Risk Reduction Strategies: Surgical Perspective

8

Lisa Renee-Palko Spiguel and Nora Hansen

Introduction

Breast cancer is estimated to affect over 200,000 women in the United States in 2012, accounting for up to 40,000 deaths [1]. Based on SEER database rates from 2006 to 2008, the cumulative lifetime risk of breast cancer for an average woman in the general US population is 12.29%, with the greatest risk occurring in the sixth decade of life [1]. Although the majority of these breast cancers are sporadic, approximately 25% of breast cancers are secondary to some inherited predisposition, commonly related to identifiable mutations in inherited genes such as BRCA1, BRCA2, *CHEK2*, and PTEN. Women born with these gene mutations are at a significantly higher risk of developing breast cancer over the general population, as well as other associated cancers, and do so typically at a younger age.

Mutations in the tumor suppressor genes, BRCA1 and BRCA2, account for the majority of known familial breast cancer risk. Studies demonstrate that women with germ line mutations in BRCA1 gene have an estimated lifetime risk of breast cancer ranging from 65–87%, with the average lifetime risk of 45–55% in BRCA2 carriers. The greatest risk occurs in women younger than the age of 40. These women are also at an increased risk of ovarian cancer with a lifetime risk in BRCA1 carriers of 39–51%, and 11–35% for BRCA2 mutation carriers. The greatest risk of ovarian cancer occurs in women over the age of 60 [2]. Although studies looking specifically at breast cancer-specific survival in women with germ line BRCA mutations have not demonstrated a decrease in overall or disease-free survival, they have demonstrated that in addition to an increase in lifetime risk of breast cancer, there is an increase in the incidence of metachronous breast cancers as compared to the general population, with up to 20% of BRCA1 carriers and over 10% of BRCA2 carriers diagnosed with a new cancer at 5 years, as compared to 2–5% for the general population diagnosed with sporadic cancer [3, 4].

Although evidence of known genetic mutations confirms a women's predilection for cancer, not all inherited conditions are known. Furthermore other factors such as a personal history of breast cancer, as well as personal history of high risk lesions such as LCIS and atypical hyperplasia, increase a woman's risk above the general population. Due to the increased risk of cancer in these patients, various options exist to either increase the detection of cancer at an earlier stage or decrease the overall risk of cancer from occurring. Options include increased surveillance which is discussed in depth in chapter 6 as well as chemoprevention strategies through the use of selective estrogen receptor modulators, such as tamoxifen, which have demonstrated a

L.R.-P. Spiguel (✉) • N. Hansen
Lynn Sage Comprehensive Breast Center,
250 East Superior Street, Prentice 4-420,
Chicago, IL 60611, USA
e-mail: lisa.spiguel@gmail.com; nhansen@nmh.org

N.M. Hansen (ed.), *Management of the Patient at High Risk for Breast Cancer*,
DOI 10.1007/978-1-4614-5891-3_8,

49% decrease in the risk of invasive cancer in healthy high risk patients with a median follow-up of 55 months. In subset analysis of BRCA mutation carriers, the use of tamoxifen demonstrated an equivalent reduction in breast cancer incidence among BRCA2 carriers; however, tamoxifen beginning at the age of 35 in healthy BRCA1 mutation carriers did not significantly reduce breast cancer risk. These results are likely related to the overall low incidence (6.6%) of BRCA carriers in the Breast Cancer Prevention trial, as well as the majority of BRCA1 cancers being ER- and PR- negative [5].

Additional options to reduce risk are surgical, consisting of prophylactic bilateral mastectomy (PBM) and prophylactic bilateral salpingo-oophorectomy (PBSO) in high risk women, as well as contralateral prophylactic mastectomy (CPM) in women with a personal history of breast cancer diagnosis. This chapter will discuss these surgical options for cancer risk reduction, focusing on the ability of surgery not only to reduce the occurrence of a primary breast cancer, but also to reduce the occurrence of subsequent metachronous cancers and associated mortality. Furthermore it will discuss safety of nipple sparing mastectomy (NSM) on risk reduction and cancer treatment in high risk women, as well as the role for sentinel lymph node biopsy (SLNB) in prophylactic surgery.

Surgical Strategies

Prophylactic Bilateral Mastectomy

Several prospective and retrospective studies have investigated the utility of PBM for the prevention of breast cancer (Table 8.1). All of these studies demonstrate a 85–100% breast cancer risk reduction following PBM with up to a 14-year median follow-up.

One of the first studies that investigated the efficacy of PBM in cancer prevention was a study looking specifically at moderate and high risk women based on family history. Hartmann and colleagues conducted this retrospective review of all women with a family history of breast cancer who underwent PBM for risk reduction—10% of which underwent total mastectomy, while 90% underwent subcutaneous mastectomy. Women were divided into two groups, high risk and moderate risk on the basis of family history. A total of 639 women were identified, 214 at high risk and 425 at moderate risk. Following a median follow-up of 14 years, a 89.5% reduction in breast cancer risk in the moderate risk group was demonstrated as compared to the predicted incidence based on the Gail risk model, and a 90–94% breast cancer risk reduction occurred in the high risk group based on incidence of breast cancer in related sisters. They also concluded a reduction in the risk of death from breast cancer in both groups up to 94% [6]. On subset analysis of 26 BRCA1 and BRCA2 mutation carriers, with a median follow-up of 13.4 years, no patients developed subsequent breast cancer following PBM, translating into a breast cancer risk reduction of up to 100% [7].

A second study investigating the role of PBM in breast cancer risk reduction specifically in BRCA patients was a prospective study conducted on 139 BRCA1 and BRCA2 carriers, 76 of which underwent PBM with 63 electing for surveillance alone [8]. Following a mean follow-up of 2.9 years, no women developed breast cancer following PBM, whereas 8 (17.7%) women developed breast cancer in the surveillance group, demonstrating a substantial breast cancer risk reduction in BRCA mutation carriers.

Table 8.1 Prophylactic bilateral mastectomy

Study	Year	Study design	F/U (years)	Patients (*n*)	Breast cancer risk reduction (%)
Hartmann et al.	1999	Retrospective	14	639	90–94
Hartmann et al.	2001	Retrospective	13.4	26	85–100
Meijers-Heijboer et al.	2001	Prospective	2.9	139	100
Rebbeck et al.	2004	Prospective	6.4	483	90–95

A larger prospective cohort study of 483 BRCA carriers with a longer mean follow-up of 6.4 years compared 105 BRCA mutation carriers who underwent PBM to 378 matched controls who underwent routine surveillance [9]. Four different statistical analyses were performed to determine breast cancer risk reduction associated with PBM, as well as the effects of concomitant PBSO on overall risk reduction. Women either underwent subcutaneous, total, or modified radical mastectomy (MRM). Following 6.4 years follow-up, 2 (1.9%) women who underwent PBM were diagnosed with breast cancer compared with 184 (48.7%) of the 378 matched controls, demonstrating up to a 95% breast cancer risk reduction in BRCA mutation carriers who undergo PBM.

A more recent study by Heemskerek-Gerritsen investigated the role of both PBM and CPM in high risk women with either known BRCA status or 50% risk carriers from a hereditary breast/ovarian cancer (HB(O)C) family [10]. Their study comprised 358 women, 65.9% of which were known BRCA mutation carriers, while the other 34.1% were from HB(O)C families. Fifty-one percent of which were affected women with a history of breast cancer, and 49% had no prior history of breast cancer. All patients underwent skin sparing mastectomies. A considerable portion of BRCA mutation carriers also opted for PBSO, with 57% of unaffected BRCA carriers and 67% of affected BRCA carriers. Following a 4.5-year median follow-up, no primary breast cancers occurred after CPM. One BRCA1 mutation carrier who underwent PBM was found to have metastatic cancer in an axillary node, as well as bone and liver metastases 3.5 years following PBM, suggesting a missed occult primary at the time of her PBM. No additional patients undergoing PBM developed subsequent breast cancer.

Although none of the studies investigating the role of PBM on breast cancer risk reduction are randomized prospective trials, they all demonstrate at least a 90% reduction in breast cancer risk following prophylactic mastectomy. Based on such provocative risk reduction, one would infer a survival benefit directly from PBM in these high risk patients; however, there has been no strong evidence to date. One of the first studies investigating PBM in high risk patients by Hartman and colleagues did confer up to a 94% reduction in the risk of death from breast cancer in both moderate and high risk groups; however, this was calculated based on the probability of breast cancer for each year of follow-up with the breast cancer-relative survival rates from the SEER database [6].

Schrag and colleagues also suggested a gain in life expectancy following prophylactic surgery among women who carry mutations in either BRCA1 or BRCA2; however, their data was calculated based on a Markov decision analysis model. They used available data on the incidence of cancer, prognosis of women with various cancer types, and the efficacy of PBM and PBSO in preventing breast and ovarian cancer to estimate the effects of prophylactic surgery on life expectancy among women with different levels of cancer risk [11]. They compared nine case scenarios based on whether patients underwent immediate prophylactic surgery, delayed prophylactic surgery, or surveillance alone. They assumed all women undergoing PBSO would continue to receive hormone replacement therapy until the age of natural menopause, hypothetically abating any effect PBSO would have on breast cancer prevention. Their results demonstrated, on average, that 30-year-old women who carry BRCA mutations would gain approximately 2.9–5.3 years of life expectancy from PBM and 0.3–1.7 years of life expectancy from PBSO depending on their cumulative risk of cancer, and that the gain in life expectancy from undergoing both prophylactic surgeries was greater than the sum of each procedure alone. In regards to optimal timing for surgery, PBSO could be delayed up to the age of 40 years with little loss of life expectancy. However the overall gain in life expectancy did decline with age, with minimal benefits for women 60 years and older.

Based on the above studies, it is evident that PBM confers over a 90% reduction in breast cancer risk in high risk women; however, there is only a suggested mortality reduction, with the overall gain being greater for younger women, and little benefit on survival for women over the age of 60.

Prophylactic Bilateral Salpingo-Oophorectomy

The impact of PBSO in regards to breast cancer and ovarian cancer risk reduction has also been well studied (Table 8.2). These studies demonstrate an approximate 50% risk reduction of breast cancer risk following PBSO and up to a 96% risk reduction of gynecologic malignancies following PBSO. The greatest effect of PBSO on both breast and gynecologic malignancies occurs in women less than the age of 50, supporting the use of PBSO as a prophylactic surgery for women soon after childbearing ages.

Rebbeck and colleagues performed one of the first retrospective case–control cohort studies investigating the reduction of breast cancer risk following PBSO in BRCA1 mutation carriers [12]. They included women with BRCA1 mutations who underwent PBSO but had no prior history of breast or ovarian cancer and had not undergone PBM. These women were matched with a control group comprising BRCA1 mutation carriers that had not undergone either PBSO or PBM, had similar date of birth, and were from the same collaborative institution from which the case cohort was ascertained. Following 9 years of postsurgical follow-up, PBSO demonstrated a 47% reduction in the risk of developing breast cancer, which persisted for greater than 10 years after surgery and was not negated by the use of postsurgical hormone replacement therapy. When further analyzing risk reduction based on age, women older than the age of 50 demonstrated little benefit, indicating that the therapeutic benefit of PBSO occurs at earlier ages.

In a later publication, Rebbeck and colleagues investigated the benefit of PBSO for both breast and ovarian cancer risk reduction in both BRCA1 and BRCA2 mutation carriers as compared to matched controls [13]. In the subgroup of 259 women studied for ovarian cancer risk reduction, only 2 (0.8%) cases of papillary serous peritoneal cancer were diagnosed 3.8 and 8.6 years after surgery, as compared to 58 (19.9%) cases in 292 matched controls, leading to an overall ovarian cancer risk reduction of 96%. The mean age of ovarian cancer diagnosis was 50 years of age supporting the role of PBSO as soon as possible after childbearing is completed. In the subgroup of 241 women studied for breast cancer risk reduction, 21 (21.2%) of the 99 patients who underwent PBSO subsequently developed breast cancer, as compared to 60 (42.3%) of the controls, constituting a 53% breast cancer risk reduction.

A prospective study by Kauff and colleagues investigated the prevention of breast and ovarian cancer in women 35 years of age or older with BRCA1 or BRCA2 mutations who underwent PBSO as compared to women who underwent surveillance [14]. With a mean follow-up of 24.2 months, 5 (6.9%) ovarian or primary peritoneal cancers developed in women who elected to undergo surveillance, compared to 1 (1.0%) woman who underwent PBSO. Eight (12.9%) women with breast tissue in the surveillance group developed breast cancer, as compared to 3 (4.3%) women who underwent PBSO. When both breast cancer and ovarian cancer occurrences were analyzed together, a 75% risk reduction of BRCA-related breast or ovarian cancer was found. When analyzed separately, a reduction in both BRCA-related breast and ovarian cancer occurred; however the risk reduction was not statistically significant.

In a more recent prospective study by Kauff and colleagues, the efficacy of PBSO for the prevention of BRCA-associated breast and gynecologic cancer was investigated in women with BRCA1 and BRCA2 mutations independently [15]. Following 33 months of follow-up, 28 (9.5%) women who underwent surveillance developed breast cancer, as compared to 19 (6.3%) women who underwent PBSO, leading to a 47% risk reduction in BRCA-related breast cancer. In BRCA1 mutation carriers, 19 (10.6%) developed a new breast cancer, as compared to 15 (7.9%) women who underwent PBSO, representing a 39% risk reduction in BRCA1 patients. In BRCA2 carriers, 9 (7.8%) patients developed breast cancer in the surveillance group, as compared to 4 (3.5%) breast cancers in the PBSO group, leading to an overall 72% risk reduction in BRCA2 carriers. The larger reduction in breast cancer risk in BRCA2 carriers following PBSO

Table 8.2 Prophylactic bilateral salpingo-oophorectomy

				BRCA1		BRCA2		Risk reduction	
Study	Year	F/U (years)	Patients (*n*)	BSO (%)	Control (%)	BSO (%)	Control (%)	Breast cancer	Gynecologic cancer
Rebbeck et al.	1999	9	122	100	–	–	–	HR 0.53 (CI, 0.33–0.84)	–
Rebbeck et al.	2002	8	551	84.6	82.2	16.2	18.2	–	HR 0.04 (CI, 0.01–0.16)
Rebbeck et al.	2002	10	241	83.8	85.2	18.2	14.8	HR 0.47 (CI, 0.29–0.77)	–
Kauff et al.	2002	2	170	57	67	43	33	HR 0.32 (CI, 0.08–1.20)	HR 0.15 (CI, 0.02–1.31)
Eisen et al.	2005	–	3,295	73.6	73.6	26.4	26.4	OR 0.46 (CI, 0.35–0.62)	–
Finch et al.	2006	3.5	1,828	79	70	20	30	–	HR 0.20 (CI, 0.07–0.58)
Kauff et al.	2008	3	1,079	63	61	37	39	HR 0.53 (CI, 0.29–0.96)	HR 0.12 (CI, 0.03–0.41)

was thought to be related to the higher proportion of ER-positive breast cancers occurring in BRCA2 mutation carriers as compared to BRCA1 carriers.

In regards to BRCA-associated gynecologic cancers, 12 (4.2%) women who underwent surveillance, as compared to 3 (0.6%) women who underwent PBSO developed gynecologic cancers, leading to an 88% risk reduction of BRCA-associated gynecologic cancers following PBSO. When their analysis was limited to BRCA1 carriers, 10 (5.8%) women developed gynecologic cancers in the surveillance group, as compared to 3 (0.9%) in the PBSO group, leading to an 85% overall risk reduction. In BRCA2 carriers, only 2 (1.8%) women developed gynecologic cancer in the surveillance group, with no patients developing cancer in the PBSO group. Risk reduction in BRCA2 carriers did not reach statistical significance related to the low incidence of BRCA2-associated gynecologic cancers. PBSO therefore appears to confer a larger risk reduction in BRCA-associated breast cancer in BRCA2 mutation carriers and a larger risk reduction in BRCA-associated gynecologic cancers in BRCA1 mutation carriers.

Eisen and colleagues performed an international case–control study also investigating the extent of protection offered against BRCA-associated breast cancer following PBSO in BRCA1 and BRCA2 mutation carriers, as well as the affect of age at PBSO [16]. They identified 1,439 matched sets in 3,295 patients, 74% were BRCA1 carriers, 26% were BRCA2 carriers. As compared to the surveillance group, PBSO was associated with a 57% reduction in breast cancer risk in BRCA1 carriers, and a 46% reduction in risk in BRCA2 patients. This protective effect was evident up to 15 years following PBSO. When investigating the effect of age at PBSO, a statistically significant reduction was seen only up to the age of 50 in BRCA1 carriers. There was no clear trend associated with timing of PBSO for BRCA2 carriers likely related to the lower number of BRCA2 carriers in their study, as well as an older age of breast cancer onset in BRCA2 carriers.

In a subsequent prospective case–control cohort study investing the effect of PBSO on BRCA-associated gynecologic malignancies, Finch and colleagues demonstrated an 80% reduction in gynecologic cancer risk in patients undergoing PBSO as compared to surveillance alone [17]. One thousand eight hundred and twenty-eight women were enrolled, with 75.5% BRCA1 mutation carriers, and 24.1% BRCA2 mutation carriers. Eight patients carried both BRCA1 and BRCA2 mutations. Thirty two (4.1%) gynecologic cancers were observed in the surveillance group, 29 (5.3%) in BRCA1 carriers and 3 (1.3%) in BRCA2 mutation carriers, as compared to 7 (1.3%) in women undergoing PBSO, 6 (1.3%) in BRCA1 carriers and 1 (1.0%) in BRCA2 carriers. After adjustment for covariates, there was an 80% reduction in risk of gynecologic cancers associated with PBSO in BRCA carriers.

As demonstrated in the above studies, there is an approximate 50% risk reduction for breast cancer and up to a 96% risk reduction for gynecologic-associated cancer in BRCA mutation carriers who undergo PBSO as compared to surveillance. In subset analysis, it appears that PBSO may confer a larger breast cancer risk reduction in BRCA2 carriers as compared to BRCA1 carriers. This greater risk reduction is likely related to the increased prevalence of ER-positive cancers in BRCA2 mutation carriers as compared to BRCA 1 carriers. On the other hand, it appears from various studies that PBSO may confer a larger gynecologic cancer risk reduction in BRCA1 carriers, which is likely related to an increased prevalence of gynecologic cancers at younger ages in BRCA1 carriers. The greatest reduction in both breast and gynecologic cancers following PBSO is shown to occur at ages less than 50, supporting the use of PBSO for prophylactic surgery soon after a woman's childbearing years.

Does breast and gynecologic cancer risk reduction following PBSO equate to a mortality benefit in these high risk women? Domcheck and colleagues performed a large prospective analysis of over 600 BRCA1 or BRCA2 mutation carriers, with the primary intent to determine whether PBSO improves overall mortality and cancer-specific mortality in these high risk patients [18].

In their matched cohort analysis, results demonstrated a 7% incidence of breast cancer in BRCA carriers following PBSO, as compared to 13% in women undergoing surveillance, leading to a breast cancer risk reduction of 64% following PBSO in BRCA patients. Subsequent mortality analysis demonstrated a statistically significant reduction in overall mortality (HR 0.24), breast cancer-specific mortality (HR 0.10), and gynecologic-specific mortality (HR 0.05) in BRCA carriers. When investigating the association between PBSO and mortality reduction in BRCA1 independent of BRCA2 mutation carriers, a statistically significant reduction in overall, breast cancer-specific, and ovarian cancer-specific mortality reduction was demonstrated in BRCA1 carriers only, likely related to the lack of cancer-specific deaths in BRCA2 mutation carriers who underwent PBSO.

In a more recent multicenter prospective cohort study by Domcheck and colleagues, the relationship of both PBSO and PBM in cancer-specific and overall mortality reduction was investigated in BRCA carriers [19]. Both PBSO and PBM resulted in breast cancer risk reduction. After 3 years follow-up, none of the women undergoing PBM developed breast cancer, while 7% of the surveillance women did. PBSO in both BRCA1 and BRCA2 mutation carriers led to a statistically significant breast cancer risk reduction, with a 37% reduction in BRCA1 carriers and 64% reduction in BRCA2 carriers. Breast cancer risk reduction was only significant in women who underwent PBSO prior to the age of 50. In regards to gynecologic cancer risk reduction, PBSO was associated with risk reduction in BRCA1 mutation carriers only, with a risk reduction of 85% in women with a prior diagnosis of breast cancer, and 69% in women with no prior history of breast cancer. No cases of gynecologic cancer following PBSO were detected in BRCA2 carriers. Furthermore, PBSO was associated with significantly lower all-cause mortality and cancer-specific mortality when all BRCA mutation carriers were combined, with the greatest gain in women younger than the age of 50. However when analyzed independently based on mutation status, all-cause mortality reduction and cancer-specific mortality remained significant only in BRCA1 mutation carriers. This is likely related to the limited number of BRCA2 mutation carriers, as well as fewer events that occurred in BRCA2 mutation carriers.

The above studies demonstrate a significant breast and gynecologic cancer risk reduction, as well as a significant lower cancer-specific mortality and increased overall survival in women who undergo PBSO as compared to women who elect to undergo increased surveillance. Importantly this overall survival benefit and lower cancer-specific mortality was found to occur in women younger than the age of 50, supporting the notion that women who elect to undergo PBSO should do so soon after childbearing years [12, 16, 19]. As mentioned above, when BRCA mutation carriers were independently evaluated based on BRCA1 vs. BRCA2 mutation status, the survival benefit was more significant in BRCA1 carriers. This is most likely related to the lower number of BRCA2 carriers enrolled in the above studies, as well as the overall lower incidence of BRCA-associated cancers occurring at younger ages in BRCA mutation carriers.

When discussing PBSO as a prophylactic option for BRCA mutation carriers, it is important to address concerns regarding premature menopause in premenopausal women. Premature menopause may lead to increased risk of osteoporosis and cardiovascular disease, as well as early symptoms of hot flashes, vaginal dryness, sexual dysfunction, and cognitive dysfunction [16]. It is important to counsel women that the use of short-term hormone replacement therapy appears safe in such women, with studies demonstrating no significant difference in breast risk cancer reduction in women who took short-term HRT following PBSO, as compared to those who did not [20, 21]. Although the data on duration of HRT is not concrete, it appears that women who undergo PBSO in their premenopausal years are safe to take short-term HRT until the age when they would have experienced natural menopause, typically at the age of 50. This allows physicians the ability to prescribe HRT until the natural age of menopause to abate premature menopausal symptoms in women following PBSO.

Contralateral Prophylactic Mastectomy

In addition to women with strong family histories or known inherited mutations, women with a history of primary breast cancer are also at higher risk of developing a subsequent primary cancer, approximating 1% per year, with some studies demonstrating a risk of contralateral breast cancer (CBC) up to 35% by 16 years after the first breast cancer diagnosis [22]. This risk is higher in women with known BRCA1 or BRCA2 germ line mutations, with up to a 27% risk at 5 years and 43% risk at 10 years depending on the specific mutation and history of endocrine therapy [23]. Due to this increased risk of metachronous cancer, more women are electing to undergo CPM for breast cancer risk reduction. Recent SEER data demonstrates that the use of CPM in the United States has more than doubled from 1998 to 2003, with up to 11% of women undergoing mastectomy for their index cancer electing to undergo concomitant CPM [24].

One of the first studies investigating CBC risk reduction following CPM, was a study by McDonnell and colleagues who retrospectively evaluated women with a family history of breast and/or ovarian cancer who underwent CPM at the time of their therapeutic mastectomy. To determine CBC risk reduction they used the Anderson statistical model calculating risk reduction based on family history and menopausal status [22]. Following a median follow-up of 10 years, only 8 (1.1%) women developed CBC post CPM. Through use of their statistical model, breast cancer risk reduction was up to 96% following CPM which varied slightly based on menopausal status, with a 94.8% reduction in premenopausal women and 96.3% risk reduction in postmenopausal women. The risk reduction was similar regardless of whether adjuvant therapy was used for the woman's primary cancer.

Metcalfe and colleagues looked specifically at CBC risk reduction in BRCA mutation-detected families. Based on their analysis, they determined a 5-year actuarial risk of CBC following the diagnosis of a first breast cancer to be 16.9% in women who saved their contralateral unaffected breast, and a 10-year risk of 29.5%. The 10-year actuarial risk of CBC was shown to be slightly higher for BRCA1 patients, 32%, as compared to BRCA2 patients, 24.5%. With a mean follow-up of 9.2 years, only 1 (0.7%) patient following CPM developed a CBC, as compared to 97 (28.9%) in women who saved their contralateral breast, leading to a 97% overall CBC risk reduction following CPM [23]. They also demonstrated a 59% CBC risk reduction in their patients who underwent PBSO, which was greater for women younger than the age of 50 at time of diagnosis.

Van Sprundel and colleagues also demonstrated a significant CBC risk reduction following CPM in BRCA mutation carriers [25]. After a mean follow-up of 3.4 years, only 1 (1.3%) patient following CPM developed a CBC, whereas 6 (14%) patients undergoing surveillance developed CBC, leading to an overall 91% CBC risk reduction following CPM, independent of the impact of PBSO. A significant overall survival was observed in the CPM groups as compared to the surveillance group; however, this was related to the effect of concomitant PBSO. Women who underwent both CPM and PBSO did demonstrate a better overall and breast cancer-specific survival than either prophylactic surgery alone.

Herrinton and colleagues also demonstrated a protective benefit of CPM on the incidence of CBC, as well as an associated decrease in breast cancer-specific mortality and all-cause mortality [26]. After a median follow-up of 5.7 years, CPM was associated with a 97% reduction in CBC risk. Furthermore, 8.1% of women who underwent CPM died of breast cancer as compared to 11.7% of women who did not, representing a 43% risk reduction in breast cancer-specific death. On further analysis, the CPM cohort did have a lower all-cause mortality suggesting a possible of selection bias for overall healthier patients undergoing CPM. CPM was also less effective against preventing subsequent distant metastasis, leading to a larger effect of CBC risk reduction than expected mortality reduction.

Boughey and colleagues also investigated the effect of CPM on recurrence and survival in high risk women with Stage I and II breast cancer [27]. High risk women were defined as any woman with history of either first- or second-degree relative. Their control cohort was matched on age of breast cancer diagnosis, year of diagnosis, tumor stage, and nodal status. After a median follow-up of 17.3 years, 2 (0.5%) patients developed a CBC in the CPM cohort as compared to 31 (8.1%) patients who did not undergo CPM, representing a 95% risk reduction of CBC. Reduction in CBC risk remained statistically significant after adjustment for age, stage, nodal status, and first-degree family history. Ten-year overall survival estimates for CPM vs. Patients undergoing only therapeutic mastectomy were 83% vs. 74%, with a 22% overall survival benefit for patients undergoing CPM. A disease-free survival benefit of 34% was also seen in women who underwent CPM. There was also a trend towards improved breast cancer-specific survival in women undergoing CPM.

In a recent large population-based study on data from the SEER registry, Bedrosian and colleagues investigated the utility of CPM on breast cancer-specific survival, with further analyses based on age, disease stage, and ER status [28]. Of 311,643 cases of breast cancer diagnosed in the 6-year study period, 107,106 women underwent mastectomy for the treatment of unilateral breast cancer. Eight thousand nine hundred and two (8.3%) underwent CPM. As compared to non-CPM patients, CPM patients were significantly younger and had earlier-stage disease. In a univariate analysis, CPM was associated with improved disease-specific survival for women with stages I-III, with an overall 47% improvement in disease-specific survival. Additional variables associated with disease-specific survival were disease stage, lymph node status, tumor grade, ER status, race, histology, and age, all of which remained statistically significant following multivariate analysis. To determine the role of selection bias for healthier women, they found that cancer-specific survival associated with CPM declined with age, with women older than 60 years having no risk reduction from CPM, which was likely related to a strong association between CPM and non-cancer causes of death in women older than 60. Among younger women, there was no association between CPM and non-cancer causes of death.

In a subset analysis investigating age, disease stage, and ER status, they demonstrated that patients diagnosed before the age of 50 years with stage I or II ER-negative breast cancer had a significant reduction in the risk of disease-specific mortality, with a risk reduction of 47%, accounting for a 4.8% increase in 5-year adjusted breast cancer-specific survival favoring CPM. This was not seen in early-stage ER-positive breast cancers in young women. Among women between the ages of 50 and 59, CPM was associated with improved breast cancer-specific survival for women who had early-stage ER-negative disease and those with later-stage ER-positive disease. No reduction in breast cancer-specific death was associated with CPM in women older than 60 years of age. As illustrated by Bedrosian and colleagues, these results may be related to the larger absolute lifetime risk of metachronous CBC combined with the low probability of competing causes of death in younger women. Furthermore the role of endocrine therapy in reducing subsequent breast cancer may have a role in the decreased effects of CPM in younger women with ER+ disease. In addition, no survival benefit was seen amongst women who underwent CPM for DCIS, pure lobular cancers, or locally advanced (stage III) disease.

Overall, the above studies demonstrate up to a 97% risk reduction of CBC in women who undergo CPM as compared to women who save their unaffected breast. This risk reduction has been shown to confer a survival benefit that seems to be affected by selection bias of healthier women who undergo for CPM. However, based on the SEER database study by Bedrosian and colleagues there may be a subset of women for which CPM would provide the greatest survival benefit, consisting of young women with early stage ER-negative disease (Table 8.3).

Table 8.3 Surgical strategies for risk reduction

Prophylactic bilateral mastectomy (PBM) • PBM has been shown to confer over a 90% breast cancer risk reduction in women at moderate to high risk based on family history alone • Subset analysis of BRCA mutation carriers continues to demonstrate a 85–100% breast cancer risk reduction following PBM • No strong evidence exists to date regarding an associated mortality benefit from breast cancer risk reduction following PBM; however, analytic decision models do suggest a gain of 2.9–5.3 years of life in BRCA mutation carriers
Prophylactic bilateral salpingo-oophorectomy (PBSO) • A 47–68% breast cancer risk reduction is demonstrated following PBSO, with a 80–96% gynecologic cancer risk reduction in BRCA mutation carriers • The greatest breast cancer and gynecologic cancer risk reduction occurred in BRCA women younger than the age of 50 years, supporting the use of PBSO soon after childbearing years • A significant reduction in overall mortality, breast cancer-specific mortality, and gynecologic cancer-specific mortality is demonstrated following PBSO alone or in combination with PBM in BRCA mutation carriers • In subset analysis investigating BRCA 1 and BRCA 2 mutation carriers independently, survival benefit was only statistically significant in BRCA 1 carriers, likely related to the limited number of BRCA 2 carriers in the studies, as well as the fewer cancer events that occurred in BRCA 2 mutation carriers as compared to BRCA1 carriers • Similar to cancer-specific risk reduction, mortality benefit following PBSO was found to be significant only in women younger than the age of 50 years
Contralateral prophylactic mastectomy (CPM) • A 91–97% contralateral breast cancer (CBC) risk reduction has been shown to occur in women undergoing CPM during the treatment of their index cancer • Several studies suggest an overall and breast cancer-specific survival benefit following CPM; however, concern exists for selection bias for younger healthier women electing to undergo CPM • In subset analysis of a large SEER registry study, young women with ER-negative tumors may demonstrate the greatest survival benefit due to the inability of the use of endocrine agents • No survival benefit following CPM is demonstrated in women undergoing CPM for DCIS, pure lobular cancers, locally advanced disease, as well as women over the age of 60

Nipple Sparing Mastectomy for Risk Reduction and Cancer Treatment

Based on the above studies, both PBM as well as CPM provide significant breast cancer risk reduction in patients undergoing both prophylactic and therapeutic surgery. However, what surgery is the best oncologic option for these patients? Over the past few years, NSM has resurfaced as a surgical option due to tighter selection criteria and advanced reconstructive options. NSM is a mastectomy technique similar to skin sparing mastectomy (SSM), however unlike SSM, NSM preserves the nipple areola complex with a small amount of retroareolar tissue. From an aesthetic standpoint, nipple areola complex preservation is thought to maintain the aesthetic integrity of the women's breast, by preserving the most symbolic component—the nipple and areola. However from an oncologic standpoint, preserving the nipple areola complex leaves the theoretical potential for occult cancer in a clinically negative nipple as well as the potential for future cancer to occur. This risk is thought to be heightened in high risk women undergoing prophylactic surgery due to their predilection for cancer, which is emphasized by Hartmann and Rebbeck's earlier studies demonstrating in-breast recurrences to only occur in women who underwent NSM as compared to total mastectomy [6, 9].

Occult Nipple Involvement

Numerous studies supporting the safety of NSM for both therapeutic and prophylactic mastectomy arise from studies investigating the incidence of occult nipple involvement in mastectomy specimens. In a recent study, Reynolds and colleagues investigated both the presence of terminal duct lobular units (TDLUs) in the nipple as well as the incidence of premalignant and malignant lesions within the NACs of BRCA carriers [29]. Sixty-two therapeutic and prophylactic mastectomy specimens from 33 BRCA mutation carriers were

sectioned and microscopically examined. Seventy-six percent of women were BRCA1 mutation carriers, while 24% were BRCA2 carriers. Twenty-eight women (85%) underwent therapeutic mastectomy, and 82% underwent concomitant CPM. Five women (15%) underwent PBM for risk reduction. Interestingly only 24% of mastectomy specimens demonstrated TDLUs in the NAC, the majority of which were in the retroareolar tissue, with only 5 (8%) specimens demonstrating TDLUs in the nipple papilla alone. There was no evidence of premalignant or invasive cancer found in the 33 NACs of prophylactic mastectomies, including both CPM and PBM specimens. Of the 29 therapeutic mastectomies, only 1 (3.5%) NAC demonstrated invasive cancer, 1 (3.5%) demonstrated DCIS, and 1 (3.5%) demonstrated atypical lobular hyperplasia.

Brachtel and colleagues then investigated clinicopathologic characteristics predictive of NAC involvement [30]. Three hundred and sixteen mastectomy specimens, 232 therapeutic and 84 prophylactic, were sectioned and analyzed. Thirty-eight percent of patients were known BRCA mutation carriers. None of the prophylactic mastectomy specimens contained invasive carcinoma or DCIS, although 5% were positive for LCIS. Twenty-one percent of the 232 therapeutic mastectomy specimens contained pathologic findings of DCIS (62%), IDC (<10%), ILC (<10%), and lymphovascular invasion (<20%). On multivariate analysis, tumor size, tumor-nipple distance, and HER2-Neu amplification were predictive of NAC involvement. No statistical correlation was found with BRCA mutation status. Furthermore they demonstrated an 80% sensitivity and 96% negative predictive value of retroareolar biopsy in determining nipple involvement.

One of the most recent and largest studies by Li and colleagues examined 2,323 mastectomy specimens to determine the frequency of occult NAC involvement as well as to identify clinicopathologic features predictive of occult NAC involvement [31]. Two hundred and forty-eight (10.7%) mastectomy specimens demonstrated occult nipple involvement, with more than half of the involved nipples occurring only at the base of the nipple margin. Only 5% of all involved nipples had a negative base with involved papillae or skin. Of the 248 involved nipples, 56.5% were DCIS only, 29.4% were invasive cancer, 3.2% LVI only, and 1.6% LCIS. Seventy-eight percent of the index cancers with occult nipple involvement were IDC or IDC accompanied with DCIS. On multivariate analysis, tumor size, tumor-to-nipple distance, central tumor location, multicentricity or multifocality, as well as lymph node involvement, LVI, and HER2-Neu amplification were statistical predictors of occult nipple involvement.

The above studies demonstrate a higher likelihood of NAC involvement in therapeutic mastectomy specimens as compared to prophylactic specimens, with both Reynolds and Brachtel demonstrating a 0% incidence of malignant or premalignant pathology involving the nipple base in prophylactic mastectomy specimens [29, 30]. In regards to therapeutic mastectomies, the likelihood of NAC involvement was as high as 21%, which was affected by factors such as tumor size, tumor-to-nipple distance, multicentricity, higher stage cancers, LVI, and the presence of HER2-Neu amplification, demonstrating the importance of patient selection in nipple areola preservation [31].

Oncologic Safety of Nipple Sparing Mastectomy

On a clinical note, numerous single-institution studies with at least 5 years of follow-up have demonstrated oncologic safety in terms of acceptable local, regional, and distant recurrence rates, as well as favorable 5-year overall survival in patients undergoing NSM [32–37] (Table 8.4). One of the largest studies with longest follow-up was published by Benediktsson and colleagues, with a median follow-up of 13.4 years [33]. Although they demonstrated one of the highest overall locoregional recurrence rates of 24.1%, 0% of their recurrences occurred at the NAC. High local recurrence rates were likely related to their patient population, in which over 50% of their patients had Stage II or Stage III disease with up to 40% having axillary node involvement. Furthermore, following subgroup analysis of patients who received adjuvant radiotherapy, the locoregional recurrence rate was decreased to 8.5% after 13 years.

Table 8.4 Nipple sparing mastectomy (NSM)

Study	Year	Patients (*n*)	F/U (years)	NAC recurrence (%)	Locoregional recurrence (%)	Distant recurrence (%)	Post-op XRT (%)	Stage II/III (%)	Five-year overall survival (%)
Caruso et al.	2006	56	5.5	2	2	10	0	38	92
Benediktsson et al.	2008	216	13	0	24.1	20.3	21.8	53.2	76.4
Gerber et al.	2009	238	8.4	1.6	13.4	23.3	27	81	76.6
Kim et al.	2010	520	5.5	1.3	2.0	–	5.3	41.5	97.1
Lim et al.	2010	897	5.2	–	4.6	–	56.3	100	79.4
Jensen et al.	2011	99	5	0	0	0	16	36.4	100

Table 8.5 Oncologic safety of nipple sparing mastectomy

- A 10–20% incidence of occult nipple areola complex (NAC) involvement has been demonstrated in women undergoing therapeutic mastectomy, with a 0% incidence of occult nipple involvement in women undergoing prophylactic mastectomy for risk reduction
- Clinicopathologic factors related to increased NAC involvement are larger tumor size, shorter tumor-to-nipple distance, central tumor location, tumor multicentricity or multifocality, presence of lymph node involvement, as well as HER2-neu amplification
- Clinical studies demonstrate locoregional recurrences to occur in 0–24% of women undergoing NSM for breast cancer treatment, with NAC recurrences only as high as 1.6%
- Intra-operative retroareolar tissue biopsy is recommended with studies demonstrating a 80% sensitivity and 96% negative predictive value of retroareolar biopsy in determining NAC involvement

A second series published by Gerber and colleagues compared 246 patients who underwent MRM, SSM, or NSM, with an average follow-up of 8.4 years [34]. Each surgical group was statistically equivalent in terms of multicentricity, AJCC staging, axillary involvement, tumor grade, as well as pre- and postoperative systemic and radiotherapy. Their results demonstrated no significant differences in locoregional recurrences, isolated distant metastases, or breast cancer-specific death. Their locoregional recurrence rates for MRM, SSM, and NSM were 14.6, 12.5, and 13.4%, respectively, with only a 1.6% incidence of NAC recurrence in their NSM patients. Of more recent studies with a minimum 5-year median follow-up, local recurrence rates ranged from 0 to 5%, with NAC recurrence rates ranging from 0 to 1.3% [35–37].

A recent study by Filho and colleagues investigated the use of NSM for both prophylactic and oncologic purposes in high risk women [38]. Fifty six percent were for breast cancer risk reduction, as compared to 44% for therapeutic mastectomies. NSM was offered as a therapeutic option to patients with clinically negative axillas, tumors less than 3 cm, and a tumor-to-nipple distance of at least 1 cm. Approximately 20% of their patients were known BRCA mutation carriers, with 70% of their patients having a positive family history. Although with a limited median follow-up of 10.4 months, there were no reported local or NAC recurrences.

Based on the above studies, NSM for prophylactic surgery appears to be oncologically safe in regards to the low probability of occult nipple involvement, as well as the acceptable recurrence rate and overall survival. Additional long-term follow-up in high risk patients would be helpful in fully elucidating the clinical outcomes in such patients. NSM for therapeutic surgery also appears safe; however, appropriate patient selection appears to be paramount and the use of intra-operative frozen section of retroareolar tissue is recommended (Table 8.5).

Role of Sentinel Lymph Node Biopsy in Prophylactic Mastectomy

SLNB in the setting of prophylactic mastectomy currently is not standard of care, although the use of SLNB has been demonstrated to occur in up to 85% of patients undergoing CPM based solely on surgeon preference [39]. Many surgeons fear the need to perform staging axillary lymph node dissection (ALND) in patients found to have occult invasive malignancies in their prophylactic specimens, when an axillary dissection potentially could have been prevented with a negative SLNB. Although some institutions do report the utility of SLNB following mastectomy, the overall accuracy is unknown [40]. Although postsurgical complications following ALND are reported in up to 70% of patients, SLNB is also not without risk, with recent data from prospective randomized trials demonstrating up to a 25% postoperative complication rate following SLNB alone, which includes up to an 8% risk of lymphedema at 6 months [41]. Furthermore the incidence of an occult invasive cancer in prophylactic specimens is reportedly low. Both Hartmann and colleagues, as well as Heemskerk-Gerritsen and colleagues demonstrated a <1% incidence of occult invasive cancer in their prophylactic mastectomy specimens of high risk women undergoing PBM [6, 10].

Since then numerous retrospective studies have investigated the role of SLNB for prophylactic surgery [42–48] (Table 8.6). The incidence

Table 8.6 Sentinel lymph node biopsy

						Mastectomy specimen		Contralateral SLNB
Study	Year	Study design	Patients (*n*)	BRCA (%)	Family history + (%)	Invasive cancer (%)	DCIS (%)	Positive (%)
Dupont et al.	2000	Prospective	57	–	–	3.5	0	3.5
Boughey et al.	2006	Retrospective	409	5.6	57	1.8	3.2	1.9
Black et al.	2007	Retrospective	173	17.0	52.6	2.6	7.3	3.6
Soran et al.	2007	Retrospective	155	7	52.3	1.3	1.9	1.3
McLaughlin et al.	2008	Retrospective	529	9.3	59	1.6	3.8	2
Laronga et al.	2009	Retrospective	449	–	53.2	1.4	2.9	2
Nasser et al.	2010	Retrospective	99	–	48.5	2	6	2
Czyszczon et al.	2011	Retrospective	184	6	6	1	5	1.3

Table 8.7 Role of sentinel lymph node biopsy (SLNB) in risk reducing surgery

- The incidence of occult invasive carcinoma found in prophylactic mastectomy is low, occurring in less than 3.5% of women undergoing PBM
- When calculating the total benefit rate of sentinel lymph node biopsy based on the number of negative sentinel lymph nodes when occult cancer is found and the number of positive sentinel lymph nodes when no cancer is found, the benefit rate is only 2.8%—in turn not supporting the use of routine SLNB during prophylactic surgery
- Some studies investigating sentinel lymph node biopsy in CPM also demonstrate an increased risk of cross metastasis to contralateral sentinel nodes, questioning the utility of routine SLNB in this subset of patients

of occult invasive carcinoma in prophylactic specimens has been shown to occur between 1 and 3.5% of the time. Furthermore the majority of occult disease if found, is typically in situ disease. In a recent meta-analysis incorporating 1,251 patients undergoing routine SLNB in 1,343 prophylactic mastectomies from 6 retrospective studies, occult invasive cancer was found in 21 specimens, representing an occult invasive cancer rate of only 1.7% [49]. Of these 21 cases, only 4 cases had positive SLNs, therefore only 17 patients of 1,343 pooled prophylactic mastectomies were able to avoid potential ALND. Eighteen cases demonstrated positive SLNs where no occult cancer was identified. A total benefit rate of SLNB was calculated, which was defined as the number of negative SLNs at the time of prophylactic mastectomy in cases with occult cancer plus the number of positive SLNs at the time of prophylactic mastectomy in cases where no invasive cancer was identified divided by the number of prophylactic mastectomies. The overall benefit rate was 2.8%.

Although Zhou and colleagues demonstrated only an overall 2.8% benefit rate, is there a patient population that would benefit from routine SLNB? Of the studies reviewed, the majority demonstrate a higher incidence of occult cancer in CPM specimens for known index cancers as compared to PBM for risk reduction. Therefore patients undergoing PBM for risk reduction may not be suitable candidates for routine SLNB. However in CPM patients, clinicopathologic factors have been identified as predictive in both contralateral occult disease as well as contralateral sentinel lymph node involvement. Boughey and colleagues demonstrated postmenopausal status, age over 60 years, or history of either ILC or LCIS to be predictive of contralateral occult disease. They did not demonstrate BRCA mutation status to be a predictive variable [43]. Laronga and colleagues found that larger index cancer size, ipsilateral nodal metastases, higher index tumor grade, skin and nipple involvement, and LVI did play independent roles in contralateral nodal involvement in the absence of contralateral occult disease [46]. This was true in 6 of the 8 studies and likely represented cross metastasis from locally advanced or inflammatory index cancers, as well as patients undergoing delayed CPM in the face of an ipsilateral recurrence with prior axillary dissection. Such clinicopathologic characteristics may be helpful in patient selection for SLNB in patients undergoing CPM [39, 43, 44, 46–48] (Table 8.7).

Conclusion

The decision to undergo prophylactic surgery for risk reduction remains complex. Although prospective randomized clinical trials would be ideal to truly evaluate the efficacy of prophylactic surgeries on risk reduction and survival, these studies would be difficult for accrual and would take years of follow-up. Based on numerous prospective and retrospective studies, PBM, PBSO, as well as CPM demonstrate significant cancer-specific risk reduction. Although only analytical models demonstrate expected survival benefit for patients undergoing PBM, stronger retrospective and prospective studies demonstrate an overall survival and cancer-specific survival in younger women undergoing PBSO. Furthermore, a recent population-based analysis demonstrates a potential survival benefit in younger patients with

ER-negative tumors undergoing CPM. In regards to type of prophylactic surgery, total mastectomy, SSM, and NSM all appear to be safe options for prophylactic surgery. Patient selection remains imperative for NSM decision in patients undergoing NSM for therapeutic mastectomy, with tumor characteristics and anatomical factors of clinical importance. Whereas the routine use of SLNB is not fully supported based on the available literature, the use of SLNB in selected patients undergoing CPM may appear clinically appropriate, such as patient with locally advanced index cancers.

References

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
2. Antoniou A, Pharoah PDP, Arod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117.
3. Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet. 1998;351:316–21.
4. Verhoog LC, Brekelmans CTM, Seynaeve C. Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol. 1999;17: 3396–402.
5. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001;286:2251–6.
6. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340:77–84.
7. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93:1633–7.
8. Meijers-Heijboer H, van Geel B, van Putten WLJ, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345:159–64.
9. Rebbeck TR, Friebel T, Lynch H, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol. 2004;22:1055–62.
10. Heemskerek-Gerritsen BAM, Brekelmans CTM, Menke-Pluymers MBE, et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of Hereditary Breast Cancer: long-term experiences at the Rotterdam Family Cancer Center. Ann Surg Oncol. 2007;14:3335–44.
11. Schrag D, Kuntz KM, Garber JE, et al. Decision analysis-effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Eng J Med. 1997;336:1465–71.
12. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst. 1999;91:1475–9.
13. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1616–22.
14. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609–15.
15. Kauff ND, Domcheck SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2- associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26:1331–7.
16. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case–control study. J Clin Oncol. 2005;23:7491–6.
17. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. JAMA. 2006;296:185–92.
18. Domcheck SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 2006;7:223–9.
19. Domcheck SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967–75.
20. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465–77.
21. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol. 2005;23:7804–10.
22. McDonnell SK, Schaid DJ, Myers JL, et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J Clin Oncol. 2001;19:3938–43.
23. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2004;22:2328–35.
24. Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25:5203–8.

25. Van Sprundel TC, Schmidt MK, Rookus MA, et al. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. Br J Cancer. 2005;93:287–92.
26. Herrinton LJ, Barlow WE, Yu O, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol. 2005;23:4275–86.
27. Boughey JC, Hoskin TL, Degnim AC, et al. Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. Ann Surg Oncol. 2010;17:2702–9.
28. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst. 2010;102:401–9.
29. Reynolds C, Davidson JA, Lindor NM, et al. Prophylactic and therapeutic mastectomy in BRCA mutation carriers: can the nipple be preserved? Ann Surg Oncol. 2011;18:3102–9.
30. Brachtel EF, Rusby JE, Michaelson JS, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. J Clin Oncol. 2009;27:4948–54.
31. Li W, Wang S, Guo X, et al. Nipple involvement in breast cancer: retrospective analysis of 2323 consecutive mastectomy specimens. Int J Surg Pathol. 2011;19:328–34.
32. Caruso F, Ferrara M, Castiglione G, et al. Nipple sparing subcutaneous mastectomy: sixty-six months follow-up. Eur J Surg Oncol. 2006;32:937–40.
33. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy in immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. Eur J Surg Oncol. 2008;34:143–8.
34. Gerber B, Krause A, Dieterich M, et al. The oncological safety of skin paring mastectomy with conservation of the nipple-aerola complex and autologous reconstruction: an extended follow-up study. Ann Surg. 2009;249:461–8.
35. Kim HJ, Park EH, Lim WS, et al. Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaenous flap reconstruction is an oncologically safe procedure: a single center study. Ann Surg. 2010;251(3):493–8.
36. Lim W, Ko BS, Kim HJ, et al. Oncological safety of skin sparing mastectomy followed by immediate reconstruction for locally advanced breast cancer. J Surg Oncol. 2010;102:39–42.
37. Jensen JA, Orringer JS, Guiliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. Ann Surg Oncol. 2011;18:1665–70.
38. Filho PA, Capko D, Barry J, et al. Nipple-sparing mastectomy for breast cancer risk-reducing surgery: The Memorial Sloan-Kettering Cancer Center experience. Ann Surg Oncol. 2011;18:3117–22.
39. Soran A, Falk J, Bonaventura M, et al. Is routine sentinel lymph node biopsy indicated in women undergoing contralateral prophylactic mastectomy: Magee-Womens hospital experience. Ann Surg Oncol. 2007;14:646–51.
40. Karam A, Stempel M, Cody HS, et al. Reoperative sentinel lymph node biopsy after previous mastectomy. J Am Coll Surg. 2008;207:543–8.
41. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol. 2007;25:3657–63.
42. Dupont EL, Kuhn MA, Mcann C, et al. The role of sentinel lymph node biopsy in women undergoing prophylactic mastectomy. Am J Surg. 2000;180:274–7.
43. Boughey JC, Khakpour N, Meric-Bernstam F, et al. Selective use of sentinel lymph node surgery during prophylactic mastectomy. Cancer. 2006;107:1440–7.
44. Black D, Specht M, Lee JM. Detecting occult malignancy in prophylactic mastectomy: preoperative MRI versus sentinel lymph node biopsy. Ann Surg Oncol. 2007;14:2477–84.
45. McLaughlin SA, Stempel M, Morris EA, et al. Can magnetic resonance imaging be used to select patients for sentinel lymph node biopsy in prophylactic mastectomy? Cancer. 2008;112:1214–21.
46. Laronga C, Lee MC, McGuire KP. Indications for sentinel lymph node biopsy in the setting of prophylactic mastectomy. J Am Coll Surg. 2009;209:746–52.
47. Nasser SM, Smith SG, Chagpar AB. The role of sentinel node biopsy in women undergoing prophylactic mastectomy. J Surg Res. 2010;164:188–92.
48. Czyszczon IA, Roland L, Sahoo S. Routine prophylactic sentinel lymph node biopsy is not indicated in women undergoing prophylactic mastectomy. J Surg Oncol. 2012;105:650–4.
49. Zhou WB, Liu XA, Dai JC, et al. Meta-analysis of sentinel lymph node biopsy at the time of prophylactic mastectomy of the breast. Can J Surg. 2011;54:300–6.