

# THE REALITY OF PROPHYLACTIC NIPPLE-SPARING MASTECTOMY IN BRAZIL

Realidade da adenomastectomia redutora de risco no Brasil

Antonio Luiz Frasson<sup>1\*</sup>, Martina Lichtenfels<sup>2</sup>, Alessandra Borba Anton de Souza<sup>2</sup>

**S**urgical treatment of breast cancer has evolved over the past decades, from radical mastectomy to the acceptance of conservative techniques. In recent years, several studies have demonstrated the oncological safety and good aesthetic result of the skin-sparing mastectomy. Skin-sparing mastectomy consists in removal of the entire glandular breast tissue and the nipple-areola complex (NAC), preserving the skin of the breast<sup>1-4</sup>. Consequently, it favors immediate breast reconstruction using autologous tissue, expanders or silicone prosthesis. Based on this technique, researchers started to question the oncological safety and therapeutic indications to also preserve the NAC.

Nipple-sparing mastectomy involves surgical excision of the whole mammary gland, preserving the subcutaneous fat, the skin, and the NAC. As the breast envelope remains intact, it is extremely important to preserve the subcutaneous blood vasculature for the survival of skin and especially of NAC. In 1951, Rice and Stickler described this surgical technique for the first time for the treatment of a benign breast disease<sup>5</sup>. Currently, NSM has been performed for the treatment of patients in high-risk to develop breast cancer as a prophylactic surgery and in patients with malignant neoplasms<sup>6</sup>.

Prophylactic nipple-sparing mastectomy has been proven a safe and effective technique for women with high risk of developing breast cancer<sup>7-9</sup>. Prophylactic surgeries become more widespread in society every day, with an increase in demand in recent years due to the development of models that calculate estimated risk of neoplasms, the increase in access to genetic tests to identify mutations associated with breast neoplasm, and the improvement of techniques and materials for surgical reconstruction.

Positive oncological family history can be very common in women diagnosed with breast or ovarian cancer, but heritable mutations are related to less than 10% of neoplasms of all patients with breast cancer, and less than 15% among patients with ovarian cancer. Mutations in BRCA1 and BRCA2 genes cause approximately 40 to 50% of hereditary syndromes related

to breast and ovarian cancer, while mutations in genes such as TP53, PTEN, PALB2, CHEK2, STK11 are responsible for only 10%<sup>10,11</sup>. Remaining causes correspond to unknown genetic variants and mutations in other genes that are already known, but extremely rare<sup>10,12,13</sup>. Women with mutations in BRCA1 and BRCA2 genes presents an increased chance to develop breast and ovarian cancers. Throughout their whole life, the risk of developing breast cancer is about 55 to 85% and for ovarian cancer this number is around 15 to 65%<sup>14,15</sup>. These genes are also correlated with more aggressive tumors, increased risk for second cancer diagnosis, and the development of triple-negative breast tumors<sup>16,17</sup>. Salpingo-oophorectomy reduces the risk in patients with proven mutation for hereditary syndromes related to breast and ovarian cancers, and it was indicated as prophylactic surgery in the National Comprehensive Cancer Network (NCCN) Guideline. Since mastectomy only reduces the risk of breast neoplasm, the NCCN Guideline suggests a case-by-case discussion rather than formally indicating it as a prophylactic approach for the mentioned patients<sup>18</sup>.

In Brazil, this technique has also been increasingly used, but data about it are scarce, as the literature lacks publications on the practice in Brazilian centers. To increase knowledge about prophylactic nipple-sparing mastectomy in Brazil and the opinion of mastologists on the subject, we conducted a survey using a questionnaire sent by *e-mail* to the members of the Brazilian Society of Mastology (BSM).

In all, 183 mastologists answered our questionnaire on prophylactic nipple-sparing mastectomy in Brazilian clinical practice. Out of these 183 participants, more than 50% were from the Southeast region, 18.6% from the South region, 17.5% from the Northeast region, and 11% from the Midwest and North regions. Most participants — approximately 70% — work in cities with more than 500 thousand inhabitants, that is, the large cities of Brazil where reference hospitals are located. Only 6% of them work in cities with less than 100 thousand inhabitants. Career lengths of mastologists who answered the questionnaire were:

<sup>1</sup>Medical School of Pontifícia Universidade Católica do Rio Grande do Sul (PUC-RS) – Porto Alegre (RS), Brazil.

<sup>2</sup>Mastology Center of PUC-RS - Porto Alegre (RS), Brazil.

\*Corresponding author: [alfrasson.af@gmail.com](mailto:alfrasson.af@gmail.com)

Received on: 01/23/2018. Accepted on: 02/04/2018.

19% with 1 to 5 years, 21% with 5 to 10 years, 15% with 10 to 15 years, 17% with 15 to 20 years, and 29% with more than 20 years of experience. This information is interesting because it shows that both new and experienced mastologists took the survey, thus making it more heterogeneous. Most participants work in private (45.9%) and private/academic hospitals (39.9%), and 14.2% work in public hospitals.

A substantial number of mastologists who answered our questionnaire perform less than 5 nipple-sparing mastectomies per year (34.6%); approximately 25% perform 5 to 10 surgeries per year; 22%, 11 to 20 surgeries per year; and 19%, over 20 surgeries per year. The vast majority of nipple-sparing mastectomies were performed in patients with breast neoplasms (70% of patients had undergone less than 10% of prophylactic surgeries), and only 13.2% of mastologists had performed more than 50% of prophylactic surgeries out of the total number of nipple-sparing mastectomies.

The interest in prophylactic breast surgery had a significant increase by the Angelina Jolie effect, in 2013<sup>19</sup>. Patients all around the world sought doctors to get information on genetic testing and possible practices to prevent breast cancer development. Our data show that prophylactic surgeries still account for the minority of indications for nipple-sparing mastectomy in Brazil, but also that this number is increasing.

Another important characteristic is the small number of bilateral therapeutic surgeries when the patient does not have a neoplasm in the contralateral breast. Approximately 75% of mastologists perform bilateral surgery in only 20% of cases of therapeutic nipple-sparing mastectomies. A minority of surgeons (13%) perform bilateral surgeries with prophylactic surgery in contralateral breast in most of nipple-sparing mastectomies they conduct.

In the United States, the use of prophylactic nipple-sparing mastectomy in the contralateral breast has increased significantly in recent decades, despite bringing little benefit for patients with low risk of developing cancer in contralateral breast<sup>20,21</sup>. This phenomenon could be possibly related to greater access to high-quality screening tests, the availability of better techniques in breast reconstruction, as well as the choice of patients to undergo prophylactic surgery, motivated mainly by the fear of disease recurrence and by esthetic reasons (symmetry)<sup>22,23</sup>.

In our study, we found that most mastologists do not perform bilateral nipple-sparing mastectomy, contrary to the trend in developed countries. The prophylactic surgery in contralateral breast prolongs patients' hospital stay, increases surgery costs, can lead to postoperative complications, and, so far, it has not demonstrated higher overall survival rate in patients with sporadic breast cancer who underwent this procedure<sup>24,25</sup>. We believe that these are the reasons why mastologists do not perform bilateral surgery in most patients in Brazil. However, not performing the surgery may influence the recurrence of breast neoplasm and

also have unsatisfactory esthetic results, leading the patient to new surgical procedures and higher treatment costs. Therefore, discussing this topic is of great importance to find the best treatment for patients.

According to our questionnaire, paying patients and patients holding a health insurance have more access to genetic evaluation compared to those who rely on the Brazilian public health system (SUS). While 17% of the participants answered that all of their paying and/or insured patients have access to genetic evaluation, only 1% reported the same for their patients at SUS. Another striking fact is the poor access to genetic evaluation for the vast majority of SUS patients (85.6%). As most mastologists who took our survey are from major cities, we expected a greater number of SUS patients with access to geneticists.

When asked about the most common reason to indicate prophylactic bilateral nipple-sparing mastectomy, 64.8% of the participants declared that they only suggest prophylactic surgery for patients with BRCA1 and/or BRCA2 mutations. Only 7.7% stated recommending prophylactic surgery if the patient has a negative genetic test result for mutations in these genes, but positive family history of breast and/or ovarian cancer, and 11.5% usually indicate the technique for patients who did not undergo genetic testing, but have a family history of breast and/or ovarian cancer. A positive genetic test result for other genetic high-penetrance mutations lead only 1.1% of the participants to indicate prophylactic nipple-sparing mastectomy, and 9.3% of surgeons suggest prophylactic surgery when they find bilateral precursor lesions. These data demonstrate how the access to genetic testing is important before conducting this kind of procedure, and as many patients assisted at SUS institutions do not have such access, indication of prophylactic nipple-sparing mastectomy is limited.

In the questionnaire, the following hypothetical case was described: 45-year-old female patient, last menstrual period 15 days earlier, nulliparous, menarche at age 10, multiple bilateral breast nodules (category 3 in last breast imaging test), great-aunt with breast cancer at age 50, previous breast biopsy resulting in fibroadenoma, with 48% of risk throughout her life according to the International Breast Intervention Study (IBIS) Breast Cancer Risk Evaluation Tool. Negative test for mutations for *breast cancer gene* (BRCA — sequencing and *multiplex ligation-dependent probe amplification* — MLPA). In accordance with previous findings, most mastologists would not indicate prophylactic nipple-sparing mastectomy in this case (76%). As the patient presented no BRCA mutation, neither strong family history, which were the most common causes of recommendation of this type of surgery reported by participants, most mastologists did not consider it necessary.

This survey has contributed to increase the knowledge about indications, use and limitations of nipple-sparing mastectomy. However, these informations should be more deeply discussed in further studies.

## REFERENCES

1. Medina-Franco H, Vasconez LO, Fix RJ, Heslin MJ, Beenken SW, Bland KI, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. *Ann Surg*. 2002;235:814-9.
2. Carlson GW, Styblo TM, Lyles RH, Jones G, Murray DR, Staley CA, et al. The use of skin-sparing mastectomy in the treatment of breast cancer: The Emory experience. *Surg Oncol*. 2003;12:265-9.
3. Uriburu JL, Vuoto HD, Cogorno L, Isetta JA, Candas G, Imach GC, et al. Local recurrence of breast cancer after skin-sparing mastectomy following core needle biopsy: case reports and review of the literature. *Breast J*. 2006;12:194-8. <https://doi.org/10.1111/j.1075-122X.2006.00240.x>
4. Warren PA, Foster RD, Stover AC, Itakura K, Ewing CA, Alvarado M, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. *Ann Surg Oncol*. 2012;19(11):3402-9. <https://doi.org/10.1245/s10434-012-2362-y>
5. Rice CO, Strickler JH. Adeno-mammectomy for benign breast lesions. *Surg Gynecol Obstet*. 1951;93:759-62.
6. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol*. 2008;34(2):143-8. <https://doi.org/10.1016/j.ejso.2007.06.010>
7. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med*. 1999;340:77-84. <https://doi.org/10.1056/NEJM199901143400201>
8. De Felice F, Marchetti C, Musella A, Palaia I, Perniola G, Musio D, et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. *Ann Surg Oncol*. 2015;22:2876-80. <https://doi.org/10.1245/s10434-015-4532-1>
9. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *Am J Surg*. 2016;212:660-9. <https://doi.org/10.1016/j.amjsurg.2016.06.010>
10. Castera L, Krieger S, Rousselin A, Legros A, Baumann JJ, Bruet O, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Human Genet*. 2014;22:1305-13. <https://doi.org/10.1038/ejhg.2014.16>
11. Silva FC, Lisboa BC, Figueiredo MC, Torrezan GT, Santos EM, Krepischi AC, et al. Hereditary breast and ovarian cancer: assessment of point mutation and copy number variations in Brazilian patients. *BMC Med Genet*. 2014;15:15:55. <https://doi.org/10.1186/1471-2350-15-55>
12. Campeau PM, Foulkes WD, Tischkowitz MD. Hereditary breast cancer: new genetic developments, new therapeutic avenues. *Hum Genet*. 2008;124:31-42. <https://doi.org/10.1007/s00439-008-0529-1>
13. Lhota F, Zemankova P, Kleiblova P, Soukupova J, Vocka M, Stranecky V, et al. Hereditary truncating mutations of DNA repair and other genes in BRCA1/BRCA2/PALB2 negatively tested breast cancer patients. *Clin Genet*. 2016;90(4):324-33. <https://doi.org/10.1111/cge.12748>
14. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*. 1994;266:66-71.
15. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature*. 1995;378:789-92. <https://doi.org/10.1038/378789a0>
16. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304(9):967-75. <https://doi.org/10.1001/jama.2010.1237>
17. Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol*. 2015;33:304-11. <https://doi.org/10.1200/JCO.2014.57.1414>
18. National Comprehensive Cancer Network. NCCN Clinical practice guidelines in Oncology [Internet]. Disponível em: [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)
19. Evans DGR, Barwell J, Eccles DM, Collins A, Izatt L, Jacobs C, et al. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Res*. 2014;16(5):442. <https://doi.org/10.1186/s13058-014-0442-6>
20. Yao K, Stewart AK, Winchester DJ, Winchester DP. Trends in contralateral prophylactic mastectomy for unilateral cancer: a report from the National Cancer Data Base, 1998-2007. *Ann Surg Oncol*. 2010;17:2554-62. <https://doi.org/10.1245/s10434-010-1091-3>
21. Tuttle T, Jarosek S, Habermann E, Arrington A, Abraham A, Morris TJ, et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. *J Clin Oncol*. 2009;27(9):1362-7. <https://doi.org/10.1200/JCO.2008.20.1681>
22. Ager B, Butow P, Jansen J, Phillips KA, Porter D; CPM DA Advisory Group. Contralateral prophylactic mastectomy (CPM): A systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. *The Breast*. 2016;28:107-120. <https://doi.org/10.1016/j.breast.2016.04.005>
23. Brewster AM, Parker PA. Current knowledge on contralateral prophylactic mastectomy among women with sporadic breast cancer. *Oncologist*. 2011;16:935-41. <https://doi.org/10.1634/theoncologist.2011-0022>
24. Mortenson MM, Schneider PD, Khatri VP, Stevenson TR, Whetzel TP, Sommerhaug EJ, et al. Immediate breast reconstruction after mastectomy increases wound complications: however, initiation of adjuvant chemotherapy is not delayed. *Arch Surg*. 2004;139:988-91. <https://doi.org/10.1001/archsurg.139.9.988>
25. Murphy JA, Milner TD, O'Donoghue JM. Contralateral risk-reducing mastectomy in sporadic breast cancer. *Lancet Oncol*. 2013;14:e262-9. [https://doi.org/10.1016/S1470-2045\(13\)70047-0](https://doi.org/10.1016/S1470-2045(13)70047-0)