

No Cancer Occurrences in 10-year Follow-up after Prophylactic Nipple-sparing Mastectomy

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Background: Prophylactic nipple-sparing mastectomies (NSM) have become increasingly common, although there is little long-term data on its efficacy in prevention of breast cancer. The objective of this study was to assess the incidence of breast cancer in a cohort of patients undergoing prophylactic NSM with a median follow-up of 10 years.

Methods: Patients receiving prophylactic NSM at a single institution from 2006 to 2019 were included in a retrospective nature. Patient demographics, genetic mutations, operative details, and specimen pathology were recorded, and all post-operative patient visits and documentation were screened for cancer occurrence. Descriptive statistics were performed where appropriate.

Results: Two hundred eighty-four prophylactic NSMs were performed on 228 patients with a median follow-up of 120.5±15.7 months. Roughly, a third of patients had a known genetic mutation, with 21% BRCA1 and 12% BRCA2. The majority (73%) of prophylactic specimens had no abnormal pathology. The most commonly observed pathologies were atypical lobular hyperplasia (10%) and ductal carcinoma in situ (7%). Cancer was identified in 10% of specimens, with only one case of lymphovascular invasion. Thus far, there have been no incidences of locoregional breast cancer occurrence in this cohort.

Conclusions: The long-term breast cancer occurrence rate in this cohort of prophylactic NSM patients at the time of this study is negligible. Despite this, continued surveillance of these patients is necessary until lifetime risk of occurrence following NSM has been established. (*Plast Reconstr Surg Glob Open* 2023; 11:e5087; doi: 10.1097/GOX.0000000000005087; Published online 14 June 2023.)

INTRODUCTION

Prophylactic mastectomies have been performed at higher rates in recent years secondary to several trends.¹ These include more widely available genetic testing for both hereditary breast cancer and genes with heightened breast cancer susceptibility, which inform patients of potential future oncologic risk.^{2,3} The refinement of nipple-sparing mastectomy (NSM) techniques occurred simultaneously, offering a treatment modality for risk

reduction that provides improved aesthetic outcomes and preserves the nipple-areola complex (NAC).^{1,4,5}

Given their risk-reducing role, prophylactic NSMs must be scrutinized in the long term, to determine safety of achieving cancer-free survival among patients. This is particularly important as it helps to justify the use of NSMs for improved aesthetics given that well-established alternatives to NSMs for breast cancer exist and are known to reduce the risk of subsequent disease.⁶ The current literature documents few to no cases of oncologic locoregional occurrence following prophylactic NSM, although these studies are limited by follow-up intervals of less than 3 years.^{7,8} Studies describing cohorts with follow-up beyond 5 years are lacking. This is largely in part to the relatively recent adoption of nipple-sparing mastectomies, which only started to receive widespread use in the early to mid-2000s.⁹ The primary concern with NSM is residual breast tissue left posterior to the NAC to preserve its viability

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that may pose future oncologic risk.⁶ As patients receiving prophylactic NSMs often carry an increased risk for breast cancer, it is important to inform patients what this risk may be when discussing risk-reducing therapy and subsequent reconstructive options.^{6,10,11} To date, the longest follow-up after prophylactic NSM documented in the literature is 5 years.^{8,12-14} The objective of this study was to assess for locoregional oncologic occurrence in a cohort undergoing prophylactic NSM with a median follow-up of 10 years.

METHODS

All patients receiving NSMs between 2006 and 2019 at a single institution were screened to determine whether mastectomy was performed for prophylactic or therapeutic indications. Therapeutic mastectomies, defined as mastectomies in patients with established or assumed cancer based on presurgical biopsy or patients with preoperative imaging indicative of breast cancer, were excluded from analysis.

Prophylactic mastectomies occurring in patients receiving either bilateral NSM for identified genetic predisposition for breast malignancy or patients with extensive family histories of breast malignancy were included. Patients undergoing bilateral mastectomies, comprised of a unilateral therapeutic mastectomy and a contralateral prophylactic mastectomy, were included.

Pathology from all prophylactic NSMs that met inclusion criteria was included in this study. Thus, patients with malignancies identified in mastectomy specimens or patients requiring nipple excision were not removed from the study. The mastectomies were performed by a total of five breast surgeons.

Patient medical records were reviewed in October 2021. Extracted data included demographics and operative details. Documented genetic mutations and mastectomy specimen pathology were also noted. Cancer staging was based on reviewing the pathology report in conjunction with the *American Joint Committee on Cancer 7th Edition Cancer Staging Manual*.¹⁵ All subsequent patient visits and documentation were screened for discussion of breast cancer occurrence or potential breast cancer development. Local occurrence was defined as cancer identified in the breast following initial mastectomy. Regional disease was defined as oncologic breast disease after initial mastectomy on the ipsilateral chest wall or in the regional lymph nodes. Metastatic disease was defined as a cancer originating in the breast, though identified in a remote solid organ or lymph node following initial mastectomy.⁴

Evaluation of patients for mastectomy type occurred independently by both breast and plastic surgeons. In cases of unilateral cancer, indications for NSM were based on the oncologic breast meeting appropriate criteria including an absence of NAC involvement of the tumor. For patients seeking bilateral prophylactic NSM, candidacy included various patient factors, including size of the breast, ptosis, smoking history, and remaining comorbidities. Patients were counseled on the risk of residual breast tissue as a result of maintaining the

Takeaways

Question: What long-term oncologic risk is associated with prophylactic nipple-sparing mastectomies?

Findings: Reviewing a single institution experience with 284 prophylactic nipple-sparing mastectomies and a median follow-up of over 120 months, there have been no incident cases of breast cancer occurrence.

Meaning: Although prophylactic nipple-sparing mastectomy appears to effectively reduce subsequent oncologic risk, continued surveillance throughout the life of these patients is required to determine the true incidence.

NAC. Frozen subareolar biopsies were variably performed among the breast surgeons throughout the study period but were performed with greater frequency over time. When a subareolar biopsy was performed, a slice of tissue several millimeters in thickness by several millimeters in diameter was removed from just under the nipple—superficial to the plane of the mastectomy. Patients were offered and counseled on all breast reconstructive options including free tissue transfer and prosthetic breast reconstruction.

Our current surveillance protocol is primarily based on our experience of managing patients following therapeutic mastectomy. This protocol includes biannual visits with a clinical examination with the breast surgeons for the 3–5 years following mastectomy. Patients then transition to annual examinations for the remainder of their life. Imaging is performed for patients with a physical examination concerning for a breast mass or nodule. This decision is deferred to the oncologic surgeons. Additionally, patients with implant-based breast reconstruction may receive breast imaging when monitoring the implants or in cases of suspected implant rupture.

Microsoft Excel (Version 7; Microsoft Corp, Seattle, Wash.) was used for performing descriptive statistics where appropriate. In addition, total woman years and breast years of follow-up were also calculated.¹⁶ This study was conducted in concordance with the Declaration of Helsinki.

RESULTS

A total of 228 patients underwent a total of 284 prophylactic NSMs with a mean \pm standard deviation and median follow-up of 121 ± 16 and 120 months, respectively. Mean age at the time of NSM was 47 ± 9 years and mean age at the time of analysis was 57 ± 9 years. This denotes a follow-up period of 2289 woman years and 2861 breast years.

A majority of patients received bilateral NSMs (91%); however, only the prophylactic mastectomy was included in the analysis. Six percent of patients had previous breast surgery. Eight percent of patients smoked at the time of mastectomy or had a history of tobacco use. History of chemotherapy and radiation was present in 6% and 3% of patients, respectively. Roughly, one-third of patients carried a known genetic susceptibility for breast cancer (34%). BRCA1 mutation was present in 21% of patients,

Table 1. Patient Demographic Factors of Patients Undergoing Prophylactic Nipple-sparing Mastectomy

Variable	Percentage (%)
Mean age at time of surgery \pm SD, y	46.9 \pm 9.0
Mean current age \pm SD, y	57.0 \pm 9.0
Mean body mass index \pm SD, kg/m ²	23.9 \pm 4.9
Smoking	
Current	6 (2.6)
Former	13 (5.7)
Diabetes mellitus	7 (3.1)
Prior radiation therapy	6 (2.6)
Prior chemotherapy	13 (5.7)
Mastectomy laterality	
Unilateral	20 (8.8)
Bilateral	208 (91.2)
Prior breast augmentation	
Yes	6 (2.6)
No	222 (97.4)
Prior breast reduction/mastopexy	
Yes	8 (3.5)
No	220 (96.5)
Genetic predisposition	
BRCA1	48 (21.1)
BRCA2	28 (12.3)
CDKN2A	1 (0.4)
None	151 (66.2)

SD, standard deviation.

and BRCA2 mutation was present in 12% of patients (Table 1). Fifty-eight percent of patients initially underwent tissue expander-based breast reconstruction, 32% received immediate autologous reconstruction, and the remaining 10% underwent direct-to-implant reconstruction. (See table, Supplemental Digital Content 1, which shows pathologic and operative details of patients undergoing prophylactic nipple-sparing mastectomy, <http://links.lww.com/PRSGO/C622>.)

Each mastectomy specimen was examined by pathology. Seventy-three percent of specimens did not exhibit any pathologic histology. Of the identified pathologic histologies, atypical lobular hyperplasia was the most common (10%), followed by ductal carcinoma in situ (7%). Cancer was identified in 28 (10%) pathology specimens. Mean tumor size was 0.67 \pm 0.43 cm. Only one case of both multifocal/multicentric disease and lymphovascular invasion was observed. Three patients had sentinel lymph node biopsies performed with no positive nodes identified. These were performed in a subsequent procedure following mastectomy after final pathology revealed cancer or atypia.

Of the specimens that demonstrated cancer, 41% of tumors exhibited estrogen receptor positivity and 47% displayed progesterone receptor positivity. Twelve percent demonstrated human epidermal growth factor receptor 2 positivity. Intraoperative frozen subareolar biopsies were performed in the majority of prophylactic NSMs (56%). Three (2%) frozen sections were positive for atypia or cancer. Six (3%) patients had positive subareolar tissue specimens on permanent pathology for either atypia or cancer, and each required NAC resection. No patients required

adjuvant radiation therapy, while five ultimately necessitated adjuvant chemotherapy. Stage 0 and stage I tumors were most common among patients with cancer in prophylactic mastectomy specimens. (See table, Supplemental Digital Content 1, <http://links.lww.com/PRSGO/C622>.) In this cohort receiving prophylactic nipple-sparing mastectomies, there have been no incidences of locoregional breast cancer occurrence to date.

DISCUSSION

Prophylactic mastectomies have been established in disease-free patients with genetic or familial predispositions for breast malignancy as a mechanism for reducing subsequent development of breast cancer.⁶ While there are data beyond 10 years of follow-up for other prophylactic mastectomy techniques, no literature describes patients receiving NSMs at this long of an interval following surgery. In this cohort of patients with prophylactic NSMs, there have not been any breast cancer occurrences to date. With the rise in volume of prophylactic mastectomies, it is important to assess patients for the long-term oncologic safety of these techniques to appropriately counsel patients on the risk reduction of the procedure and establish appropriate screening guidelines.¹ Advantages of NSM include improved aesthetic outcomes of breast reconstruction and higher reported levels of patient satisfaction.^{4,17} These benefits, however, must be balanced against the residual risk of breast cancer occurrence following NSM secondary to remaining breast tissue associated with the NAC.⁶

The effectiveness of prophylactic mastectomy in patients with predispositions to breast cancer has been well established. Long-term data are limited to patients who have undergone either total or subcutaneous prophylactic mastectomies.¹² Current studies of patients receiving prophylactic NSM have established rates of locoregional breast cancer occurrence to be 0%–1% with follow-up intervals of fewer than 5 years.^{8,13,14} Data examining prophylactic NSM beyond 5 years of follow-up are not available. Given the paucity of literature describing the long-term safety and efficacy of prophylactic NSM, this study reports a patient cohort with 10 years of median follow-up after prophylactic NSM. This cohort of 284 prophylactic NSMs in 228 patients represents the longest median follow-up of any study to date in the literature. We identified no cases of breast malignancy following prophylactic NSM.

Given the lack of control groups in the present study, it is not possible to discern the effectiveness and safety of prophylactic NSM compared to other prophylactic mastectomy surgical techniques. However, these results suggest that NSM offers an aesthetically pleasing and oncologically safe option for prophylactic mastectomy. Continual education of patients for the risk of breast cancer occurrence following NSM remains critical as these results do not suggest a 0% risk of subsequent breast malignancy following NSM. While an exact estimate of lifetime risk is outside the scope of this study, it is certainly nonzero. Until more studies from others corroborate the findings of this article, we will continue to follow

our current clinical surveillance protocol. These protocols are primarily based on our experience of managing patients following therapeutic mastectomy. Although this study suggests there is a low risk of cancer occurrence following prophylactic NSM, appropriate caution and follow-up with patients after prophylactic NSM are warranted until lifetime risks of oncologic locoregional occurrence are established.

Other studies have established that for some patients, prophylactic NSM may remove clinically concealed breast malignancies. Incidental breast cancers have been found in 2% to 12% of prophylactic mastectomy specimens.^{7,18} In this cohort, we found histological evidence of breast malignancy in 10% of specimens. There have been no cases of oncologic locoregional recurrence in patients with an incidentally discovered breast malignancy.

This study has several limitations. First, its retrospective nature introduces the potential for this study to have not accurately captured all data points. Although the follow-up interval is the longest interval to be reported to date for prophylactic NSMs, it is ultimately inadequate for establishing safety and risk-reducing ability in patients receiving prophylactic NSMs. Breast cancer can occur at any time; thus, true evaluation of prophylaxis can only be determined when examining the entirety of the patient's life.⁶ Continuing to follow this cohort will be critical to understanding the efficacy of lifetime oncologic prophylaxis. Furthermore, this study is limited by the size of the cohort. As NSMs grew in popularity in the mid-2000s, there are a limited number of patients with sufficient follow-up time for inclusion. Thus, future studies should continue to examine the outcomes of these patients as they accrue time since their prophylactic NSMs. Patients receiving prophylactic mastectomies have differential risk for subsequent breast cancer. These differences were not assessed or controlled for in this analysis. Variability may exist in the fidelity of individuals maintaining follow-up appointments among patients receiving any form of surgical care, particularly prophylactic breast surgery based on the patient's risk factors or their personal preferences. However, establishing long-term safety profiles of prophylactic NSMs may help mold clinical follow-up guidelines and assist in educating patients on subsequent oncologic risk.

CONCLUSIONS

Assessing a cohort of patients with 10 years of follow-up from prophylactic NSM, there have been zero incidences of locoregional breast cancer occurrence. While this finding supports the safety of this technique for this indication, the ultimate effectiveness of prophylaxis must continually be assessed throughout the entirety of the patient's life.

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DISCLOSURES

The authors have no financial interest to declare in relation to the content of this article.

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