Trends in the uptake of nipple sparing mastectomy in BRCA1/2, PALB2, and other pathogenic variant carriers undergoing risk-reducing mastectomy

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BACKGROUND

- Germline pathogenic variants (in *BRCA1/2, PALB2,* and other high penetrance genes) confer up to a 70% lifetime breast cancer risk, making risk-reducing mastectomy (RRM) a key preventive strategy;
- Nipple-sparing mastectomy (NSM) has recently gained popularity over total or skin-sparing mastectomy (SSM) due to superior cosmetic results and increased patient satisfaction;
- Limited data exist on NSM adoption trends among high-risk carriers; understanding these trends supports informed decision-making and standardized preventive care.

OBJECTIVES

To assess temporal trends in the uptake of NSM compared to SSM and total mastectomy among carriers of *BRCA1/2, PALB2*, and other pathogenic variants and identify clinical and demographic factors associated with NSM.

COHORT SELECTION

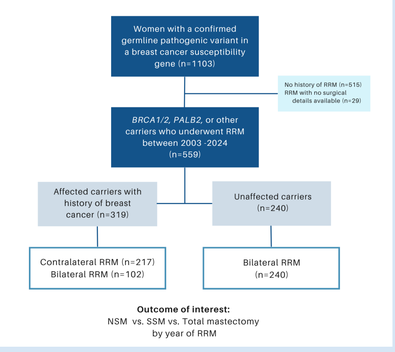


Figure 1. Cohort selection and outcome of interest
We performed a retrospective cohort study of female germline pathogenic variant carriers who underwent RRM between 2003-2024 at two McGill University-affiliated academic centers in Montreal, QC, Canada. The cohort included *BRCA1/2, PALB2, TP53, CDH1*, and *PTEN* carriers with or without a history of breast cancer. The cohort included 559 carriers, including 217 (39%) who underwent contralateral RRM and 342 (61%) who underwent bilateral RRM.

METHODS

Study design: Multi-institutional retrospective cohort study;
Primary outcome of interest: Type of RRM performed with or without reconstruction, including NSM, SSM or total mastectomy;
Statistical Analysis: The proportion of patients undergoing each type of RRM over time were evaluated using the Mantel-Haenszel test for trend. Univariate analysis of factors associated with each type of RRM was performed using Chi-squared tests. Multivariable logistic regression was then used to assess factors independently associated with receipt of NSM using all factors significant (p<0.05) on univariate analysis.

RESULTS

TABLE Univariate analysis of factors associated with nipple sparing mastectomy in *BRCA1/2, PALB2* and other carriers undergoing risk reducing mastectomy

Characteristic	Cohort No. (%)	Proportion undergoing NSM %	*p-value*
Age Group			**0.03**
<30 years	51 (9.1)	56.9	
30-39 years	137 (24.5)	60.6	
40-49 years	179 (32.0)	60.9	
50-59 years	123 (22.0)	48.8	
60+ years	69 (12.3)	42.0	
Germline Pathogenic Variant (GPV)			**0.002**
BRCA1	261 (46.7)	51.0	
BRCA2	248 (44.4)	55.7	
PALB2, TP53, CDH1 or *PTEN*	50 (8.9)	78.0	
Parity			**0.028**
Nulliparous	130 (23.3)	63.9	
Parous	429 (76.7)	52.9	
Menopausal status			**0.005**
Premenopausal	225 (42.0)	64.9	
Post-menopausal: premenopausal RRSO	186 (34.7)	52.7	
Post-menopausal: natural menopause (±RRSO)	125 (23.3)	46.4	
BMI at surgery			**0.004**
<18.5	177 (31.7)	44.1	
18.5-24.9	197 (35.2)	66.0	
25-29.9	102 (18.3)	56.9	
30 or more	83 (14.9)	53.0	
Smoking			0.72
Never smoker	433 (77.5)	55.0	
Former smoker	68 (12.2)	54.4	
Current smoker	58 (10.4)	60.3	
Diabetes			0.16
Yes	22 (3.9)	40.9	
No	537 (96.1)	56.1	
Breast cancer			**<0.001**
Affected carrier	319 (57.1)	47.0	
Unaffected carrier	240 (42.9)	66.7	
Prior Radiation			**<0.001**
Yes	143 (25.6)	34.3	
No	416 (74.4)	62.7	
Year of RRM			**<0.001**
Prior to 2012	84 (15.0)	11.9	
2013-2015	101 (18.1)	33.7	
2016-2018	126 (22.5)	62.7	
2019-2021	119 (21.3)	76.5	
After 2022	129 (23.1)	74.4	

RESULTS

Of 559 RRM patients:
75 (13.4%) underwent total mastectomy;
174 (31.1%) underwent skin-sparing mastectomy (SSM);
310 (55.5%) underwent nipple-sparing mastectomy (NSM)

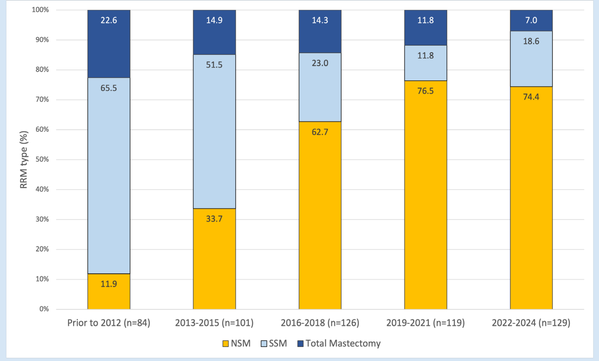


Figure 2. Type of risk-reducing mastectomy performed by year of surgery.
SSM was the most common type of RRM performed early in the study period (65.5% before 2012), following which there was a clear trend towards increasing use of NSM, from 12% of cases performed before 2012 to 74% of cases after 2022 (p<0.001). After 2016, it remained the dominant RRM approach for *BRCA1/2* and *PALB2* carriers.

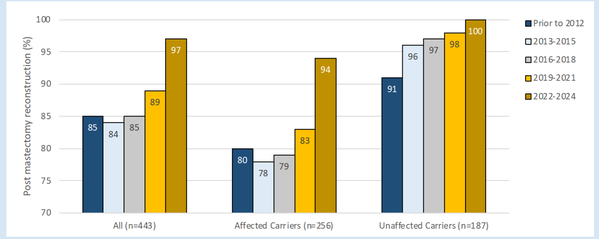


Figure 3. Proportion of patients undergoing reconstruction, by year of surgery and stratified by personal history of breast cancer.
Reconstruction was used in 85% of carriers undergoing reconstruction before 2012, compared to 97% of carriers undergoing RRM after 2022 (p<0.001). Reconstruction was considerably more common in unaffected carriers undergoing bilateral RRM.

FACTORS ASSOCIATED WITH NSM

Characteristic	OR (95% CI)	p-value
Age Group		0.38
<30 years	Ref	
30-39 years	1.26 (0.56-2.84)	
40-49 years	1.50 (0.65-3.47)	
50-59 years	0.90 (0.34-2.32)	
60+ years	0.66 (0.22-1.94)	
Germline Pathogenic Variant		0.13
BRCA1	Ref	
BRCA2	1.01 (0.65-1.57)	
PALB2, TP53, CDH1, PTEN	2.36 (0.99-5.63)	
Parity		0.53
Nulliparous	Ref	
Parous	0.85 (0.51-1.42)	
Menopausal status		0.32
Premenopausal	Ref	
Post-menopausal after premenopausal RRSO	1.47 (0.85-2.55)	
Post-menopausal after natural menopause (±RRSO)	0.82 (0.35-1.91)	
BMI at surgery		**0.046**
<18.5	Ref	
18.5-24.9	**1.83 (1.07-3.13)**	
25-29.9	1.38 (0.74-2.59)	
30 or more	0.84 (0.44-1.61)	
Breast cancer		0.09
Affected carrier	Ref	
Unaffected carrier	1.53 (0.93-2.54)	
Prior Radiation		**<0.001**
Yes	Ref	
No	**2.94 (1.69-5.12)**	
Year of RRM		**<0.001**
Prior to 2013	Ref	
2013-2015	**3.45 (1.43-8.34)**	
2016-2018	**13.9 (5.75-33.45)**	
2019-2021	**28.1 (11.3-69.6)**	
After 2022	**22.5 (9.17-55.2)**	

CONCLUSIONS

- NSM uptake has risen dramatically among high-penetrance carriers, becoming the predominant RRM approach over the past two decades;
- Year of surgery and absence of prior radiation were the strongest independent predictors of undergoing NSM;
- Understanding these evolving trends enhances patient counselling, supports standardized preventive care, and promotes patient-centred surgical decision-making.

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