

# NSM for BRCA-mutated patients

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Growing numbers of asymptomatic women who become aware of carrying a breast cancer gene (BRCA) mutation are choosing to undergo risk-reducing bilateral mastectomies with immediate breast reconstruction. We reviewed the literature with the aim of assessing the oncological safety of nipple-sparing mastectomy (NSM) as a risk-reduction procedure in BRCA-mutated patients.

Keywords: breast cancer ; BRCA mutations ; risk reduction ; nipple-sparing mastectomies

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## 1. Introduction

Fifty-five to sixty-five percent of women with BRCA1 mutation and 45% of women with BRCA2 mutations will develop breast cancer by the age of 70 years <sup>[1][2]</sup>. Growing numbers of asymptomatic women who become aware of carrying a BRCA mutation are choosing to undergo risk-reducing bilateral mastectomies with immediate breast reconstruction <sup>[3]</sup>, due to the so-called Angelina Jolie effect <sup>[4]</sup>. For these patients NSM is the preferred option, allowing better patient-reported outcomes <sup>[5][6]</sup>. Based on current evidence, risk-reducing mastectomies in BRCA mutations carriers reduce the risk of subsequent breast cancer by 89–95% <sup>[7]</sup>. As NSMs have been associated with residual glandular breast tissue, in particular underneath the nipple-areolar complex <sup>[8][9][10][11][12]</sup>, the oncological safety in terms of risk reduction in BRCA mutated patients is of particular concern.

## 2. Results and Discussion

Nine retrospective studies have investigated the safety of NSM as a risk-reducing procedure in asymptomatic BRCA carriers. All studies, except the one from Hartmann and colleagues <sup>[13]</sup>, have a relatively short follow-up (range 18.5–41.8 months). Additionally, all but two studies by Jakub and Domchek <sup>[14][15][16][17][18][19]</sup> included a small number of patients (range 20–150).

The majority of the studies also included subgroups of patients with a history of breast cancer who underwent therapeutic NSM. Although the percentage of BRCA1/2 for the group of patients who underwent prophylactic NSM was not always reported <sup>[17][18][19]</sup>. The median age at surgery was similar across the studies (range 36.5–41 years). The incidence of primary breast cancer post-NSM in asymptomatic BRCA mutated patients who underwent risk-reducing bilateral procedures was low and consistent across all studies.

According to a recent systematic review, residual glandular breast tissue is reported in up to 100% of patients undergoing mastectomy and is mainly associated with the type of surgical procedure, indication, and surgeon's expertise <sup>[8]</sup>. Residual breast tissue can be found in all areas of the remaining chest wall, mostly in the skin-flaps and more frequently underneath the nipple-areolar complex <sup>[8]</sup>. This poses a risk for subsequent breast cancer development. In a study by Papassotiropoulos, 2019 <sup>[22]</sup>, residual breast tissue (RBT) was detected in 82/160 (51.3%) mastectomies. The median RBT percentage per breast was 7.1%. Of all factors considered, only the type of surgery (40.4% for SSM vs. 68.9% for NSM;  $p < 0.001$ ) and surgeon's case load ( $p < 0.001$ ) were significantly associated with RBT. This evidence is particularly relevant when considering the generalizability of the results of our review, as all the included studies have been conducted in highly specialized breast centers with dedicated breast surgeons, treating a high volume of patients.

The probability of nipple involvement by premalignant lesions (i.e., ductal carcinoma in situ) in the nipple-areolar complex of BRCA mutation carriers is low at the time of risk-reducing procedures <sup>[23]</sup>. Manning et al. highlighted the importance of focused retro areolar tissue assessment and designation of a separate nipple margin even in BRCA carriers undergoing prophylactic NAC-sparing mastectomy. However, the practice of focused retro areolar tissue assessment in asymptomatic BRCA mutation carriers undergoing risk-reducing NSM is currently not recommended by international guidelines <sup>[24][25]</sup>.

According to the results of our literature review, NSM appears to be a safe option for BRCA mutation carriers from an oncological point of view, as the reported rates of postoperative complications are low in all the included series. However, surgical training and surgeon experience are crucial in limiting complications and the amount of breast tissue left behind.

An important aspect to consider is the impact of NSM on quality of life. Unfortunately, none of the studies in this review included data on patient-reported outcomes (PROMs). However, other studies have looked explicitly at PROMs in BRCA carriers who underwent risk-reducing surgery. Metcalfe and colleagues reported that women who underwent NSM have better body image and sexual functioning compared with SSM, while both groups had comparable levels of cancer-related distress and perception of breast cancer risk [26]. Keller and colleagues conducted a retrospective study of 39 BRCA1/2 carriers, half of whom were asymptomatic at the time of surgery. The great majority (87%) underwent NSM. At a median follow-up of 5.6 years after surgery, most patients were satisfied or very satisfied with the cosmetic outcome (33/39; 85%). Only four patients reported discontentment (4/39; 10%) with the cosmetic outcome, and two (2/39; 5.1%) would elect a different type of operation. Improvement in quality of life was seen in 78% of patients, with a reduction in anxiety being the most important factor. None of the 39 patients reported regrets despite approximately 50% experiencing some degree of pain and a minority (7/39; 18%) reporting moderate limitations in everyday life and limitations in leisure time activities (4/39; 10.3%) [27]. Salibian and colleagues evaluated patient satisfaction in 22 very young (<30 years) BRCA carriers who underwent NSM and found similar results. At an average follow-up of 37 months, none of the patients regretted their decision, and 83.3% of patients would have the procedure at the same age, 8.3% at an earlier age, and 8.3% at a later age. Twelve patients also completed the BREAST-Q surveys: average scores for satisfaction with breasts and information were 73 and 77.8, respectively. Average well-being scores were 79 (Physical), 78.2 (Psychosocial), and 79.6 (Sexual) [28]. These findings are in line with a recent Cochrane meta-analysis that evaluated the efficacy of risk-reducing mastectomy and its impact on the quality of life in both BRCA and non-BRCA carriers [29].

### 3. Conclusions

Nipple-sparing mastectomy appears to be an oncologically safe option for BRCA mutation carriers, with low reported rates of new breast cancers, low rates of postoperative complications, and high levels of satisfaction and postoperative quality of life. However, larger multi-institutional studies with longer follow-up are needed to establish this procedure as the best surgical option in this setting.

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