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CLINICAL TRIAL

Risk-reducing mastectomy: a case series of 124 procedures in Brazilian patients

Antônio Luiz Frasson[1,2] · Martina Lichtenfels[1] · Alessandra Anton Borba de Souza[1] · Betina Vollbrecht[1] · Ana Beatriz Falcone[2] · Mônica Adriana Rodriguez Martinez Frasson[1,2] · Fernanda Barbosa[2]

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Abstract

Purpose Women with mutations in breast cancer predisposition genes have a significantly higher lifetime risk of developing breast cancer and can opt for risk-reducing mastectomy. Women with positive family history of cancer can also opt for prophylactic surgery as a preventive method in selected cases. Current studies showed reduced risk of developing breast cancer after prophylactic nipple-sparing mastectomy, however, despite the good clinical outcomes, one of the main concerns regarding nipple-sparing mastectomy (NSM) is the oncological safety of nipple-areola complex preservation. In this study, we aimed to evaluate the indications, complication rates, and unfavorable events of 62 Brazilian patients that underwent risk-reducing NSM from 2004 to 2018.

Methods Patient data were reviewed retrospectively and descriptive statistics were utilized to summarize the findings.

Results The mean patients age was 43.8 years. The main indication for risk-reducing NSM was the presence of pathogenic mutation (53.3%), followed by atypia or lobular carcinoma in situ (25.8), and family history of breast cancer and/or ovarian cancer (20.9%). There were four (3.2%) incidental diagnosis of ductal carcinoma in situ and one invasive ductal carcinoma (0.8%). From the 124 prophylactic NSM performed, two (1.6%) complications had occurred: one (0.8%) infection and one (0.8%) partial nipple necrosis. In a mean follow-up of 50 months, there was one (1.6%) newly diagnosed breast cancer in the 62 patients undergoing prophylactic NSM.

Conclusions Our findings demonstrated efficacy and safety to perform NSM as prophylactic surgery with good oncological outcomes and low complication rates in a case series of Brazilian patients.

Keywords Prophylactic surgical procedures · Genetic predisposition to disease · Subcutaneous mastectomy · Breast neoplasm

Introduction

Approximately 40–50% of hereditary breast and ovarian cancer syndromes are associated with mutations in the *BRCA1* and *BRCA2* genes, while only 10% is related to mutation in other moderate and high-risk genes, such *TP53*, *PTEN*, *PALB2*, *CHECK2*, and *STK11* [1, 2]. Women with mutations in *BRCA* genes have a significant increased lifetime risk of developing breast cancer. The risk of breast cancer at the age of 80 years is 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers [3].

Patients presenting inherited breast cancer syndromes can opt for intensive clinical surveillance or prophylactic surgery with the aim of early detection and of reducing cancer development and mortality. Nipple-sparing mastectomy (NSM) has been successfully performed for the treatment of breast cancer and for women at high risk of developing breast cancer [4, 5]. The number of prophylactic mastectomies have been increasing after the press noticed worldwide that actress Angelina Jolie performed a bilateral risk-reducing mastectomy (BRRM) due to an inherited pathogenic *BRCA1* mutation [6]. However, not only mutation carriers can choose the surgery as a preventive method. Women with strong family history of breast and/or ovarian cancer,

✉ Antônio Luiz Frasson
alfrasson.af@gmail.com

[1] Breast Cancer Center, Hospital São Lucas, Pontifical Catholic University of Rio Grande Do Sul (PUCRS), Ipiranga 6690, Porto Alegre, Brazil

[2] Breast Cancer Group, Albert Einstein Hospital, Albert Einstein avenue 627, São Paulo, Brazil

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without genetic mutations, can also opt for prophylactic surgery in selected cases [7].

Current studies showed reduced risk of breast cancer with the use of prophylactic NSM, however, despite the good esthetic and clinical outcomes one of the main concerns regarding NSM is the safety of nipple-areola complex preservation [4, 8–12].

This study aimed to evaluate the characteristics, complication rates and outcomes of 62 Brazilian patients that underwent 124 bilateral risk-reducing NSM with immediate breast reconstruction from 2004 to 2018.

Methods

Design and participants

This retrospective study was performed according to the ethical guidelines and received approval from the ethics committee of the São Lucas Hospital and Albert Einstein Hospital. Patients with completed medical records were included in our study and all patients were operated by a senior surgeon. Informed consent was waived by the institutional review board because of the retrospective characteristic of the study.

Between January 2004 and December 2018, 124 bilateral risk-reducing NSMs were performed in 62 women with high risk of developing breast cancer. The mean age of the patients was 43.8 years (range 23–67). Clinicopathological characteristics are listed in Table 1.

Surgical technique

All procedures were performed under general anesthesia. The NSM skin incision was chosen in accordance with the method of reconstruction and physician consideration, being the majority a hidden scar inframammary incision. The glandular tissue was removed leaving only fat tissue to preserve blood flow and reduce the risk of flap necrosis. It is important to highlight that flap thickness varies among patients since it is based on the amount of subcutaneous fat present in the breast.

Patients diagnosed previously with suspected lesions underwent intraoperative histopathological examination of frozen sections of the retroareolar tissue to confirm the absence of malignancy in the retroareolar margin. Immediate breast reconstruction was performed in all patients with a definitive implant (Fig. 1).

Statistical analyses

Quantitative variables were described in means, while categorical variables were described by absolute and relative frequencies. Analyses were performed using the SAS statistical software (version 9.4; SAS Institute, Inc. Cary, NC) and TABLEAU software (version 2019.1.2)."

Table 1 Patient characteristics ($n = 62$)

	N (%)
Number of women	62
Number of NSM	124
Age, years	
< 35	12 (19.3)
35–49	34 (54.9)
> 49	16 (25.8)
Mean age	43.8
Menopause status	
Premenopausal	47 (75.8)
Postmenopausal	13 (21)
Postpartum	2 (3.2)
Genetic test	
Yes	40 (64.5)
Positive for mutations	33 (82.5)
BRCA1	12 (36.4)
BRCA2	18 (54.6)
P53	1 (3)
PALB2	1 (3)
CHEK2	1 (3)
Negative	7 (17.5)
No	22 (35.5)
Family history	
Breast cancer	52 (64.5)
Ovarian cancer	3 (4.9)
Breast and ovarian	9 (14.5)
No history of breast and/or ovarian	10 (16.1)

NSM nipple-sparing mastectomy, *BRCA* breast cancer genes, *P53* tumor protein p53, *VUS* variant of uncertain significance, *ATM* ataxia-telangiectasia mutated, *PALB2* partner and localizer of BRCA2, *CHEK2* checkpoint kinase 2

Results

In our study, we observed an increase in NSM performed during the last years and also an increasing number of bilateral risk-reducing NSM after 2013 (Fig. 2).

We analyzed 62 patients who underwent 124 risk-reducing NSM between 2004 and 2018. No patient underwent skin sparing/total mastectomy as prophylactic surgery. The mean patients age was 43.8 years (range, 23–67), including 12 (19.3%) patients under the age of 35 years. The indications for the bilateral risk-reducing NSM were mutations in breast cancer predisposition genes in 33 patients (53.3%), diagnosis of atypia or lobular carcinoma in situ (LCIS) in 16 patients (25.8%) and strong familial history

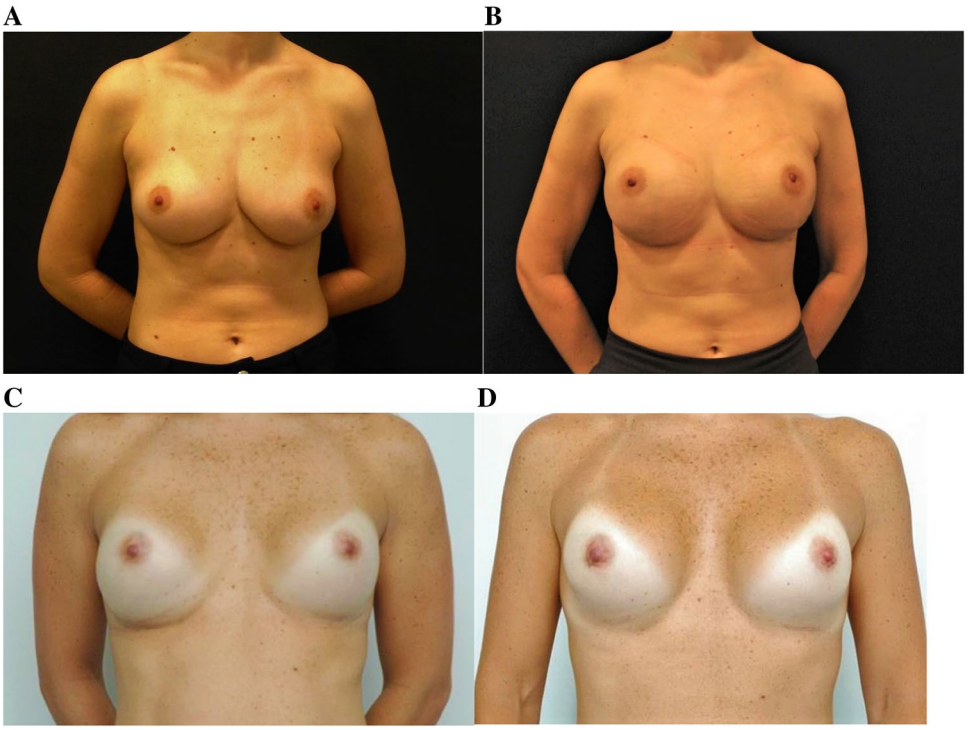

Fig. 1 Cosmetic result of risk-reducing NSM in BRCA mutation carriers. **a**, **c** Preoperative; **b**, **d** postoperative: immediate reconstruction with permanent implants and inframammary incision

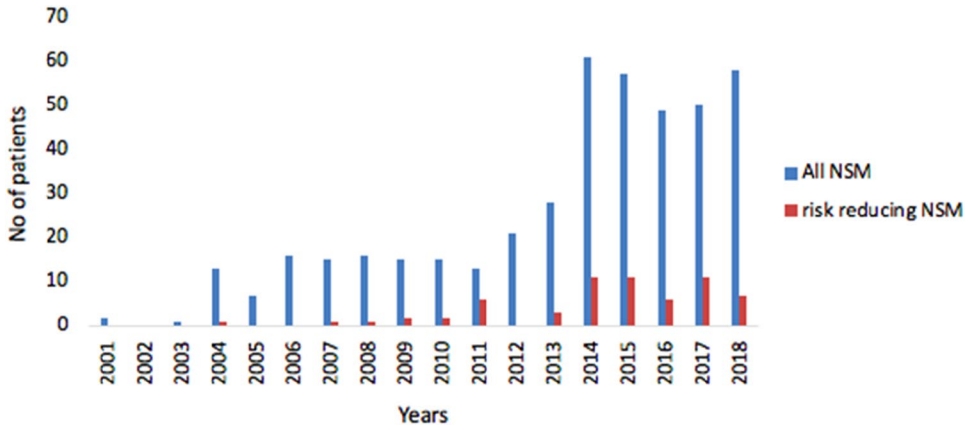

Fig. 2 Trends over time of all NSM performed and only bilateral risk-reducing NSM

Table 2 Indications of risk-reducing NSM

	N	%
No. of patients	62	100
Genetic mutation	33	53.3
Atypia or LCIS	16	25.8
Positive family history	13	20.9

LCIS lobular carcinoma in situ

of breast and/or ovarian cancer in 12 patients (20.9%) (Table 2). Forty (64.5%) patients were submitted to genetic testing: twelve (36.4%) were *BRCA1* mutation carriers, eighteen (54.6%) *BRCA2* mutation carriers, one (3%) presented Li-Fraumeni syndrome (*TP53* mutation), one (3%) presented *CHEK2* gene mutation, one (3%) presented *PALB2* gene mutation, and seven (17.5%) patients were negative for known mutations. One patient with negative genetic test presented VUS in *ATM* gene. The majority of patients (64.5%) reported a history of breast cancer in family, 14.5% ovarian cancer and 4.9% both cancers. Three (6%) patients had previous personal history of other cancers, two of them with endometrial cancer (4%) and one (2%) with kidney cancer.

There were four (3.2%) occasional findings of DCIS and one of IDC (0.8%) (Table 3) in the 124 risk-reducing NSM performed. Follow-up of all patients was performed with clinical examination and ultrasound every year.

Table 3 Occult findings in risk-reducing NSM

Occult primary breast cancer	*N*	%
No. of NSM	124	
IDC	1	0.8
DCIS	4	3.2

NSM nipple-sparing mastectomy, *IDC* invasive ductal carcinoma, *DCIS* ductal carcinoma in situ

Table 4 Unfavorable events and complications rates

	N	%
No. of NSM	124	100
Complications		
Infection	1	0.8
NAC necrosis	1	0.8
No. of Patients	62	100
Vital status		
Alive	62	100
Events		
Tumor development	1	1.6

NSM nipple-sparing mastectomy, *NAC* nipple-areola complex

In the 124 prophylactic surgeries performed two (1.6%) complications occurred, one (0.8%) infection and one (0.8%) partial nipple necrosis. The patient presenting nipple necrosis was treated clinically and no nipple resection was necessary.

During the mean follow-up of 50 months, one (1.6%) newly breast cancer was diagnosed in the 62 patients undergoing risk-reducing NSM. This patient was not diagnosed with incidental breast cancer at the surgery, she presented a *BRCA2* mutation carrier with family history and developed breast cancer 18 months after the surgery with lymph node micrometastasis. At the end of follow-up, all patients were alive. Unfavorable events and complications rates are shown in Table 4.

Discussion

NSM has been successfully used for both risk reduction and cancer treatment [4, 5, 13, 14]. NSM is a conservative approach for breast cancer that provides good esthetic satisfaction, however, the oncological safety of nipple preservation is still controversial. The main concerns regarding the use of NSM are nipple necrosis and local and nipple recurrences.

The number of prophylactic mastectomies has been increasing after the "Angelina effect" [6]. The actress Angelina Jolie discovered that she is a *BRCA1* mutation carrier and was submitted to bilateral risk-reducing mastectomy in 2013. This decision was worldwide publicized and increased the interest of women in hereditary breast cancer and prophylactic surgery even in Brazil. This is one of the reasons that can be attributed to the increasing number of risk-reducing surgery. Other factors include easier access to genetic counseling, advance in reconstructive strategies and better surgical outcomes [15]. In accordance, Grobmyer and colleagues showed an increase in the number of bilateral NSM for mutation carriers over time (2001–2017) [13]. We also observed an increasing in number of bilateral risk-reducing NSM after 2013. From 2001 until 2013, 16 bilateral risk-reducing NSM were performed and between 2014 and 2018 this number increased 2.9 times, with 46 bilateral prophylactic surgeries performed. Another explanation for the increasing number of prophylactic surgeries after 2013 is the cost of the genetic test. In 2013, with the overturned of the patent for BRCA 1/2 and the introduction of next-generation sequencing (NGS) [16], the cost of genetic testing dropped from $2000 to $5000 per test to approximately $250 per test [17], increasing the uptake of genetic testing for mutations related to breast cancer risk. In our study 40 women were indicated to genetic counseling and underwent genetic testing for inherited predisposition mutations in genes contributing to breast cancer risk. Thirty-three (82.5%) women presented a hereditary genetic mutation, being the majority *BRCA1* (36.4%) and *BRCA2* (54.6%) mutation carriers. Seven (17.5%) from 40 women presented a negative genetic test for known pathogenic mutations. These results demonstrated the importance of genetic counseling for patients at high risk of developing breast cancer.

Genetic counseling is an important component of the risk assessment and genetic testing process [18]. After the genetic counseling, high-risk surveillance must be employed and risk-reducing surgeries can be discussed as a therapy option [19]. The process of familial risk assessment is complex, requires careful interpretation of information, consideration of future risk and a shared decision-making [20]. Therefore, the services must be well integrated and individualized to benefit the patient and family [21]. For healthy *BRCA1/2* mutation carriers, risk-reducing mastectomy (RRM) might be a good option, however, the indication for surgery can`t be applied for patients with other moderately penetrant gene mutations, for whom insufficient data are available. In the case of highly penetrant genes and/or highly burdened family history, risks and benefits must be carefully considered and discussed with the patient to individualize the treatment. Most of the patients with strong family history of breast and/or ovarian cancer or BRCA mutations opt for risk-reducing surgery [22].

The decision to undergo prophylactic surgery is attributed to several factors, being the most important the diagnosis of inherited breast cancer syndromes, family history and relationship, including marital status, and number of children [23]. Our main indication for bilateral risk-reducing NSM was the presence of mutation (53.3%), followed by patients with diagnosis of atypia or LCIS (25.8%) and women with strong positive family history of breast and/or ovarian cancer (20.9%). These findings demonstrated that most of bilateral risk-reducing NSM performed in our service were in women with diagnosed hereditary breast cancer syndrome.

Manning and colleagues showed no newly diagnosed breast cancer and 6% of incidental finding of DCIS in 151 prophylactic NSM performed in *BRCA1/2* mutations carriers or with diagnosis of uncertain significance at short-term follow-up [8]. Incidental finding of DCIS in our patients was lower than reported in previous literature [8], with only 4 (3.2%) cases of DCIS diagnosed in 124 prophylactic procedures performed. We also reported 1 (0.8%) occult finding of IDC. This patient presented a small 2.2 mm Luminal A tumor.

Only 0.8% of NAC necrosis occurred in the 124 bilateral risk-reducing NSM and it is important to emphasize that no nipple-areola complex was resected. The complications rates found in our study were lower (1.6%) than reported by Isaksson and colleagues that demonstrated 22.7% surgical site infection and 22.2% partial skin necrosis in 185 women undergoing bilateral risk-reducing mastectomy with immediate breast reconstruction [7].

Meta-analysis including 2635 patients from four prospective studies indicated that bilateral risk-reducing mastectomy achieve a significant risk reduction of breast cancer in *BRCA1* and *BRCA2* mutation carriers [24]. Analysis of 150 *BRCA1/2* mutation carriers that underwent NSM for risk reduction demonstrated only one new primary breast tumor development and no event on NAC at a mean follow-up of 32.6 months [25]. Jakub and colleagues showed no breast cancer development in *BRCA1* or *BRCA2* mutation carriers that underwent risk-reducing NSM. The authors retrospectively evaluated 346 *BRCA1* or *BRCA2* mutation carriers from 9 institutions, and demonstrated that none patient undergoing contralateral risk-reducing NSM or bilateral risk-reducing NSM presented diagnosis of breast cancer during a mean follow-up of 56 moths [11]. Corroborating with previous studies, at a mean follow-up of 50 months, we found only one (1.6%) new primary breast cancer. Based on our findings, we suggest that NSM is an effective risk-reducing strategy to mutation carriers and also to patients with strong family history of breast cancer. The limitations of our study include it`s retrospective nature and the small sample.

Innovative techniques for surgical treatment of breast cancer and prophylactic surgeries have been emerged aiming to reduce morbidity and scars, including endoscopic NSM (E-NSM) and robotic (R-NSM). E-NSM presented limitations related to the use of two-dimensional endoscopic inline camera and the rigid tip instruments. Robotic-assisted surgery, on the other hand, incorporated three-dimensional imaging system and offered the flexibility of robotic arms [26]. R-NSM can be discussed as the next step in the evolution of minimally invasive breast surgery. However, a recent US Food and Drug Administration (FDA) safety communication seemed to be more cautious and has published against its practice outside clinical studies until more data ensure the oncological safety [27]. R-NSM was first reported in 2015 by Toesca et al. that presented the feasibility, safety and good esthetic outcomes [27]. Preliminary data of robotic nipple-sparing mastectomy (R-NSM) with immediate prosthetic breast reconstruction to treat selected breast cancer and as prophylactic procedure showed low complication rate, no skin flap, or nipple-areola complex necrosis [28]. Robotic latissimus dorsi-flap breast reconstruction (RLDFR) is also a safe and reproducible procedure that provides breast reconstruction by a single incision [29]. The indications of prepectoral breast reconstruction using dermal matrix have increased as one-stage and minimally invasive technique for breast cancer patients with oncological safety and good esthetic results. However, adverse events such rippling might be associated with the technique [30, 31]. The deep inferior epigastric artery perforator flap is a minimally invasive autologous breast reconstruction, cost-effective associated to good esthetic outcomes [32]. Although, for bilateral procedures, the technique was related to higher complication rate and flap loss [33].

There is evidence that R-NSM and robotic reconstruction will be part of future strategies for prophylactic and breast cancer surgeries. As the use of dermal matrix, we still need to understand when offering these approaches for patients without augmented cost, larger laterally scar and with oncological safety. A future option can be mix standard surgery with minimal inframammary incision and experienced surgeons hands touching the plan with robotic technology to access difficult surgical plans. New surgeries and reconstruction techniques have been highlighted as the future for breast cancer patients and high-risk women, however, long-term outcomes are lacking to confirm the efficacy and safety of the procedures.

Conclusion

To the best of our knowledge this is the first study regarding bilateral risk-reducing NSM in a Brazilian population. The results of our study demonstrated efficacy and safety of performing risk-reducing surgery for high-risk patients with good outcomes and low complication rates. Therefore, we

support the use of NSM to reduce the risk of breast cancer development in mutation carriers and high-risk patients.

Author contributions All authors contributed to the study conception and design. Material preparation and writing the manuscript were performed by ALF, MAMRF, ABF, BV and FB; data collection, analysis and writing the manuscript were perfomed by ML and ABAS. The first draft of the manuscript was written by MLs and all authors commented on previous versions of the manuscript. Supervision was performed by ALF.

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Data availability All data analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards by the Institutional Ethics Committee of Pontifical Catholic University of Rio Grande do Sul (PUCRS), Hospital Albert Einstein and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study (retrospective study) formal consent is not required.

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