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# MASTOLOGY

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# Neuromuscular bandage for the prevention of post-mastectomy seroma: a clinical trial protocol

Erica Alves Nogueira Fabro<sup>1,\*</sup> , Rejane Medeiros Costa<sup>1</sup> , Flávia Oliveira Macedo<sup>1</sup> ,  
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## ABSTRACT

**Introduction:** Seroma is the most common early complication after breast cancer surgery and is associated with other complications and adjuvant therapy delays. A potential hypothesis for its prevention is the obliteration of dead space between tissues, which can be achieved by external compression. To assess whether the use of a neuromuscular bandage employing the compressive technique during the first postoperative week is effective in preventing seroma. **Methods:** This study comprises a two-arm randomized superiority clinical trial to evaluate the following as primary outcomes: seroma incidence, volume and duration using a suction drain and bandage safety and satisfaction as secondary outcomes. Women aged  $\geq 18$  years submitted to a mastectomy as breast cancer treatment will be included, while women submitted to bilateral mastectomies, immediate breast reconstruction or surgical flap rotation closure, who present hematomas or surgical wound infections at the time of recruitment or autoimmune diseases that lead to skin lesions and/or allergy to tape, as well as those exhibit difficulties in understanding the study will be excluded. Randomization will be performed by lots at study enrollment. Coded envelopes will be available for intervention or control group allocations. Patients allocated in the intervention group will be submitted to the bandage application for seven days. All patients will use a suction drain according to the institution's routine. **Ethics and disclosure:** This study was approved by the Brazilian National Cancer Institute, Research Ethics Committee under no. 2,774,824 and it is registered in the ClinicalTrials.gov (NCT04471142).

**KEYWORDS:** breast neoplasm; seroma; prevention; physiotherapy; taping.

## INTRODUCTION

Seroma is the most common early complication following surgical breast cancer treatment<sup>1,2</sup>. Incidence rates range from 2.5% to 85%<sup>1-3</sup> and the condition is directly associated to extensive surgical dissection procedures, such as mastectomies and axillary lymphadenectomies, due to the generation of more dead space between tissues<sup>4</sup>.

There are some known risk factors for the development of seroma in women undergoing surgical treatment for breast cancer, such as older age, higher body mass index (BMI), high blood pressure, large breast volume, breast biopsy prior to surgical treatment, neoadjuvant chemotherapy, thromboprophylaxis, presence of lymph node metastasis, greater number of removed lymph nodes, longer surgery times, electrocautery, type of drainage and longer suction drain durations<sup>5-9</sup>.

Although seroma formation is not life threatening, it may comprise a risk factor for the development of necrosis and dehiscence, predisposition to sepsis, upper limb movement restriction, lymphedema and a prolonged recovery period and, consequently, delays in beginning adjuvant therapy<sup>10,11</sup>.

The obliteration of the dead space between the tissues left by the breast and axillary content removal is discussed among approaches applied to seroma prevention, mainly by two methods, namely surgical flap fixation or external compression<sup>3</sup>.

Neuromuscular taping and the Kinesio® Taping method have been recently introduced into the clinical practice to reduce pain and swelling, also ensuring muscle activity stability<sup>12,13</sup>.

The purpose of neuromuscular bandage treatment during the postoperative period is to facilitate the body's natural healing process by relieving tension in the muscles involved in the

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**Conflict of interests:** nothing to declare. **Funding:** The neuromuscular bandage used in this study will be donated by the company Fisio Vital Comércio de Artigos Ortopédicos Ltda, which signed a commitment agreement with the Research Ethics Committee (CEP-INCA) waiving access to data and results analysis and dissemination interference.

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surgical trauma, increasing proprioception through mechanoreceptor excitation, improving blood circulation and lymphatic drainage and decreasing inflammation and pain<sup>12,14</sup>.

Neuromuscular bandages are composed of 100% cotton fibers and heat-sensitive acrylic glue. They do not contain any chemical substances, are hypoallergenic, and their length reaches up to 140% of their original size. They must always be expanded longitudinally, and their weight and thickness are very similar to skin, both porous and resistant to water, thus allowing for gas exchanges. These bandages are manufactured with digital printing technology, so that, once applied, they present better skin adherence<sup>13,15</sup>.

This type of bandage application in women with breast cancer has been shown to be safe and effective. Martins et al.<sup>16</sup>, for example, evaluated the safety and tolerability of the Kinesio® Taping bandage in the control of upper limb lymphedema secondary to breast cancer, and found that no patient developed skin lesions, blisters, hyperthermia, or skin scaling and/or redness at the application site. A meta-analysis of randomized clinical trials also concluded that kinesio taping was effective and safe in the control of lymphedema secondary to breast cancer<sup>17</sup>.

The use of neuromuscular banding for seroma treatment, although with still little scientific evidence available, may be an option for seroma prevention and treatment following breast surgery. In this regard, Bosman and Piller<sup>18</sup> conducted a pilot study demonstrating the use of bandaging employing the lymphatic taping technique as a non-invasive approach for seroma treatment.

Furthermore, a Phase I study, in which the safety of a compressive bandage was evaluated in patients presenting seroma secondary to surgical breast cancer treatment reported this approach as a safe method, in which only 8.8% of patients developed a skin reaction and the bandage had to be removed, while 85.7% of women felt satisfied and 68.5% reported safe use<sup>19</sup>.

In this context, the aim of this clinical trial is to evaluate the effectiveness of a neuromuscular compressive bandaging in seroma prevention following mastectomy.

## METHODS

### Hypotheses

This study protocol describes a randomized clinical trial in which the application of a neuromuscular compressive bandage in women with breast cancer submitted to a mastectomy was compared to routine therapy. The hypothesis is that the use of a compressive bandage during the first postoperative week associated to a drain is effective in preventing seroma. The second hypothesis is that the compressive bandage influences the length of suction drain use, the number of aspiration punctures (when indicated), and the volume of the punctured seroma.

### Study design

This is a randomized controlled clinical trial of superiority with two arms, a control group and intervention group, carried out in a single reference center for breast cancer treatment.

### Patients and study site

This study was carried out in the city of Rio de Janeiro, at the Cancer Hospital III of the National Cancer Institute (HCIII/INCA), concerning women diagnosed with breast cancer submitted to mastectomy.

### Eligibility criteria

Women aged 18 years or older submitted to mastectomy as surgical breast cancer treatment will be included in the study.

The exclusion criteria are: patients submitted to bilateral mastectomies as well as those submitted to immediate breast reconstruction or surgical closure with skin flap rotation, presenting hematoma or surgical wound infections at the time of recruitment, presenting autoimmune diseases that generate skin lesions and/or allergy to tape, as well as patients with difficulties in understanding the study.

### Sample size

The sample size was calculated by considering the occurrence of the outcome (seroma) in 60% of the control group patients<sup>1</sup> and in 45% of the intervention group, at a 5% significance level and 80% test power through a one-tailed hypothesis test. This calculation indicated the inclusion of 270 patients, 135 in each group.

### Randomization

Randomization will be performed by drawing lots at the moment the patient enters the study (Figure 1). A total of 27 blocks containing 10 envelopes will be made available, 5 of which will contain a code that allocates patients in group A and 5 in group B. This was established to avoid therapist or patient preferences concerning the intervention. The patients will be guided concerning their group and the follow-up will be carried out while the patient is under dressing care. All assessments, intervention and data collection will be carried out by professionals trained and qualified for this purpose.

### Treatment protocols

According to the HCIII/INCA routine, a closed system used for postoperative (PO) drainage will be inserted intraoperatively in patients undergoing mastectomies or axillary dissections for seroma prevention. This system remains between seven and fourteen days, depending on the drainage volume. On the first postoperative day, all patients will be submitted to dressing at the scarring points, with the suction drain being pointed and oriented by the nursing team to clean the drain ostium only with filtered, boiled and cold water, and to apply the dressing daily,

in addition to emptying the closed drainage system and counting the drained volume twice a day.

All patients will be scheduled to return in seven days to the physiotherapy outpatient clinic for kinetic-functional, skin and healing reassessments. The drain volumes noted at home and the drain conditions will be evaluated at the nursing outpatient clinic, which assesses and cares for the dressing, in order to proceed with drain removal. The suction drain will be removed on the 7<sup>th</sup> PO day if the total volume drained on the previous day according to the patient's notes is  $\leq 50$  mL or, at the most, on the 14<sup>th</sup> PO day, regardless of the drained volume, or in the emergency cases (infection and drain externalization).

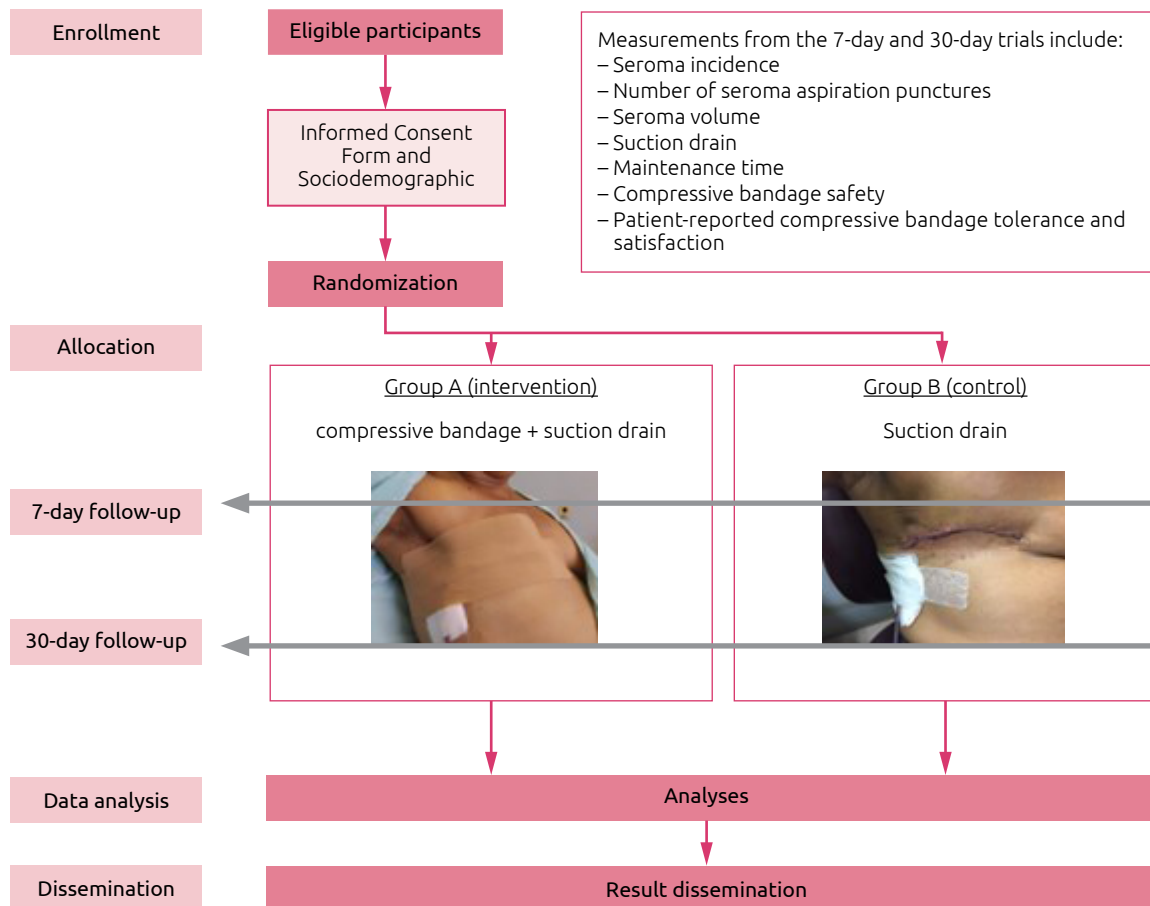
On the first postoperative day, patients may be randomized to the following groups:

- **Group A (Intervention with neuromuscular banding):**  
Patients allocated in this group will undergo neuromuscular compressive bandage on the hospital discharge day. The bandage will be removed on the 7<sup>th</sup> day, when the patient will be scheduled to return to the nursing clinic. The patients

will be instructed to remove the material at home in case of any symptom such as itching, redness, discomfort and/or any other occurrence due to bandage use.

- For bandage application:
  1. Assessment and scarring care by the nursing team.
  2. Placement of the sterile microporous tape over the scarring region to avoid contact with the bandage glue, and protect the scar points if the patient needs to remove the bandage at home. This adhesive tape is a sterile material used to protect the scarring points.
  3. Application of the 7.5 cm wide Vitaltape® neuromuscular bandage, through maximum stretching on the plastron, armpit, and lateral thorax portion regions. The bandage will be placed without stretching at both ends, using between two and three centimeters. The necessary number of bandage bundles will be applied according to the trunk height and width of each patient.

All applications will be performed by trained physiotherapists for proper neuromuscular bandage placement employing the



**Figure 1.** Study randomization protocol.

compressive technique. Research participants will receive a home guidance manual with instructions on bandage use and a home checklist that must be completed with daily observations and collected at the end of seven days (the Complementary document).

- Grupo B (control):  
The patients allocated in this group will follow the institutional routine using only the suction drain, and will be instructed by the nursing team to maintain the scarring points uncovered and wash them daily with filtered, boiled, and cold water, returning to the nursing clinic in 7 days for reassessment.

## Blinding

As this survey aims to assess the use of a medical device, blinding is not possible due to the intervention characteristics. Thus, neither participants nor researchers who will assess the outcomes and collect the data will be blinded.

## Data collection

Data will be collected through interviews and physical examinations, and complemented by an active search using both electronic and physical medical records. Information regarding type of oncological treatment, histopathological reports and clinical data on dressing care will be obtained from hospital records.

## Patient follow-ups

Interviews and physical examinations will be performed during the study enrollment moment, and after 7 and 30 days of surgery. Data on sociodemographic characteristics and life habits will be obtained during the initial interview. After 7 days, patients in the intervention group (Group A) will be asked about local symptoms due to bandage use (concerning compressive bandage safety), as well as bandage use tolerance and satisfaction.

## Outcomes parameters and statistical analysis

### Primary outcome

The primary outcomes of this study will be assessed considering physical and/or electronic medical records obtained by the nursing team responsible for dressing care.

- Seroma incidence: seroma will be considered as the presence of local fluctuations with aspiration puncture indication condition for resolution, regardless of drained volume.
- Number of punctures: considered as the number of times the patient returned to the Institution to perform seroma puncture aspiration until complete resolution.
- Seroma volume: considered as the sum of all punctured volumes at each patient visit.
- Suction drain maintenance time: the time the suction drain must be maintained, in days.

### Secondary outcomes

Secondary outcomes will only be evaluated in the intervention group (Group A) on the 7<sup>th</sup> postoperative day, as they are directly associated to compressive bandage use (Figure 2).

- Compressive bandage safety: any dermal alterations caused by the bandage will be evaluated.
- Compressive bandage tolerance: reports on the sensations of patient using the compressive bandage.

## Descriptive and control variables

The following variables will be employed: patient characteristics (age, marital status, education, skin color, body mass index, arterial hypertension, Diabetes Mellitus status, smoking and alcohol consumption), as well as tumor characteristics, oncological treatment (clinical staging, molecular subtype, type of breast biopsy, neoadjuvant treatment (chemotherapy, targeted therapy, hormone therapy), type of breast surgery, number of removed lymph nodes, number of involved lymph nodes, use of an electric intraoperative scalpel, surgical laterality and breast weight, and postoperative complications characteristics (spontaneous dehiscence of the surgical stitches, epidermolysis, necrosis, instrumental debridement, surgical wound infection and hematoma, delayed healing, paresthesia along the course of the intercostobrachial nerve, paresthesia in the plastron, intercostobrachialgia, plastron pain, axillary net and early edema in the upper limb ipsilateral to the surgical treatment)).

## Data analyses

Descriptive analysis will be performed concerning the selected variables and the main outcomes. Numerical variables will be presented using central tendency and dispersion measures, and categorical variables will be presented as frequency distributions.

The Shapiro-Wilk test will be applied to assess data distribution normality, considering a significance level of 5%. The comparison of continuous variables between the intervention groups will be performed using the Student's t test, while for categorical variables the chi-square test or Fisher's exact test will be performed. Outcome assessments for dichotomous variables will be carried out using odds ratios at a 95% confidence interval.

Multiple logistic regressions and multiple linear regressions will be performed to control confounding variables. The variables to be included in the model will be selected by the Stepwise Forward method (progressive variable inclusion), maintaining those presenting  $p < 0.05$ .

The SPSS version 24.0 will be used for the data analysis.

## Ethics and dissemination

### Data collection and confidentiality

Patients who meet the inclusion criteria will be informed about the purpose of the study, its duration, possible side effects and

**Dermal alterations:**

- Color alterations (redness): defined according to the presence of hyperemia at the bandage application site.
- Local temperature increases: defined according to the presence of hyperthermia at the bandage application site.
- Peeling: the presence of dry or wet desquamation at the bandage application site will be assessed, graded as mild, moderate or intense.
- Wounds: the presence of continuity solution (wounds) at the bandage application site will be assessed, being graded as mild, moderate or intense.
- Bullous lesions: the presence of blisters at the bandage application site will be assessed, graded as mild, moderate or intense.

**Patient sensations:**

- Pain at the application site: considered by patient reports and graded according to a Numerical Visual Scale (0-10).
- Pruritus: reports on itching or irritation at the bandage application site will be assessed, graded according to the Numeric Visual Scale (0-10).
- Burning: report on burning at the bandage application site will be assessed, graded according to a Numerical Visual Scale (0-10).
- Discomfort: discomfort at the application site will be assessed, graded according to a Numerical Visual Scale (0-10).
- Feeling of tightness: uncomfortable tightness will be assessed, graded according to a Numeric Visual Scale (0-10).

**Figure 2.** Dermal alterations and sensations referred to during the intervention period.

non-mandatory participation. Upon participation acceptance, confidentiality will be guaranteed through the confidential filing of information concerning patient health and personal data, and an informed consent form will be provided.

Patients participating in the intervention group may report discomfort at the bandage application site (itching, local heat, burning, redness, swelling, pain). Upon any complication, the intervention will be suspended. Possible discomfort monitoring and follow-up will be carried out until full patient recovery by the physiotherapy and nursing services, and by the Emergency Care Service assistance team, as this service may comprise the main gateway in case of any local discomfort due to bandage use.

## Ethics

This study was approved by the National Cancer Institute Research Ethics Committee (CEP-INCA), Rio de Janeiro, Brazil, under No. 2,774,824, in accordance with attributions defined in CNS Resolution No. 466/2012 and CNS Operational Standard No. 001/2013.

This clinical trial is registered at Clinical Trials.gov under identifier No. NCT04471142.

## Withdrawal

All participants are free to withdraw from the study at any time and for any reason.

## Dissemination plan

This study protocol intends to answer whether the use of a compressive bandage during the first postoperative week

associated with the use of a drain is effective in preventing seroma. The results of this research will be published in scientific publications, national and international scientific events, and other media portals. The study protocol will be presented to healthcare professionals and shared with patient groups through workshops and webinars.

## DISCUSSION

Seroma stands out as the most common complication arising from breast cancer treatment. Its presence can increase the likelihood of developing infections, edema, and limitations in joint amplitude. This can result in setbacks for adjuvant treatment, as well as causing discomfort when engaging in daily tasks, leisure, and work.

The utilization of a compressive bandage was deemed a secure approach for patients experiencing seroma after undergoing surgical treatment for breast cancer, necessitating aspiration to alleviate discomfort.

A clinical trial was designed to explore the potential effectiveness of utilizing a compressive bandage during the initial week following mastectomy surgery, as part of the surgical treatment for breast cancer. This approach aims to offer a cost-effective strategy for preventing seroma formation.

## CONCLUSIONS

The application of compressive bandage can be an effective and non-invasive strategy to prevent seroma in patients after mastectomy surgery.

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## AUTHORS' CONTRIBUTIONS

EANF: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project

administration, Writing – original draft. RMC: Data curation, Investigation, Methodology, Project administration, Writing – original draft. FOM: Investigation, Methodology, Writing – original draft. DMT: Investigation, Methodology, Writing – original draft. SSA: Formal analysis, Writing – review & editing. LCST: Supervision, Writing – review & editing. AB: Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing.
















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# Assessment of pathological response of breast cancer in patients undergoing neoadjuvant chemotherapy in a referral hospital in Amazonas State

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## ABSTRACT

**Introduction:** The therapeutic options for breast cancer are diverse. Increasingly, treatments are established on an individual basis, depending on a series of variables ranging from age to the molecular profile of the tumor. When neoadjuvant chemotherapy (NAC) is necessary, adequate clinical evaluation (CE) and control examinations, such as breast ultrasound (US) and mammography (MMG), are of fundamental importance, as it is necessary to reevaluate the tumor lesion to determine an individualized surgical treatment, with the aim of performing breast-conserving surgery within the available techniques. This study sought to evaluate the pathological response of patients undergoing neoadjuvant chemotherapy, analyzing the presence or absence of tumor reduction by relating the physical examination with imaging methods (MMG and US), taking the anatomopathological examination measurements as the gold standard, thus intending to identify the best method for evaluating the pathological response. **Methods:** This was a prospective, observational, analytical cohort study. The study included 41 patients diagnosed with breast cancer detected by mammography and ultrasound (MMG and US) followed by biopsy, who underwent neoadjuvant chemotherapy (NAC) and surgery. The measurements of the malignant breast lesions obtained by CE, MMG and US were compared with the anatomopathological measurements on biopsy as the gold standard. **Results:** Pearson's correlation coefficient was the statistical method used for evaluation, finding a value of 0.49 between the anatomopathological examination and CE, 0.47 between the anatomopathological examination and MMG and 0.48 between the anatomopathological examination and US ( $p < 0.05$ ). **Conclusions:** CE, MMG and US showed a moderate correlation with anatomopathological measurement, in addition to a moderate correlation between them, demonstrating equivalence in the pre-surgical definition of the size of the breast tumor after NAC, being complementary to each other to define a measure of greater accuracy of the tumor in breast cancer.

**KEYWORDS:** mammography; ultrasound; clinical examination; neoadjuvant chemotherapy.

## INTRODUCTION

Breast cancer is one of the challenges in the current scenario of population aging and combating chronic non-communicable diseases in Brazil<sup>1</sup>. It is the type of cancer that most affects women in the country, except for non-melanoma skin tumors, and also the one that kills the most<sup>1</sup>. According to Brazil's National

Cancer Institute (INCA), about 73,610 new cases of breast cancer are expected in Brazil for the three-year period from 2023 to 2025, and in the case of the state of Amazonas, 500 new cases are expected per year, which corresponds to an estimated risk of 61.66 new cases for every 100 thousand women in Brazil<sup>2,3</sup>. The therapeutic options for breast cancer are diverse and range

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from surgery and radiotherapy to systemic drug treatment (chemotherapy, hormone therapy)<sup>4</sup>.

Neoadjuvant chemotherapy (NAC), that is, chemotherapy started before breast cancer surgery, was introduced in the 1970s, with the aim of reducing the stage of locally advanced (inoperable) disease and making it operable<sup>5</sup>. Since then, it has been gaining more and more ground, mainly in the presence of HER2-positive and triple-negative neoplasms associated with increased disease-free survival, and as a mechanism of tumor cytoreduction, which can occur partially or completely, allowing in some cases surgical procedures with greater preservation of breast tissue, so that the pathological complete response (pCR) after neoadjuvant treatment, in most cases, determines a better prognosis in the treatment of breast cancer<sup>5,6</sup>.

Therefore, adequate clinical evaluation and performance of control examinations, such as ultrasound, mammography and MRI, are essential for the treatment of neoplastic breast lesions. The diagnostic accuracy of imaging tests to detect pCR is as high as 74% in MMG and 79% in US, with the former being more sensitive than physical examination, although less specific<sup>7</sup>. As for MRI, it is known that in addition to being the gold standard for evaluating response to NAC, it has been the most used to determine pCR in most studies<sup>8-12</sup>.

This work was established as a method of elucidating clinical data in complementary association with imaging methods, in the quest to generate data with information that provides better monitoring for patients treated at the Fundação Centro de Controle de Oncologia do Estado do Amazonas (FCECON). Its objective was to evaluate the pathological response of patients undergoing NAC, analyzing tumor reduction and relating the size of the lesion through physical examination and the imaging methods MMG and US, taking the anatomopathological examination measurements as the gold standard, thus seeking to identify the best method to evaluate the pathological response in these patients in question. Although MRI is the gold standard test for evaluating pathological response, it was not applied in the study due to its unavailability in the Unified Health System (SUS).

## METHODS

A prospective, observational, analytical cohort study was conducted. The study included 41 patients admitted to the Mastology Service of FCECON (Amazonas State Oncology Control Center Foundation) from May 1, 2021 to October 30, 2021; the patients were diagnosed with breast carcinoma and underwent NAC and surgery, where the metric results of malignant breast lesions acquired using CE, MMG and US methods after completion of NAC were compared, taking measurements from the anatomopathological examination as the gold standard.

CE was performed during hospitalization for the implementation of a surgical procedure, with the patient sitting in

bed with her arms relaxed and loose at her sides to evaluate the armpits and supra- and infraclavicular fossae. Afterwards, the patient was positioned in a horizontal supine position with the arm above the head, using the oblique-lateral position when the nodules were in the lateral quadrants, close to the anterior axillary line. Therefore, the tumor was fixed between the examiner's fingers, who measured it using manual calipers. The size considered was the longitudinal and transversal measurement found. Regarding imaging examinations (US and MMG), these were analyzed both in relation to the report and in relation to the image, also using the largest tumor measurement as a reference for statistical evaluation.

All surgeries were performed by the FCECON Mastology Service, and pathological measurements were obtained by pathologists working at the service. In relation to the histopathological examination, the size of the tumor considered was the longitudinal and transverse measurement taken with a millimeter ruler in the macroscopic examination or, in cases where there was no visualization with the naked eye, through the largest measurement obtained by microscopic examination of the histological slide, being defined as zero when no neoplastic disease was observed in the surgical specimen. The acquired measurements were stored in a computerized database for later analysis.

The analysis of the drugs used in NAC was not the focus of this study, but the patients had standard treatment with doxorubicin, cyclophosphamide and paclitaxel, and when the c-erbB2 proto-oncogene expressed, trastuzumab was associated with the treatment, as well as double blockade with trastuzumab and pertuzumab in special cases.

Patients who did not undergo NAC and/or did not undergo control examinations after NAC were excluded.

For statistical analysis, Pearson's correlation coefficient ( $r$ ) was used as a statistical analysis to evaluate the measurements obtained by each diagnostic method (CE, MMG and US and anatomopathological examination). The mean, median, standard deviation, minimum, maximum, absolute and relative frequency of data were also calculated to analyze the characteristics of the population. The data were presented in the form of tables, and  $p < 0.05$  was considered statistically significant.

The study was approved by the FCECON Research Ethics Committee (COEP) under No. 4.894.078.

## RESULTS

In the group of 41 patients studied, the age ranged between 28 and 75 years, with a mean of 49 and a median of 47 years; only one patient was not Brazilian (2.4%), 23 patients (56%) were from the capital of Amazonas, while 13 (31.7%) were from the state's countryside. Histopathological analysis by biopsy confirmed the diagnosis of malignancy in all 41 patients, with invasive ductal

carcinoma being the most common histological type, present in 85.3% of cases, as shown in Table 1.

Regarding the immunohistochemistry pattern, four cases were diagnosed as luminal A (9.7%) Ki-67 <14%, ten as luminal B (24.3%) Ki-67 >14%, ten as hybrid luminal (24.3%), six pure HER2+ (14.6%) and eleven as triple-negative (26.8%).

The interval between the end of NAC and the surgical procedure was 57.1 days. The time elapsed between the evaluation of patients using work-up methods after NAC and surgery ranged from a minimum of 25 days to a maximum of 201 days, with a mean of 57.1 days and a median of 46 days. In three cases, the time between the end of NAC and surgery was more than 95 days, and in these cases, the delay was associated with personal reasons described by the patients, which increased the overall average attributed to the study.

The diameter of the lesions varied according to each method adopted, with ultrasound showing a lower standard deviation compared to the other findings (CE and MMG), according to Table 2.

The neoplastic lesions identified through CE, MMG and US were compared with the anatomopathological examination to determine which examination had the greatest association with the result found in the surgical specimen. Regarding CE, the tumor measurement was greater than that found in the anatomopathological examination in 46.3% of cases, being the same in 17% of cases, and lower in 36.5% of cases.

When analyzing the mammogram, the measurement found was greater than the anatomopathological measurement in 29.2% of cases, the same in 56% of cases and lower in 14.6% of the analyzed population. In the comparison for US, the lesion was larger than the pathological finding in 46.3% of cases, the same in 41.4%, and smaller in 12.1%.

**Table 1.** Distribution according to histological type identified in the breast biopsy.

Histological type	n	%
Invasivo ductal carcinoma	35	85.37
Lobular	4	9.76
Metastatic adenocarcinoma	1	2.44
Mucinous	1	2.44
Total	41	100.00

Pearson's correlation coefficient was determined using the average between the longitudinal and transversal measurements of the tumor diameter obtained by the anatomopathological examination and for each preliminary examination conducted. The correlation coefficient found is highlighted in Table 3.

Pearson's correlation coefficients were also calculated between the non-surgical methods, obtaining  $r=0.40$  for the comparison between CE and MMG,  $r=0.54$  between CE and US, and  $r=0.41$  between MMG and US, with all values being significant ( $p<0.005$ ).

The pharmacological treatment used in NAC was through cycles of anthracycline + cyclophosphamide + taxane (AC x T) associated with trastuzumab in the presence of HER2+ tumors. Five patients underwent double blockade (trastuzumab and pertuzumab) combined with AC x T, and only two showed pCR.

The histopathological analysis of the surgical specimen identified residual presence of disease in 32 patients (78%); it was not possible to evaluate in 5 patients (12.1%) - Tx, and in 4 patients (9.7%), there was complete remission of the disease.

## DISCUSSION

The individualization of therapies for the treatment of breast cancer is directly associated with technological advances, so that several imaging methods are used to define breast lesions, especially when it is necessary to assess the presence or absence of pCR. The present study sought to determine the best preliminary method to evaluate the pathological response to treatment with NAC in 41 patients, all women treated at a referral hospital in Amazonas State. Accordingly, the residual lesions were analyzed through physical examination and imaging methods (MMG and US), taking the anatomopathological examination

**Table 3.** Pearson correlation coefficient ( $r$ ) for comparison between anatomopathological examination and clinical examination, mammography and ultrasound ( $n=41$ ). Correlation with statistical significance ( $p<0.05$ ).

Correlation	R
Anatomopathological <i>versus</i> clinical examination	0.49
Anatomopathological <i>versus</i> mammography	0.47
Anatomopathological <i>versus</i> ultrasound	0.48

**Table 2.** Description of tumor size according to preliminary assessment.

Method	Tumor measurements (cm)				
	Mean	Standard deviation	Median	Minimum	Maximum
Clinical examination	3.5	4.1	2.9	0	16.1
Mammography	2.6	2.5	2.4	0	9.5
Ultrasound	2.4	1.9	2.2	0	11
Anatomopathological	2.8	3.4	1.6	0	14

measurements as the gold standard, demonstrating the equivalence of the methods in the pre-surgical determination of breast tumor size post-NAC.

There are several trials that have sought to verify the most reliable method for evaluating the pathological response of breast cancer after NAC. In these studies, a histological predominance of invasive ductal-type carcinoma is noted, with samples exceeding 60% in most of the articles evaluated, in agreement with the data we found, since 60.9% of our patients had histological involvement of the ductal type<sup>5,6,8-11,13</sup>. Regarding the immunohistochemical profile, the predominance of the luminal profile stands out, which was also evidenced in our study, where we observed this finding in 34% of patients<sup>9,10,12-16</sup>.

NAC can be performed in any molecular profile, among which we can highlight tumors with expression of the c-erbB2 protein, which as a result of pharmacological advances has been associated with excellent results related to pCR, especially after the introduction of double blockade therapy (pertuzumab + trastuzumab)<sup>15</sup>. Of the 41 patients evaluated in our study, 32 (78%) showed no complete pathological response to neoadjuvant chemotherapy. When individualizing patients with c-erbB2 protein expression who underwent double blockade, we found two patients (40%) with pCR among the five who underwent treatment with trastuzumab and pertuzumab, a result that is similar to the findings described in the literature<sup>14</sup>.

Analyses of measurements obtained through CE, MMG and US are also described in various publications; in some cases, in comparison with the findings of the anatomopathological examination, mostly determining the existence of a single method, superior to the others, for carrying out the evaluation of the pathological response to NAC<sup>6-11,13</sup>. Among the studies we analyzed, only one attributed MMG as a highly sensitive and reproducible method for evaluating the persistence of disease after NAC, with an accuracy estimated at 73%<sup>7</sup>. In our study, the mammogram showed lesions with a mean value equivalent to 2.6 cm, which is close to the mean value described in the anatomopathological analysis, in this case, equal to 2.8 cm, a finding that confirms the results of this study, indicating MMG to be a reliable method<sup>7</sup>.

There is evidence of greater precision in measurements obtained through US when compared to those obtained through MMG, which is evidenced by various statistical methods<sup>6,9,11,13</sup>. As well as high accuracy when combined with MMG and US<sup>7</sup>. In our study, the diameter of the lesions varied according to each method used, with breast US having a lower standard deviation in relation to the other methods compared.

Pre-existing studies also confirmed a tendency for imaging methods to underestimate tumor size<sup>6,10,17</sup>. In the present study, this was verified in relation to CE, considering that imaging methods had less interference in measuring tumor size. There is evidence that CE could underestimate the size of the

lesion, especially in circumstances in which the tumor is located in very deep regions, such as in large breasts or breasts that are very dense on palpation, which would make it difficult to distinguish between tumor and normal breast tissue. It can be inferred that we sought to minimize errors in relation to measuring the tumor during the physical examination, taking into account the rigor in positioning the patient correctly and using a millimeter ruler to better define the size of the lesion.

In recent years, no articles demonstrated CE, individually, to be the best method for evaluating the size of the residual tumor, when compared to imaging methods in relation to pathology. This fact is probably due to radiology evolution, which, through various methods, has been able to determine pathological response findings with greater precision through imaging tests<sup>6-11,13-15,17</sup>. It is interesting to note that when evaluating these studies, there is a lack of standardization in relation to the statistical evaluation method, thus using different correlation tests, which represent a difficulty in comparing results.

In our research, only two studies used Pearson's correlation coefficient to evaluate the pathological response: the first finding US to be the best method, with findings of 0.68<sup>6</sup>; the other demonstrating equivalence between the three evaluation methods, with a Pearson correlation coefficient of 0.8 between the anatomopathological examination and the CE, 0.7 between the anatomopathological examination and MMG, and 0.7 between the anatomopathological examination and US ( $p < 0.05$ )<sup>18</sup>. In our study, we found a Pearson correlation coefficient equal to 0.49 between the anatomopathological measurement and that determined through physical examination; 0.47 when comparing the anatomopathological and MMG; and 0.48 between pathology and US ( $p < 0.05$ ).

In a study by Paris et al., the evaluation used was through the kappa index, which evaluated a similar relationship as ours with a coefficient of 0.4, not establishing superiority in relation to any method evaluated (US, MMG and CE), a finding also evidenced in our study<sup>5</sup>. We also found data associated with the interclass correlation coefficient, used to compare US and MMG in relation to MRI, finding superiority for the latter in this evaluation<sup>9,11</sup>. One hundred and seventy-four patients were statistically evaluated using the ROC curve with the aim of comparing the pathological response to NAC using MRI, CE and MMG, also demonstrating superiority in relation to MRI<sup>10</sup>. Spearman's correlation coefficient was also described in the search to compare the relationship between MRI, MMG and US, attributing superiority to MRI with a value of 0.786<sup>15</sup>.

It is important to highlight that, despite the importance of all the methods used to measure the size of the tumor, MRI is increasingly presented as a more reliable method, being used as the main examination to evaluate pathological response<sup>8-10,12,15</sup>. In our search for articles for this discussion, we were forced to include MRI data due to the absence of publications that



exclude this imaging method from pathological response analysis. MRI was not introduced in our study because it is not possible in the context of the SUS, as it is not standard in the public health network, and it is not possible to use it as a comparison parameter with other imaging methods in the services of SUS.

Although this study evaluated preoperative measurements and the final tumor size, several limitations can be noted, among which the sampling data are shown, since it was a study with few patients, selection criteria, varying sizes of lesions, multiple histological types, and lack of comparison with the gold standard, namely MRI. Also, there were various chemotherapy regimens, types of cycles, and intervals between examinations, which were not performed on the same day but without a very long interval.

Despite all the limitations, we believe that the tumor measurements obtained by CE, MMG and US displayed a moderate correlation with that obtained by anatomopathological examination.

## CONCLUSIONS

The results of this study demonstrate that tumor measurements obtained by CE, MMG and US displayed a moderate correlation with that obtained by anatomopathological examination, being similar in determining the size of the breast tumor after NAC, and complementary to each other to obtain a more accurate measurement of the tumor in breast cancer. Through these results, we can demonstrate the importance of this work in contributing to the treatment of patients diagnosed with breast cancer who undergo NAC and surgery.

## AUTHOR'S CONTRIBUTIONS

KCXP: Investigation, Validation, Visualization, Writing – review & editing. GVP: Data curation. HAMS: Data curation. HVP: Data curation. JNB: Data curation. KFO: Data curation. LIAC: Data curation. MHCR: Data curation. LMCM: Data curation. LBA: Data curation. IAA: Data curation. MMLYM: Data curation. TCFS: Data curation. JGM: Data curation. HFES: Investigation, Validation, Visualization, Writing – review & editing.

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## ERRATUM

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### On page 1 it was included:

José Guilherme Maia<sup>2</sup> 

### On page 5 it was included:

## AUTHOR'S CONTRIBUTIONS

JGM: Data curation.



# Survival of patients with de novo metastatic breast cancer

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## ABSTRACT

**Introduction:** For the 2020-2022 triennium more than 2 million cases of breast cancer were estimated worldwide. De novo metastatic breast cancer is so called when metastasis is diagnosed at the same time as the primary tumor. It affects approximately 3.5 to 10% of breast cancer patients and only 25% of these will be alive after 5 years. **Methods:** We conducted a retrospective cohort study of women with de novo metastatic breast cancer treated at a single center from January 1, 2000 to December 31, 2012. Cases were identified in the Hospital Cancer Registry. Overall survival (OS) was estimated at 5 years with the Kaplan-Meier product limit, and the log-rank test was used to test differences between curves; Cox multiple regression and all tests were considered significant with  $p < 0.05$ . **Results:** Of the 265 patients in the study, the estimated 5-year OS was 31.3%. There was a difference in survival according to the following: age group ( $p < 0.046$ ); having had breast surgery ( $p < 0.001$ ); having undergone chemotherapy simultaneously with radiotherapy, hormone therapy, targeted therapy or surgery ( $p < 0.088$ ); use of exclusive or multimodal hormone therapy ( $p < 0.001$ ); education ( $p < 0.001$ ); luminal tumors ( $p < 0.003$ ); and being treated between 2006 and 2012 ( $p = 0.043$ ). In the multiple model adjusted by age group and education, the following factors remained as predictors of a better prognosis: having undergone surgery (hazard ratio — HR=0.46, 95% confidence interval — 95%CI 0.32–0.66); luminal tumors (HR=0.34, 95%CI 0.23–0.50); and targeted therapy (HR=0.27, 95%CI 0.15–0.46). **Conclusion:** The risk of death in patients with de novo metastatic breast cancer was lower than in those undergoing local surgical treatment as part of multimodal treatment, as well as the luminal molecular subtype and the introduction of better systemic treatment strategies, such as target.

**KEYWORDS:** breast cancer; survival; metastasis.

## INTRODUCTION

For the 2020-2022 triennium, more than 2 million cases of breast cancer were estimated worldwide, with just under 700,000 deaths, which represents a significant 15.5% of total cancer deaths in women<sup>1,2</sup>. In Brazil, the estimate was more than 73 thousand new cases and 18,068 deaths, with cancer being the first cause of death among women, which corresponds to 16.3% of all cancer deaths<sup>3</sup>. De novo metastatic breast cancer is so called when metastasis is diagnosed at the same time as the primary tumor. It affects approximately 3.5 to 10% of breast cancer patients and only 25% of these will be alive after 5 years<sup>4-6</sup>. It is a systemic disease that requires multimodal treatment and is classified, like the initial disease, into clinically relevant groups for treatment, according to the positivity or negativity of estrogen, progesterone and HER2 receptors<sup>6-8</sup>. The most frequent sites of metastases in these patients

are bone, lung, liver and central nervous system<sup>8,9</sup>. The mutation profile is of greater complexity and heterogeneity than the initial stages<sup>10-12</sup>. Surgical treatment is considered in selected cases, with precise indication to control symptoms with the intention of hygienic surgery<sup>12</sup>. Some studies observed a positive impact on quality of life and others found an increase in overall survival (OS) when compared to patients who did not undergo surgery in the metastatic setting. A retrospective cohort analysis was conducted on the survival of de novo metastatic patients who underwent surgical treatment in relation to those who did not undergo surgery.

## METHODS

This was a hospital-based retrospective cohort study with data extracted from the Hospital Cancer Registry (RHC); it

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was composed of women with de novo metastatic breast cancer treated in a single Brazilian center from January 1, 2000 to December 31, 2012. The sociodemographic variables analyzed were age group ( $\leq 50$  years, 51–69 years and  $\geq 70$  years), education (complete and incomplete primary education, and complete secondary education and higher education), and health care (supplementary or public health care system). The molecular subtypes (luminal, HER2-positive luminal B, overexpressed HER2 and triple-negative), the histological grade (1, 2 and 3), the number of lines of chemotherapy and hormone therapy, and the topography of the metastases were analyzed. Treatment was stratified according to modality (yes and no), breast-conserving surgery (segmental resection and quadrantectomy), total mastectomy, axillary sentinel lymph node investigation, axillary dissection, chemotherapy, radiotherapy, hormone therapy and targeted therapy.

The cases were staged according to the American Joint Commission of Cancer (AJCC), 8th edition, in 2018, which added histological grade, presence of estrogen/progesterone/HER2 receptors and multiple gene panel<sup>13</sup>. For qualitative variables, absolute (n) and relative frequency (%) were evaluated.

Survival time was calculated by subtracting the date of last information (alive or dead) by the date of diagnosis. The Kaplan-Meier product limit estimator was used to compare survival curves, and the log-rank test was applied. The semiparametric Cox proportional hazards model was used to evaluate the prognostic potential, and the hazard ratio (HR) and 95% confidence interval (95%CI) were calculated for all variables. For the multiple model, variables were selected using the log-rank test, from the highest to lowest level of statistical significance. The survival analysis was divided into two periods (2000–2005 and 2006–2012) because of the importance of the introduction of taxane drugs and targeted therapy in treating patients more effectively from 2006 onwards. The proportional hazards assumption was based on Schoenfeld residuals. The significance level for all tests was set at 0.05. All statistical analyses were performed in STATA 15 (College Station, Texas, 2017).

This study was approved by the Research Ethics Council (CEP) under No. 2660/19.

## RESULTS

Between 2000 and 2012, 265 patients with de novo metastatic breast cancer were identified. Of these, 42.5% (n=90) were aged 61 or over and 78.5% (n=208) received care through the supplementary health care system. Regarding clinical staging, 51.4% (n=136) of patients were T4; 34.3% (n=91), N1; histological grade 2 was the most common, present in 47.5% (n=126) of patients (Table 1).

The molecular subtypes of the cases evaluated were: luminal (58%; n=153), HER2-positive luminal B (21%; n=56),

**Table 1.** Sociodemographic characteristics, clinical staging and molecular subtype of 265 patients with de novo metastatic breast cancer treated at the A. C. Camargo Cancer Center, from 2000 to 2012.

Variable	n=265	%
Age group (years)		
$\leq 50$	90	33.8
51–60	63	23.7
$\geq 61$	112	42.5
Education		
Primary, complete and incomplete	47	18.1
Secondary, complete, and Higher Education	77	28.9
Unknown	141	53.0
Health care		
Public health care system	50	18.8
Supplementary care health system	208	78.5
Not reported	7	2.6
Year of diagnosis		
2000–2005	90	33.8
2006–2012	175	66.2
T – Clinical tumor size		
Tx	4	1.5
T1	12	4.5
T2	68	25.7
T3	43	16.2
T4A/C/D	28	10.6
T4B	108	40.8
Not reported	2	0.8
N – Lymph node status		
N0	61	23.0
N1	91	34.3
N2	83	31.3
N3	28	10.5
Not reported	2	0.7
Molecular subtype		
Luminal	153	58.0
Luminal B HER2-positive	56	21.0
HER2-overexpressing	25	9.4
Triple-negative	19	7.1
No information	12	4.5
HER2*		
Negative	171	64.5
Positive	82	31.0
Not reported	12	4.3

Continue...

**Table 1.** Continuation.

Variable	n=265	%
Estrogen receptor		
Negative	56	21.0
Positive	202	76.0
No information	7	3.0
Progesterone receptor		
Negative	85	32.0
Positive	170	64.0
No information	10	4.0
Histological grade		
1	15	5.6
2	126	47.5
3	106	40.0
Not reported	18	6.8
Metastases (n=324)		
Bone	199	99.4
Lung	97	64.0
Liver	86	56.1
Central nervous system	40	28.5
Others	76	66.1

\*HER2 + (IHC 3+ or 2+ with ISH amplified).

HER2-overexpressing (9.4%; n=25) and triple-negative (7.1 %; n=19) (Table 1).

When evaluating metastases, all patients had involvement in multiple organs, with bone being the most affected, followed by the lung and liver (Table 1).

In multimodal treatment, chemotherapy was performed in 81.9% (n=217) of patients, radiotherapy in 76.7% (n=204), hormone therapy in 66.8% (n=177); targeted therapy in 15.8% (n=42) and surgery in 32.5% (n=86) (Table 2).

The 5-year OS in patients with de novo metastatic breast cancer from 2000 to 2012 was 31.3%: 20.22% in the period of 2000 to 2005 and 34.95% in the period of 2006 to 2012. The highest survival rates were identified in women with age under 50 years (35.89%), higher education (42.2%), luminal molecular subtype (34.4%), surgical breast treatment (47.7%), axillary surgery (49.3%), radiotherapy (34.5%) and targeted therapy (54.2%) (Table 3 and Figure 1).

In the multiple regression model adjusted by age group and education, a reduction in the risk of death was observed in patients who underwent surgical treatment in the breast (HR=0.46, 95%CI 0.32–0.66), with luminal tumors (HR=0.34, 95%CI 0.23–0.50) and with HER2 tumors using targeted therapy (HR=0.27, 95%CI 0.15–0.46). An increased risk of death was also observed in patients with N2 and N3 axillary involvement (HR=1.71, 95%CI 1.12–2.62) (Table 4).

**Table 2.** Treatment modalities in 265 patients with de novo metastatic breast cancer at A. C. Camargo Cancer Center, from 2000 to 2012.

Treatment	n	%
Primary surgery – breast		
Yes	86	32.5
No	179	67.5
Type of breast surgery – primary		
Mastectomy (total)	71	82.5
Conservative surgery	15	17.4
Axillary surgery		
Yes	79	30.0
No	186	70.0
Type of axillary surgery		
Axillary dissection	76	96.2
Sentinal lymph node	3	3.8
Chemotherapy		
Yes	217	81.9
No	48	18.1
Hormone therapy		
Yes	177	66.8
No	88	33.2
Targeted therapy		
Yes	42	15.8
No	223	84.2
Radiotherapy of primary lesion – breast		
Yes	68	25.6
No	244	78.2
Radiotherapy of metastases		
Yes	136	51.1
No	108	40.7
Bone	76	28.6
Central nervous system	40	15.1
Others*	20	7.4

\*plastron, neuroaxis, ocular, lymph nodes.

## DISCUSSION

In this study, it was possible to verify a 31.3% probability of survival of *de novo* metastatic patients within 5 years in the period from 2000 to 2012. It was observed that, among these, patients who underwent surgical treatment of the primary tumor had an increase in survival, but it was found that the most common tumor profile was luminal, which are usually tumors with a better prognosis and great possibility of drug treatment.

**Table 3.** Probability of survival according to sociodemographic and clinical characteristics of 265 patients with de novo metastatic breast cancer.

Variable	Death (total)	OS – 5y	p-value
Age group (years)			
≤50	68 (89)	35.89	0.046
51–69	103 (124)	28.79	
≥70	41 (51)	21.65	
Education			
Primary incomplete/complete	41 (47)	12.77	<0.001
Secondary	23 (32)	28.13	
Higher education	25 (45)	42.20	
Unknown	141		
Year of diagnosis			
2000–2005	71 (89)	20.22	0.004
2006–2012	111 (176)	34.95	
Health care			
Public health care system	41 (50)	26.18	0.897
Supplementary health care system	164 (208)	31.82	
Not determined	7		
Clinical staging – cT			
T0/1	9 (16)	43.75	0.016
T2	40 (68)	39.93	
T3	25 (43)	38.03	
T4 A/C/D	21 (28)	25.00	
T4B	85 (108)	20.01	
Not determined	2		
Clinical staging – cN			
N0	34 (63)	44.18	<0.001
N1	56 (91)	36.44	
N2	69 (82)	15.85	
N3	21 (27)	22.22	
Not determined	2		
Topography of metastases			
Bone	101 (152)	31.92	0.466
Lung	30 (45)	32.15	
Liver/central nervous system	51 (69)	23.92	
Luminal			
Yes	136 (212)	34.44	<0.001
No	46 (52)	11.92	
Not determined	1		
HER2			
Yes	54 (82)	33.84	0.496
No	116 (171)	30.09	
Not determined	12		

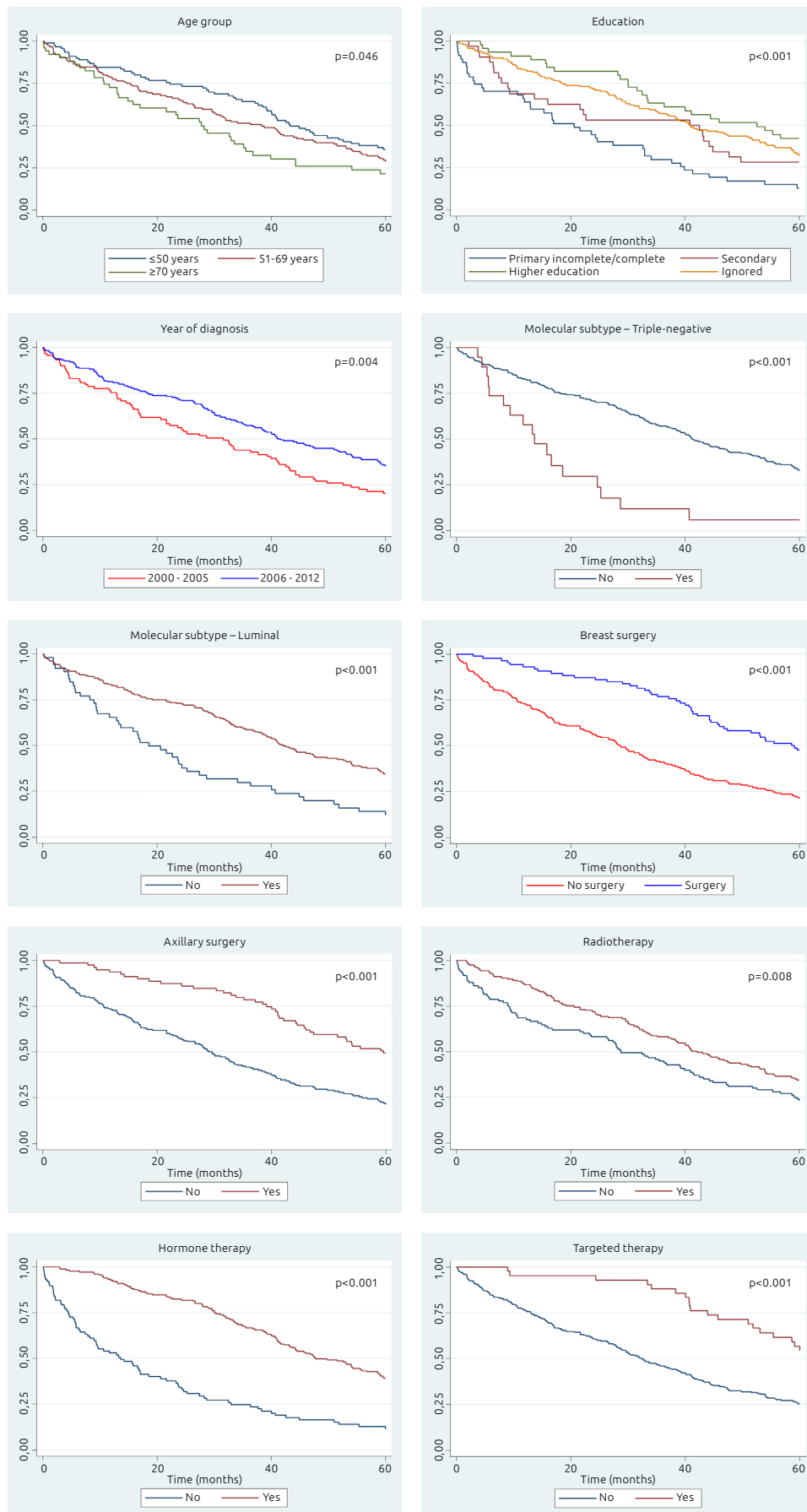
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**Table 3.** Continuation.

Variable	Death (total)	OS – 5y	p-value
Triple-negative			
Yes	17 (19)	5.92	<0.001
No	156 (237)	32.87	
Not determined	9		
Histological grade			
1	11 (15)	25.28	0.223
2	95 (126)	35.62	
3	88 (106)	28.62	
Not determined	18		
Breast surgery			
Yes	57 (86)	47.67	<0.001
No	137 (179)	21.05	
Type of breast surgery			
Mastectomy	36 (71)	49.3	0.586
Conservative surgery	9 (15)	40.00	
Axillary surgery			
Yes	51 (79)	49.37	<0.001
No	142 (186)	21.33	
Type of axillary surgery			
Axillary dissection	38 (76)	50.00	0.801
Sentinel lymph node	2 (3)	33.33	
Chemotherapy			
Yes	173 (217)	30.77	0.088
No	35 (48)	25.89	
Radiotherapy			
Yes	124 (157)	34.53	0.008
No	101 (108)	23.12	
Targeted therapy			
Yes	26 (42)	54.19	<0.001
No	163 (223)	25.23	
Hormone therapy			
Yes	135 (177)	39.11	<0.001
No	76 (88)	11.41	
Not determined	1		
Hormone therapy lines			
0	74 (74)	10.60	<0.001
1	43 (59)	39.07	
2	43 (54)	32.67	
3	40 (56)	52.80	
Not determined	12		
Chemotherapy lines			
0	42 (44)	24.31	0.016
1	50 (69)	36.79	
2	36 (46)	30.09	
3	60 (74)	35.91	
Not determined	25		

The significance level for all tests was set at 0.05.





**Figure 1.** Estimated overall survival of 60 months for patients with de novo metastatic breast cancer.

**Table 4.** Prognostic factors associated with the survival of patients with metastatic breast cancer de novo at A. C. Camargo Cancer Center, from 2000 to 2012.

Variable	HR	HRa* (95%CI)
Breast surgery		
No	1.00	1.00
Yes	0.42 (0.29–0.59)	0.46 (0.32–0.66)
Luminal		
No	1.00	1.00
Yes	0.46 (0.33–0.65)	0.34 (0.23–0.50)
Targeted therapy		
No	1.00	1.00
Yes	0.38 (0.23–0.61)	0.27 (0.15–0.46)
cN		
N0	1.00	1.00
N1	1.25 (0.81–1.91)	1.21 (0.78–1.87)
N2	2.15 (1.42–3.25)	1.71 (1.12–2.62)
N3	1.80 (1.04–3.10)	1.87 (1.06–3.28)
Age group (years)		
≤50	1.00	1.00
51–69	1.25 (0.89–1.74)	0.90 (0.62–1.29)
≥70	1.67 (1.11–2.53)	0.98 (0.62–1.55)
Education		
Illiterate	1.00	1.00
Primary incomplete/complete	0.59 (0.35–0.98)	0.72 (0.41–1.27)
Secondary	0.36 (0.22–0.60)	0.50 (0.29–0.85)
Higher education	0.48 (0.33–0.69)	0.73 (0.48–1.09)

HR: hazard ratio; 95%CI: 95% confidence interval. \*Test of proportional-hazards assumption ( $p=0.218$ ). Adjusted for schooling and age group.

Analyzing how these patients access care, there was no difference in survival between those treated in the public health care system and those treated in the supplementary health care system. Despite the treatment limitations imposed in the public system, access to chemotherapy and hormone therapy, at the time considered, was quite similar in our service, which was not the reality in Brazil as a whole. In the Amazona III study, a nationwide retrospective cohort that carried out an epidemiological analysis of breast cancer at all stages and evaluated the difference between patients treated by the public health care system and the supplementary health care system, it was observed that patients treated in the public system had tumors at more advanced stages and greater difficulty in accessing screening tests, which had a negative impact on their prognosis<sup>14</sup>.

In our study, all patients were multimetastatic, with the main sites being bone, lung, liver and central nervous system,

and no difference in survival was observed when evaluating the metastasis sites, which can be explained by the multiplicity of metastatic sites. In the work of Tian et al.<sup>15</sup>, who evaluated mutations and possible biomarkers in patients with metastatic tumors and correlated them with impact on treatment and survival, liver metastases had a worse prognosis compared to other sites<sup>15–17</sup>.

In this study, approximately 35.89% of patients were under 50 years of age, 80% belonged to the luminal subtype and regarding the combined treatment of chemotherapy, radiotherapy and surgery, 81.9% underwent chemotherapy and 32.5% surgery. This patient profile was similar to that studied in ECOG – ACRIN 2108, which evaluated surgical treatment in this group and observed no difference in OS or progression-free survival at 3 years<sup>15</sup>. In patients with de novo metastatic breast cancer, surgery is an option, but in the classic indication of controlling local complications, such as bleeding and infection<sup>16</sup>. Badwe et al.<sup>17</sup> found an improvement in survival in patients operated on with luminal profiles and single bone metastasis, while the ACRIN study did not observe an impact on survival<sup>15,17</sup>.

It was observed in this study that the inclusion of surgery as part of the treatment showed an increase in survival. Our findings are consistent with those of Badwe et al.<sup>17</sup> and Soran et al. regarding the use of breast surgery in these patients<sup>17,18</sup>. It is important to note that the majority had the luminal molecular subtype, which has a better prognosis, a fact that may have influenced the results.

In clinical practice, however, the survival benefit of local treatments in de novo metastatic breast cancer is controversial. Retrospective studies have shown that local treatments increase survival, as shown in this study<sup>17,18</sup>. Recent randomized clinical trials<sup>19,20</sup> that investigated the survival benefit of primary site surgery revealed contradictory conclusions<sup>14,15,21,22</sup>. The reasons for this greater survival need to be studied by exploring possible mutations and genetic biomarkers, as identified in the study by Bertucci et al., from 2019, which determined the presence of mutations in nine controlling genes, such as TP53 and GATA3, among others, which impact the prognosis and survival of these patients<sup>23</sup>. The study concluded that metastatic disease has more mutations and greater complexity than the initial disease. Therefore, the identification of these mutations would help in conducting individualized and efficient treatment<sup>15,23,24</sup>.

Analyzing the literature, it is possible to observe that the indication for surgery in de novo metastatic patients went through three phases: in the first, all patients underwent surgery; in the second, no patient underwent surgery; and in the third, at the moment, we individually evaluate each patient, each tumor type, disease control or progression and define cases that may benefit from surgery and those that, in fact, do not need surgery on the primary tumor<sup>25–29</sup>.

Therefore, the study has limitations inherent to retrospective studies. However, it is a referral center specialized in cancer treatment in which data are systematically reviewed.

## CONCLUSIONS

Greater survival was observed in de novo metastatic breast cancer patients whose multimodal treatment included breast surgery. However, factors such as luminal molecular subtype may have influenced these results. As the understanding of the biology of tumors evolves and treatments become more accessible to the population, our challenges will be greater in determining

for whom and at what time each treatment should be carried out. What, in fact, is causing the best survival of our patients seems to us to be this quality multidisciplinary treatment.

## AUTHORS' CONTRIBUTION

FPML: Investigation, Data curation, Writing – review & editing. GAF: Formal analysis, Methodology, Writing – review & editing. MPC: Formal analysis, Methodology, Writing – review & editing. SMS: Writing – review & editing, Supervision. LPF: Writing – review & editing. FBAM: Conceptualization, Project administration, Supervision, Writing – review & editing.

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# Assessment of the relationship between metabolic syndrome and breast cancer

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## ABSTRACT

**Introduction:** Metabolic syndrome (MS) affects approximately 30% of women aged over 50 years. It is known to have a direct relationship with carcinogenesis and, therefore, with breast neoplasia. **Methods:** Retrospective longitudinal observational cohort study carried out at the Gynecology and Obstetrics Service of the São Paulo State Public Servant Hospital. The rates of local recurrence, distant metastases and overall survival of patients with malignant breast neoplasia in each group were evaluated. **Results:** Between 2017 and 2020, 375 patients underwent surgical treatment for breast cancer, of which 335 were eligible for the study, with an average age of 63.4 years old. MS is present in 32.5% of patients. Regarding the prognostic factor, patients with MS have a very similar distribution. The molecular profile in patients with MS is 39.4% of Luminal A patients, while in those without MS it is 42.5% of Luminal B. Regarding clinical staging, patients with MS have initial clinical stage I and IIA in 54.1% of cases, while patients without MS present an initial clinical stage in 65% of cases. The average overall survival of the sample was 37.3 years, with a CI of 1.1 years; disease-free survival was 35.9 years, with CI 1.2 years; and invasive disease-free survival was 36.9 years, with CI 1.3 years. **Conclusions:** The presence of MS at diagnosis does not worsen survival.

**KEYWORDS:** malignant breast neoplasm; metabolic syndrome; prognosis; survival.

## INTRODUCTION

Metabolic syndrome (MS) can be defined as a set of conditions — central obesity (waist circumference), high blood pressure, reduced HDL cholesterol, increased triglycerides and impaired glucose intolerance — which is known to be associated with a greater risk in development of cardiovascular disease and type 2 diabetes. It affects approximately 30% of the population of women over 50 years old<sup>1,2</sup>.

Currently, breast cancer (BC) is the most common in Brazil, after skin cancer, and is the one that causes the most deaths in the female population<sup>3</sup>. According to the National Cancer Institute (INCA), in 2021, around 66,280 new cases were estimated, and in 2019, more than 18,000 deaths.

The risk of developing the disease becomes higher after the age of 50, and the risk factors are numerous: behavioral (sedentary lifestyle, obesity or overweight after menopause); hormonal (early menarche, late menopause, absence of children/breastfeeding, prolonged use of oral contraceptives and hormone replacement); and hereditary (family history of ovarian or breast cancer in males, or breast cancer in women before

the age of 50, in addition to genetic alterations in the BRCA1 and BRCA2 genes)<sup>3</sup>.

In view of the aforementioned risk factors, it is important to seek, in addition to the screening recommended by the Ministry of Health (a mammogram every two years in women aged 50 to 69 years), ways to reduce the risk of BC with regard to behavioral factors. Maintaining an adequate weight and performing physical activities can contribute to reducing this pathology.

Therefore, in the pathophysiology of breast neoplasia, its relationship with MS can also be seen, which is often its cause and even its consequence. Women treated for BC seem to have an additional risk of MS, resulting from excess adiposity and the effect of treatments<sup>4</sup>.

MS is one of the most common public health problems worldwide, and its incidence has been continuously increasing, in a pandemic manner, over the last two decades, in both developed and developing countries. Epidemiological data confirm that MS is independently associated with an increased incidence of several tumors, including BC, and is a poor prognostic factor in patients with early and metastatic BC<sup>5</sup>.

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The mechanism underlying the effects of MS remains unknown. Most researchers believe that MS is related to higher concentrations of sex hormones, insulin and insulin-like growth factor, which lead to a distortion of the normal balance between cellular differentiation and apoptosis and the progression and proliferation of BC cells<sup>6-8</sup>.

It is also noteworthy that patients with MS, with or without breast cancer, have a higher cardiovascular risk. MS is well established as a prothrombotic state associated with increased levels of inflammatory markers<sup>1,9</sup>, which constitutes an increased risk for cardiovascular disease.

Based on this context, the present study sought to correlate prognosis in patients with malignant breast cancer undergoing surgical treatment, whether or not they had previous MS; only deaths due to BC were evaluated, and not from other causes related to metabolic complications.

## METHODS

This is a retrospective longitudinal observational cohort study. Epidemiological information was collected from the database of patients in the Mastology sector of Hospital do Servidor Público Estadual (HSPE), from January 2017 to December 2020, and the patients were divided into two groups: group 1 (those who had MS) and group 2 (those who did not have these characteristics).

To define MS, the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criterion was based on: in order to establish the diagnosis of the syndrome, the patient must present at least three of the following five criteria: increased waist circumference (men:  $\geq 102$  cm; women:  $\geq 88$  cm); triglycerides  $\geq 150$  mg/dL; low HDL cholesterol (men  $< 40$  mg/dL; women:  $< 50$  mg/dL); high blood pressure ( $\geq 130 \times 85$  mmHg) and fasting blood glucose  $\geq 100$  mg/dL.

The epidemiological data obtained were many: age, date of BC diagnosis, previous comorbidities related to MS, date of recurrence or appearance of metastases, date of death due to BC, clinical staging and breakdown of the respective receptors present in each pathology.

The exclusion criteria were patients who were lost to follow-up for more than 12 months, due to an initial diagnosis of metastases, or who had missing data in the electronic medical record. All patients underwent surgical treatment at HSPE.

In both groups, the rates of local recurrence, distant metastases and overall survival of patients with malignant breast cancer were evaluated. Data were recorded in an Excel<sup>®</sup> spreadsheet and statistical analysis was conducted using the Mann-Whitney, Equality of Two Proportions and  $\chi^2$  tests.

The work was submitted to Plataforma Brasil and, as it was a retrospective study, the Free and Informed Consent Form (ICF) was waived (Figure 1).

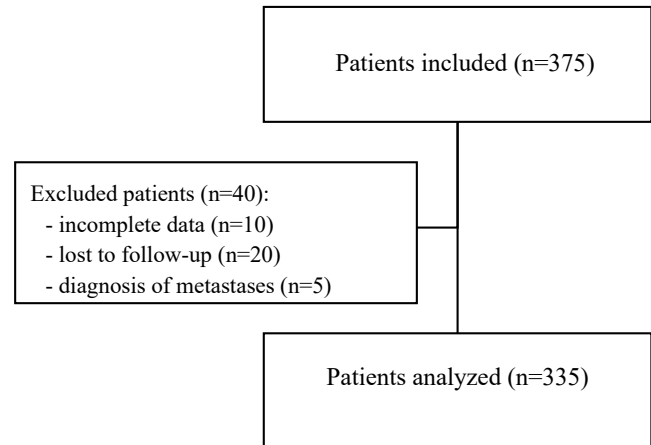


Figure 1. Patients included in the study.

## RESULTS

From January 2017 to December 2020, 375 patients underwent surgical treatment for BC at HSPE, of which 25 were excluded due to loss to follow-up; 10, due to incomplete data; and five, due to diagnosis of metastases.

After exclusion, the medical records of 335 patients eligible for the study were analyzed, with mean age of  $63.4 \pm 1.4$  years and an average follow-up time of  $48 \pm 1.4$  years.

MS is present in 109 (32.5%) patients. The criteria used for MS are: waist circumference above 88 cm, HDL below 50 mg/dL, triglycerides above 150 mg/dL, diabetes mellitus or systemic arterial hypertension.

The mean age of patients with MS was  $63.5 \pm 10.7$  years, and of patients without MS,  $65.1 \pm 10.0$  years, with no significant difference. Of the patients evaluated with MS, 81.1% were menopausal, whereas of those without MS, 83.6% were menopausal. As expected, hypertension, diabetes, obesity, low HDL cholesterol, high triglycerides and waist circumference  $> 88$  cm are more recurrent among patients with MS, all with significant differences. These characteristics are shown in Table 1.

Regarding the characteristics of prognostic factors, i.e., Ki-67, molecular classification and staging, Table 2 shows that patients with MS have a very similar distribution, whereas those without MS present Ki-67  $\geq 14\%$  in 62.4% of patients with a significant difference. In patients with MS, the molecular profile is 39.4% Luminal A patients, and in patients without SM, 42.5% Luminal B, with a significant difference in distribution. Regarding clinical staging, patients with MS present initial clinical stage I and IIA in 54.1% of the cases, advanced stage IIB in 20.2% and III in 25.7%, whereas patients without MS present initial clinical stage in 65% of cases, advanced stage IIB in 11.1% and III in 23.9%, results with a significant difference. When we evaluated the presence of obesity as a factor that worsens prognostic factors, we did not find significant differences. Table 2 shows these characteristics.

**Table 1.** Comparison of groups with and without metabolic syndrome.

	With MS		Without MS		p-value
	(n=109)		(n=226)		
Age (mean ± standard deviation) – years	63.5±10.7		65.1±10.0		0.85
BMI (mean ± standard deviation)	28.2±4.1		27.9±4.0		0.85
	n	%	n	%	
Menopausal <i>status</i>					
Pre-menopause	20	18.4	37	16.4	<0.001
Post-menopause	89	81.6	189	83.6	
Low HDL cholesterol (<50)	37	33.9	9	3.4	<0.001
Waist circumference >88 cm	49	44.9	42	18.6	<0.001
High triglycerides (>150)	82	75.2	13	5.7	<0.001
DM	81	74.3	21	9.3	<0.001
SAH	101	92.2	78	34.5	<0.001
Obesity	59	54.1	41	18.1	<0.001

MS: metabolic syndrome; BMI: body mass index; DM: diabetes mellitus; SAH: systemic arterial hypertension.  
Source: database of the Mammary Pathology sector of Hospital do Servidor Público Estadual.

In the assessment of recurrences, diagnosis of metastases and deaths, there was a significant difference between the groups of patients with and without MS — relapses occurred in 4.6% of patients with MS and in 4.0% of patients without MS; metastases, in 8.3% of patients with MS and in 10.2% of patients without MS; and deaths, at 4.5% and 4.0%, respectively. When we re-evaluated obesity as a factor in worsening of recurrences, metastases and deaths, we found no differences, as can be seen in Table 3.

To evaluate the relationship between MS and adverse prognosis, a factor called “Prognosis” was created, which is the joint analysis of information on metastasis, recurrence and death. If the person presents at least one of these three factors, the prognosis is not considered a Good Prognosis, that is, only those who do not present these three factors will have a Good Prognosis. Therefore, a multivariate Logistic Regression analysis was carried out to determine the probability of a person having a Bad Prognosis based on the results of two independent factors: Ki-67 and Immune. This multivariate analysis was carried out for each MS group, that is, there are two statistical models, as shown in Table 4.

Since the two independent factors are qualitative, one of their classifications is the reference response. Thus, in KI-67, the reference is the classification of <14%, and in molecular profile, it was the best of them, that is, LUMINAL A.

Analyzing both models, it can be seen that only the TNBC classification proved to be statistically significant in the multivariate analysis — the coefficient was positive and, consequently, the odds ratio (OR) was greater than 1.00. In the non-MS model, the OR of triple negative tumors (TNBC) was 9.30, which shows that a patient with a TNBC molecular profile is 9.30 times more likely to have a poor prognosis than a LUMINAL A patient.

The temporal outcomes of overall survival, disease-free survival and invasive disease-free survival were assessed. The average overall survival of the sample was 37.3 years, with CI of 1.1 years; disease-free survival was 35.9 years, with CI of 1.2 years; and invasive disease-free survival was 36.9 years, with CI of 1.3 years. When these outcomes were compared with the presence of MS, a significant difference was observed in all outcomes.

## DISCUSSION

Metabolic syndrome (MS), also known as insulin resistance syndrome or syndrome X, is a type of multifactorial metabolic disease<sup>9</sup>. Pathologically, patients with MS are characterized by chronic inflammation and oxidative stress, both involved in the process of carcinogenesis<sup>10</sup>. In the study in question, MS was present in 109 (32.5%) patients, while 226 (67.5%) were not carriers.

A literature review by Li et al., from March 2021<sup>11</sup>, evaluates that MS and its components exert a great influence on the breast tumor and its microenvironment. In obese individuals — represented, in the present study, by 54% of patients with MS and 18% of patients without MS —, this tumor microenvironment presents a higher production of fibroblasts, immune and endothelial cells.

In the mammary gland, the interaction between obese adipocytes and BC cells leads to the transformation of mammary adipocytes into cancer-associated adipocytes, the so-called CAAs, which secrete more leptin and reduce adiponectin production<sup>9</sup>. These alterations show a close relationship between obesity and more aggressive BC phenotypes — increased size, high-grade tumors, triple negative tumors or tumors with multiple metastases<sup>12</sup>.

**Table 2.** Distribution of prognostic factors (Ki-67, molecular profile and clinical staging) and the relationship with metabolic syndrome.

	With MS		Without MS		Total		p-value
	n	%	n	%	n	%	
General							
TNBC	23	21.1	26	11.5	49	14.6	0.010
HER-2 +	6	5.5	12	5.3	18	5.4	
Luminal HER	7	6.4	26	11.5	33	9.9	
Luminal B	30	27.5	96	42.5	126	37.6	
Luminal A	43	39.4	66	29,2	109	32.5	
Not obese							
TNBC	12	24.0	20	10.8	32	13.6	0.030
HER-2 +	3	6.0	8	4.3	11	4.7	
LUminal HER	4	8.0	22	11.9	26	11.1	
Luminal B	12	24.0	81	43.8	93	39.6	
Luminal A	19	38.0	54	29.2	73	31.1	
Obese							
TNBC	11	18.6	6	14.6	17	17.0	0.578
HER-2 +	3	5.1	4	9.8	7	7.0	
Luminal HER	3	5.1	4	9.8	7	7.0	
Luminal B	18	30.5	15	36.6	33	33.0	
Luminal A	24	40.7	12	29.3	36	36.0	
General (%)							
<14	54	49.5	85	37.6	139	41.5	0.038
≥14	55	50.5	141	62.4	196	58.5	
Not obese (%)							
<14	24	48.0	70	37.8	94	40.0	0.193
≥14	26	52.0	115	62.2	141	60.0	
Obese (%)							
<14	30	50.8	15	36.6	45	45.0	0.159
≥14	29	49.2	26	63.4	55	55.0	
General							
I	24	22.0	83	36.7	107	31.9	0.041
IIA	35	32.1	64	28.3	99	29.6	
IIB	22	20.2	25	11.1	47	14.0	
IIIA	13	11.9	30	13.3	43	12.8	
IIIB	9	8.3	19	8.4	28	8.4	
IIIB I	2	1.8	3	1.3	5	1.5	
IIIC	4	3.7	2	0.9	6	1.8	
Not obese							
I	14	28.0	69	37.3	83	35.3	0.212
IIA	15	30.0	50	27.0	65	27.7	
IIB	10	20.0	21	11.4	31	13.2	
IIIA	4	8.0	24	13.0	28	11.9	
IIIB	5	10.0	18	9.7	23	9.8	
IIIB I	0	0.0	2	1.1	2	0.9	
IIIC	2	4.0	1	0.5	3	1.3	
Obese							
I	10	16.9	14	34.1	24	24.0	0.453
IIA	20	33.9	14	34.1	34	34.0	
IIB	12	20.3	4	9.8	16	16.0	
IIIA	9	15.3	6	14.6	15	15.0	
IIIB	4	6.8	1	2.4	5	5.0	
IIIB I	2	3.4	1	2.4	3	3.0	
IIIC	2	3.4	1	2.4	3	3.0	

MS: metabolic syndrome; TNBC: triple negative tumors.

Source: database of the Mammary Pathology sector of Hospital do Servidor Público Federal.

**Table 3.** Comparison of metabolic syndrome with the presence or absence of metastasis.

	With SM		Without SM		Total		p-value
	n	%	n	%	n	%	
Metastases							
General							
No	100	91.7	203	89.8	303	90.4	0.575
Yes	9	8.3	23	10.2	32	9.6	
Not obese							
No	46	92.0	163	88.1	209	88.9	0.436
Yes	4	8.0	22	11.9	26	11.1	
Obese							
No	54	91.5	40	97.6	94	94.0	0.211
Yes	5	8.5	1	2.4	6	6.0	
Relapses							
General							
No	104	95.	217	96.0	321	95.8	0.795
Yes	5	4.6	9	4.0	14	4.2	
Not obese							
No	48	96.0	177	95.7	225	95.7	0.920
Yes	2	4.0	8	4.3	10	4.3	
Obese							
No	56	94.9	40	97.6	96	96.0	0.507
Yes	3	5.1	1	2.4	4	4.0	
Deaths							
General							
No	91	83.4	206	91.1	297	88.6	?
Yes	18	16.6	20	8.9	38	11.4	
Not obese							
No	40	80	167	90.0	207	88.1	?
Yes	10	20	18	10.0	28	11.9	
Obese							
No	51	86.5	39	95.1	90	90	?
Yes	8	13.5	2	4.9	10	10	

MS: metabolic syndrome.

Source: database of the Mammary Pathology Sector of Hospital do Servidor Público Federal.

Another factor that explains the association of MS with carcinogenesis is the increase in plasma estrogen concentrations resulting from the aromatization of peripheral androgens in adipose tissue. The synthesis of estrogens is catalyzed by the aromatase enzyme, which is expressed in increased amounts in the adipose tissue of the mammary gland, abdomen, hips and muscles<sup>12</sup>. Continuous exposure to this hormone, caused by obesity, therefore favors mitotic activity at the aforementioned sites.

In the present study, diabetes mellitus (DM) was the most frequent component of MS, second only to arterial hypertension. The hyperinsulinemia found in diabetic patients also has a clear relationship with increased body mass index (BMI).

Chronic exposure to the hyperinsulinemic state stimulates DNA synthesis and, therefore, epithelial cell replication<sup>12</sup>.

In general, the inflammatory profile of MS patients is a result of the fact that adipose tissue contains a large source of inflammatory cytokines (TNF-alpha, IL-1y and IL-6). These substances promote and generate greater insulin resistance and, therefore, the overproduction of insulin and IGF-1, with direct effects on tumor genesis<sup>12</sup>.

This study evaluated 335 eligible patients, with mean age of 63.4±1.4 years and an average follow-up time of 48.0±1.4 years. Interestingly, in these patients, the majority of whom were post-menopausal, the presence of MS at diagnosis did not worsen

**Table 4.** Logistic Regression Model for worse prognosis.

	Coef. (B)	p-value	Odds ratio		
			OR	Lim. inferior	Lim. superior
With MS					
Constant	-2.277	<0.001			
KI-67 (≥14%)	-0.286	0.700	0.75	0.18	3.21
Luminal B	1.353	0.161	3.87	0.58	25.67
Luminal HER	1.604	0.170	4.97	0.50	49.24
HER-2 +	1.724	0.109	5.61	0.68	46.02
TNBC	1.871	0.036	6.49	1.13	37.20
Without MS					
Constant	-1.981	<0.001			
KI-67 (≥14%)	-0.818	0.153	0.44	0.14	1.36
Luminal B	1.027	0.135	2.79	0.73	10.72
Luminal HER	0.827	0.272	2.29	0.52	10.02
HER-2 +	1.621	0.079	5.06	0.83	30.91
TNBC	2.231	0,003	9.30	2.15	40.36

OR: odds ratio; MS: metabolic syndrome.

Source: database of the Mammary Pathology Sector of Hospital do Servidor Público Federal.

overall survival, disease-free survival or invasive disease-free survival. Despite going against what the literature shows, there are published studies that still question the real veracity of the relationship we seek to explain.

The first meta-analyses cited in the literature in 2013 and 2014 showed that MS may be a risk factor for BC, particularly in postmenopausal patients<sup>10,13,14</sup>. This conclusion was reached because the small number of studies included — only nine observational studies were available at the time — did not allow for in-depth analysis of factors such as menopausal status, ethnic groups, and histopathological characteristics of the tumor<sup>10</sup>.

To try to evaluate this information, Guo et al., in November 2019<sup>10</sup>, carried out a new updated meta-analysis seeking to better correlate MS and breast cancer. The analyses showed that MS was associated with an increased risk of BC in postmenopausal women, but this risk was reduced in premenopausal women. The 19 datasets, with 17 studies each, supported the idea that the menopausal status of patients may modify the association between MS and the incidence of BC, even under potentially unclear reasons.

When we look at TNBC, the impact of MS remains controversial. In May 2021, Yuan et al. designed a study to specifically examine mortality after diagnosis of TNBC by metabolic risk components in 544 postmenopausal women participating in the Women's Health Initiative (WHI)<sup>15-17</sup>.

The conclusion was a 27% lower overall survival in patients with metabolic components associated with TNBC. However, in this study, patients who had MS coincidentally had lower income,

were black and had lower attendance in follow-up exams, which may have indirectly contributed to the result.

In 2020, Buono et al., in a prospective observational study, observed that MS was significantly associated with an increased risk of overall death and death from BC in patients with early BC receiving neoadjuvant therapy at a median follow-up time of 7.1 years<sup>17,18</sup>. Although the results are inconsistent with the present study, it is noteworthy that, in the 2020 study, the lack of information on treatments for hypertension, dyslipidemia and diabetes may have underestimated the number of patients with BC.

Among the possible and main limitations of the present study are the small number of patients included, which led to divergence of results in relation to what is reported in the literature, and the effective treatment of MS, with compensation for associated factors (dyslipidemia, obesity, hyperinsulinemia and hypertension), which corroborates with lower tissue inflammatory and proliferative exposure of cancer cells.

It is important to remember that this study did not evaluate deaths from other causes, only from BC — the increased cardiovascular risk present in MS and its complications were not included in the statistics.

In view of these limitations, it is necessary to increase the number of medical records analyzed, as well as in-depth research, through recent laboratory tests, in order to assess the degree of real metabolic decompensation of patients with MS and breast cancer.



## CONCLUSIONS

In this study, the presence of MS at the diagnosis of BC does not worsen overall survival, disease-free survival and invasive disease-free survival.

In multivariate analysis, triple-negative tumors — with or without MS — had a worse prognosis.






## AUTHORS' CONTRIBUTION

ALG: Methodology, Writing – original draft. MA: Conceptualization, Data curation, Methodology, Writing – review & editing. OF: Validation, Visualization. JMR: Supervision. AM: Supervision. RGCL: Supervision.

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# Impact of the COVID-19 pandemic on breast surgery in a reference service for breast cancer treatment

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## ABSTRACT

**Introduction:** The pandemic caused by the spread of the SARS-CoV-2 virus posed unprecedented challenges to health systems and societies worldwide. Among the greatest challenges was the importance of balancing the treatment of patients with potentially lethal diseases alongside the pandemic. Treatment for breast cancer, a time-dependent disease, was also compromised, as financial resources, supplies, medicines, and, especially, hospital beds needed to be allocated to assist those infected with the new coronavirus. Surgeries were suspended and surgical centers closed. To compare the number of breast surgical procedures before and during the pandemic and assess their impact on the proportional number of surgeries performed. **Methods:** This is a retrospective cohort study, reviewing procedures recorded from January 2015 to June 2021. **Results:** A total of 899 patients were included, the majority of whom were female; 58.5% of cases were oncological. The most prevalent surgery in both periods was conservative oncology (sectorectomy or quadrantectomy). There was a significant difference in the number of procedures performed before and during the COVID-19 outbreak, with a 43% drop during the pandemic. There was no significant difference in the pattern of surgeries. **Conclusion:** The pandemic caused a significant reduction in the total number of elective surgical interventions in the period analyzed — a delay that the literature identifies as a potential risk factor for disease progression and increased death rates.

**KEYWORDS:** pandemics; breast neoplasms; covid-19; elective surgical procedures.

## INTRODUCTION

The first cases of severe acute respiratory syndrome 2 (SARS-CoV-2), caused by coronavirus 2019 (COVID-19), were documented in December 2019 and rapidly disseminated worldwide<sup>1</sup>. In Brazil, the first confirmed case was identified on February 26, 2020, at Albert Einstein Hospital, in São Paulo. The World Health Organization (WHO) officially declared the pandemic on March 11<sup>th</sup>, 2020<sup>1,2</sup>. The unexpected surge in demand for treating COVID-19 patients, coupled with the need to establish and sustain the treatment of other pathologies like cancer, exerted substantial pressure on healthcare services and instigated societal transformations<sup>3</sup>.

According to data from the Brazilian Society of Cancerology (*Sociedade Brasileira de Cancerologia* — SBC), cancer stands as one of the major global public health problems and the second leading cause of deaths (accounting for one in every six deaths) in the world<sup>4</sup>.

In Brazil, 625 thousand new records of the disease were projected for each year of the 2020–2022 triennium. Non-melanoma skin cancer emerged as the most prevalent, followed by breast and prostate cancer in females and males, respectively<sup>5</sup>.

One of the preventive and control measures implemented by public authorities during the COVID-19 pandemic was the provisional suspension of elective surgical procedures<sup>4</sup>. These measures aimed to redirect resources to address the pandemic, by preserving hospital beds for patients with respiratory infections, particularly in intensive care units<sup>4,6</sup>. The debate surrounding the postponement of cancer treatment is controversial, since the definition of severity depends on the type of cancer and staging<sup>7</sup>.

Data from the National Cancer Institute (*Instituto Nacional de Câncer* – INCA) estimated an incidence of 66,280 new cases of breast cancer in women in 2020, a disease responsible for around 18,000 deaths in 2019<sup>8</sup>.

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As reported by the Brazilian Society of Oncological Surgery (*Sociedade Brasileira de Cirurgia Oncológica* – SBCO), in April and May 2020, the number of cancer-related surgeries decreased by 70%, and biopsies were reduced by 50 to 90%. It is estimated that between 50 and 90 thousand Brazilians were deprived of a cancer diagnosis in the first two months of the pandemic<sup>4</sup>.

In major Brazilian hospitals like Albert Einstein, in São Paulo, the decline in the volume of oncological surgeries, from March to May 2020, amounted to a 60% reduction compared to the corresponding period in 2019<sup>2</sup>. At Hospital A.C. Camargo Cancer Center, also in São Paulo, the number of patients undergoing breast surgery during the same three months of 2020 was 13.17% lower than the figures recorded in the same quarter of 2019<sup>9</sup>.

In the United States and Europe, the decrease in cancer patient visits per week during the pandemic's peak infection rate was 44%<sup>9</sup>. In England, postponing cancer surgeries for six months is projected to elevate the mortality rate of cancer patients by 30% over five years, regardless of age, site, and stage of the disease<sup>10</sup>. In the United Kingdom, a 20% rise in mortality from cancer, including breast cancer, is expected as a result of the pandemic<sup>11</sup>.

Caxias do Sul, the second most populous city in Rio Grande do Sul, experienced its most challenging period of the pandemic between March and July 2021, according to data from the State Health Secretariat (*Secretaria Estadual de Saúde* – SES). The department recommended the cancellation of elective surgeries for 30 days on February 22<sup>nd</sup> and again on May 25<sup>th</sup> of that year<sup>12</sup>.

Delays in medical care, diagnosis, and initiation of treatment are strongly associated with a worsening of the prognosis of patients with breast cancer, potentially impacting survival rates<sup>3</sup>. Evaluating the risks and benefits of therapeutic and diagnostic measures requires personalized consideration, taking into account the oncological prognosis and the risk of COVID-19 transmission, especially in regions with high transmissibility<sup>1,3</sup>.

Thus, the primary aim of this research was to compare the number of surgical procedures performed by the mastology team at Hospital Geral de Caxias do Sul in the pre-pandemic period, from January 2015 to February 2020, in relation to the pandemic phase, from March 2020 to June 2021. Additionally, the study endeavors to ascertain the proportion of procedures performed during both periods and to compare the pattern of interventions over the years.

## METHODS

### Type of study

This is a retrospective cohort study.

### Population and sampling

The group studied consists of a review of 905 cases involving patients who underwent surgical procedures carried out by the

mastology team, from January 2015 to June 2021, at Hospital Geral de Caxias do Sul, a regional reference health facility in oncology for patients in the mountainous region of Rio Grande do Sul, Brazil.

### Inclusion and exclusion criteria

The study included 899 patients who underwent surgery by the mastology team, at Hospital Geral de Caxias do Sul, from January 2015 to June 2021, regardless of gender and the purpose of the surgery — whether therapeutic, diagnostic, reconstructive, or aesthetic. Six cases were excluded from the study due to incomplete surgical information found in the electronic medical records.

### Data collection

The data were extracted from the electronic medical records of the operated patients through a comprehensive review of the surgical maps for the period studied. These data were then tabulated in an Excel<sup>®</sup> spreadsheet, whose access was restricted to research participants, respecting the confidentiality agreement.

### Analysis and interpretation of data

The information collected was analyzed from the database created. The significance level adopted was 0.1% ( $p < 0.001$ ).

The qualitative variables were analyzed by calculating their absolute and relative frequencies and the quantitative variables, using standard deviation and central tendency (mean, mode, or median). To compare patients,  $\chi^2$  was used, based on two models. The analysis focused on comparing the number of surgical procedures conducted during the pre-pandemic years with those performed during the COVID-19 outbreak.

### Ethical aspects

The researchers involved committed to keeping the data confidential, in accordance with the confidentiality agreement. The work was submitted to the Plataforma Brasil ethics committee. The study was approved by the Scientific and Editorial Board (*Conselho Científico e Editorial* – COEDI) of Fundação Universidade de Caxias do Sul — Hospital Geral.

## RESULTS

### Population analysis

899 patients who underwent surgery between January 2015 and June 2021 were included in the study, 868 of whom were female (96.6%). Of the total cases, 58.5% referred to cancer patients. Due to the diversity in surgical names and to standardize the analysis, patients were classified into seven surgery categories:

1. Conservative: sectorectomies and quadrantectomies in patients without a diagnosis of malignant neoplasia, such as resection of fibroadenomas, intraductal papillomas, ductal

ectasia, any benign tumors, recurrent abscesses, and other benign pathologies;

2. Oncological conservative: sectorectomies or quadrantectomies with an axillary approach, as indicated, in patients diagnosed with malignant neoplasia;
3. Mastectomy: complete removal of the mammary gland, with or without preservation of the nipple-areolar complex and the skin;
4. Mastectomy + reconstruction: complete removal of the mammary gland, with or without preservation of the nipple-areola complex and skin, and invariably includes reconstruction with an expander or silicone prosthesis;
5. Aesthetic, reparative, or corrective: excision of accessory mammary glands, resection of supernumerary nipples, prosthetic implants to repair congenital defects and genetic anomalies, mastopexies, reduction mammoplasties, and correction of gynecomastia;
6. Lymphadenectomy: excision of lymph nodes for diagnostic and/or therapeutic purposes;
7. Reconstruction: implantation of a silicone prosthesis or expander following oncological surgery.

Grouped by type of procedure, the analysis revealed that 315 patients underwent breast-conserving oncological surgery, constituting 35% of the sample and representing the most prevalent surgical indication. Another 263 cases involved non-oncological conservative surgery, accounting for 29.3% of the total. Mastectomy was performed in 109 cases (12.1%), while 101 cases involved aesthetic, reparative, or corrective surgery (11.2%). Additionally, 80 cases (8.9%) involved mastectomy with reconstruction, 20 cases (2.2%) were categorized as reconstruction procedures, and 11 cases (1.2%) involved lymphadenectomies (Table 1).

When comparing periods, the number of surgeries performed each year was as follows: 124 surgeries in 2015 and, successively, 139 in 2016; 146 in 2017; 160 in 2018; 173 in 2019; 123 in 2020, and 34 in the first half of 2021 (Table 2).

It is possible to observe the number of procedures in each semester of the period in Graphic 1.

**Table 1.** Surgical procedures performed from January 2015 to June 2021.

By type of surgery	Quantity (%)
Conservative	263 (29.3)
Oncological conservative	315 (35.0)
Mastectomy	109 (12.1)
Mastectomy + reconstruction	80 (8.9)
Cosmetic, reparative, or corrective	101 (11.2)
Lymphadenectomy	11 (1.2)
Reconstruction	20 (2.2)
Total	899 (100)

## Pre-pandemic period

From January 2015 to February 2020, a total of 774 surgical procedures were recorded. Of this total, 57.1% were due to malignant breast neoplasia. Oncological conservative surgeries were also the most prevalent, accounting for 260 procedures (33.6%), followed by 232 non-oncological conservative surgeries (30%), 97 cosmetic, reparative, or corrective surgeries (12.5%), 95 mastectomies (12.3%), 65 mastectomies with immediate reconstruction (8.4%), 18 reconstructions (2.3%), and 7 lymphadenectomies (0.9%) (Table 3).

For direct comparison over the same number of months, in the 16 months immediately prior to the pandemic, from December 2018 to February 2020, a total of 220 procedures were recorded.

## Pandemic period

Since the onset of the pandemic in March 2020 until the end of the first half of 2021 (16 months), a total of 125 surgeries were performed. Among these, 91 surgeries occurred between March and December 2020, and 34 in the first half of 2021. Notably, 67.2% of these patients were diagnosed with breast cancer.

Oncological conservative surgery remained the most frequent procedure, totaling 44% of cases, followed by 31 non-oncological conservative surgeries (24.8%), 15 mastectomies with immediate reconstruction (12%), 14 mastectomies (11.2%), 4 cosmetic, reparative, or corrective surgeries (3.2%), 4 lymphadenectomies (3.2%), and 2 reconstructions (1.6%) (Table 3).

It is possible to compare the proportion of procedures in the two periods in Graphic 2.

The  $\chi^2$  test was used to analyze the number of surgeries before and during the pandemic. There was a statistically significant difference, indicating a reduction in the number of procedures during the pandemic. The likelihood ratio was 20.58 and Pearson's  $\chi^2$  was 19.21.

## DISCUSSION

The data from this research substantiated the hypothesis of a disparity between the number of surgical procedures prior to the pandemic and during the COVID-19 outbreak, wherein a 43% reduction was observed, consistent with findings from similar studies<sup>2,9</sup>.

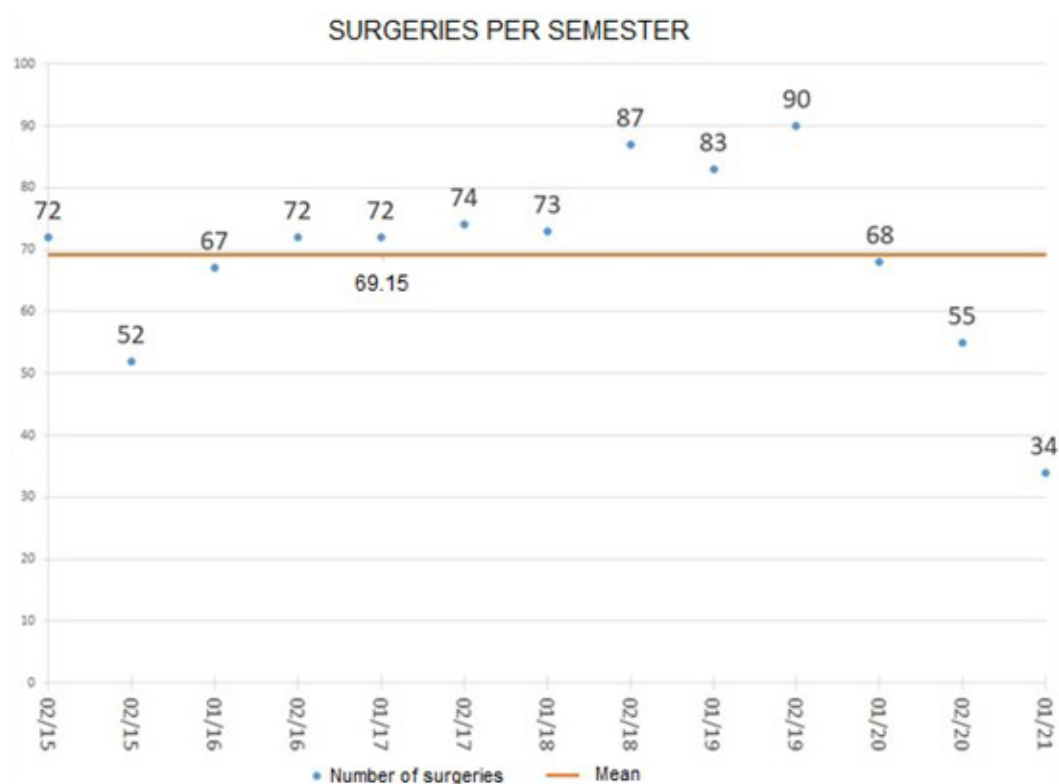
It is evident that conservative surgeries remained the most performed, especially oncological surgeries, regardless of the period evaluated. This fact reflects an evolution in increasingly earlier diagnosis, combined with advances in cancer treatment, such as neoadjuvant treatment. Furthermore, the multidisciplinary approach to patient care enables the implementation of less invasive surgical techniques.

The study also revealed a progressive increase in the total number of surgeries over the years, a phenomenon driven by population growth and the positioning of the service as a regional reference.

**Table 2.** Surgical procedures performed annually.

Surgery	2015	2016	2017	2018	2019	2020	2021*
Conservative	46	43	48	46	46	26	8
Oncological conservative	23	40	50	62	73	47	20
Mastectomy	22	13	14	22	20	16	2
Mastectomy + reconstruction	8	14	14	10	17	14	2
Cosmetic, reparative, or corrective	23	23	16	12	12	15	0
Lymphadenectomy	2	4	0	1	0	3	1
Reconstruction	0	1	4	7	5	2	1
Total	124	139	146	160	173	123	34

\*First Half of 2021.

**Graphic 1.** Frequency of surgeries per semester in the period.**Table 3.** Number of procedures performed in the pre-pandemic and pandemic periods.

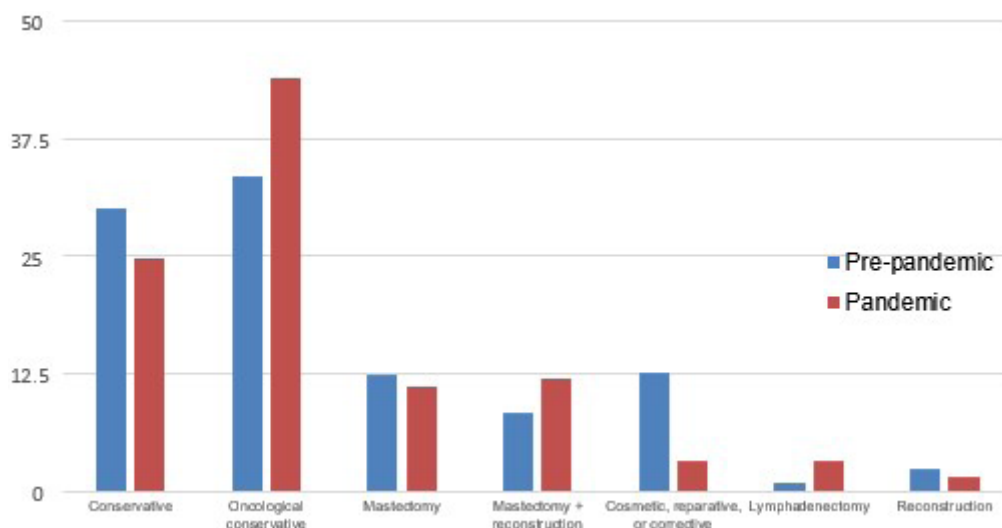
Surgery	Pre-pandemic (%)	Pandemic (%)
Conservative	232 (30.0)	31 (24.8)
Oncological conservative	260 (33.6)	55 (44.0)
Mastectomy	95 (12.3)	14 (11.2)
Mastectomy + reconstruction	65 (8.4)	15 (12.0)
Cosmetic, reparative, or corrective	97 (12.5)	4 (3.2)
Lymphadenectomy	7 (0.9)	4 (3.2)
Reconstruction	18 (2.3)	2 (1.6)
Total	774 (100)	125 (100)

In 2015, 124 surgeries were registered, which increased to 139 in 2016 (12%), 146 in 2017 (5%), 160 in 2018 (9%), and 173 in 2019 (8%).

With the onset of the pandemic, there was a 28% reduction in the number of procedures in 2020 (123) compared to 2019; in the first half of 2021, the lowest volume of surgeries was recorded within the period analyzed, applying proportionality.

Comparing the 16 months immediately prior to the pandemic with the 16 months analyzed during the pandemic, the decline in the number of procedures reached 43%. This reduction corresponds to the phase marked by the most significant restrictions on scheduling elective procedures, coinciding with the peak of the pandemic in Caxias do Sul, experienced in the first half of 2021. The impact of COVID-19 on surgery schedules underscores the harm inflicted upon breast cancer patients during this period.





**Graphic 2.** Frequency of surgeries by period.

Despite the dedication of the administration and all health-care teams to uphold care for cancer patients, the surgical schedule endured sacrifices and many procedures were suspended during the most critical periods witnessed so far. The long-term repercussions of these delays, added to delays in the diagnosis of breast cancer, will have consequences that can be quantified in new studies.

## CONCLUSIONS

The outcomes of this research converged with other studies that also demonstrated a significant reduction in the volume of surgeries during the pandemic period compared to the pre-pandemic period. There is potential for the study to progress by comparing larger samples, as the spread of COVID-19 has not yet come

to an end. Furthermore, in the long term, it may be valuable to observe whether there is any discernible impact on the survival rates of our patients.

## AUTHORS' CONTRIBUTION

LHBLT: Conceptualization, Formal analysis, Investigation, Project administration, Methodology, Supervision, Validation, Writing – review & editing. CDSMD: Data curation, Software, Visualization. COMN: Data curation, Software, Visualization. FV: Conceptualization, Formal analysis, Investigation, Project administration, Methodology, Supervision, Validation, Writing – review & editing. KSAD: Data curation, Software, Visualization. MD: Data curation, Software, Visualization. MADL: Data curation, Software, Visualization. THR: Data curation, Software, Visualization.

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# In vivo localization of occult lesions and margins in breast carcinoma using radio-fluorescence: a new hybrid technique

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## ABSTRACT

**Objective:** The aim of this study was to present a new technique for hybrid marking of non-palpable breast lesions and *in vivo* evaluation of surgical margins, called Fluorescence and Seed for Hybrid Intraoperative Evaluation. **Methods:** Seven women with non-palpable breast lesions and suspected or confirmed malignancy underwent prior iodine-125 seed implantation and peripheral intravenous administration of indocyanine green 30 min before surgery. A hybrid gamma probe with an optonuclear probe was used to detect gamma radiation in the lesions and, sequentially, the fluorescence mode, in the same lesion and its margins, after its removal. **Results:** This method distinguished, in real time, one benign and six malignant lesions, guiding the removal, identifying the remaining neoplastic area in the surgical bed, and allowing its intraoperative enlargement. **Conclusion:** This pilot study evaluates the feasibility of this new technique in identifying the primary lesion and controlling surgical margins using hybrid technology.

**KEYWORDS:** breast cancer; surgical margins; indocyanine green, nuclear medicine.

## INTRODUCTION

Breast cancer is the second-highest incidence in the world and the first among women, representing a major public health problem worldwide<sup>1</sup>.

Extreme changes in the surgical approach to breast cancer have occurred significantly in recent years. Minimally invasive surgeries emerged thanks to advances in technology, which have helped oncological surgeons to operate on increasingly smaller lesions detected only in imaging tests<sup>2</sup>.

In recent decades, nuclear medicine has become a great ally in the surgical field as a result of the development of the portable gamma radiation detector (gamma probe), which introduced studies based on the sentinel lymph node (SLN)<sup>3</sup>, extending to the radioguided localization of non-palpable breast lesions (Radioguided Occult Lesion Localization), initially using

radiopharmaceutical and, later, sealed sources of iodine-125, known as iodine-125 seeds<sup>4,5</sup>. More recently, hybrid tracers, which contain integrated radioactive and fluorescent markers, have been introduced to allow the detection of SLN<sup>6,7</sup>. Currently, the most promising tracers for this technique are considered to be colloids labeled with technetium-99m and indocyanine green (ICG).

ICG, which has been used since 1950<sup>8</sup>, is a blood pooling agent that has a different delivery behavior between normal and cancer vasculature. In normal tissue, ICG acts as an indicator of blood flow in the narrow capillaries of normal vessels. However, in tumors, it can act with a diffusible (extravascular) flow caused by greater extravasation resulting from the increase in capillarity, thus intensifying the accumulation of the substance at the site<sup>9</sup>.

This pilot study aims to describe the development of a new hybrid technique for marking and locating non-palpable lesions

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and evaluating surgical margins in real time, called Fluorescence and Seed for Hybrid Intraoperative Evaluation (FLASHIE), using hybrid gamma probes to detect seed iodine-125 and ICG.

## METHODS

This is a cross-sectional, interventional pilot study with prospective data collection from patients with suspected or confirmed non-palpable breast cancer lesions between January and February 2018, after approval by the local Research Ethics Committee.

Seven patients over 18 years of age were included, one with a pre-operative diagnosis of benignity and the other six with a malignant biopsy, after signing the informed consent form.

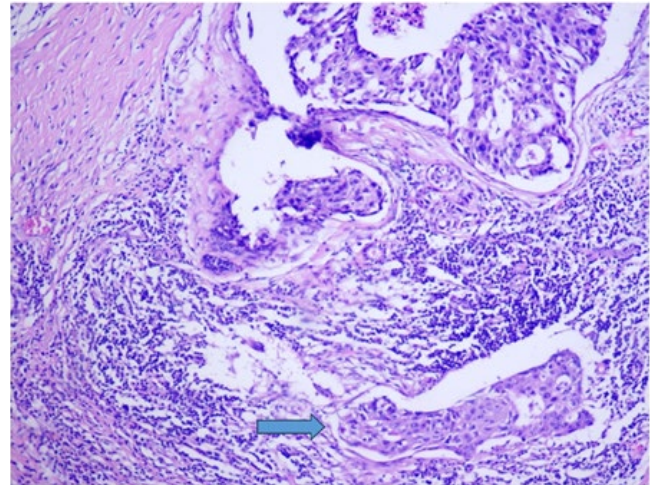
The inclusion criteria were patients investigated by fine needle aspiration, core biopsy, or mammotomy, with an indication for radioguided lumpectomy. Patients with associated excisional biopsy, liver disease, uremia, asthma, a history of allergy to iodine or seafood, and previous anaphylactic reaction to dye injection were excluded from the study.

This is a convenience sample due to the restricted research development period of 1 month, when the researchers had the Europrobe Optonuclear equipment available for the work on loan from the manufacturer Eurorad in partnership with the commercial representative in Brazil, Eckert and Ziegler. Initially, the study was scheduled to last 3 months, but due to customs delays, it was restricted to 1 month.

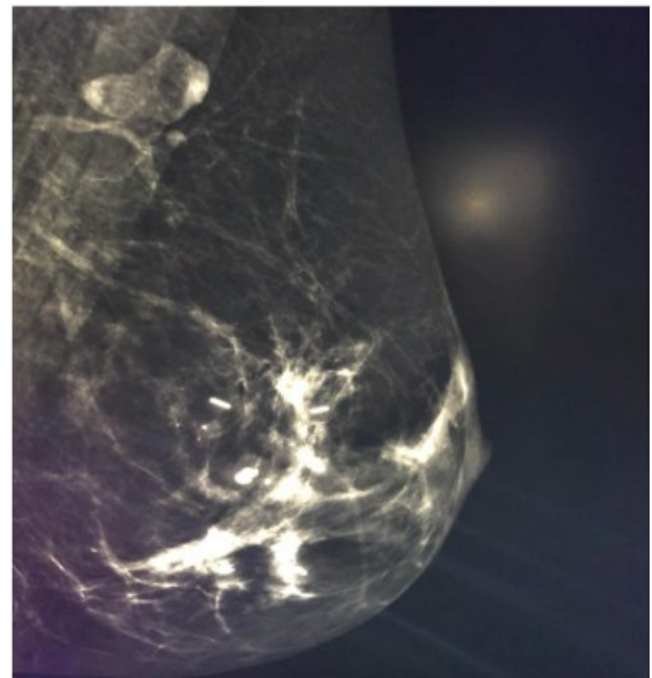
Occult lesions were marked by implanting an iodine-125 seed in the center of each patient's breast lesion in a procedure guided by ultrasound (nodules) or stereotactic (microcalcifications) between 1 and 5 days before surgery. The correct apposition of the seeds was confirmed by mammographic images in two projections and planar scintigraphic images of the thoracic region in the anterior and lateral projections ipsilateral to the affected breast, acquired on the day of implantation or 1 day before surgery.

The seeds consist of a sealed titanium source of 4×1 mm in diameter with an iodine-125 filament included with 0.2 mCi activity and energy of 27–35 KeV (IPEN, São Paulo, Brazil). Scintigraphic images were captured in Symbia E (Siemens, Germany) or Millennium MG (General Electric, USA) gamma cameras with 500 Kctg, 256×256 matrix, photopeak centered at 30 keV, and ±10 keV window.

On the day of surgery, 30 min before the surgical intervention, 5 mg of ICG (ICV® Ophthalmos, São Paulo, Brazil) was injected intravenously. During surgical exploration, an optonuclear probe for open surgery (Europrobe 3.2 Optonuclear, Euromedical Instruments, Eckbolsheim, France) was used with the combination of a traditional gamma probe and a 769 nm narrowband laser excitation source to remove the tumor lesion (Figures 1 and 2). The probe was prepared with a sterile plastic cover to be handled by the mastologist.



**Figure 1.** Anatomopathological study of the neoplastic area in the posterior region of the surgical bed (FI=15) after the removal of the primary lesion in patient 3. Color: H&E. Objective: 40×. The blue arrow indicates the presence of microinvasive carcinoma.



**Figure 2.** Mammography of patient 3 shows areas of microcalcifications marked by iodine-125 seed. No radiographically suspicious area was identified in the region posterior to the marked area.

During dissection, the lesion was localized initially, guided by the iodine-125 seed by the probe in conventional gamma-ray reading mode. Once the lesion was located, the probe's readout mode was switched to fluorescence. The areas defined in the preoperative images were analyzed by ICG fluorescence, and the reading was performed in ambient light.

Tumor fluorescence readings were performed intraoperatively (*in vivo*) and perioperatively (*ex vivo*). Once the lesion was removed, a new reading was performed at the margins of the lesion and in the tumor bed. A quantitative parameter was used to classify positivity for malignancy both in the primary lesion and in the surgical bed.

The fluorescence index (FI) was adopted, which consists of dividing the fluorescence count measured in the tumor by the fluorescence count measured in the healthy tissue surrounding the tumor and is considered positive when  $FI \geq 3$ , similar to that adopted in the study carried out by Duarte et al.<sup>10</sup> at the Universidade de Campinas – Brazil, in a technique called Radioguided Intraoperative Margin Evaluation, in which a radiopharmaceutical ( $^{99m}\text{Tc}$ -sestamibi) was also used during surgical procedures to check if the resection margins were negative.

The excised material was sent to the Pathology Service for cytology and freezing analysis by imprint. Part of the sample was submitted to a histopathological study, fixed by formalin and paraffin, and a late anatomopathological study (AP) by staining with hematoxylin and eosin. The specimen was also subjected to automated immunohistochemistry (IMHQ) with HIER PTLINK antigen retrieval incubation and development in AUTOSTAINERLINK48/DAKO.

The surgical specimens were generally classified based on the absence or presence of malignancy, whereas in this study,

the cases were classified based on whether or not the margins and surgical bed were affected. For ethical reasons, the patients were named numerically.

## RESULTS

Seven women, aged between 53 and 72 years (an average of 63.7 years), were included in this study. Seven lesions were removed, all guided by the radioactive seeds and located with the gamma probe. Most of them had a primary malignant lesion. Only one patient (n# 2) was confirmed as having a benign lesion (complex sclerosing papilloma), with  $FI=1$ . There was a predominance of nodular lesions, some with associated microcalcifications and in situ components. All primary malignant lesions presented  $FI \geq 3$ . Margins with a larger FI were malignant or small. ICG was more assertive than freezing in identifying compromised margins, based on AP. Table 1 presents this information.

Patient 3 presented  $FI=4$  in the primary lesion, marked by iodine-125 seed, and in a deeper area, relatively distant from the marked area,  $FI=15$  was measured. Due to the high FI, we opted for additional surgical expansion in this region. The AP confirmed malignancy. During the surgical procedure, in the frozen section, the margin of the enlarged region was considered compromised by the pathologist, so it was enlarged again, although there was no increase in the fluorescence reading in this surgical bed ( $FI=1$ ).

**Table 1.** Correlation between the findings of fluorescence index, anatomopathological study/immunohistochemical study, and surgical margins of breast lesions.

Patient	Characteristics of the injury	Pathology	<i>In situ</i>	Local	FI	Freezing	AP/IMHQ	Assertiveness FI	Assertiveness freezing
1	Nodule	IDC GI* Luminal A	Not observed	Lesion	3	Malignant	Malignant	Yes	Yes
				Margin	1	Free	Free	Yes	Yes
2	Nodule	Complex sclerosing papilloma	Unrealized	Lesion	1	Benign	Benign	Yes	Yes
				Margin	NA	NA	NA	NA	NA
3	Nodule	Multifocal CDml (3 foci) Hybrid luminal	Extensive (99.5% of the lesion)	Lesion	4	Malignant	Malignant	Yes	Yes
				Deep posterior region	15	Compromised	Compromised	Yes	Yes
				Margin	1	Compromised	Negative	Yes	No
4	Nodule	IDC GII* Luminal B	Scarce	Lesion	4	Malignant	Malignant	Yes	Yes
				Margin	1	Compromised	Free	Yes	No
5	Nodule	IDC Luminal A	Not observed	Lesion	7	Malignant	Malignant	Yes	Yes
				Posterior margin	6	Free	Exiguous	NA	No
6	Nodule + microcalcifications	IDC Luminal A	Extensive (>25% of the area)	Lesion	4	Malignant	Malignant	Yes	Yes
				Margin	1	Free	Free	Yes	Yes
7	Microcalcifications	IDC GII* Luminal A	Extensive (99.5% of the lesion)	Lesion	4	NR	Malignant	Yes	NA
				Posterior margin	5	NA	Exiguous	NA	NA
				Margin	4	NR	NR	NR	NR

\*Scarff-Richardson-Bloom. In situ: associated in situ component; FI: fluorescence index; AP: anatomopathological study; IMHQ: immunohistochemical study; IDC: invasive ductal carcinoma; GI: grade I; NA: not evaluated; CDml: microinvasive ductal carcinoma; GII: grade II; NR: not carried out.



After the AP with paraffin, the frozen section study was re-read, and the posterior margin was retrospectively considered free, a result reinforced by the histopathological reading of the new margin enlargement, which was also negative for malignancy. Figures 1 and 2 show, respectively, AP confirming micro-invasive carcinoma and the absence of suspicion of malignancy on mammography at the site with FI=15.

Patient 7 presented a heterogeneous area with cysts, indistinct margins, with intervening calcifications and a posterior acoustic shadow in the left breast on imaging examination, and a core biopsy was performed. The AP identified fibrocystic mastopathy containing areas of usual ductal hyperplasia and an atypical 1.0 mm area. This dubious finding indicated the removal of the entire lesion.

During the location of the suspicious area, with the iodine-125 seed, the ICG reading showed FI=4 at the seed location and FI=5 at the posterior margin in the ex vivo measurement of the piece. The reading corresponding to this region on the surgical bed also measured FI=4. As there was no diagnosis of a malignant lesion yet, freezing was not performed. Although the margin presented FI≥3, the mastologist preferred not to enlarge this area, opting not to remove it and wait for the AP result.

In this case, invasive ductal mammary carcinoma, grade III (Scarff-Richardson-Bloom), with an extensive carcinoma in situ component, corresponding to 90% of the lesion, which measured 2.0×1.8 cm in its largest dimensions, with an invasive area of 0.7×0.5 cm and multifocal lobular cancerization, was present.

This result was confirmed by immunohistochemistry (IMHQ) as invasive mammary carcinoma, luminal A subtype. The margins were free but narrow in the posterior, medial, and inferior regions, so it was decided to investigate the sentinel lymph node without enlarging the margins.

Patient 4 had infiltrating breast carcinoma, grade II (Scarff-Richardson-Bloom), which during the surgical procedure indicated FI=4 in the lesion and FI=1 in the margins, that is, without identifying malignancy. Freezing showed compromised margins on the anterior and inferior surfaces, which indicated enlargement of the margins. The AP showed free margins, indicating a false-positive result for the frozen section and a true-negative result for the ICG evaluation.

Patient 5 had infiltrating breast carcinoma, grade II (Scarff-Richardson-Bloom) on core biopsy, and during the surgical procedure, she presented FI=7 in the lesion and a small area in the posterior region of the surgical bed with FI=6, which showed a small posterior margin (1.0 mm).

Patients 1 and 6 obtained, respectively, FI=3 and FI=4 in primary lesions and frozen-free margins, with FI=1, concordant findings.

## DISCUSSION

Despite the low sample size of this pilot study, good results were obtained in the evaluation of this technique using hybrid marking.

The assertiveness of ICG in primary tumor lesions was precise, distinguishing malignant from benign lesions.

It is clear that the series must be increased, since in the literature there is a description of false-positive results due to mastitis where there is increased microvascular permeability, which allows the extravasation of macromolecules, and also in epidermal cysts, the latter being an uncommon entity<sup>11</sup>. The diagnostic association with other investigation methods helps in differentiating these lesions.

Breast-conserving surgery via partial mastectomy is an increasingly used option in the treatment of patients with invasive or in situ carcinoma<sup>3</sup>, but the assessment of margins can be difficult. Frozen freezing and AP are used to prevent residual disease after surgery and have an impact on the risk of breast tumor recurrence<sup>2,12</sup>.

In this study, three of six patients presented an extensive in situ component in a large part of the lesion, which was marked by ICG. Hagen et al.<sup>13</sup> also reported the case of a patient in whom there were two nearby lesions, identified as well-differentiated invasive ductal carcinomas, accompanied by a low-grade ductal carcinoma in situ, which was evidenced on fluorescence mammography with ICG. The presence of multifocality was observed in patient 3. Perhaps, the extremely high FI present in the remaining tissue is associated with the secondary multifocal focus.

St. John et al.<sup>14</sup> concluded in their meta-analysis that the diagnostic accuracy of frozen section and cytology studies is currently unparalleled. According to these authors, to become a disruptive technology, emerging techniques will need to compete with this level of precision and provide significant improvements, such as speed of results, cost-benefit, and accessibility of information to the surgeon, to allow rapid operational decision-making, which must be accurate and appropriate. In this context, the ICG fluorescence technique could play an important role, as it evaluates the margin in real time.

The exact determination of the extent of breast carcinoma is increasingly important for the breast surgeon. If a technique underestimates the actual size of the lesion, it may lead the surgeon to a more conservative procedure, leaving residual disease, and, if overestimated, it may induce the removal of normal tissue, compromising the cosmetic aspect of the surgery.

Holland et al.<sup>15</sup> showed foci of carcinomas more than 2 cm away from the main tumor in 43% of cases and more than 4 cm in 10% of them. In the sample studied, although not identified by other imaging methods or frozen section studies, a distant neoplastic area was identified by the fluorescence technique when reading the surgical bed, making it possible to enlarge the margin in real time.

There were also two patients (5 and 7) who presented small margins, and the FI was high in their respective regions, favoring the good correlation of the technique with the changes seen in the AP, indicating that the clinical integration of these two powerful technologies, interventionalists with molecular imaging potential, can act in synergy and add important characteristics

of both techniques, including the ability to microscopically evaluate lesions and their margins, both in vivo and ex vivo<sup>16,17</sup>.

Furthermore, the analysis of surgical margins can potentially be expanded to evaluate other organs and even use other fluorescent dyes, as reported by Xiao et al.<sup>18</sup>, who used sodium fluorescein for fluorescent-guided surgeries for the excision of brain metastases from breast cancer.

Among the limitations of the study, the main one was the short period of availability of equipment for the project, which was scheduled for 3 months, but was carried out in 1 month due to bureaucratic problems with customs clearance, which directly impacted the sample size and, consequently, the development of research.

The small sample size, included for convenience, collected a heterogeneous sample of breast lesions, not allowing similar lesions to be grouped to investigate the existence of a pattern of accumulation of ICG and FI in different types of lesions. It seems that in multifocal and non-nodular lesions, the importance of using this technique is greater due to the limitations of other imaging techniques. New studies must be conducted to provide answers and evaluate the real impact of this technology on various breast injuries.

## CONCLUSIONS

Within the limitations of the study, it was concluded that the proposed technique, FLASHIE, is feasible and quite promising.

Preliminary results indicated the potential to advance the state of the art in cancer surgical techniques, with the possibility of accurate detection of occult primary lesions and an indication of residual disease after tumor removal, in real time, especially in those areas not detected by diagnostic techniques and management of margins already established.

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## AUTHORS' CONTRIBUTION









ACP: conceptualization, data curation, investigation, methodology, resources, project administration, visualization, writing – original draft. SMM: data curation, investigation, writing – review & editing. MCD: data curation, formal analysis, investigation, validation, writing – original draft. RBF: data curation, methodology, research, validation, visualization. AMXJ: data curation, methodology, research, validation, visualization. DMC: investigation, validation, visualization. SAP: data curation, validation, visualization. JRB: data curation, investigation, validation, writing – review & editing.

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# Epidemiology of breast cancer in a tertiary oncology hospital in the countryside of Minas Gerais

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## ABSTRACT

**Objective:** In Brazil, the characteristics of breast cancer patients who arrive at cancer treatment services are influenced by conditions related to the tumor, to the diagnostic system and navigation in the phase prior to care, with regional differences being little known as well as their seasonal variation. **Methods:** This is a retrospective study of epidemiological data of patients with breast cancer treated at the Hospital do Câncer de Muriaé (HCM), an exclusively oncology hospital (CACON II), with primarily public care, a reference for cancer treatment in the east of Zona da Mata region, Minas Gerais. Clinical and care-related characteristics were evaluated from 2010 to 2021. **Results:** During this period, 4,573 new patients were treated. The care was primarily public (80.5%) and most patients were undiagnosed (45.7%) or untreated (71.8%) at the first visit. The patients were between 40 and 69 years old (70.2%) and a significant portion were between 70 and 74 years old (7.4%). The rate of early stage (clinical stage – CS 0 + I) represented only 33.9 and 25.8% of all patients and those treated exclusively in the hospital, respectively. There was no change in clinical stage and age group over the years. **Conclusion:** When evaluating epidemiological data, the characteristics of the service and the pre-institutional diagnostic care network should be analyzed, facts that influence the results. Throughout the period, there was no great variation in relation to age group and staging. In this region, the early stage of breast cancer has unsatisfactory rates, and the 70 to 74 age group should be considered in mammographic screening. Epidemiological studies are essential to improve health strategies.

**KEYWORDS:** breast neoplasms; epidemiology; trends.

## INTRODUCTION

Breast cancer is the main type of neoplasm in women in the world<sup>1,2</sup>. In developed countries, there is a high incidence and relative mortality, which is contrary to what occurs in developing countries, where it is possible to observe a lower incidence, but a higher mortality, which is influenced by the stage of diagnosis and treatment<sup>2,3</sup>.

Breast cancer screening is associated with a decrease in mortality<sup>4</sup>, due to the increase in the number of patients in the early stage, which reflects better survival<sup>5</sup>. In addition, the increase in the Human Development Index (HDI) has repercussions on the increase in patients with the initial clinical stage<sup>6</sup>.

The early stage is sensitive to technology, thus requiring mammography, biopsy, and diagnostic flow. In Europe, mammography screening is a reality, and mammography is performed on a large scale in asymptomatic patients. Based on this concept, EUSOMA (European Society of Breast Cancer Specialists) created quality criteria for screening in Breast Units<sup>7</sup>, but for places where mammographic screening is not a reality, mainly in developing countries, such as Brazil, services are focused on the demand for treatment, with few organized experiences<sup>8,9</sup>. To assess the quality of patients who arrive at the services, indirect indicators can be used, with the clinical stage being easily assessed in Brazil<sup>6</sup>.

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With a better understanding of breast cancer, it can be evaluated through molecular subtypes, a fact that influences treatment and is associated with age, diagnosis, ethnicity/skin color, and ancestry<sup>10,11</sup>.

Hospital Cancer Registries are valuable sources for the evaluation of regional characteristics, age at diagnosis, clinical stage at diagnosis, treatment, and actuarial survival. In breast cancer, these data reflect on the quality of the healthcare service prior to the hospital unit. Unfortunately, few services have their data published<sup>12-14</sup>; these data allow to assess the quality of the public healthcare service prior to hospital admission.

The Hospital do Câncer de Muriaé (Muriaé Cancer Hospital – HCM) is an oncology hospital that preferably serves patients from the public health system, being a High Reference Center in Oncology (*Centro de Alta Complexidade em Oncologia* [Oncology Center of High Complexity] – CACON II),<sup>15</sup> located in Zona da Mata, in the countryside of Minas Gerais. It started its hospital activities in 2002 and the Hospital Cancer Registry (*Registro Hospitalar de Câncer* – RHC) only in 2010. There are no reports of epidemiological evaluation of breast cancer in this region, justifying an epidemiological study on this disease.

## METHODS

This is an observational, retrospective study of data from the HCM's RHC from 2010 to 2021. The hospital is a public institution managed by the Fundação Cristiano Varela (Cristiano Varela Foundation), with primarily public care (85%), covering about 200 cities, with an estimated population of 3.1 million inhabitants. There is no other hospital or tertiary service in Oncology in this region of Minas Gerais.

The RHC data are public and can be accessed on the hospital's website ([https://www.fcv.org.br/site/Hospital/Registro Hospitalar de Câncer](https://www.fcv.org.br/site/Hospital/Registro%20Hospitalar%20de%20Cancer)), a fact that disregards the need for evaluation by a Research Ethics Committee, due to Resolution No. 466/2012. In addition, institutionally, the RHC authorized the analysis of the data. As the data change over time, the last evaluation, carried out on May 22, 2023, was used as a reference.

The authors sought to evaluate data exclusively related to breast cancer, in view of epidemiological characteristics and temporal variations related to clinical stage and age. In the evaluation of the clinical stage, the patients were classified as early stage (clinical stage – CS 0 and I), advanced stage (CS II and III), and metastatic stage (CS IV). The age group was divided into: under 40 years, 40–74 years, and over 74 years.

Figures were created by IBM SPSS for Mac version 22.0 (Figure 1) and Excel for Mac version 16 (Figure 2 and 3). Decimal numbers were automatic separated automatic in comma and not point.

## RESULTS

We observed an increasing rise in the number of patients, potentially associated with the increase in the number of referenced cities. The care was primarily public (80.5%), patients from cities in Minas Gerais (94.3%); most patients were undiagnosed (45.7%) or untreated (71.8%) at the first visit, had a low level of education (62.8% up to elementary school), and were married (55.2%) (Table 1).

The patients were generally brown (47.7%), aged 40–69 years (70.2%) (Figure 1), and native of Minas Gerais (81.1%). Attention should be given to the 70–74 years age group because there are controversies regarding screening, representing 7.4% of tumors (Table 2).

The main histological type identified was invasive ductal carcinoma (80.1%), followed by invasive lobular carcinoma (7.9%). Carcinoma *in situ* was present in 6.0% of the patients; only 33.9% had an early clinical stage (CS 0 + I). When evaluating only the cases initially treated at the hospital, 5.4% of the patients had CS 0, and 25.8% had an early stage (Table 2).

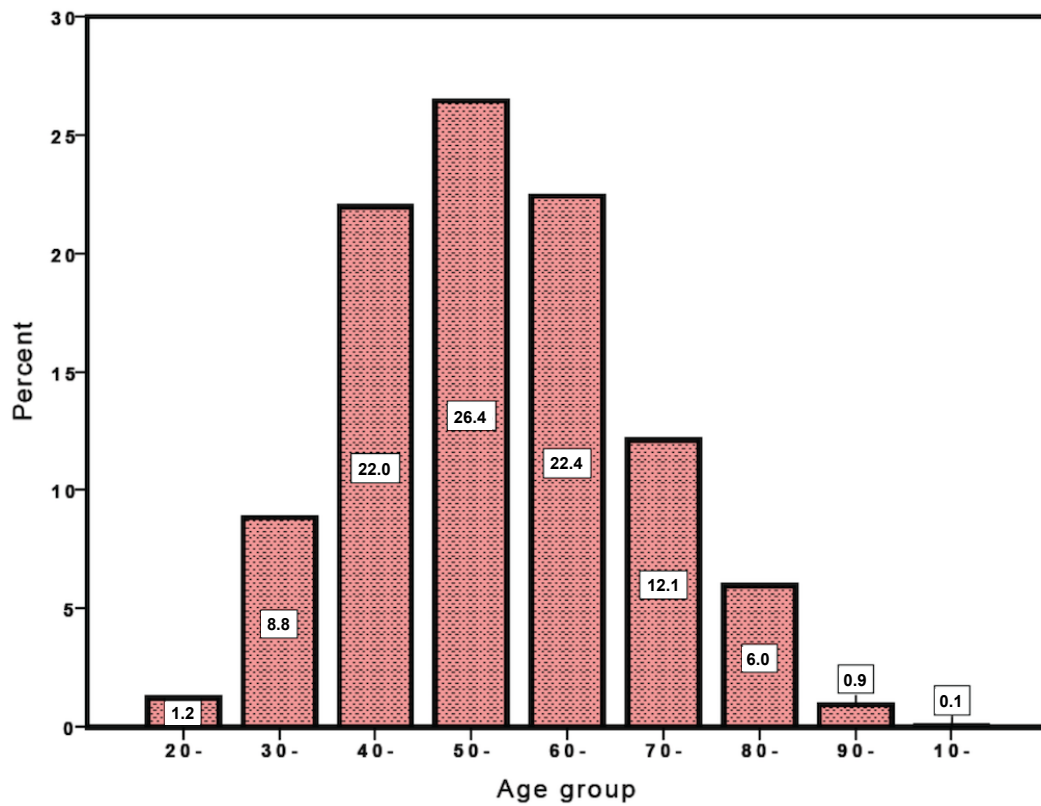
In addition, we evaluated the main characteristics of the patients treated by the Brazilian Unified Health System (SUS) in relation to the private system (Table 3): most of the patients without a diagnosis were from the SUS (47.2%), while in the private system, most patients already had a previous diagnosis ( $p < 0.001$ ). The clinical stage was also influenced by the type of care: patients with early stage (0 + I) came mainly from the private system (31.1% *versus* 26.2%;  $p < 0.001$ ). The patient's age was not influenced by the care system.

With the temporal evaluation, we observed, over the years, the maintenance of the age group at diagnosis and the clinical stage, and a small increase in the number of patients with clinical stage IV in the years of the new coronavirus (Covid-19) pandemic (Figures 2 and 3).

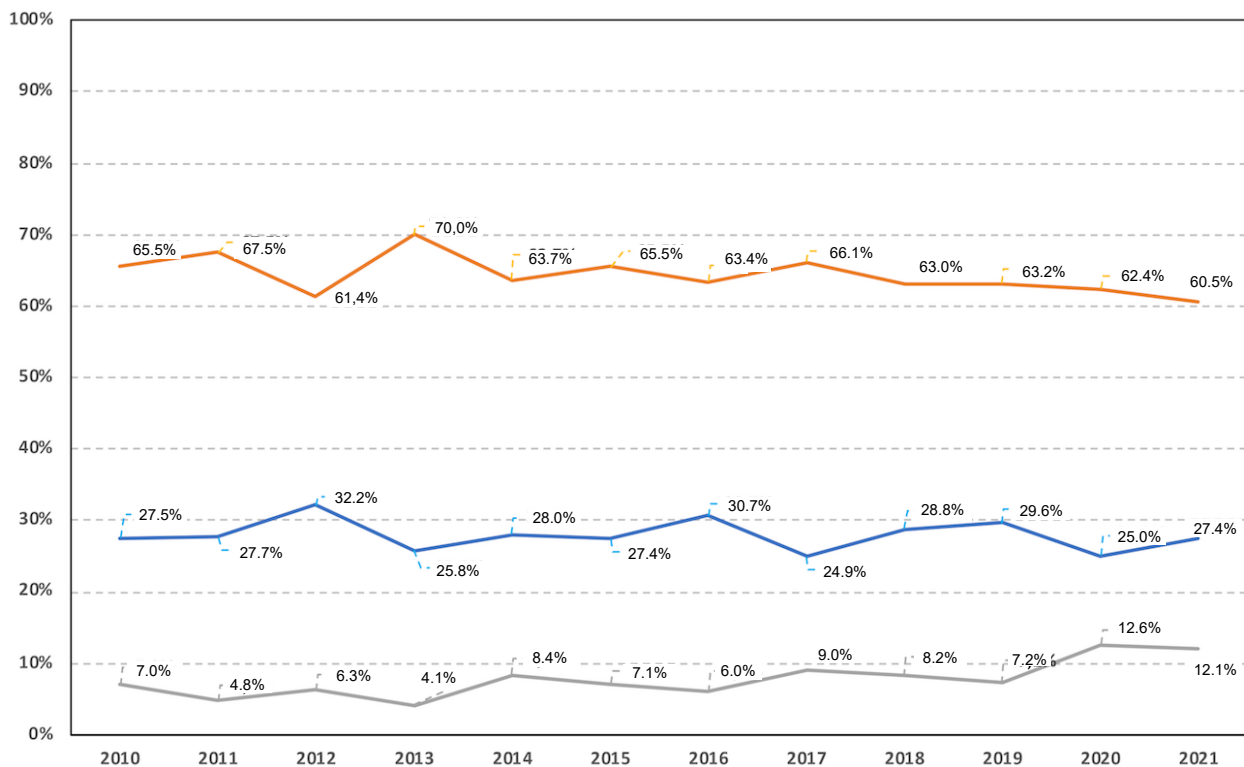
## DISCUSSION

The literature is limited with regard to epidemiological data on breast cancer-related RHC. There are experiences of cancer hospitals<sup>12</sup>, oncology units<sup>14,16</sup>, Specialty Reference Centers<sup>17,18</sup>, and the Regional League<sup>19</sup>. When evaluating epidemiological data related to breast cancer, derived from hospitals or reference services, the regional characteristics, the referral flow, the existence of other services in the region, and the characteristics of the accreditation of the oncology unit should be analyzed, a fact that may impact the presented results. The HCM serves a region referenced in the east of Zona da Mata where there is no other Oncology unit, public or private, constituting itself as a regional reference for cancer treatment. It is established as a CACON II Hospital<sup>15</sup>, as it contains all types of treatment related to cancer care, from diagnosis to palliative care, with a high rate of resolution.



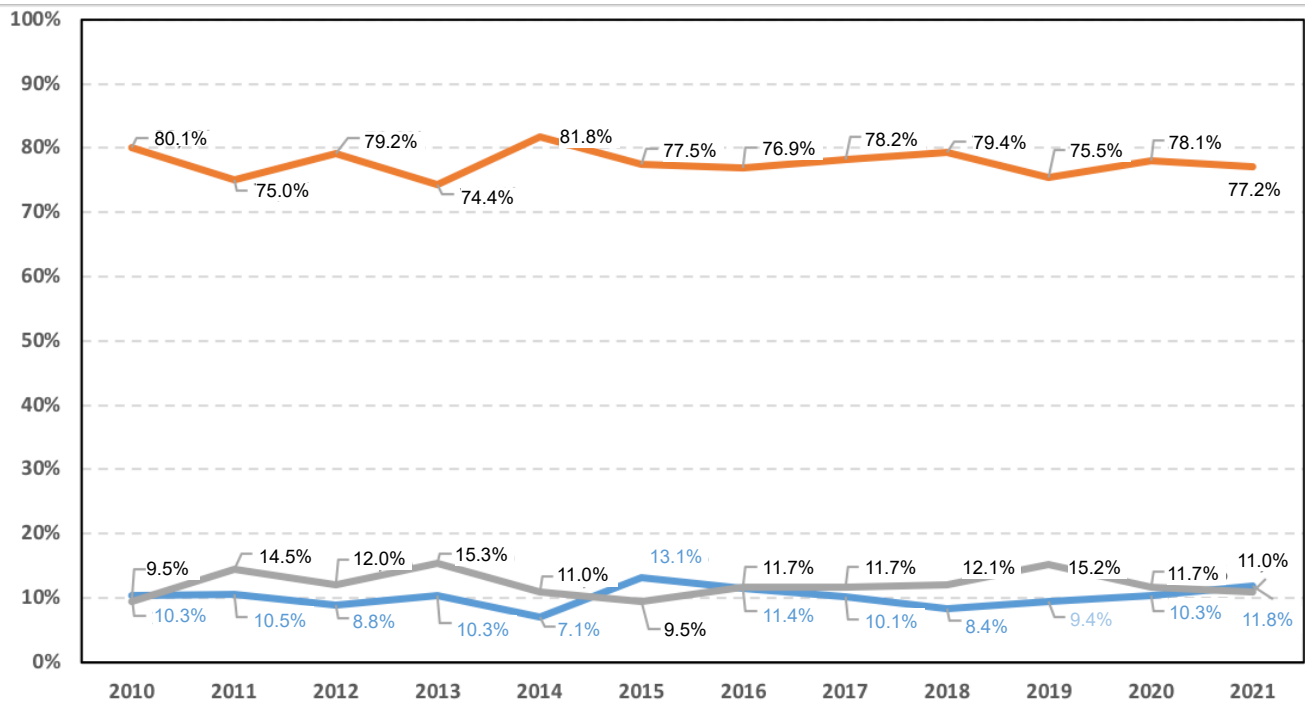


**Figure 1.** Age distribution.



CS: clinical stage; Early: CS 0 and I; Advanced: CS II and III; Metastatic: CS IV.

**Figure 2.** Time curve from the clinical stage (%) to diagnosis.



**Figure 3.** Time curve of the distribution of the age group at diagnosis

We observed an increasing rise in the number of patients, a fact that reflects the efficiency and organization of the cancer treatment network. Historically, the hospital served patients from other nearby states, a fact that has changed over time — currently, care is exclusive to patients from the state of Minas Gerais. As for breast cancer, since 2010 there has been an increase in the annual rate, which ranged from 259 women in the first triennium to 492 women in the last triennium. The HCM is a public hospital, privately managed, preferably serving SUS patients (80.5%), and private care is limited (13.1%).

With regard to breast cancer, the main access for patients is through the Mastology Division and Clinical Oncology sectors. Initially, Mastology was served together with Oncological Surgery, a fact that was modified due to the growth and the need for a team dedicated to this specialty. The inclusion of patients in the Mastology Division occurs due to the high suspicion lesions or confirmation of neoplastic disease, and patients with BI-RADS 4 and 5 lesions or confirmed breast neoplasms are evaluated. Due to limitations in the regional health system, many suspected cases are diagnosed at the hospital level. The structuring and resolution of the regional healthcare system have an impact on the type of referred patient, and there is also a high rate of patients who need complementary diagnostic evaluation and diagnostic breast biopsy. When assessing breast cancer, 45.7% of the patients were diagnosed at the institution, 26.1% arrived with a diagnosis and without treatment, and 27.4% had already undergone some type of oncological treatment.

Assessing patients' age characteristics is essential to understand potential changes related to risk factors as well as screening strategies. The Brazilian Ministry of Health suggests that screening should

be carried out in the age group of 50 to 69 years, which would benefit 49.2% of patients. The Brazilian Society of Mastology (*Sociedade Brasileira de Mastologia* – SBM), in turn, suggests starting it at 40 years of age, which would benefit 70.2% of patients. The age group of 70–74 years represents about 7.4% of patients. When evaluating the Brazilian population pyramid, there is a gradual decrease in the number of patients according to age group, and a significant number of patients in the age group of 70–74 years was observed, a fact that should be taken into account, especially in relation to those with high life expectancy, as suggested by the SBM.

Comparing the age groups, we observed no changes in the analyzed period, nor any differences in age group and clinical stage in patients from the public or private systems. Another factor that can influence the age group is the hospital characteristic. Private hospitals, which depend on health insurance plans, may have a younger population with higher income, which is associated with the availability of resources to maintain the health insurance — this fact must be better evaluated. The rate of patients under 50 years of age was 40% in a private hospital in the city of São Paulo<sup>12</sup> and 31.2% in the study's hospital.

The quality and care in staging is reflected in the quality of the RHC data. In this sample, 8% of data were ignored, and levels lower than 10% were acceptable. Another important finding is the rate of patients with stage IV, which is usually less than 10% — higher rates reflect serious limitations in the healthcare system. As it is an oncology hospital, 7.4% of the patients were diagnosed at this stage, a result influenced by the characteristics of the service, similar to that observed in oncology hospitals<sup>12,13</sup> and oncology units<sup>14,16</sup> (5.3% to

**Table 1.** General information on breast cancer patients treated at the Hospital do Câncer do Muriaé (MG).

Variable	Category	Number	%
Year of diagnosis	2010 to 2012	777	17.0
	2013 to 2015	1,023	22.4
	2016 to 2018	1,295	28.3
	2019 to 2021	1,478	32.3
Location	Minas Gerais	4,315	94.3
	Rio de Janeiro	246	5.4
	Espírito Santo	12	0.3
Type of service	Brazilian Unified Health System	3,682	80.5
	Health insurance	576	12.6
	Private	70	1.5
	Other	245	5.4
Clinic – admission*	Mastology	1,772	38.7
	Clinical oncology	1,578	34.5
	Radiotherapy	487	10.6
	Surgical oncology	480	10.5
	Other	14	0.4
Place of origin – birthplace	Southeast – Minas Gerais	3,708	81.1
	Southeast – other states	777	17.0
	Northeast	59	1.3
	South	18	0.4
	North	7	0.2
	Midwest	4	0.1
Level of education	Absent	345	7.5
	Some elementary school	2,031	44.4
	Elementary school	499	10.9
	High school	901	19.7
	College degree	606	13.3
	No information	191	4.2
Marital status	Single	1,017	22.2
	Married	2,524	55.2
	Common-law marriage	25	0.5
	Divorced	436	9.5
	Widow(er)	571	12.5
Total	–	4,573	100.0

\*Patients initially treated at another institution were excluded from this study.

8.0%), and lower than that observed in regional outpatient reference centers<sup>17,18</sup>. In a national study whose authors evaluated only invasive tumors, the national rate was 9.3%<sup>20</sup>. At the HCM, during the Covid-19 pandemic, there was an increase in the number of patients with stage IV, reaching 12.1%, a fact potentially influenced by serious limitations in patient navigation at the care level prior to hospitalization<sup>21</sup>.

Another factor associated with the quality of services is the rate of patients with early stages (CS 0 + I): 25.8%. Stage zero corresponds to carcinoma *in situ*, usually diagnosed by mammographic screening, evidencing the impact of this test as a diagnostic tool for breast cancer. In a place with organized screening, in a small city of the State of São Paulo, Brazil, three phases were observed: prior to screening (CS 0 + I = 13%); in the

**Table 2.** Data related to presentation at hospital admission.

Variable	Category	Number	%
Sex	Women	4,551	99.5
	Men	22	0.5
Ethnicity/skin color	Brown	2,183	47.7
	White	1,841	40.3
	Black	526	11.5
	Asian	4	0.1
	Ignored	19	0.4
Age group (years)	<40	466	10.2
	40–49	962	21.0
	50–59	1,227	26.8
	60–69	1,023	22.4
	70–74	339	7.4
	≥75	556	12.2
Diagnosis	ND, NT	2,091	45.7
	WD, WT	1,192	26.1
	WD, WT	1,254	27.4
	Other	36	0.8
Histological type	IDC	3,662	80.1
	ILC	359	7.9
	DCIS	213	4.7
	Other	339	7.3
CS–TNM*	CS 0	251	6.0
	CS I	921	27.9
	CS II	1,625	38.6
	CS III	1,066	25.3
	CS IV	343	8.2
CS–TNM†	CS 0	168	5.4
	CS I	639	20.4
	CS II	1,245	39.7
	CS III	854	27.2
	CS IV	231	7.4

ND: no diagnosis; NT: no treatment; WD: with diagnosis; WT: with treatment; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ; CS: clinical stage. \*Ignored data were excluded (n=367; 8%); †Ignored data and data on patients with previous treatment were excluded.

first two years of mammographic screening (43.3%); and after consolidation of screening (60%), in which asymptomatic patients had better rates of early stage (84.3% *versus* 31.9%)<sup>22,23</sup>. At an oncology hospital in Curitiba (state of Paraná, Brazil)<sup>13</sup>, from 2000 to 2009, this rate was 14.3%, but the rate of incomplete data was 16.9% and the study did not present numerical data, making it difficult to evaluate absolute data. In a private oncology hospital in the state of São Paulo<sup>12</sup>, this rate was 46.7%. If the numbers were evaluated by the HDI, we would have, in descending order: Curitiba/State of Paraná (HDI = 0.823) > São Paulo/State of São Paulo (HDI = 0.805)

> Barretos/State of São Paulo (HDI = 0.798) > Muriaé/State of Minas Gerais (HDI = 0.734). It is observed that the HDI is important, but it is also relevant how it actually reaches the SUS population, through health initiatives. Different results are observed depending on the presence and structure of the screening program, location, type of population served, and hospital characteristics. By comparing the numbers, we can observe the need to improve the regional public health system, the importance of organized mammography screening, and the need for improvements in the navigation of patients in the diagnosis of breast cancer in the SUS.

**Table 3.** Patient characteristics in relation to patient type\*.

		SUS (%)	Private (%)	Total (%)	p-value
Type of Diagnosis	ND–NT	1,335 (79.0)	355 (21.0)	1,690 (42.9)	<0.001
	WD–WT	745 (71.5)	300 (28.5)	1,052 (26.7)	
	WD–WT	728 (61.1)	445 (37.9)	1,173 (29.8)	
	Other	11 (44.4)	14 (56.0)	25 (0.6)	
Age group (years)	<40	270 (68.0)	127 (32.0)	397 (10.1)	0.419
	40–49	603 (72.1)	233 (27.9)	836 (21.2)	
	50–59	758 (71.6)	300 (28.4)	1,058 (26.9)	
	60–69	644 (73.7)	230 (26.3)	874 (22.2)	
	70–74	215 (72.4)	82 (27.6)	297 (7.5)	
	≥75	336 (70.3)	142 (29.7)	478 (12.1)	
Clinical stage	CS 0	158 (74.5)	54 (25.5)	212 (5.8)	0.001
	CS I	532 (67.1)	261 (32.9)	793 (21.8)	
	CS II	1,013 (72.4)	386 (27.6)	1,399 (38.4)	
	CS III	717 (76.4)	221 (23.6)	938 (25.7)	
	CS IV	213 (70.3)	90 (29.7)	303 (8.3)	
Total		2,633 (72.2)	1,012 (27.8)	3,645 (100)	

SUS: Brazilian Unified Health System; ND: no diagnosis; NT: no treatment; WD: with diagnosis; WT: with treatment. \*Patients whose origin is ignored were excluded from this study.

Authors of the Amazona III Study<sup>24</sup> evaluated patients with stages I to IV, coming from public and private services. When comparing the public and private systems, differences were observed in stages I, II, and IV: there was a higher rate of patients with stage I in the private service (40.6% *versus* 18.5%), and the diagnosis in this sector was mainly made by screening (53.0% *versus* 23.1%); there were no differences in relation to age group.

HCM has mixed characteristics, with partial private care. Patients from the private system generally arrived at the hospital with a confirmed diagnosis and/or previous treatment, with a higher rate of early clinical stage (31.1% *versus* 26.2%, compared to rates of patients treated by the SUS). This fact corroborates previous studies whose authors compared the public and private systems, but these numbers are lower than the rate of 46.7% observed in a private cancer hospital in São Paulo, which makes us ponder that other local cultural factors and adherence to mammography may influence the observed results. Another analyzed factor was age, which was not influenced by the preferred type of care at the hospital unit, in which there is a high rate of patients with health insurance from the Civil Servants of Minas Gerais.

Recently, there have been experiments showing associated numbers of hospital records<sup>25</sup>, represented by newsletters; however, such data, usually raw, need to be better analyzed and contextualized. Likewise, the results should be compared over

time in order to assess seasonal changes, such as the COVID-19 pandemic, or those associated with the structuring of the health system.

Thus, the main characteristics of our service were presented, with the limitations of the use of raw data, the lack of evaluation of molecular subtypes and survival, which can be presented in future studies.

## CONCLUSIONS

When observing patients treated in the Zona da Mata, in the countryside of Minas Gerais, in a tertiary oncology hospital, there are also limitations associated with diagnosis in the public service; the hospital still provides secondary care, due to the high number of cases still diagnosed at the institutional level.

## AUTHORS' CONTRIBUTION

LCNO: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. SMOC: Data curation, Visualization, Writing – original draft, Writing – review & editing. CSMF: Data curation, Visualization, Writing – original draft, Writing – review & editing. RCJDS: Data curation, Visualization, Writing – original draft, Writing – review & editing. FFV: Formal analysis, Visualization, Writing – original draft, Writing – review & editing.



RBT: Data curation, Visualization, Writing – original draft, Writing – review & editing. BLGM: Visualization, Writing – original draft, Writing – review & editing. RACV: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.









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# Breast cancer and public healthcare: survey and proposals from Brazilian Society of Mastology (SBM)

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## ABSTRACT

**Introduction:** High rates of breast cancer mortality have been reported for patients from public healthcare, in Brazil. This study aimed to obtain a panorama of breast cancer in public healthcare, based on a questionnaire sent to breast specialists. **Methods:** Active members of the Brazilian Society of Mastology (SBM) were invited to participate anonymously, from Aug-Oct 2023. Possible answers ranged from “This is not a problem” to “This is a very serious, very common problem”. The primary endpoint of the study was the relative frequency of the answers. **Results:** Overall, 767 (44% of all SBM affiliated members) completed the questionnaire. Access to modern drugs was considered the most concerning problem, with 81.36% of respondents classifying this as “serious, frequently” or “very serious, very frequently”, followed by access to diagnostic methods (64.53%), access to breast reconstruction (60.24%), delay in starting treatment (60.11%) and access to screening (51.76%). **Conclusions:** This is the first study to evaluate the perceptions of breast specialists on breast cancer care within SUS. The SBM has issued considerations and proposals aimed at reestablishing a minimally adequate standard of breast cancer diagnosis and treatment in public healthcare in Brazil.

**KEYWORDS:** public health surveillance; breast neoplasms; healthcare disparities; health inequities; socioeconomic factors.

## INTRODUCTION

Approximately 72% of the Brazilian population relies exclusively on the public healthcare system (*Sistema Único de Saúde* – SUS) for medical care. The remaining population relies on a variety of healthcare insurance plans offered by private companies<sup>1</sup>.

In oncology, there is currently an unprecedented crisis of inequality in the quantity and quality of care provided within the public healthcare sector compared to the private sector. Among women with breast cancer who depend on the public healthcare sector, disease-related mortality rates are particularly high<sup>2,3</sup>. The issues that contribute to this inequality are mostly related to screening and treatment<sup>4,5</sup>.

The objective of the present study was to obtain a comprehensive overview of breast cancer care in public healthcare in Brazil through a questionnaire sent to breast specialists across the country.

## METHODS

### Study population

This online survey was conducted between August and October 2023. All 1,759 breast specialists affiliated with the Brazilian Society of Mastology (*Sociedade Brasileira de Mastologia* – SBM) were invited to participate anonymously in the study. Invitations to visit the web page hosting the questionnaire were sent via e-mails and messages, restricted to affiliates. Access to the questionnaire was not attached to any identification, e-mail, or personal contact. Non-respondents either did not visit the webpage, did not answer, or did not complete the questionnaire. An estimation of non-respondents was made, comparing data from the total number of SBM affiliates.

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## Intervention

The online questionnaire consisted of eight objective questions:

- In which state do you live?
- How big is the population of the city/town in which you live or work?
- How is the situation regarding breast cancer screening within public healthcare where you live or work?
- How is the situation regarding delays in initiating breast cancer treatment in public healthcare where you live or work?
- How is the situation regarding breast reconstruction in the public healthcare where you live or work?
- How is the situation regarding breast cancer diagnostic methods (imaging, pathology, and genetic testing) in public healthcare where you live or work?
- How is the situation regarding treatment modalities such as access to targeted drug therapy, cyclin-dependent inhibitors, and immunotherapy in public healthcare where you live or work?

For each question, the possible answers were:

- I don't know
- This is not a problem
- This is a minor, infrequently occurring problem
- This is a moderate, occasionally occurring problem
- This is a serious, frequently occurring problem
- This is a very serious, very frequently occurring problem

## Endpoints

The primary outcome of the study was the relative frequency of the answers to each question. The secondary outcome was the relative frequency of “*serious, frequently*” and “*very serious, very frequently*”, according to region and state.

## Statistical analysis

This is a descriptive study without comparative analyses. Qualitative variables are expressed as relative frequencies. Tables, figures and maps were built with Microsoft® Excel.

## RESULTS

A total of 767 breast specialists answered the questionnaire, representing 44% of all the physicians affiliated with SBM (Table 1). All respondents completed the questionnaire. The only state without representation was Acre.

Access to modern drugs was the most concerning problem, with 81.36% of respondents classifying it as a “*serious, frequently*” or “*very serious, very frequently*” problem, followed by access to diagnostic methods (64.53%), access to breast reconstruction (60.24%), delay in starting treatment (60.11%), and access to screening (51.76%) (Table 2). The proportion, by state, of answers “*serious*” and “*very serious*”, is represented in Figures 1-3.

## DISCUSSION

This is the first study to evaluate how breast specialists perceive the major problems involved in breast cancer control within the public healthcare system. The survey addressed five aspects: access to screening, delays in initiating treatment, access to breast reconstruction, access to diagnostic methods, and access to modern treatment modalities such as targeted drug therapy, cyclin-dependent kinase inhibitors, and immunotherapy. The aspect that was considered most concerning was the lack of access to modern drugs.

The issues that contribute to this inequality are mostly related to screening and treatment. Screening in Brazil is opportunistic, and highly dependent on adherence, which is historically

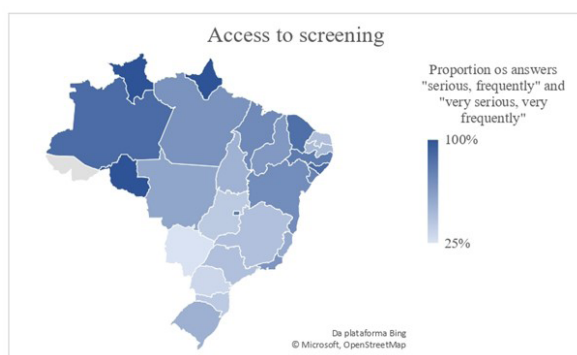
**Table 1.** Characteristics of the breast specialists from Sociedade Brasileira de Mastologia: respondents and non-respondents.

State	Respondents n (%)	Non-respondents n (%)	Total
Acre	0 (0)	2 (100)	2
Alagoas	8 (42)	11 (58)	19
Amazonas	8 (50)	8 (50)	16
Amapá	2 (40)	3 (60)	5
Bahia	43 (39)	67 (61)	110
Ceará	28 (45)	34 (55)	62
Distrito Federal	23 (36)	41 (64)	64
Espírito Santo	11 (50)	11 (50)	22
Goiás	21 (36)	38 (64)	59
Maranhão	7 (26)	20 (74)	27
Minas Gerais	96 (48)	102 (52)	198
Mato Grosso do Sul	8 (57)	6 (43)	14
Mato Grosso	7 (54)	6 (46)	13
Pará	9 (31)	20 (69)	29
Paraíba	13 (33)	26 (67)	39
Pernambuco	28 (49)	29 (51)	57
Piauí	11 (61)	7 (39)	18
Paraná	29 (39)	45 (61)	74
Rio de Janeiro	46 (37)	80 (63)	126
Rio Grande do Norte	16 (43)	21 (57)	37
Rondônia	1 (14)	6 (86)	7
Roraima	1 (50)	1 (50)	2
Rio Grande do Sul	41 (35)	76 (65)	117
Santa Catarina	29 (35)	54 (65)	83
Sergipe	4 (20)	16 (80)	20
São Paulo	273 (52)	257 (48)	530
Tocantins	4 (44)	5 (56)	9
Total	767 (44)	992 (56)	1759

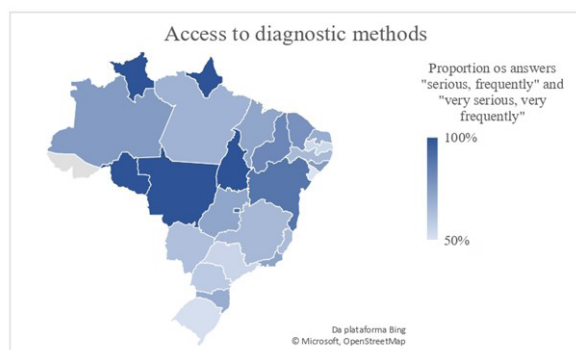
**Table 2.** Main problems in public health according to the breast specialists who completed the questionnaire

Answer to Question	Access to screening n (%)	Delay in initiating treatment n (%)	Access to breast reconstruction n (%)	Access to diagnostic methods n (%)	Access to modern drugs n (%)
I don't know	24 (3.13)	18 (2.35)	28 (3.65)	12 (1.56)	44 (5.74)
This is not a problem	15 (1.96)	10 (1.30)	42 (5.48)	11 (1.43)	5 (0.65)
This is a minor, rarely occurring problem	67 (8.74)	74 (9.65)	79 (10.30)	61 (7.95)	25 (3.26)
This is a moderate, occasionally occurring problem	264 (34.42)	204 (26.60)	156 (20.34)	188 (24.51)	69 (9.00)
This is a serious, frequently occurring problem	298 (38.85)	287 (37.42)	208 (27.12)	274 (35.72)	177 (23.08)
This is a very serious, very frequently occurring problem	99 (12.91)	174 (22.69)	254 (33.12)	221 (28.81)	447 (58.28)

A)

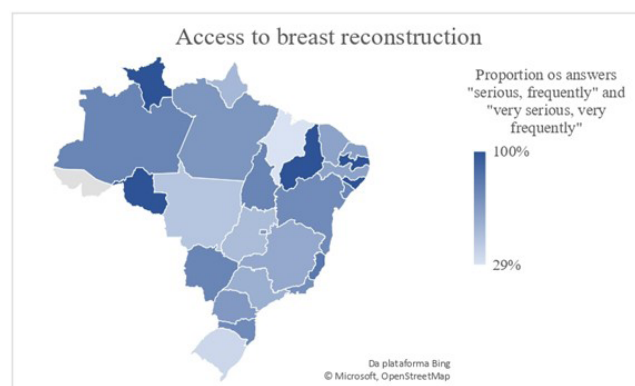


B)

**Figure 1.** Perceptions as "serious, frequently" and "very serious, very frequently", regarding screening (A) and diagnostic methods (B), by state, according to breast specialists.

low<sup>6</sup>. Mammography coverage is estimated to reach only 30% of women<sup>7</sup>. Women in public healthcare are less likely to be diagnosed at stage 1<sup>4</sup>. After undergoing mammography, women then experience difficulty in accessing diagnostic tests. Comparing the number of biopsies and mammograms performed within the public healthcare system suggests that only 16.8% of biopsies are carried out within SUS<sup>5,8</sup>. The difficulty in scheduling a biopsy within SUS forces many women to undergo the procedure in private healthcare services.

There is an inverse association between the time interval until initiating treatment and a better breast cancer prognosis.

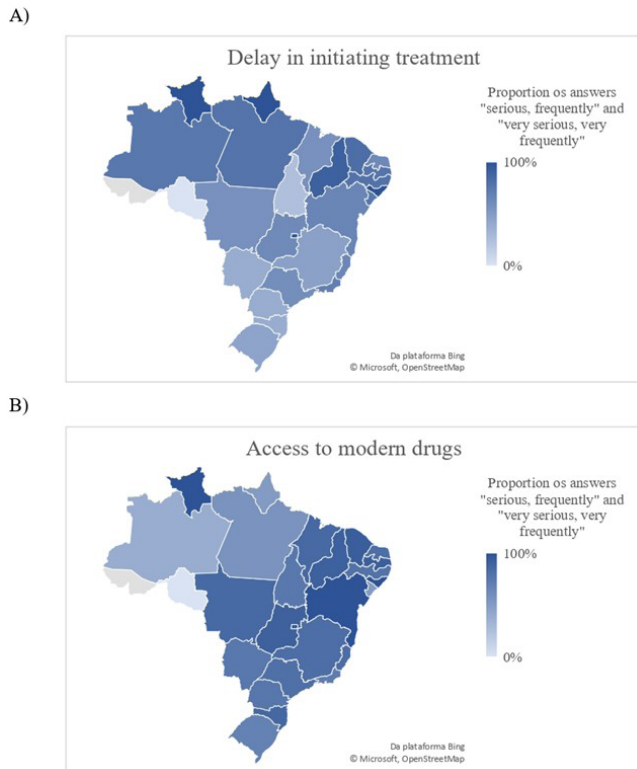
**Figure 2.** Perceptions as "serious, frequently" and "very serious, very frequently", to breast reconstruction, by state, according to breast specialists.

Ideally, time for surgery should not exceed eight weeks<sup>9</sup>. In relation to systemic treatment, a systematic review with meta-analysis showed that for every four weeks of delay, there is a reduction in overall survival and disease-free survival<sup>10</sup>. In Brazil, despite legislation that limits the initiation of treatment to 60 days, recent data show that the median waiting time is 59 days, with 49% of women waiting longer than that for treatment to begin<sup>5</sup>.

Few data are available on access to breast reconstruction in Brazil. Although national legislation approved in 1999 guarantees the right to breast reconstruction, the number of surgeries performed is low. Studies estimate that only 20–29% of women who have undergone mastectomy within the public healthcare system are able to access breast reconstruction<sup>11,12</sup>. The causes are manifold and may include a lack of public service inspection, non-existent infrastructure, shortage of materials, and lack of trained surgeons. A study found that 20% of breast specialists had received no training in breast reconstruction during medical residency<sup>13</sup>.

Currently, there are numerous unmet needs in breast cancer treatment within the SUS. Molecular testing to forecast the benefit of chemotherapy is unavailable, as is genetic testing.





**Figure 3.** Perceptions as “serious, frequently” and “very serious, very frequently”, to delay in initiating treatment (A) and access to modern drugs (B), by state, according to breast specialists.

The Ministry of Health’s most recent updated Guidelines on the Diagnosis and Treatment of Breast Cancer does not include ovarian suppression, pertuzumab for cases of early breast cancer in neoadjuvant setting, cyclin-dependent kinase inhibitors, PARP inhibitors for early or metastatic breast cancer, or immunotherapy<sup>14</sup>. Some public hospitals offer treatment that is even inferior to those minimum recommended guidelines<sup>15</sup>.

This is the first study to evaluate the perceptions of breast specialists, distributed throughout most of the country, on the problems associated with breast cancer treatment within the Brazilian public healthcare system. A limitation of the study is that the survey consisted of interviews that were dependent on individual perceptions rather than on primary data obtained from patients. Nevertheless, the present study should serve as an alert to this unprecedented crisis in the public healthcare sector.

SBM has issued the following considerations and proposals aimed at reestablishing a minimally adequate standard of breast cancer diagnosis and treatment within SUS:

1. *Compliance with legislation 14,335 of 2022 that establishes a lower limit of 40 years as the age at which to initiate breast cancer screening in Brazil, with mammograms to be performed annually thereafter.* We recommend a review of the Ministry of Health’s recommendations on initiating screening at 50 years of age, with mammograms to be performed once every two years. The incidence of cancer in individuals

under 50 years of age is increasing worldwide<sup>16</sup>. In Brazil, in particular, the proportion of cases in young women is high<sup>17,18</sup>. Epidemiological studies have shown that the onset of cancer risk occurs ten years earlier in black women compared to white women<sup>19</sup>, who were underrepresented in screening trials. These are, in fact, the reasons why the United States Preventive Services Task Force changed its recommendation, reducing the age at which to start breast cancer screening from 50 to 40 years<sup>20</sup>.

2. *Compliance with legislation 12,732 of 2012, which determines a maximum delay of 60 days until initiating treatment within SUS.* Delays in initiating treatment affect prognosis and entail more aggressive treatment, also resulting in financial toxicity<sup>9</sup>.
3. *Compliance with legislation 9,797 of 1999, which requires corrective breast reconstruction surgery to be offered within SUS in cases of mutilation resulting from cancer treatment.* Likewise, it is paramount to ensure that cancer centers have a breast reconstruction team.
4. *Establishing equivalence between the procedures approved by ANVISA in the National Commission for the Incorporation of Technology within the National Health Service (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde – CONITEC) and the National Agency of Supplementary Healthcare (Agência Nacional de Saúde Suplementar – ANS) with respect to diagnostic methods and treatment modalities.* Strategies must be drawn up to enable the incorporation, acquisition and adequate remuneration of diagnostic methods, including germline genetic testing, positron emission tomography (PET), breast magnetic resonance imaging (MRI), and vacuum-assisted biopsy. Likewise, modern treatment modalities should be incorporated, particularly trastuzumab emtansine (approved by CONITEC but still not available in SUS), cyclin-dependent kinase inhibitors (approved by CONITEC but still not available in SUS), pertuzumab (approved but available exclusively for cases of metastatic disease), pembrolizumab, trastuzumab deruxtecan, PARP inhibitors, goserelin, and sacituzumab govitecan.

## CONCLUSION

This study shows how breast specialists perceive major problems involved in breast cancer control within public healthcare system in Brazil. Lack of access to modern treatment modalities was considered the most concerning aspect, followed by access to diagnostic methods, access to breast reconstruction, delay in starting treatment and access to screening. Breast specialists are concerned that their SUS patients could be receiving insufficient screening and treatment. An agenda to deal with rising rates of breast cancer mortality should be drawn up without delay.

## AUTHORS' CONTRIBUTION

ATH: Conceptualization, Supervision, Visualization, Writing – original draft. JFB: Formal analysis, Methodology, Software, Visualization, Writing – original draft. GGN: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review &

editing. SG: Validation, Visualization, Writing – review & editing. AM: Formal analysis, Visualization, Writing – review & editing. FPC: Formal analysis, Visualization, Writing – review & editing. RFJ: Conceptualization, Data curation, Supervision, Visualization, Writing – original draft. CAR: Supervision, Validation, Visualization, Writing – review & editing.

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# Immediate reconstruction with implant post-mastectomy with prepectoral versus submuscular technique: experience of a public oncological treatment center

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## ABSTRACT

**Introduction:** Reconstruction techniques after mammary adenectomy with implant placement in the prepectoral space without the use of cell dermal matrix have been attracting more interest recently. However, data on the risk of complications, especially in patients treated in Brazil by the Brazilian Unified Health System, are scarce. **Methods:** This is a retrospective cohort study on women who underwent mammary adenectomy and immediate reconstruction with implants in a public hospital in Brazil, with survival analysis for implant extrusion and its associated factors. **Results:** Prepectoral and submuscular implant-based reconstruction had similar clinical outcomes. High axillary involvement (four or more lymph nodes) was the only factor associated with implant extrusion, regardless of the implant reconstruction techniques used. **Conclusions:** Tumor burden might interfere with the immediate implant-based breast reconstruction.

**KEYWORDS:** breast cancer; breast implants; oncoplasty.

## INTRODUCTION

Breast cancer is the disease that most affects women in the world. About one million cases are diagnosed per year<sup>1</sup>. In Brazil, there are approximately 73,610 new cases per year, with an estimated risk of 73.61 cases per 100 thousand women<sup>2</sup>.

Breast cancer treatment is multimodal, encompassing systemic therapy (chemotherapy, endocrine therapy, immunotherapy, targeted therapies, etc.), surgery, and radiotherapy. However, the main therapeutic strategy for localized disease is surgical intervention<sup>3</sup>. Although radical and conservative surgeries have comparable survival rates, breast conservation combined with radiotherapy is the standard treatment<sup>3,4</sup>. Nevertheless, there are still classic indications for mastectomy: presence of previous thoracic radiation (due to previous breast cancer or Hodgkin's lymphoma), unfavorable tumor-breast relationship, extensive calcifications, multicentric disease, or in carriers of some high-penetrance genetic mutations<sup>4</sup>.

Mastectomies that spare the skin and the nipple-areola complex (adenomastectomy) provide better aesthetic results in immediate reconstructions and are oncologically safe. Silicone implants can be positioned in the submuscular plane or in the prepectoral space<sup>5,6</sup>.

The advantages of placing the implant in the submuscular plane are minimal visibility and palpability of the prosthesis, in addition to reduced rippling. As disadvantages, this technique can cause animation deformities, functional loss of the pectoralis major muscle, capsular contracture in varying degrees, and more postoperative pain<sup>5,6</sup>.

The reconstruction technique with implants in the prepectoral space was initially used in the 1980s, but was promptly rejected due to high complication rates<sup>5</sup>. However, as of 2015, the technique aroused increasing interest, as noted in the literature, mainly in Italian centers<sup>7</sup>.

The advent of dermal matrices has given rise to discussion regarding new possibilities for post-mastectomy reconstructions.

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Initially, they were used in a complementary way, covering the lower and lateral part, with the upper end sutured to the lower edge of the pectoralis major muscle, reducing the tension of the muscle bag. Nonetheless, this option maintained a potential risk for shoulder joint dysfunction and animation deformities associated with dissection of the pectoralis to create the muscle bag.

Aiming to remedy such damage, the prepectoral reconstruction technique with total or partial coverage of the implant by the acellular dermal matrix (ADM) has emerged. This consisted of including the prosthesis covered by the mesh in the glandular cavity itself, fixing it to the pectoralis major<sup>5</sup>.

Although the prepectoral technique using ADM has proven to be safe and advantageous in terms of reducing complications, the use of biological meshes or synthetic materials increases its costs<sup>8</sup>. This fact may limit its use by paying sources, especially in the Brazilian Unified Health System (SUS) scenario. Thus, prepectoral reconstruction without coverings emerged as an alternative, showing satisfactory initial results<sup>9,10</sup>.

This technique, however, may have disadvantages such as greater visibility and palpability of the implant, rippling, and implant extrusion. Some authors argue that undue weight and tension of the implant may put pressure on the mastectomy flap, preventing tissue perfusion<sup>11</sup>.

Currently, there has been interest in the results of prepectoral breast reconstruction techniques and their comparison with subpectoral ones. Therefore, in this study we aim to describe the profile of patients undergoing adenomastectomy followed by immediate reconstruction technique with pre- and subpectoral implants, without the use of dermal matrix, as well as factors associated with the risk of implant extrusion.

## METHODS

### Study design

This is a retrospective, observational, cohort, analytical study.

### Study location

High Complexity Oncology Assistance Center (*Centro de Assistncia de Alta Complexidade em Oncologia* – CACON) of the state of Maranho, Brazil, Hospital do Cncer Aldenora Bello [Aldenora Bello Cancer Hospital], maintained by the Fundao Antnio Dino [Antnio Dino Foundation], which assists patients from the Brazilian Unified Health System (SUS), health insurance plans, and private individuals.

### Inclusion criteria

Women who underwent skin-sparing mastectomy or skin- and nipple-sparing mastectomy followed by immediate single-stage reconstruction with silicone implants, between January 2021 and December 2022, treated exclusively by the SUS.

### Exclusion criteria

Women who underwent immediate reconstruction, using myocutaneous flaps, fat grafting, or who had an unviable area of the skin flap.

### Sampling method

The sample was obtained by convenience within the proposed period, with data collection after approval by the research ethics committee, through the analysis of electronic and physical medical records, which took place from March to July 2023.

### Description of surgical technique

The procedures were performed by five mastologists from this oncology reference unit, and the surgical technique was defined individually. Based on the indication profile for each technique, the sample was distributed between the prepectoral reconstruction and subpectoral reconstruction subgroups.

In the prepectoral technique, the anatomical limits were previously demarcated. The incision in the lateral third of the inframammary fold up to the muscular plane and then the dissection of the subglandular space up to signaled limits with preservation of the fascia of the pectoralis major muscle. Subsequently, the anterior glandular surface was dissected, preserving the skin flap and subcutaneous cellular tissue.

Biopsies of the retroareolar region were performed intraoperatively to rule out neoplastic involvement of the papilla. After checking hemostasis, the pocket was washed and the microtextured round silicone prosthesis was inserted, the size defined according to anatomical measurements and testing by placing molds.

Subpectoral reconstructions had different incisions according to the assessment of the attending mastologist. Some of the patients had large breasts with increased ptosis due to significant skin sagging. In these cases, a reduction mammoplasty-type incision with excision of the nipple-areola complex (NAC) was chosen, resulting in an inverted T-type scar, or a wedge incision to resect the NAC and excess skin in patients with signs of nipple-areola involvement. In the others, a periareolar or radial incision was chosen. In all cases, the gland was carefully dissected with the care already reported in the previous technique. Subsequently, the submuscular pocket was made by elevating the pectoralis major muscles and the fascia of the serratus anterior. Finally, the implant was included in this space and, subsequently, partial synthesis of the access to the pocket was performed to avoid lateral migration of the prosthesis.

In both techniques, the pocket was washed and the microtextured round silicone prosthesis was inserted, the size defined according to anatomical measurements and testing by placing molds.

### Study variables

The numerical variables are: age (years), body mass index (BMI), prosthesis size (cc), breast weight (g), surgery time (minutes), and time until implant extrusion (days).



The categorical variables are: age group, BMI category, smoking habit, clinical staging (TNM), type of surgery, laterality, type of incision, histology, histologic grade, immunohistochemical profile (IHC), focality, assessment of margin involvement, type of axillary surgery, number of dissected lymph nodes, number of involved lymph nodes, contralateral breast symmetrization, adjuvant radiotherapy, neoadjuvant chemotherapy (CT), implant extrusion, and staff (anonymized by the letters A to E).

## Statistical analysis

In the descriptive analysis, categorical variables are presented by frequencies and numerical variables by absolute numbers, medians, and interquartile ranges.

In the univariate analysis, Fisher's exact or Wilcoxon tests were used to associate the classification variables with the type of reconstruction technique used (prepectoral or subpectoral) and with the implant extrusion event (yes and no).

The logrank test was used to measure the difference in implant extrusion-free survival curves for each variable.

In the Cox survival model, the binary qualitative dependent variable used was the occurrence of extrusion: yes or no. The independent variables included were selected based on clinical criteria endorsed in the literature as factors associated with post-breast surgery complications.

## Ethical aspects

This research was approved by the Research Ethics Committee under the CAAE (Certificate of Presentation for Ethical Consideration) consubstantiated opinion number: 69155623.9.0000.8907.

## RESULTS

The study included 61 women, five of whom underwent bilateral mastectomies, one for bilateral breast cancer (synchronous tumor), and the others for risk reduction in the contralateral breast, totaling 66 mastectomies.

In Table 1 we describe the characterization of the sample stratified by surgical technique. This is a sample of young women, most of whom were over 45 years old, overweight/obese, who underwent surgery for stage II and III breast cancer, with invasive tumors of intermediate histologic grade, and a positive immunohistochemical profile of hormone receptors without overexpression of the HER-2 protein. Most tumors were unifocal, achieving free margin status at surgery. Regarding the axillary approach, sentinel lymph node biopsy (SLNB) was the most frequently performed procedure, most had up to four lymph nodes dissected and only 4.5% of the sample showed involvement of more than four lymph nodes. Most women underwent neoadjuvant chemotherapy and a smaller proportion required adjuvant radiotherapy.

In the analysis by subgroups, as shown in Table 1, the majority of patients underwent prepectoral reconstruction without

the use of acellular dermal matrix (55%). Patients in this subgroup had an inframammary fold with the incision of choice and had lower values of BMI, breast weight, prosthesis size, and surgery time, with a statistically significant difference ( $p < 0.05$ ) in all these variables. The proportion of implant extrusion was similar in the prepectoral and submuscular techniques; however, we verified a tendency in the prepectoral group toward later extrusion (median of 180 days) in relation to the group with prepectoral reconstruction (median of 48.5 days), but this relationship was not statistically relevant ( $p = 0.066$ ). In the other variables analyzed, we found no statistically relevant difference between the groups.

In Table 2 we present the univariate analysis data of the sample stratified by the outcome extrusion versus no implant extrusion. We can observe that only the variables type of axillary surgery and number of involved lymph nodes showed statistical difference between the subgroups.

In Figure 1 we present the curves for implant loss-free survival analysis. Only patients with massive axillary involvement, i.e., four or more involved lymph nodes, were associated with the risk of implant loss (logrank  $p < 0.05$ ).

In Table 3 we show the Cox survival model, whose dependent variable is implant extrusion. In the model, it was possible to verify that only the degree of axillary involvement (four or more involved lymph nodes) was associated with an increased risk of implant extrusion.

## DISCUSSION

Recently, skin-sparing mastectomies have been widely used worldwide for the treatment of breast cancer patients, recognized for the impact of breast reconstruction on the quality of life of female cancer survivors<sup>5</sup>.

For decades, reconstruction with a submuscular prosthesis was considered the most viable<sup>7-9</sup>. The first reports of the prepectoral technique date back to the 1970s, when it was strongly associated with the occurrence of implant loss, capsular contracture, and flap necrosis<sup>12,13</sup>. In recent years, however, its improvement has led to new discussions on the subject, as its application has less relation to postoperative pain and there are no repercussions on the functionality of the pectoralis major muscle, in addition to the techniques having comparable complication rates<sup>8,14-16</sup>.

In this study, acellular dermal matrix or similar material was not used to cover the implant in any of the reconstruction subgroups, considering that there is already research data that supports such practice, demonstrating that there is no increase in the complication rate, in addition to reducing costs and surgery time<sup>8,9,16</sup>. The implant loss rate (12%) in the general population of this study is compatible with that observed in other publications and does not present a statistically significant difference between the subgroups of each technique ( $p = 0.3$ )<sup>15-20</sup>.



**Table 1.** Epidemiological and clinical characteristics stratified by surgical reconstruction technique used.

Variables	Total n=66* (%)	Prepectoral n=36* (%)	Subpectoral n=30* (%)	p-value†
Age (years)	48 (41–53)	48 (41–54)	48 (44–52)	0.7
Age group (years)				
≤45	28 (42)	15 (42)	13 (43)	0.9
>45	38 (58)	21 (58)	17 (57)	
BMI (kg/m <sup>2</sup> )	25.8 (23.7–27.9)	24.5 (22.2–26.8)	27.0 (25.1–28.8)	<b>0.002</b>
BMI category (kg/m <sup>2</sup> )				
<25	25 (38)	19 (53)	6 (20)	<b>0.006</b>
≥25	41 (62)	17 (47)	24 (80)	
Smoking habit				
No	61 (94)	33 (92)	28 (97)	0.6
Yes	4 (6.2)	3 (8.3)	1 (3.4)	
Unknown	1	0	1	
Clinical staging (TNM)				
Stages 0 and I	18 (30)	11 (32)	7 (26)	0.6
Stages II and III	43 (70)	23 (68)	20 (74)	
NA	5	2	3	
Type of surgery				
Prophylactic	5 (7.6)	2 (5.6)	3 (10)	0.7
Therapeutic	61 (92)	34 (94)	27 (90)	
Laterality				
Right	31 (47)	17 (47)	14 (47)	>0.9
Left	35 (53)	19 (53)	16 (53)	
Type of incision				
Periareolar	14 (21)	3 (8.3)	11 (37)	<b>&lt;0.001</b>
Radial	6 (9.1)	0 (0)	6 (20)	
Inframammary fold	33 (50)	33 (92)	0 (0)	
Inverted T	13 (20)	0 (0)	13 (43)	
Histology				
Normal breast	5 (7.6)	2 (5.6)	3 (10)	0.8
Invasive carcinoma	53 (80)	29 (81)	24 (80)	
DCIS	8 (12)	5 (14)	3 (10)	
Histologic grade				
I	15 (25)	7 (21)	8 (30)	0.5
II	33 (54)	18 (53)	15 (56)	
III	13 (21)	9 (26)	4 (15)	
NA	5	2	3	
IHC				
HR(-)/HER2(3+)	10 (16)	4 (12)	6 (22)	0.2
HR(-)/HER2(neg)	5 (8.2)	4 (12)	1 (3.7)	
HR(+)/HER2(3+)	12 (20)	9 (26)	3 (11)	
HR(+)/HER2(neg)	34 (56)	17 (50)	17 (63)	
NA	5	2	3	

Continue...

**Table 1.** Continuation.

Variables	Total n=66* (%)	Prepectoral n=36* (%)	Subpectoral n=30* (%)	p-value†
Focality				
Multifocal	15 (25)	9 (26)	6 (22)	0.7
Unifocal	46 (75)	25 (74)	21 (78)	
NA	5	2	3	
Margin assessment				
Free	59 (97)	32 (94)	27 (100)	0.5
Involved (superficial)	2 (3.3)	2 (5.9)	0 (0)	
NA	5	2	3	
Axillary surgery				
Not performed	7 (11)	3 (8.3)	4 (13)	0.4
SLNB	47 (71)	28 (78)	19 (63)	
Lymph node excision	12 (18)	5 (14)	7 (23)	
Number of dissected lymph nodes				
≤4	47 (71)	27 (75)	20 (67)	0.5
>4	19 (29)	9 (25)	10 (33)	
Number of involved lymph nodes				
≤4	63 (95)	35 (97)	28 (93)	0.6
>4	3 (4.5)	1 (2.8)	2 (6.7)	
Prosthesis size (cc)	418 (360–475)	380 (339–429)	440 (414–508)	<0.001
Breast weight (g)	352 (262–482)	276 (222–347)	499 (387–663)	<0.001
Surgery time (minutes)	145 (116–199)	123 (110–153)	195 (145–253)	<0.001
Symmetrization				
No	40 (61)	27 (75)	13 (43)	0.009
Yes	26 (39)	9 (25)	17 (57)	
Adjuvant radiotherapy				
No	40 (61)	22 (61)	18 (60)	>0.9
Yes	26 (39)	14 (39)	12 (40)	
Neoadjuvant CT				
No	35 (53)	18 (50)	17 (57)	0.6
Yes	31 (47)	18 (50)	13 (43)	
Implant extrusion				
Yes	8 (12)	6 (17)	2 (6.7)	0.3
No	58 (88)	30 (83)	28 (93)	
Time until extrusion (days)	146.8 (27–391)	180 (84–391)	48.5 (27–70)	0.066
Staff				
A	21 (32)	15 (42)	6 (20)	0.074
B	21 (32)	8 (22)	13 (43)	
C	9 (14)	7 (19)	2 (6.7)	
D	7 (11)	2 (5.6)	5 (17)	
E	8 (12)	4 (11)	4 (13)	

BMI: Body Mass Index; NA: Not applicable; DCIS: ductal carcinoma in situ; IHC: immunohistochemical profile; SLNB: sentinel lymph node biopsy; CT: chemotherapy.

\*Absolute numbers: interquartile range and frequencies; †Student's t-test or Mann-Whitney test; Fisher's Exact Test or  $\chi^2$  of independent samples. Bold indicates statistically significant p-values.

**Table 2.** Characterization of variables according to the outcome of extrusion versus no implant extrusion.

Variables	Total n=66* (%)	With extrusion n=8* (%)	No extrusion n=58* (%)	p-value†
Age (years)	48 (41–53)	51 (43–54)	48 (41–53)	0.8
Age group				
≤45	28 (42)	3 (38)	25 (43)	>0.9
>45	38 (58)	5 (63)	33 (57)	
BMI (kg/m <sup>2</sup> )	25.8 (23.7–27.9)	26.1 (24.5–27.6)	25.8 (23.5–27.9)	0.8
BMI category				
<25	25 (38)	3 (38)	22 (38)	>0.9
≥25	41 (62)	5 (63)	36 (62)	
Smoking habit				
No	61 (94)	7 (88)	54 (95)	0.4
Yes	4 (6.2)	1 (13)	3 (5.3)	
Unknown	1	0	1	
Type of surgery				
Prophylactic	5 (7.6)	0 (0)	5 (8.6)	>0.9
Therapeutic	61 (92)	8 (100)	53 (91)	
Histology				
Normal breast	5 (7.6)	0 (0)	5 (8.6)	0.6
Invasive carcinoma	53 (80)	8 (100)	45 (78)	
DCIS	8 (12)	0 (0)	8 (14)	
Histologic grade				
I	15 (25)	1 (13)	14 (26)	0.6
II	33 (54)	6 (75)	27 (51)	
III	13 (21)	1 (13)	12 (23)	
NA	5	0	5	
IHC				
HR(-)/HER2(3+)	10 (16)	2 (25)	8 (15)	0.7
HR(-)/HER2(neg)	5 (8.2)	0 (0)	5 (9.4)	
HR(+)/HER2(3+)	12 (20)	2 (25)	10 (19)	
HR(+)/HER2(neg)	34 (56)	4 (50)	30 (57)	
NA	5	0	5	
Clinical staging (TNM)				
Stages 0 and I	18 (30)	1 (13)	17 (32)	0.4
Stages II and III	43 (70)	7 (88)	36 (68)	
NA	5	0	5	
Focality				
Multifocal	15 (25)	2 (25)	13 (25)	>0.9
Unifocal	46 (75)	6 (75)	40 (75)	
NA	5	0	5	
Laterality				
Right	31 (47)	2 (25)	29 (50)	0.3
Left	35 (53)	6 (75)	29 (50)	

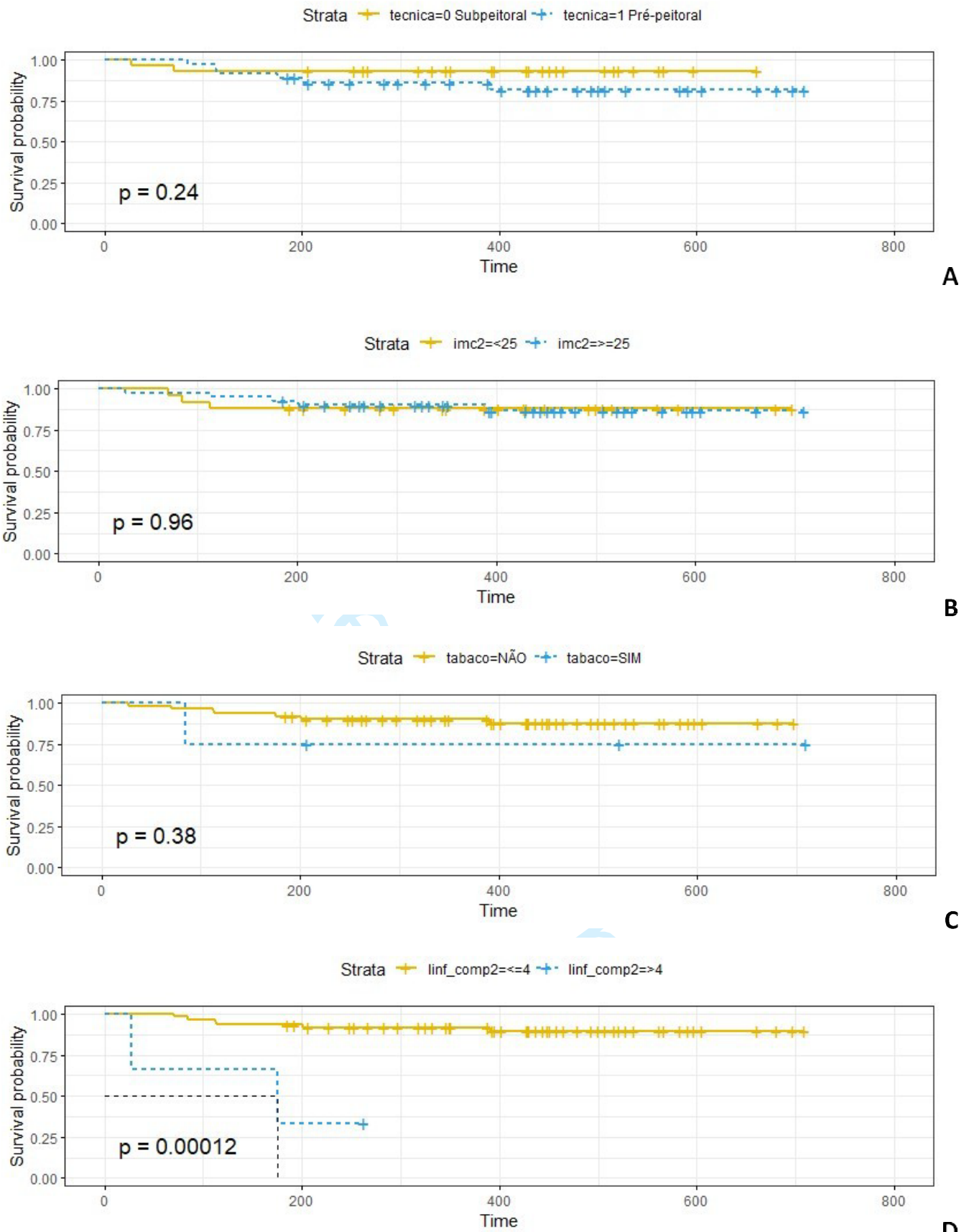
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**Table 2.** Continuation.

Variables	Total n=66* (%)	With extrusion n=8* (%)	No extrusion n=58* (%)	p-value†
Type of incision				
Periareolar	11 (17)	1 (13)	10 (17)	0.8
Radial ULQ	6 (9.1)	0 (0)	6 (10)	
Inframammary fold	36 (55)	6 (75)	30 (52)	
Inverted T	13 (20)	1 (13)	12 (21)	
Margin				
Free	59 (97)	7 (88)	52 (98)	0.2
Involved (superficial)	2 (3.3)	1 (13)	1 (1.9)	
NA	5	0	5	
Axillary surgery				
Not performed	7 (11)	0 (0)	7 (12)	0.010
SLNB	47 (71)	3 (38)	44 (76)	
Lymph node excision	12 (18)	5 (63)	7 (12)	
Number of dissected lymph nodes				
≤4	47 (71)	5 (63)	44 (76)	0.7
>4	19 (29)	3 (38)	16 (28)	
Number of involved lymph nodes				
≤4	63 (95)	6 (75)	57 (98)	0.037
>4	3 (4.5)	2 (25)	1 (1.7)	
Prosthesis size (cc)	418 (360–475)	465 (370–506)	410 (360–469)	0.4
Breast weight (g)	352 (262–482)	407 (243–455)	349 (262–508)	>0.9
Breast weight				
<425	43 (65)	4 (50)	39 (67)	0.4
≥425	23 (35)	4 (50)	19 (33)	
Surgery time (minutes)	145 (116–199)	160 (119–209)	145 (116–195)	0.7
Symmetrization				
No	40 (61)	6 (75)	34 (59)	0.5
Yes	26 (39)	2 (25)	24 (41)	
Adjuvant radiotherapy				
No	40 (61)	4 (50)	36 (62)	0.7
Yes	26 (39)	4 (50)	22 (38)	
Neoadjuvant chemotherapy				
No	35 (53)	2 (25)	33 (57)	0.13
Yes	31 (47)	6 (75)	25 (43)	
Technique				
Subpectoral	30 (45)	2 (25)	28 (48)	0.3
Prepectoral	36 (55)	6 (75)	30 (52)	
Staff				
A	21 (32)	3 (38)	18 (31)	0.2
B	21 (32)	1 (13)	20 (34)	
C	9 (14)	3 (38)	6 (10)	
D	7 (11)	0 (0)	7 (12)	
E	8 (12)	1 (13)	7 (12)	

BMI: Body Mass Index; DCIS: ductal carcinoma in situ; NA: Not applicable; IHC: immunohistochemical profile; ULQ: upper lateral quadrant; SLNB: sentinel lymph node biopsy.

\*Median (interquartile range); †Wilcoxon test; Fisher's exact test. Bold indicates statistically significant p-values.



**Figure 1.** Implant loss-free survival. A: prepectoral technique vs. subpectoral technique; B: BMI 25; C: smoking habit yes vs. no; D: No. of involved lymph nodes  $\leq 4$  vs.  $> 4$ .



**Table 3.** Cox survival model analysis relating time to outcome (implant extrusion) with independent variables.

Variables	No. of events	HR	95%CI	p-value	q-value*
Age group (years)	8			0.25	0.56
≤45		—	—		
>45		2.91	0.44–19.1		
BMI (kg/m <sup>2</sup> )	8			0.51	0.57
<25		—	—		
≥25		0.52	0.07–3.71		
Neoadjuvant CT	8			0.24	0.56
No		—	—		
Yes		3.60	0.38–34.0		
Adjuvant radiotherapy	8			0.40	0.57
No		—	—		
Yes		2.25	0.33–15.2		
Surgical technique	8			0.28	0.56
Subpectoral		—	—		
Prepectoral		5.19	0.20–135		
Surgery time (minutes)	8	1.00	0.99–1.02	0.48	0.57
Number of dissected lymph nodes	8			0.31	0.56
≤4		—	—		
>4		0.26	0.01–4.71		
Number of involved lymph nodes	8			<b>0.007</b>	<b>0.075</b>
≤4		—	—		
>4		76.6	2.29–2-558		
Clinical staging (TNM)	8			0.43	0.57
0-I		—	—		
II-III		2.61	0.21–32.1		
Smoking habit	8			0.090	0.49
No		—	—		
Yes		16.3	0.91–294		
Breast weight (g)	8	1.00	1.00–1.01	0.71	0.71

\*False discovery rate for multiple tests.

HR: hazard ratio; CI: confidence interval; BMI: Body Mass Index; CT: chemotherapy; Bold indicates statistically significant p-values.

Among the factors linked to the demographic profile that may be associated with an increased rate of complications are high BMI (over 30 kg/m<sup>2</sup>) and breast weight<sup>3,14,16</sup>. In the present analysis, the general profile of the sample was similar to that of other publications and there was no statistical relevance in the comparison of patients who had or did not have extrusion ( $p=0.51$  for BMI and  $p>0.71$  for breast weight), similar to the results demonstrated by Hassan et al., 2021 who, despite finding a higher occurrence of implant loss in the group with higher BMI, did not demonstrate statistical significance<sup>21</sup>.

In the comparative analysis of the subgroups, it was evident that patients who underwent subpectoral reconstruction had significantly higher BMI and breast weight, with  $p=0.002$  and

0.001, respectively, as described by Sbitany et al.<sup>22</sup> The prosthesis size was also relevant in this comparison, with a larger prosthesis size in the subpectoral reconstruction group, with  $p<0.05$ . As this is a real-life, retrospective, cohort study, the selection of patients for each reconstruction technique was at the surgeon's discretion. Thus, there is selection bias between the groups, with a predominance of smaller breasts and implants in the prepectoral group. This fact was expected because this reconstruction technique is more commonly indicated for patients with smaller breasts and absent ptosis or ptosis up to grade 2<sup>9</sup>.

Based on morphological criteria, patients with larger breasts require larger volume prosthesis for reconstruction. This fact alone has a greater relationship with the risk of flap ischemia due

to compression of the subdermal vessels<sup>22</sup>. Greater volume and increased ptosis are other factors that lead to an increased risk of ischemia and necrosis of the skin and NAC, therefore requiring an additional layer for protection, suggesting the indication for submuscular reconstruction<sup>14</sup>.

The median age in the assessed population was 48 years and, in the subgroup analysis, there was no statistical difference in this regard ( $p=0.7$ ). The relationship between age above or below 45 years of women with or without extrusion was also not significant ( $p=0.8$ ). Advanced age is a recognized factor associated with a higher incidence of complications<sup>23</sup>. However, although this population demonstrated similarity with those of other studies, the relevance of this factor for extrusions was not demonstrated in these studies<sup>21,23</sup>. In the present research, advanced age did not represent a contraindication for reconstructions. The evaluation of indication depended on the surgeon's judgment regarding the performance status of each individual and the observation of other associated risk factors.

Smoking habit was reported by only 6.2% of patients, having low representation in this sample. The rates for this datum vary according to the time and location of the study<sup>24</sup>. In Brazil, the prevalence of smoking has decreased over the years<sup>25</sup>. Its greater association with the risk of ischemic complications and implant loss makes it a relative contraindication, which may also have impacted the decision regarding the indication for reconstruction in this population<sup>9,14,23,26</sup>.

Prepectoral reconstructions were associated with a lower rate of contralateral symmetrization when compared to subpectoral reconstructions (25% versus 57%,  $p=0.009$ ), in addition to shorter surgical time ( $p=0.001$ ), as shown by Franceschini et al.<sup>9</sup> The correlation of shorter time of the prepectoral technique can be justified by the lack of need for dissection of the submuscular space for insertion of the prosthesis and by the lower number of contralateral breast symmetrization. In this technique, the occupation of the gland's own anatomical space by the prosthesis provided a more natural aesthetic appearance, simulating contour and ptosis similar to its previous conformation<sup>14-16</sup>.

In subpectoral reconstructions, the least common incision was the radial one (9.1%), possibly due to its recurrent relationship with displacement of the NAC due to scar retraction that is apparent in the anterior view, leading to an unfavorable aesthetic result<sup>20,27,28</sup>. Periareolar incisions (37%), still highly recommended due to good access for mastectomy, axillary approach, and creation of the submuscular pocket, maintain the inconvenience of the scar in the anterior view and are losing preference<sup>29</sup>.

In the subpectoral reconstruction population, there was a greater number of women with large breasts and, consequently, higher levels of ptosis, as such factors are related to a greater risk of complications in prepectoral reconstruction<sup>9,14,22</sup>. These characteristics indicate a greater possibility of the need for resection

of excess skin, justifying a high rate of reduction mammoplasty-type incisions (43%) for a better aesthetic result<sup>20,30</sup>.

Incisions through the inframammary fold were sometimes associated with greater risks due to the supposed greater tension in the suture line, as well as the possibility of venous congestion and circulatory deficit in the lower area of the flap, but in this population this datum was not relevant regarding the risk of extrusion ( $p=0.46$ )<sup>31</sup>. This incision was the most commonly chosen, applied in all prepectoral reconstructions, and it was not significant regarding the association with risk of extrusion (OR 2.00; 95%CI 0.29–40.2 and  $p=0.46$ ), as shown in other publications<sup>10,32</sup>. This preference is justified by providing good access for performing the procedure, a scar in a barely visible location, and preservation of the positioning of the NAC<sup>20,27,28</sup>.

Variables linked to complementary treatment, such as exposure to radiotherapy and chemotherapy, are known risk factors for prosthesis extrusion<sup>3,8,21</sup>. In this research, neither of these two factors had statistical relevance regarding extrusion, either through univariate analysis or the Cox model, results similar to recent publications<sup>9,31,33</sup>. The decrease in the effects of complementary therapies on implant loss rates may be related to the evolution of surgical techniques used, as well as the consolidation of knowledge of oncological safety in conservative mastectomies<sup>5,22</sup>.

Researchers of most publications demonstrate correlations of factors linked to the individual or the treatment regarding their influence on complications or describe complication rates in a population undergoing one of the reconstruction techniques<sup>3,34,35</sup>. As for tumor characteristics, there are few studies discussing their relevance regarding the influence on complication rates. In this context, characteristics — such as tumor type, histologic grade, immunohistochemical expression, and focality — were detailed in the present study. Invasive ductal carcinoma of no special type (IDC) was the most frequent type (61%), as described in other populations<sup>3,31,35</sup>. In the univariate analysis, this aspect was not statistically significant ( $p=0.2$ ), corroborating Blok et al.<sup>35</sup>. Histologic grade, immunohistochemical expression, and focality were also irrelevant for the analyzed outcome. These results allow us to assume that tumor characteristics are in the background regarding the influence on the risk of extrusion.

Among other aspects evaluated in this analysis, the type of axillary approach has statistical relevance according to the univariate analysis, as 63% of prosthesis losses occurred in patients who underwent axillary lymph node excision ( $p=0.01$ ) and in those who presented a greater number of involved lymph nodes ( $p=0.037$ ). Jafferbhoy et al., demonstrated similar data, however, they did not analyze characteristics such as staging or volume of tumor involvement, variables directly linked to the indication of this type of axillary approach<sup>6</sup>. Within this context, women who had only neoplasia *in situ* (12%) did not have extrusion, and among those clinically staged at 0 and I, only one evolved with implant loss. Thus, when the clinical stage was related to

the outcome, more than half of the events occurred in patients classified as stage II and III. Elswick et al., reached conflicting results regarding complication rates, such as higher necrosis and dehiscence rates in the group of patients undergoing adjuvant radiotherapy, in a population in which 50% of patients were classified as stage III<sup>34</sup>.

Another relevant aspect was the degree of axillary involvement in the histopathological analysis. In this case, there was a significance with a predominance in those who had a smaller volume of axillary disease, that is, up to four involved lymph nodes ( $p=0.037$ ). However, only three women had high lymph node involvement. Therefore, these factors were included in the multivariate analysis in order to clarify discordant results.

Based on preestablished clinical criteria, variables related to a higher risk of postoperative breast complications were included in a multivariate analysis using the Cox survival model, in which a statistical correlation was observed with the degree of axillary involvement, reinforcing the assumption linked to the clinical stage. The group with greater axillary involvement ( $>4$  lymph nodes) presented a higher risk ratio (HR 2.29; 95%CI 2.5–58). This datum indicates that axillary tumor volume may represent a risk factor for implant loss in single-stage immediate breast reconstructions. Nonetheless, individuals with this involvement profile are also included in the list of indications for chemotherapy and radiotherapy, possible confounding factors<sup>36,37</sup>.

These aspects, despite not having demonstrated significance in this analysis, are widely correlated with the outcome according to previous analyses<sup>31,38</sup>. Therefore, it is necessary to include variables linked to the clinical stage and tumor volume in the final histopathological analysis, in studies with a larger population and more extrusion events.

## CONCLUSIONS

Immediate reconstruction after skin- and nipple-sparing mastectomy with prepectoral implant placement without the use of cell dermal matrix was not associated with a higher risk of extrusion when compared with the submuscular technique. Large axillary involvement was the only factor associated with implant loss in this population. The study results may be limited by sample selection bias.

## AUTHORS' CONTRIBUTION

PLC: Data curation, Formal analysis, Writing – original draft. YCMSR: Supervision, Validation. GMC: Supervision, Validation, Writing – review & editing. AGCO: Supervision, Validation, Writing – review & editing. RAV: Supervision, Validation. JPG: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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


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# Temporal changes in the incidence of ductal carcinoma *in situ* in Goiânia, Brazil: a population-based study

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## ABSTRACT

**Introduction:** Mammography screening has resulted in a considerable increase in the diagnosis of early-stage tumors in various countries. However, most available data refer to high-income countries, hospital-based studies, or studies with limited follow-up. Therefore the aim of this study was to determine the incidence of ductal carcinoma in situ (DCIS) in Goiânia, Brazil. **Methods:** Ecological study among residents of the city of Goiânia, Brazil. We included all the DCIS cases registered at the Goiânia population-based cancer registry between 1994 and 2010. Crude incidence and age-standardized incidence rates (using the world standard population) were calculated. Poisson regression was used to analyze temporal changes, with the average annual percent change (AAPC) in the crude and age-standardized incidence rates being calculated. **Results:** There were 261 cases of DCIS, with an annual incidence rate that ranged from 0.58 to 4.21 per 1,000 women (crude and standardized) over the period. The number of cases of DCIS in the 40–49 and 60–69-years age groups increased significantly ( $p < 0.01$ ). The AAPC of the crude incidence rate for the period was 11.88% per year (95%CI 9–15;  $p < 0.01$ ) and the standardized rate was 11.89% per year (95%CI 9–15;  $p < 0.01$ ). **Conclusions:** The incidence of DCIS in Goiânia increased between 1994 and 2010, possibly due to improved mammography screening. The present study, which was conducted in a consolidated population-based cancer registry (PBCR) and involved an extensive follow-up time, could contribute towards increasing epidemiological knowledge on DCIS and its variations around the world.

**KEYWORDS:** breast carcinoma in situ; breast neoplasms; incidence; epidemiology; cesium.

## INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is a form of breast cancer characterized by abnormal cell proliferation confined within the basement membrane. It may present with extensive ductal involvement and lesions that render differential diagnosis difficult.<sup>1,2</sup> Since DCIS is considered a precursor lesion, a reduction was expected in breast cancer incidence and mortality following the advances made in the approach to DCIS over recent decades.

However, even with an estimated 50,000–60,000 surgical procedures performed annually to resect DCIS, controversies remain regarding the progression of the disease and its epidemiological variations.<sup>3,4</sup>

The incidence of DCIS has increased expressively over recent years, perhaps as the result of the consolidation of population-based mammography screening programs and of the advances made in diagnostic methods.<sup>2,5,6</sup> Nevertheless, there are major

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differences in the rates found in different countries, with less developed countries tending to have relatively lower values. However, in less developed countries, most of the data on DCIS originate from retrospective, hospital-based studies, with incidence rates that range from 2.5 to 24.4%.<sup>7-9</sup> In this respect, the lack of data originating from population-based studies hampers understanding of the disease and the creation of specific public policies.<sup>8</sup>

Since PBCRs record incident cases of cancer in a defined population over a period of time, their use in real-world studies allows a wider exploratory data analysis to be conducted and includes the possibility of external validation. The city of Goiânia, situated in midwestern Brazil, has the longest continuously operating PBCR in the country.<sup>10</sup> Therefore, the objective of the present study was to determine the temporal changes in the incidence of DCIS at a PBCR in midwestern Brazil.

## METHODS

An ecological study was conducted between January 1994 and December 2010 on women with DCIS. This period was chosen due to the completeness of the 10-year overall survival data, which will be reported in another study. The cases were extracted from the database of the Goiânia PBCR where data on all new cases of cancer in the municipality are collected and recorded. This PBCR was developed in 1986, and has uninterruptedly been registering all new cases of cancer in residents of the municipality of Goiânia since its creation.<sup>10</sup>

### Cases

All cases registered as DCIS that were diagnosed in the city of Goiânia between 1994 and 2010 were included in the study. Following analysis, cases in which the women had only moved to the city after being diagnosed (untrue city residents), cases for which there was a bias in data collection (inconclusive information), and any cases in which DCIS was associated with an invasive or micro-invasive carcinoma were excluded from the study sample.<sup>11</sup>

### Variables

The patients were divided into the following age groups: 30–39 years, 40–49 years, 50–59 years, 60–69 years and ≥70 years. Data regarding the size of the lesion (taking into consideration the largest measurement in centimeters) and nuclear grade were obtained from the surgical pathology reports. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expressions were classified as positive or negative with respect to the initial *in situ* lesion, in accordance with the description on the immunohistochemical report.

### Statistical analysis

The database was created using Excel, version 2003 (Microsoft Corporation, Redmond, WA, USA). The frequency of all the

variables was determined and the analysis of central tendency was performed whenever pertinent.

The crude incidence rate was defined as the ratio between the number of new cases of breast cancer *in situ* diagnosed annually and the number of women exposed to the risk of developing the disease at the midpoint of the respective year, with the result being expressed as a coefficient per 100,000 women.<sup>12</sup> The female population of Goiânia considered to have been exposed to the risk of cancer was calculated for each respective year based on the population census data for 1991, 2000 and 2010 and on the intercensal data for the other years.<sup>13</sup> The annual standardized incidence rate was calculated for each age group based on the world standard population according to Doll and Cook.<sup>14</sup>

The temporal changes in the incidence of DCIS were analyzed using Poisson jointpoint regression model (JoinPoint Regression, version 4.3.0, the National Cancer Institute, USA).<sup>15</sup> The average annual percent change (AAPC) in the crude incidence rate and in the age-standardized incidence rate was calculated. The 95% confidence intervals (95%CI) were calculated and p-values < 0.05 were considered statistically significant. Statistical Package for the Social Sciences (SPSS) for Windows, version 13.0 (IBM Corp, Armonk, NY, USA) was used for the other statistical analyses.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Ethics Committee approved the study protocol with the register number 1.940.921 (CAAE 64258216.5.0000.5078). This study fully complies with the current law of the country in which it was conducted.

## RESULTS

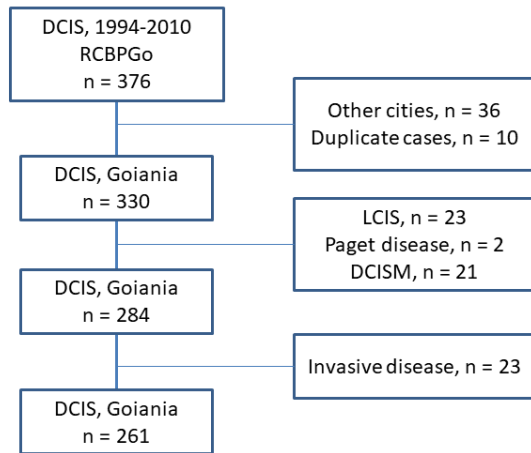
### Characterization of the sample

Between 1994 and 2010, 376 cases of carcinoma *in situ* were identified; however, 115 of these cases (44%) were excluded either because they did not comply with the classification of DCIS or due to missing data. A total of 261 cases of DCIS were included in the analysis (Figure 1).

Most of the cases of DCIS registered in Goiânia occurred in women of 40 to 49 years of age (n=80), with peak registration occurring in 2009 (n=38). Tumor size was described in 51% of the surgical pathology reports, with mean size being 1.4 cm. The classification of nuclear grade was described in 68% of the reports, with 19% of the cases of DCIS being classified as grade I, 44% as grade II, and 37% as grade III. Immunohistochemical reports were available from 139 cases (49%). Of these, 56% were estrogen receptor (ER) and/or progesterone receptor (PR) positive, 26% were HER-2 positive, and 4% were triple-negative (Table 1).

## Incidence

While in the 1994-2010 period 5,277 cases of invasive breast cancer were registered, with an increase from 155 cases in 1994 to 425 in 2010, there were four cases of DCIS in 1994 and 21 in 2010. For the cases of DCIS, an increase of 425% was found in relation to the first year, while cases of invasive breast cancer had an increment of 174% over the same period (Figure 2). Considering the total



DCIS: ductal carcinoma *in situ*  
RCBPGO: Registro de Câncer de Base Populacional de Goiânia  
LCIS: Lobular Carcinoma *in situ*

**Figure 1.** Flowchart of patients included in the study.

**Table 1.** Characteristics of the primary tumor as retrieved from the surgical pathology and immunohistochemical reports.

Characteristics	n (%)
Age (years)*	54.21±12.30
Tumor size (cm)*	1.39±1.69
Nuclear grade	
Low (I)	31 (18.3)
High (II/III)	138 (81.7)
Total	169
Estrogen receptor	
Positive	94 (75.8)
Negative	30 (24.2)
Total	124
Progesterone receptor	
Positive	80 (66.1)
Negative	41 (33.9)
Total	121
HER2	
Positive	36 (30.8)
Negative	81 (69.2)
Total	117

\*Mean±standard deviation. HER2: human epidermal growth factor receptor 2.

number of cases, the relative rate of DCIS was 4.94% (261/5,277). This increase was confirmed from the AAPC, both for DCIS and for invasive carcinomas, corresponding to 15.5 (95%CI 12.5–18.7) and 7.2 (95%CI 6.0–8.5), respectively ( $p<0.01$ ).

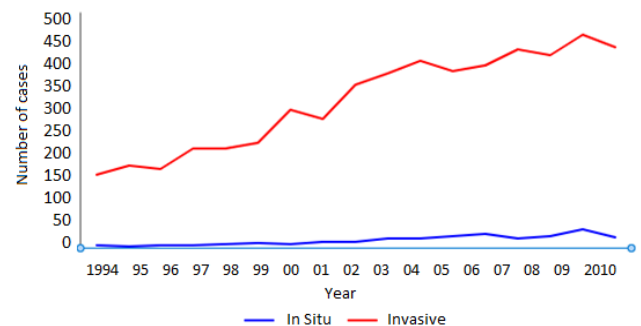
The crude annual incidence rate of DCIS was 1.33/100,000 in 1994, and 4.21/100,000 in 2010. The incidence rate adjusted for the Doll and Cook<sup>14</sup> world standard population was 0.58/100,000 in 1994, and 1.85/100,000 in 2010. There was an annual increase both in the crude incidence rate of 11.93% (95%CI 9–15;  $p<0.01$ ) and in the standardized rate of 11.94 (95%CI 9–15;  $p<0.01$ ).

Stratifying the incidence for each 10-year age group, a significant growth was found in the number of cases of DCIS for the 40-49 years and 60-69 years age groups ( $p<0.01$ ). The crude incidence rates and those standardized according to age are shown in Table 2 for 1994 and 2010 according to age groups and with the respective AAPC for each rate.

## DISCUSSION

The incidence of DCIS has increased expressively in recent years, possibly as a result of the consolidation of population-based mammography screening programs and the advances made in diagnostic methods.<sup>2,6,8</sup> In Brazil, according to a telephone survey conducted with almost 268,000 individuals, mammography coverage in the country increased from 71% to 78% between 2007 and 2016.<sup>16</sup> Nevertheless, there is a huge difference between the rates found in different countries, with low-to-middle income countries tending to have a relatively low incidence rate compared to developed countries.<sup>3,7-9</sup> The present study, which was conducted in a consolidated PBCR and involved an extensive follow-up time, could contribute towards elevating epidemiological knowledge on DCIS and its variations around the world.

In the United States, according to data from the Surveillance, Epidemiology and End Results (SEER) program, the incidence of DCIS had a rapid growth following the introduction of mammography screening in the 1980s. Nevertheless, despite the stabilization



**Figure 2.** Evolution of the number of cases of carcinoma in situ and invasive carcinoma, in residents of Goiânia, over the years studied.

**Table 2.** The average annual percent change in the crude incidence rate and in the age-standardized incidence rate of ductal carcinoma *in situ* in the city of Goiânia (GO) between 1994 and 2010.

Age group (years)	Crude rate by age group*				Age-standardized incidence rate*			
	1994	2010	AAPC (95%CI)	p-value	1994	2010	AAPC (95%CI)	p-value
30–39 <sup>†</sup>	1.24	1.71	-	-	0.15	0.21	-	-
40–49	1.99	5.23	6.19 (2.0–10.5)	<0.01	0.24	0.63	6.21 (2.0–10.6)	<0.01
50–59	6.06	6.36	7.46 (-0.3–15.8)	0.07	0.55	0.57	7.49 (-0.3–15.9)	0.07
60–69	0	12.40	10.35 (4.3–16.8)	<0.01	-	0.87	10.35 (4.2–16.8)	<0.01
≥70	0	12.69	10.13 (-2.5–24.4)	0.11	-	0.51	10.31 (-2.5–24.8)	0.09

AAPC: average annual percent change; 95%CI: 95% confidence interval; \*Incidence rates per 100,000 women; <sup>†</sup>For the 30-39 years age group, analysis of the AAPC proved impossible since no cases were registered in some of the periods analyzed; There was only one case under 30 years of age over the entire period evaluated, making analysis of the AAPC impossible.

of screening rates over the past ten years, an AAPC of 0.8% was seen in the incidence of DCIS between 1992 and 2011.<sup>3</sup> In the present study, an increase of 425% was found in the standardized incidence rate of DCIS, which ranged from 0.58/100,000 in 1994 to 1.85/100,000 in 2010. Over the same period, the incidence of invasive carcinoma increased 174%. Possible explanations for this difference in proportion include the transition from analogical mammography to digital mammography and the improvement of other diagnostic methods, which could have increased the detection of early lesions.<sup>2,3</sup> In low-to-middle income countries, this improvement in technology occurred much later and is still occurring in some regions, explaining the elevated trend of a rise in relation to the US data for the same period.<sup>3</sup> Furthermore, expanded knowledge on the histology of the disease and other initiatives involving quality control in mammography could also have contributed to this increase in incidence between 1994 and 2010.<sup>1,2,17</sup>

The incidence of DCIS also varied according to age, race and other clinical factors. In the United States, where there is less racial miscegenation compared to the Brazilian population, a different distribution of prognostic factors was found between the racial groups analyzed, together with different incidence rates.<sup>3,5</sup> In the evaluation by age group, the correlation between the reduction in DCIS in women of 50-69 years of age between 2002 and 2006 and the reduction in the prescription of combined hormone replacement therapy following publication of the Women's Health Initiative (WHI) study merits particular attention.<sup>3,18</sup> In the same period, there was no statistically significant difference in the incidence curve in women of 40 to 49 years of age.<sup>18</sup> These data differ from those found in the present study, possibly due to different genetic factors or risk exposures.<sup>19</sup> Furthermore, the occurrence of DCIS in the over-70s (9.5%), an age group that is excluded from the majority of screening guidelines worldwide is also noteworthy.<sup>20,21</sup> Despite questioning on

over-diagnosis and overtreatment in this population,<sup>22</sup> this is a very heterogenous group in which screening should be individualized in accordance with clinical status rather than chronological age alone.<sup>23</sup>

Considering age at diagnosis, women with DCIS also tend to be diagnosed at a younger age compared to those with an invasive carcinoma. While invasive disease is more prevalent in the 50 to 59-year age group,<sup>9,24</sup> DCIS appears to be more prevalent in women of 40 to 49 years of age. These data reinforce the theory that DCIS is a precursor lesion that could take up to ten years to invade the basement membrane and the breast stroma. Nevertheless, the possibility that the carcinogenesis of DCIS is different from that of invasive carcinoma and that different factors could sometimes affect the biological behavior of these pathologies cannot be ruled out.<sup>1,2,25</sup>

Another interesting point in the incidence of DCIS in the city of Goiânia involves the radioactive contamination accident that occurred in 1987 and the possible increase in cancer cases resulting from exposure to ionizing radiation.<sup>26-28</sup> Considering a latency time of 10 years, peak incidence would be expected to occur in 1997, and this was not seen. Furthermore, the incidence rate of DCIS in the city of Goiânia was found to be similar to that of the other Brazilian state capital cities where the higher incidence over time has occurred gradually.<sup>29</sup> These data, along with the findings of other epidemiological studies conducted in the region, suggest that there is no association between the accident involving cesium-137 and the incidence of breast cancer and DCIS.<sup>27,28</sup>

In recent years, in addition to the growth in the incidence rates of DCIS, a favorable change has also been seen in tumor stage at the time of diagnosis. Different studies have evaluated breast cancer staging in Brazil and, despite the inherent limitations of retrospective studies, a wide variation was found in the effectiveness of mammography screening. In the city of Barretos,<sup>8</sup>

which has the best organized screening system in the country, the incidence rate of DCIS was much higher than that seen in the cities of Curitiba<sup>7</sup> and São Paulo,<sup>30</sup> with rates of 16.5%, 2.9% and 8.1%, respectively. In Goiânia, the relative rate of DCIS was only 5%, which is also proportional to the poor mammography coverage (14.7%) within the public healthcare system in the mid-western region of the country.<sup>31</sup>

The limitations of the present study include its retrospective design and the loss of 44% of the sample due to missing or contradictory data in the Goiânia PBCR database. These limitations, however, are inherent to population-based studies,<sup>14,32</sup> and do not affect the credibility or the relevance of the results found. On the other hand, the strongpoints of the study were the long follow-up time and the secondary verification of the surgical pathology data that give greater robustness and innovativeness to the study.

## CONCLUSIONS

The incidence of DCIS in the city of Goiânia increased between 1994 and 2010, possibly due to improved mammography screening. This increase differed as a function of the age groups analyzed and was relatively higher than the increase in the incidence of invasive carcinoma. Finally, the observed incidence was similar to the average in other regions, according to the literature.

## AUTHORS' CONTRIBUTION

NAFL: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing. CMBS: Conceptualization, Data curation, Formal analysis, Project administration, Software, Validation, Visualization, Writing – review & editing. MARM: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – review & editing. ECP: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – review & editing. NMAF: Conceptualization,

Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. JCO: Conceptualization, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. CMRG: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. MNB: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. JRMBJ: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. RFS: Conceptualization, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. RRP: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. LFPO: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. LRS: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RMSR: Conceptualization, Data curation, Methodology, Validation, Supervision, Writing – review & editing.

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# CDH1 methylation and expression of E-cadherin and other markers in breast cancer

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## ABSTRACT

**Introduction:** E-cadherin, encoded by the CDH1 gene, is a glycoprotein involved in cell adhesion, and the methylation of CDH1 can prevent the protein expression favoring tumor invasion. This study investigated the methylation of CDH1 in the DNA extracted from tumor and non-tumor tissues of breast cancer patients. In addition, the expression of E-cadherin, human epidermal growth factor receptor-2 (HER-2), estrogen receptor (ER), progesterone receptor (PR), and the marker of proliferation Ki-67 (Ki-67) was analyzed by immunohistochemistry. **Methods:** Samples of tumor and non-tumor breast tissues were collected from 15 women diagnosed with breast carcinoma at the time of mastectomy to analyze CDH1 methylation. The DNA was extracted, modified by the sodium bisulfite method, and amplified by polymerase chain reaction (PCR). The expression of E-cadherin, HER-2, ER, PR, and Ki-67 was evaluated by immunohistochemistry. **Results:** All the 15 patients had CDH1 methylation in the tumor tissue, and nine had CDH1 methylation in the non-tumor breast tissue. The immunohistochemical analysis showed that one patient had E-cadherin expression, three had HER-2, five had ER, six had PR, and nine had Ki-67. **Conclusions:** Our findings suggest that CDH1 gene methylation prevented E-cadherin expression in breast tumors once only one of the nine patients tested by immunohistochemical analysis showed the protein. The methylation of CDH1 in non-tumor breast tissues observed in nine patients may suggest the presence of infiltrating neoplastic cells or non-neoplastic genetically transformed cells.

**KEYWORDS:** cadherin-1; methylation; breast neoplasms; immunohistochemistry.

## INTRODUCTION

Cadherins, a large superfamily of transmembrane glycoproteins, are integral to cell adhesion and the maintenance of tissue architecture. Among them, E-cadherin, encoded by the *CDH1* gene, is an invasion suppressor, and its dysregulation or mutation can lead to cancer development<sup>1-3</sup>. E-cadherin imbalance is characteristic of several malignancies and is involved in tumor metastasis<sup>2,4</sup>. The protein is particularly significant in the context of invasive lobular carcinoma (ILC), which accounts for 10-15% of all breast cancers<sup>5</sup>. The absence of E-cadherin expression is a characteristic feature of *in situ* and ILCs.

DNA methylation is a biochemical process in which a methyl group (CH<sub>3</sub>) is added to the cytosine of a CG dinucleotide in the DNA sequence<sup>2</sup>. This epigenetic phenomenon can alter the gene

expression without modifying the base sequence. Aberrant methylation of *CDH1* can inactivate the gene, preventing E-cadherin expression<sup>2</sup>. A study demonstrated the inverse relationship between *CDH1* gene methylation and E-cadherin expression in 50 cases of both ductal-type breast cancer and normal breast samples. The study showed that 94% of ductal-type breast cancers had *CDH1* promoter methylation, and that 95% of full-methylated tumor samples had no E-cadherin expression<sup>6</sup>.

In addition to E-cadherin, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2), and the marker of proliferation Ki-67 (Ki-67) are essential markers in breast cancer. ER plays a critical role in the growth and development of breast tumors. More than 70% of breast cancers are ER positive, based on immunohistochemical analysis<sup>7,8</sup>. In these cases, the survival of patients can be improved

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by ER-positive therapy<sup>8</sup>. PR is a prognostic marker in breast cancer, and its high expression is more frequent in tumors with a better prognosis (luminal A) than in tumors with a worse prognosis (luminal B)<sup>9</sup>. HER-2 is a growth-promoting protein, and its excess or amplification of the *HER-2* gene is related to a poor prognosis of breast cancer<sup>10</sup>. Ki-67 is a protein associated with cell proliferation, and a high level of Ki-67 is often indicative of a more rapidly growing breast tumor<sup>11</sup>.

This study aimed to analyze the methylation status of the *CDH1* gene in tumor and non-tumor tissues of breast carcinoma patients. Furthermore, the expression of E-cadherin, ER, PR, HER-2, and Ki-67 was examined by immunohistochemistry. We investigated whether *CDH1* methylation inhibited the expression of E-cadherin in the studied patients.

## METHODS

### Study design and selection of patients

This prospective hospital-based study involved 15 women treated at the *Instituto de Ginecologia* of the *Universidade Federal do Rio de Janeiro*, Brazil. The age of the patients varied between 44 and 78 years (average age: 56.7±9.6 years). All of them were diagnosed with breast carcinoma and underwent mastectomy. Before the surgery, patients were interviewed and invited to participate in the study. Those who agreed to participate were provided with all the necessary information and signed a consent form.

### Data collection and ethical aspects

Patient recruitment occurred from October 2018 to July 2021. Demographic and clinical data were gathered from the patients' medical records. The study was approved by the Research Ethics Committee of the *Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro* (Certificate: CAAE #91406118.6.0000.5257, dated September 29, 2018).

### Collection of tissue samples

Tumor and non-tumor surrounding tissue fragments of around 1-2 cm in each axis were collected from the breast of patients at the time of mastectomy. The tissue samples were collected at the *Instituto de Ginecologia, Universidade Federal do Rio de Janeiro*.

### Extraction of DNA from tumor and non-tumor breast tissues

DNA extraction from tumor fragments and non-tumor breast tissues was performed using the phenol:chloroform method, as previously described by McCormick et al.<sup>12</sup>, using the UltraPure™ Phenol:Chloroform:Isoamyl Alcohol (Invitrogen, USA, Cat. No. 15593-031).

## Methylation mechanism

The DNA samples were modified by the sodium bisulfite conversion method and then analyzed by the methylation-specific polymerase chain reaction (MSP) technique. DNA modification was performed using the EZ DNA Methylation-Gold™ Kit (Zymo Research, USA, Cat. No. D5005), according to the manufacturer's instructions.

## Polymerase chain reaction

After the DNA modification, a fragment of exon 5 of the *P53* gene was amplified by polymerase chain reaction (PCR) to confirm the DNA integrity. The amplification reaction was performed as previously described by Pestaner et al.,<sup>13</sup> generating a 274-base-pair product. In the next step, the *CDH1* gene was amplified by PCR. For the *CDH1* amplification, two pairs of primers were used as follows: *CDH1*-U (unmethylated) forward, 5'-GGTAGGTGAATTTTGTAGTTAATTAGTGGTA-3' and *CDH1*-U reverse, 5'-ACCCATACTAACCAAAAACACCA-3', producing a fragment of 211 base pairs, and *CDH1*-M (methylated) forward, 5'-GGTGAATTTTGTAGTTAATTAGCGGTAC-3' and *CDH1*-M reverse, 5'-CATACTAACCGAAAACGCCG-3', producing a fragment of 204 base pairs<sup>14</sup>. The polymerase used was the GoTaq G2 Hot Start Green Master Mix (Promega, USA, Cat. No. M7422). The cycling included an initial denaturation at 96°C for 7 min, followed by 35 cycles of 95°C for 1 min, 62°C for 1 min, 72°C for 1 min, and a final extension at 72°C for 5 min.

## Gel electrophoresis and staining

The PCR products were run by electrophoresis in 10% polyacrylamide gel. A negative control and a DNA marker were included in each electrophoretic run. Gels were stained by the silver nitrate method involving DNA fixation with ethanol and acetic acid, impregnation with silver nitrate, and revelation of the DNA bands with sodium hydroxide (NaOH) and formaldehyde<sup>15</sup>.

## Histopathological and immunohistochemical analysis

The tissue samples were fixed in 10% formalin and embedded in paraffin wax. The tissue blocks were sectioned into 4 µm thickness sections. The hematoxylin-eosin staining was used for the histopathological analysis. The immunohistochemistry was accomplished with monoclonal antibodies for all antigens. The primary antibodies used were rabbit anti-E-cadherin (clone EP700Y, 1:200, Cell Marque), mouse anti-HER-2 (clone CB11, 1:600, Cell Marque), rabbit anti-ER (clone SP1, 1:200, Cell Marque), mouse anti-PR (clone 16, 1:100, Cell Marque), and rabbit anti-Ki-67 (clone SP6, 1:300, Spring). The secondary antibody applied was from the Novolink Polymer Detection System® (Leica Biosystems, UK, product code: RE7280-K), following the manufacturer's instructions.

## RESULTS

Table 1 shows the methylation panel of the *CDH1* gene in the tumor and non-tumor breast tissues. All the 15 patients had *CDH1* methylation in the tumor tissue. Nine patients had *CDH1* methylation in the non-tumor breast tissue.

Out of the 15 patients, samples from nine patients were analyzed by histopathology and immunohistochemistry. As indicated in Table 2, E-cadherin expression was detected only in patient

**Table 1.** Methylation panel of the cadherin 1 (*CDH1*) gene in tumor and non-tumor breast tissues.

Patient number	Tumor breast tissue	Non-tumor breast tissue
1	M	U
2	M	M
3	M	U
4	M	M
5	M	U
6	M	M
7	M	M
8	M	U
9	M	M
10	M	M
11	M	U
12	M	M
13	M	M
14	M	M
15	M	U

M: *CDH1* methylated. U: *CDH1* non-methylated.

five. All the nine patients tested positive for Ki-67. As determined through the immunohistochemical analysis, the classification of tumor subtypes was as follows: luminal A (patients 2, 7, and 8), luminal B (patients 6 and 10), HER-2-positive (patient 5), and triple-negative (patients 3, 4, and 14). The histopathological grades and types of breast carcinomas are described in Table 3.

Table 4 shows the age and TNM stage of the patients. It is noteworthy that all patients with this information available fell within a tumor category of 3 or 4, representing an advanced disease. Photomicrographs of the histological sections of tumors are displayed in Figures 1 and 2.

## DISCUSSION

Our study investigated the methylation status of the *CDH1* gene in tumor and non-tumor tissues of breast cancer patients. Additionally, we analyzed the expression of E-cadherin, ER, PR, HER-2, and Ki-67 by immunohistochemistry.

The results showed that *CDH1* gene methylation was detected in the tumor of all the 15 patients and in the non-tumor breast tissue of nine patients (Table 1). Otherwise, only patient number five presented E-cadherin protein expression in the immunohistochemical analysis, suggesting that *CDH1* methylation prevented E-cadherin expression in the other patients. This aligns with the findings of Shargh et al.<sup>6</sup>, who reported that, in a group of 50 breast cancer patients, 94% had *CDH1* methylation and 95% of full-methylated tumor samples had no E-cadherin expression. In another study, Corso et al. emphasized that the detection of *CDH1* epigenetic alterations in a diagnostic/pre-operative biopsy may be helpful to improve patient management and to infer the prognosis of breast cancer and the pattern of tumor dissemination<sup>16</sup>.

**Table 2.** Invasive ductal and invasive lobular carcinoma: Immunohistochemical analysis reports.

Patient number	Invasive Ductal Breast Carcinoma – Patients 2, 3, 4, 7, 8, 10, and 14 Papillary intraductal carcinoma – Patient 6 ILCs – Patients 5 and 6				
	ER Positive (%)	PR Positive (%)	Ki-67 Positive (%)	HER-2 Positive (%)	E-cadherin Positive (%)
2	100	100	1–5	0	0
3	0	0	80–90	0	0
4	0	0	80–90	0	0
5	Not available	20–30	20–30	Score 3 (>30%)	Positive
6	100	90–95 (infiltrating) 20–30 (intraductal)	30–40	0	0
7	60–70	10–20	5–10	0	0
8	100	100	5–10	0	0
10	100	90–95	50–60	Score 1 (≤10%)	0
14	0	0	80–90	Score 1 (≤10%)	0

ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor-2; Ki-67: marker of proliferation Ki-67; ILCs: invasive lobular carcinomas.



**Table 3.** Histopathological analysis reports (breast carcinoma types).

Patient number	Ductal infiltrating carcinoma, non special type	Ductal carcinoma <i>in situ</i>	Ductal carcinoma <i>in situ</i> Grade 1 without comedonecrosis	Ductal carcinoma <i>in situ</i> Grade 2 with comedonecrosis	Intraductal papillary carcinoma	ILC
2	Grade 2	Grade 1	P	-	-	-
3	P	-	-	-	-	-
4	Grade 3	-	-	-	-	-
5	-	-	-	-	-	P
6	-	-	-	-	P	P
7	Grade 1	-	-	-	-	-
8	Grade 1	Grades 1 and 2	P	-	-	-
10	Grade 2	Grade 2	-	P	P	-
14	Grade 3	-	-	-	-	-

P: positive for the types of carcinomas of the study patients. Grade 1: well differentiated. Grade 2: moderately differentiated. Grade 3: poorly differentiated. ILC: invasive lobular carcinoma.

**Table 4.** Age and TNM stage of patients.

Patient number	Age (years)	TNM stage
1	53	T4b N2 Mx
2	73	WD
3	50	WD
4	44	T3 N0 M0
5	49	CT3 CN2 CM0
6	59	T4 N0 Mx
7	44	T4B N1 Mx
8	49	T3 N1 Mx
9	78	WD
10	57	T4 N0 Mx
11	57	T4 N1 Mx
12	56	T4B N0
13	59	T3 N1 M0
14	54	T4b N2 Mx
15	69	T3 N0 M0

TNM acronym refers to TNM Classification of Malignant Tumors, where "T" refers to primary tumors, "N" refers to nearby lymph node involvement, and "M" refers to distant metastasis. WD: TNM stage not described in the records.

Three patients (2, 7, and 8) were diagnosed with luminal A subtype carcinoma, characterized by a strong positivity for ER and PR, a negativity for HER-2, and a weak positivity for Ki-67 (Table 2). As pointed out by De Santo et al.<sup>17</sup>, the luminal A subtype is associated with less biologically aggressive neoplasms and is responsive to anti-estrogenic therapy. However, over time, neoplastic cells can develop resistance to this therapy due to mutations in the genes of ERs. This resistance can interfere with the action of anti-estrogen drugs, such as tamoxifen, thereby favoring cancer progression.

Three patients (3, 4, and 14) were diagnosed with the triple-negative subtype, characterized by a high Ki-67+ (80-90%) due

to the elevated degree of the proliferation of neoplastic cells. This subtype presents an aggressive clinical behavior, as pointed out by Derakhshan and Reis-Filho<sup>18</sup>. Furthermore, the triple-negative subtype is associated with neoplasms of high combined histopathological grade, which agrees with our findings reported in Table 3 (patients 4 and 14 had Grade 3). This characteristic favors response to neoadjuvant chemotherapy.

Patient number five, diagnosed with ILC, was HER-2+. This patient showed *CDH1* methylation and E-cadherin expression only in the tumor and not in the non-tumor tissue, confirming the heterogeneity of E-cadherin expression in lobular carcinomas<sup>5</sup>.

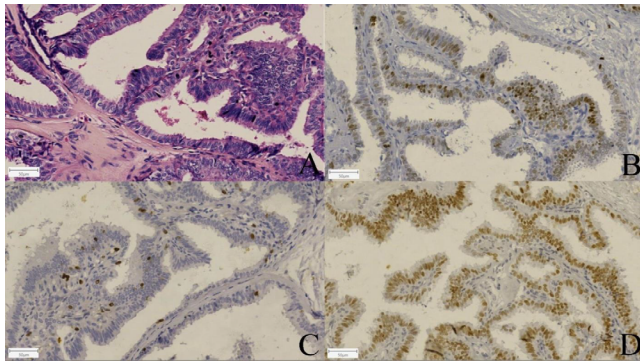
The histopathological diagnosis summarized in Table 3 allowed an initial prognostic assessment. Histopathological analysis is indispensable to direct complementary molecular studies (including immunohistochemistry and methylation analysis). These studies are essential to improve diagnosis and assist in choosing the most appropriate treatments, allowing a better evaluation of the final prognosis in patient survival.

TNM stage information was available for 12 out of the 15 patients (Table 4). All of them had advanced tumors (seven had T4 and five had T3), which is related to late diagnosis, delay in treatment start, and reduced survival, as emphasized by Rivera-Franco and Leon-Rodriguez<sup>19</sup>.

To our knowledge, this is the first study that simultaneously explored *CDH1* gene methylation and E-cadherin protein expression in a cohort of Brazilian breast cancer patients.

## CONCLUSIONS

Our findings suggest that *CDH1* gene methylation prevented E-cadherin expression in breast tumors once only one of the nine patients tested by immunohistochemical analysis showed the protein. The methylation of *CDH1* in non-tumor breast tissues observed in nine patients may suggest the presence of



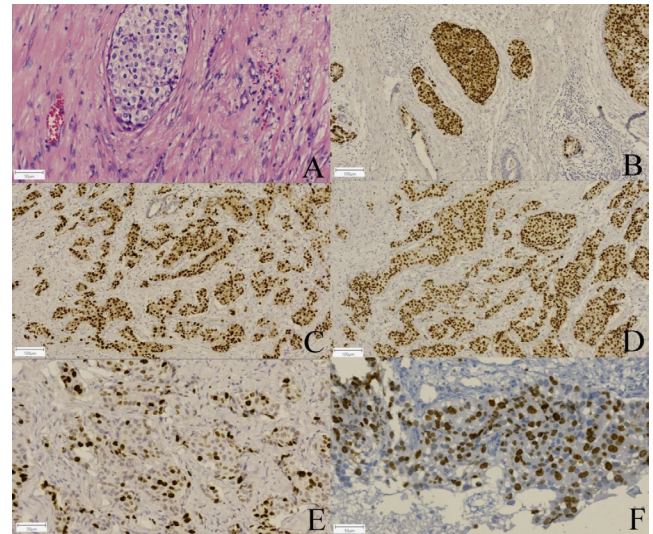
**Figure 1.** Histological sections of papillary carcinomas. The scales correspond to 50  $\mu$ m in length. HE: hematoxylin-eosin staining. A: Intraductal papillary carcinoma, HE. B: Intraductal papillary carcinoma with nuclear PR positivity, IH. C: Intraductal papillary carcinoma with nuclear Ki-67 positivity, IH. D: Intraductal papillary carcinoma with nuclear ER positivity, IH.

IH: immunohistochemistry. PR: progesterone receptor. Ki-67: marker of proliferation Ki-67. ER: estrogen receptor.

infiltrating neoplastic cells or non-neoplastic genetically transformed cells. New studies are needed to analyze the methylation of other genes that encode markers for breast cancer, such as ER, PR, HER-2, and Ki-67. Furthermore, these studies should investigate the relationship between gene methylation and the respective marker expression.

## AUTHORS' CONTRIBUTION

LFQ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MSMS: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. FCR: Data curation,



**Figure 2.** Histological sections of ductal carcinomas. A: in situ ductal carcinoma, HE. B: in situ ductal carcinoma with nuclear PR positivity, IH. C: invasive ductal carcinoma with nuclear PR positivity, IH. D: invasive ductal carcinoma with nuclear ER positivity, IH. E: invasive ductal carcinoma with nuclear Ki-67 positivity, IH. F: invasive ductal carcinoma with nuclear Ki-67 positivity, IH. In A, E, and F, the scales correspond to 50  $\mu$ m in length. In B, C, and D, the scales correspond to 100  $\mu$ m in length.

HE: hematoxylin-eosin staining, IH: immunohistochemistry. PR: progesterone receptor. Ki-67: marker of proliferation Ki-67. ER: estrogen receptor.

Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SBLR: Formal analysis, Investigation, Methodology, Writing – review & editing. HSPS: Funding acquisition, Resources, Writing – review & editing. MGCC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.


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# Retrospective analysis of the epidemiological profile of patients undergoing breast reconstruction in a public hospital in Northeastern Brazil

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## ABSTRACT

**Introduction:** Breast reconstruction is a right guaranteed by the public health system to patients undergoing mastectomy. The present study aimed to understand the epidemiological profile of women with breast cancer who underwent breast reconstruction at a referral hospital in the Northeast region of Brazil. **Methods:** Observational, retrospective study with an analytical character and descriptive approach. Data were collected through a sociodemographic questionnaire and clinical-surgical history, and were subsequently analyzed using SPSS version 18, with the percentages of the categories evaluated by the  $\chi^2$  test, considering a significance level of 5%. The comparison of the analyses was significant ( $p < 0.005$ ), demonstrating that the profile described was the most frequent in the group of patients evaluated. **Results:** A non-probabilistic sample of 400 medical records was obtained from a public referral hospital in the unified health system of the Northeast Region. The majority had a mean age between 46 and 59 years (45.3%) and brown skin color (61.1%), and were married (79.1%), with education up to high school (60.7%); they were housewives (45.0%), non-smokers (84.9%), non-alcohol drinkers (94.9%) and underwent immediate reconstruction after mastectomy (70.3%). **Conclusions:** The findings support that patients with high education levels are likely to undergo immediate breast reconstruction, indicating that socioeconomic level significantly influences the rates of breast reconstruction after radical or conservative breast surgery.

**KEYWORDS:** breast cancer; mastectomy; epidemiology

## INTRODUCTION

Breast cancer is a significant public health problem, widely recognized as a disease that most frequently affects women over 45 years of age, and it is the leading cause of cancer death in women worldwide, including women in high- and low-income countries<sup>1,2</sup>. There are several factors that are linked to the emergence of this condition, including the lifestyle adopted by those affected<sup>3-7</sup>.

There are several ways for treating breast cancer, and the treatment is multidisciplinary. Depending on the stage of the disease, local or systemic treatments may be used, with more radical or conservative approaches. In recent decades, surgical treatment has evolved from the more radical Halsted surgery to more conservative surgeries with immediate reconstruction<sup>8,9</sup>. Given the aggressiveness of the procedure, a search began for new, less aggressive techniques and ways to build a new breast for women who have undergone mutilating surgeries<sup>10,11</sup>.

Access to information about breast reconstruction in women who have undergone such reconstruction depends on the

sociodemographic profile of these patients. It is also noted that underprivileged populations and those with lower levels of education have lower rates of breast reconstruction, which demonstrates that mastologists are less willing to give advice for immediate or delayed reconstruction<sup>12,13</sup>.

In 2021, the Brazilian Society of Mastology published a note stating that, in the last decade, more than 110,000 Brazilian women underwent mastectomy through the Unified Health System (SUS) as part of their treatment for breast cancer. However, only 25,000 underwent breast reconstruction, with an increase in absolute numbers observed up to 2014, with a slight reduction up to 2017. In 2020, with the COVID-19 pandemic, there was an even sharper drop in the number of these procedures performed, worsening an already unfavorable scenario<sup>14</sup>.

It is clear that breast reconstruction and its evolution are related to several factors, namely economic, social, and psychological, which contributed to delaying its acceptance for several decades. Thus, the objective of our study was to understand the

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epidemiological profile, socioeconomic factors, clinical pathological characteristics, and the relationship between immediate and delayed breast reconstruction in a referral public health hospital in the state of Pernambuco, with the aim of understanding the association of these factors in the best way possible and changing the lives of these women.

## METHODS

This was an observational, retrospective, analytical study with a descriptive approach. Four hundred patients diagnosed with breast cancer who underwent breast reconstruction and were admitted to the mastology and breast reconstruction service of the Barão de Lucena Hospital in Recife (PE) were evaluated.

To analyze the data, a database was created in a Microsoft Excel spreadsheet, which was exported to SPSS, version 18, where the analysis was performed. To evaluate the personal and clinical profile of the patients studied, the percentage frequencies were calculated, and the respective frequency distributions were constructed.

To evaluate which factors influence the histological type and the classification of the tumor, lymph nodes and metastasis (TNM), contingency tables were constructed and the  $\chi^2$  test for independence was applied. In cases where the prerequisites for applying the  $\chi^2$  test were violated, Fisher's exact test was applied. In the evaluation of the relationship between the molecular subtype and the type of surgery and reconstruction, the  $\chi^2$  test for homogeneity was applied; as well as in the evaluation of the distribution of the type of reconstruction according to the molecular subtype. All conclusions were drawn considering a significance level of 5%.

The project was submitted to and approved by the Human Research Ethics Committee of the Amaury de Medeiros Foundation, CAAE: 35568920.0.0000.5191. Data collection began in September 2021, after approval by the ethics committee.

## RESULTS

Table 1 shows the distribution of the sociodemographic profile of the patients evaluated. The majority of patients were from Recife (36.0%), between 46 and 59 years old (45.3%), brown-skinned (61.0%), married (79.3%) and with completed/incomplete high school (60.7%), and they worked from home (45.0%), did not smoke (85.0%) and did not consume alcoholic beverages (95.0%).

Table 2 shows the distribution of the clinical profile of the patients evaluated. Most patients showed: delay of more than one to three months of treatment (44.2%), ductal histological type (89.0%), TNM type II (51.0%), immediate reconstruction (70.3%), chemotherapy (80.5%), radiotherapy (73.8%), and Luminal A molecular subtype (60.8%).

**Table 1.** Distribution of the sociodemographic profile of the patients evaluated.

Evaluated factor	n	%
Place of origin		
Recife	144	36.0
Metropolitan area	117	29.2
Interior	139	34.8
Age (years)		
Up to 30	25	6.2
31 to 45	129	32.3
46 to 59	181	45.3
60 or older	65	16.2
Skin color		
White	136	34.0
Brown	244	61.0
Black	20	5.0
Marital status		
Married	317	79.3
Single	53	13.3
Widowed	11	2.7
Divorced	19	4.7
Level of education		
No education	5	1.3
Literate	13	3.3
Elementary compl./incompl.	94	23.4
Secondary compl./incompl.	243	60.7
Higher education compl./incompl.	45	11.3
Profession		
Unemployed	14	3.4
Paid work	167	41.8
Student	15	3.8
Housewife	180	45.0
Retired	24	6.0
Smoker		
Yes	60	15.0
No	340	85.0
Alcohol drinker		
Yes	20	5.0
No	380	95.0

Table 3 shows the distribution of the type of reconstruction according to the molecular subtype. The most frequent type of reconstruction was oncoplastic flap (45.0%), followed by breast reconstruction with myocutaneous flap (GD) (23.5%) and reconstruction with prosthesis (10.3%). When analyzing the distribution of the type of reconstruction according to molecular subtype



**Table 2.** Distribution of the clinical profile of the patients evaluated.

Evaluated factor	n	%
Delay time (1 missing)		
Up to 1 month	148	36.8
More than 1 to 3 months	176	44.2
More than 3 to 6 months	62	15.5
More than 6 months to 1 year	2	0.5
More than 1 year	12	3.0
Histological type		
Ductal	356	89.0
Lobular	15	3.7
Others	29	7.3
TNM		
Stage 0	25	6.2
Stage I	107	26.8
Stage II	204	51.0
Stage III	60	15.0
Stage IV	4	1.0
Type of surgery		
Mastectomy	169	42.3
Quadrantectomy	231	57.7
Reconstruction time		
Immediate	281	70.3
Late	119	29.7
Chemotherapy		
Yes	322	80.5
No	78	19.5
Radiotherapy		
Yes	295	73.8
No	105	26.2
Molecular subtype		
HER 2	34	8.4
Luminal A	243	60.8
Luminal B	65	16.3
TN	58	14.5

TNM: tumor, lymph nodes and metastasis.

group, it was observed that in patients with molecular subtypes HER2, Luminal A and TN there was a higher prevalence of the oncoplastic reconstruction type with flap (41.2%, 44.9% and 36.2%, respectively), followed by the type of breast reconstruction with myocutaneous flap (GD) (35.3%, 22.2% and 34.5%, respectively). For the group of patients with molecular subtype B, the majority of patients underwent oncoplastic reconstruction with flap (55.4%), followed by the type of reconstruction with prosthesis (18.5%) (Figure 1).

## DISCUSSION

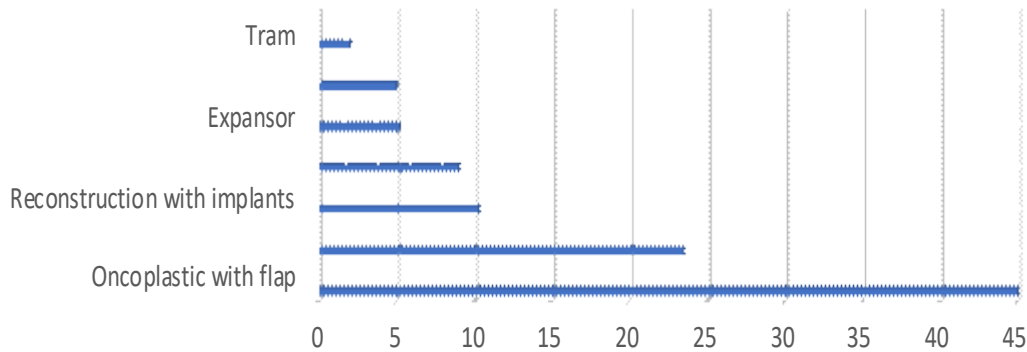
We have seen significant surgical developments in breast cancer in recent years, from Halsted mastectomy to conservative surgery and the advances in breast reconstruction that occurred in the 20th century. However, with the introduction of different oncoplastic techniques, women have had a new option to improve the psychological trauma of breast loss. Breast reconstruction surgery has been widely used in the treatment of breast cancer, as it allows for the resection of large tumors while maintaining aesthetics and oncological results. Research has shown that patients who choose breast reconstruction are motivated by body image for reasons of femininity and sexuality<sup>45,16</sup>.

Our results demonstrated that indicators such as socioeconomic status, origin, educational level and race did not influence the use of breast reconstruction and were considered independent factors for this type of procedure. Clough et al. found data similar to ours, as did Cristian in a study analyzing socioeconomic determinants in breast reconstruction<sup>17,18</sup>. The high level of patient satisfaction in psychosocial, sexual and physical terms is associated with immediate reconstruction compared to mastectomy alone<sup>19,20</sup>.

The rate of patients who underwent immediate reconstruction was 70.3%, while 29.7% underwent delayed reconstruction. These data are positive when compared to data in the literature, in which 18.5% underwent immediate reconstruction, while 9.5% underwent delayed reconstruction<sup>21,22</sup>. Morrow et al. reported that approximately 25% of their patients refused to undergo breast reconstruction after mastectomy because they were afraid of

**Table 3.** Distribution of reconstruction type according to molecular subtype.

Reconstruction type	n	%	Molecular subtype			
			HER2 (%)	Luminal A (%)	Luminal B (%)	TN (%)
MS/Prosthesis	36	9.0	5 (14.7)	23 (9.5)	4 (6.2)	4 (6.9)
Breast reconstruction with myocutaneous flap (GD)	94	23.5	12 (35.3)	54 (22.2)	8 (12.3)	20 (34.5)
Flap with autologous tissue: TRAM	8	2.0	0 (0.0)	7 (2.9)	0 (0.0)	1 (1.7)
Reconstruction with Expander	21	5.2	1 (2.9)	14 (5.8)	2 (3.1)	4 (6.9)
Lipofilling	20	5.0	2 (5.9)	12 (4.9)	3 (4.6)	3 (5.2)
Reconstruction with prosthesis	41	10.3	0 (0.0)	24 (9.9)	12 (18.5)	5 (8.6)
Oncoplastic reconstruction with flap	180	45.0	14 (41.2)	109 (44.9)	36 (55.4)	21 (36.2)



**Figure 1.** Distribution of patients according to type of reconstruction.

the likelihood of interference in the detection of cancer recurrence<sup>23,24</sup>. The data from Morrow et al. differ from the findings of Natalie et al.: of 866 patients, 768 did not undergo conservative surgery (88.7%) and 98 (11.3%) underwent oncoplastic surgery<sup>25</sup>.

A Brazilian study by Freitas-Júnior et al. from 2017 on the trend of surgeries for the treatment of breast cancer in Brazil revealed that, between January 2008 and December 2014, 193,596 surgeries were performed for the treatment of breast cancer in SUS, indicating a tendency towards a reduction in the number of simple mastectomies with some stability in the numbers of breast-conserving surgery and radical mastectomies. In addition, there was an increase in breast reconstructions using both implants and myocutaneous flaps. This study found a rate among patients who underwent mastectomy and reconstructive surgeries of 15% in 2008, with a significant increase in 2013 and 2014, of 23.7% and 29.1%, respectively<sup>26</sup>.

Another interesting fact was that most of our patients were in clinical stage 0, I, and II, with 84% of patients, which allowed for more conservative surgeries and immediate reconstruction than radical mastectomy. Wu et al., in a survey of 47,123 patients treated with mastectomy alone or mastectomy followed by breast reconstruction, the staging 0, I, and II was 85%, similar to our findings, but these data were not obtained by Mansell et al.<sup>27</sup>.

The most common histological type was ductal, and most patients underwent mastectomy (43.0%). In the group of patients with lobular histological type, the distribution of the type of surgery was homogeneous (33.3% for all types of surgery) and the time for immediate reconstruction was longer (73.3%). For other histological types, the majority underwent mastectomy (38.0%) and with immediate reconstruction time (79.3%). The homogeneity test was not significant in the comparison of the distribution of the type of surgery and the time for reconstruction between the different histological types ( $p=0.834$  and  $0.513$ , respectively), indicating that the distribution of the type and time of surgery is similar in different histological types<sup>28</sup>.

Regarding the molecular subtype of our patients, Luminal A was the most common, with 60% of cases, followed by Luminal B in 16%, triple-negative in 15% and HER-2 in 9%; These data are

very similar to those reported by Wu et al. in the SEER survey of the National Cancer Institute program in the United States, in which Luminal A was found in 68% of patients, with HER-2 in 6.1% and triple-negative in 13%. We observed that there was no difference between the type of breast reconstruction with the different molecular subtypes. Patients with HER-2 and triple-negative molecular subtypes underwent less immediate breast reconstruction compared to luminal tumors, and they also had a relatively higher risk of local recurrence<sup>29</sup>.

In the majority of our patients who underwent oncoplastic techniques, locoregional flaps (45%), breast implants and expanders (25%) were used in almost 70% of cases, leaving reconstruction with myocutaneous flaps with the latissimus dorsi or Tram and fat grafting for selected cases and later reconstructions. Offodile et al., in a retrospective study by the American College of Surgeons, demonstrated that the most commonly used reconstruction was with breast implants and that reconstruction using flaps and implants was rarer<sup>30,31</sup>.

Regarding the level of education, it was noted that patients who underwent breast reconstruction had completed high school (60.7%), and 11.3% had higher education. Thus, it was noted that the higher the level of education of the patients, the greater the search for reconstruction, as in Albrecht et al.<sup>32</sup>.

In addition, it was noted that most of the women who underwent breast reconstruction had some type of employment. The study demonstrated that 41.8% of the patients had some kind of paid job. Therefore, we can infer that women who are in the job market seek out reconstruction procedures more often<sup>33</sup>.

## CONCLUSION

The findings support the idea that patients with high levels of education are likely to undergo immediate breast reconstruction. It was also inferred that the histological type of carcinoma and the molecular subtype did not interfere with breast reconstruction. We observed that the number of immediate breast reconstructions in patients with breast cancer increased significantly.

## AUTHORS' CONTRIBUTION

DLFF: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation. NCFLF: Methodology, Project

administration, Resources, Software, Supervision, Validation. TLF: Visualization, Writing – original draft, Writing – review & editing.

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# Breast cancer mortality in Brazilian men: an age-period-cohort study

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## ABSTRACT

**Introduction:** Male breast cancer is a rare malignancy whose health impacts remain unknown, notably in countries like Brazil. The purpose of this article was to evaluate breast cancer mortality in Brazilian men by an age-period-cohort study. **Methods:** This ecological study evaluates the mortality of Brazilian men due to breast cancer using an age-period-cohort model. Data were sourced from the public, open-access Brazilian database DATASUS, available at <https://datasus.saude.gov.br>, covering the period from 1996 to 2021. Demographic data represent the total population of Brazilian males, while clinical data focus on patients whose cause of death was coded as 175 (ICD-9) or C50 (ICD-10). The age-period-cohort effects were analyzed following the classic model and its adaptations. The analysis was performed using R 4.4.0. Alpha<sup>®</sup> software. **Results:** It was noted an increasing mortality trend with aging, peaking in men over 80 years old. From 1996 to 2009, no statistically significant changes were observed in the hazard ratio (HR). However, from 2010 onward, a significant increase in HR was found, reaching a peak in 2020–2021 (HR 2.79634; 95%CI 2.37121–3.29770). A total of 34 birth cohorts (1919–2011) were analyzed. Cohorts from 1919–1964 and 1981–2011 did not show statistically significant results, while those from 1966–1979 exhibited a decreasing HR, with the lowest HR seen in the 1979 cohort (HR 0.91323; 95%CI 0.83545–0.99825). **Conclusions:** This study identifies a growing trend in male breast cancer mortality in Brazil, particularly after 2010, with variations across birth cohorts.

**KEYWORDS:** epidemiology; breast cancer; age-period-cohort.

## INTRODUCTION

Male breast cancer (MBC) is a rare malignancy, representing less than 1% of all breast carcinomas diagnosed annually in the United States<sup>1</sup>. The lifetime risk of a man developing breast cancer is estimated to be approximately 1 in 1,000, significantly lower than the 1 in 8 observed in women<sup>1,2</sup>.

Some risk factors associated with MBC include a family history of breast cancer, black ethnicity, exposure to radiation, genetic mutations (such as the breast cancer genes BRCA1 and BRCA2), use of exogenous estrogen, and conditions like Klinefelter's syndrome, which are linked to elevated estrogen levels<sup>1-3</sup>.

Globally, the incidence of MBC remains much lower than that of female breast cancer (FMC)<sup>3</sup>. Data from population-based studies in countries such as Denmark, Finland, Norway, and Sweden have shown world-standardized incidence rates of

0.40 per 100,000 person-years for men, in stark contrast to 66.7 per 100,000 person-years for women<sup>2-5</sup>.

In Brazil, the epidemiology of MBC mirrors global trends, but with notable regional variations. Between 2005 and 2015, 1,521 deaths were attributed to MBC, with the most significant rise in mortality seen among patients aged 80 years or older<sup>6</sup>.

Despite the growing recognition of MBC in Brazil, data on mortality and disease trends remain limited<sup>6</sup>. The paucity of comprehensive mortality data in Brazil presents a significant challenge in understanding the full scope of the disease<sup>6</sup>. Expanding research efforts to capture and analyze more robust mortality data is crucial for developing effective public health strategies<sup>6</sup>.

Therefore, this research was developed with the aim to evaluate breast cancer mortality in Brazilian men by an age-period-cohort (APC) study.

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## METHODS

### Study characterization

This study employs an ecological approach to evaluate mortality among Brazilian men due to breast cancer, utilizing an APC modeling framework to explore temporal and generational effects on mortality rates.

### Data source

Data for this analysis were extracted from DATASUS, an open-access and publicly available Brazilian health information database, accessible at <https://datasus.saude.gov.br>. The dataset was categorized into two components: demographic data, which includes the total male population in Brazil during the study period, obtained from the Brazilian Institute of Geography and Statistics (IBGE) census data and demographic projections; and, clinical data, whose records pertain to male individuals whose cause of death was attributed to breast cancer, identified using the International Classification of Diseases in its ninth edition (ICD-9) code 175 and the ICD-10 code C50. Variables analyzed included age at death, year of death, and cause of death.

### Temporal classification

To assess temporal trends, data were stratified by birth cohorts and defined periods. The periods were categorized as 1996–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2019, and 2020–2021. Age groups were arranged at five-year intervals, ranging from 10–14 to 75–79 years, with a final category for individuals aged 80 years and older. Finally, birth cohorts were calculated by subtracting the age at death from the year of death, adhering to the classical Lexis diagram framework.

### Statistical modeling

Given that mortality data represent count-based outcomes, they were modeled using a Poisson regression framework, suitable for count data<sup>7-9</sup>. The APC model was constructed to disentangle age, period, and cohort effects, incorporating the following equation<sup>7-9</sup>:

$$\log(\lambda_{ijk}) = \mu + \alpha i + \beta j + \gamma k$$

Where: the mortality rate ( $\lambda_{ijk}$ ) for age ( $i$ ), period ( $j$ ), and cohort ( $k$ ) was modeled and  $\mu$  represents the global average mortality rate;  $\alpha$  represents the average age effect;  $\beta$  represents the average period effect, and  $\gamma$  represents the average cohort effect<sup>7-9</sup>.

Recognizing that Poisson regression assumes the equality of the mean and variance, the presence of overdispersion was assessed using a likelihood ratio test comparing the Poisson model to a negative binomial model<sup>7-9</sup>. Where overdispersion was detected, adjustments were made by employing the negative binomial model to provide robust standard error estimates, ensuring the validity of the results.

Submodels were sequentially tested to assess the relative contributions of age, period, and cohort effects using likelihood ratio tests and the Akaike Information Criterion for model selection. The final model was evaluated for goodness-of-fit through deviance statistics. All statistical analyses were conducted using R (version 4.4.2), with the Epy package facilitating APC modeling.

APC interactions were analyzed within the broader epidemiological and societal context. For instance, age effects were interpreted in light of physiological vulnerability, while period effects considered advancements in diagnostic technologies and healthcare access. Cohort effects were evaluated for their potential linkage to generational exposures, such as environmental or occupational risks.

Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated and reported with precision. An HR between 0 and 1 suggests that independent variables (age, period and/or birth cohorts) act as a protective factor for the dependent variable, in this case, MBC mortality, thereby reducing the likelihood of its occurrence. An HR equal to 1 indicates that the independent variable has no measurable impact on MBC mortality, reflecting a neutral association. Conversely, an HR greater than 1 implies that the independent variable functions as a risk factor, increasing the likelihood of mortality from MBC. The CIs of the HR provide insight into its statistical significance and precision. If the entire CI falls below 1 (e.g., 0.5–0.9) or above 1 (e.g., 1.2–1.8), the result is considered statistically significant. In contrast, a CI that crosses 1 (e.g., 0.8–1.2) indicates a lack of statistical significance, as it includes the possibility of no effect.

## RESULTS

A total of 3,913 deaths were observed along the evaluated time. In all age subgroups assessed, the number of deaths showed a growing absolute pattern; that is, the number of deaths increased as age increased.

An increasing trend in mortality rates of Brazilian men from breast cancer was observed with individual aging, with mortality peaks reached in men after 80 years old (Table 1; Figures 1 and 2).

The years between 1996 and 2009 did not demonstrate statistical significance in their mortality HR. Since 2010, a growing and statistical significant HR has been observed, with HR peaks identified in the final evaluated period, 2020 to 2021 (HR 2.79634; 95%CI 2.37121–3.29770) (Table 2; Figure 3).

A total of 34 cohorts were analyzed, from 1919 to 2011. The cohorts born between 1919 and 1929, as well as between 1944 and 1964, and from 1981 onwards did not present statistical significance in their HR. On the other hand, the cohorts from 1966 to 1979 showed a decreasing HR with a peak of lower HR observed in the 1979 cohort (HR 0.91323; 95%CI 0.83545–0.99825) (Table 3; Figure 4).

**Table 1.** Brazilian men's breast cancer mortality rates for 100,000 individuals by age groups.

Age groups (years)	Mortality rates for 100,000	95% Confidence interval
10–14	0.00135	0.00092–0.00198
15–19	0.00255	0.00181–0.00359
20–24	0.00478	0.00352–0.00650
25–29	0.00899	0.00686–0.01179
30–34	0.01690	0.01333–0.02143
35–39	0.03177	0.02583–0.03908
40–44	0.05972	0.04980–0.07161
45–49	0.11225	0.09535–0.13213
50–54	0.20719	0.17758–0.24173
55–59	0.34308	0.29437–0.39984
60–64	0.47872	0.40243–0.56948
65–69	0.63591	0.51314–0.78805
70–74	0.91911	0.71637–1.17922
75–79	1.44000	1.08386–1.91314
Over 80	2.35234	1.72271–3.21209

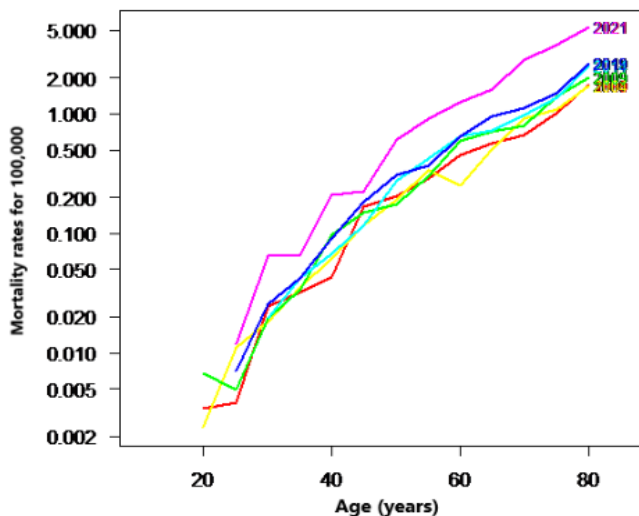
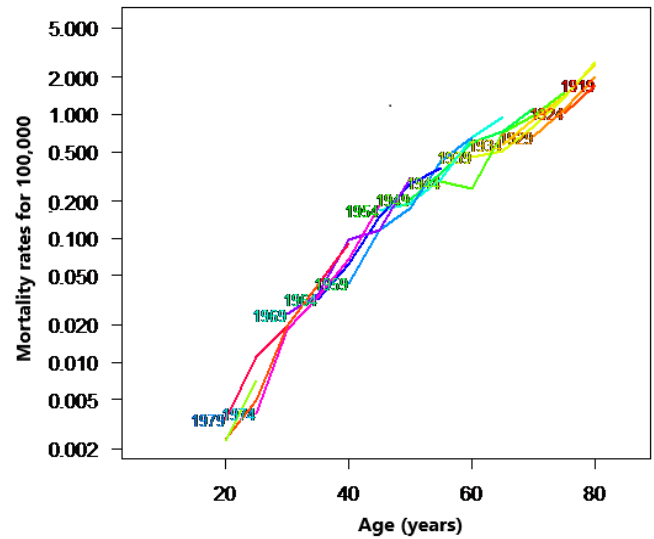
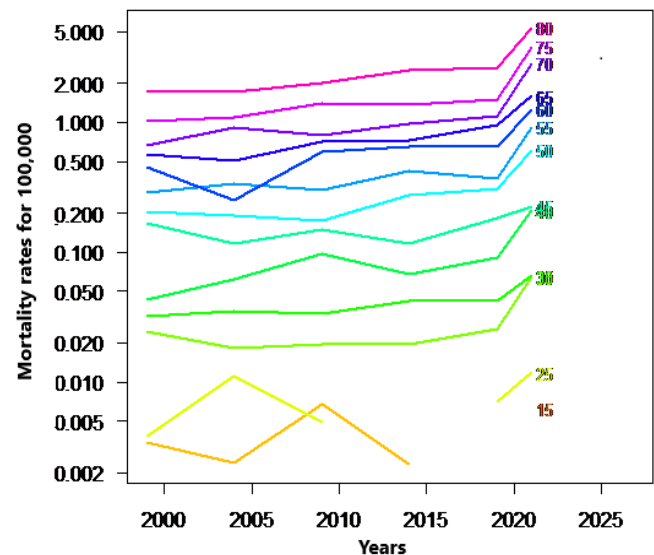
**Figure 1.** Brazilian men's breast cancer mortality rates for every 100,000 individuals by age and period.

Figure 5 summarizes the main results of this study; that is, an increase in mortality with population aging, especially among those who died over 80 years. In addition, since 2010, an increase in HR was noted, with a peak in the period 2020–2021. Finally, during the cohorts from 1966 to 1979, a progressive reduction in HR was noted among the evaluated groups.

The figure shows on its Y-axis (vertical) the mortality rate due to MBC for every 100,000 individuals. The X-axis (horizontal) specifies the age at which individuals died. Each line on the

**Figure 2.** Brazilian men's breast cancer mortality rates for every 100,000 individuals by age and birth cohort.**Table 2.** Brazilian men's breast cancer hazard ratio by evaluated periods.

Period	Hazard ratio	95% Confidence interval
1996–1999	0.99486	0.97560–1.01450
2000–2004	1.02082	0.94405–1.10384
2005–2009	1.11184	0.96396–1.28241
2010–2014	1.25725	1.08620–1.45523
2015–2019	1.35218	1.15330–1.58536
2020–2021	2.79634	2.37121–3.29770

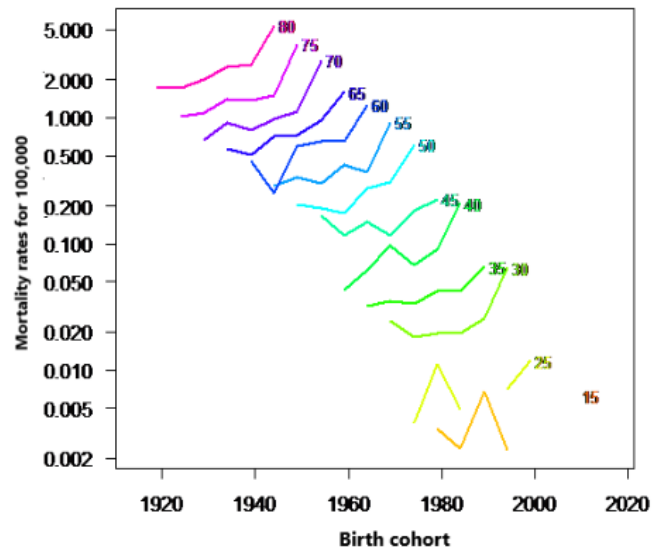
**Figure 3.** Brazilian men's breast cancer mortality rates for every 100,000 individuals by the evaluated years.

**Table 3.** Brazilian men's breast cancer hazard ratio by evaluated cohorts.

Cohort	Hazard ratio	95% Confidence interval
1919	0.76110	0.53993–1.07287
1924	0.77237	0.57619–1.03535
1929	0.78381	0.61167–1.00439
1934	0.79541	0.64376–0.98280
1939	0.81451	0.67595–0.98147
1941	0.83231	0.69732–0.99343
1944	0.87588	0.74373–1.03151
1946	0.91115	0.77802–1.06707
1949	0.96061	0.82907–1.11301
1951	0.98371	0.86503–1.11868
1954	1.00220	0.92114–1.09038
1956	1.00585	0.95581–1.05850
1959	1.00256	0.99344–1.01177
1961	0.99693	0.99041–1.00350
1964	0.98530	0.97008–1.00076
1966	0.97613	0.95783–0.99478
1969	0.96143	0.93280–0.99094
1971	0.95159	0.91342–0.99136
1974	0.93702	0.88380–0.99345
1976	0.92743	0.86423–0.99526
1979	0.91323	0.83545–0.99825
1981	0.90389	0.81671–1.00037
1984	0.89005	0.78931–1.00364
1986	0.88094	0.77152–1.00588
1989	0.86745	0.74555–1.00928
1991	0.85857	0.72872–1.01157
1994	0.84543	0.70415–1.01505
1996	0.83678	0.68823–1.01738
1999	0.82396	0.66501–1.02091
2001	0.81553	0.64996–1.02328
2004	0.80305	0.62802–1.02685
2006	0.79483	0.61381–1.02924
2009	0.78266	0.59308–1.03284
2011	0.77465	0.57965–1.03525

graph represents a specific time. From the figure, it is possible to observe that MBC mortality increases with age, regardless of the evaluated period. It is worth noting that 2021 presents the highest mortality rates.

The figure shows on its Y-axis the mortality rate due to MBC for every 100,000 individuals. The X-axis specifies the age at which individuals died. Each line on the graph represents a specific birth cohort. From the figure, it is possible to observe that MBC

**Figure 4.** Brazilian men's breast cancer mortality rates for every 100,000 individuals by birth cohort.

mortality increases with age, regardless of the birth cohort. It is worth noting that more recent birth cohorts present lower mortality rates than older birth cohorts.

The figure shows on its Y-axis the mortality rate due to MBC for every 100,000 individuals and on the X-axis, the evaluated periods. Each line on the graph represents a specific age group. From the figure, it is possible to observe that MBC mortality is greater in older individuals and that they maintained a practically constant trend throughout the entire evaluated period.

The figure shows on its Y-axis the mortality rate due to MBC for every 100,000 individuals and on the X-axis, the birth cohorts. Each line on the graph represents a specific age group. From the figure, it is possible to observe that MBC mortality is higher in older individuals, which corresponds to older birth cohorts, whereas MBC mortality is lower in younger individuals, which represents more recent birth cohorts.

The figure is composed of two distinct parts. On the left, the mortality rate for MBC for every 100,000 individuals (Y-axis) is evaluated according to the age group (X-axis), and an increase in the mortality rate can be observed as age progresses. On the right, it is possible to observe the relative risk (Y-axis) between each birth cohort and period evaluated. Since the unit of measurement for both variables is years (X-axis), they can be represented together. It can be abstracted from the graph that from 1996 to 2009, no statistically significant changes in the HR were observed. However, from 2010 onward, a significant increase in HR was found, reaching a peak in 2020–2021. As previously indicated in the results section and Table 3 many birth cohorts did not present a statistically significant HR. However, among the statistically significant cohorts, the ones from 1966 to 1979 demonstrated a decreasing HR with a peak of the lowest HR observed in the 1979 cohort.

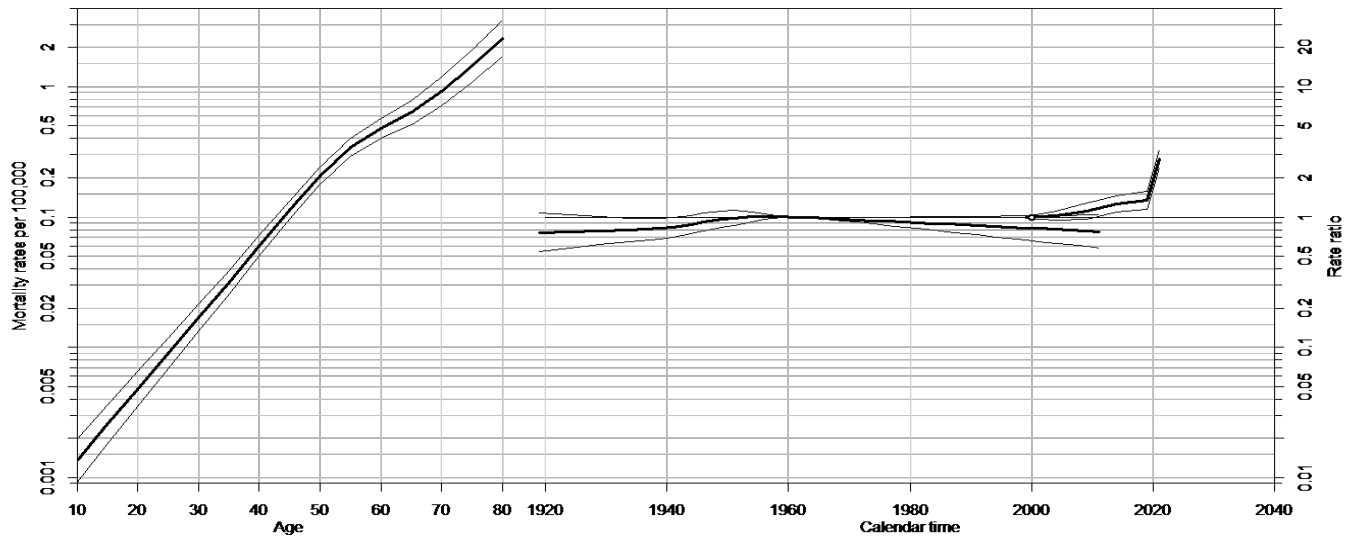


Figure 5. Summary of key findings.

## DISCUSSION

### Sex disparities

Sex-related disparities in breast cancer are notable, with MBC demonstrating distinct clinicopathological features and prognostic outcomes when compared to FBC<sup>10-17</sup>. MBC is a rare condition, accounting for approximately 0.5% to 1.0% of all breast cancer cases<sup>10</sup>.

Men are typically diagnosed at a later age, ranging between 60–70 years median, as opposed to 48–61 years in women<sup>10,11,13</sup>. This delayed diagnosis in men is often associated with more advanced disease stages and higher tumor grades at presentation, contributing to treatment challenges<sup>10,11,13</sup>.

The histological landscape of MBC also differs from that of FBC<sup>11,14</sup>. While invasive ductal carcinoma is the most prevalent histological subtype in both sexes, MBC presents with fewer instances of lobular carcinoma due to the lack of lobular tissue in the male breast<sup>11,12,14</sup>. Men are also more likely to present with hormone receptor-positive tumors, particularly estrogen receptor (ER)-positive, with higher rates than those observed in women<sup>11-14</sup>. This receptor positivity underpins the widespread use of endocrine therapies in MBC, yet, despite these interventions, outcomes remain less favorable than in FBC<sup>11-14</sup>. Cytokine-mediated inflammation, driven by tumor-associated macrophages and IL-6 (interleukin-6), may exacerbate tumor progression in both sexes but manifests distinct immunological signatures in men, likely influenced by androgen suppression of immune surveillance mechanisms<sup>14</sup>.

Prognostically, MBC generally exhibits poorer outcomes<sup>12,15,16</sup>. Studies indicate that men experience lower overall survival (OS) and breast cancer-specific survival (BCSS) rates as compared to women<sup>12,13,15,16</sup>. For example, one study revealed a 5-year OS of 73.9% in men, compared to 86% in women, with a 5-year BCSS of 78.9% in

men versus 94.7% in women<sup>13</sup>. This gap in survival is partially attributed to the higher burden of comorbidities in older male patients, such as diabetes mellitus, atrial fibrillation, and end-stage renal disease, all of which exacerbate mortality risks<sup>13,16</sup>. Additionally, male patients tend to present with larger tumors, higher tumor tissue invasion, greater lymph node involvement, and higher tumor grades at diagnosis, further complicating their prognosis<sup>13,16</sup>.

The social and historical dimensions of breast cancer research have long skewed toward FBC, resulting in delayed recognition and underfunding of MBC studies<sup>15,16</sup>. Sociocultural stigmas surrounding MBC, compounded by limited public awareness, contribute to diagnostic delays and poorer outcomes<sup>15,16</sup>. Addressing these disparities requires not only equitable resource allocation but also public health initiatives to deconstruct gendered misconceptions and promote early detection<sup>15,16</sup>.

Treatment modalities also differ significantly between the sexes<sup>10-13,17</sup>. Men are more frequently subjected to total mastectomy, whereas women often undergo breast-conserving surgery<sup>12,17</sup>. The higher prevalence of hormone receptor-positive tumors in men drives the increased use of endocrine therapy, particularly tamoxifen<sup>10,17</sup>. Despite these therapeutic approaches, men continue to experience poorer survival rates, a disparity that may stem from late-stage diagnoses, the aggressive nature of their tumors, and the underutilization of systemic therapies<sup>17</sup>.

### MBC particularities

MBC arises from a multifaceted interplay of genetic predispositions, lifestyle factors, and therapeutic disparities, each contributing to its unique pathogenesis and outcomes<sup>14</sup>. Genetic mutations, most notably in BRCA2 and less frequently in BRCA1, are central to the etiology of MBC, conferring significantly elevated lifetime risks<sup>14,15</sup>. Additional genomic alterations, such as TP53 (tumor

protein) mutations in Li-Fraumeni syndrome and PTEN (phosphatase and TENsin homolog deleted on chromosome 10) mutations associated with Cowden syndrome, underscore the hereditary predispositions inherent to this malignancy<sup>14</sup>. The androgen receptor pathway, distinct from the estrogen-driven mechanisms predominant in FBC, also plays a pivotal role, influencing tumor proliferation and therapeutic responsiveness<sup>15</sup>. Finally, epigenetic modifications, such as hypermethylation of tumor suppressor genes, have also been implicated, revealing a complex interplay between inherited and acquired genetic factors<sup>14</sup>.

Lifestyle factors exacerbate these genetic susceptibilities<sup>10-17</sup>. Obesity, linked to higher aromatase activity and subsequent estrogen production, stands as a significant modifiable risk factor for MBC<sup>15</sup>. Similarly, alcohol consumption, implicated in epigenetic modifications of DNA (deoxyribonucleic acid) repair pathways, and smoking, associated with oxidative DNA damage, have been identified as contributors to tumorigenesis<sup>16</sup>. Chronic comorbidities, such as liver cirrhosis, which disrupts sexual hormone metabolism, further complicate the landscape of risk<sup>15,16</sup>.

Treatment paradigms for MBC often reflect those established for FBC, despite evidence suggesting differential responses<sup>17</sup>. For example, tamoxifen—a cornerstone of hormone therapy—elicits higher rates of adverse effects in men, including thromboembolism and weight gain, potentially impacting adherence, possibly driven by its overinteraction with androgen receptors<sup>17</sup>. Furthermore, limited data on the efficacy of targeted therapies like CDK4/6 (cyclin-dependent kinase) inhibitors or immune checkpoint inhibitors in MBC underscore the critical need for sex-specific clinical trials to refine treatment algorithms and optimize outcomes<sup>17</sup>.

## Age

Age is a significant prognostic factor in MBC<sup>1,10-17</sup>. Sogunro et al. observed that older age at diagnosis, particularly  $\geq 76.1$  years, was linked to higher mortality, with an HR of 1.13 ( $p=0.004$ )<sup>1</sup>. Similarly, it was found that younger men ( $\leq 40$  years) have better survival outcomes than those  $>40$  years, with 5-year overall survival rates of 97.4% versus 86.4%, respectively<sup>1</sup>. The authors suggest that this survival difference may stem from biological changes associated with aging, such as decreased immune function and increased comorbidities, which negatively impact outcomes<sup>1</sup>. These findings align with other literature, noting that the age of onset plays a critical role in determining the prognosis of MBC, and younger men tend to present with less aggressive disease compared to their older counterparts<sup>10-17</sup>.

Conversely, better survival in younger men may also result from earlier-stage diagnoses and potentially more aggressive treatment strategies<sup>1</sup>. The authors suggest that older patients might experience delays in diagnosis, contributing to the poorer outcomes observed<sup>1,17</sup>. This highlights the importance of age-specific screening and tailored treatment strategies to improve survival in older men diagnosed with MBC<sup>1,17</sup>.

## Period

The impact of distinct time periods on MBC incidence has been increasingly recognized<sup>5,14,16</sup>. Peng et al. identified a period effect contributing to rising MBC incidence between 2010 and 2019 in Taiwan and the USA<sup>5</sup>. The authors noted that societal changes, such as dietary shifts and greater exposure to environmental estrogens, might explain this trend<sup>5</sup>. The rise in incidence over these years possibly results from increased industrialization and the accompanying exposure to chemicals, such as xenoestrogens, which are known to interfere with hormone regulation and are potential carcinogens<sup>6,10,13,18</sup>. This is consistent with similar trends observed in FBC, suggesting shared environmental risk factors across the sexes<sup>5,10,13,18</sup>.

Additionally, the authors highlight the role of improved diagnostic techniques and heightened awareness, which may have contributed to the apparent increase in MBC cases over recent decades<sup>5,13-15,19</sup>. Period effects, therefore, reflect not only actual rises in incidence but also enhanced detection rates<sup>5,13-15,18,19</sup>. While these findings underline the importance of monitoring environmental changes over time, they also suggest that public health efforts should focus on mitigating these modifiable risks to reduce future incidence rates<sup>11,19</sup>.

## Birth cohort

The authors of a Taiwanese study identified a cohort effect, suggesting that men born after the 1960s exhibited higher MBC rates, likely due to increased exposure to Westernized lifestyles, including high-fat diets and obesity<sup>5,12,15,16</sup>. This cohort effect aligns with global trends showing that men from industrialized nations are more susceptible to MBC due to higher exposure to risk factors such as environmental estrogens and poor dietary habits<sup>5,15,16</sup>. These findings suggest that lifestyle changes over generations may partly explain the rising MBC incidence among younger birth cohorts<sup>13,16,20</sup>.

Additionally, the authors discuss that earlier birth cohorts were less exposed to industrial chemicals like alkylphenols and bisphenol A, commonly found in household products and industrial waste, which have been linked to breast cancer risk<sup>5,12,13,21</sup>. The increased prevalence of obesity and Western dietary patterns among younger cohorts has further contributed to the cohort effect observed in MBC incidence, particularly in industrialized countries<sup>5,15,16,20,21</sup>. This underscores the necessity of addressing modifiable lifestyle factors across generations to mitigate future increases in MBC cases<sup>5,15,16,20,21</sup>.

## Men breast cancer global trends

Integrating the findings of this study within the context of global trends in MBC reveals both shared challenges and unique opportunities for public health interventions in Brazil<sup>16,20</sup>. MBC incidence, while consistently low worldwide, has exhibited slight upward trends in certain regions, likely attributable to improved diagnostic capabilities, heightened awareness, and changing environmental



exposures<sup>16,20</sup>. These global shifts underscore the need for proactive surveillance systems in Brazil, particularly as its demographic and epidemiological transition brings an aging male population at higher risk for malignancies, including breast cancer<sup>16</sup>.

### Men breast cancer impact on Brazilian public health:

Public health strategies in Brazil must also contend with socioeconomic and geographic disparities that influence access to care<sup>16</sup>. While high-income nations have embraced routine genetic screening for BRCA mutations among high-risk individuals, such practices remain limited in Brazil due to resource constraints<sup>14,16,21</sup>. Additionally, delayed diagnosis, frequently observed in low-resource settings, exacerbates the already poor prognosis associated with MBC<sup>14,16,21</sup>. To address these gaps, tailored strategies such as awareness campaigns targeting primary care providers, integration of genetic counseling services, and prioritization of early-stage treatment in national oncology guidelines are imperative<sup>14,16,21</sup>.

Furthermore, the intersection of MBC with Brazil's epidemiological landscape—characterized by increasing rates of obesity, alcohol consumption, and metabolic syndromes—necessitates a multi-pronged approach<sup>13,16</sup>. Leveraging insights from global health initiatives, including lifestyle intervention programs and enhanced hormonal therapy accessibility, can serve as a framework for national policy adaptations<sup>13,16</sup>. Such strategies, bolstered by robust data collection and cross-regional collaborations, would not only align Brazil with global best practices but also ensure equitable and effective management of this rare but impactful malignancy<sup>13,16</sup>.

### Data lack on individual's level and its potential biases

The absence of individual-level data introduces significant potential biases, necessitating a sensitivity analysis to assess the robustness of the study's findings. Missing data often result in selection bias, particularly if the absence of records correlates with unobserved variables such as socio-economic status, comorbidities, or healthcare access<sup>16</sup>. For instance, in the context of MBC, underreporting may disproportionately affect rural or underserved populations where diagnostic infrastructure is limited, skewing mortality trends toward urbanized, better-resourced areas<sup>16</sup>.

Sensitivity analyses employing multiple imputation techniques or inverse probability weighting could elucidate the extent to which these biases influence the results<sup>15</sup>. For example, imputing missing covariates such as tumor grade, genetic mutation status, or treatment regimens might reveal hidden associations or mitigate the overestimation of certain risk factors<sup>15</sup>. Additionally, employing stratified analyses by geographic region or income quintile could uncover systematic disparities masked in aggregate data, offering a more granular understanding of the biases introduced<sup>15</sup>.

Moreover, the lack of granular data on individual-level treatment responses complicates the interpretation of survival

outcomes<sup>16</sup>. Differential access to therapies such as tamoxifen or trastuzumab, coupled with variability in adherence rates, may distort apparent survival disparities<sup>14</sup>. Incorporating probabilistic sensitivity analyses to simulate scenarios of treatment allocation could provide a clearer picture of the extent to which these factors confound the results<sup>14,16</sup>. Addressing these gaps is not merely a statistical necessity but a scientific imperative, as it ensures that the conclusions drawn are not only statistically valid but also reflective of the lived realities of MBC patients across diverse contexts<sup>14</sup>.

### Reliance on death certificate data

The use of death certificate data as a primary source for studying MBC mortality is associated with inherent biases that may compromise the accuracy and interpretability of findings<sup>16,22</sup>. Death certificates, often completed under time constraints and with limited clinical insight, are prone to misclassification and/or underreporting the cause of death, particularly in less prevalent conditions like MBC<sup>16,22</sup>. This is exacerbated by the overlap of symptoms and complications with other prevalent conditions, such as cardiovascular disease or secondary malignancies, which can obscure the attribution of mortality to breast cancer itself<sup>16,22</sup>.

Such inaccuracies carry profound implications for epidemiological analyses. Misclassified data may underestimate the true burden of MBC, skewing mortality rates and obscuring trends<sup>16,22</sup>. For instance, cases where metastatic breast cancer contributes to death might be recorded under related organ failures, such as hepatic or pulmonary causes, thereby diminishing the visibility of breast cancer as an underlying or contributory cause<sup>16,22</sup>. Moreover, differences in the thoroughness of death certification between urban and rural settings, or across socioeconomic strata, could introduce disparities that are falsely attributed to demographic or biological factors rather than systemic inconsistencies<sup>16,22</sup>.

A nuanced discussion on the ramifications of these biases is essential to contextualize findings and guide future research. Incorporating data from cancer registries, autopsy reports, or hospital records could mitigate these limitations<sup>16,22</sup>. Additionally, leveraging molecular autopsy techniques, which identify specific oncogenic markers like BRCA mutations or HER2 (human epidermal growth factor receptor-type 2) amplification in deceased patients, could refine the classification of deaths and ensure a more accurate representation of MBC's impact on mortality statistics<sup>16,22</sup>.

## CONCLUSIONS

This study highlights a significant increase in male breast cancer mortality in Brazil over the past decade, particularly in men aged over 80. Cohorts from the late 20th century exhibited lower mortality risks. These findings underscore the importance of increased awareness and targeted interventions for this rare but impactful disease.

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# Analysis of delayed core biopsy results during COVID-19 pandemic: the experience of a single public center

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## ABSTRACT

**Introduction:** To observe and analyze the waiting time for breast biopsy and the impact of this time on the early diagnosis of breast cancer in Santa Catarina. **Methods:** Observational cohort study. Data collection was performed through direct observation with the application of a questionnaire and subsequent quantitative analysis. A convenience sample was used, in which data were computed through a questionnaire administered to patients in cases where a breast biopsy with a thick needle was requested due to the existence of a suspicious lesion in the physical examination or in imaging examinations requested as breast cancer screening. Data from the collection instrument were extracted through direct interviews with patients in the office and completion of a questionnaire, after their correct guidance and signing of an informed consent form. The percentage of malignant versus benign lesions and the pain scale during core biopsy were evaluated. **Results:** The questionnaire was submitted to 71 women who attended the mastology outpatient clinic at the Hospital Regional de São José – Dr. Homero de Miranda Gomes (HRSJ-HMG) between October 2021 and May 2022. Of these, 7 did not undergo breast biopsy due to the lesion not being identified, 39.1% resulted in malignant neoplasia and 60.9% in benign lesion. Regarding the assessment of pain during core biopsy, 57.8% experienced mild or no pain, 21.8% moderate pain and 10.9% severe pain. **Conclusions:** Through this study, it was possible to diagnose malignant lesions and treat patients who had the chance of early follow-up.

**KEYWORDS:** breast neoplasms; core biopsy; descriptive epidemiology; referred pain; menopause; early diagnosis.

## INTRODUCTION

Breast cancer is among the most common malignant neoplasms in women in several countries, including Brazil, where, excluding non-melanoma skin cancers, it is the most common type of cancer in women, with the highest number in the South and Southeast regions<sup>1,2</sup>. Data from the National Cancer Institute<sup>2</sup> show breast cancer as the leading cause of death from malignant neoplasms in women in all regions of Brazil, with the exception of the North region, where it is second only to cervical cancer. Additionally, 73,610 new cases of breast cancer were estimated in Brazil in 2023, with an estimated risk of 66.54 cases per 100,000 women. The mortality rate in 2021 was 11.71 deaths/100,000 women<sup>2</sup>.

According to Concord-3<sup>4</sup>, there was a drop in the five-year survival rate for women with breast cancer, falling to 76.9% (75.5–78) from 2005 to 2009 and 75.2% (73.9–76.5) from 2010 to 2014<sup>3,4</sup>.

These data reflect the speed with which these women are able to access early diagnosis, which includes access to medical care, screening mammograms (MMG) and biopsies of lesions detected as suspicious, as well as the conditions of systemic treatment.

In recent years, the COVID-19 pandemic has led to a reduction in routine consultations for the prevention of female cancer. A questionnaire distributed among specialists in Santa Catarina estimated that there was a reduction of more than 50% in consultations and screening examinations during this period<sup>5</sup>. National estimates show that more than 40,000 cases of breast cancer were not diagnosed in 2020.

It is extremely important that, as soon as a lesion suspected of malignancy is detected, patients are able to undergo a breast biopsy procedure in a timely manner for pathological and immunohistochemical analysis, followed by appropriate referral and

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admission to specialized centers for treatment. Such consultations and procedures were also hindered by the COVID-19 pandemic<sup>6</sup>.

The most commonly used procedures for breast biopsies are: fine-needle aspiration biopsy (FNA), percutaneous core biopsy, vacuum-assisted biopsy (mammotomy), and surgical, incisional or excisional biopsy. The method chosen will depend on a clinical and imaging evaluation of the lesion and the patient's clinical analysis<sup>6,7</sup>. Image-guided biopsy has brought greater practicality and reduced morbidity for patients, similar to the efficacy and precision seen with surgical biopsy<sup>8</sup>. Currently, less than 9% of core needle biopsies diagnose high-grade lesions; however, this number tends to increase with the improvement of breast imaging techniques<sup>3</sup>.

A comprehensive review of the literature assesses the conduct of high-grade lesions and observes the diversity of existing results, demonstrating the importance of increasing the number of core biopsies for lesions suspected in imaging tests or clinically so that strategies can be defined and there is a reduction in the incidence of cancers or an improvement in cure and survival rates<sup>9</sup>.

Institutional differences in excision rates for high-grade lesions, once diagnosed in the core biopsy, demonstrate the need for further studies and improvements in the number of lesions detected for the appropriate indication of these biopsies<sup>10</sup>.

The role of the mastologist includes strategies for surveillance and risk reduction, as well as defining methods for screening and diagnosing these lesions<sup>6</sup>. In this scenario, MMG and core biopsy, which are essential for monitoring patients, are allies in the diagnosis of high-grade or malignant lesions.

In view of this, the present study aimed to analyze the results of breast biopsies of patients recruited because of suspicious lesions after the COVID-19 pandemic. In addition, the objective was to assess the waiting time between the request and the performance of the core needle biopsy and the degree of discomfort with the procedure.

## METHODS

A retrospective cohort study was conducted. Data collection was performed through direct observation with the administration of a questionnaire and subsequent quantitative analysis.

The study took place at the Mastology Service of the Maternity Ward of the Dr. Homero de Miranda Gomes Regional Hospital of São José (HRSJ-HMG), in the city of São José, state of Santa Catarina.

Data were computed through a questionnaire applied to patients who underwent breast biopsy with a thick needle due to the existence of a suspicious lesion in the physical examination or in imaging tests, requested as breast cancer screening, according to the BI-RADS classification by the Basic Health Unit (UBS). All patients were referred from primary care for biopsy

at a tertiary service with mastology care, as shown in the flowchart presented in Figure 1.

During a six-month period, data from patients on the SUS waiting list for breast biopsy in 18 cities in Santa Catarina were evaluated. The primary objective was to evaluate the pathological results of the core needle biopsy and the waiting time for the biopsy from the time the request was made by the primary care physician. The secondary objectives were to analyze the pain related to the procedure, as well as the epidemiological characteristics. To perform the breast biopsies, the BARD needle, models MN1413 and MN1410, and the BARD Magnum gun were used.

After authorization by the HRSJ and approval by the institution's Research Ethics Committee (CEP), a questionnaire was administered to patients seen at the HRSJ-HMG mastology outpatient clinic.



**Figure 1.** Flowchart of patient care.



The collected data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS), version 20.0, and Minitab 16. Statistical tests were performed with a significance level of  $\alpha=0.05$  and, therefore, a confidence level of 95%. Qualitative variables were expressed as frequencies and percentages using Microsoft Excel, version 2010.

## RESULTS

In a seven-month period between October 2021 and May 2022, 185 women were waiting for a breast biopsy through SUS, in a corresponding list of 18 municipalities in the state of Santa Catarina, because of suspicious changes in breast imaging examinations, BI-RADS category 4 or 5, or through physical examination by the UBS. During this period, of the total of 185 patients, only 71 (38.4%) chose to be seen in the HRSJ-HMG Mastology Outpatient Clinic to undergo the procedure through active recruitment. There was no information on the progress of the situation of the remaining 114 patients. Of the women treated, 6 did not undergo a breast biopsy because the lesion designated as suspicious was not identified in screening examinations. Of the 64 patients who underwent the examination, the biopsy of 25 (39.1%) resulted in malignant breast neoplasm and 39 (60.9%) presented with a benign lesion in the histopathological result (Figure 2). Of the 39 benign lesions, 2 were categorized as risk lesions such as flat epithelial atypia, atypical ductal hyperplasia, papillary lesions with atypia, radial scar with atypia, atypical lobular hyperplasia and lobular carcinoma *in situ*.

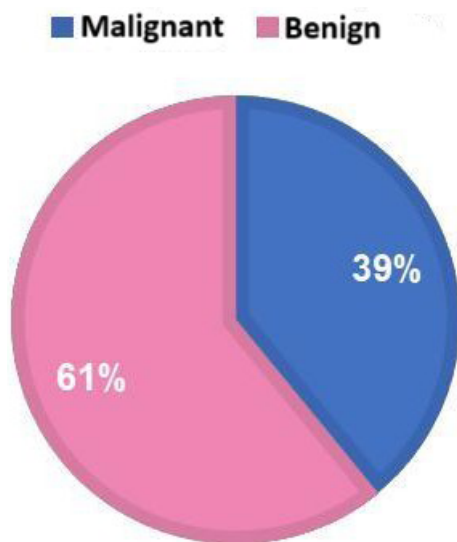
After the procedure, patients were asked about their pain, using a visual analogue scale from 0 to 10 to measure each patient's pain level. Of these, 40 (62.5%) had mild or no pain, 17

(26.5%) had moderate pain, and only 7 patients (11%) reported severe pain, as shown in Figure 3.

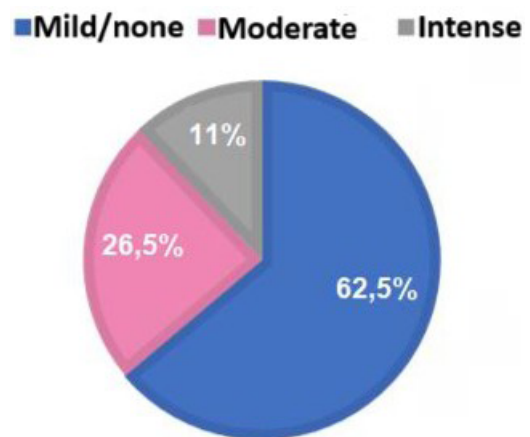
In the group of patients who had pain during core biopsy, 35% had a malignant result in the pathological examination and 65% had a benign result.

Table 1 shows the relationship between the variables analyzed during the administration of the questionnaire to the patients. Comparing age groups, a total of 28 women aged 50 or younger obtained 22 (78.6%) benign results and 6 (21.4%) malignant results. In women over 50 years of age, 16 (47%) biopsies with benign lesions and 18 (53%) with malignant lesions were obtained. Age over 50 years was a statistically significant factor for the presence of malignancy ( $p=0.006$ ).

Also in Table 1, the relationship between the result obtained and the menopausal status at the time of perception of the breast lesion can be noted. This variable was found in 35 patients after the onset of menopause, of which 16 (45.7%) were benign lesions and 19 (54.3%) were malignant lesions. A total of 28 women reported being in menopause, with 22 (78.6%) showing benign results and 6 (21.4%) malignant results of the biopsied lesion.



**Figure 2.** Histopathological result of biopsies performed because of suspicious changes.



**Figure 3.** Pain scale in core biopsy procedure.

**Table 1.** Clinical profile of patients undergoing breast biopsy at a tertiary care facility.

	PE – Benign	PE – Malignant	p-value
	n (%)	n (%)	
Age (years)			
≤50	22 (78.6)	6 (21.4)	0.006
>50	16 (47)	18 (53)	
Menopause			
Yes	16 (45.7)	19 (54.3)	0.006
No	22 (78.6)	6 (21.4)	
Palpable			
Yes	10 (50)	10 (50)	0.13
No	28 (65.1)	15 (34.9)	

PE: result of the pathological examination.



Table 1 also sought to relate the pathological results found with the presence of palpable lesions or by finding in screening examination. The study included 20 women with palpable lesions at the time of biopsy; of these, 50% obtained malignant results. There were 43 patients with suspicious non-palpable changes in the breast; of these, 28 (65.1%) showed benign lesions and 15 (34.9%) were diagnosed malignant. Within the group of non-palpable breast lesions, in which the biopsy was guided by imaging, with MMG and breast USG being available for this study, a total of 30 were guided by USG, of which 63.3% had benign lesions and 36.7% had malignant lesions. A total of 13 patients underwent MMG-guided biopsy, of which 69.2% were benign and 30.8% were malignant. There was no statistical correlation between the malignancy result and the type of malignant lesion, whether palpable or a finding on physical examination ( $p=0.13$ ).

The time between the identification of the suspicious lesion and the time the biopsy was performed was analyzed. Most patients (31–47%) had access to the biopsy more than 90 days after the lesion was found, either through clinical examination of the breasts or through imaging. It was noted that 12 (18.2%) patients had their lesion biopsied between 30 and 90 days and 23 patients (34.8%) in less than 30 days. Of the 20 palpable lesions, 40% of the women were over 50 years of age. It was recorded that 45% had palpable lesions and were in menopause, while 55% were in menarche. Among the 43 patients without palpable lesions on clinical examination, 37.2% were 50 years of age or younger, while 11.4% of postmenopausal patients were 50 years of age or younger and 88.6% were over that age.

Six patients were lost to follow-up, did not return with the results for management and were not found in the active search. One patient, of the 71 referred for a suspicious lesion, did not attend the outpatient clinic.

## DISCUSSION

Several studies conducted in recent years have shown that breast cancer in young women under 40 years old accounts for approximately 7% of all cases of the disease<sup>11</sup>. A retrospective study demonstrated a more severe prognosis for breast cancer in patients under 40 years of age. This makes early diagnosis necessary, since these are usually more aggressive tumors that grow more rapidly<sup>11</sup>.

On the other hand, it is worth noting that, with regard to age, the present study addresses the occurrence of breast cancer in patients over 50, who account for the majority of cases, and whose samples have a highly significant p-value compared to younger women. Likewise, it is noted that cases of breast cancer are more prevalent after menopause, with 54.3% of diagnoses for breast cancer occurring in this scenario and 21.4% before this period. Regarding the clinical finding of palpable lesions, no

association was found between palpable nodules or alterations in screening tests and the diagnosis of malignancy in the pathological examination.

It was noted in the present study that the majority of patients who presented to the service with a palpable lesion (60%) were under 50 years of age, in addition to the finding of 55% in the menarche period, which is in agreement with the current literature that indicates that young women have more palpable breast nodules<sup>12</sup>.

We observed that 47% of patients presented to the service for biopsy after 90 days from the moment of detection of the suspicious lesion, a period whose compliance is crucial for the success of the treatment and the respective achievement of cure. Since the time until the beginning of treatment for malignant breast neoplasia is directly related to the cure rates, it is of utmost importance that it begin as soon as possible.

In view of this, it is important to emphasize that palpable lesions can be biopsied simply and efficiently in an outpatient setting, with appropriate training and equipment. In other words, a total of 10 (14%) patients in this study — who had palpable lesions and were diagnosed with breast cancer — would have had access to definitive treatment services more quickly and earlier if they had been available. For this reason, it is extremely important that UBS teams be familiar with the types of procedures available and their indications, as well as providing the necessary information to the pathologist<sup>6</sup>.

One of these procedures is the core biopsy, a method appropriate for nodules, architectural changes or breast density<sup>6</sup>. FNA is indicated for cystic lesions that are well defined on imaging as benign or malignant, in cases of suspected recurrence in the chest wall or for analysis of lymph node metastasis<sup>6,13</sup>. A meta-analysis demonstrated that USG-guided core biopsy was superior to FNA in the axillary staging of breast cancer<sup>14</sup>.

One of the justifications for performing FNA instead of core biopsy is the less discomfort of the fine needle compared to the thick needle and the lower operating cost. However, we demonstrated that 54 patients reported mild or moderate pain. Furthermore, none of the biopsied lesions had insufficient material, which could frequently occur when cytological analysis alone was performed.

Therefore, immediate performance of a thick needle biopsy ensured that the waiting time for diagnosis — in most cases, more than three months — was not delayed by insufficient material or inconclusive examination generated by cytology.

Furthermore, delays in diagnosis, especially of palpable lesions, could be reduced by training primary care teams to perform core needle biopsies in these cases — which, in this sample, corresponded to 20 patients treated at a tertiary hospital for the procedure. This would reduce the cost of patient care and travel, as well as delays in diagnosis.

Among the limitations found in FNA, we have the underestimation of invasion, as well as the failure to recognize components of ductal carcinoma in situ in cases of papillary and atypical lesions<sup>8,13</sup>. Cases like these may be alleviated as the core biopsy procedure becomes more routine, with the training of professionals qualified to perform it.

In comparison with open surgical biopsy, biopsy guided by imaging methods, such as USG, MMG or magnetic resonance imaging, is equally accurate and has a complication rate of less than 1%, such as infection, hematoma and pneumothorax. In addition, image-guided biopsies generate lower final costs, since they imply fewer surgical procedures necessary to obtain adequate free margins<sup>7</sup>.

It is noted that there are lesions that need to be surgically removed, based on diagnosis in breast biopsies, due to the high risk of progression to breast cancer. These are: atypical ductal hyperplasia, flat epithelial atypia, papillary lesions with atypia, radial scar with atypia, atypical lobular hyperplasia and lobular carcinoma in situ<sup>9,10,13</sup>.

Studies show that these lesions can underestimate breast cancer, especially when they are large and when a small-gauge needle is used for biopsy<sup>6,9</sup>. In this study, we found 5.1% of high-risk benign lesions, which were referred for surgical excision.

Although clinical protocols are highly effective and briefly guide the techniques to be used, knowing the work environment, the patient, her limitations, her traumas and her expectations is essential when trying to reduce the potential pain impact inherent to a biopsy experience.

Furthermore, it is essential to pay attention to the presence of physical disabilities, which may make it difficult to position the patient during the examination, and other limitations for the correct planning of the method, which will result in greater practicality, safety and efficacy in the final result<sup>7</sup>.

It is important to conduct further studies comparing the cure and survival rates between women with palpable lesions who had them biopsied at the UBS and those who need to travel to another service to undergo the examination. Research is also suggested that relates the fear of pain when performing a core biopsy to the speed of diagnosis, as well as the waiting time in the SUS line to reach the referral service.

## CONCLUSION

This study is the result of a seven-month follow-up period, between October 2021 and May 2022, during a period of high relevance due to the COVID-19 pandemic. Since breast cancer is highly sensitive to the time it takes to evolve, especially from the discovery of the lesion to the biopsy followed by

treatment, it was convenient to analyze the results of the core needle examinations in this pandemic scenario. It is worth mentioning that the study involved 71 women, all of whom were previously awaiting a breast biopsy through SUS, either because of suspicious changes in breast imaging examinations (BI-RADS category 4 or 5) or because of physical examinations performed at the UBS. The 71 women were seen at the mastology outpatient clinic at the Hospital Regional de São José – Dr. Homero de Miranda Gomes to undergo the procedure through active recruitment.

In terms of the main results of the core biopsy itself, a high propensity for malignant lesions was found in women over 50 years old (53% of cases), while only 21.4% for women under 50. Furthermore, it was understood that these lesions are more frequent in postmenopausal patients, compared to menstruating patients, with the incidence of malignant lesions being 54.3 and 21.4%, respectively.

The above results were in fact expected, given the history of the neoplasm. However, an important analysis regarding the time between the identification of the suspicious lesion and the performance of the biopsy is noteworthy: 47% of the patients had access to the biopsy more than 90 days after the lesion was found; 18.2% in a period between 30 and 90 days; and 34.8% in less than 30 days. It is important to note that six patients were lost to follow-up and did not return with the result for the management. Therefore, this study demonstrates the importance of preparing UBS teams to perform core biopsies of breast lesions suspected of malignancy, aiming at early diagnosis and direct referral to centers for oncological treatment. Although the COVID-19 pandemic has been greatly mitigated, other similar critical scenarios could require greater diagnostic agility in UBS in a similar way, since the present study highlighted possible losses that delayed results could cause in terms of delaying the start of treatment — consequently, reducing the chance of cure.

In addition, the study reinforces the need to carefully outline the concerns and limitations of each patient, with the aim of reducing fear of undergoing breast biopsy, so that treatment is not delayed.

## AUTHORS' CONTRIBUTION





MAF: Conceptualization, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft. NFR: data curation, formal analysis, Writing – original draft. GAOA: Data curation, Formal analysis, Writing – original draft. PC: Data curation, Formal analysis, Writing – original draft. AF: Methodology, Validation, Writing – revision & editing. RH: Project administration, Supervision, Validation, Visualization, Writing – revision & editing.

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# Association between obesity and triple-negative breast cancer: a systematic qualitative review

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Edmund Baracat<sup>1</sup> , Sérgio Masili-Oku<sup>2</sup> 

## ABSTRACT

**Introduction:** The relation between obesity and triple-negative breast cancer (TNBC) is not totally elucidated. TNBC represents a heterogeneous group of aggressive growth neoplasms. The concepts related to the development of hormone receptor-positive tumors cannot be directly extended to this group. To evaluate the association between obesity and TNBC, considering as primary outcome the assessment of the incidence of this tumor subtype in this population and as secondary outcomes the specific pathophysiology, prognosis, and treatment in this context. **Methods:** This was a systematic review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses — PRISMA statement. PubMed/MEDLINE and Cochrane were the databases used as primary paper sources. Inclusion according to titles and abstracts allowed a secondary selection by reference list revision. The final full-text review was done on the most opportune studies identified. **Results:** A total of 52 articles were included. **Epidemiology:** A higher frequency of obesity among TNBC patients compared to other subtypes and TNBC in obese women was observed in the literature. It is uncertain whether premenopausal status is an aggravating factor. **Pathophysiology:** Several studies identified the production of different factors by obese adipose tissue and their regulation of genes related to the expression of stem-like cell properties, mainly leptin, IL-6, and IL-8. **Prognosis:** Most studies pointed out that disease-free survival and overall survival are independent of body mass index. **Treatment:** Weight reduction showed no significant power in improving prognosis but may favor primary incidence prevention. Drugs based on obesity-related pathways are still in research, and various potential targets were raised. **Conclusions:** Obesity is a risk factor for TNBC. Obese-related inflammatory cytokines may contribute to tumor development. Once TNBC is established, the prognosis does not differ according to initial body mass index changes. No target drug for obesity-related tumorigenic pathways is currently available for clinical use.

**KEYWORDS:** obesity; breast neoplasm; triple negative breast cancer.

## INTRODUCTION

The relationship between obesity and breast cancer is an old topic of discussion and investigation. Over years of epidemiological research and observation, it has become clear that the interaction of body mass index (BMI) with breast tumorigenesis could not be simplified into one unique conclusion. This binomial showed itself to be complex and heterogeneous. Different associations were found depending on multiple context factors such as ethnicity, menstrual status, and anatomopathological tumor type.

The well-established association is obesity in postmenopausal women as a risk factor for hormone receptor-positive breast cancer. Pathophysiology justifying this influence was initially

well-understood and supposedly simple. The higher and maintained estrogenic synthesis, by aromatase enzyme conversion of adrenal androgens in adipose tissue, could stimulate the breast cells proliferation that expressed those hormone receptors<sup>1</sup>. However, past decade data already point to other factors synthesized by adipose tissue that could have a synergistic carcinogenic effect on the breast and other organs, as well.

The connection between triple-negative breast cancer (TNBC) and obesity is not entirely intuitive. TNBC consists of the most aggressive subtype and stands for 20% of breast cancer cases. The absence of hormone or HER2 expression reflects the difficulty to treat the cancer, as no targeted therapy has been developed to date<sup>2</sup>.

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Recently, numerous lines of research have been interested in this subtype of tumor. Pro-inflammatory activity related to adipose tissue has brought to light more consistent data concerning the possibility of obesity as a risk factor for TNBC development.

This systematic review aimed to concentrate on and explore the prior global knowledge already published in the scientific literature about the association between obesity and TNBC.

As a primary outcome, we intended to evaluate whether the incidence of TNBC is proportionally higher in the obese population. As secondary outcomes, we evaluated the pathophysiology that could explain such an association, the prognostic effect of obesity in a patient with this tumor subtype, and the targeted treatments that could be applied in this specific associative context.

The data presented in this article were designed to concisely report to generalists and specialists what is known about this issue so that they can improve their practice based on available evidence.

## METHODS

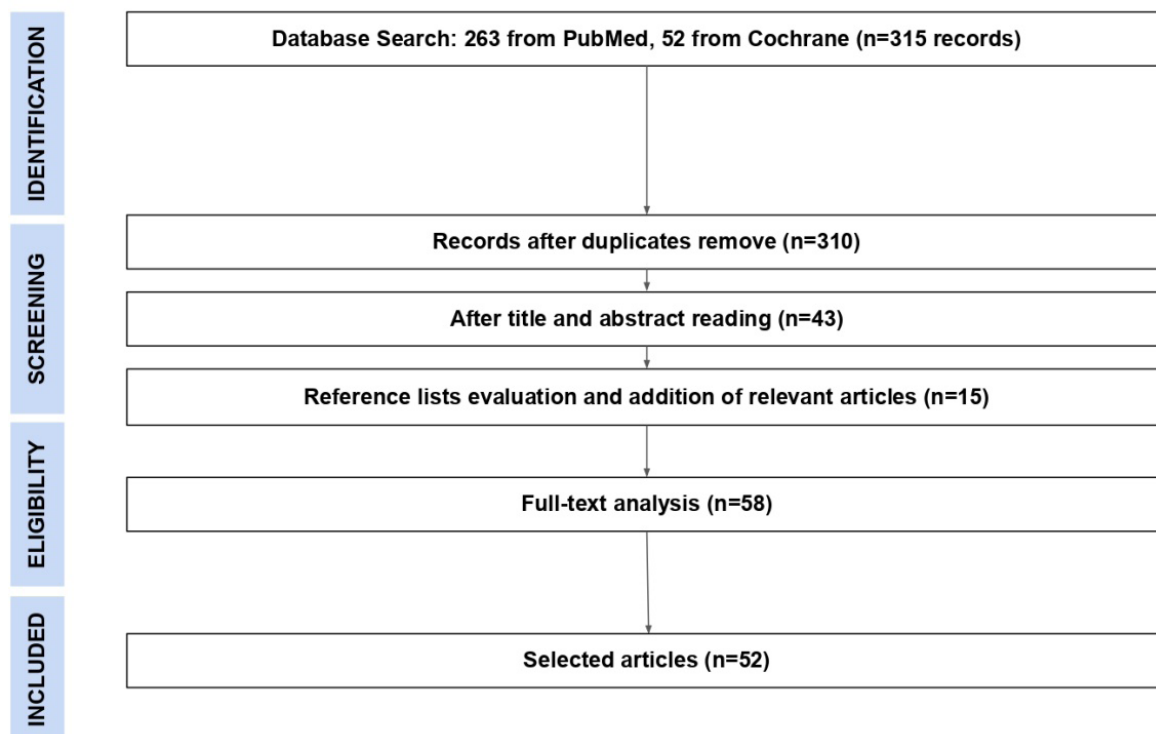
This review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>3</sup> (Figure 1). A systematic search was conducted to determine relevant articles published until July 1, 2022, using two

primary biomedical literature databases: PubMed/MEDLINE and Cochrane. The following terms were used to access papers of interest broadly: ((triple-negative breast cancer) OR (basal-like)) AND ((BMI) OR (obesity)). No limits were placed on the country or publication date. All types of studies, descriptives or analytics were accepted. Studies in process or only published in conference annals were not included.

Only articles in English were selected. Studies in which TNBC was analyzed, among other types of breast tumor, were also considered. Studies with women across both premenopausal and postmenopausal status were considered for analysis. Animal model studies were also included. After the initial exclusion of duplicates, titles and abstracts were revised, allowing the first filtration of our bibliography, selecting the articles with probably the highest impact for the full-text review.

A secondary selection of opportune papers for analysis was performed. Additional studies were identified by reviewing the reference lists of the first listed studies that met the inclusion criteria.

After full-text evaluations, the last refinement was concluded, finishing the selection process of adequate literature for this topic review. This systematic review was performed from this condensed but relevant group of articles. Thereafter, the study's samples, methods, results, and conclusions were qualitatively described. No statistical analysis was conducted on these data.



**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for systematic review articles selection.



This article's discussion of the relationship between obesity and TNBC was carefully and objectively detailed based on the most consistent data available. Aiming for a straightforward approach, we organized epidemiology, pathophysiology, prognosis, and interventions.

## RESULTS

The primary literature search yielded 310 articles, considering 263 from PubMed, 52 from Cochrane, and the removal of five duplicates. After the title and abstract reading, 43 studies directly related to the association between obesity and TNBC were selected. We added 15 other opportune studies by their reference lists evaluation, reaching 58 articles for full-text analyses. After reading all 58 texts, we ended up with 52 primary studies covering epidemiology, pathophysiology, prognosis, and treatment subtypes.

### Epidemiology

There are multiple studies concerning TNBC patients' characteristics. However, the pathophysiology of this tumor subtype has not been elucidated yet. Therefore, populational analyses have always been a first step in bringing to light this disease mechanism.

Through extensive sample studies, including initially its different subtypes, breast cancer incidence showed itself to be directly related to obesity frequency, and over years of detailed research comparing individual characteristics between breast cancer subtypes, TNBC alone also presented a frequent association with obesity in concordance with general tendency.

Millikan et al. found an increasing waist-hip ratio positively associated with basal-like tumors, even though no relation was observed with BMI<sup>4</sup>. After that, several studies pointed to a higher frequency of obesity among TNBC patients compared to other subtypes or obesity as a significant risk factor for TNBC<sup>5-12</sup>. Somali et al., Enger et al., and Maiti et al., found no relationship between obesity and TNBC<sup>13-15</sup>.

Pierobon's meta-analysis with 3,845 patients diagnosed with TNBC, which evaluated breast cancer, obesity, and menopausal status, concluded that this association between obesity and TNBC was only valid for women with premenopausal status<sup>10</sup>. This corroborated a previous study by Gaudet, which comprised women under 56 years old and restricted its conclusion of TNBC increased risk by obesity only to premenopausal status<sup>9</sup>. Also, in a pooled analysis of 34 studies comprising 35,568 patients, of which 1,997 had TNBC, Yang et al. identified an association between obesity and breast cancer confined to TNBC cases in women younger than 50 years old<sup>8</sup>. An epidemiological difference was then established with the protective effect obesity imposes over hormone receptor-positive tumors in premenopausal women<sup>11</sup>.

Concerning racial differences in this context, Siddharth et al. suggested a higher frequency of obesity among African-American women compared to European-American ones as one of the factors that could explain the TNBC earlier onset and more advanced stage at diagnosis in that population. Other factors related would be a genetic risk, low income, and inadequate screening<sup>16</sup>.

In Table 1, we listed and summarized the main epidemiological studies that evaluated the association between TNBC and obesity. It is observed that the correlation is positive in the majority of the studies (8 out of 11), with a particular emphasis on the premenopausal period.

### Pathophysiology

Obesity has already been linked to the development of different types of cancer. Concerning TNBC, a couple of articles examined molecular factors and pathways that may favor this tumor's emergence in obese patients, as summarized in Figure 2. Most of these studies are *in vivo* research using TNBC cells inoculated in animal models.

The main primary changes in an obese organism described as possible triggers for TNBC tumorigenesis are adipose tissue mechanical stress and hypoxia, with adipocyte death and consequent systemic inflammation. A second pathway recurrently explored is the high leptin levels observed in obese individuals, being directly associated with TNBC severity<sup>15,17,18</sup>.

Adipose tissue is responsible for inflammatory cytokines release, including IL-6, IL-8, IL-12, CCL2, and IL-1 $\beta$ <sup>19</sup>. Leptin and IL-6 are related to increased macrophage migration to adipose tissue and their subtype change from type 1 to type 2. Type 2 macrophages secrete IL-6 (dependent on NADPH oxidase 2 activity), IL-8, TGF- $\beta$ , and EGF. Also, leptin stimulates T cell release of IL-2 and IFN- $\gamma$ <sup>20,21</sup>.

Leptin, IL-2, and IFN- $\gamma$  from T cells, IL-6, and TNF- $\alpha$  (through glycoprotein 130) from type 2 macrophages can activate STAT3/JAK2, NF- $\kappa$ B, and Wnt/EZH2<sup>17,20,21</sup>. These transcription factors regulate the expression of NANOG, SOX2, and OCT4 — genes that are shown to induce stem-like properties in TNBC cells, including renewal capacity<sup>18,21</sup>.

In addition, obese individuals present low natural killer (NK) cell number and activity that have already been associated with poor prognosis in TNBC<sup>22</sup>. NK cells play a role against tumor cells' survival, and chronically elevated leptin levels can decrease leptin receptor sensibility, resulting in the downregulation of cytotoxic activity<sup>23</sup>. Naik et al. described this immune pathway by which obesity could favor TNBC progression<sup>24</sup>.

Teslow et al. reported that inflammation and reactive oxygen species derived from the obesity context can regulate splicing factor serine/arginine-rich splicing factor 2 (SRSF2), which augments the expression of methyl-CpG-binding domain variant 2 (MBD2-v2) that is another inductor of NANOG overexpression<sup>25</sup>. Additionally, Kolb et al. presented that inflammation enhances the

**Table 1.** Previous articles that evaluated the association of triple-negative breast cancer incidence with obesity.

Studies	Country	Sample size	Study design	Main findings	Odds ratio or p-value	Risk of bias
Enger et al. <sup>14</sup>	U.S.A.	1,184 cases; 272 TNBC	Case-control (two groups: pre and postmenopause)	Body mass index was not associated with TNBC, including BMI>27	No association was found regarding BMI	Low cut point regarding BMI>27
Milikan et al. <sup>4</sup>	U.S.A.	1,424 cases; 225 basal-like	Case-control	Elevated WHR was associated with increased risk of basal-like breast cancer in pre and postmenopausal women compared to luminal A cases and controls.	WHR 0.77–0.83: OR 2.3 (95%CI 1.5–3.5)/≥0.84: OR 2.3 (95%CI 1.4–3.6) (referent to controls)	Higher incidence of basal-like tumors among African-Americans
Vona-Davis et al. <sup>5</sup>	U.S.A.	620 cases; 117 TNBC	Retrospective cohort	Obesity was present in 49.6% of those with triple-negative tumors but in only 35.8% of those with non-triple-negative tumors.	p=0.0098	No analysis according to age subgroups
Kwan et al. <sup>7</sup>	U.S.A.	2,544 cases; 288 TNBC	Prospective cohort	Compared with luminal A cases, triple-negative cases tended more likely to be overweight or obese if premenopausal	Overweight: OR 1.82 (95%CI 1.03–3.24)/Obese: OR 1.97 (95%CI 1.03–3.77)	Higher incidence of TNBC among African-Americans
Maiti et al. <sup>15</sup>	U.S.A.	176 cases; 86 TNBC	Retrospective cohort	Triple-negative breast cancer is associated with a higher prevalence of the metabolic syndrome but not with higher BMI	No association was found regarding BMI	Reduced population, retrospective study
Trivers et al. <sup>6</sup>	U.S.A.	476 cases, 135 TNBC	Case-control	Women with TN tumors were more likely to be obese than normal/underweight	OR 1.89 (95%CI 1.22–2.92)	Tumor specimens were available only on a subset of eligible cases
Yang et al. <sup>8</sup>	U.S.A.	35,568 cases; 1,997 TNBC	Pooled analysis 34 studies/Case control	Association in women <50 years between obesity and breast cancer confined to TNBC cases	OR 1.80 (95%CI 1.42–2.29)/p=0.000002	Differences in study populations, designs and methods of collecting risk factors, and marker data
Gaudet et al. <sup>9</sup>	U.S.A.	890 cases; 246 TNBC	Case-control	Larger body size among premenopausal women was associated with higher risk of luminal B and TNBC	OR 1.67 (95%CI 1.22–2.28)/p=0.026 (compared to luminal A)	Biased observed findings for unmeasured risk factors, staining obtained by a single pathologist
Pierobon et al. <sup>10</sup>		24,479 cases; 3,845 TNBC	Systematic review and meta-analysis	The case-case and case-control comparisons showed a significant association between TNBC and obesity	Case-case: OR 1.2 (95%CI 1.03–1.4)/p=0.003 Case-control: OR 1.43 (95%CI 1.23–1.65)/p=0.913	

Continue...

**Table 1.** Continuation.

Studies	Country	Sample size	Study design	Main findings	Odds ratio or p-value	Risk of bias
Somali et al. <sup>13</sup>	Turkey	882 cases; 132 TNBC	Retrospective cohort	No significant difference was observed in terms of BMI between postmenopausal and premenopausal patients in the TNBC group	p=0.08	Patients with unknown menopausal status, >50 years old were considered postmenopausal
Chen et al. <sup>11</sup>	U.S.A.	2,659 cases; 1,275 TNBC	Case-case-control	Obese premenopausal women had an increased risk of TNBC while obese postmenopausal women had a reduced risk of TNBC	Pre: OR 1.82 (95%CI 1.32–2.51)/ p=0.004 Post: OR 0.74 (95%CI 0.54–1)/ p=0.032	Case-case comparison should not be extended to a cancer-free population

U.S.A.: United States of America; TNBC: triple-negative breast cancer; BMI: body mass index; CI: confidence interval; WHR: waist-hip ratio; OR: odds ratio.

upregulation of angiopoietin-like 4 (ANGPTL4) in adipocytes. This condition leads to angiogenesis and progression of breast cancer<sup>19</sup>.

High levels of leptin and leptin receptor activity have also been shown to promote Serpine-1 gene expression that codifies serine protease inhibitors in vascular epithelial cells. Through binding vitronectin, this protein favors the detachment of cancer cells, facilitating metastasis. Leptin knockdown resulted in a diminution of metastasis<sup>26</sup>.

A third pathway described by which obesity could be associated with TNBC development is chronic hyperglycemia. D'Esposito et al. showed that TNBC cells become more invasive when cultivated with adipocytes and even more when exposed to a hyperglycemic environment. Hyperglycemia increases CCL5 produced by adipocytes that bind to CCR5, which activates STAT3/JAK2, mTOR, and p38MAP kinase. CCL5 presence in adipose tissue was associated with lymph node positivity and metastasis<sup>27</sup>. In concordance, Dietze et al. showed that hyperglycemia through induced hyperinsulinemia and IGF-1 raise could activate AKT/mTOR cascade, resulting in elevated glucose uptake by the cell ending on the Warburg effect<sup>20</sup>.

## Prognosis

Previously, it has already been shown that obesity appears to be a factor in poor prognosis for breast cancer in general. Ewertz et al., in a large sample Danish study with 18,967 patients, revealed an increase in metastasis and death frequency in obese patients with breast cancer compared to non-obese ones; however, cancer subtypes were not discriminated<sup>28</sup>.

Despite a general investigation of obesity and breast cancer development, researchers have been specifically interested in evaluating the influence of obesity according to each cancer subtype. In the last decade, a couple of studies were dedicated to analyzing if obesity could or could not be confirmed as a possible factor for a poor prognosis in TNBC. The results found were not always homogeneous.

In a systematic review and meta-analysis including nine studies comprising 4,412 TNBC patients, Mei et al. concluded

that disease-free survival (DFS) and overall survival (OS) were independent of BMI<sup>29</sup>. This was consistent with other studies not included in this meta-analysis<sup>30–34</sup>. It is valid to point out that Dawood et al. and Tait et al. analyzed their sample by menopausal status and still found no significant influence of BMI over TNBC prognosis between pre and postmenopausal groups<sup>31,33</sup>. Schmidt et al., however, presented similar results but with a 70% postmenopausal sample<sup>34</sup>. Also, Mowad et al., despite finding larger tumor size and grade staging, DFS and OS remained indifferent among obese and non-obese individuals<sup>32</sup>.

In counterpoint, some authors found a positive association between obesity and TNBC's poor prognosis, including DFS and OS. Through these studies, attention should be taken to Turkoz et al. presenting an all-premenopausal sample and Loi et al. a 74% one<sup>35,36</sup>. Also, Hao et al., Bao et al., and Al Jarroudi et al. found a worse prognosis exclusively among the premenopausal group<sup>37–39</sup>. However, Choi et al. described no difference according to menopausal status, comprising only 50 patients<sup>40</sup>. Chen et al., independent of menopausal status, similarly presented a decrease in DFS and OS in the obese group and were the first, to our knowledge, to include in the analyses the abdominal circumference, not only the weight, finding a worse prognosis in the group with both general obesity associated with central obesity<sup>41</sup>.

Additionally, Maehle et al. described a better prognosis for their obese negative hormone receptor group than the non-obese one, considering that the sample was 75% composed of postmenopausal women and TNBC individuals were not isolated<sup>42</sup>.

## Treatment

Since there is no available well-established target therapy for TNBC, modifiable risk factors, such as weight intervention, have been a source of interest in the last years for prevention or even cancer progression impairment.

Eliassen et al., in a large prospective cohort study within the Nurses' Health Study, including 87,143 postmenopausal patients followed up for 24 years, observed an increased risk for general breast cancer associated with weight gain since the age of 18

years. This pointed to weight maintenance or loss as a possible prevention method. However, TNBC was not evaluated separately<sup>43</sup>.

Enger et al. precisely found a tendency of risk increase of breast cancer by weight gain during the menarche restricted to hormone receptor-positive tumors. Hormone receptor-negative tumor risk was independent of weight change, and physical activity frequency was also evaluated. Weight loss or physical activity after diagnosis was not evaluated<sup>14</sup>.

First, *in vivo* studies showed reverse TNBC progression and delayed tumor latency in obese mice submitted to weight loss on a low-fat diet. This phenomenon was associated with a reduction in kinases (PKC- $\alpha$ , PKD1, PKA, and MEK3) and an increase in AMPK $\alpha$  activity<sup>44,45</sup>.

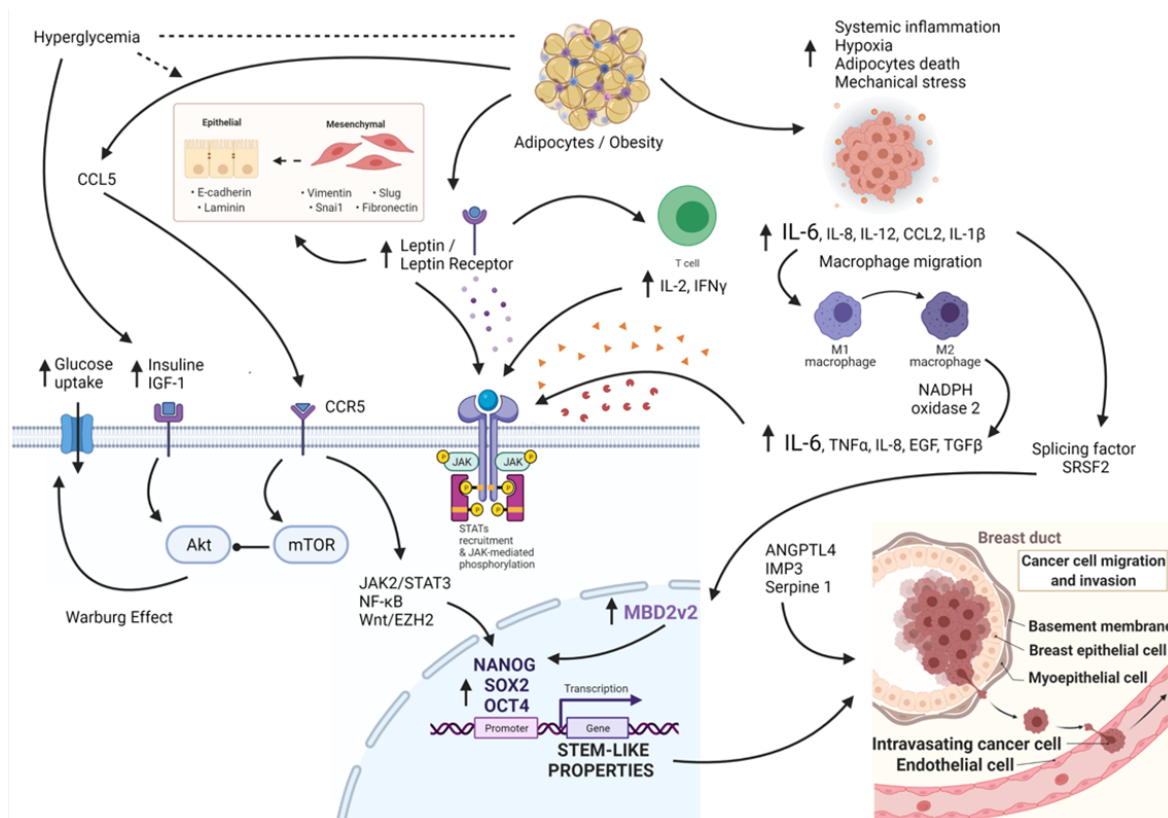
However, studies with TNBC patients did not show that clear correlation. In a 518 Chinese patients study, weight loss was associated with higher tumor recurrence and mortality than stable weight<sup>38</sup>. In a second study with 173 patients, weight change — gain or loss — did not correlate with Ki67 or pathologic complete response change during neoadjuvant chemotherapy<sup>46</sup>. In counterpoint, Wang et al. described JAK/STAT3-regulated fatty acid  $\beta$ -oxidation as critical for cancer stem cell self-renewal and chemoresistance, which could be more evident in obese patients<sup>47</sup>.

Finally, some authors tested therapeutic drug alternatives for TNBC related to obesity pathophysiology. Otvos et al., in a mouse xenograft model for TNBC, found a significant average survival

increase by subcutaneous Allo-aca (a leptin receptor antagonist) administration compared to conventional intraperitoneal cisplatin<sup>48</sup>. Similarly, Gourgue et al. described a reduction in TNBC growth with apelin antagonist F13A. This substance reduces apelin activity, an adipokine increased in adipose tissue of obese mouse tumors<sup>49</sup>.

Naik et al., in an extensive discussion about immune pathways related to TNBC development and progression in obese organisms, suggested some hypothetical points of possible therapeutic interventions to be studied:

- 1) PD-1/PD-L1 suppression, since in a study with 250 patients, obese ones got the major benefit of this intervention than lean individuals. Being PD-L1 a mark of immunosuppression, it becomes a possible target for blocking;
- 2) Adoptive NK cell therapy, since obese have low NK cell number and activity;
- 3) Inhibition of IL-6 or its receptor related to a tumorigenic pathway;
- 4) Inhibition of CCL2/CCR2 and CSF/CSF-1R related to macrophage type 2 polarization and accumulation, also favoring stem cell properties development;
- 5) Blocking of myeloid-derived suppressor cells that also express PD-L1 and are stimulated by obesity-related cytokines; and
- 6) TGF- $\beta$ 1 blocking since its increment in obese individuals hinders a sustained effective T cell response against tumor cells<sup>24</sup>.



**Figure 2.** Pathways linking obesity and breast cancer development (created with BioRender).

## DISCUSSION

After some years of research and many studies focused on exploring the specific effect of obesity on TNBC development and progression, we are beginning to identify concordant results that point to the establishment of initial consistent knowledge on this topic. In the past, breast cancer was considered a unique disease. Today, we understand that different subtypes make breast cancer notably a heterogeneous disease.

Concerning TNBC, the majority of studies agree that obesity is a risk factor for tumor development. Just one study focused on evaluating menopausal status directly, and it suggested that this association is limited to the premenopausal period<sup>10</sup>. The authors gave no hypothesis to explain why the prejudicial effect of obesity would be reduced after menopause, especially considering its supposed independence from hormone influence.

A temporality bias, however, could be a reasonable hypothesis. TNBC presents itself as an early-onset tumor, possibly based on the significant influence of genetic factors. Thereby, incidence at older ages would naturally be lower, as most susceptible individuals had already developed and manifested it at a younger age. Also, a higher incidence of obesity and TNBC among African-Americans should be considered as a possible bias regarding the influence of confounding genetic and social factors in this population.<sup>4,7</sup>

Mamidi et al. identified the main pathways activated in premenopausal women with TNBC in a whole genome transcriptome analysis, including unfolded protein response, endoplasmic reticulum stress, B cell receptor, and autophagy signaling<sup>50</sup>. Despite that, more investigation should be conducted to explain the possible influence of hormonal status on these specific mechanisms. As for hormone receptor-positive breast cancer, it is valid that the opposite association is observed: obesity showed itself as a protective factor among premenopausal women. Potischman et al. suggested that in premenopausal women, obesity is associated with a more significant number of anovulatory cycles, thus, lower estradiol levels and less incidence of hormone-dependent tumors<sup>51</sup>.

Inflammation is a new focus of interest for all diseases epidemiologically associated with obesity. Pathophysiology studies revealed a world of obesity-related inflammatory and genetic cascades that could justify developing cancers independently of estrogen, such as TNBC. Almost all of the articles consisted of *in vivo* research and elucidated different pathways that could be more investigated to offer new potential therapeutic targets.

Studies related to obesity and TNBC prognosis presented conflicting findings. The authors do not exclude possible bias considering the aggressiveness of this tumor subtype. Once this cancer is established, its progression is possibly little or nothing different comparing an obese or not-obese environment. However, some authors found a worse prognosis, especially in premenopausal groups. This condition may be associated with significant incidence of TNBC in premenopausal obese women.

Concerning the still absence of specific treatment, lifestyle modifiable factors have been evaluated. Sun et al. pointed to the maintenance of an optimal body weight as a valuable primary prevention for TNBC — the only clear, effective measure currently available<sup>52</sup>.

Even though obesity seems to favor the development of TNBC, studies investigating weight loss as a possible factor for tumor control after diagnosis did not reach concordant conclusions; tumor stage, chemotherapy side effects, or diet may influence weight loss. Further investigation in more homogeneous groups is necessary to differentiate cases in which diet and consequent weight loss could be used to break the disease from those in which weight loss occurs due to advanced tumor itself or palliative treatment. Weight loss could contribute to the reduction of hormones and inflammatory cytokines that eventually figure as stimulants for tumor cell perpetuation.

The impact of physical activity still needs to be specifically better evaluated for TNBC. Few studies analyzed it as a risk reducer for this tumor incidence. No consistent evidence has been observed, as it was reported by The Women's Health Initiative concerning breast cancer in general<sup>53</sup>.

The complexity of inflammatory pathways and immune system regulation is a current challenge and an opportunity for improving or developing treatment for different types of cancer. Little literature is currently available, but specific targets for obese-related environmental factors seem promising, including leptin, IL-6, PD-1/PD-L1, and NK cells.

As a qualitative review, we emphasize that this study presents the risk of bias related to a subjective joint analysis of articles. The absence of a meta-analysis weakens the power of its evidence. Results remain based on the global impression of a team of experts over a systematic selection of studies.

## CONCLUSIONS

There is consistent evidence supporting obesity as a risk factor for TNBC. Inflammatory cytokines related to an obese environment may contribute to tumor development. It is uncertain if the premenopausal status is a worsening factor. Obese patients with already diagnosed TNBC have a similar prognosis to non-obese ones, and their weight loss does not seem to be a disease course modifier. Few target drugs directed to obesity-related tumorigenic pathways began to be tested and showed initial encouraging results. More investigations concerning the pathophysiology and new treatment possibilities need to be performed.

## AUTHORS' CONTRIBUTIONS

LLI: data curation, formal analysis, visualization, writing – original draft, writing – review & editing. SRM: investigation, software, writing – review & editing. JRF: funding acquisition, resources, supervision, validation. EB: funding acquisition, project administration, resources. SMO: conceptualization, methodology, project administration.




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## REFERENCES

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# The influence of germline mutations on breast cancer

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## ABSTRACT

The ability to evade protection mechanisms and uncontrolled cell growth can lead to the development of mutations, whether somatic or germline, and consequently to the dreaded diagnosis of cancer. Breast cancer is considered the most common type of cancer in women in several regions of Brazil, mainly in the South and Southeast, second only to non-melanoma skin cancer. Approximately 5% to 10% of neoplasms are related to germline alterations that lead to hereditary predisposition. There is evidence of an association with mutations in nine genes, the highest risk being breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2). Due to its epidemiological importance, in this narrative review we observed the main genetic mutations and syndromes associated with breast carcinoma, the recommendations for screening in high-risk patients, and the indication for genetic counseling. Bibliographic research on the PubMed and Cochrane databases and analysis of the *Guidelines Breast Cancer Risk Reduction* and *Breast Cancer Screening and Diagnosis*, from June 2022 to September 2023. In this review, we observed a greater influence of germline mutations on breast cancer related to the genes BRCA1, BRCA2, PALB2, PTEN, CDH1, STK11 and, in Brazil, considered a country of ethnic-racial diversity, to TP53. As cancer screening in the country is opportunistic, knowledge of germline mutations associated with breast cancer offers specific screening recommendations for high-risk patients, indications for genetic counseling, and guidelines for prophylactic surgery, in addition to impacting the formulation of public screening policies.

**KEYWORDS:** genetic predisposition to disease; germ-line mutation; breast neoplasms; genes; genes, BRCA1; genes, BRCA2.

## INTRODUCTION

The human genome is composed of approximately 20 to 25 thousand genes, capable of producing functional molecules, and are considered the units of genetic information. This production results from the processes of transcription and translation<sup>1</sup>.

Exposure to various endogenous and exogenous factors can generate changes in DNA, causing the so-called mutations<sup>2</sup>, which can occur in somatic or germline cells. There are protective mechanisms capable of correcting them, but when these mechanisms are ineffective, they lead to the development of malignant cells<sup>3</sup>.

Female breast carcinoma is prevalent in all regions of the country, mainly in the Southeast and South, second only to non-melanoma skin cancer. An estimated 73,610 new cases were reported each year in the 2023–2025 triennium. The risk increases with age, but it has been observed that the number of young patients diagnosed with the disease has exponentially increased<sup>4</sup>.

Researchers indicate that between 70% and 80% of breast carcinomas are related to environmental factors and 5% to 10% to germline genetic alterations<sup>5</sup>.

When a pathogenic germline variant alone is associated with a significantly increased risk of cancer, it is a hereditary predisposition syndrome. Most of these syndromes result from a mutation in one of the two alleles of a given gene present in the genome. Therefore, they present an autosomal dominant inheritance pattern, with a 50% risk of transmission to offspring<sup>6</sup>.

Risk stratification for the development of breast cancer in a consultant depends on a detailed anamnesis, starting from personal history, analyzing factors such as age, habits, sedentary lifestyle, smoking, alcohol use, gynecological and obstetric history, personal and family history of cancer in first-degree relatives. In addition, there are mathematical models that quantify the risk of breast cancer, the most widely used being those of Gail and Tyrer-Cuzick<sup>7</sup>.

Authors of a recent publication by the Breast Cancer Association Consortium found strong evidence for the association of pathogenic variants in nine genes with breast cancer risk. The genes considered high risk are TP53, BRCA1, BRCA2, PALB2, and ATM; BARD1, CHEK2, RAD51C, and RAD51D are moderate risk. ATM

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and CHEK2, in turn, are related to estrogen receptor-positive breast cancer, and the others, to hormone receptor-negative<sup>8</sup>.

Pathogenic variants in BRCA1 and BRCA2 are the most common, being associated with almost 50% of the risk attributable to the family component for the development of the disease. These patients have a cumulative increase in the risk of invasive breast cancer, from 55% to 85%, up to the age of 70 years and a 15% to 65% increase in the risk of developing ovarian cancer<sup>8</sup>.

It is worth familiarizing oneself with other hereditary diseases, such as Li-Fraumeni syndrome (mutation in the TP53 gene), Cowden syndrome (PTEN), and those in which other sites of involvement are more common, but which also present a risk for breast cancer such as Peutz-Jeghers syndrome (STK11) and hereditary diffuse gastric cancer (CDH1)<sup>9</sup>.

Due to their epidemiological importance, in this study we described the main genetic mutations and syndromes associated with breast cancer and the risks of developing the disease as well as screening recommendations, strategies for early diagnosis, classification of high-risk patients, and genetic counseling.

The main objective of the study was to identify the importance and influence of germline genetic mutations on breast cancer in the literature. As secondary objectives, we sought to outline strategies for tracking the disease in the high-risk population.

## METHODS

For this narrative review, the bibliographic research was based on the described objectives. The starting point consisted of the questions: what is the importance of the hereditary component in the risk of breast cancer? What syndromes are most associated with breast cancer? What are the risks of a person with a hereditary predisposition developing breast cancer? What are the screening strategies for patients classified as high risk? Searches were conducted on the PubMed and Cochrane databases and analysis of the *National Comprehensive Cancer Network Breast Cancer (NCCN)*, *Guidelines Breast Cancer Risk Reduction*, and *Breast Cancer Screening and Diagnosis*, from June 2022 to September 2023.

## RESULTS AND DISCUSSION

The human genome is composed of DNA, and we are exposed daily to several endogenous and exogenous factors capable of affecting and changing our genetic code, giving rise to somatic or germline mutations<sup>10</sup>. Somatic, or acquired, mutations occur during DNA replication, preceding a mitotic division, and are generally limited to a specific tissue. They affect all cells generated from the mutated cell, and this mechanism is one of the hallmarks of cancer. Germline cells occur during DNA replication, preceding meiosis. The mutation affects gametes and all cells that originate from them and are transmitted to offspring<sup>10</sup>.

Breast cancer is categorized into subtypes based on molecular identification from immunohistochemical evaluation. In this process, the presence or absence of hormone receptors (estrogen and progesterone) and overexpression of the HER2 protein are identified. Perou and Sorlie (2000) developed *in situ* hybridization techniques for detecting HER2 amplification, leading to greater accuracy in dividing breast cancer into four subgroups<sup>11</sup>:

- Luminal A (KI 67, which corresponds to a cell proliferation index<10%);
- Luminal B (KI 67>10%);
- HER2 overexpressed (3+);
- Triple-negative (tumor without all three standard molecular markers).

Although most neoplasms are the result of complex interactions between the genetic component and the environment, a percentage of cases can be attributed to inherited genetic alterations, which lead to a greater predisposition to the development of tumors. Currently, it is estimated that approximately 5% to 10% of carcinomas are associated with hereditary predispositions such as breast, prostate, colorectal, and pancreatic cancer. Furthermore, certain tumors that occur predominantly in childhood may be hereditary, as is the case with retinoblastoma, considered the paradigm of familial cancer<sup>12</sup>.

There are support tools, such as mathematical models, that can be used to numerically predict the risk of breast cancer. The most widely used are the Gail, Claus and Tyrer-Cuzick models. The Gail model is the best known and focuses primarily on personal background, but is limited to family background. The Claus model focuses almost exclusively on family background. Conversely, the Tyrer-Cuzick model is the one that covers information the most<sup>13</sup>.

Gail assesses the risk of breast cancer occurring in the next five years, reaching the age of 90 (lifetime risk). Using this method, eligibility for the use of tamoxifen is calculated (greater than 1.67% in five years). The Claus model assesses the lifetime risk of breast cancer and determines eligibility for breast MRI (greater than 20%). Tyrer-Cuzick assesses the ten-year risk of breast carcinoma and polygenic genetic inheritance and guides genetic counseling in patients with a lifetime risk above 20%.

Genes associated with hereditary breast cancer are subdivided into high-risk genes (relative risk – RR>or equal to 5), moderate-risk genes (RR>or equal to 1.5 and<or equal to 5), and low-risk genes (RR<or equal to 1.5)<sup>8,14</sup>.

In the last decade, significant advances have been made in the knowledge of molecular mechanisms that give rise to cancer, identifying several genes directly involved in the development of neoplasias, including oncogenes (which predispose to cancer when overexpressed), tumor suppressor genes (which can give rise to a tumor when inactivated), and genes of the DNA repair system (inactivation leads to the accumulation of mutations). This culminated in the identification of genes associated with specific hereditary cancer predisposition syndromes<sup>15</sup>.



The most frequently mutated genes are BRCA1 (27.4%), BRCA2 (20.3%), TP53 (10.5%), ATM (8.8%), CHEK2 (6.2%), and PALB2 (5.1%) (Figure 1). BRCA1 and BRCA2 account for approximately 50% of all pathogenic/likely pathogenic germline variants. The multigene panel was responsible for doubling the identification of germline variants in predisposition genes other than BRCA1 and BRCA2 as well as increasing the chance of finding a variant of unknown significance (VUS) by 12 times<sup>16</sup>.

Genes considered moderate risk, which increase the risk of breast cancer by at least two times, are identified in 2% to 3% of women diagnosed with breast carcinoma and in approximately 1% of the general population. ATM, CHEK2, and PALB2 are the most common in this subgroup<sup>17</sup>.

For ATM and CHEK2 variants, odds ratios were higher for breast cancer with estrogen receptor-positive disease than for hormone receptor-negative disease. For BARD1, BRCA1, BRCA2, PALB2, RAD51C, and RAD51D variants, odds ratios were higher for estrogen receptor-negative than for hormone receptor-positive disease<sup>18</sup>.

Among the high-risk syndromes, we can mention hereditary breast and ovarian cancer (HBOC), related to BRCA1 and BRCA2. Female patients with a BRCA1 mutation have a risk of approximately 70% of developing breast cancer by the age of 80 and a 9% to 20% risk of developing a second breast cancer. In patients with a BRCA2 mutation, the risk remains the same until the age of 80, but the risk of developing a second cancer within five years is reduced by 3% to 12%. The risk of developing ovarian cancer by the age of 70 in patients with a BRCA1 mutation is approximately 44% and with a BRCA2 mutation, 17%<sup>9</sup>.

Li-Fraumeni syndrome is also mentioned, associated with a germline mutation in the TP53 gene, in which international

case studies estimate a risk of up to 90% of carriers developing cancer by the age of 60. When developing breast cancer, the risk would be approximately 85% by the age of 70. The syndrome is considered to be at high risk for the development of multiple primary tumors<sup>16</sup>.

In Brazil, special attention should be given to the p.(Arg337His) variant in the TP53 gene. It is estimated that it is found in around 2.7 out of a thousand individuals born in the Southern region of the country. Researchers associate a more aggressive phenotype of Li-Fraumeni, with a mutation in an expression-modifying gene, XAF1. As a consequence, the high prevalence of this variant in TP53 significantly impacts screening strategies and risk reduction in the country<sup>19</sup>.

Knowledge of genetic mutations related to breast cancer predisposition has a strong impact on the creation of screening and early diagnosis strategies.

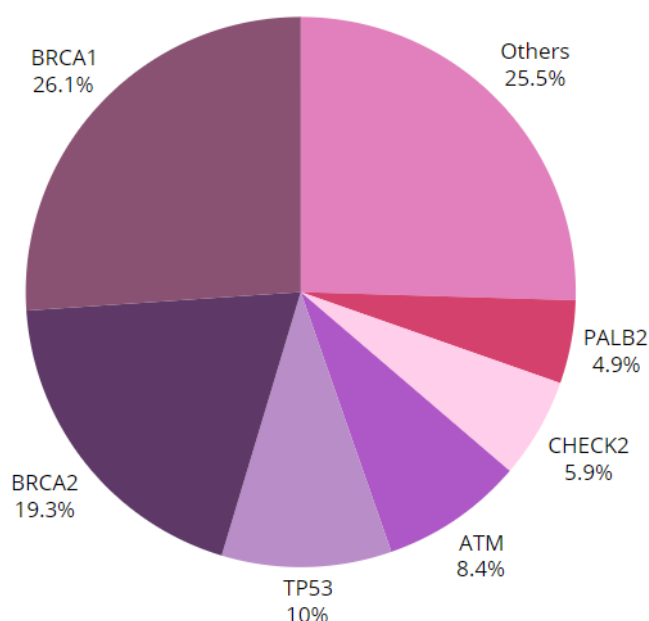
According to the NCCN, screening for patients with BRCA1 and BRCA2 mutations begins at the age of 25, with a biannual clinical examination and annual breast MRI, and at age of 30, with annual mammography and MRI. According to the North American organization, risk-reducing mastectomy or prophylactic tamoxifen should be considered; salpingo-oophorectomy should be indicated as of the age of 35 in BRCA1 and as of the age of 40 in BRCA2; and, above the age of 75, management should be individualized.

For men, an annual clinical breast exam is recommended as of the age of 35 and mammography should be considered at the age of 50 or ten years before the earliest diagnosis in the family. For patients with TP53 mutation, breast screening is recommended as of the age of 20, with biannual clinical examination and annual MRI, and as of the age of 30, annual breast MRI and mammography<sup>20,21</sup>.

Genetic testing to assess susceptibility to breast cancer has been an important aspect of disease prevention. Since the 1990s, with the description of the BRCA1 and BRCA2 genes, there has been a continuous improvement in guidelines for screening for breast cancer and reducing the risk for high-risk women and their families<sup>22</sup>.

Genetic counseling is a fundamental part of the national cancer policy, being responsible for identifying individuals at high risk of developing tumors. This is the communication process that deals with the problems associated with the occurrence or possibility of a genetic disorder occurring in a family. Families with multiple cases of cancer, bilateral tumors, or tumors diagnosed at very early ages compared to the average age of diagnosis in the general population should be referred to genetic counseling. Among the foundations of this counseling are:

- voluntary use of services;
- informed decision-making;
- nondirective and noncoercive counseling;
- protection of privacy and confidentiality of genetic information;
- attention to psychosocial aspects associated with the impact and management of genetic information<sup>9</sup>.



**Figure 1.** Graph with the main genes related to breast cancer and their frequency.



During a genetic evaluation, the patient's ancestry and region of origin must be taken into account. Individuals with *Ashkenazi* Jewish ancestry, for example, have a higher prevalence of mutations in the BRCA1 and BRCA2 genes, given that one in every 40 patients (2.5%) carries the mutation compared to one in every 400 patients (0.25%) in the general population<sup>9</sup>.

In genetic counseling, risk-reducing surgeries, traditionally known as prophylactic surgeries, are considered prevention strategies. This term should be used with caution, as it suggests the false idea that mastectomy guarantees total prevention against breast cancer. This procedure may be indicated for high-risk patients, however, its role is better defined in women carrying deleterious mutations, especially BRCA1 and BRCA2. These surgeries are highly complex and have a considerable risk of complications, and should therefore be reserved for special situations and after careful assessment of risks and benefits in a multidisciplinary environment<sup>23</sup>.

In the guideline published in 2024 by the American Society of Clinical Oncology (ASCO)<sup>24</sup>, germline genetic testing is recommended for any patient up to 65 years of age who is newly diagnosed with breast cancer or has a history of this neoplasia, regardless of family history. This will allow patients to seek genetic counseling, allowing changes to be made in the way they and their families are monitored. It is also recommended that all patients with a history of breast cancer diagnosed over the age of 65 with any of the following criteria be tested:

1. Personal or family history suggesting the presence of a pathogenic variant;
2. Patient with triple-negative breast cancer histology;
3. Male patient;
4. Patient of *Ashkenazi* Jewish descent or member of a population with a higher prevalence of founder mutations.

In Brazil, Bill No. 265/2020 is currently being processed in the National Congress, which amends Law No. 11.664/2008, which provides for the implementation of health actions that ensure prevention, detection, treatment, and follow-up of cervical and breast cancers within the scope of the Brazilian Unified Health System (SUS), to also ensure tests for detecting genetic mutations<sup>25</sup>.

The right has already been assisting women in the supplementary system operated by health insurance plans since 2014. In 2015, through the law known as the "Angelina Jolie Law," an agreement was signed between the government of Rio de Janeiro and the SUS for tests to detect genetic mutations of the BRCA1 and BRCA2 genes in women with a family history of neoplasia diagnosis. In 2019, Minas Gerais was the second Brazilian state to formulate legislation with the same purpose, followed by the states of Goiás, the Federal District, and Amazonas.

The NCCN 2024 includes the possibility of risk-reducing mastectomy for women carrying mutations in other genes, such as TP53, PTEN, PALB2, and salpingo-oophorectomy for those with

mutations in RAD51C, RAD51D, and BRIP1. The first consistent data regarding the benefit of risk-reducing surgery in women at high risk for breast cancer come from the study by Hartmann et al., which showed a risk reduction after 14 years of follow-up in 90% of cases<sup>26</sup>.

A study published in the Breast Cancer Research and Treatment in 2019 evaluated 2,857 asymptomatic women carrying a BRCA1 or BRCA 2 mutation and the benefit of risk-reducing surgery. At the end of the average follow-up of ten years, there were 268 cases of breast cancer in the BRCA1 group, which did not undergo surgery, and a higher mortality rate compared to those patients who underwent surgery (99.7% vs 93.2%,  $p=0.002$ )<sup>21</sup>.

In view of the complexity of hereditary cancer in public health programs in 1996, in the USA, the National Cancer Institute (NCI) proposed the creation of a national cancer genetics network through the joint effort of doctors and researchers from various health institutions. The Cancer Genetics Network (CGN) was officially announced in September 1998 as a network of eight centers specializing in the study of hereditary predisposition to cancer<sup>27</sup>.

## CONCLUSIONS

The Brazilian population has unique ethnic characteristics. The miscegenation observed in the country offers an opportunity to advance in the understanding of the genetic characteristics of cancer without the bias of studies with isolated populations<sup>28</sup>.

Identifying individuals with a higher genetic susceptibility to developing neoplasms is important, considering that there are education, screening, and risk reduction measures that can be indicated for this specific group<sup>12</sup>. Screening strategies should be followed with clinical and imaging tests in patients of all social conditions.

In Brazil, there are still few public or private actions aimed at identifying, guiding, and monitoring individuals and families at high risk for hereditary cancer. Larger and more prospective studies are necessary to observe and measure more effective interventionist — or even observatory — methods with greater certainty of execution.

## AUTHORS' CONTRIBUTION









MFSVG: Conceptualization, Literature review, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. LLSC: Data curation, Formal analysis, Writing – review & editing. CA: Formal analysis, Investigation, Writing – original draft. JPCA: Validation, Writing – review & editing. HRG: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. ADS: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. JTCA: Conceptualization, Project administration, Methodology, Visualization, Writing – original draft.

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# Hyperbaric oxygen therapy for complications of breast cancer surgery

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## ABSTRACT

In 2020, there were approximately 2.3 million new cases of breast cancer worldwide. Breast-conserving surgery followed by adjuvant radiotherapy has replaced radical and modified radical mastectomy as the standard treatment for patients with early-stage breast cancer, with equivalent overall survival and disease-free survival rates. Oncoplastic techniques consist in removing the tumor from the breast and applying plastic surgery techniques for breast reconstruction. The use of oncoplastic techniques may increase the number of women who experience postoperative complications or who are recalled for biopsy. Complication rates of around 16% can be considered acceptable, with the most common immediate complications being delayed wound healing, fat necrosis, and infection, while late complications being fibrosis and breast asymmetry. The use of hyperbaric oxygen therapy (HBOT) appears as an alternative for the treatment of these conditions. The Undersea and Hyperbaric Medical Society recognizes 14 valid medical indications for HBOT. Among these, those that stand out with interest in mastology are: chronic wounds; compromised flaps and grafts; radiotoxicity and soft tissue infections. Although most of the evidence is the result of observational studies or is extrapolated from the use of HBOT in other areas, its use may contribute to better outcomes in patients undergoing surgical treatment for breast cancer.

**KEYWORDS:** hyperbaric oxygenation; mastectomy; breast neoplasms; mammaplasty.

## INTRODUCTION

In 2020, there were approximately 2.3 million new cases of breast cancer worldwide, equivalent to an estimated risk of 47.80 cases per 100,000 women. In the same period, in Brazil, there were 17,825 deaths from female breast cancer, corresponding to a risk of 16.47 deaths per 100,000 women<sup>1</sup>. Breast-conserving surgery techniques followed by adjuvant radiotherapy have replaced radical and modified radical mastectomy techniques as standard treatment in patients with early-stage breast cancer, with equivalent overall survival and disease-free survival rates<sup>2</sup>. Oncoplastic techniques consist of removing the tumor from the breast and applying plastic surgery techniques to reconstruct the breast. When comparing the use of oncoplasty with traditional breast-conserving surgery techniques, no significant differences were observed in overall and disease-free survival<sup>3</sup>.

The use of oncoplastic techniques may contribute to reducing the number of surgical approaches required for oncologic resection and result in greater patient satisfaction and better assessment by the surgeon of the appearance of the breast after the procedure. However, it may increase the number of women who have complications in the postoperative period or who are recalled for biopsy<sup>4</sup>. Complication rates of approximately 16% can be considered acceptable, with the most common immediate complications being delayed wound healing, fat necrosis, and infection, while late complications being fibrosis and breast asymmetry<sup>2</sup>. Common strategies for managing complications in reconstructive surgeries include wound care, debridement, vacuum dressings, and new reconstruction procedures. The use of hyperbaric oxygen therapy (HBOT) appears as an alternative for the treatment of these conditions<sup>5</sup>. The use of HBOT in the

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treatment of chronic wounds is a well-established practice, and recent studies suggest benefit in acute or developing lesions<sup>6</sup>.

The aim of this review is to discuss the applications of hyperbaric oxygen therapy in postoperative complications of patients treated for breast cancer.

## METHODS

This work is a narrative review of the scientific literature based on several medical publications related to the application of HBOT in patients undergoing breast surgery. The initial search was performed in PubMed, using the MeSH descriptors: “breast neoplasms” and “hyperbaric oxygenation”, with a filter for articles in English, Spanish and Portuguese published in the last 10 years. A total of 20 studies were found, most of them reports or case series related to flap ischemia and radiotoxicity. Articles listed in the bibliography of these studies were also consulted, as well as books and publications related to HBOT and the surgical treatment of breast cancer carried out by Cochrane, professional councils and specialist societies for contextualization purposes.

## RESULTS AND DISCUSSION

### Hyperbaric oxygen therapy

The first report of the use of HBOT dates back to 1662, when the British physicist Henshaw first used compressed air for hyperbaric therapy in a chamber called “Domicilium”. Its use began to expand in the early 20th century, and in the 1960s it began to be used in the treatment of chronic wounds<sup>7</sup>.

HBOT consists in subjecting the patient to an environment with high pressure and 100% oxygen concentration. The minimum value usually applied is 1.4 atmospheres absolute (ATA), which can be simplified as a 40% increase in atmospheric pressure at sea level. HBOT treatment is generally applied in hyperbaric chambers that can be individual (only 1 patient) or collective (multiple patients). The standard treatment consists in exposing the patient to 2 to 3 ATA for approximately 90 minutes<sup>8</sup>.

Exposure to this environment leads to greater diffusion of oxygen gas into the blood, with an increase in the partial pressure of O<sub>2</sub> (pO<sub>2</sub>) in arterial blood, and consequently, greater oxygen supply to the tissues. The increase in oxygen concentration in the tissues stimulates neovascularization and has an immunomodulatory effect, activating fibroblasts, reducing inflammation, increasing the synthesis of growth factors, potentiating antibiotics, improving antioxidant response and alleviating ischemia-reperfusion injury<sup>7</sup>.

HBOT is a technique considered safe, with few reported contraindications. Its side effects are related to pressure variation and oxygen toxicity and include auditory barotrauma and transient visual changes. The most worrisome complications are

pulmonary toxicity, practically nonexistent with current protocols, and neurotoxicity, which has a low incidence (1:10,000 treatments)<sup>9</sup>. Undrained pneumothorax is the main absolute contraindication due to the risk of transforming a simple pneumothorax into a tension pneumothorax<sup>8</sup>.

### Complications of post-treatment surgery

Oncoplastic surgeries are complex procedures that combine two different procedures at the same surgical site, accumulating the risk of complications from both procedures. In addition, the defect provides areas of fragility and thinner flaps compared to non-oncological surgeries, because of the resection of the tumor. The risk of postoperative complications is also related to the surgeon's experience and the patient's characteristics, such as body mass index (BMI), breast size, history of smoking and skin care<sup>3</sup>.

Immediate complications include surgical wound dehiscence, ischemia and necrosis of the dermoglandular flap, necrosis of the nipple-areola complex, hematoma, seroma and surgical wound infection, while the most frequent late complications are fat necrosis and breast asymmetry<sup>3</sup>.

In addition, patients with breast cancer are often subjected to radiotherapy, adding the sequelae of this treatment to the risks already described. Among the complications of radiotherapy is late radiotoxicity, which is characterized by pain, fibrosis, edema, reduced mobility of the arms and unsatisfactory aesthetic results<sup>3,10</sup>.

### When to indicate HBOT

The Undersea and Hyperbaric Medical Society recognizes 14 valid medical indications for HBOT (Table 1). Among these are indications of interest in mastology: chronic wounds, flap and graft involvement, radiotoxicity and soft tissue infections. The above-mentioned indications are also recognized by the Brazilian Society of Hyperbaric Medicine and the Federal Council of Medicine<sup>11,12</sup>.

The application of HBOT in chronic wounds is well established in cases of diabetic foot and venous ulcers. A meta-analysis carried out by Cochrane in 2020 demonstrated that the use of HBOT in diabetic feet improves healing in the short term (relative risk [RR]=2.35; 95% confidence interval [95%CI] 1.19–4.62; p=0.01), but did not observe any difference in the long term. HBOT may also be beneficial in reducing wound size in patients with venous ulcers (mean difference [MD]=33.00%; 95%CI 18.97–47.03; p<0.00001) or with different types of ulcers (MD=61.88%; 95%CI 41.91–81.85; p<0.00001)<sup>13</sup>. Regardless of the etiology of chronic wounds, tissue hypoperfusion is a common mechanism in their pathophysiology, and HBOT corrects oxygen deficiency. HBOT improves oxygenation of the wound bed by providing adequate oxygen to the surrounding vascularized tissue, stimulating the local immune response, tissue repair and angiogenesis<sup>11</sup>.

The pathophysiology of late radiotoxicity is a complex and only partially understood process. The mechanisms suggested in



**Table 1.** Indications for Hyperbaric Oxygen Therapy per Undersea and Hyperbaric Medical Society.

Air or Gas Embolism	Severe Anemia
Acute Thermal Burns	Compromised Grafts and Flaps
Refractory Osteomyelitis	Intracranial Abscess
Decompression Sickness	Acute Traumatic Ischemia
Arterial insufficiency: Central Retinal Artery Occlusion and Selected Problem Wounds	
Delayed Radiation Injuries: Soft Tissue and Bony Necrosis	
Carbon Monoxide and Cyanide Poisoning	
Idiopathic Sudden Sensorial Hearing Loss	
Necrotizing Soft Tissue Infections	
Clostridial Myositis and Myonecrosis (Gas Gangrene)	

Adapted from: Indications for Hyperbaric Oxygen Therapy<sup>11</sup>.

its pathophysiology include obliterative endoarteritis and fibrosis associated with tissue atrophy. Thus, the benefit of HBOT would be the result of stimulating neoangiogenesis and consequently tissue oxygenation. Basic research studies have shown that the prophylactic use of HBOT can reduce tissue fibrosis and stimulate the mobilization of stem cells to irradiated tissues<sup>11</sup>.

Another meta-analysis conducted by Cochrane in 2023 evaluated the use of HBOT in the prevention and treatment of late complications of radiotherapy, observing complete resolution or significant improvement in cases associated with necrosis or tissue damage (RR=1.39; 95%CI 1.02–1.89; I2=64%; number needed to treat=8). However, only 2 studies included patients with breast cancer, and no benefit of HBOT was found in the primary outcomes evaluated: improvement in lymphedema and brachial plexopathy<sup>14</sup>. In contrast, two more recent observational studies observed an improvement in quality of life, even without objective improvement in lymphedema<sup>15,16</sup>. Although HBOT is the recommended treatment for late radiotoxicity, it still lacks high-level evidence. The Honey Trial is an ongoing randomized study to evaluate the efficacy of HBOT in patients with late radiotoxicity treated for breast cancer and should provide new information to this field<sup>10</sup>.

HBOT is not indicated in cases of viable grafts and flaps; however, it can be applied in the recovery of patients who have graft or flap compromise<sup>11</sup>. A case series of women undergoing NSM included 17 patients and 25 breasts that presented with early signs of ischemia and venous congestion or partial tissue necrosis postoperatively. Flap recovery was observed in 22 breasts, and only 3 breasts required a new surgical approach<sup>17</sup>. Another case series included 44 patients and 50 breasts with mastectomy flap necrosis referred to an HBOT referral center in the Netherlands. The outcomes evaluated included the need for surgical reapproach and reduction of tissue necrosis using the SKIN score. Despite the worsening of necrosis depth observed during the study, the affected area was significantly reduced with HBOT. Twenty-one breasts (42%) required a

new surgical approach, a rate that is within the range found in the literature for patients who received other treatments for ischemia (5%-67%)<sup>18</sup>.

In addition to therapeutic use, HBOT can be used in the peri-operative period in cases of flap or graft compromise to reduce the risk of progression to necrosis and the need for new surgical approaches<sup>5</sup>. A retrospective case series of 8 women who underwent nipple-areola complex-sparing mastectomy and immediate reconstruction followed by HBOT showed a >6-fold increase in pre- and post-HBOT perfusion. Tissue viability was assessed intraoperatively with indocyanine green angiography (ICGA). Intraoperative fluorescence values in IVGA <20%, relative to the control area, indicated a risk of postoperative tissue ischemia and immediate referral for HBOT<sup>6</sup>.

Although breast surgery is considered a clean procedure, rates of surgical site infections range from 1% to 20% after mastectomy and from 1% to 35% after breast augmentation with implants. Standard treatment consists in antibiotic therapy and debridement of devitalized tissue in selected patients<sup>19,20</sup>. However, necrotizing soft tissue infections are rare, with only 20 cases described in the literature, including cases without prior breast surgery and unrelated to cancer<sup>21-23</sup>. The use of HBOT in the treatment of these infections contributes to reducing mortality, the need for amputation and other complications<sup>11,24</sup>.

## CONCLUSION

The development of oncoplastic techniques, allowing for better aesthetic results and ensuring oncological safety, has led to an increase in the number of procedures performed. Consequently, complications related to this procedure have occurred more frequently, which requires that mastologists have knowledge of the methods available to manage them, providing better outcomes for patients. HBOT appears to be a possible intervention in cases of complications associated with oncoplasty and other surgical treatments for breast cancer. Although most of the evidence is



the result of observational studies or extrapolated from the use of HBOT in other areas, its use can contribute to better outcomes in patients undergoing surgical treatments for breast cancer. Cases associated with late radiotoxicity and compromise of grafts and flaps stand out because they present more solid evidence compared to other applications of HBOT in mastology. Difficulties regarding cost and availability should also be considered. Knowledge about HBOT by specialists and the public in general is another limiting factor for expanding the use of the method. However, offering HBOT in the management of these

conditions expands the therapeutic arsenal available to patients who present with complications at this fragile time in their life.

## AUTHORS' CONTRIBUTIONS

CBF: Data curation, Methodology, Writing – original draft. RJSV: Conceptualization, supervision, writing – Review & editing. MB: Writing – review & editing. EN: Writing – Review & editing. MAB: Writing – review & editing. CRC: Conceptualization. MHRRK: Conceptualization. MAP Conceptualization.

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# Malignant phyllodes tumor of the breast in a young patient – case report

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## ABSTRACT

**ABSTRACT:** Phyllodes tumor (PT) is an uncommon form of breast tumor. It occurs most commonly in women aged 35 to 65 years. The benign form represents about 85–90% of cases and only 10–15% of PTs are malignant. Clinically and radiologically, malignant phyllodes tumor (MPT) presents as regular, well-delimited, mobile nodules that are difficult to distinguish from fibroadenomas of the breast. The most important differential diagnoses of MPT include fibroadenoma, metaplastic carcinoma, and sarcoma. The prognosis of MPT exhibits a higher frequency of local recurrence and metastatic rate with larger tumors and inadequate surgical margins. The case presented here refers to a 24-year-old female patient, with a vast tumor in the right breast, with rapid and progressive growth, associated to local pain, and histological diagnosis of MPT. Surgery was the initial treatment, followed by adjuvant chemotherapy and radiotherapy. The purpose of this article was to report an atypical case of MPT of the breast in a very young woman as well as to make a brief literature review on this infrequent and dangerous disease.

**KEYWORDS:** phyllodes tumor; malignant phyllodes tumor; breast neoplasm; case reports.

## INTRODUCTION

Phyllodes tumor (PT) of the breast is uncommon, representing 0.3–1.0% of all breast neoplasms and 2.5% of all fibroepithelial breast tumors<sup>1,2</sup>. The estimated incidence is 2.1 cases per million women<sup>2</sup>.

It occurs most commonly in women aged 35 to 65 years. The benign form represents about 85–90% of cases. Only 10–15% of PTs are malignant (MPTs), and only 10–26% of MPTs are found with metastasis<sup>3</sup>.

The presence of a painless unifocal mass with a history of fast growth, reaching a large size, and in advanced age may be clinical findings favorable to the diagnosis of the PT<sup>3</sup>. Tumor size can vary between 1–45 cm, with an average size of 4–5 cm, although MPTs can reach larger dimensions<sup>3,4</sup>. There are no specific clinical manifestations to distinguish benign from malignant subtypes<sup>1</sup>.

The World Health Organization classifies these tumors as benign, borderline, or malignant according to a combination of histological features, including stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor margin<sup>1,3</sup>.

Clinically and radiologically, they present as regular, well-delimited, mobile nodules that are difficult to distinguish from fibroadenomas of the breast.

Surgery is the standard treatment. Generally, local excision is performed for benign and small tumors, while total mastectomy is considered for borderline, large, malignant, and recurrent tumors. Overall, segmental resection with adequate margins is the treatment of choice<sup>5</sup>. The role of radiotherapy and chemotherapy remains controversial. Adjuvant radiotherapy has been shown to increase disease-free survival in MPTs treated with segmental resection. However, available data on increased overall survival in the literature are inconclusive<sup>6</sup>.

This article aimed to report a case of MPT of the breast in a very young woman as well as to make a brief literature review on this infrequent and dangerous disease.

## CASE REPORT

This is a 24-year-old female patient referred for evaluation of a nodule in the right breast, with rapid and progressive growth, for about two months, associated with local pain. Nulligest, without comorbidities or use of medication, she had a history of bilateral reduction mammoplasty eight years ago. Family history revealed

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two maternal great-aunts with breast cancer. On clinical examination, the patient presented a bulging and voluminous nodule in the upper lateral quadrant (ULQ) of the right breast, measuring 8.0 x 6.0 cm, with fibroelastic consistency and mobile; and non-palpable axillary lymph nodes. Ultrasound image evidenced a large oval, regular, and circumscribed mass, containing aneugenic areas inside, measuring approximately 7.0 x 6.0 x 5.0 cm in the ULQ. Breast magnetic resonance imaging showed a solid-cystic, oval, heterogeneous nodule with indistinct margins, early enhancement, and predominantly peripheral, in the ULQ/axillary extension of the right breast, measuring 7.0 x 5.0 x 4.0 cm, without plane of clear cleavage between the nodule and the pectoralis major muscle, in addition to right axillary adenopathy - Breast Imaging Reporting and Data System (BI-RADS 4®). A core biopsy of the lesion was performed, with anatomopathological findings: pleomorphic neoplasm with a tubulosarcomatoid disposition, with the possibility of a MPT.

Subsequently, the patient evolved with rapid lesion growth, significant local pain, and skin suffering in the region of the lesion (Figure 1). Chest and abdomen tomography showed no relevant changes. Surgical treatment was indicated and, after discussing the case, the patient opted for conservative surgery. Thus, a partial mastectomy was performed, with resection of the tumor with margins of the pectoralis major muscle fibers due to tumor infiltration, and of enlarged lymph nodes in the right axillary region, associated with the creation of a glandular and cutaneous flap for closure (Figures 2 and 3). Anatomopathological and immunohistochemical results revealed high-grade pleomorphic/spindle cell malignancy, with myogenic differentiation, measuring 7.5 x 7.0 x 4.5 cm, free margins, and absence of metastasis in the five dissected lymph nodes, with a probable diagnosis of MPT.

Finally, patient recovered well in the postoperative period, with preserved right upper limb mobility, and, after evaluation of clinical oncology, adjuvant chemotherapy with six cycles of doxorubicin and ifosfamide was indicated. Adjuvant radiotherapy was performed with a hypofractionated protocol of 15 sessions, and a concomitant boost in the surgical area (total dose of 40 Gy in the breast and 48 Gy in the operative site). Germline genetic panel was not performed. Before the chemotherapy treatment, the medical team discussed with the patient and a fertility preservation technique was performed, through ovulation induction with gonadotropins and oocyte collection for cryopreservation.



**Figure 2.** Intraoperative – post-tumor resection.



**Figure 1.** Tumor clinical presentation.



**Figure 3.** Intraoperative – post-final suture.



## DISCUSSION

PT is a rare form of breast tumor. It was first described by Johannes Muller in 1838 and constitutes 0.3–1.0% of all breast tumors<sup>1</sup>. MPTs are extremely rare and can imitate benign tumors such as fibroadenomas on clinical examination. The median age for presentation of MPT is 50 years old<sup>7</sup>.

Regarding histopathological aspects, PTs are defined as a group of circumscribed biphasic tumors, similar to fibroadenomas, composed of periductal stroma and ductal epithelium, with a double-layered foliar growth pattern with hypercellular stroma, characterized by pleomorphism and stromal overgrowth, infiltrative borders, and usual mitoses<sup>1,2</sup>. Clinically, the most common finding is the breast lump — mobile and painless. Dilated veins can be seen overlying large PTs. Axillary metastases are uncommon, and most palpable axillary lymph nodes are reactive, not metastatic<sup>8</sup>.

Diagnosis should preferably be made by histopathological study, obtained by core needle biopsy or excisional biopsy. Fine needle aspiration (FNA) does not provide the information necessary for a differential diagnosis. Due to the similarity of cytological features for benign PT and cellular fibroadenoma, these two biphasic fibroepithelial lesions cannot be properly differentiated on FNA<sup>9</sup>. A PT with a bland stromal component can mimic a fibroadenoma; whereas a PT with a stroma that appears overtly sarcomatous can be challenging to differentiate from a sarcoma. MPT is defined by the combination of marked nuclear pleomorphism of stromal cells, stromal overgrowth (defined by the absence of epithelial components in one low-power microscopic field), diffuse stromal cellularity with increased mitotic activity (>10 per 10 HPF [high-power fields]), and infiltrative borders<sup>3</sup>. The most important differential diagnosis of MPT includes fibroadenoma, metaplastic carcinoma, and sarcoma<sup>10</sup>. The immunohistochemical findings are characterized by the expression of p53, CD117, p16, EGFR, Ki-67, and VEGF, which reveal low positivity in benign PT and high in MPT<sup>11</sup>.

Although PT is primarily treated by surgical excision, literature data demonstrate that all PTs can recur regardless of their histology, with lower incidences of recurrence evidenced in benign tumors and higher rates observed in borderline and malignant ones. Local recurrence (LR) rates vary by 15–40% among different types of PT<sup>12</sup>. The risk factors most commonly associated with LR comprehend not only positive margins but also the existence of necrosis, stromal overgrowth, and a larger tumor size. No difference was found in terms of LR among patients undergoing mastectomy or breast-conserving surgery<sup>7</sup>. Our patient underwent partial mastectomy and margins were free on anatomopathological analysis. A large retrospective and multicenter study on MPT management demonstrated that a 3 mm margin threshold was appropriate, with no impact of larger margins on overall survival. Hence, they recommended re-excision to achieve wider margins in cases with 0–1–2

mm margins<sup>13</sup>. The National Comprehensive Cancer Network (NCCN) guideline recommends wide excision with clean margins  $\geq 1$  cm for MTP<sup>14</sup>. Axillary lymph node dissection showed no added benefit on the recurrence or disease-free survival in MPT. Most lymphadenopathy in MPT is usually either reactive to tumor necrosis or to infected ulcerated skin lesions, with less than 1% of pathological involvement<sup>15</sup>.

The role of adjuvant radiotherapy in MPT is still controversial. Several studies have shown that radiation therapy is associated with reduced LR but did not have any impact on overall survival<sup>16</sup>. The use of adjuvant chemotherapy is more questionable and its effect on PTs is doubtful. Adjuvant cytotoxic chemotherapy lacks evidence of benefits both for reducing LRs and for improving overall or disease-free survival. Owing to the low frequency of distant metastasis, only a small number of retrospectively analyzed cases have been reported and a treatment strategy for MPT has not been established. Nevertheless, it can be considered for large tumors, when adjacent structures such as the chest wall are involved, or unresectable distant metastasis<sup>17</sup>. In these cases, chemotherapy regimens of soft tissue sarcomas are generally employed. NCCN guideline recommends anthracycline plus ifosfamide as the first line of treatment<sup>14</sup>. Although pathologically, they express estrogen receptors in 58% and progesterone receptors in 75% of cases; endocrine therapy has not proven to be beneficial in the treatment of PTs<sup>18</sup>.

The prognosis of MPT exhibits a higher frequency of LR (12–65%) and metastatic rate (up to 27%) with larger tumors and inadequate surgical margins<sup>13</sup>. The most common spots for metastasis are the lungs, pleura, and bone. The 5-year survival is around 65%<sup>7</sup>. Kapiris et al. reported a 5-year survival rate of 54% and a 10-year survival rate of 23%, with a significant association of results according to tumor size and surgical margins<sup>12</sup>.

Germline genetic panel is not routinely ordered for patients with PT. The NCCN practice guidelines do not include PT as criteria for genetic counseling or as testing criteria for any of the known heritable cancer syndromes<sup>14</sup>. Recently, in a multi-center contemporary cohort of 550 PTs, Rosenberger et al. found that roughly 10% of PT patients tested for germline cancer predisposition genes carried a deleterious mutation, similar to that seen among women with breast adenocarcinoma<sup>19</sup>.

## CONCLUSIONS

MPTs are rare entities. These tumors should be correctly recognized and effectively treated at first diagnosis since they have an elevated risk of recurrence. The PT diagnostic hypothesis should be raised in tumors with benign characteristics, rapid growth, and large dimensions. Accurate pathological classification of PTs is relevant to foresee the risk of recurrence and survival rate. Benign and borderline PTs have less aggressive disease behavior



than MPT. Excision with adequate margins is the recommended therapy. There is no stated consensus concerning the optimal type of surgery and indications for radiotherapy and chemotherapy in these cases. The establishment of adequate and standardized therapeutic strategies for MPTs is needed to reduce the risk of local and distant tumor recurrence.

## AUTHORS' CONTRIBUTION

CFH: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. ACOP: Investigation, Validation, Writing – review & editing. JPSS: Formal analysis, Investigation, Writing – original draft. ITR: Formal analysis, Investigation, Writing – original draft.

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# A Rare Case of Syringomatous Tumor of the Nipple and Breast Reconstruction

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## ABSTRACT

Syringomatous tumor, first described in 1983, is a rare benign clinical condition that can affect the breast. Its infiltrative form is often misidentified as malignant pathologies, as it can present as a subareolar lesion with suspicious clinical, mammographic, and ultrasound findings for malignancy. The exact origin of these lesions remains uncertain; however, they may manifest as a unilateral or bilateral subareolar nodule with symptoms such as pain, edema, nipple enlargement, and nipple discharge. Despite local infiltration, there is no evidence of regional or distant metastases. Local complete excision appears to be an adequate therapy, with only cases that were incompletely excised showing recurrence. Below is a case report of a syringomatous adenoma infiltrating the nipple, with complete resection and nipple reconstruction using oncoplastic techniques.

**KEYWORDS:** breast reconstruction; breast tumor; breast neoplasms.

## INTRODUCTION

The areola-nipple complex (ANC) is the origin of various morphologically distinct tumors and related changes, stemming from the unique structures of the nipple, especially the intramammary ducts, adjacent structures, and intramammary stroma<sup>1</sup>. The syringomatous tumor of the nipple, a rare benign condition<sup>2</sup>, was first described by Rosen in 1983<sup>3</sup>.

Although benign, its tendency to infiltrate locally and recur if not completely excised can lead to it being mistaken for a malignancy.

The disease typically presents as a unilateral or bilateral subareolar nodule, accompanied by clinical manifestations such as erythema, pain, edema, nipple distension, and papillary discharge<sup>4</sup>. This case report aimed to address both the rarity of the condition and the significance of differentiating it from breast neoplasms, as well as to describe an alternative technique for nipple reconstruction.

## CASE REPORT

A 55-year-old female patient, who experienced menarche at 11 years old and has had three children, her first at age 20, with breastfeeding lasting for 8 months. She had been using hormonal contraceptives for 12 years. She had been regularly consulting a

mastologist to monitor nodules since March 2021. A mammogram (MMG) in November 2022 revealed nodular images and focal asymmetries (BI-RADS 3). An ultrasonography (USG) performed the same month showed a heterogeneous area of 2 cm at 9 o'clock and 4 cm from the nipple, which could correspond to either breast tissue or a solid nodule in the right breast (NRB), and another NRB of 0.8 cm at 6 o'clock and 3 cm from the nipple (BI-RADS 3); these nodules had been stable since August 2022. A fine needle aspiration (FNA) of the NRB at 9 o'clock revealed rare groups of typical ductal cells. During a routine consultation in November 2022, increased hardness was observed in the right nipple, covering more than two-thirds of its surface (Figure 1).

A magnetic resonance imaging (MRI) scan was requested, revealing intra-nipple enhancement in the right nipple extending 0.9 cm, categorized as BI-RADS 4. Additionally, a solid nodule in the left breast (NLB) was detected at 5 o'clock, 4.7 cm from the nipple, with a type II curve (Figure 1).

In February 2023, she underwent excision of two mammary nodules in her right breast and an incisional biopsy of the right nipple. The anatomopathological examination revealed that the nodules were fibroadenomas, measuring 1.2 cm and 0.6 cm. The nipple biopsy showed a syringomatous tumor of the nipple with compromised margins (specimen: 0.8 cm). Immunohistochemistry

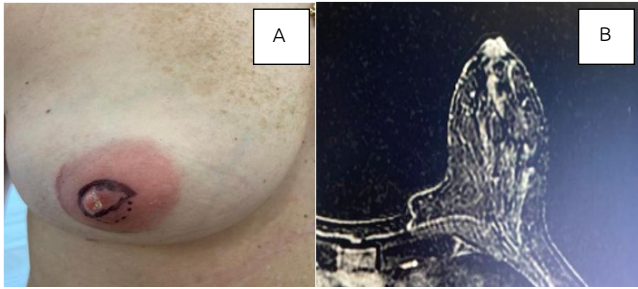
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**Figure 1.** (A) Lesion in the right nipple affecting more than half of its volume and (B) MRI showing enhancement within the right nipple.

confirmed the diagnosis, showing positivity for markers p63, cytokeratins 5/6, 14, and 8/18, estrogen receptor (ER) positive, and ki67 at 5%.

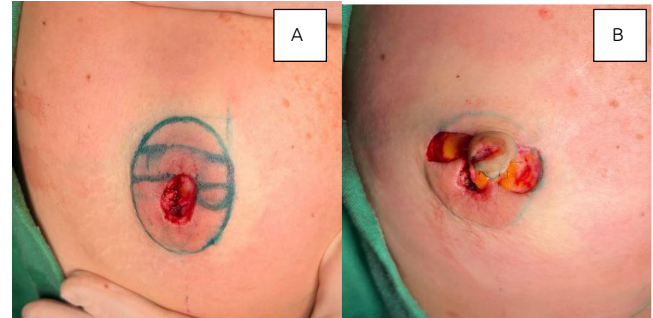
After analyzing the exams and reassessing the patient, it was decided to perform a complete resection of the tumor with margins and immediate nipple reconstruction. The surgery took place on July 20<sup>th</sup>, 2023. The entire right nipple and part of the base of the areola were resected (Figure 2).

After removing the nipple, it was sent for freezing and evaluated macroscopically, showing free margins. For nipple reconstruction using local flaps, and considering the patient did not have a contralateral donor nipple, the double-opposed periareolar/pouch flap technique was chosen. Modifications were made to the technique, positioning the upper closure portion of the nipple projection, which is normally central, laterally. The wings of the flap were marked with measurements of 1 cm in width and 1 cm at the base. Dissection began with the external wings, elevating them with a thin layer of subcutaneous fat. The papilla was then assembled and sutured together (Figure 2). The areolar flaps were sutured to the base of the papilla, and the incisions were approximated using single stitch sutures (Figure 3).

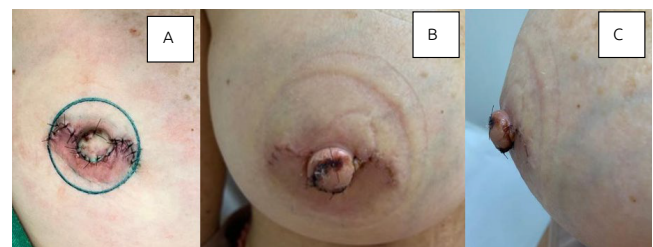
On the seventh postoperative day (POD), the areola stitches were removed (Figure 3), and on the 14<sup>th</sup> day, the stitches on the nipple were removed. The anatomopathological examination revealed a 1.5 cm syringomatous tumor of the nipple with free margins. The patient is currently scheduled for areola micropigmentation.

## DISCUSSION

A syringomatous tumor typically presents as a solitary firm mass in the subareolar region or on the nipple and can occur within the breast parenchyma<sup>2</sup>. It may be clinically asymptomatic, sensitive, and painful on palpation, and/or present with itching and ulceration. The size varies from 1 cm to 3 cm in diameter<sup>4</sup>. The average age at presentation is 40 years, with an age range from 11 to 76 years<sup>3</sup>. Nipple inversion or discharge may be present<sup>5</sup>. It can be pathologically misdiagnosed as ductal breast carcinoma, which can lead to delays or errors in diagnosis. Timely management



**Figure 2.** (A) Right breast after nipple resection with planned incision for the neomamilo and (B) assembly of the nipple after bringing the cylinder together.



**Figure 3.** (A) Neomamilo after approximation of the areolar flaps to the nipple (immediate) and seventh postoperative day, (B) frontal view, and (C) lateral view.

with histopathological correlation is essential, as it allows for less invasive surgical methods.

The imaging findings of a syringomatous tumor often resemble those of malignant tumors, making it difficult to distinguish from carcinoma on imaging studies such as MMG, USG, and MRI<sup>2</sup>. On MMG, it may appear as a high-density mass in the subareolar region with an irregular contour, spicules, or microcalcifications. On USG, it typically presents as a poorly defined mass with heterogeneous internal echoes<sup>4</sup>. Since fine needle aspiration or needle biopsy often fails to provide a definitive diagnosis, many cases are reported as suspected malignancies<sup>4</sup>.

Some researchers have reported the usefulness of immunohistochemical staining for p63 or S-100 protein<sup>5,6</sup>. However, in the present study, staining was performed for Ki-67, a prognostic and predictive marker for breast cancer<sup>7</sup>. Ki-67 is expressed during the G1, S, G2, and M phases of the cell cycle but not during the resting G0 phase. Therefore, high levels of Ki-67 indicate a tumor with high proliferative potential. In other words, Ki-67 staining helps differentiate between benign and malignant tumors and predict prognosis.

The presence of a myoepithelial layer in syringomatous tumors is not completely indisputable, but it is commonly mentioned in the literature due to positive reactions for “myoepithelial cell markers” such as p63 or Ck5/6. Recently, however, immunohistological findings have demonstrated that syringomatous tumors of the nipple are p63+ Ck5/14+ proliferations of progenitor cells in the nucleus,

which differentiate into glandular (Ck8/18) and squamous cells (Ck10/13). Differentiations into myoepithelial cells (actin, CD10, calponin, etc.) are much rarer and usually only focal in these tumors. Therefore, in the context of syringomatous tumors, the expression of p63 and high molecular weight cytokeratins Ck5 and/or Ck14 cannot be used as an indication of myoepithelial differentiation<sup>1</sup>.

Pathologically, the tumor appears grossly ill-defined, with a firm to resistant consistency and a gray or white cut surface<sup>8</sup>. Histologically, the lesion is composed of tubules, ducts, and strands of small, uniform, generally basophilic cells that infiltrate the dermis of the surrounding skin and the stroma of the nipple<sup>8</sup>. Proliferating ducts, lined by one or multiple layers of metaplastic squamous cells, may be present. These cellular nests often have a teardrop or comma-shaped appearance, and tumor cells can infiltrate the stroma between smooth muscle bundles and even into the perineural region<sup>4</sup>.

Histologically and clinically, syringomatous adenoma of the nipple is often mistaken for tubular carcinoma or low-grade adenosquamous carcinoma of the breast. Special attention from pathologists and clinicians is crucial to avoid incorrect diagnoses and unnecessary treatments<sup>4</sup>.

The histopathological diagnostic criteria for syringomatous tumor include:

- Location in the dermis and subcutaneous tissue of the nipple or areola;
- Irregular tubules, compressed or comma-shaped, infiltrating into bundles and/or smooth muscle nerves;
- Presence of myoepithelial cells around the tubules;
- Presence of cysts lined with stratified squamous epithelium and filled with keratinized material;
- Absence of mitotic activity and necrosis<sup>4</sup>.

Due to its rarity, the syringomatous tumor presents an intriguing diagnostic challenge. Differential diagnoses include primary malignant breast carcinomas such as low-grade adenosquamous carcinoma and tubular carcinoma. Tubular carcinoma typically occurs deep in the breast, often located in the upper quadrant, lateral to or away from the nipple. If it extends to the nipple, it may cause nipple retraction or Paget's disease. Tubular carcinoma is also more commonly ER positive, whereas syringomatous tumors are usually ER negative. Syringomatous tumors are benign and have not been reported to metastasize. However, they can exhibit local recurrence if not completely resected<sup>6</sup>. Therefore, the ideal initial management involves complete resection with histologically negative margins. If the margins appear involved, reexcision is recommended.

In patients with negative margins after removal of the entire syringomatous tumor, there was no evidence of recurrence during a follow-up period of 1 to 6 years<sup>9</sup>. However, patients with positive margins after local surgical excision experienced tumor recurrence<sup>10</sup>. Therefore, careful monitoring to detect local recurrence is considered necessary<sup>5</sup>. Most recurrences were treated

with local reexcision. However, since syringomatous tumors of the nipple generally occur in the dermal and subcutaneous regions of the nipple or areola<sup>3</sup>; appropriate management often requires total resection of the ANC.

If the tumor is so close to the nipple that preserving it is impossible, and the patient wishes to preserve it, an appropriate treatment regimen must be selected. In these cases, however, careful postoperative monitoring is mandatory<sup>2</sup>. Jones et al.<sup>10</sup> reported recurrence times ranging from 1.5 months to 4 years. Therefore, the duration of follow-up should exceed 5 years if complete resection is not performed.

We opted for complete resection of the lesion, which occupied more than 2/3 of the nipple. This resulted in the excision of the entire nipple and part of the areola, yielding a 1.6 cm specimen with free margins. We also chose to perform immediate nipple reconstruction.

## CONCLUSION

Nipple adenoma, also known as syringomatous cystadenoma, is a rare type of benign tumor that can occur on the skin or cutaneous appendages, such as sweat glands and sebaceous glands. Clinically, it mimics Paget's disease of the nipple or malignant breast lesions. Due to its rarity, nipple adenoma can easily be overlooked as a differential diagnosis in clinical practice.

The possibility of a syringomatous tumor should be considered when a patient presents with nipple discharge and erosion, with or without a palpable nodule beneath the nipple. This condition also presents a challenge for histological diagnosis. Accurate histological and immunohistochemical analysis is important to distinguish nipple adenoma from invasive carcinoma.

Due to the risk of recurrence, resection with clear margins should generally be recommended. In cases where resection results in compromised margins, follow-up may be required.

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. This report was approved by the Ethics Committee under number 6.639.583.

## AUTHORS' CONTRIBUTIONS

JLAA: Writing – original draft, Writing – review & editing, Supervision, Validation. UWS: Project administration, Resources, Software. MLMD: Formal analysis, Investigation, Funding acquisition. WP: Formal analysis, Conceptualization, Data curation, Investigation, Funding acquisition. DTSMN: Project administration, Formal analysis, Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Investigation, Methodology, Funding acquisition, Resources, Software, Supervision, Validation, Visualization.








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# The challenging diagnosis of granular cell tumor of the breast: a case report

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## ABSTRACT

Conventional granular cell tumors, derived from Schwann cells, occur in soft tissues and are mostly benign. It is also recognized as Abrikossoff's tumor or granular cell myoblastoma, and the most common locations are found in the head, neck, arms, esophagus, and respiratory tract. The incidence in the breast is rare, representing only 8% of granular cell tumors. However, it is important to consider it as a differential diagnosis when investigating breast nodules due to its misleading presentation. This is a challenging diagnosis considering that the clinical examination and imaging workup may suggest signs of malignancy. Therefore, the lack of histopathological analysis may lead to erroneous conclusions and therapies. Due to non-specific imaging and physical examination findings, a biopsy of the lesion is mandatory for diagnosis. The tumor's microscopic criteria consist of the presence of large polygonal cells, with eosinophilic, granular, and abundant cytoplasm. The cell borders are indistinct and the growth pattern is infiltrative, with perineural and possible perivascular involvement; however, mitotic figures are rare. The present case report demonstrates the importance of anatomopathological analysis for this diagnosis. It refers to a female patient, 28 years old, complaining of a breast node. She was followed up in the Mastology Department for further investigation, with a mammography report identifying a speculated nodule, with undefined margins, classified as Bi-Rads 5 in the right breast, and an ultrasound reporting a Bi-Rads 4C solid nodule. The clarification was made through biopsy, which determined microscopy compatible with the rare tumor of granular cells in the breast, in addition to the immunohistochemical profile, which differentiated the tumor variant of non-neural origin, composed of ovoid cells with eosinophilic granules, presenting nuclear pleomorphism, atypia, and mitotic figures.

**KEYWORDS:** granular cell tumor; breast tumor; breast neoplasms; Schwann cells.

## INTRODUCTION

Conventional granular cell tumors occur in soft tissues and are mostly benign<sup>1</sup>. It is also recognized as Abrikossoff's tumor or granular cell myoblastoma, whose most common locations are the head, neck, arms, esophagus, and respiratory tract<sup>2,3</sup>. The incidence in the breast is rare, representing only 8% of granular cell tumors<sup>3</sup>. However, it is important to consider it a differential diagnosis when investigating breast nodules due to its misleading presentation. After all, conventional granular cell tumors of the breast may mimic malignant tumors, both in clinical manifestation and in imaging examinations, leading to diagnostic errors and inadequate radical treatments<sup>2</sup>.

On mammography, a granular cell tumor may reveal a solid nodule with spiculated or irregular margins, and on ultrasound, it may define a heterogeneous, vascularized nodule, with anisotropy and acoustic shadow, determining non-specific findings more associated with malignancy<sup>1</sup>. Therefore, as imaging tests do not exclude a malignant neoplasm, the differential diagnosis can be challenging and induce major psychosocial disorders in the patient. As a rule, definitive identification depends on the anatomopathological analysis of the lesion<sup>4</sup>. In macroscopy, it appears as an irregular and firm mass, with or without skin retraction and nipple inversion<sup>3</sup>. Microscopically, it is characterized by the composition of epithelioid cells with granular eosinophilic cytoplasm with abundant lysosomes<sup>5</sup>.

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## CASE REPORT

A 28-year-old female patient was admitted to the Mastology service at a regional hospital in Sete Lagoas, Minas Gerais, complaining of a nodule in her right breast, which she initially noticed six months ago. She claimed to be previously healthy, without comorbidities or allergies. Furthermore, she reported a history of two previous pregnancies, the last one in 2020 with breastfeeding for a year. Her menarche was at age 12, and she currently has regular cycles, using a copper intrauterine device (IUD) implant since 2021. Regarding her family history, she reported an aunt with ovarian cancer and two uncles with bowel cancer.

In a subsequent ultrasound examination, a breast imaging reporting & data system (Bi-Rads) 4C nodule was diagnosed, identifying a solid, hypoechoic, spiculated, non-circumscribed nodular image, with a posterior acoustic shadow, located in the retroareolar region of the right breast, measuring 1.8 x 1.9 x 1.3 cm. The mammogram, performed some months later, presented a poorly defined spiculated nodule in the right breast, with Bi-Rads 5 classification, and another nodule in the left breast with Bi-Rads 2 characteristics. Following the propaedeutic investigation, a guided core biopsy was performed using ultrasound. The result indicated a granular cell tumor.

A sectorectomy of the right breast was performed on the patient, with total resection of the tumor. The macroscopic examination revealed a firm, brown nodule measuring 2.5 x 2.4 cm, located 0.3 cm from the deep margin (Figure 1). The microscopy confirmed the diagnosis of neural granular cell tumor, with proliferation of polygonal cells, without atypia, with large and granular cytoplasm supported by dense, fibrous connective tissue, and no signs of malignancy (Figures 2 and 3).

An immunohistochemical study was requested, which demonstrated the panel: AE1/AE3 antigen and AE1/AE3/PCK26 antibody negative; CD68 antigen and KP-1 antibody positive; negative

GATA3 antigen and L50-823 antibody; negative P63 antigen and 4A4 antibody; and S100 antigen and positive polyclonal antibody.

The patient evolved in good general condition, without lymphadenopathy or phlogistic signs on post-operative examination. She was advised about the rarity of the condition and the need for follow-up with a new ultrasound in six months.

## DISCUSSION

The conventional granular cell tumor, derived from Schwann cells, is most common in soft tissues, mainly found in the head, neck, arms, or chest wall. Its occurrence in the breast is rare, representing

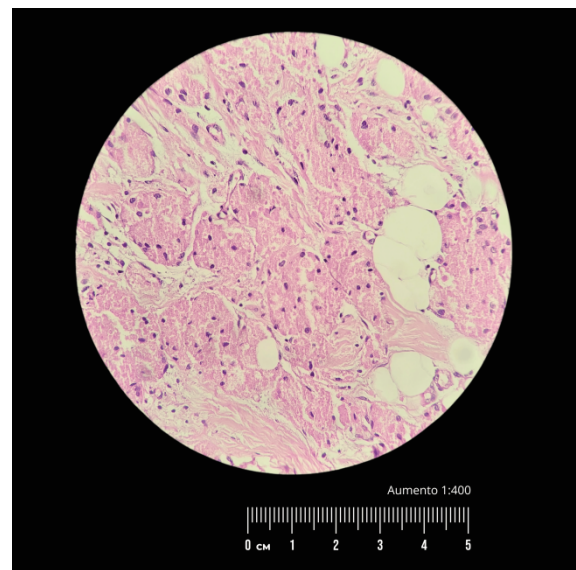


Figure 2. Microscopy of the lesion.

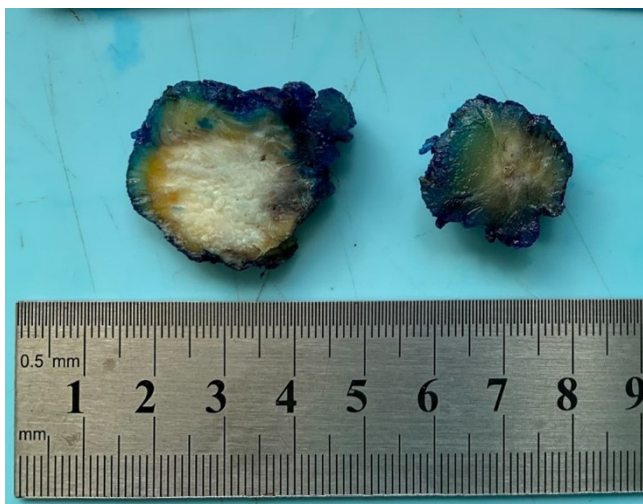


Figure 1. Macroscopy of the lesion.

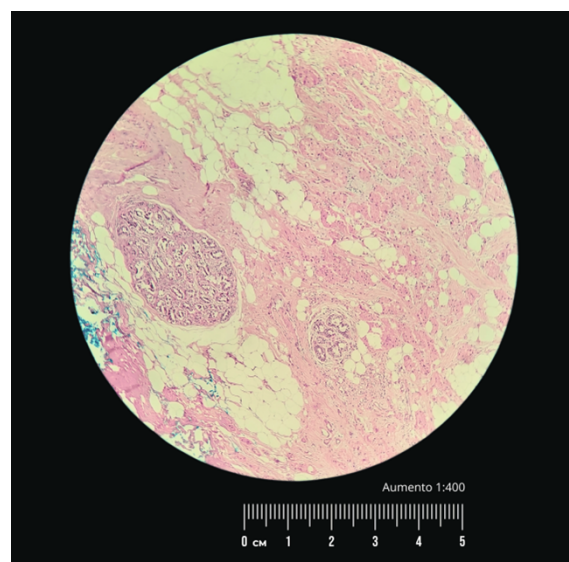


Figure 3. Microscopy of the lesion.

less than 10% of all granular cell tumors<sup>5,6</sup>. Considering tumors that affect the breast in general, granular cell tumors represent less than 0.1%<sup>5,6</sup>. Regarding the incidence in malignant form, it represents 1% to 2% of the category<sup>1,3,5</sup>. Epidemiologically, the tumor affects more women, across a wide age range from 19 to 77 years, and when it eventually affects men, it's more common in young adults of African descent<sup>3</sup>.

Thus, granular cell tumors, which represent 1 in every 1,000 breast tumors, should be considered as a differential diagnosis for the investigation of breast nodules<sup>3</sup>. Mainly, because it is a challenging diagnosis considering that the clinical examination and imaging exams can suggest signs of malignancy, and the lack of histopathological analysis may lead to erroneous conclusions and therapies<sup>2,5,7</sup>. Therefore, due to non-specific imaging and physical examination findings, the lesion biopsy is mandatory for diagnosis<sup>1,2</sup>.

The microscopic criteria of this tumor consist of the presence of polygonal large cells, with eosinophilic, granular, and abundant cytoplasm<sup>3,5</sup>. The cell borders are indistinct and the growth pattern is infiltrative, with perineural and perivascular possible involvement; however, mitotic figures are rare<sup>3</sup>. The present case obtained decisive histological confirmation with core biopsy analysis and the biopsy after the right breast sectorectomy. After all, the imaging tests were suggestive of malignancy, with a Bi-Rads 5 report mammography, and an ultrasound, with a Bi-Rads 4C result.

The variant of granular cell tumor of non-neural origin, unlike the conventional presentation, is composed of ovoid cells with eosinophilic granules, presenting nuclear pleomorphism, atypia, and mitotic figures, conferring a greater potential for lymphatic dissemination<sup>8</sup>. Immunohistochemistry is essential to determine a differential diagnosis, as the non-neural tumor is negative for S100 protein and other neural or melanocytic markers<sup>9</sup>.

The immunohistochemical profile of conventional granular cell tumors shows positive for S100, CD68, CD63 (NKI/C3), and NSE, which may be related to cytoplasmic lysosomes reactivity, but the Ki-67 proliferation index is usually low<sup>3</sup>. As 10% of malignant cases are also positive for the S-100 marker, it is essential to search for other markers, such as CD68, which demonstrates lysosomal activity associated with the perineural Schwann cell<sup>10</sup>. In the reported case, we have a corresponding panel result, showing positivity for S100 and CD68.

The recommended treatment for the case is local surgical excision with free margins, without total mastectomy or sentinel lymph node biopsy, due to its mostly benign nature<sup>2,3,10</sup>. The prognosis for granular cell tumors of neural origin is good, and the recurrence rate is less than 10% after resection with appropriate margins<sup>2,3,10</sup>. The statistics regarding non-neural granular cell tumors are also positive, characterized by an indolent evolution, despite some worrying histopathological signs<sup>9</sup>. However, the malignant form can metastasize, including distant dissemination, which requires attention to worse prognostic characteristics of conventional granular cell tumors, such as a size greater than 5 cm, pleomorphism, prominent nucleoli, mitotic figures and necrosis<sup>5</sup>.

## CONCLUSIONS

The correct diagnosis of a conventional granular cell tumor of the breast is decisive for its psychosocial impact and for defining appropriate therapeutic management. It is a rare pathology, mostly benign, but challenging to diagnose. Due to non-specific imaging and physical examination findings, histopathological study is mandatory to rule out malignancy, along with immunohistochemical analysis of the lesion, which is important to differentiate from non-neural granular cell tumor.

## AUTHORS' CONTRIBUTIONS

JFAR: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. GJS: Conceptualization, Data curation, Investigation, Supervision, Visualization. AT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. AALL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. CASR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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# Capecitabine-related death in triple negative breast cancer: a case report

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## ABSTRACT

Triple-negative breast cancer (TNBC) is an immunohistochemical subtype of breast neoplasia characterized by the absence of hormonal receptor and HER2 expression. Capecitabine has been increasingly used in the treatment of TNBC patients who did not achieve a pathological complete response (pCR) after neoadjuvant therapy, showing favorable survival outcomes. Adverse effects related to capecitabine use are common, including gastrointestinal, hematologic, and dermatologic toxicity. However, the drug is generally well tolerated, and fatal outcomes related to treatment are infrequent. Due to its atypical nature, this study reports a death associated with therapy. In the case presented, the patient developed pancytopenia and febrile neutropenia (FN) 18 days after starting chemotherapy, progressing to alveolar, gastrointestinal, vaginal, and urethral hemorrhage, followed by hemodynamic instability, cardiopulmonary arrest, and death. Mortality occurring so early after capecitabine initiation may be linked to genetic alterations in certain individuals, such as dihydropyridine (DPD) deficiency. Genetic testing to identify DPD gene defects could allow for chemotherapy dose adjustments and reduce toxicity prevalence; however, such testing is not routinely performed. Further studies are needed to substantiate and assess the degree of benefit of this investigation before capecitabine chemotherapy, as well as the appropriate course of action based on the results. In these patients, FN prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) may also be considered, although it is primarily recommended for chemotherapeutic agents with a higher risk of myelotoxicity. Additional research is necessary regarding the actual application of capecitabine in TNBC cases to evaluate effectiveness, tolerability, and improve patient management.

**KEYWORDS:** breast neoplasms; triple negative breast neoplasms; capecitabine; drug toxicity.

## INTRODUCTION

Breast cancer is the most common neoplasm in women and the most frequently diagnosed malignancy<sup>1</sup>. Among the intrinsic subtypes classified by immunohistochemistry, triple-negative breast cancer (TNBC) is characterized by the absence of hormone receptor and HER2 expression. It has an incidence of 15 to 20% and is generally associated with a poorer prognosis, accounting for 5% of breast cancer-related deaths annually<sup>2</sup>.

The absence of all three receptors precludes the use of targeted therapy, making chemotherapy the current standard systemic treatment for this type of tumor. Various therapies have been investigated to improve pathological complete response (pCR) rates in TNBC and enhance patient prognosis. Among these, the immunotherapeutic agent pembrolizumab has been shown to increase disease-free survival (DFS)<sup>2,3</sup>. In this context,

capecitabine has emerged as another alternative; it is an oral pro-drug of 5-fluorouracil, primarily used in the treatment of metastatic breast cancer<sup>4,5</sup>. Recent studies have highlighted it<sup>5-8</sup> as a potential option for adjuvant therapy in TNBC patients, particularly those who did not achieve pCR following neoadjuvant treatment, demonstrating improved overall survival (OS) and DFS outcomes.

Fatal outcomes associated with capecitabine are rare, with mortality due to adverse effects occurring in approximately 1 to 3% of breast cancer patients<sup>9</sup>. Capecitabine has a relatively safe pharmacological profile and is generally well tolerated<sup>10</sup>. Given the rarity of such events, this study aimed to report and analyze a case of a patient with TNBC who received capecitabine as adjuvant therapy and subsequently experienced a therapy-related fatal outcome.

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## CASE REPORT

A 44-year-old woman from the Baixo Amazonas region in Pará. G2PC2A0. Menopause occurred at 43 years of age. She used combined oral contraceptives (COCs) for seven years and received quarterly contraceptive injections for eight years. She smoked for 13 years, 1.3 pack/year, but quit 13 years ago. She denies any family history of cancer or other significant pathologies.

The patient was referred to the mastology outpatient clinic for evaluation of a nodule in the left breast. Breast ultrasound (BUS) revealed a hypoechoic, irregularly shaped, vascularized nodular lesion measuring 2×2.3×2.4 cm, located at the 12 o'clock position, 0.7 cm from the skin, and classified as BIRADS® 4. A biopsy of the left breast confirmed the neoplasm as a poorly differentiated, grade III invasive ductal carcinoma, associated with a comedo-type intraductal component. Immunohistochemical analysis showed the carcinoma to be negative for hormone receptors and HER2, confirming the triple-negative subtype. The tumor exhibited 90% Ki-67 expression. The initial clinical staging was T2N0M0.

Neoadjuvant chemotherapy was initiated, consisting of 4 sessions of carboplatin AUC 5 and paclitaxel 175 mg/m<sup>2</sup>, followed by 4 sessions of doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>. During treatment, the patient experienced only mild toxicity, including nausea, asthenia, and headache. Subsequently, she underwent left quadrantectomy and sentinel lymph node biopsy, which led to left axillary lymphadenectomy. The residual tumor after chemotherapy measured 1.5 cm, and of the 20 lymph nodes removed, 3 demonstrated carcinomatous metastases with capsular leakage.

After adjuvant radiotherapy, the patient began oral therapy with capecitabine at a dose of 1,000 mg/m<sup>2</sup> twice daily for 14 days, administered in 8 cycles of 21 days each. Eighteen days after starting the first cycle, the patient developed severe diarrhea and diffuse abdominal pain, categorized as grade 3 by the Common Terminology Criteria for Adverse Events Version 5.0 (CTC-AE) classification of adverse effects of diarrhea and colitis, with more than 10 daily bowel movements<sup>10</sup>, as well as vomiting and oral lesions consistent with moniliasis. The blood count revealed hemoglobin (Hb) 10.9 g/dL, leukocytes 210/mm<sup>3</sup> (neutrophils 83.58/mm<sup>3</sup>), and platelets 29,000/mm<sup>3</sup>, leading to a diagnosis of febrile neutropenia (FN) due to chemotherapy toxicity. The patient was admitted to the referral hospital, where empirical antibiotic therapy with cefepime, for antipseudomonal coverage, and ciprofloxacin, to broaden the spectrum of gastrointestinal bacterial coverage, was initiated. Fluconazole was also started due to oral moniliasis. A blood culture was performed three days after the initiation of antibiotics and yielded negative results. Platelet transfusions were administered to manage thrombocytopenia during hospitalization, along with filgrastim, a granulocyte colony-stimulating factor. No imaging or genetic tests for dihydropyridine dehydrogenase deficiency were conducted during this period. After 6 days of hospitalization, the blood count showed

Hb 9.27 g/dL, leukocytes 122/mm<sup>3</sup> (neutrophils 8.18/mm<sup>3</sup>), and platelets 2,000/mm<sup>3</sup>. The patient experienced significant clinical deterioration, with alveolar, digestive, vaginal, and urethral hemorrhage, followed by hemodynamic instability, cardiorespiratory arrest, and death.

## DISCUSSION

In patients with TNBC and residual disease following neoadjuvant chemotherapy, the role of capecitabine was recently established through the randomized phase III clinical trial CREATE-X<sup>6</sup>. In this study, 887 patients with HER2-negative breast cancer who did not achieve pCR after neoadjuvant therapy were randomized into either a control group or a capecitabine group (1,250 mg/m<sup>2</sup>, orally, twice daily, on days 1–14 of each 3-week cycle, for a total of 8 cycles). This patient population was selected based on the association between failure to achieve pCR and poorer prognosis, including reduced survival outcomes. The study demonstrated five-year OS and DFS benefits, which, after subgroup analysis, were primarily observed in patients with TNBC (DFS 68.9% vs. 56.1%, HR 0.58, 95%CI 0.39–0.87; OS 78.8% vs. 70.3%, HR 0.52, 95%CI 0.30–0.90), who comprised approximately 30% of the study population. Capecitabine was well tolerated, with no fatal outcomes reported.

A meta-analysis by Li et al.<sup>5</sup> evaluated seven clinical trials involving patients with early-stage TNBC and found a significant increase in OS and DFS with the addition of adjuvant capecitabine to standard chemotherapy with anthracyclines and taxanes. Similarly, another meta-analysis by Li et al.<sup>8</sup> reported comparable results, demonstrating that adjuvant capecitabine is the most effective therapeutic strategy compared to other chemotherapy-based interventions.

Adverse effects associated with capecitabine use are common and include gastrointestinal, hematologic, and dermatologic toxicities<sup>4,9,11</sup>. According to a meta-analysis evaluating the safety profile of capecitabine in TNBC across 11 studies, the most frequently reported adverse effects were diarrhea, hand-foot syndrome, and leukopenia, which were generally tolerable<sup>11</sup>. Two studies assessed the tolerability of capecitabine in real-world clinical practice, following the recommendations of the CREATE-X trial. A retrospective analysis conducted in the United States involving 23 TNBC patients, with a mean dose of 1,871 mg/m<sup>2</sup>/day, found that 47.8% of patients required dose reductions, 69.6% experienced dose interruptions, and 34.8% discontinued treatment early due to toxicity, primarily caused by hand-foot syndrome, gastrointestinal symptoms, and pain/fatigue<sup>12</sup>. Another multicenter observational study of 129 Caucasian patients reported better tolerability, with 10.4% of the general population discontinuing treatment due to toxicity. Hand-foot syndrome, diarrhea, and neutropenia each affected 1.85% of patients. The initial dose administered was 1,250 mg/m<sup>2</sup> twice daily for 14 days, every 21 days, across 6–8 cycles<sup>13</sup>. None of the studies reported fatal outcomes related to the drug.

Lower doses of capecitabine may reduce toxicity<sup>9</sup>; however, few studies have evaluated the efficacy of lower-dose regimens in TNBC patients. Wang et al.<sup>7</sup> investigated the use of adjuvant capecitabine at a reduced dose (650 mg/m<sup>2</sup>, twice daily) but with a longer treatment duration (one year) in patients with early-stage TNBC. The study demonstrated an improvement in five-year DFS, although no significant impact on OS was observed. Among the 221 patients in the capecitabine group, 4.1% discontinued treatment due to unacceptable toxicity, primarily hand-foot syndrome. Additionally, leukopenia and diarrhea/abdominal pain were reported in 23.5 and 6.8% of patients, respectively.

Fatal outcomes so early in the use of capecitabine may be the result of genetic alterations in certain individuals. Dihydropyridine (DPD) deficiency is an important factor that increases the risk of toxicity to fluoropyrimidine (FP) drugs, such as 5-fluorouracil and capecitabine. This deficiency is related to a genetic variation that increases the concentration of the drug in the body. Complete DPD deficiency is extremely rare, while between 3 and 5% of cancer patients may have partial deficiency. In patients with complete deficiency, the mortality rate is almost 100% in exposure to FP. On the other hand, although less fatal, partial deficiency may be responsible for 43 to 59% of cases of serious or life-threatening toxicity due to the substance<sup>14</sup>.

In this sense, genetic testing to identify defects in the dihydropyridine dehydrogenase (DPYD) gene could indicate adjustments in the chemotherapy dose and reduce the prevalence of toxicity. However, studies in the United States show that this genetic screening is generally not indicated in oncology guidelines and is also not usually adopted by specialists. This is because there is still a lack of studies to indicate when, how and which genetic tests to apply, as well as information on how to interpret the tests and how to modify the dose according to their results<sup>15</sup>.

The definition of FN includes an oral temperature exceeding 38.3°C or two consecutive readings above 38°C within two hours, along with an absolute neutrophil count below 500/μL or below 1,000/μL with a predicted decline within the next 48 hours in patients undergoing systemic chemotherapy. Clinical signs of sepsis may also be considered in the diagnosis of this condition<sup>16</sup>. FN is a serious complication that typically arises 7 to 10 days after the last chemotherapy dose and has a mortality rate that can exceed 50%<sup>17</sup>. Therefore, identifying the infectious focus

through clinical evaluation or cultures, along with the prompt initiation of antibiotic therapy, is essential to improving patient prognosis and reducing mortality rates<sup>18</sup>.

Recombinant granulocyte colony-stimulating factors (G-CSFs), such as filgrastim and pegfilgrastim (PFG), a recombinant G-CSF protein, can be used as prophylaxis for FN. Ideally, all patients undergoing chemotherapy with an FN risk greater than 20% should receive one of these prophylactic agents; however, this would entail significant costs. Therefore, their use is primarily recommended in therapies associated with substantial myelosuppression, such as those involving docetaxel (DCX) and doxorubicin<sup>19</sup>. Although myelotoxicity and FN are less common with capecitabine, prophylaxis with PFG may also be considered<sup>20</sup>.

## CONCLUSIONS

Capecitabine is an important therapeutic option for patients with TNBC. Currently, its primary indication is for patients with residual disease following neoadjuvant chemotherapy, demonstrating benefits in survival and mortality outcomes. The drug is generally well tolerated and has lower toxicity compared to other chemotherapeutic agents. However, careful monitoring of adverse effects is necessary, particularly given the recent expansion of its use in TNBC patients. Investigating DPD deficiency may be valuable in predicting severe toxicity and could be crucial for dose adjustments in higher-risk patients. Further studies are needed to determine the benefits of routine DPD deficiency screening before initiating capecitabine therapy, as well as to establish appropriate management strategies based on test results. FN remains a serious complication, for which prophylactic measures may also be considered in these patients. Additionally, further research is required to evaluate the real-world application of capecitabine in TNBC, assessing its effectiveness, tolerability, and optimal patient management.

## AUTHORS' CONTRIBUTION

GMMVJ: writing – original draft, writing – review & editing. ACSES: writing – original draft, writing – review & editing. DSACC: project administration, supervision, writing – review & editing. JCS: validation, writing – review & editing.

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# Breast lobular carcinoma metastatic to the cervix: case report

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## ABSTRACT

Breast cancer is the most common cancer among women, with 5 to 15% of these cases classified as invasive lobular carcinoma (ILC). Metastases can occur at any stage of the disease, with the most common sites being bones, lungs, lymph nodes, liver, and brain. However, extragenital metastasis to the uterus is rare. This study describes a case of a 52-year-old woman with breast pain for over a month. Mammography indicated a suspicious nodule (BIRADS 5). Physical examination revealed a breast nodule, *peau d'orange* skin, and axillary mass. Core biopsy diagnosed invasive lobular carcinoma. Tomographies suggested bone metastases. Additionally, she presented with abnormal uterine bleeding, and ultrasonography showed a suspicious uterine nodule, confirmed as a metastasis of ILC by immunohistochemical analysis. She had been treated with anastrozole since November 2023, with symptom reduction and clinical follow-up. It is known that ILC is the breast cancer most likely to metastasize to the genital tract. Previous reports mention difficulties in differentiation through imaging exams, with definitive differentiation achieved by biopsy of the cervix and/or later by surgery for tumor excision, with histopathological analysis and immunohistochemical profiling. There is limited scientific data on treatment options and prognosis in these cases. A study of approximately 1,650 patients with metastatic lobular carcinoma showed an overall survival of about 34 months. Thus, it is concluded that metastasis of invasive lobular carcinoma to the cervix is a rare entity, and this study aimed to contribute to the understanding of this condition and increase scientific evidence on the topic.

**KEYWORDS:** breast neoplasms; neoplasm metastasis; cervix uteri.

## INTRODUCTION

Breast cancer is the most commonly diagnosed malignant disease in women (with an estimated 2.1 million new cases in 2018) and is the leading cause of cancer-related death in women in over 100 countries<sup>1</sup>. The National Cancer Institute (INCA) projects approximately 73,000 new cases in Brazil for the 2023–2025 triennium, with an adjusted incidence rate of 41.89 cases per 100,000 women. The age-adjusted mortality rate from breast cancer in women in Brazil, based on the world population, was 11.71 deaths per 100 women, with higher rates observed in the Southeast and South regions and a progressive increase with age<sup>2</sup>.

Invasive lobular carcinoma accounts for 5 to 15% of all breast carcinomas. While the incidence rates of invasive ductal carcinoma have remained stable, those of lobular carcinoma have been steadily increasing since 1980. This rise presents a significant clinical challenge, as lobular carcinoma is

more difficult to detect through both physical examination and mammography<sup>3</sup>.

Metastases can occur in both early-stage and locally advanced breast cancer, with the most common sites of dissemination being the bones, lungs, lymph nodes, liver, and brain<sup>4,5</sup>. Metastases of extragenital origin to the uterus are rare, typically affecting the uterine body, while metastases to the uterine cervix represent an extremely rare site for this neoplasm<sup>4,6,7</sup>.

Metastasis is the stage of cancer progression associated with the highest mortality, making knowledge of rare metastatic sites crucial for the early detection and interpretation of symptoms.

This study aims to report a case of lobular carcinoma in a 52-year-old female patient, presenting with metastases to the cervix and ovaries. Specifically, it focuses on a case of breast lobular carcinoma metastasizing to an exceptionally rare site, the cervix.

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## CASE REPORT

A 52-year-old female patient, previously healthy and in her reproductive years, G2C2, with menarche at 14 years, was referred to Hospital Erasto Gaertner (HEG) in May 2023, presenting with breast pain, changes in skin appearance, and a palpable nodule in the right breast. Symptoms began one month prior to her referral to this facility. Mammography revealed diffuse increased breast density, nipple retraction, diffuse architectural distortion, extensive radiodensity in the middle third of the breast, an ill-defined radiodensity in the right axillary region, and a slightly lobulated nodule, approximately 9 mm, in the right axillary region. These findings were classified as BIRADS 5.

During her first consultation with a breast specialist in July, physical examination revealed a locally advanced tumor in the right breast. The skin displayed a *peau d'orange* appearance and thickening throughout the breast, with firmer areas in the upper quadrants and retroareolar region, as well as nipple and skin retraction in the inferolateral quadrant. Additionally, a palpable mass was detected in the ipsilateral axilla, suggestive of lymph node involvement. A core biopsy was performed, and staging tests were ordered.

Core biopsy identified invasive lobular carcinoma, with additional immunohistochemical studies showing positivity for hormone receptors (estrogen and progesterone), negativity for HER2, and a proliferative index (Ki67) of 5%. Staging via computed tomography scans revealed predominantly sclerotic oval lesions scattered throughout the skeleton, which are suspicious for metastatic disease.

In addition to the breast complaint, the patient reported abnormal uterine bleeding, specifically menometrorrhagia. A transvaginal ultrasound was performed (Figure 1), which showed an anteroverted uterus with smooth contours and a uniform myometrial texture, except for a well-defined, hypoechoic, heterogeneous

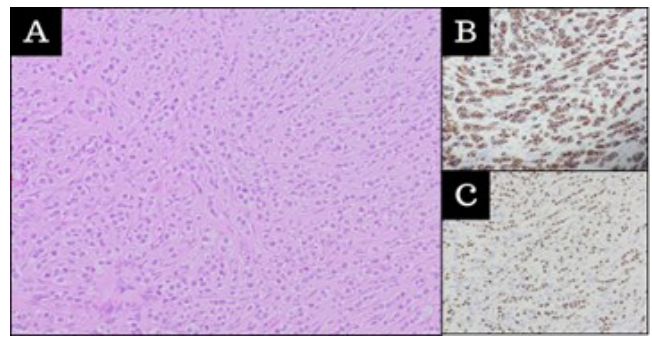


**Figure 1.** Transvaginal ultrasound showed increased uterine dimensions, along with the reported parity (11.1 x 5.5 x 8.2 cm. Volume: 250 cm<sup>3</sup>), a patulous uterine cavity of 14 mm, and heterogeneous content within it. Source: the authors.

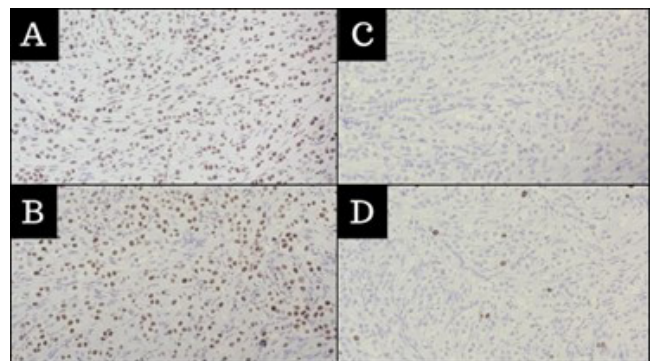
nodular image on the posterior uterine wall, suggestive of an intramural myoma, measuring 19 x 18 x 20 mm. Uterine dimensions were increased, in addition to the reported parity (11.1 x 5.5 x 8.2 cm. Volume: 250 cm<sup>3</sup>). The uterine cavity was patent, measuring 14 mm, with heterogeneous contents inside, and no flow detected on Doppler, which may indicate blood content. The ovaries were of normal dimensions for the age group, and no free fluid was observed in the pelvic fundus or tubal collections. The cervix appeared normal, measuring 4.3 cm in its longitudinal axis.

Hysteroscopy was conducted, and the curetted material was sent for histological analysis. The results revealed atypical cell proliferation in the endocervical stroma. Immunohistochemical analysis identified metastasis of lobular breast carcinoma (Figure 2), with positive hormone receptors and negativity for HER2 (Figure 3).

The patient underwent laparotomy for salpingo-oophorectomy, aimed at achieving castration, along with peritoneal biopsy and peritoneal lavage cytology. Histological analysis of these samples also confirmed metastases of lobular breast carcinoma, with immunohistochemical findings consistent with those previously observed (cervix and breast).



**Figure 2.** A: Neoplasia with cord-like distribution, featuring small cells with low nuclear grade (optical microscopy, hematoxylin and eosin, 400x); B: positivity for cytokeratin 7; and C: positivity for GATA3 (optical microscopy, immunohistochemistry, 200x).



**Figure 3.** Immunohistochemical study showing positivity for hormonal receptors (estrogen (A) and progesterone (B)) and negativity for HER2 (C). The Ki67 proliferative index (D) was approximately 5% (optical microscopy, immunohistochemistry, 400x).



The patient is being monitored by professionals from the clinical oncology and mastology services; she developed anemia secondary to menometrorrhagia and is currently using ferrous sulfate, which has led to improvement in her hematimetric indices. For the treatment of breast neoplasia, anastrozole was prescribed and began in November 2023. The patient has tolerated the medication well, and during the last consultation (in December), she reported a significant reduction in right axillary lymph node enlargement, “softening” of the breast, and a decrease in right breast hyperemia.

## DISCUSSION

Lobular carcinoma is the primary malignant breast neoplasm most commonly metastasizing to the genital tract, although extragenital metastases to the uterus are rarely observed<sup>7</sup>.

Histologically, lobular carcinoma is characterized by cells with minimal cohesion, either embedded in fibrous tissue or arranged in linear cords. These cells have rounded or oval nuclei with a rim of cytoplasm. Typically, mitoses are absent<sup>4,5</sup>.

Immunohistochemical studies are conducted to distinguish metastatic lobular carcinoma from primary cervical neoplasms<sup>4</sup>. The panel for metastatic lobular carcinoma typically shows positive CK-7 and negative CK-20, with the breast-specific marker GCDFP-15 also positive. Lobular carcinoma is usually characterized by a loss of the adhesion protein E-cadherin. However, approximately 15% of lobular carcinomas do not exhibit this loss of expression<sup>4,5</sup>.

Breast and gastrointestinal tumors are the most common extragenital cancers that metastasize to the uterus, with lobular carcinoma being the most prevalent histopathological type to do so<sup>6,7</sup>. Uterine and vaginal metastases typically present with vaginal bleeding, while ovarian metastases often appear as asymptomatic ovarian masses<sup>8</sup>.

The ovaries are the most common sites of metastasis within the female genital tract, due to their extensive vascularization and lymphatic drainage<sup>9</sup>. In contrast, the cervix has limited vascular supply and only an afferent lymphatic drainage system, which may account for the relative rarity of metastases to the cervix compared to the ovaries<sup>6</sup>.

Lobular carcinomas exhibit a distinct pattern of metastasis distribution compared to non-special type carcinomas (ductal, not otherwise specified). They show a lower frequency of regional lymph node metastases and a higher incidence of metastases to distant sites, including the gastrointestinal tract, bones, skin, meninges, uterus, and ovaries<sup>3</sup>.

The clinical characteristics of uterine involvement are often nonspecific, typically presenting as vaginal bleeding and abdominal discomfort<sup>6</sup>. Anatomopathological findings from a previously published study reporting a case of lobular carcinoma with metastasis to the cervix indicated that the metastasis appeared as a

protruding mass with a whitish appearance on section, resembling the pattern found in leiomyomas<sup>10</sup>.

Differentiating metastatic tumors from primary reproductive system tumors is essential for accurate staging and treatment, though it can be challenging. Previous reports highlight difficulties in distinguishing these tumors through imaging tests, with some cases of metastatic lobular carcinoma presenting as lesions that mimic leiomyomas<sup>10</sup>.

Definitive differentiation can be achieved through cervical biopsy and/or post-surgical tumor removal, with histopathological analysis revealing the linear pattern characteristic of lobular carcinoma and an immunohistochemical profile consistent with this diagnosis<sup>3,10,11</sup>.

Treatment options for cervical metastasis are influenced by individual factors such as the extent of the disease, the presence of other metastases, and the patient's performance status. Given the rarity of lobular carcinoma metastasizing to the cervix, there is limited well-established scientific data on treatment options and prognosis for these cases.

Previously published reports have documented the isolated use of adjuvant palliative therapy with anastrozole and S-1, as well as palliative chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide, followed by hormone therapy. Additionally, the use of palliative radiotherapy for symptom management has been reported<sup>10-12</sup>.

In a study involving approximately 1,650 patients with metastatic lobular carcinoma, the overall survival rate was approximately 34 months; there are no specific studies that address the survival of patients with this type of cancer metastasizing to the cervix<sup>13</sup>.

## CONCLUSIONS

Lobular carcinoma of the breast presents diagnostic and therapeutic challenges, particularly when it metastasizes to uncommon distant organs. This case report underscores the importance of meticulous clinical follow-up and interdisciplinary collaboration for the effective management of patients with this neoplasm and cervix metastases. Further studies are required to develop specific therapeutic approaches and enhance patient outcomes.

## AUTHORS' CONTRIBUTION

JWB: writing – original draft, writing – review & editing. MTBR: data curation, investigation, writing – original draft, writing – review & editing. MMCV: data curation, investigation, writing – original draft, writing – review & editing. SOI: conceptualization. JCL: conceptualization, data curation, investigation, supervision, project administration, writing – original draft, writing – review & editing.

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# Giant epidermal cyst in the breast requiring reconstruction with the bilobed flap technique — case report

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## ABSTRACT

Epidermal cysts are one of the most common benign skin lesions, originating in the pilosebaceous unit, and are very common on the scalp, back, and trunk. They usually measure from millimeters to a few centimeters and require surgical treatment only depending on the patient's discomfort. Cases that mimic breast neoplasms are rare. Treatment consists of a minimal incision, with removal of the contents and their capsule, without major complications. We report here the case of a woman with an epidermal cyst in her left breast, which had grown progressively over the years, reaching 6 cm. Because of its size, location, and unfavorable relationship between tumor size and breast size, surgery using an oncoplastic breast remodeling technique was chosen, opting for the use of a bilobed flap to achieve a satisfactory cosmetic result, without loss of breast volume.

**KEYWORDS:** epidermal cysts; surgical flaps; breast-conserving surgery; breast diseases.

## INTRODUCTION

Epidermal cysts originate in the pilosebaceous unit and are most commonly found on the scalp, back, and trunk. Their presentation in the breast is rarely reported, appearing mainly in the peri-areolar cutaneous and subcutaneous region<sup>1-4</sup>. As of 2021, only ten cases had been reported in the English literature<sup>4</sup>. There are no published studies detailing surgical options for large lesions.

The importance of reporting this benign lesion, in addition to its surgical approach, lies in the clinical-radiological differentiation of other non-neoplastic and neoplastic breast lesions. However, the incidence of malignant potential of this lesion is highly variable (0.045–19%), and the true incidence remains uncertain<sup>3</sup>.

It is a retention cyst of the sebaceous gland derived from the infundibulum of the hair follicle or by traumatic inclusion (e.g., core needle biopsy or breast surgeries that can cause epithelial implantation or stimulation of epithelial proliferation). The epidermal cyst is lined by true stratified squamous epithelium, with proliferation and implantation of epidermal elements within a circumscribed space in the dermis, and its growth results from the accumulation of epithelial and keratinous debris<sup>2,3</sup>.

Wide excision does not always have an aesthetic impact, as it often does not reach large volumes; in situations where there is a forewarning of resection of more than 20% of the breast volume, partial breast reconstruction is indicated using a variety of techniques.

The objective of this case report was due to the unusual shape of the epidermal cyst in the breast and its size but also due to the need to use an alternative surgical technique to repair the cosmetic deformity caused by its wide and adequate excision<sup>5,11-13</sup>.

## CASE REPORT

Female patient, 58 years old, menarche at 13 years old, three children, postmenopausal, with no personal history of hormone replacement therapy and no family history of breast cancer, but with a sister's history of ovarian cancer. She presented with a palpable lesion in her left breast, which she had for eight years, showing progressive growth. Mammography (MMG) in June 2023 showed a large, isodense, circumscribed nodule, located predominantly in the middle third of the central region of the left breast,

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palpable, measuring approximately 6.2 x 5.5 cm, and classifying BI-RADS 4. An ultrasound was performed in June 2023, which showed a hypoechoic, oval, circumscribed nodule, with major axes parallel to the skin, located in the lower lateral quadrant (LLQ) of the left breast at 4 o'clock, measuring 5.5 x 2.7 x 5.3 cm, 0.9 cm from the papilla, with discrete central vascularity on color Doppler, palpable and BI-RADS 4. On physical examination, the breasts were of small to moderate volume, with a soft nodular area of 5.5 cm in LLQ of the left breast, periareolar (Figure 1).

A core biopsy was performed in June 2023, with sebaceous secretion being released during the procedure. The clinical and histopathological diagnosis was epidermal cyst. As a surgical plan, it was decided to perform complete resection of the breast lesion and breast reconstruction using a bilobed flap (Figure 2).

After excision of the lesion in the left breast with margins, aiming at the integrity of the capsule, an incision of the flap was made at a previously marked site (Meadows marking<sup>10</sup>). With this technique, it was possible to transpose part of the mammary

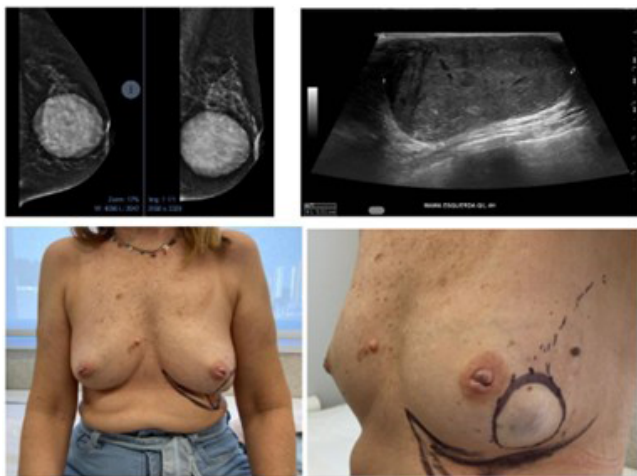
glandular tissue to cover the area with defect; the geometric structure of the flap allowed the maintenance of the breast volume.

In the immediate postoperative period, a slight depression could be seen in the flap, but with maintenance of the shape of the breast, and the unusual appearance of the scar. During the evolution and accommodation of the flap, the aesthetic aspect showed significant improvement (Figure 3), and the patient was satisfied with the surgical result. The patient remains well, with no complaints four months after surgery, in clinical and outpatient follow-up.

## DISCUSSION

Epidermal cysts are known to be benign lesions, with no association with breast cancer. They are believed to arise through several possible mechanisms. These include the derivation of a congenital anomaly resulting from cellular nests remaining from the embryonic mammary ridge, as a sequela of traumatic or surgical alterations, or as squamous metaplasia in an area of fibrocystic alteration or fibroadenoma<sup>1</sup>.

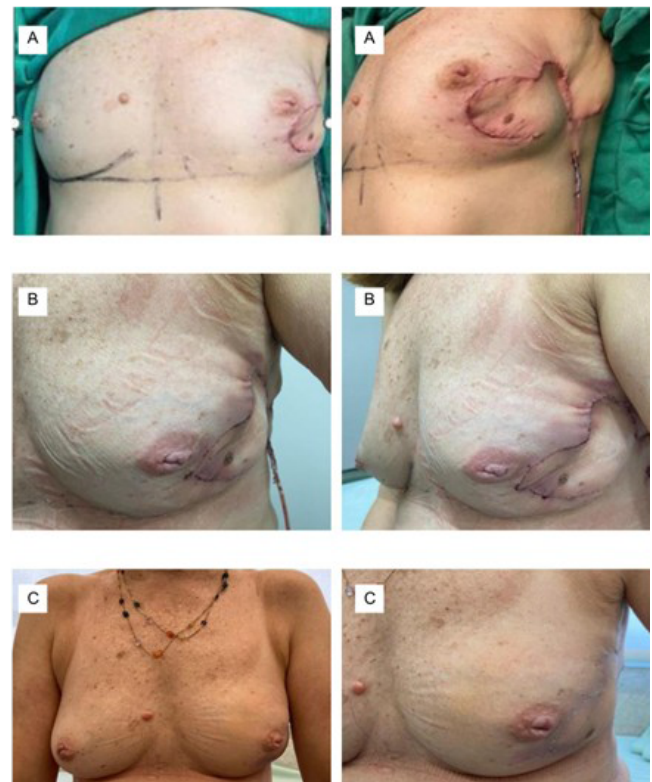
Typically, they grow naturally slowly, with their rupture responsible for secondary reactions such as foreign bodies, granulomatous reactions or abscess formation<sup>3</sup>. Paliotta et al.<sup>3</sup> described the following clinical findings: palpable mass in the breast in 79% of cases, local discomfort in 67%, inflammation



**Figure 1.** Clinical-radiological presentation of the case.



**Figure 2.** Wide resection of the lesion, highlighting the intact capsule of the epidermal cyst, and creation of a bilobed flap to correct the breast defect.



**Figure 3.** Postoperative appearance. (A) Immediate postoperative, (B) 7th day and (C) final appearance.



in 33%, spontaneous rupture in 12% and ulceration in 4% of the 65 patients studied.

The importance of recognizing this lesion lies in the fact that it can be confused with any benign or malignant lesion of the breast, both clinically and radiologically.

Clinically, an epidermal cyst presents as a firm nodular protrusion of the skin; in the breast, the lesion usually grows deep into the subcutaneous tissue and is indistinguishable from other types of breast lesions. Classically, an ultrasound scan shows a solid, circumscribed, complex mass<sup>2</sup>. A mammogram shows a well-circumscribed mass with homogeneous increased density<sup>5</sup>. Calcification of an epidermal cyst may occur mainly in older lesions<sup>6,7</sup>. An incisional biopsy typically shows the release of proteinaceous material that is highly suggestive of this entity. Histopathological examination shows that these lesions are lined with stratified squamous epithelium containing an agranular layer<sup>2,3</sup>.

The treatment of choice is surgical excision with preservation of the integrity of the capsule, minimizing complications such as recurrent infections and recurrence of the lesion due to inadequate excision. Simple excision techniques are generally used, with small scars, which do not require advanced technical knowledge of flap rotation and reconstruction of large defects. There is no need for additional treatments after surgical excision, which is curative<sup>1-5</sup>.

The case report presents a large lesion, requiring an advanced oncoplastic surgical technique as an alternative for breast remodeling used in breast-conserving surgeries more commonly used in the treatment of malignant lesions, in which free surgical margins are required.

The emergence of oncoplastic surgical techniques has enabled not only oncological safety but also the preservation of breast cosmesis, with acceptable aesthetic results<sup>8,11-13</sup>. Individual aspects should be respected and guided by variables such as lesion location, breast size, skin type, patient's body shape and symmetrization in relation to the other breast when making a decision regarding the technique to be used. The bilobed flap was initially described by Esser in 1918, who designed it for closing defects in the nasal tip. However, it was Zimany, in 1953, who published the description of this flap in the English literature and made it popular. It is a double transposition flap with a single pedicle, in which the first flap is transposed into a defect and the second and smaller flap is transposed to fill the secondary defect caused by the transposition of the larger flap, distributing the tension forces in several directions and reducing the distortions and skin redundancies generated by a simple transposition flap or primary closure<sup>9</sup>. It is used in cases of volume replacement and can be a choice when opting for a thoracic-lateral transposition flap.

There are several ways to draw the markings, the most common being the Meadows technique. It involves transporting part

of the glandular tissue to the region of the defect, and a lateral thoracic flap is used to correct the area adjacent to the tumor<sup>9,10</sup>. The larger lobe corresponds to 75% of the defect and the smaller lobe, to 75% of the larger one. The flaps are detached and rotated so that the first fills the primary defect, the second fills the secondary defect and, finally, the defect left by the smaller lobe is closed primarily.

Its main complications are necrosis, epitheliolysis and infection, which in most cases can be resolved in an expectant way or with surgical debridement or the use of antibiotics.

Advanced breast reconstruction techniques using flaps can be best used in association with breast fat grafting, a very promising and safe technique, which has established itself as an important technical-surgical refinement<sup>13</sup>.

## CONCLUSIONS

Epidermal cysts in the breast do not always require complex excision without loss of a large amount of glandular tissue. The alternative surgical technique to repair the deformity left after excision is uncommon and can be performed by surgeons with expertise in breast oncoplasty.

The choice of the appropriate surgical technique for treating breast lesions requires careful evaluation, with very individualized criteria, and the possibility of changing the previously chosen technique may exist if a better technique favors cosmesis and surgical safety. The use of one or more associated techniques can favor a safe and aesthetically acceptable way for patients, regardless of the nature of the breast lesion.

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the consent form is available for review by the editor-in-chief of this journal. This report was approved by the ethics committee under No. 6.995.223.

## AUTHORS' CONTRIBUTION

JLAA: Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DTSMN: Conceptualization, Data curation, Investigation, Funding acquisition, Methodology, Supervision. MLMMD: Formal analysis, Funding acquisition, Investigation. GSB: Conceptualization, Formal analysis, Investigation, Software. LSLF: Data curation, Project administration, Software, Validation. UWS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.



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# Desmoid tumor in the male breast refractory to systemic treatment: case report

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## ABSTRACT

Desmoid-type fibromatosis, an intermediate soft tissue tumor known for its local infiltrative behavior and high recurrence rate, is uncommon in the male breast. The report outlines the clinical journey of a 44-year-old male presenting with a rapidly growing breast mass, initially managed with a watchful waiting approach and subsequent systemic therapies including celecoxib, sorafenib, and a combination of methotrexate and vinblastine, all of which proved ineffective. Genetic testing revealed a catenin beta 1 (CTNNB1) mutation, indicative of a sporadic tumor. Despite various treatment attempts, significant tumor progression was observed, necessitating surgical intervention followed by radiotherapy. This case underscores the challenges in managing desmoid tumors, emphasizing the importance of multidisciplinary approaches and the potential need for surgical resection when conventional therapies fail.

**KEYWORDS:** breast; male; desmoid fibromatosis; diagnostic imaging; MRI.

## INTRODUCTION

Desmoid-type fibromatosis is classified as an intermediate soft tissue tumor characterized by clonal fibroblastic proliferation originating from deep soft tissues<sup>1</sup>. This tumor is known for its local infiltrative behavior and high recurrence rate, though it rarely metastasizes<sup>2</sup>. These factors have led to the exploration of alternative treatment modalities beyond surgery, including radiation therapy, chemotherapy, and anti-hormonal therapies. Currently, surgical resection remains the gold standard for desmoid tumor management<sup>3,4</sup>. Desmoid fibromatosis is exceedingly uncommon in the breast, accounting for only 0.2% of all breast tumors, and this condition's incidence in males is sporadic<sup>5</sup>.

## CASE REPORT

A 44-year-old male patient complained of weight loss and a lump in the left breast. Percutaneous biopsy diagnosed a desmoid tumor, estrogen receptor (ER)-negative. Breast magnetic resonance imaging (MRI) demonstrated an oval mass with irregular margins, which showed heterogeneous enhancement, with a type I (persistent) kinetic curve in the left breast's lower quadrants, measuring 67 x 48 x 36 mm (estimated volume of 60 cc). It was in close contact with the skin and showed signs

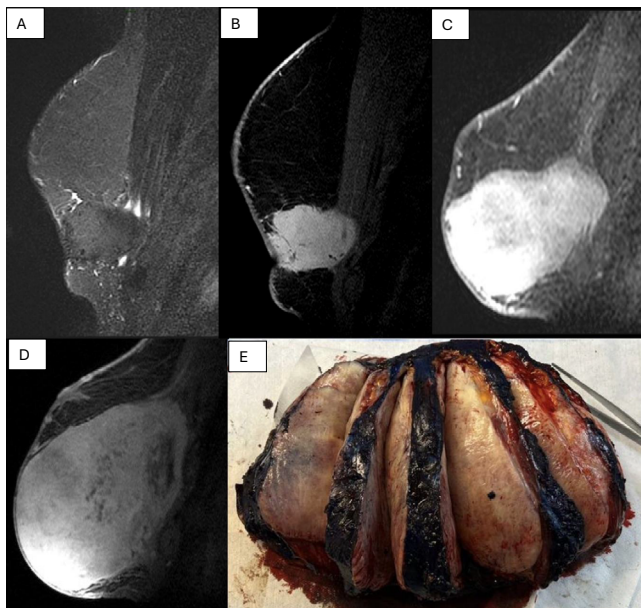
of infiltration into the pectoralis major muscle (Figure 1A-B). After discussion in the multidisciplinary tumor board, a watchful waiting approach was chosen with imaging control for three months after continuous use of celecoxib 200 mg/day. Upon return after this period, a significant increase in the lesion was noted, which was consistent with the results of the breast MRI performed in the same month, with the tumor volume estimated at 321 cc. A catenin beta 1 (CTNNB1) positive variant was detected at somatic genetic testing, with a sporadic origin of the desmoid tumor, without family risks. The case was meticulously reviewed during a multidisciplinary meeting, aiming at a tumor-reducing approach through targeted therapy with tyrosine kinase inhibitors. In this context, celecoxib was discontinued, and sorafenib was prescribed at an initial dose of 400 mg/day. However, due to the manifestation of cutaneous toxicity, the dose of sorafenib was adjusted to 200 mg/day. After four months, new imaging tests revealed a dimensional increase in the lesion, with the tumor volume estimated at 631 cc (Figure 1C). Given this scenario, the case was submitted to a SELNET (Sarcoma European & Latin-America Network) meeting for evaluation, resulting in a consensus to maintain systemic therapy. Methotrexate was then prescribed at a dose of 30 mg/m<sup>2</sup> and vinblastine at a dose of 5 mg/m<sup>2</sup>,

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**Figure 1.** Contrast-enhanced sagittal T2-weighted sequence at breast MRI demonstrating an oval mass with irregular margins, presenting low signal and peri tumoral edema on T2-weighted images (A), infiltrating the pectoral muscle, and showing heterogeneous enhancement in sagittal fat-suppressed contrast-enhanced T1-weighted images (B). The lesion progressed despite the systemic treatment after seven months (C) and eleven months (D). The patient underwent a mastectomy with a partial resection of the underlying musculature (E).

administered weekly with a continuation plan for six months. After two months, another imaging examination was conducted, revealing further progression of the disease, with the tumor volume estimated at 1,146 cc (Figure 1D). Given this scenario, the decision was made to proceed with a surgical approach followed by radiotherapy. At that time, the patient experienced sporadic pain in the lower region of the tumor mass but denied dyspnea, chest pain, and other relevant symptoms. The tumor resection surgery, using an abdominal fasciomyocutaneous flap, was successful (Figure 1E). The patient remains asymptomatic at a seven-month follow-up, undergoing clinical and imaging surveillance with no signs of recurrence.

## DISCUSSION

Desmoid neoplasia is characterized by its lack of metastatic potential, displaying a notable propensity for local growth, invasion of adjacent structures, and high recurrence rates<sup>1</sup>. The etio-pathogenesis of desmoid tumors remains unknown. Although there have been reports of breast desmoid tumors following surgical procedures with breast implants and traumas, it is clear that isolated physical factors are not sufficient to trigger fibromatosis in the breast<sup>6</sup>. Although most cases have been observed

in postmenopausal women, the issue of hormonal receptors in mammary fibromatosis remains controversial<sup>2</sup>.

Breast imaging tests do not provide specific features to detect desmoid fibromatosis, which makes it difficult to distinguish this condition from breast malignancies<sup>7</sup>. However, imaging and histopathological examinations are essential for treatment planning and follow-up. Desmoid tumors often appear in mammography as high-density, irregular, non-calcified masses with spiculated margins. Chest computed tomography (CT) and MRI are valuable tools to determine the extent of the tumor's infiltration into adjacent tissues<sup>8</sup>.

Managing desmoid tumors depends on various factors, including location, size, extent of invasion, and individual characteristics. Surgery has traditionally been the gold standard of treatment for desmoid tumors, aiming at complete resection with negative margins<sup>3</sup>. However, the high local recurrence rate post-surgery necessitates careful patient screening. A conservative "watch and wait" approach may be adopted in asymptomatic patients, with active surveillance employed to monitor for signs of progression, leveraging the tumor's potential for spontaneous stabilization or regression<sup>5</sup>.

In some cases, neoadjuvant therapy may be indicated. In a study by Kaspar et al., desmoid tumors treated with imatinib demonstrated promising results. At six months, the progression arrest rate was 65%; subsequent rates were 59%, 53%, and 45% at 12, 15, and 24 months, respectively<sup>9</sup>. A retrospective study investigating the efficacy of apatinib, a tyrosine kinase inhibitor, revealed an objective response rate of 45.5%, with a notable disease control rate of 95.4%<sup>10</sup>. An additional study examined the use of tamoxifen and sulindac in treating desmoid tumors in adults. The results indicated an overall response rate of 60%, with complete response observed in 8% of cases and partial response in 52%<sup>11</sup>.

Various chemotherapy drugs may be administered, including tyrosine kinase inhibitors (imatinib, sunitinib, and sorafenib), methotrexate and vinblastine (MTX/VBL), doxorubicin, and other agents like cyclophosphamide and pazopanib. Hormonal treatments, such as selective estrogen receptor modulators (tamoxifen, raloxifene, toremifene) and luteinizing hormone-releasing hormone analogs (leuprolide), can also be indicated in ER-positive tumors. Non-steroidal anti-inflammatory drugs like sulindac and celecoxib may also be prescribed. Radiation therapy may be used to target and shrink the tumor, particularly in cases where surgery is not feasible, or to reduce the risk of recurrence after surgery<sup>12</sup>.

In the presented case, the patient experienced significant tumor progression over nine months, from 60 to 1,146 cc (approximately 20 times larger), despite multiple systemic treatments performed. Given this lack of efficacy, surgical resection emerged as the most appropriate method for resolving the disorder, corroborating literature data. Additionally, considering that adjuvant

radiation therapy can positively influence the disease-free survival rate, this option was also performed<sup>4</sup>.

High-intensity focused ultrasound (HIFU) and ablation techniques are two other types of local treatment. HIFU represents an emerging, non-invasive therapeutic option, deploying targeted ultrasound waves to induce thermal ablation of tumor cells, with preliminary studies showing promising outcomes. Cryoablation and radiofrequency ablation offer minimally invasive alternatives to traditional surgery, providing benefits in selected cases, particularly for patients with small, localized tumors and those unsuitable for extensive surgical procedures<sup>3,4</sup>.

## CONCLUSION

We presented a rare case of desmoid tumor in a male breast with chest wall invasion, which showed progression after neoadjuvant

systemic treatment. Imaging was important in diagnosis, staging, and response evaluation, supporting multidisciplinary meetings for proper treatment planning.

## AUTHORS' CONTRIBUTION

CLLR: conceptualization, formal analysis, investigation, writing – original draft. SQD: conceptualization, formal analysis, investigation, writing – original draft. CMAS: formal analysis, investigation, writing – original draft. BML: data curation, formal analysis, writing – review & editing. JAS: conceptualization, data curation, resources, writing – review & editing. LG: data curation, resources, writing – review & editing. CSG: data curation, resources, writing – review & editing. AGVB: project administration, conceptualization, data curation, methodology, writing – review & editing.

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# Malignant phyllodes tumor of the breast with lymph node metastasis: a case report

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## ABSTRACT

In the present case report we aim to describe a rare case of malignant phyllodes tumor in a young patient who presented with a fast-growing mass in the right breast, with an enlargement in the axillary lymph node ipsilateral to the lesion. Perioperative histopathological analysis confirmed malignancy in two out of five excised lymph nodes. Modified radical mastectomy was performed in the right breast, with axillary dissection levels I and II. One month after the first consultation, surgical margins were increased. The patient underwent adjuvant chemotherapy as a complement to surgical treatment. She had tumor recurrence 56 days after surgical treatment. The patient passed away six months after diagnosis.

**KEYWORDS:** malignant phyllodes tumor; lymphatic metastasis; modified radical mastectomy.

## INTRODUCTION

Phyllodes tumors (PTs) are rare tumors, accounting for less than 1% of all primary breast neoplasms. They usually present as fast-growing breast nodules, affecting women in the fourth or fifth decades of life.

PTs are classified as benign, borderline (low grade), and malignant (high grade)<sup>1</sup>. Differentiating PT and fibroadenoma by mammography can be difficult, in such a way that fine-needle aspiration (FNA) and core biopsy are the basis for preoperative diagnosis<sup>2</sup>.

Clinically, PT presents as an extensive and painless unilateral breast mass, distending the overlying skin and superficial veins. Bloody nipple discharge may occur due to tumor infarction. Axillary lymph node enlargement is common, but the presence of lymph node metastasis is rare<sup>3</sup>.

Treatment is based on complete excision of the lesion, with 1-cm margins. Surgical success, reduction of local recurrence rates, and the emergence or not of metastases depend on surgical tumor resection with free margins<sup>2,3</sup>.

In this study we describe a case of a young patient with a fast-growing lesion in the right breast, with a palpable ipsilateral axillary lymph node. The perioperative anatomopathological examination of sentinel lymph nodes showed involvement in two of five lymph nodes, positive for malignancy. Modified radical

mastectomy surgery on the right side was performed with axillary dissection levels I and II and deep margin enlargement one month after the first consultation. The immunohistochemical profile demonstrated characteristics compatible with malignant phyllodes tumor with a proliferation index of 50%. The patient underwent complementary chemotherapy.

## CASE REPORT

P.T., 29 years old, woman, smoker (34 pack-years), with no family history of cancer, was referred to the consultation by the Health Center with a diagnosis of breast cancer on the right side. She presented with an ulcerated lesion on the central region of the right breast, reporting acute local pain. She reported having a breast lesion since the age of nine and receiving hospital follow-up and nodulectomy, losing the follow-up after ten years. She reported an increase in the breast injury in the last two months associated with intense mastalgia. She had the result of an anatomopathological examination, showing a poorly differentiated, pleomorphic, infiltrating neoplasm in the breast parenchyma, with the observation that the poor differentiation of the lesion did not allow physicians to determine whether it corresponded to a poorly differentiated carcinoma, lymphoma, or neoplasm of another histogenesis.

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On physical examination, she presented asymmetrical pendulous breasts due to the large increase in volume of the right breast, absence of palpable nodules in the left breast or axillary lymph node enlargement, right breast with a lesion measuring 9.0 x 9.0 cm, affecting the central region of the breast, with distortion of the nipple-areola complex and presence of palpable lymph node in the right axillary region, measuring about 1 cm, mobile, and painless (Figure 1).

At first, bone scintigraphy, computed tomography of the chest, pelvis, and abdomen were requested for staging. The chest tomography showed two solid, contiguous nodules, measuring 17 x 15 mm and 8 x 8 mm, with a suspicious aspect for metastatic disease, located in the periphery of the lateral basal segment of the right lower lobe. The other tests were within normal parameters.

Modified radical mastectomy surgery on the right side was performed with axillary dissection levels I and II and deep margin widening one month after the first consultation. The peri-operative anatomopathological examination of sentinel lymph nodes showed involvement in two of five lymph nodes, positive for malignancy.

The anatomopathological examination of the lymph nodes showed the presence of six nodules, the largest measuring 3.5 x 1.5 x 1.0 cm and the smallest, 0.5 x 0.3 x 0.2 cm. When cut, they were firm, elastic, and brownish. Two of them came

positive for poorly differentiated metastatic malignant neoplasm. The specimen resulting from the right mastectomy measured 14 x 13 x 9 cm, with 731 g and skin without signs of retraction or macroscopic lesion. In the parenchyma, a whitish, hardened, poorly-delimited, and nodular lesion measuring 10 x 8 x 8 cm was observed, in addition to a deep margin of 2 x 2 x 2 cm.

The immunohistochemical profile demonstrated characteristics compatible with malignant phyllodes tumor with a proliferation index of 50%. Moreover, in a note from the immunohistochemical study in a right axillary lymph node specimen, it is suggested that the positivity only for the P53, P63, and  $\beta$ -catenin markers and the high proliferation index (Ki-67) may correspond to high-grade metastatic phyllodes tumor. We listed the markers of the surgical specimens in Tables 1 and 2.

After surgical treatment, the patient was referred to clinical oncology to undergo adjuvant chemotherapy. Tumor recurrence was observed 56 days postoperatively (Figure 2). The patient underwent two chemotherapy cycles, the first with anthracycline and cyclophosphamide, without satisfactory clinical response, and the second with doxorubicin and ifosfamide, but she developed significant toxicity and febrile neutropenia. The patient passed away about six months after the initial diagnosis.



**Figure 1.** Preoperative diagnosis: ulcerated lesion on the right breast.

**Table 1.** Immunohistochemical markers of the right breast and axillary lymph node.

Marker	Right mastectomy specimen	Right axillary lymph node
GCDFP-15	Not applicable	Negative
CKAE1/AE3	Negative	Negative
ER	Negative	Negative
PR	Negative	Negative
CK5/6	Not applicable	Negative
BCL2	Not applicable	Negative
Vimentin	Positive	Not applicable
CK7	Negative	Not applicable
CK20	Negative	Not applicable
GATA-3	Negative	Not applicable
E-cadherin	Negative	Not applicable
HER-2	Negative	Not applicable
Ki-67	Positive 50%	Not applicable
AMS	Multifocal positive	Not applicable
CD68	Negative	Not applicable
CD34	Negative	Not applicable

**Table 2.** Right axillary lymph node markers — frozen section.

Marker	Right axillary lymph node — frozen section
P53	Diffuse positive
P63	Diffuse positive
$\beta$ -catenin	Diffuse positive
CD34	Negative
CD117/c-KIT	Negative
Ki67	Positive 90%

**Figure 2.** Local recurrence of the lesion on the right breast.

## DISCUSSION

Phyllodes tumors are rare, accounting for less than 1% of all primary breast neoplasms. Composed of stromal and epithelial elements, they usually present as fast-growing and clinically-benign breast nodules in women in the fourth or fifth decades of life. When malignant, the lung is the organ most affected by distant metastases, which can be represented by solid nodules or thin-walled cavities<sup>4</sup>.

They are classified as benign, borderline, or malignant, according to several histological parameters (degree of cell stroma and atypia, number of mitoses, growth and nature of tumor borders), local recurrence capacity, and risk of metastasis. In addition, benign phyllodes tumors are very similar to fibroadenomas, making their differentiation difficult<sup>1,5</sup>.

Recognizing the subtypes of phyllodes tumors is important because it allows predicting the clinical behavior of the disease: benign tumors can recur locally; borderline tumors can recur locally and have a very low risk of metastasis, while malignant tumors have a higher risk of metastatic behavior<sup>1</sup>.

Sometimes, there may be doubts about the differentiation of borderline and malignant types. The most practical way to differentiate malignant tumors from borderline tumors is: when the lesion presents all histological changes, it should be considered malignant; and when it presents only some of the characteristics, borderline. The presence of heterogeneous malignant elements, such as liposarcoma, chondrosarcoma, or osteosarcoma, categorizes the tumor as malignant, regardless of other histological parameters. The most important microscopic pattern to determine the clinical behavior of these tumors is the impairment of surgical margins.

Borderline and malignant PTs have a metastasis rate between 25 and 31%, whereas the metastasis rate of benign forms is approximately 4%<sup>1,2</sup>.

Histologically, the purely-benign forms have very little nuclear atypia and a mitotic capacity of less than 5/10 high-power fields, while malignant tumors have fibroepithelial architecture with a leaf-like intracanalicular pattern, projecting into dilated cystic spaces, accompanied by atypical stromal hypercellularity, with irregular margins and mitotic activity of at least 10/10 high-power fields<sup>1,5</sup>.

Clinically, the phyllodes tumor presents as an extensive and painless unilateral breast mass, distending the overlying skin and superficial veins. Its size can occupy the entire breast. In addition, bloody nipple discharge caused by tumor infarction may occur.

Axillary lymph node enlargement is common; however, the presence of lymph node metastasis is rare as well as ulceration and retraction of the nipple. About 20% of patients have palpable axillary lymph nodes on physical examination, but only 5% are demonstrably metastatic. In mammography, it is possible to identify a round, lobulated, and dense mass, with circumscribed margins, and it may rarely present calcifications.

Nonetheless, these findings are also compatible with fibroadenoma, and it is not possible to differentiate them at mammography, in such a way that FNA and core biopsy are the basis for preoperative diagnosis.

At ultrasound, a hypoechoic mass with circumscribed or partially defined edges is identified; in the malignant phyllodes tumor, usually there is an associated cystic component, making ultrasound the method of choice for initial investigation<sup>2,3</sup>.

Treatment is based on complete excision of the lesion, with 1-cm margins, which is often curative and reduces the risk of recurrence. According to the literature, routine lymph node excision is not recommended, as PTs most commonly present hematogenic and rarely lymph node dissemination (<1%)<sup>3,6</sup>. Surgical success, reduction of local recurrence rates, and the emergence or not of metastases depend on surgical tumor resection with free margins, a less aggressive technique and equally effective when compared to mastectomy. The treatment decision — wide local excision vs. mastectomy — should be guided by lesion size and surgical feasibility<sup>2,3</sup>. In cases of local recurrence, the treatment is wide-margin resection. To date, there are no direct guidelines as for the use of radiotherapy or chemotherapy<sup>6</sup>.

There are five cases of phyllodes tumor with lymph node metastasis described in the literature, confirming the rarity of the finding. The patients were young and initially presented with a fast-growing painless breast mass, as in the present report<sup>7-11</sup>.

## CONCLUSIONS

Malignant phyllodes tumors rarely spread to the lymphatic system, although axillary lymph node enlargement is a common finding. At the beginning of the investigation, mammography and breast ultrasound are of great value, but FNA and core biopsy are the tests that support the preoperative diagnosis.

Treatment is based on complete excision of the lesion with free surgical margins, considering the high risk of recurrence of these tumors. Routine lymph node excision is not recommended, as lymphatic dissemination in this type of tumor is rare (<1%). When there is recurrence, the treatment is still wide-margin resection. To date, there is no consensus on the use of adjuvant chemotherapy or radiotherapy.

Thus, in view of the rarity of the case and its poor prognosis, its notification in the medical literature is paramount.

## AUTHORS' CONTRIBUTION

GV: conceptualization, data curation, investigation, methodology, resources, project administration, supervision, visualization, writing – review & editing. JCL: conceptualization, resources, project administration, visualization, writing – review & editing. HZL: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, visualization, writing – original draft, writing – review & editing. GB: conceptualization, data curation, investigation, methodology, writing – original draft, visualization, writing – review & editing.

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# Knowledge and indications of mindfulness practices among breast surgeons: results of a survey conducted in Brazil

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## ABSTRACT

**Introduction:** Breast cancer is the second most prevalent neoplasm affecting women in the world. The risk of mental disorders in cancer patients is about 30% higher, with a 21% prevalence of depression and anxiety. A complementary and integrative technique of psychic support is mindfulness practice. **Objective:** To assess breast surgeons' knowledge of mindfulness practices. **Methods:** A cross-sectional study of the knowledge and indication of this practice among Brazilian breast surgeons was carried out through an electronic questionnaire. **Results:** A total of 204 surgeons answered the survey. Of them, 76% reported having some knowledge or knowledge of the existence of these practices and 15% were completely unaware of mindfulness practices. The vast majority (n=177; 86.8%) did not refer any patients to perform mindfulness, and among those who did (n=27; 13.2%), most recommended fewer than ten patients in the last year. Despite including a significant sample of professionals working in oncological and academic institutions, nearly all cited not having full knowledge of mindfulness practices and their impacts, which may reflect the higher numbers of patients not being referred. **Conclusion:** Data from this study may indicate that training and dissemination of these practices are necessary among breast surgeons.

**KEYWORDS:** breast neoplasms; mindfulness; breast; surgeons; knowledge.

## INTRODUCTION

Breast cancer is the second most prevalent neoplasm that affects women worldwide; an estimated 2.3 million new cases are diagnosed annually, with increased incidence regardless of country development pattern<sup>1</sup>. In Brazil, according to data from the National Cancer Institute (INCA, *Instituto Nacional de Câncer*), the forecast is 73,610 new cases of the disease in the three-year period 2023–2025, representing an incidence rate of 41.9 new cases per 100,000 women<sup>2,3</sup>. In contrast to the increased incidence, we are witnessing a decrease in mortality in this group of patients due to advances in early diagnosis and the increasingly effective treatment portfolio<sup>4</sup>.

The United States data published this year showed a decline in breast cancer mortality between 1975 and 2019; from 48 to 27 deaths per 100,000 women<sup>5,6</sup>. Thus, with a higher incidence

and lower mortality, there is an increasingly positive balance of women who live with breast cancer or are survivors of the disease. According to Carlson et al.<sup>7</sup>, in the United States this prevalence reached about 26 million women.

With this rising number of female survivors, in addition to the physical sequelae, the psychological consequences may become evident and of significant concern. The risk of mental disorders in cancer patients is about 30% higher, with a 21% prevalence of depression and anxiety<sup>8</sup>. A complementary and integrative technique of psychic support that has become popular in recent years is the therapeutic use of mindfulness practices, defined as a meditation practice that cultivates mindfulness in the moment; in the present.

From an initial Buddhist origin, the goal of mindfulness is to maintain awareness at every moment, getting rid of strong

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attachment to beliefs, thoughts, or emotions, thus developing a greater sense of emotional balance and well-being<sup>9-13</sup>. Meditative techniques, such as mindfulness, can influence the susceptibility or treatment of diseases by reducing stress, anxiety, or depression, in addition to decreasing the use and reducing the adverse effects of analgesic, anxiolytic, or antidepressant medications<sup>14-16</sup>.

Therefore, mindfulness practices could assist in the psychic symptoms of cancer patients<sup>17-19</sup>. A systematic review published in 2019 showed that the indication of complementary therapies in cancer patients reached proportions of 51%, demonstrating the importance and consideration of these practices by clinicians who promote care<sup>20-23</sup>. The American Society of Integrative Oncology, the American Society of Clinical Oncology (ASCO), and the North American National Comprehensive Cancer Network (NCCN) recommend mindfulness as a complementary treatment for psychological problems in cancer survivors<sup>24-26</sup>.

Given this high incidence of psychological symptoms in cancer patients, the need for complementary therapies to treat

these symptoms in this group, and the efficacy and indications in international protocols of mindfulness practices, it is necessary to evaluate the knowledge and indication of mindfulness practices by Brazilian breast surgeons.

## METHODS

A descriptive cross-sectional study was conducted through a structured electronic questionnaire sent to breast surgeons associated with the Brazilian Society of Mastology (SBM, *Sociedade Brasileira de Mastologia*). The SBM membership criteria require medical residency and/or certification in clinical/surgical treatment of breast diseases through a specialist title.

The questions and answer options are described in Table 1, and consist of demographic data, such as age, gender, region of residence in Brazil, certification of specialist in breast diseases, years after graduation, work in an oncology hospital, educational institution, and city of capital or countryside; and data on

**Table 1.** Questionnaire applied with the available answer possibilities.

Questions		Possible Answers					
Demographic Characteristics							
1	How old are you?	<30 years	31–40 years	41–50 years	51–60 years	61–70 years	>70 years
2	What is your gender?	Male	Female	Other			
3	Where in Brazil do you live?	North	Northeast	Midwest	Southeast	South	
4	Do you have a Specialist in Mastology (TEMA) title?	Yes	No				
5	How many years have you graduated in Medicine?	<5 years	5–10 years	>10 years			
6	Do you work in an institution dedicated to oncology treatment?	Yes	No				
7	Do you work in an academic institution (teaching hospital, university, educational institution)?	Yes	No				
8	Do you work most of your time in the capital of your state or in a non-capital city?	Capital	Non-capital				
Working with Mindfulness							
9	Are there interactive and complementary practices services at your hospital?	Yes	No	I do not know			
10	What is your level of knowledge regarding mindfulness?	Great knowledge	Some knowledge	Only knowledge of existence	Lack of knowledge		
11	Have you ever referred patients undergoing or post-treatment for breast cancer for mindfulness practices?	Yes	No				
12	If so, how many patients in the last year?	<10 patients	10–50 patients	>50 patients	No Referred to		
13	Are you aware of the impacts described in the literature of mindfulness practices for: Depression / Anxiety / Sleep / Stress / Quality of Life / Pain?	Yes	No	No referred to			
14	Do you practice mindfulness?	Yes, daily	Yes, rarely	I know, but I do not practice	I do not practice, because I do not know		



clinical performance with mindfulness: presence in the service of integrative practices, degree of knowledge about mindfulness, clinical indication of mindfulness to patients, number of patients referred, knowledge about the impacts of mindfulness practices, and personal use of practices.

The email contacts of breast surgeons from all over Brazil were retrieved from the SBM database and records. Only Brazilian surgeons and partners registered at SBM and those who accepted participation in the study after reading and acknowledging the informed consent form were included in the study. SBM also provided data on age, gender, region of residence, and whether or not they were certified as specialists in the total number of associated surgeons; thus, allowing the comparison of those who answered the questionnaire (sample) with the total number of associates (general population). SBM's list of partners was updated in 2023 and is considered complete and reliable.

Therefore, we assume that all associates were considered eligible for the questionnaire and the concept of unknown eligibility was not applied. Those who did not return the questionnaires were considered non-responders. The response rate was calculated by the number of returned responses divided by the number of eligible subjects (SBM-associated members). For this calculation, complete responses (above 80%) were used.

On the other hand, questionnaires with a proportion of responses less than 80%, but with responses above 50% were considered partial, not entering into the calculation of response rate, but were considered for analysis of the study's objective.

The study stages include three phases:

Phase 1) Sending the electronic address of the questionnaire in Google Forms format. The questionnaire does not contain any identification data of the candidate participant, only demographics and questions about clinical practice with mindfulness. The invitation to participate in the research together with the direct access shortcut, without intermediary or identification, was sent via email by SBM to the associated mastologist physicians registered at this institution. Four emails were sent to all associates, within 15 days between them, during the period of June and July/2024.

All emails were the same and had the same body content.

The emails were sent by the SBM secretary, always by the same person, through the company's electronic address unique digital platform. In the "Reply" email field and in the "To" field, there was only and exclusively the email of the responsible researcher. The addresses of all guests to participate were exclusively included in the "Bcc" field which allows sending the email to several people while keeping the addresses private, safe, and confidential.

Phase 2) Tabulation of Google Forms data in a Microsoft Excel for Windows spreadsheet, duly adapted for statistical analysis.

Phase 3) Analysis of the results from the R for Windows software, version 4.2, by the Research Support Office of the Faculty of Medicine of Botucatu.

The demographic profile of the study sample was assessed using absolute (n) and relative (%) frequency measures. Relative frequencies were analyzed according to the number of participants who answered each question. The association between the demographic characteristics of the sample and the population (all breast surgeons associated with SBM) was analyzed using contingency tables and proportion testing. Significance was set at 5% (p-value [p]<0.05).

The protocol and the informed consent form of the study were approved by the SBM internal ethics council and the Medical Ethics Committee of the Botucatu School of Medicine of the Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP) under number 77508524.5.0000.5411.

## RESULTS

Among the 1,893 SBM members, 204 breast surgeons accepted and completed the questionnaire in full; their demographic data are presented in Table 2. Most respondents were aged between 31–40 years (27.9%), followed by 41–50 (27.5%), and 51–60 (25.5%). In a comparative analysis, there was no statistical age difference between the group of responders and the general population of associated members, except in the population between 51–60 years old which was more represented in our study (25.5% versus 19%; p=0.02).

Of the total 204 surgeons in the sample, 111 (54.4%) were female, similar to the general study population.

As for the region of the country of residence, we observed a divergence of our sample with the general population associated with SBM. There was similar representation only concerning the Northeast and Midwest regions.

We did not obtain answers from the North region. The Southeast region, which despite concentrating the majority of associated members (n=962; 50.8% of the total), in our study, was represented by the majority of the questionnaires answered (63.7%), a percentage above the general population (50.8%; p=0.001).

Regarding certification as a specialist, the study was statistically representative of the general population and the majority of the sample had certification (166 versus 38; 81.4%). Data on clinical and professional performance are described in Table 3. As for the time after graduation, 81.4% answered that they had graduated for more than ten years and the majority (n=107; 52.5%) worked in an exclusive oncological institution.

Those surgeons in the sample who worked in an academic or educational institution represented 61.8% (n=126). As for the city of acting, the majority (n=125; 61.3%) worked in the capital of their state of residence. Regarding the existence of an integrative practices service in the institution where the surgeons in the sample worked, 45.6% did not have this service for referral of patients, 38.7% had this service, and 15.7% were unaware of the availability of integrative practices in the institution.

In an analysis of the responses about specific knowledge regarding mindfulness practices, summarized in Table 4, 76%

**Table 2.** Demographic characteristics of responders (sample) and general population of surgeons associated with Brazilian Society of Mastology.

Characteristics	n sample (204)	%	n SBM members (1,893)	%	p-value
Age					
<30 years	5	2.50	31	1.68	0.58
31–40 years	57	27.90	554	30.14	0.69
41–50 years	56	27.50	549	29.80	0.64
51–60 years	52	25.50	350	19.00	0.02
61–70 years	26	12.70	213	11.58	0.63
>70 years	8	3.90	141	7.67	0.08
Gender					
Male	93	45.60	831	44.00	0.78
Female	111	54.40	1,062	56.00	0.59
Region of Residence					
North	0	0	73	3.85	0.007
Northeast	45	22.10	413	21.80	1.00
Midwest	11	5.40	155	8.18	0.19
Southeast	130	63.70	962	50.80	0.001
South	18	8.80	290	15.30	0.01
Specialist certification					
Yes	166	81.40	1,462	77.00	0.31
No	38	18.60	431	23.00	0.18

**Table 3.** Demographic characteristics of the respondents' performance.

Characteristics	n (204)	%
Years after Graduation		
<5 years	7	3.50
5–10 years	31	15.20
>10 years	166	81.40
Work in an Exclusive Oncology Institution		
Yes	107	52.50
No	97	47.50
Work in an Academic Institution		
Yes	126	61.80
No	78	38.20
Work in the Capital City		
Yes	125	61.30
No	79	38.70
Existence of Integrative Practice in the Institution of Activity		
Yes	79	38.70
No	93	45.60
I do not know	32	15.70

**Table 4.** Knowledge of mindfulness practices and referral of patients by breast surgeons.

Knowledges	n (204)	%
Knowledge of mindfulness practices		
Great knowledge	17	8.30
Some knowledge	73	35.80
Knowledge of existence	82	40.20
Lack of knowledge	32	15.70
Knowledge of mindfulness impacts		
Yes	62	30.40
No	69	33.80
Some knowledge	73	35.80
Referral of patients to mindfulness		
Yes	27	13.20
No	177	86.80
How many patients were referred in the last year		
< 10 patients	21	10.30
10–50 patients	10	4.90
> 50 patients	2	1.00
No referred to	171	83.80
Practice of Mindfulness by the surgeon		
Yes, daily	18	8.80
Yes, rarely	49	24.00
I know, but I do not practice	49	24.00
I do not practice, because I do not know	88	43.10

reported having some knowledge or awareness of the existence of these practices and 15% cited complete ignorance of mindfulness practices.

Studies indicate the impact of mindfulness practices on the treatment of depression, anxiety, sleep, stress, quality of life, and pain. When participants were asked about the knowledge of these impacts, we obtained a similar proportion among those who reported not having knowledge (33.8%), having knowledge (30.4%), and partially knowing the impacts (35.8%).

One of the questions in the questionnaire was about the referral of patients to mindfulness practices. The vast majority ( $n=177$ ; 86.8%) did not refer any patients to perform mindfulness and, among those in the sample who did ( $n=27$ ; 13.2%), most referred fewer than ten patients in the last year.

Finally, another question addressed knowing about the performance of mindfulness practices by the breast surgeon

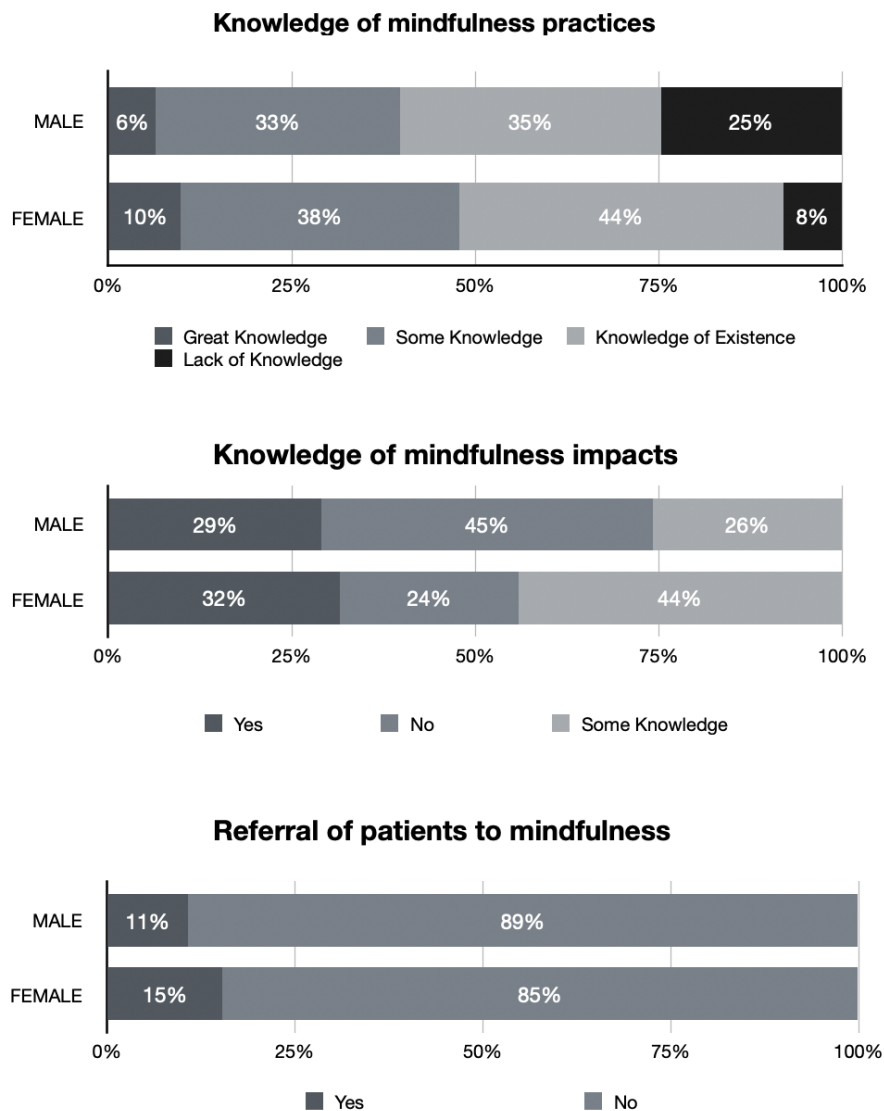
professionals. Only 8.8% reported practicing the techniques daily and 24%, despite knowing mindfulness, reported not practicing them.

Subgroup analyses were performed based on the complete data collection and decision of the authors.

Regarding age group, respondents were subdivided into 50 years of age or less and over 50 years of age, resulting in a younger majority (58% and 42%, respectively).

As for the gender subgroups, a statistical majority was female ( $p=0.09$ ), and of the total number of respondents who reported complete ignorance of mindfulness, the majority was male ( $p<0.05$ ).

Concerning knowledge of mindfulness impacts, the highest statistical proportion of the response was partially in the female group and not in the male group. The proportion that reported yes to the knowledge of impacts was statistically similar between genders (Figure 1).



**Figure 1.** Distribution of respondents according to gender and knowledge of mindfulness practices, knowledge of impacts, and referral of patients to mindfulness. (male=93; female=111).

In the subgroups regarding the city of residence, most respondents' statistics were concentrated in the capital and there was a statistical difference in deep knowledge of mindfulness (higher in the capital's population,  $p=0.03$ ) and complete inexperience (higher in the countryside's population,  $p<0.05$ ).

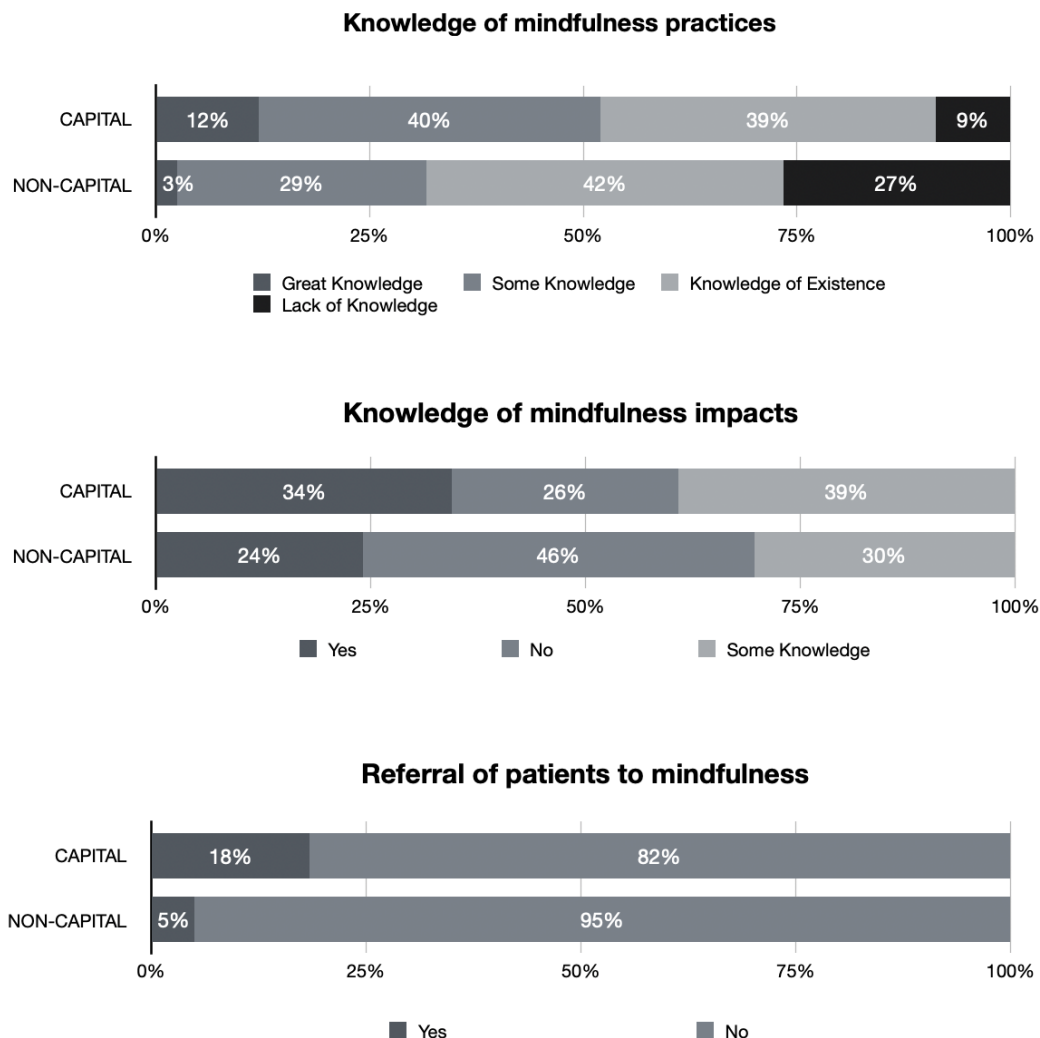
Considering the populations of the countryside and the capital, there was a similarity regarding the knowledge of mindfulness impacts and greater referral of patients by the responders of the capitals, as shown in Figure 2.

Figure 3 exhibits the distribution of respondents according to time since graduation, where the vast majority were concentrated in surgeons with more than ten years, with knowledge of mindfulness being similar between the groups, except for those who responded "awareness of the existence of mindfulness", which was greater in the group with longer graduation time (27% versus 73%;  $p=0.02$ ). Even so, there was no statistical difference between the groups for referral of patients to practices ( $p=1.00$ ).

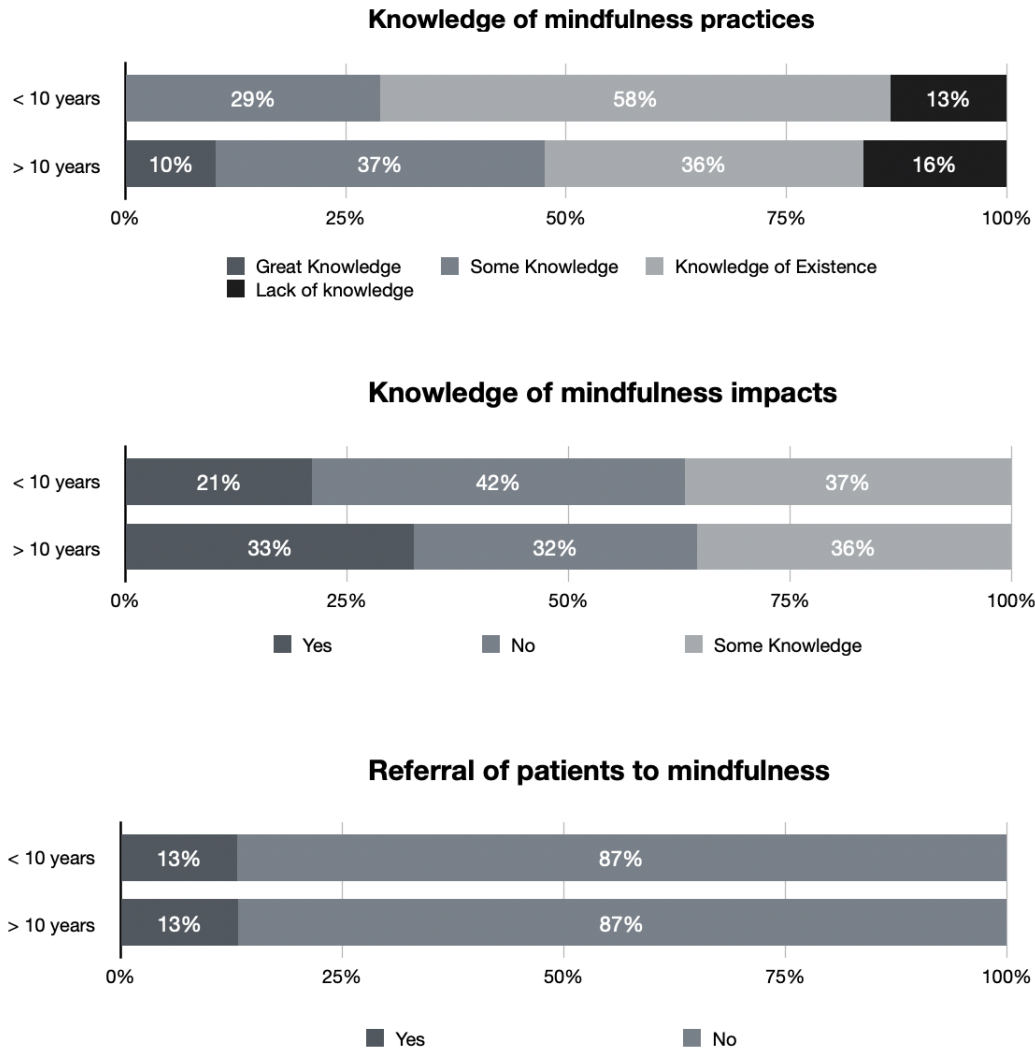
In an analysis of the subgroup that has or does not have a specialist certificate, where most have the certification, no statistical difference was found between the groups for knowledge of the practices, their impacts, and referral of patients to therapy.

Regarding the question of performance in an academic institution, although most respondents were linked to educational institutions, there were also no statistical differences regarding the responses of knowledge of the practices, their impacts and referral of patients. For work in exclusive cancer care institutions, no differences were observed between the groups of responders regarding the knowledge and indication of mindfulness.

In the subgroup regarding the existence or not of a mindfulness service in the institution of the responding surgeons, the statistical majority reported not having the availability of mindfulness and also represented the majority who did not know the impacts ( $p=0.01$ ). Despite this, no statistical difference was found between the groups regarding the referral or not of patients to mindfulness practices.



**Figure 2.** Distribution of respondents according to city of residence and knowledge of mindfulness practices, knowledge of impacts, and referral of patients to mindfulness (capital=125, non-capital=79).



**Figure 3.** Distribution of respondents according to time since graduation and knowledge of mindfulness practices, knowledge of impacts, and referral of patients to mindfulness (<10 years=38; >10 years=166).

## DISCUSSION

The population of Brazilian breast surgeons who participated in this study had a homogeneous distribution in relation to age groups and gender.

The vast majority were certified by SBM and graduated more than ten years ago. They were in the capital cities of the country and had links with educational institutions or cancer care institutions. These demographic data suggest and may indicate adequate training and experience of the population of surgeons in the study regarding the treatment and specific management of patients with breast cancer.

Despite this probable indication of the scientific and clinical preparation of the respondents, most considered themselves to have insufficient knowledge of mindfulness practices. More than half said they were only aware of the existence of the practices or were completely unaware. Associated with this, we also obtained complementary data regarding the knowledge about mindfulness, which was the lack of complete or partial information on

the impacts of mindfulness for patients with breast cancer by the responding surgeons.

In an older meta-analysis by Halle et al.<sup>23</sup>, which evaluated ten studies and 1,709 women with breast cancer, mindfulness had a positive impact soon after intervention in relation to quality of life, fatigue, sleep, stress, anxiety, and depression. After six months, these results held for symptoms of anxiety and depression.

A systematic review of Cochrane, published by Schell et al. in 2019, analyzing only the Mindfulness-Based Stress Reduction (MBSR) practice in women with breast cancer, resulted in a slight improvement of mindfulness in dealing with anxiety, depression, and sleep quality after intervention of six months<sup>15</sup>. And, more recently (2024), in a Chinese meta-analysis publication with 1,644 patients, MBSR significantly reduced perceived stress, depression, anxiety, and fear of recurrence<sup>24</sup>. These secondary studies indicated the impacts and possibly beneficial effects of mindfulness practices on breast cancer patients.



From those and other data in the literature, we believe that mindfulness knowledge by professionals who work with women with breast cancer is essential for a more comprehensive, holistic treatment, aiming at the best possible quality of life for these patients during and after treatment.

Since most surgeons believe they do not know mindfulness practices and their in-depth impacts results in patients not being referred to the practices. Almost 90% of the surgeons in our survey did not refer patients to mindfulness; and among the few who did, the majority indicated mindfulness for less than ten patients in the last year. Thus, these data probably suggest that the fact that the practice is not known in detail interferes with its indication and with the non-referral of patients to mindfulness.

In this regard, it is also necessary to take into account that more than 60% of respondents did not have or were unaware of the existence of an integrative medicine or mindfulness service in their workplaces, resulting in probable lower dissemination of practices and less possibility of clinical indication.

The data of our research, in subgroup analysis, also indicated that male surgeons have a greater lack of knowledge of mindfulness and its impacts on the health of patients but this was not reflected in a higher rate of referral of patients to perform the practices. Referral was reported as very low in both genders; possibly, there was no close relationship of gender with these results.

Our population of respondents was more concentrated in state capitals and, thus, may have interfered with the statistical results of greater knowledge of mindfulness among them than residents of smaller cities, who reported greater ignorance. Again, this factor should not represent interference in the causes of patients' referral to mindfulness, since the rates were low and similar between the two groups.

As for the subgroup analysis considering the time since graduation, although we obtained more respondents with more than ten years, the lack of statistical difference regarding in-depth knowledge and mindfulness impacts did not also reflect on the referral rate. That is, it is likely that the hypothesis of longer clinical experience has not resulted in greater knowledge and offer of practices to patients. Associated with this, we also noted similar knowledge of mindfulness and low referral of patients even though most responders are specialists in breast diseases or work in academic and oncology services.

The fact of longer experience, proven specialty, and greater contact and possible access to scientific information (academic or oncological services) may not have interfered with greater knowledge of mindfulness and the use of these practices in clinical care.

We also analyzed data regarding the use of mindfulness by the breast surgeons themselves. As there is evidence of practices in various psychic symptoms, we believe that they can also impact the professional.

As expected, considering the previous data regarding the lack of full knowledge of practices, 75% of the professionals do

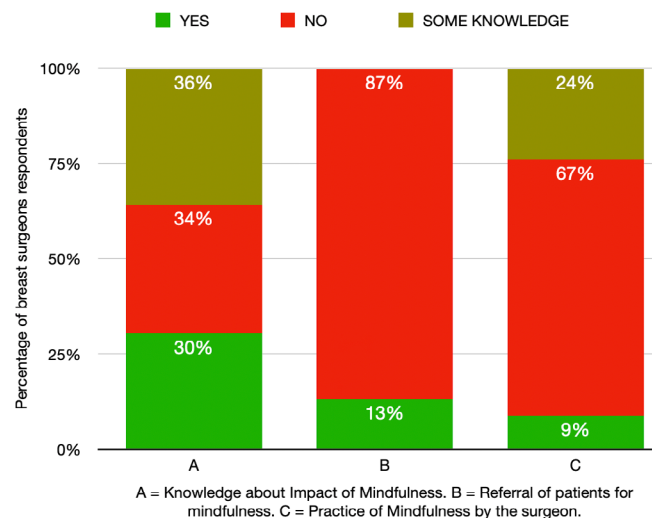
not perform any mindfulness practice. Figure 4 illustrates the comparison of these data in a graph.

One primary limitation of our study includes the low response rate nationwide; we had 204 responses from a total population of 1,893 surgeons. The fact that it is a cross-sectional observational study based on electronically sent questionnaires is also a limitation. Additionally, we know that in this type of research, there is the possibility of selection bias, where those professionals most likely to participate or interested in the subject in question come to answer the survey.

Another limitation was that our sample was not statistically significant to represent the population aged 51–60 years; however, we do not believe it is of major importance since the highest concentration of the general population of breast surgeons associated with SBM are in younger age groups.

A divergence in our study was the disproportionality of participants according to the Brazilian State regions where the breast surgeons participating in the research reside.

We did not have the participation of the North region but there was a greater representation from the Southeast region. This imbalance could affect the data, but according to our analysis, the final result would not have a considerable impact since the great concentration of health professionals throughout the scope occurs in the Southeast region. Despite the small divergences in the representativeness of the sample in relation to the general population of breast surgeons, the data indicate that knowledge of mindfulness practices as well as their impact on breast cancer women's health was considered insufficient by the participants and possibly impacted the referral of patients to mindfulness and its use by the surgeons themselves.



**Figure 4.** Distribution of breast surgeon respondents regarding knowledge of the impact of mindfulness, referral of patients to mindfulness, and practice of mindfulness by the surgeon (n=204).

Considering the positive impacts that mindfulness can bring to women with breast cancer, it is necessary, in view of these data, to promote the dissemination and training of breast surgeons. With this, we could increase the indication of mindfulness among patients and results in better quality of life.

## CONCLUSION

Our study indicates that, among the Brazilian breast surgeons who answered the questionnaire, despite including a considerable sample of professionals working in oncological and academic institutions, the vast majority judged that they did not have full knowledge about mindfulness practices and their impacts.

This may be reflected in the higher numbers of patients not being referred to the practices and not being carried out by the professionals themselves.

Thus, considering the impacts that mindfulness practices can have on patients' treatments, the data from this study may

indicate that further training and dissemination of these practices are necessary among breast surgeons.

## AUTHORS' CONTRIBUTION

PGTA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FPC: Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. GTT: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DABB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## ERRATUM

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**On page 1 it was included:**

José Guilherme Maia<sup>2</sup> 

**On page 5 it was included:**

**AUTHOR'S CONTRIBUTIONS**

JGM: Data curation.



