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Oncologic Safety of Prophylactic Nipple-Sparing Mastectomy in a Population With *BRCA* Mutations
A Multi-institutional Study

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Invited Commentary page 129

IMPORTANCE Nipple-sparing mastectomy (NSM) offers superior cosmetic outcomes and has been gaining wide acceptance; however, its role among patients with *BRCA* mutations remains controversial.

OBJECTIVE To report on the oncologic safety of NSM and provide evidence-based data to patients and health care professionals regarding preservation of the nipple-areolar complex during a risk-reducing mastectomy in a population with *BRCA* mutations.

DESIGN, SETTING, AND PARTICIPANTS We retrospectively reviewed the outcomes of 9 institutions' experience with prophylactic NSM from 1968 to 2013 in a cohort of patients with *BRCA* mutations. Patients with breast cancer were included if they underwent contralateral risk-reducing mastectomy; however, only the prophylactic side was considered in the analysis. Patients found to have an occult primary breast cancer at the time of risk-reducing mastectomy, those having variant(s) of unknown significance, and those undergoing free nipple grafts were excluded.

MAIN OUTCOMES AND MEASURES The primary outcome measure was development of a new breast cancer after risk-reducing NSM. Three reference data sources were used to model the expected number of events, and this was compared with our observed number of events.

RESULTS A total of 548 risk-reducing NSMs in 346 patients were performed at 9 institutions. The median age at NSM was 41 years (interquartile range, 34.5-47.5 years). Bilateral prophylactic NSMs were performed in 202 patients (58.4%), and 144 patients (41.6%) underwent a unilateral risk-reducing NSM secondary to cancer in the contralateral breast. Overall, 201 patients with *BRCA1* mutations and 145 with *BRCA2* mutations were included. With median and mean follow-up of 34 and 56 months, respectively, no ipsilateral breast cancers occurred after prophylactic NSM. Breast cancer did not develop in any patients undergoing bilateral risk-reducing NSMs. Using risk models for *BRCA1/2* mutation carriers, approximately 22 new primary breast cancers were expected without prophylactic NSM. Prophylactic NSM resulted in a significant reduction in breast cancer events (test of observed vs expected events, $P < .001$).

CONCLUSIONS AND RELEVANCE Nipple-sparing mastectomies are highly preventive against breast cancer in a *BRCA* population. Although the follow-up remains relatively short, NSM should be offered as a breast cancer risk–reducing strategy to appropriate patients with *BRCA* mutations.

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The superior cosmetic results of nipple-sparing mastectomies (NSMs) has been the primary factor driving the procedure's wide dissemination; however, NSM for patients with deleterious *BRCA* mutations is controversial. As testing for hereditary cancer syndromes and NSM are simultaneously being used with increased frequency,[1,2] understanding the oncologic efficacy of this procedure is critical.

In a large *BRCA* cohort, skin-sparing prophylactic mastectomy has been shown to be a powerful means of risk reduction.[3] Several retrospective series and meta-analyses of 4 prospective studies have supported prophylactic mastectomy in *BRCA* mutation carriers, demonstrating a 93% relative risk reduction.[4,5] Prophylactic mastectomies were shown by Hartmann et al[6] in a large series with 14-year follow-up to be an effective method of risk reduction. Notably, most of these cases were NSM[6]; however, only 26 of these patients were identified to have a *BRCA* mutation.[7] We sought to define the frequency of breast cancer events after NSM in patients with deleterious *BRCA* mutations and to provide evidence to facilitate informed decision-making between patients and health care professionals.

Key Points

Question Is prophylactic nipple-sparing mastectomy oncologically safe for patients with *BRCA* mutations?

Findings This review included a cohort of 346 patients from 9 institutions who underwent 548 risk-reducing nipple-sparing mastectomies. At a median and mean follow-up of 34 and 56 months, respectively, no breast cancers developed.

Meaning Nipple-sparing mastectomy is a highly effective breast cancer prevention strategy in patients with *BRCA* mutations, and nipple-sparing mastectomy should be offered as a risk-reducing approach.

Methods

We performed a retrospective review of patients with deleterious *BRCA* mutations who underwent risk-reducing NSM at 9 institutions from 1968 to 2013. After institutional review board approval from each site, all female patients with deleterious *BRCA* mutations and were aged 18 years and older undergoing NSM were identified. Informed consent was waived by the institutional review boards because this study was a retrospective review of existing material in medical records. Patients with high-risk lesions (ie, lobular carcinoma in situ, atypical ductal hyperplasia, atypical lobular hyperplasia, flat epithelial atypia, and atypical ductal proliferation) were included. Patients with breast cancer undergoing a contralateral prophylactic mastectomy had only the side of the risk-reducing procedure analyzed for events. We assumed that development of distant metastatic events in such patients resulted from the known primary cancer.

We excluded patients with occult invasive cancer or ductal carcinoma in situ in the prophylactic breast, as well as patients with a free nipple graft or variant of unknown significance. Only patients with a successful NSM were included in the analysis. Complications, such as nipple-areolar complex (NAC) loss, have been well described in the literature[8-10] and are beyond the scope of this study. Any patient who had been previously treated for breast cancer was not considered to have a prophylactic procedure and was excluded. The principle investigator or study coordinator at each institution reviewed the medical records to capture the cases and entered the data into a standardized data collection form. No specific training, interrater reliability assessment, or blinding to the study hypothesis was performed. Data collection from each site was conducted through institutional or investigator databases of either patients with *BRCA* mutations or patients who have had NSM. As this is a multi-institutional retrospective trial, each site approached their data collection slightly differently based on the most efficient process for their respective site. Descriptive statistics were used to report the incidence of primary breast events.

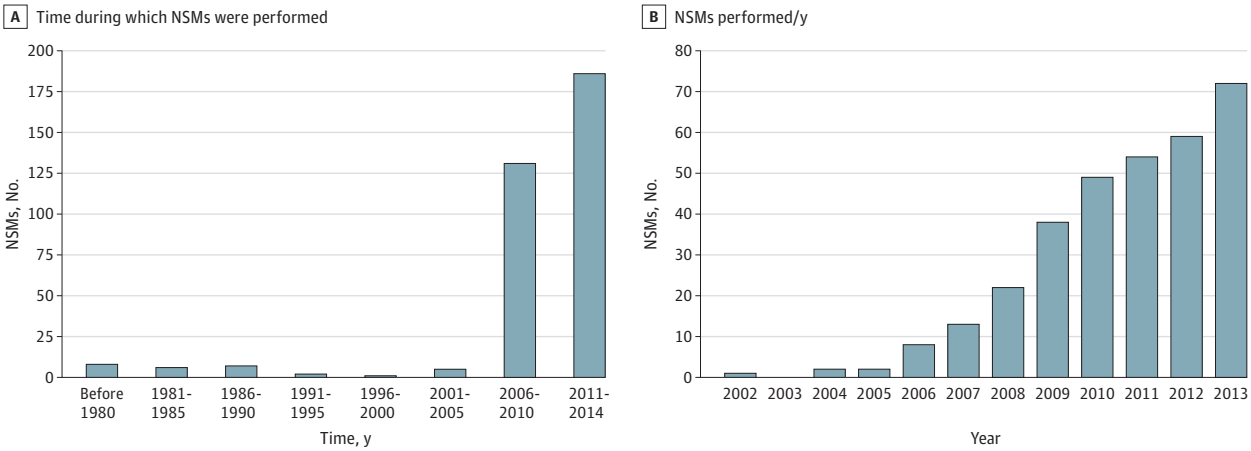
Development of invasive breast cancer or ductal carcinoma in situ after risk-reducing NSM was the primary end point, including events involving the NAC, ipsilateral skin flaps, subcutaneous tissue, chest wall, or regional lymph nodes ipsilateral to the risk-reducing mastectomy. Among the cohort of patients undergoing bilateral prophylactic procedures, development of stage IV disease was also considered a primary event.

Follow-up was calculated as the number of days from NSM to the earliest of development of a new primary breast cancer, death, or last contact. We used the indirect rate standardization method to estimate the number of expected new primary breast cancers,[11] applying the cumulative number of person-years of follow-up in our cohort to published[12-14] breast cancer incidence rates for patients with *BRCA* mutations after accounting for the effects of age and cohort period. Specifically, person-years and incidence were categorized by age and cohort period based on the same categories used in published incidence rates. We then calculated the expected number of events for each category by multiplying the incidence rate by number of person-years. Finally, we summed all category-specific expected events together to calculate 1 overall expected number.

Three such data sources were used. First, we used incidence rates derived from the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model,[12] which included women from various study sites primarily ascertained between 1980 and 1997. Rates were available in 1-year age and 10-year birth cohort period increments (defined as 1930-1939, 1940-1949, and 1950 and later), and separate rate estimates were provided for *BRCA1* and *BRCA2* mutation carriers. Rates did not distinguish between women undergoing bilateral prophylactic NSM or contralateral NSM. Thus, primary analyses assumed that both sets of women accrued breast cancer events according to the BOADICEA model, but we performed a series of sensitivity analyses assuming incidence rates for contralateral events ranged from 0.25 to 2 times the BOADICEA rates in increments of 0.25.

Second, we used incidence rates reported by Chen and Parmigiani[13] with a meta-analysis of 10 studies examining

Figure 1. Use of Nipple-Sparing Mastectomy (NSM) in the Study Population of Patients With *BRCA* Mutations



breast cancer risk in women with known *BRCA* mutations. Rates were available in 10-year increments starting at age 20 years and ending at age 70 years, and separate rates were provided for *BRCA1* and *BRCA2* mutation carriers. Rates were not provided by cohort period. To make our data set congruent with this reference data, we excluded 3 women who underwent NSM prior to age 20 years, and we truncated person-years of follow-up at age 70 years. Similar to the BOADICEA model, primary analyses assumed all women accrued events according to the published rates, but sensitivity analyses were performed assuming that incidence rates for contralateral NSM ranged from 0.25 to 2 times that of the published rates.

Third, we used data reported by van den Broek et al[14] from a cohort of 6294 patients with *BRCA* mutations who were diagnosed as having invasive breast cancer prior to age 50 years between 1970 and 2003. These patients were followed up after their initial breast cancer diagnosis to assess incidence of breast cancer in the contralateral breast. Rates were available at 5 and 10 years after initial breast cancer, in age strata of 40 years and younger and 41 to 49 years at initial breast cancer. One set of incidence rates was provided, pooled across *BRCA1* and *BRCA2* mutation carriers. Rates were not provided by cohort period. For these analyses, we subset our cohort to the 103 women undergoing a contralateral NSM after an initial breast cancer diagnosis prior to age 50 years, and we truncated person-years of follow-up at 10 years.

For each of the 3 sets of rates described,[12-14] formal, 2-sided exact tests of hypothesis comparing the observed number of new primary breast cancer events to the expected number were carried out using properties of the Poisson distribution. Data were maintained in a secure location and password-protected for each institution. From this, a limited data set was created. Patient information was protected and deidentified except for operative date. Institutional data were sent to the central study site, where they were collated, electronically stored, and password-protected.

Results

A total of 346 patients underwent 548 risk-reducing NSMs from 9 institutions between 1968 and 2013. The number per institution was 1, 11, 20, 31, 52, 84, 89, 125, and 135. Bilateral prophylactic NSMs were performed in 202 patients (58.4%), and 144 (41.6%) underwent a unilateral risk-reducing NSM secondary to a prior or concurrent cancer in the contralateral breast. Within the study cohort, 201 patients (58.1%) were diagnosed as having a *BRCA1* mutation and 145 (41.9%) with a *BRCA2* mutation. The median age at NSM was 41 years (interquartile range, 34.5-47.5 years). Median follow-up was 34 months (interquartile range, 18-58 months), and mean follow-up was 56 months (95% CI, 48-64) with 23% of patients (n = 79) having at least 60 months of follow-up. There were 1611 person-years of follow-up, and among the 548 NSMs, there were 2662 years of follow-up, a mean of 47 months per NSM in the unilateral group (95% CI, 38-56) and 62 months (95% CI, 54-71) in the bilateral group. After prophylactic NSM, no breast cancers developed in the ipsilateral NAC, skin flaps, subcutaneous tissue, mastectomy scar, chest wall, or regional lymph nodes on the side of the risk-reducing procedure. No breast cancer events occurred at any site in patients who underwent a bilateral risk-reducing NSM. Twelve patients died during follow-up (3.5%): 7 from breast cancer, 3 from ovarian or fallopian tube cancer, and 2 from other causes. Of the 7 deaths from breast cancer, all had a synchronous or previous breast cancer at the time of their contralateral prophylactic mastectomy, and the stage IV disease was determined to be related to their known cancer. The use of NSM in the population of patients with *BRCA* mutations has steadily increased at the participating centers during the past decade (**Figure 1**).

Using incidence rates from the BOADICEA model[12] and from Chen and Parmigiani,[13] we would have expected 21.8 and 22.1 new primary breast cancer events, respectively, had our patients not undergone prophylactic mastectomies, com-

Table. Expected Number of New Primary Breast Cancers for Different Prediction Models and Contralateral NSM Assumptions[a]

Prediction Model	Group	Women, No.	Expected New Primary Breast Cancers, No.							
			0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00
BOADICEA[12]	*BRCA1* mutation carriers	201	10.6	11.7	12.8	13.9	15.0	16.1	17.2	18.3
	BRCA2 mutation carriers	145	5.7	6.4	8.2	7.9	8.7	9.5	10.2	11.0
Chen and Parmigiani[13]	Women aged 20-70 y at NSM	343	16.4	18.3	20.2	22.1	24.0	25.9	27.8	29.7
van den Broek et al[14]	Women aged <50 y with primary breast cancer and contralateral NSM	103	NA	NA	NA	9.7	NA	NA	NA	NA

Abbreviations: BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; NA, not applicable; NSM, nipple-sparing mastectomies.

[a] The BOADICEA[12] and Chen and Parmigiani[13] models do not distinguish between bilateral NSM and contralateral NSM. Thus, sensitivity analyses were run (1) assuming breast cancer incidence for women with bilateral NSM equaled the model-based rates and (2) varying rates for women with contralateral NSM from 0.25 to 2 times that of the model-based rates by increments of 0.25. For instance, the column labeled "0.50" assumes incidence of a new primary breast cancer in women with contralateral NSM is half that of the model-based rate. Each test comparing the observed number of new primary breast cancer events (n = 0) with the expected numbers listed above were highly significant ($P < .001$ for each).

pared with 0 observed events in our study group (comparing observed number of events to expected number of events, $P < .001$; **Table**). Results remained highly significant when assuming women undergoing contralateral NSM had risk ranging from 0.25 to 2 times that of those undergoing bilateral NSM ($P < .001$ for each). For the 103 women undergoing contralateral NSM younger than age 50 years, we would have expected 9.7 new breast cancers on the risk-reducing side, using incidence rates provided by van den Broek et al[14] ($P < .001$; Table).

Because of concerns that screening techniques, surgical procedures, and genetic testing have changed over time, we ran sensitivity analyses subset to women undergoing NSM during or after 1995 using the BODICEA model.[12] Results were similar to our primary analyses: 0 observed events and 13.1 expected events ($P < .001$). Because of potential decreased efficacy of NSM for older women, we ran sensitivity analyses excluding the 6 women aged 65 years or older. Results were nearly identical to our primary analyses: 0 observed events and 21.4 expected events ($P < .001$).

Discussion

BRCA mutation carriers face a cumulative lifetime breast cancer risk of approximately 60% in *BRCA1* and 50% in *BRCA2* by age 70.[13,15] Multiple strategies are effective in managing the risk of breast cancer in these women, including bilateral salpingo-oophorectomy, chemoprevention, surveillance, and risk-reducing mastectomy. Risk-reducing bilateral salpingo-oophorectomy offers an approximate 50% relative reduction in breast cancer risk,[16] while the risk-reducing benefit of chemoprevention is not as well defined.[17] Although a risk-reducing bilateral salpingo-oophorectomy offers a survival benefit,[18,19] the overall survival benefit of bilateral prophylactic mastectomy is not as clearly defined.[3,19] More intensive screening programs, including magnetic resonance imaging, have significantly improved early detection among patients with deleterious *BRCA* mutations.[20-22] Ultimately, prophylactic mastectomy provides the greatest reduction in risk of breast cancer development.

Our analysis of 548 risk-reducing NSMs in 346 patients with deleterious *BRCA* mutations identified no cases of a primary breast cancer developing on the side of the prophylactic procedure. Based on risk models developed for *BRCA1/2* carriers, we would have expected approximately 22 new breast cancer events, suggesting that NSM is an oncologically effective approach, even in this high-risk population. We used 3 different prediction models to determine expected number of breast cancers that would develop in this population during the follow-up period had a prophylactic NSM not been performed. Furthermore, we used variations of expected events within 2 of these models for contralateral events ranging between 0.25 and 2 times the model-based estimates. For each of these combinations, the 0 observed breast cancer events were statistically significantly lower than expected, demonstrating that our findings are robust to variability both within and across model-based estimates. In the context of the cumulative published literature, our data support the use of prophylactic NSM as a safe risk-reducing option in a *BRCA* population.

Our study population is similar to the Prevention and Observation of Surgical Endpoints (PROSE) study.[18] The PROSE study was a multi-institutional prospective study that included 1372 women with a *BRCA* mutation who did not undergo risk-reducing mastectomy. At a similar follow-up of 3 years, breast cancer developed in 7% of patients in the PROSE study. It is worth noting the PROSE study had a younger population but a higher proportion of *BRCA1* mutation carriers. Translating this to our cohort, we would expect 24 of 346 patients (6.9%) to develop breast cancer (very similar to the formal estimate of 22 events derived from the BOADICEA[12] and Chen and Parmigiani[13] models). Considering only the 202 unaffected individuals in our study (bilateral prophylactic procedure), we would have expected 14 events. For the patients younger than age 50 years undergoing a contralateral prophylactic mastectomy, 10 events would have been expected. Thus, an estimated 24 events would be expected from these subgroups that encompass 305 of 346 patients (88%). We did not use the PROSE study for our modeling because age was not accounted for in that trial; however, this prospective multi-institutional study provides further evidence for the number

of breast cancer events the current cohort of patients with *BRCA* did not have by undergoing prophylactic NSM.

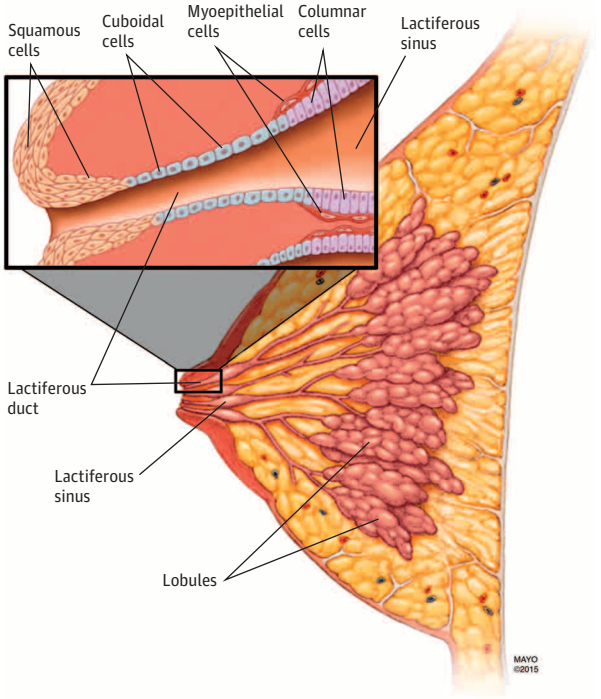
To our knowledge, there is a growing body of literature on the oncologic safety of NSM, although most of these data are among patients with no known genetic mutation, and most publications are single-institution retrospective reviews with somewhat limited follow-up. Yao et al[23] reported on a series of NSMs in women with *BRCA* mutations that included 150 prophylactic patients. No NAC events occurred, and 1 new primary breast tumor developed at a mean follow-up of 32.6 months. Sakurai et al[24] reported a low rate of NAC recurrence (3.7%) in 788 patients who underwent NSM. There was no difference in local recurrence between NSM and non-NSM cohorts (8.2% vs 7.6%, $P = .81$).[24]

A mastectomy of any type never removes 100% of the breast tissue; however, consciously leaving behind additional ductal tissue with an NSM can cause the patient and clinician pause, especially among *BRCA* carriers in which all somatic cells carry the genetic mutation. Most breast cancers arise in the terminal duct lobular units (TDLUs), which are concentrated in the deep central portions of the breast but do not exist in the dermis or epidermis of the NAC. A pathologic study of non-NSM nipple and retroareolar tissue specimens in *BRCA* carriers demonstrated TDLUs in the retroareolar tissue but few in the nipple.[25] Terminal duct lobular units were present in only 8% of nipple papillas and in the immediate retroareolar tissue of 16% of nipple specimens. Other series report TDLUs in approximately 10% to 15% of nipple specimens, rarely near the tip of the nipple and most commonly at the base.[26,27] The nipple and areola are covered by squamous epithelium. The squamous cells lining the ducts extend a short distance[25] where they transition to columnar cells. This transition normally occurs 1.2 mm and 3.6 mm from the nipple surface[28] and distal to the lactiferous sinus, which is a dilated segment of the lactiferous duct, respectively (**Figure 2**).[29] Thus, the cutaneous portion of the NAC does not have the same biologic risk for developing a primary breast tumor, and NSM can be a safe prophylactic procedure. The amount of at-risk tissue preserved is primarily dependent on retroareolar and skin flap thickness.[27,30]

Although contemporary NSMs differ from the previous subcutaneous mastectomy, the fact remains that ducts exiting the nipple are preserved. There remains a balance during NSM between being surgically aggressive to remove as much at-risk tissue (ie, TDLUs) as possible and limiting the flap necrosis rate, which can impair cosmesis. The current approach at our centers is to follow the subcutaneous-glandular breast tissue plane until that plane is lost in the retroareolar space, where the ducts exit the nipple orifice. Here, sharp division of the ducts is performed in a plane that leaves the underside of the nipple dermis as the final margin. We do not routinely core out the nipple ducts. When performing a contemporary prophylactic NSM, breast parenchyma behind the NAC is not intentionally preserved, and mastectomy after radiation is not advised.

Nipple-sparing mastectomy with reconstruction has been well incorporated into clinical practice, and a randomized clinical trial is unlikely. Choosing prophylactic mastectomy is a major decision for women with *BRCA* mutations, and surgical treatment options that optimize cosmesis have the potential to improve quality of life, with NSM patients reporting higher psychosocial ($P = .01$) and sexual well-being ($P = .02$) scores.[31]

Figure 2. Magnification View of Nipple Ducts



The inset demonstrates the transition of the lining of the nipple ducts from squamous at the orifice to cuboidal and eventually columnar at the lactiferous sinus. This figure is adapted from Chiba et al[29] with permission from *Current Surgery Reports*.

Limitations and Strengths

Our series is limited by its retrospective design and approximate 3-year median follow-up. The data abstractors were not blinded, as the medical record reviews were focused on identifying patients who underwent an NSM and/or had a *BRCA* mutation. This study spanned over 4 decades and 9 institutions; thus, there is likely variation in technique and indications for NSM. Because there is not a unique procedural code for NSM compared with simple or skin-sparing mastectomy, retrospectively abstracting this data can be a challenge as it could require manual review of all mastectomies. Thus, many high-volume centers maintain databases of NSM procedures and/or *BRCA* mutation carriers, and these were the sources used for the searches. It is possible that some cases were missed secondarily to this method. Despite this, we demonstrate robust results, finding no cancers after NSM. Our findings suggest that variations in surgical approach and potentially evolving indications did not affect oncologic outcomes. On the contrary, we believe these results are generalizable to high-volume breast surgeons most likely to routinely perform NSM. Results of our study are also limited by the inputs used in our model. We do

not have data on risk-reducing oophorectomy, adjuvant chemotherapy or endocrine therapy, or family history, which are all known to be associated with development of breast cancers. Finally, a statistical limitation to observing no cancers after NSM is the lack of variability that prevents us from calculating confidence intervals or other measures of precision. Notably, if instead of 0 events we observed 1 event, the resulting 95% CI would range from 0 to 3.7 events, still well below the expected numbers we calculated.

The strengths of the current study are the multiinstitutional collaboration and the number of patients included. To our knowledge, this represents the largest series of prophylactic NSM in *BRCA* mutations carriers in the literature, representing more than 1611 person-years of follow-up and 2662 years of surveillance among 548 NSMs.

Conclusions

Nipple-sparing mastectomies are highly preventive against breast cancer in a *BRCA* population. Although the follow-up remains relatively short, the cumulative evidence to date supports NSM as an appropriate risk-reducing procedure for patients with deleterious *BRCA* mutations.

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Author Contributions: Dr Jakub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jakub, Gray, Sacchini, Degnim.
Acquisition, analysis, or interpretation of data: Jakub, Peled, Gray, Greenup, Kiluk, Sacchini, McLaughlin, Tchou, Vierkant, Willey.
Drafting of the manuscript: Jakub, Sacchini, Tchou, Vierkant.
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Invited Commentary

When Is a Little Breast Tissue Too Much?
Nipple-Sparing Risk-Reducing Mastectomy in *BRCA* Carriers

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Whether a proportional reduction in the volume of breast tissue proportionately reduces the risk of developing breast cancer has been seriously debated in light of the recognition that most patients undergoing prophylactic mastectomy have residual breast tissue, including terminal ductal units in the skin flaps.[1,2] Animal studies[3] from 1986 suggested that the risk of developing mammary tumors was not proportionately reduced by the amount of breast tissue removed. Thus, it was recommended that if absolute protection was desired, a total mastectomy, including the nipple-areolar complex, was required.[3]

Related article page 123

However, several observational studies[4,5] have shown a greater than 90% reduction in the risk of developing breast cancer in women who underwent prophylactic mastectomy, usually either total mastectomy or skin-sparing mastectomy. Given the superior cosmetic results of nipple-sparing mastectomy (NSM) with immediate reconstruction,[6] NSM has become an increasingly popular risk-reduction strategy.

The study by Jakub and colleagues[7] demonstrates the benefit of risk-reducing surgery extended to patients with known *BRCA* gene mutations and who have undergone NSM. In this study, no breast cancer events occurred in patients who underwent bilateral risk-reducing NSM at a median follow-up of 36 months, a period in which using several predictive models, up to 22 breast cancers would have been predicted to have been diagnosed in their cohort.

Can this risk reduction be attributed solely to reduction in the number of breast cancer cells? All of these individuals were known *BRCA* carriers, and it is likely many had risk-reducing salpingo-oophorectomy. What, if any, effect this may have on the risk of developing breast cancer was not examined in this report.

Although it seems intuitive that reducing the volume of breast tissue would likely reduce the risk of developing breast cancer, *BRCA* carriers have germline mutations. Any residual breast tissue remains at the same inherent risk of developing breast cancer. *BRCA* mutations result in potentially harmful breaks in DNA strands that can promote genomic instability and lead to cancer. Does the reduction in the number of breast cancer cells at risk simply represent a reduction in the statistical chance of a harmful event occurring? If so, might a longer period of follow-up demonstrate just a delay in the future development of breast cancer after a statistical increase in the number of harmful events attains a certain threshold? The report by Jakub and colleagues[7] is reassuring that, at least in the short-term, NSM provides substantial risk reduction in *BRCA* mutation carriers. Because many of these procedures are performed in younger individuals with a substantial future cumulative risk of developing breast cancer, continued and long-term follow-up is critical.

ARTICLE INFORMATION

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