

Prophylactic mastectomy for the prevention of breast cancer: Review of the literature

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ABSTRACT

The high incidence and recurrence rate of breast cancer has influenced multiple strategies such as early detection with imaging, chemoprevention and surgical interventions that serve as preventive measures for women at high risk. Prophylactic mastectomy is one of the growing strategies of breast cancer risk reduction that is of a special importance for breast cancer gene mutation carriers. Women with personal history of cancerous breast lesions may consider ipsilateral or contralateral mastectomy as well. Existing data showed that mastectomy effectively reduces breast cancer risk. However, careful risk estimation is necessary to wisely select individuals who will benefit from preventing breast cancer.

Key words: BRCA, breast neoplasms, ductal carcinoma *in situ*, prophylactic mastectomy, risk reduction

INTRODUCTION

Breast cancer continues to be the most common cancer occurring in women with an annual incidence of 252,710 cases in the United States, resulting in 41,070 deaths, only second to lung cancer.^[1] The prevalence in 2014 had reached 3,346,387 cases with a probability of 12.4% for a women to be diagnosed with breast cancer during her lifetime that increases with age.^[1,2] Based on the surveillance, epidemiology, and end results (SEER) database, there has been a change in breast cancer incidence between the years 1975 and 2014. The reported annual percent changes in the years 1975–1980 and 2004–2014 were –0.5 and 0.3, respectively. A surge of breast cancer incidence during the 1980s can be explained by changes in female reproductive patterns and the adoption of more aggressive screening techniques that have led to increased detection of the disease.^[2] Risk factors for developing breast cancer occurrence or recurrence are multiple and complex, including family history, genetic mutations, lifestyle, radiation exposure, parity, previous history, etc., The clinical features and the type of primary cancer treatment can affect the risk of the recurrence as well.^[3] In general, the rate of recurrence is higher in the first few years after the initial

breast cancer diagnosis, and it drops down after that.^[4] Multiple strategies have been implemented to reduce the risk of breast cancer occurrence, and recurrence. These interventions include lifestyle modification, early detection with imaging, chemoprevention and surgical intervention.^[3] Prophylactic mastectomy is one of the growing strategies for breast cancer risk reduction.^[5] In this review, we are going to discuss the current evidence for prophylactic mastectomy in regard to types, indications and its role in breast cancer prevention.

HIGH-RISK POPULATION

Assessing breast cancer risk is based on both endogenous and exogenous factors. Mutations affecting known genes, compelling family history, having benign breast diseases with specific histologic features, previous history of breast cancer or radiation therapy to the breast all increase the

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risk of developing breast cancer. Familial susceptibility to breast cancer accounts for <25% of all breast cancer cases.^[6] Several genes have been implicated in familial cases. Mutations in breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) genes explain ~20% of the familial clustering of breast cancer.^[6] BRCA1 is a tumor suppressor gene mapped to chromosome 17. Its protein product is part of a complex compound responsible for repairing double-strand breaks in deoxyribonucleic acid (DNA) that contribute to genomic instability and drive cancer development.^[7,8] These breaks can be induced by radiation exposure or chemotherapy.^[9] BRCA2 gene is located on chromosome 13 and has a similar function to BRCA1 gene.^[10,11] These genes are important for the stability of the genome. The predisposed subject carries a defective allele of a tumor suppressor gene. Meanwhile, a second hit, a loss of the second gene copy, is a necessary step to cause tumor cell growth.^[12] Thus, women carrying BRCA1 or 2 gene mutations are thought to have a significantly higher risk of developing breast cancer, usually diagnosed at a younger age compared to general population.^[13-16] It is estimated that the average cumulative risk of breast cancer by age 70 years is 57%–65% for BRCA1 gene mutation carriers and 45%–49% for BRCA2 gene mutation carriers with 20-times increase in the risk of breast cancer compared to general population.^[13,14,17] Similarly, mutations in other genes account for only a small fraction of the familial cases. The p53 gene is located on chromosome 17, and like BRCA, it is a tumor suppressor gene. Mutations in this gene are found in 50% of all cancer types.^[18] They are associated with a high lifetime risk of cancer and involved in 1% of hereditary breast cancer cases.^[19] The absolute lifetime risk of breast cancer in p53 gene mutation carriers is estimated to be 24%.^[20] The phosphatase and tensin homolog (PTEN) gene located on chromosome 10 is widely expressed throughout the body. It regulates cell cycle and triggers apoptosis. Mutations in this gene underlie a number of tumor syndromes: Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus and Proteus-like syndromes. These syndromes increase the risks for several types of cancer, with female breast cancer being the highest.^[21] It is estimated that the absolute lifetime risk of breast cancer for PTEN mutation carriers is 25%.^[22] Apart from familial susceptibility, sporadic cases that show no familial clustering are mainly due to the accumulation of poorly penetrant mutations in a number of genes affected by environmental factors. In general, genetic mutations are considered high risk for developing breast cancer when they show a 4-fold increased risk of breast cancer in carriers compared to general population. Some benign breast diseases have been reported to increase the risk of subsequent development of breast cancer. Noticeably, the risk is higher with proliferative

diseases than nonproliferative histological changes. A cohort of 4970 women with biopsy-proven benign breast diseases was studied retrospectively for the determination of subsequent development of breast cancer.^[23] The estimated overall breast cancer incidence rate was 452/100,000 person years at risk. Age >50 years increased the risk by 80%. Breast cancer risk was significantly higher in women with proliferative lesions with an incidence rate ratio of 1.7, reaching 5.0 in atypical ductal hyperplasia (ADH). Similarly, the relative risk associated with nonproliferative lesions was estimated to be 1.28, compared to 1.88 for proliferative lesions and 4.24 for atypia. However, women with nonproliferative lesions and negative family history showed no increased risk.^[24] The results of two other studies are consistent with the previous study and show comparable estimates of the risk ranging from 1.6 to 1.9 for women with proliferative disease without atypia and from 3.7 to 5.3 for atypical hyperplasia, all compared to women having nonproliferative lesions. They also reported elevated risk associated with calcification in proliferative lesions and in premenopausal women with atypical hyperplasia.^[25,26] Estimated 10-year cancer risks were 17.3% with ADH, 20.7% with atypical lobular hyperplasia, 23.7% with lobular carcinoma *in situ* (LCIS), and 26% with severe ADH.^[27] In addition to the benign breast diseases, ductal carcinoma *in situ* (DCIS) is a noninvasive breast cancer composed of malignant epithelial cells completely bounded by a basement membrane of mammary ducts, which typically does not metastasize to lymph nodes. The proportion of DCIS is about 20% of screening-detected breast cancers, and it carries a higher risk for developing invasive disease.^[28,29] One study found that low-grade DCIS has 9 times increased risk of developing cancer at the same site within 30 years after diagnosis (95% confidence interval, 4.7–17).^[30] The final diagnosis of a group of 241 women who underwent a mastectomy following a preoperative biopsy showing DCIS revealed that 14% of the patients had microinvasive carcinoma, and 21% had invasive ductal carcinoma.^[31] An earlier study reported that 26% of the patients were found to have an invasive disease.^[32] Another similar study showed comparable results.^[33] The previous studies identified predictors correlated with infiltration and all agreed on palpable tumor and large size DCIS. Early thoracic radiation before the age 30 years is a significant risk factor of breast cancer. The Late Effect Study Group trial reported a 56.7-fold greater overall risk of breast cancer associated with prior mantle radiotherapy at young age compared to general population.^[34] Women treated for unilateral breast cancer have an increased risk to develop contralateral breast cancer with a 5-fold increased incidence of new cancer compared to general population.^[35-37] The estimates are listed in Table 1.

Table 1: Risk of developing breast cancer

BRCA genetic mutations	Cumulative risk by age 70 years (%)
BRCA1	65
BRCA2	45
Other genetic mutations	Absolute lifetime risk (%)
p53	24
PTEN	25
Histologic risk factors	10 years risk (%)
ADH	17.3
ALH	20.7
LCIS	23.7
Severe ADH	26.0
Other factors	Overall risk
Early thoracic radiation	56.7-fold
Prior history of breast cancer	5-fold

BRCA: Breast cancer, BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, PTEN: Phosphatase and tensin homolog, ADH: Atypical ductal hyperplasia, ALH: Atypical lobular hyperplasia, LCIS: Lobular carcinoma *in situ*

PROPHYLACTIC MASTECTOMY

The use of both prophylactic bilateral and contralateral mastectomies is steadily increasing in the United States. Prophylactic mastectomy may be bilateral in healthy women at a high risk of breast cancer, or unilateral if done for a noninvasive breast lesion or in addition to a therapeutic mastectomy in the contralateral breast.^[5] The rate of prophylactic mastectomy in women at a high-risk of breast cancer had increased during the years between 2004 and 2008 to reach 35.7% for bilateral mastectomy and 22.9% for contralateral mastectomy.^[38,39] Prophylactic mastectomy could be technically performed in different ways.^[40] Total mastectomy (also called simple mastectomy) is a procedure where the majority of the breast tissue including the nipple-areola complex is removed through an elliptical skin incision, but muscle tissue beneath the breast and axillary lymph nodes are spared.^[5] It is unlikely to eradicate all breast tissue; even though, all the visible breast tissue is removed. Some of the breast tissue can be unintentionally left underneath the skin, on the inframammary fold, or near the axilla fat pad.^[40,41] In addition to total mastectomy, skin-sparing mastectomy is a way to remove the breast tissue including the nipple-areolar complex through a periareolar incision leaving most of the skin over the breast intact. This facilitates reconstruction, and the skin of the breast is preserved with no scarring.^[40] As an extension of skin-sparing mastectomy, nipple-sparing mastectomy (also called total skin-sparing mastectomy) preserves the nipple-areola complex and the skin over the breast.^[42] This is usually achieved through an inframammary incision where the skin is carefully dissected off the breast until all the anatomic boundaries of the breast are reached, and the breast in its entirety is excised. It is important to avoid leaving any breast tissue behind the nipple-areola complex. This process is technically

demanding and much effort is required to reach the uppermost deep boundaries of the breast through a small and far incision.^[41,42] Specific retractors with light sources may be used to facilitate the excision.^[43] Historically, skin-sparing mastectomy was preferred more commonly than total mastectomy. Today, total mastectomy is the preferred prophylactic procedure, because of the advantage of current nipple reconstruction techniques.^[5,38] Increased rate of postoperative complications in addition to the doubtful oncologic safety in nipple-sparing mastectomy created reluctance amongst some institutions and surgeons to adopt this technique.^[44,45] In general, there is still debate about the most appropriate type of mastectomy for high-risk women, and it should be carefully selected.^[41,42]

EFFICACY OF PROPHYLACTIC MASTECTOMY

Bilateral

Impact of bilateral prophylactic mastectomy on breast cancer incidence

BRCA

In BRCA gene mutation carriers, several studies showed a significant reduction in the incidence of breast cancer occurring in women who underwent bilateral prophylactic mastectomies. In 2001, Meijers-Heijboer *et al.*^[46] conducted a prospective cohort study of 139 women carrying BRCA1 or 2 gene mutations. Seventy-six (55%) of these women underwent prophylactic bilateral simple mastectomy, whereas the other 63 (45%) women remained under surveillance. As a result of a mean follow-up period of 2.9 years, none of the 76 women who underwent prophylactic mastectomy developed breast cancer, compared to 8 breast cancer cases diagnosed in the group under surveillance (ratio of observed to expected cases, 1.2; 95% confidence interval, 0.4–3.7). In the same year, Hartmann *et al.*^[47] identified 26 women with BRCA1 or 2 gene mutation from their previous retrospective cohort study of bilateral prophylactic mastectomies. None of the patients developed breast cancer during a median follow-up of 13.4 years after the prophylactic mastectomies. Using two models, these studies show an 85% to 100% risk reduction achieved by prophylactic mastectomy. In addition, in 2004, Rebbeck *et al.*^[48] conducted a prospective cohort study of 483 women of the same risk group. One hundred and five of these women who underwent bilateral prophylactic mastectomy were compared to 378 controls who did not undergo prophylactic surgery. With a mean follow-up of 6.4 years, breast cancer was found in two patients (1.9%) of the bilateral prophylactic mastectomy arm and in 184 (48.7%) of the matched control arm, confirming 90% to 95% reduction in breast cancer risk after bilateral prophylactic mastectomy. In a recent large prospective cohort study, Domchek *et al.*^[49] assessed the relationship between

prophylactic mastectomy and breast cancer outcomes in BRCA1 and 2 gene mutation carriers. No breast cancers were seen in 257 women who underwent bilateral prophylactic mastectomy compared to 7% of women without the surgery over 3 years of follow-up, showing decreased risk of breast cancer in BRCA1 and 2 gene mutation carriers associated with bilateral prophylactic mastectomy. Moreover, in a study conducted in 2015, 63 women carrying BRCA1 or 1 gene mutation who underwent nipple-sparing prophylactic mastectomy reported no newly diagnosed breast cancers at a median follow-up of 26 months supporting the same conclusion.^[44]

Non-BRCA

Regardless of the BRCA gene status, two retrospective cohort studies evaluated the efficacy of bilateral prophylactic mastectomy in women at high risk for breast cancer due to variable reasons. Hartmann *et al.*^[50] categorized 639 women who underwent bilateral mastectomy because of family history of breast cancer into moderated-risk and high-risk groups. Women in the high-risk group included women with a family history of breast cancer in one or more first-degree or second-degree relatives, who were diagnosed at an early age, had bilateral disease, males or had associated history of ovarian cancer. Otherwise, they would be categorized into the moderate-risk group. The study used a control group of sisters, and the Gail model to predict the number of cases of breast cancer in both cohorts. After a median follow-up of 14 years, bilateral prophylactic mastectomy was found to be associated with a reduction in the incidence of breast cancer by 90%. In 2005, Geiger *et al.*^[51] identified 276 women with family history of breast cancer in one or more first-degree or second-degree relatives, history of atypical hyperplasia or one or more biopsy with benign findings who had undergone bilateral prophylactic mastectomy and compared them to 196 women reflecting the age and geographic distribution who had not undergone the surgery. The results of this study show that breast cancer developed in 0.4% of the former group compared to 4% in the latter.

Lobular carcinoma in situ

LCIS is rarely managed by bilateral mastectomy.^[52] Only a few authors advocated it based on the equal risk of both breasts to develop invasive disease.^[53] In one study, 56 patients chose bilateral prophylactic mastectomy and all remained cancer free. That was compared to 1032 patients who remained under surveillance with or without chemoprevention where 14% developed breast cancer after a median follow-up of 81 months. Notably, patients who opt for mastectomy had a stronger family history.^[52]

Impact of bilateral prophylactic mastectomy on breast cancer survival

Despite the confirmed reduction in breast cancer risk after bilateral prophylactic mastectomy, it is reasonable to question whether this preventive procedure results in improved overall survival in the light of modern detection and treatment modalities. In 1997, Schrag *et al.*^[54] compared prophylactic bilateral mastectomy with no prophylactic surgery among women carrying BRCA1 or 2 gene mutation carriers. They calculated that 30-year-old women gain from 2.9 to 5.3 years of life expectancy after bilateral prophylactic mastectomy on average. They also reported that increased age at the time of the procedure results in a declined gain in life expectancy reaching its minimal for 60-year-old women. In 2002, Grann *et al.*^[55] conducted a similar simulated cohort of 30-year-old women carrying BRCA1 or 2 gene mutation using Markov model. They reported that these women could prolong their survival 3.5 years with bilateral prophylactic mastectomy with a decrease in benefit according to age. More recently, in 2010, Kurian *et al.*^[56] developed a Monte Carlo model to simulate and compare different strategies for reducing cancer mortality in BRCA1 and 2 gene mutation carriers. This study reported that in BRCA1 gene mutation carriers, bilateral prophylactic mastectomy at age 25 years yields a 13% gain relative to no intervention, whereas delaying prophylactic mastectomy to age 40 years yields a small (2%) decrement in gain compared with prophylactic mastectomy at age 25 years. In BRCA2 gene mutation carriers, the reduction in mortality decreases to 8% (from 79% to 71%) only at age 25 years compared with no intervention; postponing prophylactic mastectomy to age 40 years reduces gain by 1%. This study considers prophylactic mastectomy the most effective single intervention in overall survival in BRCA2 gene mutation carriers. Moreover, in 2012, Sigal *et al.*^[57] applied their previously developed Monte Carlo simulation model to measure the effect of many factors on the gains in life expectancy resulted from conducting prophylactic strategies. Delaying prophylactic mastectomy by 5–10 years could decrease the gain in life expectancy by a range from 1 to 9.9 years in BRCA1 gene mutation carriers and from 0.5 to 4.2 years in BRCA2 gene mutation carriers. In conclusion, all these studies suggest a substantial gain in life expectancy after bilateral prophylactic mastectomy. This benefit decreases with age. Studies reporting the impact of bilateral mastectomy are listed in Table 2.

Surgical morbidity of bilateral prophylactic mastectomy

In a study in 1997 of 92 women who underwent prophylactic mastectomy followed by breast implantation, the rate of complications was 17.3% at 1 year and 30.4% at 5 years in women who received implants after prophylactic mastectomy

Table 2: Studies reporting the impact of bilateral mastectomy

Study (author, year)	Population	Main findings
Meijers-Heijboer et al., 2001 ^[46] Hartmann et al., 2001 ^[47]	BRCA1/2 BRCA1/2	Decreased incidence of BC after PM (HR=0; 95% CI=0-0.36; P=0.003) Reduction in observed risk of BC after PM=89.5% (95% CI=41.4%-99.7%)-100% (95% CI=68.0%-100.0%)
Rebbeck et al., 2004 ^[48] Domchek et al., 2010 ^[49]	BRCA1/2 BRCA1/2	Decreased incidence of BC after PM (HR=0.05-0.09; P<0.001) Decreased risk of BC after PM
Manning et al., 2015 ^[44] Hartmann et al., 1999 ^[50] Geiger et al., 2005 ^[51]	BRCA1/2 History of BC Family history, history of atypical hyperplasia, or ≥1 benign breast biopsies	No newly diagnosed breast cancers Reduction in risk of BC after PM, 89.5%; (P<0.001) Decreased incidence of BC after PM (HR=0.005; 95% CI=0.001-0.044)
King et al., 2015 ^[52] Schrag et al., 1997 ^[54] Grann et al., 2002 ^[55] Kurian et al., 2010 ^[56]	LCIS BRCA1/2 BRCA1/2 BRCA1/2	No newly diagnosed breast cancers Suggested 2.9-5.3 year gain in life expectancy after PM Suggested 3.5 years gain in life expectancy after PM Suggested 13% gain in life expectancy in BRCA1 and 8% in BRCA2 after PM at age 25 years
Sigal et al., 2012 ^[57]	BRCA1/2	1-9.9 year decreased gain in life expectancy in BRCA1 and 0.5-4.2 year in BRCA2 with delaying PM by 5-10 year

BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, BC: Breast cancer, PM: Prophylactic mastectomy, HR: Hazard ratio, CI: Confidence interval, LCIS: Lobular carcinoma in situ

during a mean follow-up of 7.8 years. The most frequent problems were capsular contraction, implant rupture, hematoma, and wound infection, respectively.^[58] However, 1 year later, a study measured the overall satisfaction rate among women who had bilateral prophylactic mastectomy, and it reported that only 5% of 370 women expressed regrets about the procedure over a median follow-up of 14.6 years.^[59]

Ipsilateral

Ductal carcinoma in situ

Most of the patients with DCIS are treated with breast-conserving surgery. However, one-third of patients undergo mastectomy. Data from SEER registries showed steady decline in the use of mastectomy for treatment of DCIS from 43% in 1992 to 28% in 1999 with significant variations among SEER sites.^[60,61] A number of recent studies have evaluated the impact of mastectomy for the treatment of DCIS regarding recurrence and survival. In 2011, a total of 496 patients with pure DCIS were prospectively followed-up a median of 83 months after treatment with mastectomy. Eleven (2%) patients with multifocal disease and comedo-type necrosis developed recurrences.^[62] A 10-year follow-up prospective study conducted in 2012 showed only one case of distant recurrence of a lesion that originally was high-grade DCIS among 54 patients. None of whom developed locoregional or local recurrence.^[63] Another retrospective study of 803 patients with DCIS followed-up for 6.3 years showed 1% 10-year rate for locoregional recurrence and 6.4% for contralateral breast cancer.^[64] A large prospective study involving 2894 women diagnosed with DCIS was conducted in 2015. As a result of a median follow-up of 9 years, 45 (1.6%) patients had an ipsilateral further event, and 83 (2.9%) had a contralateral event.^[65] In addition to recurrence, two more retrospective studies

evaluated survival in this group of patients. The first study of 637 patients with DCIS treated with mastectomy showed a cancer-specific survival of 98.0% and overall survival of 90.3%.^[66] The second study of 1546 participants showed consistent results.^[67] Other studies reporting comparable results are listed in Table 3.

Data regarding attribution of factors such as age, resection margin status, microinvasion, comedo-necrosis, tumor grade, tumor size or multifocal or multicentric tumor on the risk of recurrence are conflicting and not clear enough to guide the use of chest wall radiation post mastectomy.^[62,64,66,67,69,70,75-77]

Lobular carcinoma in situ

Unlike the current trend, women diagnosed with LCIS were often treated with mastectomy.^[78,79] The shift toward more conservative measures resulted from data suggesting a lower estimated risk of breast cancer in these women.^[80] A group of studies conducted in the 1960s and 1970s compared the results of patients treated with mastectomy and those under surveillance. A study including 124 patients with LCIS; 105 underwent mastectomy and 19 kept under follow-up, showed 1 infiltrating lobular carcinoma (IFLC) in the mastectomy group and two in the surveillance group.^[81] Similarly, in another study with a median follow-up period of 16 years, six patients treated with mastectomy were compared to 40 patients underwent diagnostic biopsy only, 15 recurrences were observed in the second group; nearly 75% of which were infiltrating and 50% appeared in the first 10 years. No recurrences were observed in the mastectomy group.^[82] In 2015, a study compared the results of 24 patients who underwent mastectomy alone, 159 patients who underwent breast conservative surgery alone and 17 patients who underwent breast conservative surgery and radiation. In

the breast conservative surgery group, 20 (13%) patients developed local recurrence by 6 years, and by 10 years, the rate increased to 17.5%. After 12 years of follow-up of the other two groups, three patients (17%) in the breast conservative surgery and radiation group developed local recurrence, while no recurrence was observed in the mastectomy group.^[83] Studies reporting the impact of ipsilateral mastectomy on recurrence in LCIS are listed in Table 4.

Phyllodes

Until the late 1970s, phyllode tumors were mainly treated with mastectomy, regardless of tumor size or grade.^[88] However, recent data consider cautious breast conservative surgery reasonably successful in providing results comparable to mastectomy.^[89] A study analyzed changes in the management of phyllodes in the period between 1952 and 2007 and correlated them to patient's outcomes showed a significant increase in a number of women undergoing breast conservative surgery instead of mastectomy. Despite this, there was no increase of disease at 5-year survival.^[90] Table 5 shows a number of studies comparing different surgical approaches to benign and borderline phyllodes.

One study conducted in 1996 evaluated the impact of wide local resection and mastectomy on the survival of patients with benign and borderline phyllodes. In the wide local resection group, 78 (98.7%) of 79 patients with benign type were found with no evidence of disease at 5-year survival, compared to 10 (76.9%) of 13 in the mastectomy group. In patients with borderline type, 12 (80%) of 15 were found with no evidence of disease at 5-year survival in the wide local resection group compared with 2 (50%) of 4 for the mastectomy.^[95] Tumor size was not correlated with histopathological type, the rate of recurrence or deaths.^[91] In conclusion, most of the evidence support the use mastectomy only when tumor size in relation to breast volume is large and cannot be resected with acceptable cosmetic and oncologic outcomes.^[91,95]

No studies evaluated the addition of postmastectomy radiation in the prophylactic use.

Contralateral BRCA

A retrospective cohort of 148 women was published by van Sprundel *et al.*^[96] shows the clinical outcome of

Table 3: Studies reporting the impact of ipsilateral mastectomy on recurrence in ductal carcinoma in situ

Study (author, year)	Type	Median follow-up	Intervention	Number of patients	Recurrences
Rubio <i>et al.</i> , 2000 ^[68]	Retrospective	3.7 years	SSM	95	3 LR
Carlson <i>et al.</i> , 2007 ^[69]	Retrospective	6.3 years	SSM	223	7 LR, 2 RR and 2 DR
Rashian <i>et al.</i> , 2008 ^[70]	Retrospective	61 months	Mastectomy	574	80 LR
Godat <i>et al.</i> , 2009 ^[71]	Retrospective	4.5 years	Mastectomy	83	0
Reefy <i>et al.</i> , 2010 ^[72]	Prospective	36 months	SSM	25	0
Kelley <i>et al.</i> , 2011 ^[62]	Prospective	83 months	Mastectomy	496	11
de Alcantara Filho <i>et al.</i> , 2011 ^[73]	Prospective	10.38 months	NSM	74	0
Chan <i>et al.</i> , 2011 ^[74]	Retrospective	8 years	Mastectomy	193	2 CWR
Childs <i>et al.</i> , 2013 ^[75]	Retrospective	7.6 years	Mastectomy	142	2
Romics <i>et al.</i> , 2012 ^[63]	Prospective	10 years	SSM	54	2 DR
Chadha <i>et al.</i> , 2012 ^[76]	Retrospective	55 months	Mastectomy	211	2 locoregional recurrences
Clements <i>et al.</i> , 2015 ^[65]	Prospective	9 years	Mastectomy	2894	45 ipsilateral and 83 contralateral recurrences
Klein <i>et al.</i> , 2015 ^[67]	Retrospective	10 years	Mastectomy	1546	36 CWR
Bannani <i>et al.</i> , 2015 ^[77]	Retrospective	39 months	Mastectomy	210	6 locoregional and 2 DR

SSM: Skin-sparing mastectomy, LR: Local recurrence, RR: Regional recurrence, DR: Distant recurrence, NSM: Nipple-sparing mastectomy, CWR: Chest wall recurrence

Table 4: Studies reporting the impact of ipsilateral mastectomy on recurrence in lobular carcinoma in situ

Study (author, year)	Median follow-up	Intervention	Number of patients	Recurrence
Benfield <i>et al.</i> , 1965 ^[84]	6.5 years	Mastectomy	13	0
Farrow, 1968 ^[85]	NA	MRM	161	0
Hutter and Foote, 1969 ^[82]	16 years	Radical mastectomy	6	0
Donegan and Perez-Mesa, 1972 ^[86]	21 months	Diagnostic biopsy	40	15; 75% infiltrating
		Mastectomy	35	9
Giordano and Klopp, 1973 ^[81]	NA	Simple mastectomy	105	1 infiltrating
		Careful follow-up	19	2 infiltrating
Wheeler <i>et al.</i> , 1974 ^[87]	15.7 months	Simple or radical mastectomy	13	0
		Careful follow-up	25	1 infiltrating
Cutuli <i>et al.</i> , 2015 ^[83]	12 years	Mastectomy only	24	0
		BCS and WBRT	17	3 (17%) LR
	6 years	BCS only	159	20 (13%) LR

NA: Not available, MRM: Modified radical mastectomy, BCS: Breast conservative surgery, WBRT: Whole breast radiation therapy, LR: Local recurrence

Table 5: Studies reporting the impact of ipsilateral mastectomy on recurrence in phyllodes

Study (author, year)	Median follow-up (benign/borderline) (months)	Intervention	Number of patients (benign/borderline)	LR (benign/borderline)
Salvadori et al., 1989 ^[91]	106/84	WLE	24/22	1/10
		MRM	1/0	0/0
		Subcutaneous mastectomy	0/2	0/0
		Total mastectomy	0/2	0/0
Moffat et al., 1995 ^[92]	135	Local excision	16/1	6/0
		Simple mastectomy	5/2	0/0
		Subcutaneous mastectomy	2/1	0/0
Acar et al., 2015 ^[93]	46	WLE	11/3	0/0
Toh et al., 2016 ^[94]	44.2/26.5	Mastectomy	0/2	0/0
		BCS	17/2	2/0
		Simple mastectomy	1/0	0/0
		Mastectomy with axillary clearance	3/2	0/0

LR: Local recurrence, WLE: Wide local excision, MRM: Modified radical mastectomy, BCS: Breast conservative surgery

contralateral prophylactic mastectomy in BRCA1 and 2 gene mutation carriers with the previous history of stage I-IIIa breast cancer. Seventy-nine of the 148 women underwent contralateral prophylactic mastectomy, while the other 69 remained under regular surveillance. After a mean follow-up of 3.5 years, one woman only developed an invasive contralateral primary breast cancer after the contralateral prophylactic mastectomy, whereas 6 women were diagnosed with breast cancer in the surveillance group. Another study compared 146 women treated with bilateral, prior, or delayed contralateral mastectomy with 336 women who retained the contralateral breast. As a result of a median follow-up of 9.2 years, only 1 contralateral chest wall recurrence was found in the first group while 97 contralateral breast cancers were found in the second (hazard ratio = 0.03).^[97] The populations of the two previous studies included variant histological types of breast cancer with infiltrating ductal carcinoma composing more than 60% in both of them. In a recent prospective study conducted by Manning *et al.*,^[44] 26 BRCA gene mutation carriers of median age 41 years had contralateral prophylactic nipple-sparing mastectomy. At a median follow-up of 28 months, there were no local or regional recurrences in any of these women.

Non-BRCA

Peralta *et al.*^[98] compared 64 women with a personal history of infiltrating ductal carcinoma (63%), IFLC (19%), LCIS (9%) or DCIS (5%) who underwent contralateral prophylactic mastectomy with 182 matching controls. After 6.2 years of follow-up, 36 contralateral breast cancers were found in the control group. While in the contralateral prophylactic mastectomy group, three occult cancers were found in the contralateral breast at the time of the surgery, but none developed subsequently ($P = 0.005$). Herrinton *et al.*^[99] conducted a large retrospective cohort comprised approximately 50,000 women in 2005. In women with

contralateral prophylactic mastectomy, 0.5% of women developed contralateral breast cancer, 10.5% of women developed metastatic disease and 12.4% developed subsequent breast cancer; 8.1% of women died of breast cancer. In comparison, 2.7% of women without contralateral prophylactic mastectomy developed contralateral breast cancer and 11.7 died of the disease. A more recent study composed of 385 patients with stage I or II breast cancer and a family history of breast cancer defined as parent, sibling, or second-degree relative with breast cancer who underwent contralateral prophylactic mastectomy and the same number of matching controls showed 2 (0.5%) contralateral breast cancers developed in the contralateral prophylactic mastectomy group and 31 (8.1%) in the control group, representing a 95% decreased risk of contralateral breast cancer (hazard ratio = 0.05, 95% confidence interval 0.01–0.22).^[100]

Infiltrating lobular carcinoma

One study published in 1997 compared the efficacy of contralateral prophylactic mastectomy to the conservative measures in IFLC specifically, by following 18 patients who underwent contralateral prophylactic mastectomy and 115 patients who did not for a median of 68 months. Three (3%) contralateral cancers were detected in the conservative group and 3 (17%) LCIS only in the contralateral prophylactic mastectomy group, concluding that careful follow-up is an acceptable choice for patients with IFLC.^[101] Studies reporting the impact of contralateral mastectomy are listed in Table 6.

QUALITY OF LIFE AFTER MASTECTOMY

Although mastectomies, in general, have low morbidity, decrease cancer-specific distress and improve symmetry in the case of contralateral mastectomies, women still experience long-term effects.^[102-104] Cosmetic, psychological,

Table 6: Studies reporting the impact of contralateral mastectomy

Study (author, year)	Population	Main findings
Metcalfe, 2004 ^[97]	BRCA1/2	Decreased occurrence of CBC after PM (HR=0.03; P=0.0005)
van Sprundel, 2005 ^[96]	BRCA1/2	Decreased occurrence of CBC after PM (P<0.001)
Manning, 2015 ^[44]	BRCA1/2	No newly diagnosed breast cancers
Peralta, 2000 ^[98]	Unilateral BC	Decreased occurrence of CBC after PM (P=0.005)
Herrinton, 2005 ^[99]	Unilateral BC	Decreased occurrence of CBC after CPM (HR=0.03; 95% CI=0.006-0.13)
Boughey, 2010 ^[100]	Stage I or II BC and family history	95% decreased risk of CBC (HR=0.05; 95% CI=0.01-0.22; P<0.0001)
Babiera, 1997 ^[101]	IFLC	No significant difference in DFS between mastectomy and conservation (P=0.98)

BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, CBC: Contralateral breast cancer, PM: Prophylactic mastectomy, HR: Hazard ratio, BC: Breast cancer, CPM: Contralateral prophylactic mastectomy, CI: Confidence interval, IFLC: Infiltrating lobular carcinoma, DFS: Disease free survival

and social domains are likely to be impacted. When patients were asked about general satisfaction with their decision, women who had mastectomies showed high satisfaction rates reaching 70% after 14.5 years of bilateral mastectomy and ranging between 83% and 90% after 10.3–20 years of contralateral mastectomies.^[105-107] However, body image issues were significantly affected, especially with bilateral mastectomies due to many factors, such as self-consciousness, feeling less sexually attractive, and dissatisfaction with the scars.^[103,104,107-109] Decreased sexual satisfaction was linked to both body image issues and loss of sensation in the breast.^[110] Even after long periods of time; one study showed that 36% of the women are still having problems with their body image after 14 years of bilateral mastectomies.^[106] Body appearance was the major issue in contralateral mastectomies as well.^[105,107] Women who underwent unilateral mastectomies were less satisfied by their appearance than women who underwent bilateral mastectomies. Some data suggest that reconstruction is associated with less satisfaction in the long-term, explained by more frequent surgical complications and concerns about implants.^[106] This side of prophylactic mastectomies should be highlighted to women considering the surgery so that they can weigh the benefits alongside the potential adverse effects.

CONCLUSION

The majority of evidence confirms 85% to 100% reduction in the incidence of breast cancer after prophylactic bilateral and contralateral mastectomy. However, prophylactic ipsilateral mastectomy has not been shown to eliminate the risk of recurrence, and in most cases, it is not supported unless surgically indicated. Because many of breast cancers are detected at an early stage where patients show good prognosis, absolute survival benefits would require studies with larger number of patients and longer periods of follow-up. Although mastectomy is generally safe and associated with high satisfaction rate, careful risk estimation, and selection of individuals who will benefit from preventing breast cancer is necessary to minimize morbidity to the remainder.

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