times in studies on the impact of CPM on survival are generally 3–7 years.

Breast Cancer-Specific Survival

Van Sprundel et al., Boughey et al., Brekelmans et al., and Babiera et al. found no significant association between CPM and breast cancer-specific survival.[70,74,79,81] However, Peralta et al. found a trend toward an association between CPM and an improved breast cancer-specific survival rate at 15 years for the subset of patients with stage 0, 1, or 2 disease (71% for CPM vs. 53% for no CPM; $p = 0.06$).[73]

Three studies found that CPM was associated with a significant improvement in breast cancer-specific survival. Lee et al. compared patients with infiltrating lobular carcinoma who did or did not undergo CPM, adjusting only for age, and found a significantly higher breast cancer-specific survival associated with CPM ($p = 0.01$).[78]

Herrinton et al. found that with a median follow-up of 4.8 years, 8.1% (74/908) of women who underwent CPM died of breast cancer, compared with 11.7% (5437/46,368) of women who did not undergo CPM.[69] The hazard ratio (HR) for breast cancer mortality was 0.57 (95% confidence interval [CI] 0.45–0.72) after adjustment for eight potential confounders. However, given that only 2.7% of women who did not undergo CPM developed contralateral breast cancer, compared with 0.5% of those who did undergo CPM (absolute reduction in rate of contralateral breast cancer, 2.2%), it is difficult to explain the absolute increase in the breast cancer-specific survival rate (3.6%) by the presumed mechanism of CPM reducing the incidence of contralateral breast cancer.

Using SEER data with a median follow-up of 47 months, Bedrosian et al. found that CPM was associated with improved breast cancer-specific survival (HR for death 0.84; 95% CI 0.76–0.92) after adjustment for eight potential confounders.[77] Furthermore, these authors determined that the association was predominantly due to improved survival in the subset of women younger than 50 years of age with stage 1 or 2, estrogen receptor (ER)-negative breast cancer (HR for death 0.68, 95% CI 0.53–0.88; $p = 0.004$). In this subset, CPM was associated with an absolute increase of 4.8% in the 5-year breast cancer-specific survival rate (83.7% for no CPM vs. 88.5% for CPM). However, given that within this subset only 0.9% of women who did not undergo CPM developed contralateral breast cancer, compared with 0.16% of women who did undergo CPM, the difference in incidence of contralateral breast cancer cannot account for this 4.8% difference in the 5-year breast cancer-specific survival rate. The authors stated that the "data strongly suggest that with increasing age, a bias exists for selecting a healthier cohort of women for CPM". Further interpretation of the data by Tuttle et al. suggest that the observations by Bedrosian and colleagues can be explained by selection bias.[82] Those patients who undergo the aggressive breast cancer surgery option of CPM are healthier, and therefore also more likely to receive chemotherapy, and thus survive their first cancer. Selection bias also accounted for the improved survival from CPM in a large ($N = 449{,}178$) study conducted by Jatoi and Parsons.[83] Lower breast cancer-specific mortality was observed in the 25,961 women who underwent CPM (HR 0.84); however, this group also had a lower mortality due to all causes (HR 0.83) and a lower non-breast cancer death rate (HR 0.71). The improved survival due to non-breast cancer-related causes in the CPM group further implicates a selection bias. Narod has argued that the majority of deaths in the first decade after breast cancer diagnosis will be from the primary cancer and that the potential survival benefit of CPM would occur much later, pointing out that it is not feasible to show any survival difference with a short-term study.[84] For women with *BRCA1/2* mutations, he estimated that the cumulative mortality rate from new contralateral breast cancer would be approximately 1.7% at 10 years and 6.8% at 20 years, such that by 20 years, 20% of all cancer deaths would be due to contralateral breast cancer. He notes that an individual must survive the first cancer, develop a contralateral cancer, and then succumb to the contralateral cancer in order to have had a survival benefit from CPM. Portschy et al. projected long-term survival after CPM for patients with unilateral breast cancer using a simulated Markov model.[85] They showed that 20-year survival differences ranged from 0.56 to 0.94% for women with stage I breast cancer and 0.36 to 0.61% for women with stage II breast cancer, depending on age and ER status. No cohort had a $> 1\%$ absolute survival difference at 20 years.

Overall Survival

Van Sprundel et al., Peralta et al., Brewster et al., Davies et al., and Babiera et al. reported no association between CPM and overall survival.[69,70,73,74,76,81,86] Pesce et al. showed that in a group of 14,627 women < 45 years of age there was no survival advantage of CPM, even in women under the age of 45 years.[87] To adjust for bias associated with factors related to the decision to undergo CPM, Brewster et al. used multivariate analysis to show that there was a significant association between CPM and overall survival after adjustment for seven variables (HR 0.74, 95% CI 0.56–0.99; $p = 0.04$).[76] However, when the authors compared 497 women who underwent CPM with 497 controls matched on their

propensity score, no significant association was seen for the entire group (HR 0.70, 95% CI 0.44–1.09; $p = 0.11$) or for the hormone receptor-positive (HR 0.63; $p = 0.12$) or hormone receptor-negative (HR 0.50; $p = 0.11$) subsets.

Herrinton et al. reported worse overall survival for women who did not have CPM,[69] noting that 13% of women who underwent CPM and 20.5% of those who did not died (HR 0.60, 95% CI 0.50–0.72). This relationship was true for women who died of breast cancer (see above discussion on breast cancer-specific survival) and for women who died of unknown and non-breast cancer causes (HR 0.69, 95% CI 0.51–0.93), suggesting that women undergoing CPM were selected for better health overall.

Boughey et al. compared 385 women who underwent CPM with 385 matched controls, with a median follow-up of 17.3 years, and found improved 10-year overall survival in the CPM group (83% vs. 74%), a survival difference that remained significant after adjustment for 11 variables (HR 0.77; $p = 0.03$).[74] Rates of contralateral breast cancer were 0.5% in the CPM group and 8.1% in the no-CPM group, again suggesting that prevention of contralateral breast cancer by CPM is not the sole explanation for the difference in overall survival.

The retrospective nature of the studies to date and the non-random nature of the decision to undergo CPM indicate that evaluation of the effect of CPM on survival is limited by selection bias. It is likely that any observed association of CPM with survival is due to CPM being performed more often on women with a better prognosis from breast cancer and better overall health. Observed differences in survival are generally larger than differences in contralateral breast cancer rates, suggesting that survival differences are not due to reduction in contralateral breast cancer. Furthermore, most studies have follow-up times expected to be too short to permit detection of a difference in survival due to prevention of contralateral breast cancer. In addition, in the modern era, the use of endocrine therapy, and even systemic chemotherapy, has decreased the rate of contralateral breast cancer.[88–90] Nichols et al. have shown a steady decrease in the occurrence of contralateral breast cancer by 3% each year since 1985, when the use of hormonal therapy became standard.[90] However, there is little evidence that women who do not undergo CPM and do develop a contralateral breast cancer are at increased risk of death from breast cancer.[91]

The potential overall survival benefit of CPM is greatest in women who have (i) the best prognosis from the index cancer; (ii) very low expected mortality from non-breast cancer causes; and (iii) the highest expected rate of contralateral breast cancer. However, even if the maximum survival benefit is expected, the difference in survival must be weighed against the negative effects of CPM.

TRENDS IN CPM RATES

There is solid population and institutional evidence that the proportion of patients diagnosed with unilateral breast cancer who choose to undergo CPM has increased dramatically over the past 20 years in North America.[2,92] This change is intriguing because the increase in CPM rates has not been a worldwide trend.[93] Güth et al. suggest that the difference between CPM rates in the US and Europe can be accounted for by different medico-social and cultural contexts which determine the public perception of breast cancer by both physicians and patients.[93]

Institutional studies examining the factors associated with undergoing therapeutic mastectomy plus CPM instead of unilateral therapeutic mastectomy have found that White women with higher education levels, a family history of breast cancer, a *BRCA* gene mutation, or a history of chest irradiation are more likely to choose CPM.[75,94–97] While most mastectomies are performed for invasive ductal carcinoma, there are studies showing increasing rates of CPM in women with lobular and non-invasive histologic subtypes.[5,95]

The use of preoperative breast magnetic resonance imaging (MRI) may also lead to the decision to undergo a CPM.[5,75,98] Additionally, most studies have found that younger women (cut-offs have varied from 40 to 55 years of age) are more likely than older women to choose CPM as part of their treatment.[4,97,99]

Variations in surgical practice,[5] and even surgeon gender,[4] appear related to the CPM choice, as does the availability of immediate breast reconstruction.[5,95,98] The desire for symmetry can play an important role in the choice of having a CPM when a unilateral mastectomy is indicated and reconstruction is being considered. Bilateral mastectomies have also increased in women with early-stage breast cancer who are candidates for breast-conserving therapy (BCT) despite data showing that there is no significant difference in overall survival between BCT plus radiotherapy and mastectomy.[1,100–103] Additionally, it has been reported that approximately half or more of the patients have chosen to undergo simultaneous breast reconstruction despite the possibility of reconstructive complications.[104]

Women undergoing CPM often perceive that the risk of developing contralateral cancer is higher than published rates, and women may also perceive that CPM is associated with improved survival.[105,106] Even when patients are educated about the actual risk of metachronous disease or death, the sentiment often expressed by those choosing CPM is that they never want to go through the surveillance, diagnosis, and treatment process again.[107] Patients often feel that having CPM is beneficial to their overall well-being as their personal cancer worry and distress regarding recurrence will be less with removal of the contralateral

breast during the same surgical procedure; however, actual documentation of distress reduction with CPM is lacking.[97,108] Several reports on the clinical considerations, counseling, and cautions regarding CPM have been published.[109–112]

Patient Satisfaction and Impact of Risk-Reducing Mastectomy on Body Image, Quality of Life, and Sexuality

Prophylactic mastectomies may have implications for patients beyond risk reduction. Considerations of body image and quality of life are important in the shared decision-making process. Data regarding the impact of prophylactic mastectomy (even with immediate reconstruction) on body image, quality of life, and sexuality have been mixed. While many women adjust well after prophylactic mastectomy and experience a reduction in cancer-related anxiety, others experience increased anxiety and distress after surgery. Post-mastectomy concerns with body image and sexuality are not uncommon.

In a recent study, Gopie et al. examined body image and sexual/partner relationship satisfaction in a prospective study of 48 patients undergoing BPM with immediate reconstruction, 36 of whom were followed serially over a median of 21 months.[113] Body image was found to decline after BPM and was lower than at baseline, even after reconstruction was complete.[113] Negative body image was associated with high preoperative cancer distress. In addition, while patients rated their sexual relationship satisfaction lower after completion of BPM and reconstruction than at baseline, partner relationship satisfaction did not change significantly.

Gahm et al. surveyed 55 patients at a mean follow-up of 29 months after BPM. Eighty-seven percent of patients reported pain or discomfort in their breasts, with 36% of all patients reporting that pain affected their sleep, and 22% reporting negative effects on their daily activities. Sexual enjoyment was decreased in 75% of patients. Although BPM was found to be associated with these negative effects, none of the women in this study agreed with the statement "I regret the decision I made". This suggests that the relief from the reduced breast cancer risk overrides the negative effects of the BPM in this small group of women.[114]

In a study of 90 women undergoing BPM, Brandberg et al. found that while anxiety decreased over time, a significant proportion of women reported body image issues after 1 year, and 48% reported increased self-consciousness.[115] In addition, nearly half of all patients felt less sexually attractive at 1 year, and sexual pleasure was lower than prior to the operation.

Most published series of women undergoing CPM show that there is widespread and long-lasting overall satisfaction with the decision to undergo this surgery.[108,116,117] However, even among women who have responded with satisfaction to specific questions, qualitative inquiry suggests that women can have some lingering doubts and concerns.[118] These doubts and concerns have generally been reported to be in the realms of body image, appearance, sexuality, and problems with reconstruction.[3,119] There has been strong support for increased professional counseling and discussions with women who have already had CPM.

Hwang et al. surveyed and compared 1598 breast cancer patients who had undergone CPM with 2379 who had not. They found no significant difference in psychosocial well-being, physical well-being, and sexual well-being in the CPM group compared with women without CPM. However, breast satisfaction was significantly better for the CPM group compared with the no-CPM group.[120]

In a study of 60 women who underwent CPM and were followed with validated questionnaires over 2 years, Unukovych et al. found no difference in health-related quality of life between these women and women in the general population.[116] In addition, anxiety, depression, and sexuality did not differ significantly between before and after the surgery, although more than half of the patients reported at least one body image issue at 2 years after CPM.

In a study of 269 women who underwent CPM who were surveyed at 10.7 years and again at 20.2 years after the surgery, the rate of satisfaction and the proportion of patients who would choose prophylactic surgery again increased slightly over time, even though a significant number of patients reported poorer body image (31%), femininity (24%), and sexuality (23%) after CPM.[117]

These data suggest that the decision to undergo prophylactic mastectomy should be carefully considered and that women should be counseled regarding potential effects on body image, femininity, and sexuality. Psychosocial support should be made available, particularly to reduce anxiety and cancer-related distress, which may have an impact on subsequent body image and satisfaction. However, with careful discussions, well-informed patients appear to be satisfied with their decisions, not express regret, and be more likely to report at long-term follow-up that they would make the same decision regarding risk-reducing surgery.

Cost versus Benefit of CPM

BPM has shown to be cost effective in women with BRCA1/2 mutations; however, it is difficult to determine the cost effectiveness of CPM due to the confounding

factors involved with indirect costs along with the direct costs, both in the short- and long-terms. Roberts et al. used a decision tree to model the costs and effects of CPM versus unilateral mastectomy in women younger than 50 years of age with sporadic unilateral, early-stage breast cancers. The impact of each surgical treatment option was measured in the form of quality-adjusted life-years (QALYs) gained. Based on the estimated costs and effects of CPM and unilateral mastectomy, treatment with CPM resulted in 0.2 QALYs less than unilateral mastectomy, and $279 less in costs over a risk period of 10 years with an expected follow-up period of 38 years. This equates to $1397 saved/QALYs lost and, according to the researchers, does not allow CPM to be considered cost effective at this time.[121] Mattos et al. estimated the lifetime costs of surveillance versus prophylactic mastectomies among different reconstruction methods, and found that lifetime prophylactic mastectomy costs were lower than surveillance costs—$1292 to $1993 lower for CPM and $15,668 to $21,342 lower for BPM, depending on the reconstruction. The authors conclude that patients should continue to be given the flexibility to opt for CPM and BPM, and the flexibility to choose the reconstructive option that best fits their needs and values.[122]

SURGICAL TECHNIQUE FOR RISK-REDUCING MASTECTOMY

Once the decision is made to proceed with BPM or CPM, two important surgical questions need to be addressed: What type of mastectomy is best for the patient? Is there a role for sentinel lymph node biopsy as part of BPM or CPM?

What Type of Mastectomy is Best for the Patient?

Two types of risk-reducing mastectomies can be performed; either total (also referred to as simple) mastectomy or nipple-sparing (also referred to as subcutaneous). In a total mastectomy, the entire breast and nipple-areolar complex are removed; these can also be skin-sparing. Questions about the need for removal of the nipple-areola complex have led to development and popularization of nipple-sparing mastectomy. This procedure preserves the entire skin envelope and can further improve the cosmetic results of breast reconstruction. Nipple-sparing mastectomy is a particularly attractive option for patients undergoing BPM and for selected patients undergoing ipsilateral therapeutic mastectomy and CPM. In a study of 583 patients undergoing CPM, 42% of women ($n = 244$) had a subcutaneous mastectomy with reconstruction, 1% ($n = 5$) had subcutaneous mastectomy without reconstruction, 27% ($n = 158$) had simple mastectomy with reconstruction, and 30% ($n = 176$) had simple mastectomy without reconstruction.[119] This study suggests that a total mastectomy was generally preferred over a subcutaneous mastectomy; however, for patients desiring immediate breast reconstruction following mastectomy, a subcutaneous mastectomy was preferred.

Although many studies have demonstrated the superior aesthetic results of nipple-sparing mastectomy over skin-sparing mastectomy,[123–125] important issues need to be considered before nipple-sparing mastectomy is selected. Complications such as partial or complete nipple necrosis can occur and loss of nipple sensation is expected with nipple-sparing mastectomy whether it is performed therapeutically or for risk reduction, and the risk of such complications should be clearly communicated to the patient before surgery.

In the therapeutic setting, the main concern with nipple-sparing mastectomy is the long-term oncologic safety of the procedure.[126,127] In older studies, the likelihood of occult nipple-areola complex involvement was relatively high (8–50%);[128–130] however, in more recent studies, such involvement was reported in only 6–11% of cases.[131–134] In a meta-analysis of 20 articles and a total of 2207 breast cancer patients who underwent nipple-sparing mastectomies, there was no significant differences in overall survival, disease-free survival, and local recurrence compared with patients who underwent total mastectomies.[135] To minimize the risk of local recurrence, careful patient selection is paramount. Optimal candidates for therapeutic nipple-sparing mastectomy can be selected on the basis of the distance between the tumor and the nipple and the results of intraoperative frozen section assessment of the retroareolar tissue.[127] Additional factors, such as primary tumor size, axillary lymph node status, lymphovascular invasion, and degree of intraductal component, are also used to determine an individuals' suitability for nipple-sparing mastectomy based on institutional protocols. The issue of poor overall operative exposure, due to small incisions that are often laterally or inferiorly placed, for the surgeon performing nipple-sparing mastectomy has not been addressed. It can be especially challenging to develop flaps from incisions along the inframammary fold. Publications reporting local recurrence after nipple-sparing mastectomy have not detailed incision placement and other technical factors that may impact recurrence.

The ideal candidate for therapeutic nipple-sparing mastectomy is a patient who (i) is aware of the possibility of loss of form and function of the nipple-areola complex; (ii) is younger with less ptosis; (iii) is a nonsmoker; (iv) has no prior history of breast irradiation; (v) will not require postoperative radiation therapy based on tumor characteristics at presentation; (vi) has a tumor smaller than 2.5 cm

that is more than 4 cm from the nipple; and (vii) has no documented lymphovascular invasion, involved axillary nodes, or extensive intraductal component.[127]

In the risk-reduction setting, the main issue with nipple-sparing mastectomy is whether the small amount of breast tissue left within and behind the skin of the nipple and areola will increase the risk for developing a future breast cancer, particularly in women with a genetic predisposition (i.e. a mutation in a breast cancer susceptibility gene). There is limited information on long-term outcomes with nipple-sparing mastectomy, particularly in women with a genetic predisposition. Indirect evidence comes from studies of skin-sparing mastectomy in which the excised nipple-areola complex was scrutinized to obtain information about the presence of terminal ductal-lobular units and premalignant or malignant lesions.

In one such study, 62 nipple-areola complexes, from 33 women with *BRCA* mutations (25 *BRCA1*, 8 *BRCA2*) who were diagnosed with breast cancer and underwent therapeutic mastectomy and CPM, were evaluated.[136] Terminal ductal-lobular units were present in 24% of nipple-areola complex specimens. There was no evidence of atypical hyperplasia, carcinoma in situ, or invasive carcinoma in any of the 33 nipple-areola complexes of prophylactic mastectomy specimens; however, among the 29 available mastectomy specimens from breasts with cancer, two (7%) had malignant findings and one (3%) had atypia identified in the nipple-areola complex. On the basis of these findings, the authors concluded that the probability of nipple involvement by premalignant or malignant lesions in *BRCA* mutation carriers is low in women undergoing prophylactic mastectomy, but higher (10%) in women undergoing therapeutic mastectomy. The authors further concluded that nipple-sparing mastectomy may be appropriate and oncologically safe for selected women with *BRCA* mutations. However, the implications of the presence of ductal-lobular units in terms of long-term breast cancer risk are unknown.

A direct assessment of the risk of subsequent breast cancer after risk-reducing nipple-sparing mastectomy was recently reported.[137] In a case–control study, 53 patients with *BRCA* mutations who underwent bilateral nipple-sparing mastectomy for risk-reduction (26 patients) or therapeutic indications (27 patients) were age-matched (for risk-reducing cases) or age- and stage-matched (for therapeutic cases) with patients without *BRCA* mutations who underwent bilateral nipple-sparing mastectomies for risk-reduction or therapeutic purposes, respectively, during the same period. Outcomes included tumor involvement of the resected retroareolar tissue, development of new breast cancers (for risk-reduction cases), and development of any local–regional recurrence (for therapeutic cases). In patients undergoing risk-reducing nipple-sparing mastectomy, in situ carcinoma was found in 1.9 and 3.8% of the retroareolar tissue specimens in the *BRCA* mutation-positive and *BRCA* mutation-negative cohorts, respectively ($p = 1$). At a mean follow-up of 56 months, no new cancers developed in patients who underwent prophylactic mastectomy. In patients undergoing therapeutic nipple-sparing mastectomy, in situ or invasive cancer was found in 0% and 3.7% of the retroareolar tissue specimens in the *BRCA* mutation-positive and *BRCA* mutation-negative cohorts, respectively ($p = 0.49$). At a mean follow-up of 33 months, there had been no local–regional recurrences in the *BRCA* mutation-positive cohort and one recurrence in the *BRCA* mutation-negative cohort. A recent review of the literature shows that recurrences after prophylactic mastectomies, including nipple sparing, rarely occur in the nipple area.[138] Additionally, whether nipple-sparing or total mastectomy, there is likely to be remaining breast tissue after surgery. A study by Griepsma et al. showed that of 206 mastectomy patients in 11 hospitals, 157 showed remaining tumor tissue in biopsy samples.[139] On the basis of these findings, the authors concluded that nipple-sparing mastectomy is an oncologically safe procedure in *BRCA* mutation carriers. However, a longer follow-up time is necessary before one can adequately assess the long-term efficacy of nipple-sparing mastectomy as a risk-reducing procedure in this high-risk cohort of patients.

Factors Related to the Discovery of an Occult Cancer in the CPM Specimen

A number of studies have examined the patient and tumor variables associated with an increased risk of finding an occult breast cancer in the CPM specimen. Lobular histologic subtype and a 5-year risk of breast cancer of at least 1.67% according to the Gail model have been associated with the discovery of cancer in the CPM specimen;[140–142] multifocality/multicentricity in the primary tumor specimen has also been a relatively consistent predictor of increased risk of finding cancer in the CPM specimen.[94,141] The relationship between patient age and the discovery of an occult cancer in the CPM specimen has been inconsistent, and observed associations are likely due to population selection of the institutions studied.[72,141] Similarly, ER status, either positive[72] or negative,[77] has been cited as a predictive factor in various series.

Is There a Role for Sentinel Node Biopsy in Patients Undergoing BPM or CPM?

The rationale for considering sentinel node biopsy in patients undergoing risk-reducing mastectomy stems from observations that occasionally occult invasive carcinoma is found on permanent pathologic evaluation of the

mastectomy specimen. In such cases, the patient will need axillary staging that can only be achieved with axillary node dissection, since the value of lymphatic mapping and sentinel node biopsy following mastectomy has not been adequately established.

Thus, some have advocated routinely performing sentinel node biopsy in patients undergoing risk-reducing mastectomy to pre-emptively address the above situation. Others have argued that the finding of occult invasive cancer in a patient undergoing risk-reducing mastectomy is so uncommon that it does not warrant routine sentinel node biopsy. Finally, others employ preoperative breast MRI to identify patients with occult invasive carcinoma and reserve sentinel node biopsy for these patients.

In the recent literature, the rates of occult malignancy in patients undergoing risk-reducing mastectomy range from 6 to 10%;[94,142–144] however, the majority of these occult carcinomas are in situ disease. The rates of occult invasive carcinoma (which would necessitate subsequent axillary staging) are quite low at 1–3%.[94,142–146] Furthermore, since these occult invasive carcinomas are usually small, the risk of involvement of the sentinel node is low (generally $< 15\%$). Thus, the probability of a positive axillary node in a patient undergoing prophylactic mastectomy should theoretically not exceed 0.5%, making the routine use of sentinel node biopsy in this setting overly aggressive.

Factors associated with the increased risk of finding occult invasive carcinoma in the CPM specimen include postmenopausal status, age older than 60 years,[142] multifocality/multicentricity,[94] and lobular histologic subtype.[142,145] Interestingly, studies that have examined factors associated with increased risk of contralateral sentinel node positivity in patients with breast cancer diagnosed in one breast have identified locally advanced stage and aggressive characteristics of the ipsilateral tumor (e.g. high number of positive nodes, high grade, lymphovascular invasion, or nipple involvement) as risk factors, suggesting that contralateral sentinel node involvement is likely due to crossover metastasis.[143,145,147] These observations further call into question the value of contralateral sentinel node biopsy in patients undergoing CPM.

Finally, in several studies, breast MRI has been found to be useful in detecting occult malignancy in the contralateral breast in patients with newly diagnosed invasive or non-invasive breast cancer.[148–152] As a result, some clinicians use breast MRI prior to CPM to limit the use of sentinel node biopsy to patients with positive MRI findings. However, others have questioned the utility of MRI in this setting, given the associated cost and low rate of finding occult invasive cancer in the contralateral breast.[144,151,153] At present, sentinel lymph node biopsy is not routinely recommended for patients who undergo CPM. Preoperative MRI can be useful in detecting occult breast cancer in the contralateral breast but it is not necessary before CPM given that identification of occult invasive disease with axillary nodal involvement at the time of CPM is quite unusual.

COMPLICATIONS AFTER RISK-REDUCING MASTECTOMY

What are the Rates of Complications After Risk-Reducing Mastectomy?

Risk-reducing mastectomy, like any surgical procedure, is associated with the potential for complications, most commonly complications related to infection, wound healing, and bleeding. Immediate breast reconstruction at the time of risk-reducing mastectomy increases the risk of complications. Implant-based reconstruction after mastectomy is associated with a higher complication rate than breast augmentation (30 vs. 12% at 5 years).[154]

The complication rate associated with risk-reducing mastectomy is similar to that associated with therapeutic mastectomy. In a series of patients undergoing therapeutic mastectomy and CPM, Goldflam et al. reported an 8.4% complication rate in the index breast, a 6.3% complication rate in the contralateral breast, and a 1.7% rate of complications in both breasts.[72] Overall, risk-reducing mastectomy was associated with a complication rate of 8.0%. The most common complications were reoperation due to bleeding, infection, and mastectomy skin flap necrosis. The authors concluded that the almost equivalent complication rates for the index and contralateral breasts indicated that patients may be doubling their risk of perioperative complications by undergoing CPM.

Similarly, Crosby et al. reported that in patients undergoing therapeutic mastectomy and CPM with immediate implant-based reconstruction, the complication rate was 22.5% in the index breast and 19.2% in the contralateral breast ($p =$ non-significant).[155] On univariate analysis, higher complication rates were associated with increased age, higher body mass index, and greater final implant volume; however, on multivariate analysis, only final implant volume was predictive of overall complications. In patients undergoing reconstruction with abdominal-based flaps, there was no difference in complication rates between the index side and the contralateral side, and multivariate analysis showed that patients with a higher body mass index were at increased risk for complications. Overall, this study showed that the risk of developing a complication is equivalent in the breast treated with CPM and the index breast in patients undergoing implant-based, abdominal flap-based, or latissimus dorsi flap-based reconstruction.

Reoperation rates have been reported to increase with the complexity of the procedure. In patients undergoing risk-reducing mastectomy, Zion et al. reported reoperation rates of 6% in patients treated without reconstruction, 37% in those undergoing CPM with reconstruction, and 52% in those undergoing BPM with reconstruction.[156] Among patients undergoing BPM with reconstruction, 27.5% had a first reoperation in the first year, 26% had a single reoperation, and 27% had two or more reoperations. Among patients not undergoing reconstruction, the reoperation rate was significantly higher with BPM than with CPM. For all groups, the rate of reoperation tended to be high in the immediate postoperative period, and then decrease to a lower rate 2 years after surgery and remain at this rate over time. Implant-related issues accounted for more than half of all reoperations, postoperative complications accounted for 9–12% of all reoperations, and 5–10% of reoperations were for removal of nodular tissue. Reported implant removal rates were 33% in patients who underwent BPM and 24% in those who underwent CPM. In the no-reconstruction group, 28% of reoperations were for postoperative problems, 36% for aesthetic concerns, and 36% to remove nodular tissue. Furthermore, use of adjuvant chemotherapy after immediate reconstruction is not associated with higher rates of surgical complications, postoperative wound healing problems, or reconstructive failure,[157] even when tissue expansion and chemotherapy are under way at the same time.[158] Adjuvant chemotherapy has not been shown to impact the aesthetic outcomes of the reconstructive surgery.[159]

In a study of 269 women undergoing BPM, 79.5% of whom had a reconstructive procedure (implants in 69% and autologous tissue in 10%), Barton et al. reported that 64% of patients had at least one complication and that the most common complications were pain (35% of patients), infection (17%), and seroma (17%).[160] Twenty-seven percent of patients had a complication that might necessitate surgical revision. The complication rate in women undergoing no reconstructive procedures was 53%, which was significantly lower than the complication rates of 75% in patients undergoing autologous tissue-based reconstruction and 66% in patients undergoing implant-based reconstruction.

Do Complications After Risk-Reducing Mastectomy Delay Initiation of Systemic Therapy?

There is sparse literature specifically addressing whether complications after risk-reducing mastectomy delay initiation of systemic therapy. Studies that have examined the impact of immediate breast reconstruction on the initiation of chemotherapy have yielded conflicting results.

Allweis et al. showed that patients who underwent mastectomy alone without reconstruction had a longer mean time to initiation of chemotherapy than patients who underwent immediate reconstruction (53 vs. 41 days).[161] However, other studies have shown no difference in the time to initiation of postoperative chemotherapy between patients undergoing mastectomy with and without reconstruction.[162,163] In one of these studies, there was no difference in time to initiation of chemotherapy despite a higher incidence of wound complications in the immediate reconstruction group (22.3 vs. 8.3%).[162]

In a more recent study by Zhong et al., the major complication rate was 3.7% in patients undergoing mastectomy alone and 15.5% in the immediate reconstruction group, and the median time from last definitive breast surgery to the start of chemotherapy was 6.8 weeks in patients undergoing mastectomy alone and 8.5 weeks in the immediate reconstruction group.[164] However, the authors noted that none of the patients who underwent immediate reconstruction had a significant delay in the initiation of adjuvant chemotherapy (time between surgery and initiation of chemotherapy, 6.39–11.0 weeks). In a study from eight National Comprehensive Cancer Network (NCCN) institutions, Alderman et al. showed that, among women under 60 years of age, immediate reconstruction was associated with a statistically significant delay in the initiation of chemotherapy; however, they questioned whether this less than 1-week delay was likely to impact long-term survival.[165]

The type of reconstruction has been shown to impact time to systemic therapy. Taylor and Kumar showed that time from surgery to initiation of chemotherapy was, on average, 5 days longer with transverse rectus abdominis myocutaneous (TRAM) flap reconstruction than without immediate reconstruction, and the delays were most commonly due to poor wound healing.[166] However, delays during chemotherapy, percentage of intended dose, and the need for antibiotics were not different between the groups with TRAM flaps, latissimus dorsi flaps, tissue expanders/implants, or no immediate reconstruction.

Does CPM Have an Impact on Radiation Delivery?

In patients with an index breast cancer who are undergoing therapeutic mastectomy and CPM, the need for postmastectomy radiation therapy (PMRT) is based on tumor size and nodal involvement. PMRT can adversely impact the aesthetic outcome of immediate breast reconstruction, and the reconstructed breast can interfere with delivery of PMRT.[167,168] In patients undergoing immediate reconstruction, complications are more common if PMRT is required (32.5% capsular contracture rate in the

irradiated group vs. 0% in the control group).[169] In general, autologous tissue-based reconstruction should be avoided when PMRT is recommended because of the possibility of late complications, including flap contraction, shrinkage, and fat necrosis,[170] although some series indicate no difference in complication rates for autologous flaps between preoperative and postoperative irradiation.[171]

CHEMOPREVENTION AS AN ALTERNATIVE TO RISK-REDUCING MASTECTOMY

Breast cancer is an ideal model for the study of cancer prevention because of its long natural history and high incidence. Lifestyle modifications for breast cancer prevention have been studied, such as low-fat diet, decreased alcohol consumption, and increased exercise, but data on the success of these strategies are limited.[172–174] Most of the prevention focus has been on developing medications for prevention, also known as chemoprevention. To date, the only agents approved for chemoprevention in high-risk women are tamoxifen, raloxifene, and exemestane. These agents reduce the incidence of ER-positive cancers and may not be appropriate for individuals at higher risk for development of ER-negative breast cancers, such as *BRCA* mutation carriers. Other agents are under investigation for breast cancer chemoprevention, including bisphosphonates, cyclooxygenase (COX)-2 inhibitors, poly(ADP-ribose) polymerase (PARP) inhibitors, metformin, and retinoids. Currently, there are insufficient data to permit recommendations regarding the use of these agents as chemoprevention agents in high-risk women.

Tamoxifen

Tamoxifen is a selective ER modulator and was initially developed in the 1960s as a contraceptive pill. It is considered as a chemopreventive agent for breast cancer for three reasons: (i) it is safe; (ii) it is effective; and (iii) studies demonstrated a decreased incidence of contralateral breast cancer in breast cancer patients treated with tamoxifen.

The National Surgical Adjuvant Breast and Bowel Project P-1 study was the first large chemoprevention trial in the US and enrolled over 13,000 participants between June 1992 and September 1997.[175] The trial targeted women between the ages of 35 and 59 years at increased risk for breast cancer and randomized them into groups taking a placebo or tamoxifen for 5 years. Tamoxifen was shown to reduce the incidence of breast cancer by 49% in all age groups. Of note, the reduced risk of breast cancer was seen only for ER-positive breast cancers. At present, there is no evidence that tamoxifen improves survival, only that it reduces the incidence of developing breast cancer.[176] Tamoxifen is associated with a reduced risk of bone fractures because of the drug's estrogen-like qualities, but it has been shown to increase the incidence of uterine cancer, venous thromboembolism, and cataracts. On the basis of the results of this trial, the US FDA approved tamoxifen (20 mg/day) as a chemoprevention agent for women at high risk for developing breast cancer.[175]

The IBIS-I (International Breast Cancer Intervention Study I) trial enrolled over 7000 women between the ages of 35 and 70 years and randomized them to tamoxifen or a placebo.[177] There was a 28% reduction in the risk of ER-positive breast cancer in the tamoxifen arm, which slightly increased beyond 10 years of follow-up.[178] Two other trials evaluating the role of tamoxifen as a chemoprevention agent did not demonstrate a benefit with this agent. The Royal Marsden trial enrolled almost 2500 healthy women between the ages of 30 and 70 years with a family history of breast cancer.[179] Participants were randomized to tamoxifen or a placebo, and the overall incidence of breast cancer was similar in the two groups. The low number of participants in the trial, and the fact that 40% of participants were also taking hormone replacement therapy, could have affected the outcome. An Italian trial randomized 5400 women who had undergone hysterectomy to tamoxifen or a placebo; however, these women were not selected on the basis of breast cancer risk.[180] The results did not demonstrate an advantage for tamoxifen, but very few participants completed the 5 years of tamoxifen, and almost half of the patients had their ovaries removed at the time of the hysterectomy, which would have lowered their breast cancer risk. However, there was a trend toward a significant reduction in breast cancer risk among women taking tamoxifen for at least 1 year.

Raloxifene

Raloxifene is also a selective ER modulator that has both estrogenic and anti-estrogenic effects. It has estrogenic effects on the skeletal system and decreases the incidence of osteoporosis. It does not have the same estrogenic effects on the uterus as tamoxifen, therefore the risk of uterine cancer is less than that with tamoxifen. Raloxifene is approved for the prevention of osteoporosis in postmenopausal women at a dose of 60 mg/day. The multiple outcomes of raloxifene evaluation (MORE) trial randomized over 7700 women to two different doses of raloxifene or placebo.[181] The investigators reported a 70% reduction in breast cancer incidence in the participants who took raloxifene. Since raloxifene was noted to be associated with fewer side effects than tamoxifen, the National Surgical Adjuvant Breast and Bowel Project initiated the Study of Tamoxifen against Raloxifene (STAR) trial, which randomized over 19,700 postmenopausal high-risk

women to tamoxifen (20 mg/day) or raloxifene (60 mg/day) for 5 years.[182] Both agents were shown to reduce the incidence of breast cancer, however tamoxifen was more effective. As expected, raloxifene has a better risk profile than tamoxifen with respect to uterine cancer, stroke, and the development of cataracts. Raloxifene was subsequently approved by the FDA as a chemopreventive agent in postmenopausal women.

Aromatase Inhibitors

The aromatase inhibitor exemestane has also been studied as a chemoprevention agent in postmenopausal women. The National Cancer Institute of Canada MAP3 (Mammary Prevention 3) trial randomized 4500 women at high risk for breast cancer to exemestane or placebo.[183] There was a 65% reduction in breast cancer incidence in women treated with exemestane. Interestingly, there were no differences in the side effects reported between the two groups. In this trial, there was no documented increase in fractures; however, the use of aromatase inhibitors has been shown to increase the incidence of fractures in older women. The follow-up time of only 35 months may have been too short to permit full evaluation of the fracture risk.

The IBIS-II trial randomized 1920 women at high risk for breast cancer to treatment with anastrozole or placebo. Significantly fewer breast cancers developed in the anastrozole group compared with the placebo group (HR 0.47, 95% CI 0.32–68; $p < 0.0001$). The 7-year cumulative incidence of breast cancer was 2.8% and 5.6%, respectively, and there was a slightly higher rate of musculoskeletal-related adverse events in the anastrozole group (64 vs. 58%). These results support the use of anastrozole for risk reduction in postmenopausal women at high risk for breast cancer.[184]

BILATERAL SALPINGO-OOPHORECTOMY AS AN ALTERNATIVE TO RISK-REDUCING MASTECTOMY

Prophylactic bilateral salpingo-oophorectomy has also been shown to reduce breast cancer risk in *BRCA 1/2* mutation carriers by approximately 50%.[185–189] Eisen et al. reported a 56 and 43% reduction in the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers, respectively.[186]

A recent meta-analysis of 15 studies estimated the pooled relative risks for cancer risk or mortality associated with and without bilateral salpingo-oophorectomy. The analysis showed a 45% reduction in breast cancer risk and a 65% reduction in all-cause mortality associated with prophylactic bilateral salpingo-oophorectomy in women who carry the *BRCA1/2* mutation with no prior history of breast cancer. A 57% reduction in all-cause mortality was reported in breast cancer patients after prophylactic bilateral salpingo-oophorectomy.[190] According to the NCCN guidelines, prophylactic salpingo-oophorectomy is recommended for all *BRCA1/2* mutation carriers once childbearing is complete. The reduction in breast cancer risk for *BRCA1/2* mutation carriers is likely due to the decreased hormonal exposure due to removal of the ovaries.

SURVEILLANCE IMAGING AS AN ALTERNATIVE TO RISK-REDUCING MASTECTOMY

Optimizing screening for women at elevated risk for developing breast cancer is critically important. Patients need to understand that the ability to detect breast cancer at an early stage is dependent on many factors. Breast size, texture, and density greatly affect both the detection of breast disease with physical examination and the detection of breast disease with imaging. Although clinical breast examination by a skilled clinician has value in detecting breast cancer, it is clear that routine surveillance imaging allows the detection of earlier, subclinical disease. The effectiveness of breast screening may significantly influence patient decision making about whether to opt for a careful surveillance program versus risk-reducing mastectomy.

The three established breast imaging approaches are mammography, breast sonography, and breast MRI. Mammography has been the gold-standard imaging modality for breast cancer screening for over three decades. In the general population, it has been reported that screening mammography has reduced the mortality rate associated with breast cancer by up to 40%.[191] However, in young women at high risk for breast cancer, dense breast tissue limits the utility of screening mammography: mammography has an overall sensitivity of 45% in women with dense breast tissue.[192] The NCCN guidelines suggest that women at increased risk for breast cancer undergo screening mammography yearly. MRI may also be used to improve screening sensitivity, particularly in young women with dense breasts.[193,194]

Substantial debate exists about the best screening protocol for women at increased risk of breast cancer. LePetross et al.[195] performed a retrospective review of 73 patients with *BRCA* mutations who underwent imaging with MRI every 6 months, alternating with mammography. Thirteen cancers were detected, 12 of which were detected on MRI but not on the screening mammography study that was obtained 6 months earlier, suggesting that the MRI should be added to the screening of women with genetic mutations known to increase the risk of breast cancer.

Several retrospective and prospective studies have revealed that screening breast MRI is an effective tool for

early detection of breast cancer in women at high risk.[196–200] In a study[200] of 1275 women with *BRCA* mutations followed for a mean of 3.2 years, breast cancer was diagnosed in 41 of 445 women (9.2%) who had screening that included MRI, compared with 76 of 830 women (9.2%) in the comparison group, who underwent screening without MRI; however, there was a significant reduction in the incidence of advanced-stage cancer in the MRI group. The long-term results of a study of 496 women with *BRCA* mutations who were enrolled in a prospective screening trial (from 1997 to 2009) and had MRI and mammography annually, as well as clinical breast examination semi-annually, demonstrated significantly improved sensitivity of MRI over mammography (86 vs. 19% during the entire study period, and 93 vs. 9% between 2003 and 2009).[201] Only 2% of the cancers detected in this study were detected between planned screenings. Of the cancers detected, 97% were stage 0 or stage 1. None of the incident cancers was associated with distant recurrence at a median follow-up of 8.4 years.[201]

Some patients at elevated risk for breast cancer are unable to undergo breast MRI because they have metal implants, such as pacemakers, defibrillators, aneurysmal clips, and certain types of metal stents. A history of claustrophobia can also make it difficult for patients to undergo breast MRI. In these individuals, ultrasound screening is an alternative. The ACRIN (American College of Radiology Imaging Network) 666 trial,[202] conducted from 2004 through 2006, recruited 2809 women with dense breast tissue from 21 sites and randomized them to physician-performed breast sonography in addition to mammography screening or mammography screening alone. Forty participants (41 breasts) were diagnosed with cancer. Eight of these patients had suspicious findings on both sonography and mammography, 12 had suspicious findings on sonography alone, 12 had suspicious findings on mammography alone, and 8 (9 breasts) had suspicious findings on neither imaging study. There was a supplemental yield of 4.2 cancers per 1000 patients screened with sonography and an associated increased rate of false-positive findings, resulting in benign ultrasound-directed biopsies. In a follow-up study, 703 women chose to have additional screening with breast MRI.[203] A total of 2662 women underwent 7473 mammogram and ultrasound screenings, 110 of whom had 111 breast cancer events: 33 detected by mammography only, 32 by sonography only, 26 by both modalities, and 9 by MRI after mammography plus sonography; 11 events were not detected by any imaging procedure. The addition of screening sonography or MRI to mammography in women at increased risk for breast cancer resulted in not only a higher cancer detection yield but also an increase in false-positive findings and the need for additional biopsies.

Breast tomosynthesis has been introduced as an adjunct to routine screening mammography and was recently demonstrated to reduce screening recall rates (ranging from 6 to 67%) in a multicenter trial.[204] The addition of tomosynthesis was also associated with increased diagnostic accuracy (6.8 to 7.2% improvement) and diagnostic sensitivity (10.7 to 16% improvement), especially for the detection of invasive carcinomas, compared with digital mammography alone. The radiation dose for tomosynthesis remains double that of mammography, but work is under way to reduce this additional radiation exposure. Other potentially promising breast imaging technologies include positron emission mammography (PEM), breast-specific gamma imaging, and optical imaging. Gamma imaging has been shown to increase the detection of breast cancer when it is used for screening women with dense breast tissue; further work to decrease the radiation dose associated with gamma imaging is under way.[205] Although these approaches have shown some merit, they have not yet been demonstrated to have a proven role in the screening of high-risk patients.

CONCLUSIONS

Since publication of the 2007 SSO position statement on the use of risk-reducing mastectomy, there have been significant advances in the understanding of breast cancer biology and treatment. The tools for risk assessment have been enhanced, and these tools can be used to develop estimates of 5-year risk and lifetime risk for breast cancer development. Genetic testing is now more readily available for appropriate individuals, and, for individuals who are found to be *BRCA* mutation carriers, information is available regarding the type of mutation and lifetime risk of breast cancer development. There is no single-risk threshold above which risk-reducing mastectomy is clearly indicated, and it is important for treating physicians and surgeons to explain to individuals not only the risk assessment but also all available treatment strategies to facilitate a shared decision-making process.

BPM reduces future breast cancer risk by approximately 90% in *BRCA* gene mutation carriers, and 95% when performed in conjunction with bilateral salpingo-oophorectomy. The available data suggest that BPM confers a survival advantage in women with the highest risk who undergo the procedure at a relatively early age. The use of bilateral salpingo-oophorectomy appears to have a greater impact on survival than BPM.

The impact of CPM in women with invasive breast cancer is more difficult to assess as the available data are largely from retrospective, single-institution or population-based studies. CPM reduces the risk of contralateral breast cancers from 90 to 100%; however, CPM does not appear to confer a survival advantage. It is clear that the use of

endocrine therapy and the use of systemic chemotherapy have an impact on the incidence of contralateral breast cancer development, and these factors should be fully considered in the decision-making process surrounding CPM. The potential benefit of CPM is more likely to be realized in women with an overall good prognosis and low expected mortality from non-breast cancer causes. Despite all of the knowledge and tools available to patients and physicians, there is no formula for predicting whether the patient will achieve peace of mind; therefore, each decision must be individualized.

Risk-reducing mastectomy affects quality of life and body image, and reconstructive surgery increases the risk of postoperative complications. High-risk women should be appropriately counseled regarding alternatives to surgery, including chemoprevention strategies and surveillance imaging. A complete discussion should cover short-term and lifetime risk for breast cancer development, risk-reduction strategies, potential complications, and the potential impact of the various approaches on survival and quality of life.

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