Published in final edited form as:

Br J Surg. 2015 October ; 102(11): 1354–1359. doi:10.1002/bjs.9884.

Nipple-sparing mastectomy in patients with *BRCA* 1/2 mutations and variants of uncertain significance

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Abstract

Background—Nipple-sparing mastectomy (NSM) is associated with improved cosmesis and is increasingly performed. Its role in *BRCA* mutation carriers has not been well described. Here indications and outcomes of *BRCA* mutation carriers undergoing NSM are studied.

Methods—*BRCA* mutations carriers who underwent NSM were identified. Details of patient demographics, surgical procedures, complications, and relevant disease stage and follow-up, were recorded.

Results—177 NSMs were performed on 89 *BRCA* mutation carriers between 9/2005–12/2013. 26 patients (median age 41 years) had NSM for early-stage breast cancer, and a contralateral prophylactic mastectomy (CPM). Mean tumor size was 1.38cm (range 0.1–3.5cm). 63 patients had NSM for prophylaxis (median age 39 years), 8 of whom had an incidental diagnosis of DCIS. In the 26 breast cancer patients, at median follow-up of 2.34 years (interquartile range (IQR) 0.45–6.06), there were no local or regional recurrences. In the 63 patients undergoing prophylactic NSM, at median follow-up of 2.15 years (IQR 0.11–8.14), there were no newly diagnosed breast cancers. All patients had immediate breast reconstruction. Five patients (5.6%) required subsequent excision of the nipple-areolar complex for oncological concerns or other reasons. Skin desquamation occurred in 68 of 177 breasts (38.4%) and resolved without intervention. Flap necrosis requiring debridement occurred in 13/177 breasts (7.3%), and tissue-expander or implant removal was necessary in 6 cases (3.4%).

Conclusion—Nipple-sparing mastectomy is an acceptable choice for patients with *BRCA* mutations, with no evidence of compromise to oncological safety at short-term follow-up. This report shows an acceptable complication rate, and patients rarely required subsequent excision of the nipple-areolar complex.

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Disclosure: The authors declare no conflicts of interest

Keywords

Nipple-sparing mastectomy; BRCA; breast surgery

Introduction

It is estimated that 55–65% of women with a *BRCA1* mutation and 45% of women with *BRCA2* mutation will develop breast cancer by age 70 years^{2,3}. Women diagnosed with breast cancer who are known to have or subsequently found to have a *BRCA* mutation usually undergo mastectomy, even for early-stage breast cancer amenable to breast-conserving therapy, due to the high risk of developing a second cancer in the ipsilateral breast, and a contralateral prophylactic mastectomy (CPM) is common⁴. In addition, many asymptomatic women known to be *BRCA* mutation carriers choose to undergo risk-reducing bilateral mastectomies with immediate breast reconstruction¹.

Nipple-sparing mastectomy (NSM) is a preferred option for many breast cancer patients when specific tumor and patient factors allow for this approach. In comparison to skin-sparing mastectomy, the nipple-sparing approach may allow for a superior cosmetic outcome and higher levels of patient satisfaction⁵, although studies comparing patient-reported outcomes (PROMs) for both techniques are lacking⁶. Several studies have shown that preservation of the nipple-areolar complex (NAC) seems to be oncologically safe without increased risk of local recurrence in women with sporadic breast cancer^{7–9}. It is also an option for many patients undergoing prophylactic mastectomy who are not limited by such tumor factors, such as asymptomatic *BRCA* mutation carriers; however, its role in this high-risk population has seldom been reported. Because NSM necessitates leaving behind a small amount of breast tissue behind the nipple areolar complex to provide a blood supply, its oncologic safety in *BRCA* mutation carriers is of particular concern. In the present study, the indications and outcomes of a large series of *BRCA* mutation carriers and some patients with Variants of Uncertain Significance (VUS) undergoing NSM at Memorial Sloan Kettering Cancer Center (MSKCC) are presented.

Methods

Patient selection for nipple-sparing mastectomy

Patients with a documented *BRCA* mutation undergoing mastectomy for treatment of breast cancer (therapeutic) or risk reduction (prophylactic) were given the option of nipple-sparing versus conventional skin-sparing mastectomy following consideration of several patient and, where relevant, tumor characteristics. Relative contraindications to NSM included smoking history, larger breast size, and ptosis. In therapeutic cases, patients with skin or nipple involvement, central tumors close to the NAC, or blood-stained nipple discharge were excluded. Tumor or microcalcifications less than 1 cm from the nipple were excluded for nipple sparing mastectomy. All patients interested in NSM discussed the risks and benefits of this approach with their breast surgeon and plastic surgeon preoperatively.

Patients were informed of the risks associated with preservation of the NAC, including risk of inadequate blood supply leading to skin desquamation or necrosis, possibly necessitating subsequent debridement or complete excision of the NAC. Concerns regarding oncological safety of nipple preservation, including limited long-term data on local recurrence rates, were discussed with all patients, including those undergoing prophylactic mastectomy. Assessment of the retroareolar tissue by frozen or permanent section was discussed as appropriate. Patients undergoing frozen section were advised that a positive result (preinvasive or invasive cancer) would require excision of the NAC at the time of mastectomy, and a positive result on permanent section would require a second operation for excision of the NAC.

Surgical technique

The most commonly performed incision for NSM was circumareolar with radial extension if required; however, the actual incision was decided on an individual-case basis following discussions between patient, breast surgeon, and plastic surgeon. Although 11 different breast surgeons performed NSMs on BRCA mutation carriers at the institution during this time period, most cases (72%) were performed by only three surgeons. Similar to conventional skin-sparing mastectomy, NSM was performed with the aim of removing all glandular breast tissue. Infiltration of the retroareolar tissue with 10 ml of saline was frequently performed following induction of anesthesia to help develop the tissue plane between the breast tissue and the NAC. A section of retroareolar tissue (“nipple margin”) was removed for either intraoperative frozen section or routine permanent section as deemed appropriate. Immediate breast reconstruction was performed by a plastic surgeon with a special interest in breast reconstruction in all cases.

Patient follow-up

Patients attended breast surgery and plastic surgery clinics postoperatively until fully recovered from surgery, and each visit was documented in the patients electronic medical record. Subsequently, patients continued to attend for annual follow-up with a breast examination performed by the breast surgeon and plastic surgeon. Imaging (by ultrasound examination) was performed only if a palpable abnormality was found on breast examination.

Data collection and outcome measures

Following approval by the MSKCC institutional review board, a prospectively maintained breast surgery database was used to identify all female patients with *BRCA* mutations who underwent NSM. The electronic medical record of each patient was accessed, and relevant data were abstracted. These included indications for surgery, type of *BRCA* mutation, family history of breast and ovarian cancer, and type of reconstruction. All progress notes and clinic notes were reviewed to identify cases with postoperative complications, including hematoma, skin desquamation, necrosis, and infection. Details of all interventions performed were recorded, such as evacuation of hematoma, surgical debridement, and removal of implant. Indications for subsequent excision of the NAC were determined. All pathology reports were reviewed to record preoperative and postoperative findings,

including frozen and permanent sections of retroareolar tissue (nipple margin). For patients undergoing NSM for breast cancer management, tumor characteristics, lymph node status, and overall American Joint Committee on Cancer disease stage were recorded. For all patients, length of follow-up was calculated, and status at last follow-up determined from review of clinic notes (i.e., no evidence of disease; alive with disease; died with disease; died other cause; or died unknown cause). Recurrence events were captured for local, regional, and distant disease.

Results

Characteristics of the study cohort

A total of 177 NSMs were performed in 89 patients with a documented *BRCA* mutation or VUS between September 2005 and December 2013, in total representing 25.5% of the NSMs performed during that period. Only one patient underwent unilateral NSM; all other patients had bilateral procedures, and immediate breast reconstruction was performed in all cases. Patient characteristics, mutation types, and indications for surgery are shown in Table 1. There were 26 therapeutic mastectomies performed in 26 patients with breast cancer; 18 as the initial surgical treatment and 8 completion mastectomies following initial lumpectomy. There were 151 prophylactic mastectomies performed in 89 patients, including 26 contralateral operations for the 26 breast cancer patients, 108 prophylactic mastectomies in 54 patients with no prior breast cancer, and 17 prophylactic mastectomies in 9 patients with a previous history of breast cancer. There was an incidental finding of ductal carcinoma in situ (DCIS) in 9 of 151 prophylactic mastectomies (6%). This included 4 patients undergoing contralateral prophylactic mastectomies, and 4 patients undergoing bilateral prophylactic mastectomy, 1 of whom was diagnosed with bilateral DCIS. In addition, there was an incidental finding of atypia in 8 prophylactic mastectomies (5.3%). There was no incidental finding of invasive breast cancer.

Assessment of retroareolar tissue and excision of the nipple-areolar complex

Assessment of the retroareolar tissue for evidence of disease differed between patients undergoing prophylactic and therapeutic NSMs. In 23 of 26 cases of therapeutic mastectomy for breast cancer, a separate nipple margin was excised for assessment, 8 were sent for intraoperative frozen section, all of which were negative and confirmed negative on subsequent permanent section. One of the 23 samples assessed by permanent section in a patient with multicentric DCIS showed DCIS present less than 1 mm from the inked resection margin. This patient returned for excision of the NAC and, of note, there was no further DCIS identified. One of 3 patients who did not have a separate nipple margin excised was found to have DCIS at the retroareolar ducts of the mastectomy specimen, and decided not to return for excision of the NAC.

For prophylactic NSM, a separate nipple margin was excised in 96 of 151 mastectomies. None were assessed by intraoperative frozen section, and there was an unexpected diagnosis of DCIS in the nipple margin permanent section in two cases. In the first case, there was an incidental finding of DCIS (single focus) in the retroareolar tissue of one breast, and the patient returned for excision of both NACs. There was no further disease evident in the

resected specimens. Similarly, in the second case, a small focus of DCIS was identified in the nipple margin, but the patient decided not to return for excision of the NAC. She has no evidence of disease after more than five years of follow-up. In addition, one further patient with an incidental diagnosis of DCIS in both breasts including retroareolar ducts on one mastectomy specimen decided to have excision of both NACs despite negative nipple margins bilaterally. There was however no further evidence of disease on the resected specimens.

One patient who underwent bilateral prophylactic NSMs complained of milk-like discharge from both nipples one year later following childbirth. This patient returned for bilateral NAC excision. Another patient required a salvage latissimus dorsi reconstruction following infection resulting in nipple necrosis and implant loss. There was no evidence of disease in any of those three resected NACs. In total, 5 of 89 patients (5.6%) underwent unilateral or bilateral excision of the NAC and the final pathology of the excised NAC was negative in all these cases.

Follow-up

Median follow-up for patients undergoing therapeutic and prophylactic NSM was 28 months (IQR 15–43) and 26 months (IQR 11–42), respectively. In the therapeutic group, there were no local or regional recurrences, but there were two deaths; one patient was diagnosed with distant metastases two years after NSM for stage IIA breast cancer and died from her disease; the second patient died from metastatic ovarian cancer three years after NSM for DCIS. In the prophylactic group, there were no new diagnoses of breast cancer and no deaths during this follow-up period.

Complications

There was some degree of skin desquamation noted following NSM in 68 breasts (38.4%) in 40 patients (44.9%) during postoperative follow-up ranging from superficial epidermolysis to full thickness necrosis requiring debridement, and most cases were fully resolved on subsequent follow-up without need for intervention. The most common complication was nipple-areolar or flap necrosis, which occurred in 13 breasts (7.3%), and there were seven cases of infection (4%). A combination of flap necrosis and infection resulted in implant loss from six breasts (3.4%). A summary of the surgical complications is shown in Table 2.

Discussion

Preservation of the NAC allows for an improved cosmetic outcome, and there is evidence that this procedure is associated with higher psychosocial and sexual well being compared to the more traditional skin-sparing mastectomy with or without nipple reconstruction (Wei CH, Price AN, Miller C et al. Psychological and sexual well-being following nipple-sparing mastectomy and reconstruction, in press). *BRCA* mutation carriers often undergo bilateral mastectomy for breast cancer treatment or as risk-reducing surgery, but the high breast cancer risk associated with these mutations understandably leads to concern among patients and physicians regarding the oncological safety of NSM. In this study, NSM was successfully performed in almost all cases, with only 8 of 177 breasts (4.5%) subsequently

requiring excision of the NAC for various reasons. This was performed for oncological reasons i.e., to out-rule residual DCIS following assessment of the separate nipple margin or the retroareolar ducts of the breast, in only three of 177 breasts (1.7%), and all excised NACs were negative for further disease. The overall rate of NAC loss of 4.5% is lower than that observed in an earlier study of NSM at our institution between 1998 and 2008, which reported a NAC loss in 8.7% of cases (10 of 115 breasts) for occult disease (6 cases) and wound-healing problems (4 cases)¹⁰. All patients in this study undergoing therapeutic NSM had early-stage breast cancer with a mean tumor size of 13.8 mm. These factors would, of course, increase the likelihood of successful NSM, and only one patient undergoing therapeutic NSM had subsequent excision of the NAC. It is interesting that for the other two patients who had excision of NAC due to concerns regarding further disease, and for one further patient who declined excision, DCIS was an incidental finding following prophylactic NSM. Although this occurred in only three cases (two in the nipple margin and one in the retroareolar ducts of the breast specimen), it highlights the importance of focused retroareolar tissue assessment and designation of a separate nipple margin even in *BRCA* mutation carriers undergoing prophylactic NSM. This procedure was performed in 96 of 151 prophylactic NSMs in this study, and the incidental diagnosis of DCIS in 2 of 96 nipple margins (2.1%) justifies sending a separate nipple margin for permanent section in all *BRCA* mutation carriers undergoing prophylactic NSM.

The type of breast reconstruction performed in this group of patients was almost exclusively implant based, with only 1 of 89 patients undergoing autologous flap reconstruction. This is consistent with a national trend in the United States toward increasing use of implant-based reconstruction and a decline in autologous reconstruction¹¹. In addition, it is known that patients undergoing bilateral mastectomy are more likely to choose implant-based reconstruction³, and 88 of 89 patients in the current study had bilateral procedures.

Careful review of all follow-up clinic notes revealed that many patients in this study had some degree of skin desquamation (38.4% of breasts); however, this was mostly superficial and reversible, with complete resolution on subsequent follow-up in most cases. Debridement was required, however, in 13 of 177 breasts (7.3%), and this was performed either in the office under local anesthesia, or in the operating room. Although this included some cases of mastectomy skin flap necrosis, separate from the NAC, these cases were in the minority. The observed rate of skin flap necrosis in the present study is higher than published rates following skin-sparing mastectomy¹², which is not an unexpected finding, as the preserved NAC is particularly prone to vascular compromise following NSM, and the rates are similar to that reported by Peled et al¹³. Patients are counseled regarding this risk preoperatively and are made aware that attempted removal of all glandular breast tissue inevitably results in thin mastectomy skin flaps, and that this is essential to minimize the risk of local recurrence or new primary breast cancer development in this high-risk population. It is reassuring, however, that only one patient in this study ultimately required excision of the NAC due to necrosis and infection (0.6%), compared to 4 cases (3.5%) in an earlier report of NSM at this institution¹⁰, possibly reflecting improvements in technique and management of skin compromise with an increasing volume of cases over time. The infection rate of 4% was similar to the expected infection rate following skin-sparing mastectomy¹². Patients can

be warned preoperatively that the risk of some degree of flap compromise is likely; however, most cases fully resolve with conservative management, and the risk of requiring debridement or removal of the NAC is low.

Twenty-six of 89 patients in this study underwent NSM for treatment of breast cancer, and there were no cases of local or regional recurrence during median follow-up of 28 months. All had early-stage node-negative disease and one patient had isolated tumour cells on sentinel lymph node biopsy. This most likely reflects intensive screening of these patients with annual MRI and mammographic surveillance leading to early diagnosis, rather than a reluctance to perform NSM in patients with node-positive disease. Although the median follow-up of 28 months is short, several studies have shown that this time period is associated with the highest risk for local recurrence following treatment of primary breast cancer^{14, 15}. A review of all mastectomies performed at the present institution during a four-year period with a median follow-up of 6 years showed that the median time to first local or regional recurrence was 1.8 years¹⁴. The absence of any cases of local or regional recurrence during our follow-up period of 28 months supports the view that NSM is oncologically safe in this patient group, but it is important to recognise the limitations of this study and that a longer follow-up in more patients is needed. In a similar study by Yao et al, three of 51 *BRCA1/2* mutation carriers undergoing NSM for breast cancer had developed local or regional recurrence at mean follow-up of 32.6 months. One patient had a local recurrence and two patients had axillary lymph node recurrence. Of note, there were no recurrences at the NAC¹⁶.

In addition to the risk of true local recurrence following mastectomy, the risk of a new primary breast cancer developing in residual breast tissue is of particular concern in the high-risk group of *BRCA* mutation carriers undergoing prophylactic or therapeutic mastectomy, and is regarded by some as a reason enough to avoid NSM in these patients. Only few studies have reported on the incidence of new primary breast cancer post mastectomy in *BRCA* mutation carriers, and these have not shown an increased risk in such patients. Domchek et al reported that none of 247 *BRCA* mutation carriers undergoing prophylactic skin-sparing mastectomy developed breast cancer during a three year follow-up¹⁷. In a smaller series of 26 *BRCA* mutation carriers undergoing skin-sparing mastectomy, Hartmann et al similarly reported that none developed breast cancer at 13 years follow-up¹⁸. More recently, Peled et al report that none of 26 patients undergoing prophylactic NSM developed a new primary breast cancer at 51 months follow-up, and Yao et al report development of a new breast cancer in merely one of 150 *BRCA1/2* mutation carriers undergoing NSM for risk reduction¹⁶. Although the present study has a relatively short follow-up of 26 months, it adds further support to this technique, with none of 89 patients undergoing prophylactic NSM developing a new primary breast cancer during this time¹³.

Within this large study of *BRCA* mutation carriers undergoing NSM, only five out of 89 (5.6%) patients and eight out of 177 (4.5%) of breasts subsequently required excision of the NAC for the finding of unexpected carcinoma or due to surgical complications. At follow-up of 26 months, there were no cases of local or regional recurrence, or new cancers, supporting the view that this procedure can be safely performed in patients with *BRCA*

mutations or VUS, although a larger cohort and longer follow-up are needed to determine the risk of subsequent cancers in the retained breast tissue.

Acknowledgments

Sources of funding: This study was funded in part through NIH/NCI Cancer Center Support Grant P30 CA008748.

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Table 1

Patient population

No. of patients	89
No. of NSMs	177
Age, years (range)	
Median age prophylactic NSM	39 (25–59)
Median age therapeutic NSM	41 (26–59)
BRCA mutation type (%) (n=89)	
BRCA1	56 (62.9%)
BRCA2	26 (29.2%)
Genetic variant of uncertain significance	7 (7.9%)
Family history (%) (n=89)	
Breast cancer	81 (91%)
Ovarian cancer	36 (40%)
Breast and ovarian cancer	32 (36%)
Neither breast nor ovarian	4 (4.5%)
Indication for NSM (n=177 NSMs)	
Therapeutic	26
Prophylactic	151
Therapeutic (n=26)	
Current breast cancer	17
Completion mastectomy	9
Prophylactic (n=151)	
Contralateral prophylactic mastectomy	26
Prophylaxis (history of breast cancer)	17
Prophylaxis (no previous breast cancer)	108
Mean tumor size, cm (range)	1.38 (0.1–3.5)
T stage (n=26)	
Tis	6
T1	15
T2	5
N stage (n=26)	
N0	25
N0(i+)	1
Breast cancer stage (%) (n=26)	
0	6 (23.1)
I	15 (57.7)
II	5 (19.2)
III	0

IV	0
Molecular profile for patients with invasive breast cancer (%) (n=20)	
ER/PR+ HER2–	11 (55%)
ER/PR+, HER2+	1 (5%)
ER–/PR–/HER2+	1 (5%)
ER–/PR–/HER2–	7 (35%)
Type of reconstruction (n=89)	
Tissue expander	80
Permanent implant	8
Autologous (DIEP) flap	1

NSM, nipple-sparing mastectomy, ER, estrogen receptor, PR, progesterone receptor, DIEP, deep inferior epigastric perforators

Table 2

Postoperative complications and reoperations in 89 patients/BRCA mutation carriers undergoing nipple-sparing mastectomy during an 8-year period

	No. of breasts	No. of patients
Excision of NAC	8 (4.5%)	5 (5.6%)
Necrosis requiring debridement	13 (7.3%)	9 (10.1%)
Infection	7 (4.0%)	7 (7.9%)
Hematoma	3 (1.69%)	3 (3.4%)
Complication requiring implant/tissue expander removal	6 (3.4%)	6 (6.7%)

NAC, nipple-areolar complex