Curr Breast Cancer Rep (2013) 5:73–85
DOI 10.1007/s12609-013-0110-3

LOCAL-REGIONAL EVALUATION AND THERAPY (KK HUNT, SECTION EDITOR)

Risk-Reducing Mastectomy: Who Is a Candidate and What Are the Outcomes?

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Published online: 19 May 2013

Abstract As genetic testing to identify hereditary susceptibility for breast cancer becomes more widely available, interest in prophylactic mastectomy is becoming more popular. Patients with unilateral breast cancer are also pursuing prophylactic contralateral mastectomy for its risk-reducing and symmetry benefits. This review discusses the selection of candidates for prophylactic mastectomy, its benefits, and data on effectiveness of this surgery.

Keywords Breast cancer · Unilateral breast cancer · Surgical oncology · Prophylactic mastectomy · Bilateral prophylactic mastectomy · BPM · Unilateral/contralateral prophylactic mastectomy · CPM · Risk reduction · Patient selection · Psychosocial considerations · Outcomes

Introduction

Breast cancer is the most common malignancy affecting American women, diagnosed in more than 280,000 patients annually, and it is second only to lung cancer as the leading cause of cancer deaths [1]. Advances in breast cancer early detection as well as treatment have resulted in improved outcomes, with nearly 90 % of patients surviving at least 5 years [1]. The armamentarium of effective systemic therapies for breast cancer is expanding at a gratifying pace, and many patients will be candidates for less disfiguring surgical procedures such lumpectomy or breast reconstruction. However, systemic therapy agents are universally associated with risks of various toxicities or adverse symptoms, and breast cancer-directed operative therapy often involves axillary surgery that is associated with lifelong risk of lymphedema and/or shoulder dysfunction. Furthermore, the threat of breast cancer mortality remains quite relevant, with nearly 40,000 American women succumbing to this disease every year [1]. It is therefore appropriate that the oncology community pursue a range of surgical as well as medical approaches designed to prevent breast cancer, thereby reducing the need for patients to face the morbidity of cancer-directed surgery, systemic therapy, and/or radiation.

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Patient Selection

Prophylactic mastectomy is the most effective strategy available today for reducing risk of breast cancer. Despite the alarming prevalence of this disease, most women are not destined to ever experience a breast cancer diagnosis and candidates for prophylactic surgery should be carefully vetted. Prophylactic mastectomy requires exposure to the inherent risks of general anesthesia, and even with the most talented of plastic/reconstruction surgeons, the end result will be an altered appearance that might exert a negative impact on body self-image and/or psychosexual satisfaction. Patients should be prepared in advance to deal with these issues, as well as the fact that prophylactic mastectomy does not confer 100 % protection from breast cancer risk.

Prophylactic surgery by definition is elective and optional; it should never be presented as a medical necessity. Alternatives to prophylactic mastectomy include chemoprevention to reduce breast cancer risk and aggressive surveillance to enhance likelihood of breast cancer early detection and successful treatment. Prophylactic mastectomy is clearly the most aggressive strategy and is associated with the greatest magnitude in risk reduction.

Given the general background issues described above, the 2 categories of patients most likely to benefit from prophylactic mastectomy would be

(1) women facing a high-risk of future breast cancer, in which case the prophylactic surgery would be performed bilaterally (bilateral prophylactic mastectomy, BPM); and
(2) women with a preexisting diagnosis of unilateral breast cancer, who would consider undergoing therapeutic mastectomy in addition to contralateral prophylactic mastectomy (CPM).

The Society of Surgical Oncology (SSO) has published a position statement on prophylactic mastectomy [2], including specific guidelines to optimize identification of the most reasonable candidates within the 2 broad categories described above (Table 1). Previously-undiagnosed women facing a high future risk of breast cancer include individuals with known or suspected hereditary predisposition (BRCA mutation carriers; Cowden's syndrome/PTEN mutation; Li-Fraumeni syndrome/p53 mutation) [3]; individuals with documented pathologic findings of abnormal proliferative activity associated with risk of malignant transformation (lobular carcinoma in situ; atypical ductal hyperplasia; atypical lobular hyperplasia) [4]; and individuals for whom conventional screening modalities such as mammography and/or clinical breast examination are less likely to achieve early detection of cancer because of extensive density or fibrocystic nodularity.

The National Comprehensive Cancer Network's (NCCN) breast cancer risk reduction guideline [5] (Table 1) includes a brief summary statement on BPM eligibility, and similar to the SSO position statement, hereditary susceptibility and LCIS are cited. Additionally, the NCCN refers to BPM as a maneuver to avoid radiation-induced cancers of the breast, a consequence of prior chest wall therapeutic radiation. Women with a history of therapeutic chest wall irradiation during adolescence or early adult life, such as mantle irradiation for Hodgkin's disease [6, 7], face a notably high risk of breast cancers that are often diagnosed in the premenopausal years, and they also have an increased risk bilateral breast cancer [8–10]. Nonetheless, limited data exist regarding prophylactic mastectomy in this setting.

Of the profiles described above, patients with documented hereditary susceptibility or family pedigrees consistent with genetically-transmitted risk are by far the most likely women to request the risk-reducing BPM. Several series have recently documented the increasing prevalence of CPM among women with unilateral disease.

Effectiveness

Animal Models and Historic Data [11]

The effectiveness of prophylactic mastectomy has been explored in rodent models with rather disappointing results. In 1 series [12], rats received the mammary carcinogen 7,12-dimethylbenz-a-anthracene followed by a 50 %, 75 %, or 100 % mastectomy 2 weeks later. Mammary cancers

Table 1 Professional/academic organizations' guidelines regarding candidates for risk-reducing mastectomy

I. Society of Surgical Oncology Position Statement on Prophylactic Mastectomy, 2007 [2]
- A. Potential indications for bilateral prophylactic mastectomies (high risk patients with no prior breast cancer diagnosis)
  1. BRCA mutation or mutation in other hereditary susceptibility gene
  2. Strong family history of breast and/or ovarian cancer (especially if breast cancer was bilateral or premenopausal)
  3. Histological risk factors (atypical ductal hyperplasia; atypical lobular hyperplasia; lobular carcinoma in situ)
  4. Difficult surveillance (extremely dense fibronodular tissue that is difficult monitor with conventional screening modalities, especially if associated with a history of multiple diagnostic biopsies)
- B. Potential indications for contralateral prophylactic mastectomy (patients with unilateral breast cancer)
  1. Risk reduction (see potential indications noted for bilateral prophylactic mastectomy)
  2. Difficult surveillance (see potential indications noted for bilateral prophylactic mastectomy)
  3. Reconstructive or chest wall symmetry issues (patients undergoing mastectomy and reconstruction for unilateral breast cancer in whom symmetry can be improved with bilateral mastectomy and bilateral reconstruction; or patients undergoing mastectomy without reconstruction in whom a large, pendulous, and/or ptotic contralateral breast would result in substantial symptomatic imbalance)

II. National Comprehensive Cancer Network breast cancer risk reduction guideline [5]
- A. Candidates in whom bilateral risk-reducing mastectomy may be considered
  1. BRCA 1/2 mutation carrier
  2. Carriers of other "strongly predisposing" gene mutations
  3. Patients with lobular carcinoma in situ
  4. "Compelling" family history
  5. Patients with prior thoracic radiation therapy delivered at age younger than 30 y

developed in nearly all rats in both mastectomy groups. In another series [13], mice with a high spontaneous incidence of mammary tumors were studied; this model was thought to more closely reflect the human breast cancer experience. Despite undergoing a 50 % vs 100 % mastectomy, there was no significant difference in the rate of cancer development at 12 months postoperative follow-up in comparison with control mice that had not undergone prophylactic mastectomy.

Human series of prophylactic mastectomy have been more promising. However, the data from historic series were difficult to interpret because all of their retrospective nature; suboptimal follow-up; and lack of detail regarding baseline breast cancer risk in patients undergoing the prophylactic surgery. These older studies likely included subsets of women who underwent the surgery because of chronic breast pain and others that may have been at low risk for breast cancer to begin with.

Pennisi and Capozzi [14] reported on results from the Subcutaneous Mastectomy Data Evaluation Center at Saint Francis Memorial Hospital in San Francisco. This database was established in 1975; in their 1989 review, it included information on 1500 patients who had undergone subcutaneous mastectomy by 165 plastic surgeons. Most of the patients were relatively young (70 % were between the ages of 35 and 55 years), and very few appeared to be at substantially high risk for breast cancer. This was evidenced by the fact that only 20 % had a first-degree relative afflicted with breast cancer and less than 15 % of the mastectomy specimens had high-risk histopathologic features, such as atypical hyperplasia or lobular carcinoma in situ. Thirty percent of these patients were lost to follow-up, and among those remaining patients who were followed for an average of 9 years, 6 breast cancers (0.6 %) were detected. Ziegler and Kroll [15] performed a critical reevaluation of this data, calculating a 1.18 % incidence of breast cancer by using only the 510 patients with documented clinical or pathologic features of a high risk for breast cancer as the denominator.

The Mayo Clinic also has extensive experience with prophylactic mastectomy. In a report on management of nipple-areolar complications following subcutaneous mastectomy, Woods and Meland [16] noted that over a 22-year period, more than 1500 prophylactic mastectomies were performed at that institution and that 5 breast cancers were subsequently detected. However, no detailed information is given regarding risk assessment or the follow-up interval for the patient population.

Contemporary Data

Table 2 summarizes the results of several studies of prophylactic mastectomy (BPM as well as CPM) published during the past 15 years. These studies mostly rely on retrospectively-acquired data and focus on the effectiveness of mastectomy in reducing incidence of new primary breast cancers. Prophylactic mastectomy fairly consistently reduces breast cancer risk in these reports by 90 %–95 %. Human data on the survival benefits of prophylactic mastectomy are mostly based upon datasets of CPM cases, and in this setting, an outcome advantage related to longevity is controversial. Potential survival benefits associated with BPM are largely derived from statistical modeling and decision-analysis studies, demonstrating up to 5 years longevity gain for high-risk patients undergoing prophylactic surgery at age 30 years. Pathology studies of the prophylactic mastectomy specimens reveal incidental findings of invasive cancer and/or ductal carcinoma in situ in fewer than 5 % of cases.

The first risk-adjusted analysis of the effectiveness of prophylactic bilateral mastectomy was reported by Hartmann et al. [17], and was based upon the Mayo Clinic experience. The records of 1065 women who underwent bilateral prophylactic mastectomy between 1960 and 1993 were reviewed, yielding 639 women (median age, 42 years) who had a family history positive for breast cancer. Ninety percent of these mastectomies were subcutaneous, and 94 % were accompanied by immediate breast reconstruction. This database was stratified into 2 groups—a high-risk group of 214 patients and a moderate-risk group of 425 patients—based on the extent of breast and ovarian cancers in the patient's family pedigree. The outcome in the high-risk group was compared with that in 403 female siblings who had not undergone prophylactic surgery. The predicted outcome in the moderate-risk group was quantified by summing individual estimates derived from Gail Model calculations [18]. At a median follow-up of 14 years, only 7 cancers developed (1.1 %): 3 in the high-risk group (1.4 %), and 4 in the moderate-risk group (1.0 %). This represented an approximately 90 % reduction in breast cancer risk for both groups as 156 cancers developed in the female siblings of patients in the high-risk group and 37.4 cancers would have been expected in the moderate-risk group. Interestingly, despite that fact that most of the mastectomies were performed using the subcutaneous technique, only 1 of the subsequent cancers was detected within the nipple-areolar complex, and only 1 additional failure was described as occurring "above areola." This innovative approach to evaluating a prophylactic mastectomy database supports the efficacy of the procedure in selected, high-risk women.

Hartmann et al. subsequently proceeded on to perform BRCA mutation testing in a subset of 176 of the highest-risk patients. Twenty-six mutation carriers (18 known deleterious mutations) were identified, and with 13.4 years median follow-up the prophylactic mastectomy was associated with an approximately 90 % risk reduction.

Effectiveness of BPM in BRCA mutation carriers has also been reported in other retrospective analyses involving

Table 2 Selected studies reporting results and risk-reducing benefits of prophylactic mastectomy (PM), including bilateral prophylactic mastectomy (BPM) as well as unilateral/contralateral prophylactic surgery in patients with unilateral breast cancer. Studies with *asterisk* include data on outcomes following contralateral prophylactic mastectomy (CPM)

Study	Type of study	Average follow-up	Pathology findings in prophylactic mastectomy specimens	Results/outcomes
Schrag, 1997 [24]	Decision-analysis; Markov model	N/A	N/A	Estimated gain in longevity for BRCA 1/2 mutation carrier undergoing BPM by age at surgery: 30-y-old: 2.9–5.3 y gained 60-y-old: no significant gain
Hartmann, 1999 [17]	Retrospective analysis: 639 BPM patients (214 high risk; 425 moderate risk)	14 y	Atypia identified in 1.5 % of cases; invasive cancer in 0.1 % of cases	BPM reduced breast cancer incidence by 90 %–94 % for high risk group (by comparison with breast cancer incidence in female siblings) and by 90 % for the moderate risk group (by comparison with breast cancer projections via Gail Model estimates)
Grann, 2000 [26]	Decision-analysis; Markov model	N/A	N/A	Estimated gain in longevity for 30 y old BRCA 1/2 mutation carrier undergoing BPM vs bilateral oophorectomy (BO) vs both vs chemoprevention: BO: 0.4–1.2 y gained BPM: 2.7–3.4 y gained BO and BPM: 3.6–4.6 y gained Chemoprevention: 0.4–1.2 y gained
*Schrag, 2000 [48]	Decision-analysis; Markov model	N/A	N/A	Estimated gain in longevity for 30-y-old BRCA 1/2 mutation carrier with early-stage breast cancer undergoing CPM: 0.6–2.1 y
*Peralta, 2000 [94]	Case-control study of 246 unilateral breast cancer cases: 64 undergoing CPM vs 182 undergoing unilateral mastectomy (noCPM)	6.8 y	Three cancers identified in CPM specimens (4.7 %)	CPM improved outcomes: 15 y DFS 55 % for CPM group vs 28 % in noCPM group (P=0.01); 15 y OS 64 % for CPM group vs 48 % noCPM group (P=0.25)
Meijers-Heijboer, 2001 [19]	Cohort study: 139 BRCA mutation carriers, 76 undergoing BPM	2.9 y	LCIS identified in one case	No primary breast cancers detected in BPM group vs 8 in the 63 noBPM group (12.7 %)
*McDonnell, 2001 [95]	Cohort study: 745 CPM patients	10 y	Invasive/in situ cancer identified in 0.5 %; atypia identified in 2.6 %	Compared with risk prediction estimates, CPM reduced breast cancer incidence by 94 % in premenopausal women and by 96 % in postmenopausal women
Hartmann, 2001 [96]	Retrospective analysis: Subset of 26 BRCA mutation carriers from prior BPM study [17]	13.4 y	N/A	Compared with risk prediction estimates, BPM reduced breast cancer incidence by 90 %
Van Roosmalen, 2002 [97]	Decision-analysis; Markov model	N/A	N/A	Estimated gain in longevity for 30-y-old BRCA 1 mutation carrier undergoing BPM vs BO vs both: BPM: 4.4–4.9 y gained BO: 5.3–9.5 y gained BO and PM: 6.6–11.7 y gained
Rebbeck, 2004 [20]	Case-control: 105 BRCA mutation carriers undergoing bilateral BPM; 378 BRCA mutation carriers not undergoing BPM	6.4 y	N/A	90 %–95 % reduction in breast cancer risk associated with BPM

Table 2 (continued)

Study	Type of study	Average follow-up	Pathology findings in prophylactic mastectomy specimens	Results/outcomes
*Herrinton, 2005 [51]	Retrospective analysis: 56,400 unilateral breast cancer patients, including 1,072 CPM cases (1.9 %)	5.7 y	N/A	CPM associated with improved outcomes: hazard ratios for contralateral breast cancer 0.03 (95 % CI 0.006–0.13); all-cause mortality 0.60 (0.50–0.72)
*Van Sprundel, 2005 [52]	Retrospective analysis: 148 BRCA mutation carriers with unilateral breast cancer; 79 undergoing CPM	3.5 y	N/A	CPM associated with 91 % reduction in breast cancer incidence; OS 94 % for CPM patients compared to 77 % noCPM group (P=0.03); survival advantage eliminated in multivariate analysis
Heemskerk-Gerritsen, 2007 [21]	Retrospective analysis: 358 high-risk women (66 % BRCA mutation carriers) undergoing PM; 177 BPM and 181 CPM	4.5 y	Invasive/in situ cancer identified in 10 cases (2.8 %)	No new primary breast cancers identified following PM
*Bedrosian, 2010 [53•]	SEER population-based study: 107,106 unilateral mastectomy patients vs 8,902 patients undergoing CPM	47 mo	N/A	CPM associated with improved disease-specific survival (mortality hazard ratio 0.63; 95 % CI 0.57–0.69; P<0.001)
*Boughey, 2010 [54]	Case–control: 770 unilateral breast cancer patients undergoing mastectomy (385 undergoing unilateral surgery compared to 385 undergoing CPM)	17.3 y	N/A	CPM associated with improved outcomes: Contralateral breast cancer detected in 2 CPM group vs 31 noCPM group (0.5 % vs 8.1 %; hazard ratio 0.05; P<0.0001). 10-y OS 83 % for CPM group vs 74 % for noCPM group (hazard ratio 0.77; P=0.03)
*Kaas, 2010 [22]	Retrospective analysis: 254 BRCA mutation carriers (147 undergoing BPM; 107 undergoing CPM)	3.7-6.1 y	Invasive cancer in one case (0.3 %); DCIS identified in 11 cases (4.3 %)	One invasive breast cancer detected 2 y following a CPM case (0.7 %); Breast cancer incidence following PM in BRCA mutation carriers estimated to be less than 0.2 % per woman-y
Arver, 2011 [23]	Retrospective analysis: 223 high-risk women (58 % BRCA mutation carriers) undergoing BPM	6.6 y	Invasive/DCIS in 8 cases (3.6 %); atypia/LCIS in 14 cases (6.3 %)	No new primary breast cancers identified following BPM, compared with 12 cases predicted to occur by risk assessment model
*Narod, 2011 [49]	Statistical model of outcome projections	N/A	N/A	CPM likely to prevent death from contralateral breast cancers that are estimated to occur in 0.4 % of breast cancer patients within 5 y, and 6.8 % deaths that are projected to occur within 20 y
*Zendejas, 2011 [50]	Decision-analysis; Markov model	N/A	N/A	CPM is cost-effective compared with surveillance for unilateral breast cancer patients younger than age 70 y; mean treatment costs for unilateral breast cancer patient diagnosed at age 45 y: $36,594 for CPM vs $35,182 for surveillance
*Brewster, 2012 [55]	Retrospective analysis: 3,889 invasive breast cancer patients (532 CPM cases; 3,357 noCPM)	4.5 y	N/A	CPM associated with improved outcomes: DFS hazard rate 0.75 (95 % CI 0.59–0.97) OS hazard rate 0.74 (95 % CI 0.56–0.99) Results strongest for patients with hormone receptor-negative breast cancer

BPM bilateral prophylactic mastectomy, CI confidence interval, CPM contralateral prophylactic mastectomy, DCIS ductal carcinoma in situ, DFS disease free survival, LCIS lobular carcinoma in situ, N/A not applicable and/or data not available, OS overall survival, PM prophylactic mastectomy, SEER Surveillance, Epidemiology, and End Results Program

patients from Europe as well the United States. Studies by Meijers-Heijboer et al. [19], Rebbeck et al. [20], Heemskerk-Gerritsen et al. [21], Kaas et al. [22], and Arver et al. [23•] collectively evaluated more than 1000 BRCA mutation carriers and with median follow-ups ranging from 2.9 to 6.6 years, those who underwent BPM had more than 90 % fewer breast cancers compared with the carriers that did not undergo the prophylactic surgery.

Markov decision-analysis models have been created by several investigators as a strategy for quantifying benefits of prophylactic mastectomy. These models are based upon projections for developing breast cancer as a consequence of BRCA mutation carrier status, likelihood of successful breast cancer treatment, and longevity estimates. These statistics are then balanced against longevity estimates given a reduced likelihood of being diagnosed with breast cancer by undergoing prophylactic mastectomy.

Schrag et al. [24] constructed one of the first decision analysis models to quantify the impact that prophylactic mastectomy is likely to have on the life span of a hypothetical woman with a *BRCA* mutation. Their calculations were based on 2 sets of assumptions. In one model, it was assumed that the presence of a *BRCA* mutation was associated with a 40 % risk of breast cancer by the age of 70 years; in the other model, the *BRCA*-mutation-associated cancer risk was 85 %. In both sets of calculations, prophylactic mastectomy was estimated to decrease breast cancer risk by 85 %. Based on this model, it was determined that an adult female *BRCA* mutation carrier undergoing prophylactic mastectomy at the age of 30 years could expect to gain 2.9 to 5.3 years of life. In contrast, if a 60-year-old *BRCA* mutation carrier underwent prophylactic mastectomy, the increase in life span would be negligible. This finding is plausible because it is likely that several factors interact with *BRCA* mutations to determine an individual's actual risk of breast cancer. The *BRCA* mutation carrier who survives to age 60 without developing a breast cancer has therefore proved to be at relatively lower risk. Additionally, by this age she is facing multiple competing causes of mortality.

In another statistical model formulated by Grann et al. [25], economic cost and quality-of-life factors were integrated with the longevity impact of prophylactic mastectomy and/or prophylactic oophorectomy in a 30-year-old BRCA mutation carrier. The overall survival effect of prophylactic mastectomy in conjunction with prophylactic oophorectomy was a gain of 3.3 to 6.0 years; for prophylactic mastectomy alone the survival benefit was 2.8 to 3.4 years. Costs associated with the surgery were based on data from the Health Care Financing Administration, and quality-of-life factors were based on surveys of 54 patients regarding the number of years of life they would trade to survive in different disease-free, disease-associated, and postoperative conditions. In this comprehensive model, combined prophylactic oophorectomy and mastectomy resulted in 1.9 quality-adjusted life years saved and was cost-effective for overall survival but not for quality-adjusted life years of survival. A follow-up decision-analysis model constructed by Grann et al. [26] accounted for the comparative risks and benefits of chemoprevention as well, and continued to find the largest-magnitude longevity gain for the combination of prophylactic oophorectomy and BPM (3.6 4.6 years gained).

A personal history of breast cancer is a well-established risk factor for development of a new primary breast neoplasm, with an incidence range of 0.5 %–1.0 % per year; this risk can be halved with adjuvant endocrine therapy, and it is 4-to-5-fold higher in patients with hereditary susceptibility [27–31]. Whether patients undergoing mastectomy for a unilateral breast cancer should routinely consider a risk-reducing CPM remains an unresolved issue. Several population-based as well as single-institution reports (as summarized in Table 3) have recently documented increasing rates of CPM in the United States and this pattern has prompted provocative questions regarding the appropriateness and cost efficiency of patients undergoing the more extensive surgery. Clinicopathologic features shown to be associated with likelihood of selecting CPM include young age at breast cancer diagnosis, lobular histology, family history, preoperative breast magnetic resonance imaging (MRI), White American background, and higher education. Interestingly, one study from Switzerland [32] suggests that the pattern of increasing CPM rates is specific to the United States compared with Europe.

CPM does have several potential benefits. For patients who undergo mastectomy with immediate breast reconstruction, improved symmetry may be achieved if the reconstruction modeling is performed bilaterally. It should also be noted that if a patient with unilateral disease undergoes a mastectomy with transabdominal myocutaneous (TRAM) flap reconstruction and then develops a contralateral metachronous lesion, she cannot undergo another TRAM flap reconstruction (although alternative sources of autogenous tissue reconstruction would be available, such as the latissimus dorsi flap). However, TRAM flap reconstruction can be used for bilateral mastectomy reconstruction if both breasts are reconstructed synchronously [33].

CPM can also be advantageous in the setting of a cancer patient with large, pendulous breasts undergoing mastectomy without reconstruction for a unilateral breast cancer. In this setting, a unilateral mastectomy can leave the patient with symptomatic discomfort from chest wall imbalance and achieving symmetry with a matched size and contour prosthesis can be both difficult and uncomfortable.

In addition to the reconstruction factors, the potential psychological benefits of avoiding a second breast cancer detection and treatment experience may also be worthwhile.

Table 3 Selected studies reporting on utilization patterns of contralateral prophylactic mastectomy in patients with unilateral breast cancer

Study	Source	Results
Tuttle, 2007 [98]	Surveillance, Epidemiology, and End Results Program database of 152,755 patients with invasive breast cancer, 1998–2003	CPM utilization increased from 1.8 % in 1998 to 4.5 % in 2003. Young age, lobular histology, and non-Hispanic white race were associated with CPM choice.
Tuttle, 2009 [99]	Surveillance, Epidemiology, and End Results Program database of 51,030 patients with DCIS, 1998–2005	CPM utilization increased from 2.1 % in 1998 to 5.2 % in 2005. Young age, white race, and lobular carcinoma in situ were associated with CPM choice.
Sorbero et al., 2009 [100]	Magee-Womens Hospital of the University of Pittsburgh Medical Center tumor registry of 3,606 patients with stage 0–III breast cancer, 1998–2000 and 2003–2005	Breast MRI use increased from 4.1 % to 23.7 % between early to recent study intervals; women undergoing breast MRI were nearly twice as likely to undergo CPM (9.2 % vs 4.7 %; $P<.001$)
Jones et al., 2009 [101]	James Cancer Hospital, Ohio State University, 1840 patients undergoing mastectomy for unilateral breast cancer, 1998–2007	CPM utilization increased from 6.5 % in 1999 to 16.1 % in 2007. Young age, higher education, and family history were associated with CPM choice.
Yao et al., 2010 [102•]	National Cancer Data Base: 1,166,456 patients with unilateral stage 0–III breast cancer, 1998–2007	CPM utilization increased from 0.4 % in 1998 to 4.7 % in 2007. Age <40 y, white race, high socioeconomic status, and private or managed care insurance were associated with CPM choice.
Stucky et al., 2010 [103]	Mayo Clinic Arizona database: 1,391 invasive breast cancer patients, 2000–2008	CPM utilization increased from 0 in 2000 to 20 % in 2008. Young age, family history, BRCA mutation status, and preoperative breast MRI associated with CPM choice.
Guth et al., 2012 [32]	University of Basel Breast Center, Switzerland: 881 invasive breast cancer patients 1995–2009	CPM utilization 7 % among mastectomy cases; no significant variation in CPM rates over study time interval. Young age, family history, and lobular histology were associated with CPM choice.
Cemal et al., 2013 [104]	Nationwide Inpatient Sample Database, n=178,603 mastectomy cases, 1998–2008	Unilateral mastectomies decreased by 2 % per y; CPM increased by 15 % per y; and BPM increased by 12 % per y.

CPM contralateral prophylactic mastectomy, DCIS ductal carcinoma in situ, MRI magnetic resonance imaging

Each patient must carefully weigh the pros and cons of CPM and make her own personal decision.

Disadvantages of CPM include the more prolonged duration of surgery. For many patients, symmetry can be optimized with lesser procedures, such as reduction mammoplasty. Common misperceptions that must be dispelled in patients considering CPM include the following: patients must understand that CPM will not affect recommendations regarding adjuvant chemotherapy for the known unilateral breast cancer; patients must understand that the CPM does not confer 100 % protection against a new primary breast cancer; CPM does not affect risk of local recurrence from the known unilateral breast cancer; and reducing risk of a second primary breast cancer does not necessarily translate into a survival advantage.

The inability of contralateral prophylactic mastectomy to favorably impact survival duration is based on data indicating that bilateral breast cancer does not necessarily result in a worse outcome compared with unilateral breast cancer. Historically, most reported series have demonstrated that the survival rates from breast cancer are generally driven by the stage and treatment of the first cancer that is diagnosed [34–42]. This finding is biologically plausible because the first cancer will have lead time advantage for establishing for micrometastatic disease, and it might be surmised that the initially presenting cancer is associated with the faster-growing pathology. Furthermore, patients with one breast cancer are likely to be observed more closely so that a second tumor will be detected at an early stage, likely to be effectively controlled, and often treatable with breast-preserving surgery. In the series reported by Robinson et al. [37] patients with bilateral locally advanced breast cancer did have a significantly worse survival than that of patients with unilateral breast cancer, which was probably related to their having an excessive total body tumor burden.

The University of Texas M. D. Anderson Cancer Center experience with 155 unilateral breast cancer patients undergoing contralateral prophylactic mastectomy was reviewed by Gershenwald et al. [43]. In this series, features that appeared to motivate the patients' surgical choice were the following: family history of breast cancer (first degree relative in 30 %, any family history in 56 %), difficulties with surveillance (48 %), associated lobular carcinoma in situ (23 %), multicentric primary breast cancer (28 %), and a mammographically occult cancer (28 %). The contralateral surgical specimens were found to be completely benign in 80 % of the cases; however, ductal carcinoma in situ was found in 2.7 %, invasive cancer was found in 1.3 %, atypical

hyperplasia was found in 12.0 %, and lobular carcinoma in situ was found in 6.5 %. Similarly, as shown in Table 2, outcome studies reporting the pathology findings in CPM specimens have generally reported low frequencies (less than 5 % of cases) of occult synchronous invasive cancers and/or ductal carcinoma in situ. King et al. [44] conducted a rigorous pathology review of nearly 500 CPM cases from the Memorial Sloan Kettering Cancer Center, and identified occult cancer in 6 % of cases; multifocality/multicentricity of the index cancer were predictive for the presence of occult contralateral breast cancer.

One logical approach to the dilemma of when to offer CPM would be to identify a subset of patients who are at particularly high risk for bilateral disease. Clinical features such as family history [27], young age at initial cancer diagnosis [37, 38, 45], and a history of radiation therapy [8, 9] as well as pathologic features such as lobular carcinoma in situ [38], invasive lobular cancer [33, 45], and multicentric cancer [44, 46, 47] have been reported to suggest an increased risk of bilateral breast cancer. One case–control study of 70 unilateral vs bilateral breast cancer performed using a central, standardized pathology review at M. D. Anderson Cancer Center [47] found 2 features to be predictive of bilateral disease: family history positive for breast cancer and multicentric tumors. These findings suggest that there is a subset of patients that may have a bilateral chest wall "field effect" of proliferative breast changes.

Schrag et al. [48] constructed an additional Markov decision-analysis model to estimate a possible survival benefit from CPM in patient with a unilateral BRCA mutation-associated breast cancer at age 30 years. Using this mathematical model, contralateral prophylactic mastectomy results in a 0.6 2.1 years gain in life expectancy. Similarly, Narod [49] and Zendejas et al. [50] have developed mathematical models demonstrating that CPM should be associated with a survival benefit and that it is also cost-effective.

Interestingly, recent retrospective studies of CPM are now suggesting that the risk-reducing benefits of prophylactic mastectomy in patients with unilateral disease are indeed associated with a longevity advantage. These data are shown in Table 2. Herrinton et al. [51], VanSprundel et al. [52], Bedrosian et al. [53•], Boughey et al. [54], and Brewster et al. [55] all identified patterns of improved survival in patients undergoing CPM. The Herrinton study [51] evaluated more than 57,000 breast cancer patients (1.9 % undergoing CPM) from the Cancer Research Network; the Bedrosian study [53] was a population-based Surveillance, Epidemiology, and End Results Program analysis; the Boughey et al. [54] study was an age- and stage-matched case–control analysis, and the Brewster et al. [55] study was a retrospective analysis of nearly 4000 breast cancer patients from the University of Texas M.D. Anderson Cancer Center.

The more recent data suggesting a survival advantage associated with CPM, which is in contrast to historic studies indicating similar survival rates for patients with unilateral vs metachronous bilateral breast cancer may be related to improved systemic therapies that are available for contemporary breast cancer patients. Patients whose micrometastatic disease from the first cancer is completely eliminated by effective systemic therapy will potentially face more of a life-threatening risk from a second cancer. Reducing likelihood of experiencing that second cancer may then provide a survival advantage. Further prospectively acquired data is needed, however, before patients can be counseled that CPM is routinely indicated. At this point in time, patients should continue to have a balanced discussion with their surgeon regarding the facts that the CPM specimen is unlikely to harbor an occult malignancy at the time of initial cancer diagnosis, and that any potential survival advantage of CPM is undefined, and that careful monitoring of the contralateral breast is a reasonable and appropriate alternative to CPM.

Patients electing to undergo prophylactic mastectomy must understand the persistent, long-term potential for future breast cancer development. The conventional prophylactic mastectomy procedure includes sacrifice of the nipple areolar skin. Numerous case reports document that primary breast cancer can be diagnosed up to several decades following prophylactic mastectomy [15, 56–59]. Historically, many patients undergoing prophylactic mastectomy underwent subcutaneous procedures with preservation of the nipple-areolar complex and interestingly, only rarely did the failed prevention surgery result in a new primary detected in the spared nipple-areolar complex [17]. This suggests that although the nipple areolar skin is indeed at higher risk for harboring microscopic foci of breast tissue compared with the more peripheral breast skin, the effectiveness of prophylactic mastectomy is still related to extent of any residual at-risk breast tissue left behind in the skin flaps, and in the axillae. Furthermore, the more limited exposure of the nipple-sparing incision can potentially compromise adequate resection of breast tissue in the peripheral portions of the chest wall. More recent series of nipple-sparing mastectomy have involved more rigorous attention to technical details of the surgery including choice of incision site [60–66]. These contemporary studies continue to demonstrate that the entire breast skin envelope must be monitored for any signs of prophylactic surgery failure. Patients opting for nipple-areolar preservation must understand that although recent data (Table 4) are promising [66–75]; this surgical technique has the potential for negating the risk-reducing benefits by some as-yet undefined degree. Other concerns are that the nipple-areolar skin will

Table 4 Selected studies of nipple-sparing mastectomy and outcomes; locoregional recurrences reported for cases of nipple-sparing mastectomy in cancerous breasts

Study	Sample size of nipple-sparing mastectomies (number prophylactic mastectomies)	Average (mean or median) follow-up	Number of locoregional recurrences	Nipple-areolar Outcome	
				Proportion with partial/any nipple-areolar necrosis	Proportion with total nipple-areolar necrosis
Caruso et al., 2006 [105]	50 (0)	5.5 y	1	NR	0.5 %
Sacchini et al., 2006 [106]	192 (97)	24.6 mo	2	11 %	NR
Benediktsson et al., 2008 [107][a]	216 (0)	13 y	52	NR	NR
Wijayanayagam et al., 2008 [108]	64 (29)	NR	NR	10 %	5 %
Sookhan et al., 2008 [109]	18 (8)	10.8 mo	0	2	0
Voltura et al., 2008 [110]	51 (24)	18 mo	2	NR	NR
Crowe et al., 2008 [72]	149 (40)	41 mo	2	2 %	1 %
Petit et al., 2009 [69][a]	579 (0)	19 mo	14	NR	NR
Sakamoto et al., 2009 [111]	89 (0)	52 mo	0	18 %	10 %
Paepke et al., 2009 [112]	109 (15)	34 mo	1	NR	1 %
Garcia-Etienne et al., 2009 [75]	42 (34)	10.5 mo	0	48 %	NR
Gerber et al., 2009 [67]	60 (0)	101 mo	7	NR	NR
Petit et al., 2009 [113] [b]	1,001 (0)	20 mo	14	5.5 %	3.5 %
Chen et al., 2009 [114]	115 (75)	22 mo	NR	13 %	3.5 %
Sakamato et al., 2010 [115]	89 (0)	52 mo	0	7.9 %	10 %
Babiera et al., 2010 [116]	54 (NR)	15 mo	0	7.2 %	NR
Kim et al., 2010 [117]	152 (0)	60 mo	3	13 %	9.6 %
Filho et al., 2011 [118]	353 (196)	10.4 mo	0	0.2 %	0 %
Jensen et al., 2011 [119]	149 (50)	60.2 mo	3	6 %	NR
Harness et al., 2011 [120]	43 (20)	18.5 mo	1	10 %	5 %
Bonetti et al., 2011 [121]	281 (NR)	25.3 mo	7	4.6 %	0.1 %
Spear et al., 2011 [122]	162 (113)	30 mo (cancer cases); 43 mo (prophylactic cases)	0	7 %	NR
Shi et al., 2012 [123]	35 (0)	68 mo	2	11 %	NR
Moyer et al., 2012 [124]	40 (16)	NR	NR	37.5 %	11.5 %
Peled et al., 2012 [125]	657 (245)	28 mo	8	2 %	1.5 %
Lohsiriwat et al., 2012 [126] [a]	861 (0)	50 mo	36 [c]	NR	NR
Wagner et al., 2012 [127]	54 (37)	NR	NR	29.6 %	7.4 %
Sakurai et al., 2013 [128]	788 (0)	78 mo	65	0	0

NR not reported

[a] Nipple-sparing mastectomy and adjuvant radiation therapy in 46 cases

[b] Nipple-sparing mastectomy and nipple-areolar intraoperative radiotherapy in all cases

[c] Including 7 cases of Paget's disease

be largely insensate, and there is an approximately 5 %–25 % risk of partial-to-complete necrosis.

Every effort should be made to ensure that patients considering prophylactic mastectomy are psychologically fit to tolerate the surgery. Even with optimal reconstruction results, this is a body-altering procedure that can negatively impact psychosocial well-being, sexual function, and quality of life [76–78]. Interestingly, there is also a case report of a patient with Munchausen's syndrome who sought bilateral prophylactic mastectomy based on a fabricated high-risk family history [79].

In selecting patients for prophylactic mastectomy, it is also important to educate patients preoperatively regarding alternative risk-reduction strategies and realistic expectations for surgical outcome. Montgomery et al. [80] reported on issues of regret in 296 women surveyed from the National Prophylactic Mastectomy Registry and found that although the incidence of regret was low (6 %), it was more common in women who were dissatisfied with their cosmetic result as well as those who felt misinformed about their options preoperatively. In addition, Stefanek et al. [81] found that women who had undergone several prior breast

biopsies were more likely to be satisfied with prophylactic mastectomy. Somewhat surprisingly, women who test positive for *BRCA* mutations are not necessarily enthusiastic about prophylactic mastectomy; in a series of *BRCA* mutation carriers surveyed by Lynch et al. [82, 83], only 35 %–52 % of respondents sought prophylactic mastectomy. Studies published within the past 10 years by Gahm et al. [78, 84], Gopie et al. [85], Frost et al. [86–88], Geiger et al. [89, 90], Graves et al. [91], Tercyak et al. [92], and Isern et al. [93] consistently report high levels of patient satisfaction and low rates of regret among women opting to undergo BPM or CPM, even among patients reporting symptoms of chronic discomfort at surgical sites.

By definition, prophylactic surgery is not an emergency. Patients considering BPM should be encouraged to seek genetic counseling when appropriate, and many patients will benefit from preoperative psychosocial counseling as well. BPM and CPM patient should thoroughly explore every option regarding the variety of reconstruction techniques and risk reduction alternatives.

Conclusion

Prophylactic mastectomy reduces breast cancer risk by 90 %–95 %. Since most breast cancers are successfully treated with contemporary therapy, it is more difficult to define a survival advantage associated with the avoidance of a breast cancer diagnosis. The Society of Surgical Oncology has developed a position statement [2] that lists conditions warranting consideration of prophylactic mastectomy for bilateral risk reduction as well as contralateral risk reduction in the setting of a biopsy-proven unilateral breast cancer. These features include family or personal history suggestive of hereditary breast cancer susceptibility; pathologic indices of increased proliferative activity and future breast cancer risk (eg, atypical hyperplasia and/or lobular carcinoma in situ), and breasts that are inherently difficult to monitor for cancer because of diffuse density or fibrocystic nodularity. These characteristics, coupled with the feature of predisposition for radiation-induced breast cancer related to prior therapeutic chest wall irradiation (as noted by the National Comprehensive Cancer Network [5]) comprise a rational framework for identifying patients that might reasonably pursue risk-reducing breast surgery, and they are summarized in Table 1. BPM is most commonly sought by patients with evidence of hereditary predisposition. CPM may be additionally motivated by reconstruction and/or symmetry advantages. CPM rates have been increasing in the United States over the past 2 decades, at least partially motivated by increasing utilization rates of preoperative breast MRI. It must be stressed that there are no absolute indications for prophylactic mastectomy. Patients interested in pursuing prophylactic surgery must understand that the surgery is risk-reducing, but does not confer 100 % protection against future breast cancer development. Candidates for this surgery should review the available breast reconstruction options, and they should be fully informed regarding alternative risk-reducing and early detection strategies, such as chemoprevention, and/or aggressive breast cancer surveillance.

Conflict of Interest Lisa A. Newman declares that she has no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Breast Cancer Facts & Figures 2011–2012. Atlanta, GA: American Cancer Society, Inc; 2012.
2. Giuliano AE et al. Society of Surgical Oncology: position statement on prophylactic mastectomy. Approved by the Society of Surgical Oncology Executive Council, March 2007. Ann Surg Oncol. 2007;14:2425–7.
3. Newman LA et al. Educational review: role of the surgeon in hereditary breast cancer. Ann Surg Oncol. 2001;8:368–78.
4. Newman LA. Surgical management of high-risk breast lesions. Problems in general surgery, benign breast disease. Vol. 20. Philadelphia PA: Lippincott, Williams, Inc; 2003. p. 99–112.
5. National Comprehensive Cancer Network Breast Cancer Risk Reduction, in NCCN Clinical Practice Guidelines in Oncology. 2012.
6. Basu SK et al. Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease. Int J Radiat Oncol Biol Phys. 2008;72:34–40.
7. Deniz K et al. Breast cancer in women after treatment for Hodgkin's disease. Lancet Oncol. 2003;4:207–14.
8. Anderson N, Lokich J. Bilateral breast cancer after cured Hodgkin's disease. Cancer. 1990;65:221–3.
9. Cutuli B et al. Breast cancer in patients treated for Hodgkin's disease: clinical and pathological analysis of 76 cases in 63 patients. Eur J Cancer. 1997;33:2315–20.
10. Cutuli B et al. Breast cancer occurred after treatment for Hodgkin's disease: analysis of 133 cases. Radiother Oncol. 2001;59:247–55.
11. Newman LA et al. Prophylactic mastectomy. J Am Coll Surg. 2000;191:322–30.
12. Wong JH et al. Analysis of the risk reduction of prophylactic partial mastectomy in Sprague–Dawley rats with 7,12-dimethylbenzanthracene-induced breast cancer. Surgery. 1986;99:67–71.
13. Nelson H et al. Effectiveness of prophylactic mastectomy in the prevention of breast tumors in C3H mice. Plast Reconstr Surg. 1989;83:662–9.
14. Pennisi VR, Capozzi A. Subcutaneous mastectomy data: a final statistical analysis of 1500 patients. Aesthetic Plast Surg. 1989;13:15–21.
15. Ziegler LD, Kroll SS. Primary breast cancer after prophylactic mastectomy. Am J Clin Oncol. 1991;14:451–4.
16. Woods JE, Meland NB. Conservative management in full-thickness nipple-areolar necrosis after subcutaneous mastectomy. Plast Reconstr Surg. 1989;84:258–64. discussion 265–6.

17. Hartmann LC et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340:77–84.
18. Gail MH et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81:1879–86.
19. Meijers-Heijboer H et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345:159–64.
20. Rebbeck T 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.
21. Heemskerk-Gerritsen BA 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 Clinic. Ann Surg Oncol. 2007;14:3335–44.
22. Kaas R et al. Prophylactic mastectomy in BRCA1 and BRCA2 mutation carriers: very low risk for subsequent breast cancer. Ann Surg. 2010;251:488–92.
23. • Arver B et al. Bilateral prophylactic mastectomy in Swedish women at high risk of breast cancer: a national survey. Ann Surg. 2011;253:1147–54. *This retrospective analysis of bilateral prophylactic mastectomy* (*BPM*) *in 223 high-risk Swedish women* (*58% carriers of BRCA mutations*) *followed cases for 6.6 years*, *with no primary breast cancers detected*. *In comparison*, *risk assessment models projected that twelve cancers would have been diagnosed in the absence of the risk-reducing surgery.*
24. Schrag D et al. Decision analysis effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med. 1997;336:1465–71.
25. Grann V et al. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. J Clin Oncol. 1998;16:979–85.
26. Grann V et al. Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2-positive women: a decision analysis. Cancer J Sci Am. 2000;6:13–20.
27. Rosen PP et al. Contralateral breast carcinoma: an assessment of risk and prognosis in stage I (T1N0M0) and stage II (T1N1M0) patients with 20-year follow-up. Surgery. 1989;106:904–10.
28. Metcalfe K et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2004;22:2328–35.
29. Pierce LJ et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol. 2006;24:2437–43.
30. Verhoo LC et al. Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer. Br J Cancer. 2000;83:384–6.
31. Frank TS et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol. 1998;16:2417–25.
32. Guth U et al. Increasing rates of contralateral prophylactic mastectomy a trend made in USA? Eur J Surg Oncol. 2012;38:296–301.
33. Kroll SS et al. Rationale for elective contralateral mastectomy with immediate bilateral reconstruction. Ann Surg Oncol. 1994;1:457–61.
34. Bloom ND et al. Bilateral mammary carcinoma; immunologic implications. N Y State J Med. 1980;80:908–10.
35. Rutqvist LE et al. Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy. J Natl Cancer Inst. 1991;83:1299–306.
36. Graham MD et al. Bilateral carcinoma of the breast. Eur J Surg Oncol. 1993;19:259–64.
37. Robinson E et al. Survival of first and second primary breast cancer. Cancer. 1993;71:172–6.
38. Healey EA et al. Contralateral breast cancer: clinical characteristics and impact on prognosis. J Clin Oncol. 1993;11:1545–52.
39. Singletary SE et al. Occurrence and prognosis of contralateral carcinoma of the breast. J Am Coll Surg. 1994;178:390–6.
40. Lee JS et al. Arguments against routine contralateral mastectomy or undirected biopsy for invasive lobular breast cancer. Surgery. 1995;118:640–7. discussion 647–8.
41. Mose S et al. Bilateral breast carcinoma versus unilateral disease. Review of 498 patients. Am J Clin Oncol. 1997;20:541–5.
42. Gajalakshmi CK, Shanta V, Hakama M. Survival from contralateral breast cancer. Breast Cancer Res Treat. 1999;58:115–22.
43. Gershenwald JE et al. Synchronous elective contralateral mastectomy and immediate bilateral breast reconstruction in women with early-stage breast cancer. Ann Surg Oncol. 1998;5:529–38.
44. King TA et al. Occult malignancy in patients undergoing contralateral prophylactic mastectomy. Ann Surg. 2011;254:2–7.
45. Broet P et al. Contralateral breast cancer: annual incidence and risk parameters. J Clin Oncol. 1995;13:1578–83.
46. Lesser ML, Rosen PP, Kinne DW. Multicentricity and bilaterality in invasive breast carcinoma. Surgery. 1982;91:234–40.
47. Newman LA et al. A case–control study of unilateral and bilateral breast carcinoma patients. Cancer. 2001;91:1845–53.
48. Schrag D et al. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. JAMA. 2000;283:617–24.
49. Narod SA. The impact of contralateral mastectomy on mortality in BRCA1 and BRCA2 mutation carriers with breast cancer. Breast Cancer Res Treat. 2011;128:581–3.
50. Zendejas B et al. Cost-effectiveness of contralateral prophylactic mastectomy versus routine surveillance in patients with unilateral breast cancer. J Clin Oncol. 2011;29:2993–3000.
51. Herrinton LJ et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol. 2005;23:4275–86.
52. van Sprundel TC 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.
53. • 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. *This Surveillance*, *Epidemiology and End Results based study compared the survival of more than 100*,*000 unilateral breast cancer patients to that of nearly nine thousand patients undergoing contralateral prophylactic mastectomy* (*CPM*) *between the years 1998 and 2003*. *Disease-specific survival was better in the CPM group* (*mortality hazard 0.63*, *95% confidence interval 0.57 0.69*).
54. Boughey JC 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.
55. Brewster AM et al. Association between contralateral prophylactic mastectomy and breast cancer outcomes by hormone receptor status. Cancer. 2012;118:5637–43.
56. Eldar S, Meguid MM, Beatty JD. Cancer of the breast after prophylactic subcutaneous mastectomy. Am J Surg. 1984;148:692–3.
57. Jameson MB et al. Metastatic breast cancer 42 years after bilateral subcutaneous mastectomies. Clin Oncol (R Coll Radiol). 1997;9:119–21.
58. Holleb AI, Montgomery R, Farrow JH. The hazard of incomplete simple mastectomy. Surg Gynecol Obstet. 1965;121:819–22.
59. Willemsen HW et al. Breast carcinoma in residual breast tissue after prophylactic bilateral subcutaneous mastectomy. Eur J Surg Oncol. 1998;24:331–2.
60. Tanna N et al. Microsurgical breast reconstruction for nipple-sparing mastectomy. Plast Reconstr Surg. 2013;131:139e–47.

61. Serra R et al. Skin-sparing mastectomy with immediate breast and nipple reconstruction: a new technique of nipple reconstruction. Plast Surg Int. 2013;2013:406375.
62. Sahin I et al. One-staged silicone implant breast reconstruction following bilateral nipple-sparing prophylactic mastectomy in patients at high-risk for breast cancer. Aesthetic Plast Surg. 2013;37:303–11.
63. Conde DM, Torresan RZ. Nipple-sparing mastectomy: What is the frontier between oncologic safety and cosmetic outcome? J Plast Reconstr Aesthet Surg. 2013;66(5):734–5.
64. Blechman KM et al. The lateral inframammary fold incision for nipple-sparing mastectomy: outcomes from over 50 immediate implant-based breast reconstructions. Breast J. 2013;19:31–40.
65. Vrekoussis T et al. Bilateral prophylactic skin-reducing nipple-sparing mastectomy with immediate breast reconstruction using only a vascularized dermal-subcutaneous pedicle: technique and possible advantages. Arch Gynecol Obstet. 2013;287:749–53.
66. Murthy V, Chamberlain RS. Nipple-sparing mastectomy in modern breast practice. Clin Anat. 2013;26:56–65.
67. Gerber B et al. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. Ann Surg. 2009;249:461–8.
68. Murthy V, Chamberlain RS. Defining a place for nipple sparing mastectomy in modern breast care: an evidence based review. Breast J. 2012. doi:10.1111/j.1524-4741.2011.01220.x.
69. Petit JY et al. Nipple-sparing mastectomy: risk of nipple-areolar recurrences in a series of 579 cases. Breast Cancer Res Treat. 2009;114:97–101.
70. Psaila A et al. Nipple sparing mastectomy with immediate breast reconstruction: a short term analysis of our experience. J Exp Clin Cancer Res. 2006;25:309–12.
71. Regolo L et al. Nipple sparing mastectomy: an innovative skin incision for an alternative approach. Breast. 2008;17:8–11.
72. Crowe JP et al. Nipple-sparing mastectomy update: one hundred forty-nine procedures and clinical outcomes. Arch Surg. 2008;143:1106–10. discussion 1110.
73. Crowe Jr JP et al. Nipple-sparing mastectomy: technique and results of 54 procedures. Arch Surg. 2004;139:148–50.
74. Garcia-Etienne CA, Borgen PI. Update on the indications for nipple-sparing mastectomy. J Support Oncol. 2006;4:225–30.
75. Garcia-Etienne CA et al. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. Breast J. 2009;15:440–9.
76. Romm S, Hutzler J, Berggren RB. Sexual identity and prophylactic mastectomy. Ann Plast Surg. 1981;7:35–7.
77. Meyer L, Ringberg A. A prospective study of psychiatric and psychosocial sequelae of bilateral subcutaneous mastectomy. Scand J Plast Reconstr Surg. 1986;20:101–7.
78. Gahm J, Wickman M, Brandberg Y. Bilateral prophylactic mastectomy in women with inherited risk of breast cancer prevalence of pain and discomfort, impact on sexuality, quality of life and feelings of regret 2 years after surgery. Breast. 2010;19:462–9.
79. Grenga TE, Dowden RV. Munchausen's syndrome and prophylactic mastectomy. Plast Reconstr Surg. 1987;80:119–20.
80. Montgomery LL et al. Issues of regret in women with contralateral prophylactic mastectomies. Ann Surg Oncol. 1999;6:546–52.
81. Stefanek ME et al. Predictors of and satisfaction with bilateral prophylactic mastectomy. Prev Med. 1995;24:412–9.
82. Lynch HT et al. A descriptive study of BRCA1 testing and reactions to disclosure of test results. Cancer. 1997;79:2219–28.
83. Lynch HT et al. Patient responses to the disclosure of BRCA mutation tests in hereditary breast-ovarian cancer families. Cancer Genet Cytogenet. 2006;165:91–7.
84. Gahm J et al. Patient satisfaction with aesthetic outcome after bilateral prophylactic mastectomy and immediate reconstruction with implants. J Plast Reconstr Aesthet Surg. 2010;63:332–8.
85. Gopie JP, Mureau MA et al. Body image issues after bilateral prophylactic mastectomy with breast reconstruction in healthy women at risk for hereditary breast cancer. Fam Cancer. 2012.
86. Fros MH et al. Contralateral prophylactic mastectomy: long-term consistency of satisfaction and adverse effects and the significance of informed decision-making, quality of life, and personality traits. Ann Surg Oncol. 2011;18:3110–6.
87. Frost MH et al. Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. JAMA. 2000;284:319–24.
88. Frost MH et al. Satisfaction after contralateral prophylactic mastectomy: the significance of mastectomy type, reconstructive complications, and body appearance. J Clin Oncol. 2005;23:7849–56.
89. Geiger AM et al. Quality of life after bilateral prophylactic mastectomy. Ann Surg Oncol. 2007;14:686–94.
90. Geiger AM et al. Contentment with quality of life among breast cancer survivors with and without contralateral prophylactic mastectomy. J Clin Oncol. 2006;24:1350–6.
91. Graves KD et al. Predictors and outcomes of contralateral prophylactic mastectomy among breast cancer survivors. Breast Cancer Res Treat. 2007;104:321–9.
92. Tercyak K et al. Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. J Clin Oncology. 2007;25:285–91.
93. Isern AE et al. Aesthetic outcome, patient satisfaction, and health-related quality of life in women at high risk undergoing prophylactic mastectomy and immediate breast reconstruction. J Plast Reconstr Aesthet Surg. 2008;61:1177–87.
94. Peralta EA et al. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg. 2000;180:439–45.
95. McDonnell SK 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.
96. Hartmann L et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93:1633–7.
97. van Roosmalen M et al. Decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: a more prominent role for oophorectomy. J Clin Oncol. 2002;20:2092–100.
98. Tuttle TM et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25:5203–9.
99. Tuttle TM et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol. 2009;27:1362–7.
100. Sorbero ME et al. Diagnostic breast magnetic resonance imaging and contralateral prophylactic mastectomy. Ann Surg Oncol. 2009;16:1597–605.
101. Jones NB et al. Contralateral prophylactic mastectomy for unilateral breast cancer: an increasing trend at a single institution. Ann Surg Oncol. 2009;16:2691–6.
102. • Yao K et al. Trends in contralateral prophylactic mastectomy for unilateral cancer: a report from the National Cancer Data Base, 1998–2007. Ann Surg Oncol. 2010;17:2554–62. *This National Cancer Data Base study analyzed trends in utilization of CPM between 1998 and 2007 in more than one million breast cancer patients. CPM utilization increased from 0.4% to 4.7% and patients most likely to select this surgical strategy were White American women younger than age 40 years residing in high socioeconomic status communities.*

103. Stucky CC et al. Increase in contralateral prophylactic mastectomy: echoes of a bygone era? Surgical trends for unilateral breast cancer. Ann Surg Oncol. 2010;17 Suppl 3:330–7.
104. Cemal Y et al. A paradigm shift in u.s. Breast reconstruction: part 2. The influence of changing mastectomy patterns on reconstructive rate and method. Plast Reconstr Surg. 2013;131:320e 6e.
105. Caruso F et al. Nipple sparing subcutaneous mastectomy: sixty-six months follow-up. Eur J Surg Oncol. 2006;32:937–40.
106. Sacchini V et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? J Am Coll Surg. 2006;203:704–14.
107. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. Eur J Surg Oncol. 2008;34:143–8.
108. Wijayanayagam A, Kumar AS, Foster RD, Esserman LJ. Optimizing the total skin-sparing mastectomy. Arch Surg. 2008;143:38–45.
109. Sookhan N et al. Nipple-sparing mastectomy initial experience at a tertiary center. Am J Surg. 2008;196:575–7.
110. Voltura AM et al. Nipple-sparing mastectomy: critical assessment of 51 procedures and implications for selection criteria. Ann Surg Oncol. 2008;15(12):3396–401.
111. Sakamoto N et al. Early results of an endoscopic nipple-sparing mastectomy for breast cancer. Ann Surg Oncol. 2009;16:3406–13.
112. Paepke S et al. Subcutaneous mastectomy with conservation of the nipple-areola skin: broadening the indications. Ann Surg. 2009;250:288–92.
113. Petit JY et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a 5 years experience at the European institute of oncology of Milan (EIO). Breast Cancer Res Treat. 2009;117:333–8.
114. Chen CM et al. Nipple-sparing mastectomy and immediate tissue expander/implant breast reconstruction. Plast Reconstr Surg. 2009;124:1772–80.
115. Sakamoto N et al. Early results of an endoscopic nipple-sparing mastectomy for breast cancer. Indian J Surg Oncol. 2010;1:232–9.
116. Babiera G, Simmons R. Nipple-areolar complex-sparing mastectomy: feasibility, patient selection, and technique. Ann Surg Oncol. 2010;17 Suppl 3:245–8.
117. Kim HJ et al. Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaneous flap reconstruction is an oncologically safe procedure: a single center study. Ann Surg. 2010;251:493–8.
118. de Alcantara FP et al. Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the Memorial Sloan-Kettering Cancer Center experience. Ann Surg Oncol. 2011;18:3117–22.
119. Jensen JA, Orringer JS, Giuliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. Ann Surg Oncol. 2011;18:1665–70.
120. Harness JK, Vetter TS, Salibian AH. Areola and nipple-areola-sparing mastectomy for breast cancer treatment and risk reduction: report of an initial experience in a community hospital setting. Ann Surg Oncol. 2011;18:917–22.
121. Boneti C et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. J Am Coll Surg. 2011;212:686–95.
122. Spear SL et al. Nipple-sparing mastectomy for prophylactic and therapeutic indications. Plast Reconstr Surg. 2011;128:1005–14.
123. Shi A et al. Subcutaneous nipple-sparing mastectomy and immediate breast reconstruction. Breast Care (Basel). 2012;7:131–6.
124. Moyer HR et al. Nipple-sparing mastectomy: technical aspects and aesthetic outcomes. Ann Plast Surg. 2012;68:446–50.
125. Peled AW et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. Ann Surg Oncol. 2012;19:3402–9.
126. Lohsiriwat V et al. Paget's disease as a local recurrence after nipple-sparing mastectomy: clinical presentation, treatment, outcome, and risk factor analysis. Ann Surg Oncol. 2012;19:1850–5.
127. Wagner JL et al. Prospective evaluation of the nipple-areola complex sparing mastectomy for risk reduction and for early-stage breast cancer. Ann Surg Oncol. 2012;19:1137–44.
128. Sakurai T et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. Med Oncol. 2013;30:481.