Oncological and Surgical Outcomes of Risk Reducing Nipple-sparing Mastectomy in Germline Pathogenic Variant Carriers

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Introduction

Nipple-sparing mastectomy (NSM) is increasingly adopted as a risk-reducing surgical approach in women with germline pathogenic variants (PVs), with the potential advantage of maintaining body image through preservation of the nipple-areolar complex. Although oncologic outcomes are well established for risk-reducing mastectomies in BRCA1/2 carriers, data are limited for NSM as well as for individuals with other high- and moderate-penetrance PVs. This study aimed to evaluate the incidence of new breast cancer, cosmetic outcomes and surgical complications following risk-reducing NSM in a genetically diverse population.

Methods and Materials

We conducted a multicenter retrospective cohort study of risk-reducing NSM performed between May 2008 and February 2025 across 12 institutions. Eligible patients had ≥1 germline PV and were classified according to the highest-risk gene. Asymptomatic patients or individuals with unilateral breast cancer were included if they underwent contralateral risk-reducing mastectomy (CRRM) or bilateral risk-reducing mastectomy (BRRM) ≥2 years after breast-conserving surgery. Patients with bilateral occult malignancy detected at NSM were excluded. Crude incidence rates were used to report new breast cancer diagnoses and surgical complications. Cosmetic outcomes were assessed using the Harvard four-point scale. Risk factors for complications were analyzed using univariable (UVA) and multivariable (MVA) analyses.

Results

A total of 524 patients underwent risk-reducing NSM: 219 BRRM and 305 CRRM, totaling 743 mastectomies. Most patients carried BRCA1 (46.0%) or BRCA2 (25.4%) PVs, followed by TP53 (15.1%), PALB2 (6.9%), CHEK2 (3.6%), and ATM (1.9%). Median age at NSM was 40 years (range 20–68). At a median follow-up of 30 months (IQR 13.1–60.3), three patients (0.6%) developed breast cancer: one nodal recurrence post-BRRM, and two flap recurrences post-CRRM. Breast cancer–related death occurred in three patients (0.6%), all following CRRM. Cosmetic outcomes were favorable, with 90% rated as excellent or good. Surgical complications occurred in 101 patients (19.3%), more frequently after CRRM (24.6%) than BRRM (11.9%) (p<.001). On UVA, complications in BRRM were associated with obesity (OR 9.15, 95% CI 2.08–40.2, p=0.003) and Wise-pattern incision (OR 35.0, 95% CI 2.57–47.3, p=0.008). In CRRM, comorbidities (OR 2.76, 95% CI 1.38–5.54, p=0.004) and Wise-pattern incision (OR 7.33, 95% CI 1.65–32.5, p=0.009) were significant. On MVA, comorbidities (OR 2.59, 95% CI 1.23–5.47, p=0.012) and Wise-pattern incision (OR 7.83, 95% CI 1.73–35.5, p=0.008) remained independently associated with complications in CRRM; no independent predictors were found in BRRM.

Conclusions

In this multicenter cohort of women with high- and moderate-penetrance germline PVs, risk-reducing NSM was associated with a very low incidence of new breast cancer (0.6%), supporting its oncologic safety. Most patients achieved favorable cosmetic outcomes. Surgical complication rates were higher after CRRM and associated with comorbidities and Wise-pattern incisions. These findings may guide surgical planning and patient counseling for risk-reducing NSM in genetically predisposed populations.

Clinical and surgical characteristics, n (%)	Overall (n=524) n / %	Bilateral risk-reducing NSM (n=219) n / %	Contralateral risk-reducing NSM (n=305) n / %
Pathogenic variant gene			
BRCA1	241 (46.0)	111 (50.7)	130 (42.6)
BRCA2	133 (25.4)	61 (27.9)	72 (23.6)
TP53	79 (15.1)	17 (7.8)	62 (20.3)
PALB2	36 (6.9)	18 (8.2)	18 (5.9)
PTEN	1 (0.2)	0 (0.0)	1 (0.3)
CHEK2	19 (3.6)	9 (4.1)	10 (3.3)
ATM	10 (1.9)	3 (1.4)	7 (2.3)
BARD1	2 (0.4)	0 (0.0)	2 (0.7)
RAD51C	1 (0.2)	0 (0.0)	1 (0.3)
RAD51D	2 (0.4)	0 (0.0)	2 (0.7)
BMI, median (range)	24.2 (17.2–39.0)	23.8 (18.0–36.3)	24.5 (17.2–39.0)
Missing	224	98	126
Obesity	29 (9.7)	9 (7.4)	20 (11.2)
Missing	224	98	126
Comorbidities	60 (11.5)	20 (9.1)	40 (13.3)
Missing	4	0	4
Age at risk-reducing NSM, median (range)	40 (20-68)	41 (20-67)	40 (22-68)
NSM incision			
Radial	41 (8.1)	16 (7.5)	25 (8.6)
Periareolar	83 (16.5)	36 (16.9)	47 (16.2)
Inframammary fold	354 (70.2)	155 (72.8)	199 (68.4)
Wise pattern	26 (5.2)	6 (2.8)	20 (6.9)
Missing	20	6	14
Breast weight in grams, median (IQR)	250.0 (185.5–325)	226.0 (46.0–670.0)	270.0 (35.0–1200.0)
Missing	150	62	88
Breast implant volume, median (range)	390.0 (175.0–675.0)	362.5 (175.0–620.0)	400.0 (175.0–675.0)
Missing	135	51	84
Reconstruction type			
Direct implant	447 (85.5)	194 (88.6)	253 (83.2)
Tissue expander	76 (14.5)	25 (11.4)	51 (16.8)
Missing	1	0	1
Implant plane			
Subpectoral	378 (72.8)	168 (77.4)	210 (69.5)
Prepectoral	141 (27.2)	49 (22.6)	92 (30.5)
Missing	5	2	3
Radiotherapy	126 (24.0)	20 (9.1)	106 (34.8)

Table 1. Clinical and surgical characteristics of patients undergoing nipple-Sparing mastectomy according to type of risk-reduction Surgery.

Surgical complications and cosmetic outcomes	Overall (n=524) n / %	Bilateral risk-reducing NSM (n=219) n / %	Contralateral risk-reducing NSM (n=305) n / %
Surgical complications			
No	423 (80.7)	193 (88.1)	230 (75.4)
Yes	101 (19.3)	26 (11.9)	75 (24.6)
Post-surgical complication type			
Partial NAC necrosis	31 (5.9)	9 (4.1)	22 (7.2)
Complete NAC necrosis	7 (1.3)	0 (0.0)	7 (2.3)
Wound dehiscence	37 (7.1)	11 (5.0)	26 (8.5)
Infection	33 (6.3)	9 (4.1)	24 (7.9)
Hematoma	20 (3.8)	4 (1.8)	16 (5.3)
Implant loss	22 (4.2)	4 (1.8)	18 (5.9)
Capsular contracture			
Missing	19 (3.6)	5 (2.3)	14 (4.6)
Baker 1	353 (67.5)	171 (78.4)	182 (59.7)
Baker 2	106 (20.3)	29 (13.3)	77 (25.2)
Baker 3	45 (8.6)	13 (6.0)	32 (10.5)
Additional reconstructive surgery	38 (7.3)	11 (5.0)	27 (8.9)
Cosmetic outcome by Harvard Scale			
Excellent	230 (59.9)	111 (71.6)	119 (52.0)
Good	113 (29.4)	40 (25.8)	73 (31.9)
Fair	25 (6.5)	1 (0.6)	24 (10.5)
Poor	16 (4.2)	3 (1.9)	13 (5.7)
Missing	140	64	76

Table 2. Surgical complications and cosmetic outcomes of patients undergoing nipple-Sparing mastectomy according to type of risk-reduction Surgery.

Oncological outcomes	Overall (n=524) n / %	Bilateral risk-reducing NSM (n=219) n / %	Contralateral risk-reducing NSM (n=305) n / %
Breast cancer after risk-reducing NSM			
No	521 (99.4)	217 (99.1)	304 (99.7)
Yes	3 (0.6)	2 (0.9)	1 (0.3)
Breast cancer death			
No	521 (99.4)	219 (0)	302 (99.0)
Yes	3 (0.6)	0 (0.0)	3 (1.0)

Table 3. Oncological outcomes of patients undergoing nipple-Sparing mastectomy according to type of risk-reduction Surgery.

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