

Title:

MRI Volumetric Analysis of Breast Fibroglandular Tissue to Assess Risk of the Spared Nipple in *BRCA 1/2* Patients Who Are Considering Prophylactic Nipple Sparing Mastectomy

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Purpose: Prophylactic nipple sparing mastectomy (NSM) in *BRCA 1/2* mutation carriers is an option for risk reduction but is controversial over concern that residual fibroglandular tissue (FGT) with malignant potential remains in the spared nipple. Since the volume of FGT in the nipple has not been formally evaluated, the objective of this study is to measure the residual volume of FGT in the spared nipple at a standard retroareolar margin (5mm) and identify sources of variability, including a greater margin and patient factors.

Methodology: A segmentation protocol was applied to breast MRIs from 105 consecutive *BRCA 1/2* patients. The MRI segmentation quantified volumes for total breast and nipple FGT. The nipple FGT volume was determined by setting the retroareolar margin (depth on MRI). The proportion of FGT in the nipple with 5mm retroareolar margin relative to the breast was calculated as the primary outcome and compared to 10mm margins. Associations between the proportion of FGT in the nipple (5mm) and patient characteristics were examined using uni- and multivariable analyses. Effect size was measured where appropriate.

Results: At 5mm and 10mm retroareolar thickness, residual FGT comprised 0.24% (0.02-0.9%) and 0.42% (0.02-0.12%), respectively, of the total breast FGT ($p < 0.001$, Cohen $d = 0.03$). Smaller breast volume, lower BMI and parity ($p < 0.001$, $p < 0.009$, $p < 0.009$ respectively) were predictive of greater proportion of residual FGT on univariate analysis, while breast volume and parity were predictive with multivariate ($R^2 = 0.28$, $F = 16.5$, $p < 0.0005$).

Conclusions: The proportion of FGT remaining in the spared nipple with a 5mm margin is extremely small, suggesting very little added risk over a skin sparing mastectomy. This proportion may be influenced by breast volume and childbearing. Doubling the retroareolar margin statistically increases the proportion, yet this likely does not translate into a clinically meaningful increase and may support a slightly thicker retroareolar margin. Overall, our findings support safety of the current trend toward increased rates of prophylactic NSM performed in the *BRCA 1/2* patient population.