# **MAST©LOGY** Official Journal of the Brazilian Society of Mastology

### Volume 32, 2022

ISSN 2594-5394







# Official Journal of the Brazilian Society of Mastology

### Volume 32, 2022

#### **EDITOR-IN-CHIEF**

Gil Facina (São Paulo, SP, Brazil)

#### **CO-EDITORS**

Francisco Pimentel Cavalcante (Fortaleza, CE, Brazil) Régis Resende Paulinelli (Goiânia, GO, Brazil) Rene Aloisio da Costa Vieira (Barretos, SP, Brazil)

#### **SPECIALTY EDITORS: MASTOLOGY**

André Mattar (São Paulo, SP. Brazil) Alfredo Carlos Simões Dornellas de Barros (São Paulo, SP, Brazil) Antonio Luiz Frasson (Porto Alegre, RS, Brazil) Benedito Borges da Silva (In memoriam – Teresina, PI, Brazil) Cassio Cardoso Filho (Campinas, SP, Brazil) César Cabello dos Santos (Campinas, SP, Brazil) Cícero de Andrade Urban (Curitiba, PR, Brazil) Daniel de Araújo Brito Buttros (Rio Claro, SP, Brazil) Daniel Guimarães Tiezzi (Ribeirao Preto, SP, Brazil) Délio Marques Conde (Goiania, GO, Brazil) Eduardo Camargo Millen (Rio de Janeiro, RJ, Brazil) Fabiana Baroni Makdissi (São Paulo, SP, Brazil) Fábio Bagnoli (São Paulo, SP, Brazil) Fabio Postiglione Mansani (Ponta Grossa, PR, Brazil) Fabrício Palermo Brenelli (Campinas, SP, Brazil) Felipe Pereira Zerwes (Porto Alegre, RS, Brazil) Gustavo Antonio de Souza (Campinas, SP, Brazil) Gustavo Zucca-Matthes (Barretos, SP, Brazil) José Luiz B Bevilacqua (São Paulo, SP, Brazil) José Luiz Pedrini (Porto Alegre, RS, Brazil) José Mauro Secco (Macapa, AP, Brazil) José Roberto Filassi (São Paulo, SP, Brazil) José Roberto Morales Piato (São Paulo, SP, Brazil) Jurandyr Moreira de Andrade (Ribeirao Preto, SP, Brazil) Luís Otávio Zanatta Sarian (Campinas, SP, Brazil) Luiz Henrique Gebrim (São Paulo, SP, Brazil) Marcelo Madeira (São Paulo, SP, Brazil) Renato Zocchio Torresan (Campinas, SP, Brazil) Roberto José S. Vieira (Rio de Janeiro, RJ, Brazil) Rodrigo Gonçalves (São Paulo, SP, Brazil) Rogério Fenile (São Paulo, SP, Brazil) Rosemar Macedo Sousa Rahal (Goiania, GO, Brazil) Ruffo de Freitas Júnior (Goiania, GO, Brazil) Vinícius Milani Budel (Curitiba, PR, Brazil) Vilmar Marques de Oliveira (São Paulo, SP, Brazil)

#### **INTERNATIONAL ADVISORY BOARD**

Marcelo Cruz (Chicago, USA) Otto Metzger Filho (Boston, USA) Bejnamin Anderson (Seattle, USA) Eduardo González (Buenos Aires, Argentina) Gail Lebovic (Dallas, USA) Luciane Cavalli (Washington, USA) Luiz Javier Gallón (Medellín, Colombia) Jaime Letzkus Berríos (Santiago, Chile) Juan Enrique Bargallo Rocha (Mexico City, Mexico) Mahmoud El-Tamer (New York, USA) Maria João Cardoso (Lisbon, Portugal) Mario Rietjens (Milan, Italy) Matthew Ellis (Houston, USA) Melissa Bondy (Houston, USA) Richard Raisburry (London, UK) Rui Manuel Reis (Braga, Portugal) Vesna Bjelic Radisic (Vienna, Austria) Virgilio Sacchini (Milan, Italy)

#### **SPECIALTY EDITORS: PATHOLOGY**

Ângela Flávia Logullo Waitzberg (São Paulo, SP, Brazil) Helenice Gobbi (Belo Horizonte, MG, Brazil)

#### SPECIALTY EDITOR: PHYSIOTHERAPY

Anke Bergmann (Rio de Janeiro, RJ, Brazil) Samantha Karla Lopes de Almeida Rizzi (São Paulo, SP, Brazil)

#### SPECIALTY EDITOR: TRANSLATIONAL RESEARCH

Gustavo Arantes Rosa Maciel (São Paulo, SP, Brazil) Tatiana Carvalho de Souza Bonetti (São Paulo, SP, Brazil)

#### **SPECIALTY EDITORS: GENETICS**

José Cláudio Casali da Rocha (Curitiba, PR, Brazil) Maria Isabel Achatz (São Paulo, SP, Brazil)

#### SPECIALTY EDITORS: MEDICAL ONCOLOGY

Carlos Barrios (Porto Alegre, RS, Brazil) Max Mano (São Paulo, SP, Brazil) Sérgio Simon (São Paulo, SP, Brazil)

#### **SPECIALTY EDITORS: RADIOTHERAPY**

Nilceana Maya Aires Freitas (Goiânia GO Brazil) Rodrigo Souza Dias (São Paulo, SP, Brazil) Samir Abdallah Hanna (São Paulo, SP, Brazil)

#### SPECIALTY EDITORS: RADIOLOGY

Helio Amâncio Camargo (São Paulo, SP, Brazil) Simone Elias Martinelli (São Paulo, SP, Brazil)

#### SPECIALTY EDITORS: EPIDEMIOLOGY AND PREVENTION

Edesio Martins (Goiânia, GO, Brazil) Luiz Cláudio Santos Thuler (Rio de Janeiro, RJ, Brazil)

#### FORMER PRESIDENTS

Alberto Lima de Morais Coutinho (1959–1961) Jorge de Marsillac (1962–1963) Eduardo Santos Machado (1964–1965) Carlos A. M. Zanotta (1966–1967) Alberto Lima de Morais Coutinho (1968–1969) Adayr Eiras de Araújo (1970–1971) João Luiz Campos Soares (1972–1973) Jorge de Marsillac (1974–1975) Alberto Lima de Morais Coutinho (1976–1977) João Sampaio Góis Jr. (1978–1982) Hiram Silveira Lucas (1983–1986) José Antonio Ribeiro Filho (1987–1989) Antônio S. S. Figueira Filho (1990–1992) Marconi Menezes Luna (1993-1995) Henrique Moraes Salvador Silva (1996–1998) Alfredo Carlos S. D. Barros (1999-2001) Ezio Novais Dias (2002-2004) Diógenes Luiz Basegio (2005–2007) Carlos Ricardo Chagas (2008–2010) Carlos Alberto Ruiz (2011–2013) Ruffo de Freitas Júnior (2014–2016) Antonio Luiz Frasson (2017-2019)



#### BRAZILIAN SOCIETY OF MASTOLOGY Praça Floriano, 55, sala 801, Centro – 20031-050 – Rio de Janeiro (RJ) Phone numbers: (21) 2220-7711 / (21) 2220-7111 E-mail: contact@mastology.org

#### NATIONAL BOARD OF DIRECTORS OF SOCIEDADE BRASILEIRA DE MASTOLOGIA

#### Triennium 2020-2022

Founder:

President National Vice President North Region Vice President Northeast Region Vice President South Region Vice President Southeast Region Vice President Midwest Region Vice President General secretary Assistant Secretary General Treasurer Assistant Treasurer Mastology Editor Escola Brasileira de Mastologia Director Deliberative Council President TFMa Committee Ethics Committee Scientific Committee

Alberto Lima de Morais Coutinho Vilmar Margues de Oliveira Vinicius Milani Budel Francianne Silva Rocha Darley de Lima Ferreira Filho Jorge Villanova Biazus César Cabello dos Santos Carlos Marino Cabral Calvano Filho Rosemar Macedo Sousa Rahal Sandra Marques Silva Gioia Felipe Eduardo Martins de Andrade Aleksandr Salamanca Mivahira Gil Facina Fabio Postiglione Mansani Antonio Luiz Frasson Eduardo Camargo Millen Clécio Ênio Murta de Lucena Alfredo Carlos Simões Dornellas de Barros

#### ABOUT

Mastology is a publication of the Brazilian Society of Mastology. The responsibility for concepts emitted in the articles is exclusive of its authors

The total or partial reproduction of the articles is allowed, provided the source is mentioned.

Founder: Antônio Figueira Filho

Submissions - mailing address: Praça Floriano, 55, sala 801, Centro – Rio de Janeiro (RJ) – 20031-050

National and international subscription and advertising: Brazilian Society of Mastology - Phone number: (21) 2220-7711 - Whatsapp (21) 98138-0034



#### ORIGINAL ARTICLE https://doi.org/10.29289/2594539420210039

# Survival analysis of patients with breast cancer and secondary brain metastasis: a retrospective cohort

Francisco Elton Coelho da Silva Filho<sup>1</sup>, Giuseppe Marques Alencar<sup>1</sup>, Lidia Lillian Santos Barbosa<sup>2</sup>, Marcos Afonso Cruz Nascimento<sup>3</sup>, Sabas Carlos Vieira<sup>4</sup>\*

#### ABSTRACT

**Introduction:** The presence of brain metastases secondary to primary breast cancer implies a worse prognosis for those affected. Therefore, the aim of this study was to determine the median survival after the diagnosis of brain metastasis in patients with breast carcinoma in a center in northeastern Brazil. **Methods:** The medical records of 345 patients diagnosed with breast cancer, treated between 1998 and July 2018, were analyzed. Those with brain metastasis along with their treatment performed and survival were identified. **Results:** Nine (2.6%) patients had brain metastasis; the mean age was 56.8 years. The mean survival time determined by the Kaplan-Meier method was 23.8 months (95%CI 6.9–40.8). Seven patients (78%) died from the disease and two were lost to follow-up (22%); invasive carcinoma of no special type was the most frequent (78%). Molecular classification by immunohistochemistry was possible in seven patients: five luminal B subtype cases, one luminal A case and one triple-negative case; luminal B subtype was associated with longer survival: 23.3 months (95%CI 3.0–43.6). As for the initial clinical staging, according to the TNM Classification of Malignant Tumors, there was one IA case, one IIA case, three IIB cases and two IIIB cases. Three patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy); there was no statistical difference in survival between the different forms of treatment (p=0.771). **Conclusion:** The median survival after diagnosis of brain metastasis from breast cancer was 23.80 months.

KEYWORDS: breast neoplasms; brain neoplasms; conservative treatment; survival rate; immunohistochemistry.

#### INTRODUCTION

Breast cancer is the most prevalent type of cancer in Brazil and worldwide<sup>1</sup>. Despite the advances that have made, mainly in the areas of prevention and treatment, breast cancer remains the main cause of cancer mortality in Brazil among women, with a mortality rate adjusted by the world population of 14.23 deaths/100,000 women, in 2019, according to Brazil's National Cancer Institute (INCA)<sup>2</sup>.

The progression of primary breast cancer to metastatic forms, especially those with cerebral involvement, is an impacting factor for the increase in morbidity and mortality of this disease<sup>3</sup>. Breast cancer is the second type of cancer with the highest risk to develop brain metastases<sup>4</sup>. In these cases, in general, the prognosis is poor and quality of life and life expectancy of patients is substantially reduced. This negative impact on life varies according to the affected location of the central nervous system and the number of metastases at the time of diagnosis. As an example of this, according to a retrospective North American cohort study, approximately 80% of the 420 patients who presented with tumor spread to the brain or another region of the central nervous system died within the first year of follow-up<sup>5</sup>. Another aggravating factor is the fact that the diagnosis is not always made in a timely manner, due to the absence of clinical manifestations of these lesions until death<sup>6</sup>.

In Piauí, the estimates for breast cancer for the 2020/2021 biennium are 590 new cases<sup>7</sup>. Despite this number of cases,

\*Corresponding author: sabas.vieira@uol.com.br

<sup>&</sup>lt;sup>1</sup>Universidade Federal do Piauí, Medical School – Teresina (PI), Brazil.

<sup>&</sup>lt;sup>2</sup>Centro Universitário Faculdade Integral Diferencial, Medical School – Teresina (PI), Brazil.

<sup>&</sup>lt;sup>3</sup>Centro Universitário de Ciências e Tecnologias do Maranhão, Nutrition College – Caxias (MA), Brazil.

<sup>&</sup>lt;sup>4</sup>Universidade Estadual de Campinas, Medical School, Postgraduate Tocogynecology – Campinas (SP), Brazil.

Conflict of interests: nothing to declare. Funding: none.

**Received on:** 07/26/2021. Accepted on: 12/08/2021.

there are not many studies in the literature on the incidence of brain metastasis and analysis of survival time in this population. Accordingly, the main objective of the present study was to evaluate the median survival after the diagnosis of brain metastasis in a retrospective cohort of patients from an oncology clinic in Teresina, Piauí, Brazil.

#### **METHODS**

The present study was conducted according to the STROBE statement for cross-sectional studies<sup>8</sup>. We analyzed the medical records of a cohort of 345 patients diagnosed with primary breast cancer, treated between January 1998 and June 2018, at a private clinic in Teresina, Piauí. The sample space had a 95% confidence level considering the female population of Piauí as 1,600,000 (according to the 2010 IBGE census), with a margin of error of 5.28%.

Those who had brain metastasis (12 cases) were identified. Three cases were excluded from the study because despite the presence of neurological symptoms, the diagnosis of tumor spread was only possible post mortem, which would compromise the determination of survival time; in addition, these cases did not have enough data regarding primary breast cancer to allow the assessment of prognostic factors. In the end, nine cases remained for descriptive analysis of variables and determination of survival rate and mean and median survival time using the Kaplan-Meier method. Median survival is understood as the time required for 50% of the sample to reach the outcome (death due to metastasis). To determine the statistical significance and confidence intervals of the influence of possible prognostic factors on survival (histological type, molecular subtype, tumor size, degree of differentiation and treatment), the log rank test was used by means of the IBM SPSS Statistics software 20. The study was approved by the Research Ethics Committee of UFPI - CAAE: 94518518.9.0000.5214. Substantiated approval :2.948.415.

#### RESULTS

Nine (2.6%) of the 345 patients had brain metastasis. The survival function determined using the Kaplan-Meier method is shown in Figure 1. The mean survival time was 23.80 months (95%CI 6.854–40.759), with a maximum value of 60.6 months and a minimum of 1 month (Figure 1); the median survival time was 9 months (95%CI 3.5–14.5); the 3-year overall survival found was 11.11%. The mean and median ages at diagnosis were respectively 56.8 and 50 years; the mean time between the diagnosis of breast cancer and the onset of brain metastasis was 36.9 months (range between 6 and 58 months). Seven patients (78%) died from the disease and two were lost to follow-up (22.22%), which were censored during the analysis.



Source: Prepared by the authors on the basis of study of online medical charts.

**Figure 1.** Survival curve of women diagnosed with brain metastasis secondary to primary breast cancer, treated at a private center in Piaui.

Invasive carcinoma of no special type was the histological type in nine cases; there was one case of papillary carcinoma (Table 1). Regarding the degree of differentiation, five cases had grade 2, two grade 3, and one grade 1. The average size of the largest dimension of the tumors in the analyzed cases was 1.96 cm (the largest with 3.5 cm and the smallest with 1 cm). There was no statistical difference in the risk of larger tumors progressing to metastasis. The presence of an undifferentiated histological grade had a median survival of 8.5 months (95%CI 7.5–9.5). There was no statistical increase in survival when comparing grades 2 and 3 (p=0.654).

Molecular classification was possible in seven patients: five luminal B subtype, one luminal A case and one triple-negative case; patients with the luminal B subtype had a longer median survival – 23.3 months (95%CI 3.0–43.6; p=0.044<0.05). The triple-negative case had a lower median survival (4.25 months) (Figure 2). There was no study of germline mutations in hereditary breast cancer susceptibility genes in any of the cases.

As for clinical staging, there was one case of IA, one IIA, three IIB and two IIIB. Three (33%) of the patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy). Three patients received neoadjuvant chemotherapy and five underwent adjuvant chemotherapy; in addition to these, three patients (30%) also used hormone therapy (tamoxifen). There was no statistical difference in survival when comparing the different treatments. (p=0.771).

Histological type	Histological grade	Molecular subtype	Treatment	Survival (months)	
ICNST	3	Luminal B	neo CT+Sur+RT	60.60	
ICNST	3	Luminal B neo CT+Sur+RT		8.00	
ICNST	3	Luminal A	Sur	9.00	
ICNST	2	Luminal B	Sur+RT+CT+TMX	12.00	
ICNST	1	NI	Sur+RT+CT+TMX	1.00	
ICNST	2	Luminal B	Sur+RT+CT	5.00	
ICNST	2	Triple-negative	Sur+RT+CT	4.25	
ICNST	2	Luminal B	Sur+RT+CT	31.00	
PC	NI	NI	NI	31.00	

Table 1. Characteristics of cases of primary breast cancer that developed brain metastasis.

ICNST: invasive carcinoma of no special type; PC: papillary carcinoma; neo CT: neoadjuvant chemotherapy; CT: adjuvant chemotherapy; Sur: surgical procedure; RT: adjuvant radiotherapy; TMX: tamoxifen.

Source: Prepared by the authors on the basis of study of online medical charts.



Source: Prepared by the authors on the basis of study of online medical charts.

**Figure 2.** Survival curve of women diagnosed with brain metastasis secondary to primary breast cancer, according to molecular subtype.

#### DISCUSSION

In the present study, the median survival of patients with brain metastasis was 23.8 months (95%CI 6.9–40.8). We identified luminal B subtype as associated with a better outcome, with a median survival of 23.3 months (95%CI 3.0–43.6; p=0.044). The presence of an undifferentiated histological grade led to a worse prognosis, with a mean survival of 8.5 months (95%CI 7.5–9.5); however, there was no significant difference in survival when comparing grades 2 and 3 (p=0.654).

The mean time between the diagnosis of breast cancer and the onset of brain metastasis was 36.9 months (range between 6 and 58 months). Among the patients analyzed, seven (78%) died from the disease and two were lost to follow-up (22%), the latter being censored during the analysis. Survival time ranged from 1 – 60.6 months (Figure 2).

A Chinese study, published in 2019, using the Surveillance, Epidemiology, and End Results Database, analyzed the survival of 18,322 American patients diagnosed with metastatic breast cancer. Patients with brain metastasis had a worse prognosis when compared to those whose cancer progressed to metastases to other organs; they had a lower breast cancer-specific survival rate and lower overall survival; p<0.001, for both)<sup>9</sup>. This was observed in our cohort: the median survival found after the Kaplan-Meier analysis in our cohort was 9 months (95%CI 3.5–14.5 months), similar to the median value found in the US population (8 months for patients with brain metastasis with 95%CI 5.7–10.4 months)<sup>9</sup>.

On the other hand, the overall 3-year survival rate found was 11%; lower than that found in the survival analysis of the US population, 19.90%<sup>9</sup>. An important limitation for this was our small number of cases of patients who developed brain metastasis in the present series.

Nine (2.6%) of the patients had brain metastasis in the present study; the mean age was 56.9 years, while the median age was 50 years. This number was similar to the median age of 56 years found in a European multicenter study that evaluated 668 patients with brain metastasis secondary to primary breast cancer. Furthermore, according to the literature, survival tends to decrease in patients with advancing age (over 40 years), when compared to younger patients (under 40 years)<sup>10</sup>. Only one patient in our sample was younger than 40 (31 years old).

Growing evidence indicates that the occurrence of distant metastases differs according to the histological subtype of primary breast cancer. According to the World Health Organization (WHO), there are 21 histological types of breast cancer, divided into non-invasive carcinomas, which include carcinomas in situ and Paget's disease, and invasive carcinomas, such as invasive carcinoma of no special type (invasive ductal carcinoma) and other rarer types<sup>11</sup>.

According to the literature, the most common histological type is invasive carcinoma of no special type<sup>11</sup>; this was also the most frequent type in patients who developed brain metastasis in the sample of the present study (88.89% of cases), as can be seen in Table 1. However, there was no statistically significant increase in risk in our sample, demonstrating that invasive carcinoma of no special type is most associated with brain metastasis (relative risk (RR) 3.75; 90%CI 0.35–18.56). However, this finding is in agreement with a multinational and multicenter cohort study, whose sample space involved 2,473 patients with primary breast cancer and brain metastasis. Invasive carcinoma of no special type was diagnosed in about 80% of these patients<sup>12</sup>.

Among the invasive cancers of no special type, it is possible to see in Table 1 that three belonged to the most undifferentiated form, with one case being grade 1 (least undifferentiated) representing 11% of cases, and five grade 2 (56%). In one of the cases, it was not possible to assess the degree of tumor differentiation. When considering the degree of differentiation as a prognostic factor, there was no statistically significant difference in survival, when we compared the survival curves for grades 2 and 3 (p=0.654). Grade 3 patients had a median survival of 8.5 months (95%CI 7.5-9.5). The literature, in turn, points out that the more undifferentiated the tumor, the worse the prognosis tends to be, and therefore, the longer survival is usually found in patients diagnosed with grade 1 and 2 cancer; however, the small number of cases in our study severely limits this analysis<sup>13</sup>. Even with this good prognostic correlation, some cases of more differentiated histological grade may develop metastases, with the invasive ductal subtype being more commonly associated with this type of tumor dissemination<sup>14</sup>.

Among the patients, there was also one case of papillary carcinoma with an unknown degree of differentiation, as shown in Table 1. Papillary carcinomas tend to have a better prognosis compared to invasive carcinoma of the no special type, and this patient had a 31-month survival rate<sup>15</sup>.

Regarding size, the mean of the largest dimension of the tumors was 1.96 cm (ranging from 1 - 3.5 cm); there was no statistical difference in the association between a larger size of the primary tumor and the probability of progressing to brain metastasis. This limitation is possibly due to the small number of patients in our series. According to Wang et al. (2019), the size of the primary tumor is one of the variables with the worst prognosis for survival (hazard ratio HR>1, p<0.001), especially those with T4 classification<sup>9</sup>.

Furthermore, the literature suggests that the survival time for patients with brain metastases differs significantly between the molecular subtypes of breast cancer. These are classified according to the presence or absence of estrogen (ER) and progesterone (PR) receptors or human epidermoid growth factor receptor 2 (HER2) in luminal A (ER+ and/or PR+ and HER2-), luminal B (ER+ and/or PR+ and HER2+), triple-negative (ER-, PR-, HER2-) and enriched or overexpressed HER2 (ER-, RP-, HER2+)<sup>13</sup>. Breast cancer subtypes with high expression of the HER2 marker and triple-negative (TN) are more prone to brain metastasis during the course of the disease, with triple-negative being associated with lower survival<sup>15</sup>. There is evidence that approximately 30% of primary breast cancers with HER2+ and about 50% of triple-negative cases progress with central nervous system invasion<sup>16</sup>. In the present study, molecular classification was possible in seven patients: luminal B subtype was the most prevalent (five cases); there was one luminal A case and one triple-negative case. There was a longer median survival (23.32 months) in those patients who had luminal B subtype (95%CI 3.01–43.63) and thereby a better outcome (Figure 2).

This result was consistent with that obtained by a retrospective French study that analyzed 4,118 patients with brain tumors secondary to breast cancer: the overall survival for HER2+/HR+ (luminal B) tumors was the highest (18.9 months; HR=0.57, 95%CI 0.50-0.64; p<0.0001)<sup>17</sup> when compared to the other molecular subtypes. Although the triple-negative subtype had a lower mean survival (4.25 months), accurate statistical analysis was not possible, because of the limiting factor of having only one patient with this characteristic in our series. Also, according to Darlix<sup>17</sup>, patients with triple-negative tumors (HER2-/HR-) had a worse outcome, with an overall survival of 4.4 months (HR=1.55, 95%CI 1.42–1.69; p<0.0001)<sup>17</sup>.

Another limitation of the present study was the fact that none of the nine cases (100%) included genetic tests, such as testing for the BRCA-1 gene. Nonetheless, five of them (55%) had an indication for genetic studies according to the NCCN (National Comprehensive Cancer Network), because primary breast cancer was diagnosed before the age of 50<sup>18</sup>. Furthermore, one of these five was within another criterion, as it met the triple-negative molecular classification. A French cohort study showed that positivity for BRCA-1 is associated with the development of high-grade tumors, as well as with a high rate of mitosis<sup>19</sup>. For a better approach, the American Society of Breast Surgeons, considering the results of a prospective multicenter study of genetic testing, currently recommends performing multigene panels in all breast cancer patients<sup>20</sup>. In addition, there are associations in the literature between this alteration and evolution with triple-negative tumors<sup>21</sup>.

Regarding clinical staging (TNM) at the time of diagnosis, there was one case of IA, one IIA case, 3 IIB cases and two IIIB cases. The more advanced the stage at diagnosis, the worse the patient's prognosis tends to be. Patients diagnosed at stage 4, for example, have a median survival of 2 - 3 years<sup>9</sup>. It is important to emphasize, however, that in the estimation of survival, the TNM classification must be evaluated together with other individual factors. Its use for prognosis disregards variables such as

genetic, pathological (cell replication rate or tumor subtype) or treatment differences<sup>22</sup>.

The factors are directly related to the therapeutic management of the patient. The spread of metastatic breast cancer makes treatment difficult, where the cancer is considered incurable and with a poor prognosis. The final objective of the treatment is therefore palliative to improve the patients' symptoms and delay the spread of the tumor<sup>23</sup>. In this cohort, 33% of the patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy); three patients received neoadjuvant chemotherapy, five underwent adjuvant chemotherapy, while three patients (30%) also used hormone therapy (tamoxifen).

For patients with metastasis, the decision to treat with systemic chemotherapy or hormone therapy depends on a few factors: tumor location and extent, the presence of hormone receptors, age, menopausal profile, and disease-free period<sup>23</sup>.

Primary tumor resection can increase patient survival when performed at early stages, and it also impacts disease recurrence<sup>24</sup>. In the management of metastatic tumors, however, evidence shows that aggressive local therapy does not lead to additional benefits to patient survival. However, in certain circumstances, surgical resection of the primary tumor of stage IV breast cancer works as palliative care in the control of ulcerations, bleeding and infections, and therefore, it should be considered in a multidisciplinary approach<sup>23</sup>. In the present study, all patients were operated on (100%), and adjuvant or neoadjuvant treatment was individualized. However, there was no statistically significant difference in survival when comparing the different forms of treatment (p=0.771).

An alternative for the treatment of brain metastasis is stereotactic surgery by radiotherapy. This type of intervention is indicated when the patient has less than four foci of brain metastasis. However, the prognosis is still guarded. In a cohort study with 50 patients, the median survival found after this approach was 33 months<sup>25</sup>.

#### CONCLUSION

The median survival after diagnosis of brain metastasis from breast cancer was 23.8 months. The luminal B subtype was associated with a better outcome, with a mean survival of 23.3 months

#### **AUTHORS' CONTRIBUTIONS**

SCV: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. FECSF: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft. GMA: Investigation, Data curation, Methodology, Writing – original draft, Visualization. LLSB: Investigation, Data curation, Formal Analysis, Writing – original draft, validation. MACN: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft.

#### REFERENCES

- World Health Organization. Cancer Today. International Agency for Research on Cancer [internet]. Geneva: World Health Organization [cited on May 4, 2020]. Available at: http://gco.iarc.fr/today/home
- Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Mortalidade [Internet]. Rio de Janeiro: INCA; 2020 [cited on Nov 24, 2021]. Available at: https://www.inca.gov.br/controle-do-cancer-demama/dados-e-numeros/mortalidade
- Martin AM, Cagney DN, Catalano PJ, Warren LE, Bellon JR, Punglia RS, et al. Brain metastases in newly diagnosed breast cancer: a population-based study. JAMA Oncol. 2017;3(8):1069-77. https://doi.org/10.1001/jamaoncol.2017.0001
- Cunha MLV, Grosbelli L. Profile of patients with intracranial tumors undergoing surgical resection at a neuro-oncology referral hospital. Arq Bras Neurocir. 2018;37:19-26. https://doi. org/10.1055/s-0038-1639588
- Altundag K, Bondy ML, Mirza NQ, Kau SW, Broglio K, Hortobagyi GN, et al. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with

central nervous system metastasis. Cancer. 2007;110(12):2640-7. https://doi.org/10.1002/cncr.23088

- Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer. 1983;52(12):2349-54. https://doi.org/10.1002/1097-0142(19831215)52:12<2349::aid-cncr2820521231>3.0.co;2-b
- Instituto Nacional do Câncer (INCA). Estatísticas de câncer [Internet]. Brasil: INCA [cited on May 4, 2020]. Available at: https://www.inca.gov.br/numeros-de-cancer
- STROBE. STROBE Checklists [Internet]. Switzerland: Institute of Social and Preventive Medicine; 2021 [cited on Feb 21, 2021]. Available at: https://www.strobe-statement.org/index. php?id=available-checklists
- Wang R, Zhu Y, Liu X, Liao X, He J, Niu L. The Clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. BMC Cancer. 2019;19(1):1091. https://doi.org/10.1186/s12885-019-6311-z
- Mustillo A, Ayoub JP, Charpentier D, Yelle L, Florescu M. Prognosis in young women less than 40 years of age with brain metastasis from breast cancer. Curr Oncol. 2020;27(1):39-45. https://doi.org/10.3747/co.27.5621

- 11. World Health Organization. Breast Tumours. WHO Classification of Tumours [Internet]. Geneva: World Health Organization. [cited on May 4, 2020]. Available at: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Breast-Tumours-2019
- 12. Sperduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, et al. Beyond an updated graded prognostic assessment (Breast GPA): a prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys. 2020;107(2):334-43. https://doi. org/10.1016/j.ijrobp.2020.01.051
- Aquino RGF, Vasques PHD, Cavalcante DIM, Oliveira ALS, Oliveira BMK, Pinheiro LGP. Invasive ductal carcinoma: relationship between pathological characteristics and the presence of axillary metastasis in 220 cases. Rev Col Bras Cir. 2017;44(2):163-70. https://doi.org/10.1590/0100-69912017002010
- Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer. 2006;107(4):696-704. https://doi.org/10.1002/cncr.22041
- Oehrlich NE, Spineli LM, Papendorf F, Park-Simon TW. Clinical outcome of brain metastases differs significantly among breast cancer subtypes. Oncol Lett. 2017;14(1):194-200. https://doi.org/10.3892/ol.2017.6166
- 16. Griguolo G, Jacot W, Kantelhardt E, Dieci MV, Bourgier C, Thomssen C, et al. External validation of modified breast graded prognostic assessment for breast cancer patients with brain metastases: a multicentric european experience. Breast. 2018;37:36-41. https://doi.org/10.1016/j.breast.2017.10.006
- 17. Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, Debled M, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer. 2019;121(12):991-1000. https://doi.org/10.1038/s41416-019-0619-y

- Manahan ER, Kuerer HM, Sebastian M, Hughes KS, Boughey JC, Euhus DM, et al. Consensus guidelines on genetic testing for hereditary breast cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26(10):3025-31. https:// doi.org/10.1245/s10434-019-07549-8
- De Talhouet S, Peron J, Vuilleumier A, Friedlaender A, Viassolo V, Ayme A, et al. Clinical outcome of breast cancer in carriers of BRCA1 and BRCA2 mutations according to molecular subtypes. Sci Rep. 2020;10(1):7073. https://doi.org/10.1038/ s41598-020-63759-1
- 20. The American Society of Breast Surgeons. Consensus Guideline on Genetic Testing for Hereditary Breast Cancer [Internet]. Columbia: The American Society of Breast Surgeons; 2019 [cited on May 4, 2020]. Available at: https://breastsurgeons. org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf
- 21. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012;21(1):134-47. https://doi.org/10.1158/1055-9965.EPI-11-0775
- Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173-80. https://doi.org/10.1016/S1470-2045(14)71116-7
- Tosello G, Torloni MR, Mota BS, Neeman T, Riera R. Breast surgery for metastatic breast cancer. Cochrane Database Syst Rev. 2018;3(3):CD011276. https://doi.org/10.1002/14651858. CD011276.pub2
- 24. Feig BW, Ching CD. The M.D. Anderson Surgical Oncology Handbook. 6th ed. London: Wolters Kluwer Health Adis (ESP); 2018.
- 25. Sledge GW. Curing metastatic breast cancer. J Oncol Pract. 2016;12(1):6-10. https://doi.org/10.1200/JOP.2015.008953



## Changing the molecular profile of primary and metastatic breast cancer identified by Foundation One: case report

Izabella Fernandes Viana Montechi<sup>1</sup>\* <sup>(b)</sup>, Patrícia Werlang Schorn<sup>2</sup> <sup>(b)</sup>, Amanda Damazio Cabral<sup>1</sup> <sup>(b)</sup>, Juliana Sinezio Santos<sup>1</sup> <sup>(b)</sup>, Alessandra Vanessa Leite e Silva<sup>2</sup> <sup>(b)</sup>

#### ABSTRACT

**Objective:** To describe a case report of a patient who presented with bilateral breast cancer with progression to metastatic disease, in which immunohistochemical profile of the primary and metastatic tumor was divergent. **Methods:** This was a study with a descriptive narrative and reflective design, of the case report type, based on secondary data, with information and images obtained from the electronic medical records of the MVSoul system used in the oncology center of a private hospital in the Federal District in Brazil. Data collection was derived from the analysis of data and images of the electronic medical record. **Case report:** A patient presented with bilateral metastatic breast cancer, and the primary and metastatic breast tumors showed a difference in immunohistochemical profile. Accordingly, we highlight the rarity of the case, the need for biopsies of metastatic lesions because of the molecular heterogeneity of breast cancer and possible discrepancy between the primary tumor and metastases. Spreading knowledge about diagnostic tests and personalized treatment according to tumor molecular characteristics is also essential, especially when the patient does not have a satisfactory therapeutic response, as in the reported case, since the patient had metastases with different molecular profiles confirmed only by of tumor DNA sequencing.

KEYWORDS: breast neoplasms; metastasis; biopsy; cytogenetic analysis.

#### INTRODUCTION

Breast cancer is the most common type of malignant neoplasm in Brazilian women, with an annual incidence of 66,280 cases (29.7%), and it was the main cause of cancer death In 2020, where 18,068 (16.4%) deaths from breast cancer were registered<sup>1</sup>. According to international guidelines, breast cancer is uncommon in women under 40 years of age, representing less than 7% of all diagnosed cases<sup>2</sup>. Even rarer is the involvement of a second contralateral primary breast cancer, corresponding to a mean annual incidence rate of 0.5%<sup>3,4</sup>. Over the years, scientific discoveries have shown that this neoplasm has significant molecular heterogeneity, and an immunohistochemical evaluation of the disease is essential to characterize the status of the progesterone (PR) and estrogen (ER) receptors, HER2 expression and Ki67 cell proliferation index<sup>2,5</sup>. According to these data, breast carcinoma is classified as luminal A, luminal B, HER2-positive or triple-negative (TN).

Breast cancer has extensive molecular heterogeneity, so it cannot be seen as a single entity, since patients with different molecular subtypes have differences in survival and different therapeutic possibilities<sup>6</sup>. Luminal tumors are those enriched by hormone receptors (ER and/or PR) and include special types, such as tubular, cribriform, lobular and mucinous carcinomas. On the basis of Ki67, a cut-off point of 14% was established to distinguish luminal A and B tumors. By definition, luminal A tuors are those that are hormone receptor positive, HER2-negative and Ki67-positive up to 14%, while luminal B ones are those that are hormone receptor-positive and HER2-positive or -negative and have a Ki67 index greater than 14%<sup>7</sup>. Those tumors that do not express the HER2 protein or hormone receptors are called triple-negative tumors, and they are more aggressive<sup>8-10</sup>.

Generally, the characteristics of metastatic breast cancer, like other types of cancer, are similar to those of the initial disease. However, more and more studies demonstrate a

 <sup>&</sup>lt;sup>1</sup>Hospital Santa Lucia Sul, Clinical Oncology – Brasília (DF), Brazil.
 <sup>2</sup>Hospital Santa Lucia Sul, Oncologist – Brasília (DF), Brazil.
 \*Corresponding author: izamontechi@hotmail.com
 Conflict of interests: nothing to declare. Funding: none.
 Received on: 10/29/2021. Accepted on: 12/31/2021.

divergent molecular profile between the initial breast tumor and the recurrent or<sup>11</sup> metastatic one, which can be attributed to the cellular heterogeneity of the cancer, as well as the selective expression of receptors by cell clones at the end of the initial treatment<sup>11</sup>. All this makes it often necessary to biopsy the new lesion, especially when the patient does not have a satisfactory therapeutic response<sup>12</sup>.

A study carried out with a large cohort of patients in the Stockholm region (Sweden) estimated that, at relapse, 32%, 41% and 15% of patients showed a change in ER, PR and HER2 status, respectively<sup>11,13,14</sup>. It also highlights that women with initially ER-positive tumors who transformed into ER-negative had a significantly increased risk of death by 48% compared to stable ER patients<sup>11</sup>.

Another multicenter cohort study, PriMet, retrospectively evaluated 635 breast cancer patients between 1980 and 2010. Discrepancies in hormone receptors and HER2 status between primary tumor and recurrent disease were observed in 18.7% and 21.6% of cases, respectively<sup>15,16</sup>. Regarding hormone receptor presence, positivity in the primary tumor and its absence in the relapsed disease were more frequent, while for the expression of HER2, the opposite was observed<sup>16</sup>.

Cancer treatment is undergoing an essential shift with the use of molecularly targeted drugs for selected subsets of patients with various tumor types, resulting in more effective and safer treatment. Diagnostic tests that show individual genomic alterations are essential for the successful application of personalized therapy<sup>17</sup>. Parallel (or "next generation") DNA sequencing, successfully applied in the research environment to elucidate the complexity of the cancer genome, is becoming an attractive clinical diagnostic technology because it can accurately detect most genomic changes in all therapeutically relevant cancer genes in a single trial<sup>18</sup>.

Given the complexity of this disease, it is necessary to promote effective interventions, and it is essential to better understand the relevant molecular characteristics and their influence on prognosis. Likewise, it is essential to know the therapeutic possibilities to achieve the best possible prognosis and longer disease-free survival for the patient.

Therefore, the present work is justified by the importance of disseminating knowledge about a cancer whose prognosis and treatment depend on its molecular characteristics.

#### METHODS

This was a study with a descriptive design of a narrative and reflective character, of the case report type, based on secondary data, with information and images obtained from the electronic medical record of the MVSoul system used in the oncology center of a private hospital in the District Federal. The information was collected through the analysis of data and images from the electronic medical record.

#### **CASE REPORT**

A 39-year-old patient came to the outpatient clinic in 2004 with a complaint of a palpable lump in the right breast. Breast ultrasound revealed two breast nodules, which were biopsied: 1. Invasive ductal carcinoma (IDC), grade II, 0.7x0.5 cm in the lower left quadrant. 2. IDC, grade II, 0.3x0.2 cm in the upper left quadrant. Clinical status T1N0M0. Immunohistochemistry showed ER+, PR++, HER2++, Ki67++, FISH negative. Patient underwent left quadrantectomy with negative sentinel lymph node (SL) investigation, followed by radiotherapy and use of tamoxifen for five years.

She was under clinical follow-up when, in 2009, at the age of 44, after ending the use of tamoxifen, she had recurrence of the skin neoplasm. We opted for a right radical mastectomy with axillary dissection and a left prophylactic mastectomy with negative SL. Anatomopathology (AP) of the right breast surgical specimen showed IDC, grade II, 3x2x1.5 cm, skin infiltration, with four compromised lymph nodes of 15 resected, pT4pN2 M0, ER+, PR+, HER2-negative and Ki67 10%, while the AP prophylactic mastectomy of the left breast found a second primary tumor: IDC, grade I, 1.4 cm, luminal B, LS negative. Chemotherapy was started with AC-T (docetaxel) regimen, external radiotherapy in the breast plastron and use of adjuvant anastrozole for five years (until 2014), because at that time the patient was postmenopausal.

In May 2017, three years after anastrozole was discontinued, follow-up examinations showed suspected disease progression to the bones, lungs, and mediastinum. Bone biopsy (sternum) showed AP compatible with metastatic adenocarcinoma, immunohistochemistry: ER 80%, PR negative, Ki67 50%, HER2 negative. At this point, she was on faslodex for five cycles, showing clinical worsening and rapid progression of the disease to the liver. She then opted for the Foundation One genetic test, which indicated no detectable genetic alterations. There was a change of treatment to chemotherapy with paclitaxel+bevacizumab for six cycles, when there was new disease progression to the bones during treatment.

The regimen was changed to eribulin for four cycles, with a good initial response, but followed by a new one for progression, this time for the lungs and mediastinum. With the arrival of CDK4/6 inhibitors, palbociclib with letrozole was chosen for four cycles, however, with further worsening of the disease in bones, lungs and liver.

In view of the extensive history and lack of therapeutic response, a new bone biopsy (iliac) was performed, where AP confirmed IDC with ER 60%, PR negative and HER2 negative. Material was sent again to Foundation One, and the result was different from the previous ones, including HER2 amplification. Once HER2 amplification was verified, the patient started using trastuzumab emtansine every 21 days, combined with letrozole and denosumab, with excellent clinical, metabolic and radio-logical complete response for a year and a half. There was then focal progression of the disease in the central nervous system, where she underwent radiosurgery and then started a double block with Herceptin and Perjeta. To date, the patient uses double HER2 blockade, with clinical stability and no evidence of disease (Figure 1).

#### DISCUSSION

Breast cancer is the most common type of malignant neoplasm in Brazilian women, with an annual incidence of 66,280 cases (29.7%), and the main cause of cancer death. In 2020, 18,068 (16.4%) deaths from breast cancer were identified<sup>1</sup>. According to international guidelines, breast cancer is uncommon in women under 40 years of age, accounting for less than 7% of all diagnosed cases<sup>2</sup>. The involvement of a second contralateral primary breast cancer is even rarer, corresponding to an average annual incidence rate of 0.5%<sup>3</sup>.

Research carried out by the Cooperative Breast Cancer Group in Denmark evaluated 68,466 patients with breast cancer between 1978 and 2012, of which only 4% had a second contralateral primary tumor, and the prognosis was considerably worse when compared to unilateral disease<sup>4</sup>. There are many risk factors for breast cancer; however, for contralateral disease, these factors are not well established<sup>5</sup>.

Over the years, scientific discoveries have also shown that breast tumors have remarkable molecular heterogeneity, and an immunohistochemical evaluation of the disease is essential to characterize PR and ER status, HER2 expression and Ki67<sup>2</sup> index.



**Figure 1.** A) PETCT of the patient before starting treatment with trastuzumabe entansina combined with letrozol and denosumabe; B) PETCT of the patient at the end of treatment with trastuzumabe entansina combined with letrozol and denosumabe.

And it is according to each molecular subtype that survival rate is determined and therapeutic possibilities defined<sup>6</sup>.

Luminal tumors are those enriched by hormone receptors (ER and/or PR) and include special types such as tubular, cribriform, lobular and mucinous carcinomas. On the basis of the Ki67 level, a cohort point of 14% was established to distinguish luminal A and B tumors. By definition, luminal A tumors are those that are hormone receptor-positive, HER2-negative and Ki67-positive up to 14%, while luminal B ones are those that are hormone receptor-positive or -negative with Ki67 index greater than 14%<sup>7</sup>. Those that do not express the HER2 protein and do not have hormone receptors are called triple-negative (TN) tumors and are more aggressive<sup>8-10</sup>.

Luminal A tumors are those with the lowest metastatic potential, while luminal B and HER2-positive tumors have as main metastatic sites the central nervous system, liver and lung, as well as bones. TN tumors metastasize to any location<sup>11</sup>.

The British Columbia Cancer Agency followed patients with early-stage breast cancer diagnosed between 1986 and 1992 and found high rates of brain metastases in the HER2 overexpressed (28.7%) and TN (22%) groups<sup>15</sup>.

A retrospective cohort performed at Seoul National Hospital (South Korea) analyzed 1,432 patients with stage I to III breast cancer who underwent surgery and systemic treatment when indicated, with a mean follow-up of 53 months. The five-year breast cancer-free interval, according to subtype, was 93.9% for luminal A, 94.2% for luminal B with HER2 positive, 91.4% for luminal B with HER2 negative, 83.1% for HER2 positive and 81.9% for TN. The overall five-year survival rate was 98.3%, 95.8%, 98%, 90.8% and 89.9% for luminal A, luminal B with HER2 negative, luminal B with HER2 positive, HER2 positive and TN, respectively<sup>12</sup>.

An Asian study evaluated recurrence rates according to molecular subtype and found: 5% for luminal A, 7.8% for luminal B with HER2 negative, 6.6% for luminal B with HER2 positive, 13.1% for HER2 positive and 16.7% for TN<sup>13</sup>. Kennecke and coworkers (2010) followed 313 women with breast cancer for 93 months and observed that the site of distant recurrence varied according to molecular subtype: in luminal A and B, the most common pattern of recurrence was in the bones, while for HER2-positive and TN, visceral involvement was more common<sup>14</sup>.

The molecular characteristics of metastatic breast cancer, like other types of cancer, are often similar to those of the initial disease. However, more and more studies have shown a divergent molecular profile between the initial tumor and the recurrent or metastatic one. This can be attributed to the cellular heterogeneity of cancer and the selective expression of receptors by cell clones after the initial treatment<sup>11</sup>. Because of this, biopsy of the new lesion is often necessary, especially when the patient does not have a satisfactory therapeutic response. A large cohort study of patients in the Stockholm region estimated that, at relapse, 32%, 41% and 15% of patients showed a change in ER, PR and HER2 status, respectively.

It is noteworthy that women with initially ER-positive tumors who transformed into ER-negative had an increased risk of death by about 48% when compared with stable ER patients<sup>11</sup>. PriMet, a multicenter cohort study, evaluated 635 breast cancer patients between 1980 and 2010. Discrepancies in hormone receptors and HER2 expression between primary tumor and recurrent disease were observed in 18.7% and 21.6% of cases, respectively. The positivity in the primary tumor and its absence in the recurrent disease were more frequent for hormone receptors, while for HER2 expression, the opposite was observed<sup>16</sup>.

The treatment of breast cancer is undergoing an essential change with the use of molecular-targeted drugs, based on a better understanding of this molecular heterogeneity and resulting in a more effective and safer treatment. Diagnostic tests that show individual genomic alterations are essential for the successful application of personalized therapy<sup>17</sup> based on tumor DNA sequencing. This clinical diagnostic technology has been extremely attractive because it can accurately detect most genomic changes in all therapeutically relevant tumor genes<sup>18</sup>. Speeding up the selection of effective drugs based on the identification of gene mutations in tumor DNA becomes essential, since patients with metastatic breast cancer carry a history of several previously received therapeutic lines, as in this case, resulting in reduced tumor cell sensitivity to the drugs used<sup>19</sup>.

#### CONCLUSIONS

A patient presented with tumors in both breasts, metastatic and with different immunohistochemical profile between the primary tumor and the metastasis. Thus, the rarity of the case, the need for rebiopsy of metastatic or recurrent lesions due to the molecular heterogeneity of breast cancer and possible discrepancy between the primary and recurrent tumors are highlighted. Spreading knowledge about diagnostic tests and personalized treatment, considering their molecular characteristics, is also essential, especially when the patient does not have a satisfactory therapeutic response, as in the case reported, since the patient had lesions with different molecular profiles confirmed only with tumor DNA sequencing.

#### **AUTHORS' CONTRIBUTION**

IFVM: Data curation, Methodology, Writing – original draft, Writing – review & editing. PWS: Methodology, Writing – original draft. ADC: Methodology, Writing – original draft. JSS: Data curation, Writing – original draft. AVLS: Data curation, Writing – original draft.

#### REFERENCES

- 1. Brazil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estatísticas de Câncer [internet]. Rio de Janeiro: Inca; 2021. [cited on October 10, 2021]. Available at: https://www.inca.gov.br/numeros-de-cancer
- Franzoi MA, Rosa DD, Zaffaroni F, Werutsky G, Simon S, Bines J, et al. Advanced stage at diagnosis and worse clinicopathologic features in young women with breast cancer in Brazil: a subanalysis of the AMAZONA III study (GBECAM 0115). J Glob Oncol. 2019;5:1-10. https://doi.org/10.1200/JGO.19.00263
- Spronk I, Schellevis FG, Burgers JS, Bock GH, Korevaar JC. Incidence of isolated local breast cancer recurrence and contralateral breast cancer: a systematic review. Breast. 2018;39:70-9. https://doi.org/10.1016/j.breast.2018.03.011
- Langballe R, Frederiksen K, Jensen MB, Andersson M, Cronin-Fenton D, Ejlertsen B, et al. Mortality after contralateral breast cancer in Denmark. Breast Cancer Res Treat. 2018;171(2):489-99. https://doi.org/10.1007/s10549-018-4846-3
- Rasmussen CB, Kjær SK, Ejlertsen B, Andersson M, Jensen MB, Christensen J, et al. Incidence of metachronous contralateral breast cancer in Denmark 1978-2009. Int J Epidemiol. 2014;43(6):1855-64. https://doi.org/10.1093/ije/dyu202
- Provenzano E, Ulaner GA, Chin SF. Molecular classification of breast cancer. PET Clin. 2018;13(3):325-38. https://doi. org/10.1016/j.cpet.2018.02.004
- Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736-50. https://doi.org/10.1093/jnci/djp082
- Bitencourt AGV, Lima ENP, Chojniak R, Marques EF, Souza JA, Luciana Graziano L, et al. Correlação entre resultado do PET/CT e achados histológicos e imuno-histoquímicos em carcinomas mamários. Radiol Bras. 2014;47(2):67-73. https:// doi.org/10.1590/S0100-39842014000200006
- Caldarella A, Buzzoni C, Crocetti E, Bianchi S, Vezzosi V, Apicella P, et al. Invasive breast cancer: a significant correlation between histological types and molecular subgroups. J Cancer Res Clin Oncol. 2013;139(4):617-23. https://doi.org/10.1007/ s00432-012-1365-1
- Corben AD. Pathology of invasive breast disease. Surg Clin North Am. 2013;93(2):363-92. https://doi.org/10.1016/j. suc.2013.01.003

- Lindström LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012;30(21):2601-8. https:// doi.org/10.1200/JCO.2011.37.2482
- 12. Lee Y, Kang E, Lee AS, Baek H, Kim EK, Park SY, et al. Outcomes and recurrence patterns according to breast cancer subtypes in Korean women. Breast Cancer Res Treat. 2015;151(1):183-90. https://doi.org/10.1007/s10549-015-3390-7
- Shim HJ, Kim SH, Kang BJ, Choi BG, Kim HS, Cha ES, et al. Breast cancer recurrence according to molecular subtype. Asian Pac J Cancer Prev. 2014;15(14):5539-44. https://doi. org/10.7314/apjcp.2014.15.14.5539
- 14. van Uden DJP, van Maaren MC, Strobbe LJA, Bult P, van der Hoeven JJ, Siesling S, et al. Metastatic behavior and overall survival according to breast cancer subtypes in stage IV inflammatory breast cancer. Breast Cancer Res. 2019;21(1):113. https://doi.org/10.1186/s13058-019-1201-5
- Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28(20):3271-7. https://doi.org/10.1200/ JCO.2009.25.9820
- 16. Kolberg-Liedtke C, Wuerstlein R, Gluz O, Heitz F, Freudenberger M, Bensmann E, et al. Phenotype Discordance between Primary Tumor and Metastasis Impacts Metastasis Site and Outcome: Results of WSG-DETECT-PriMet. Breast Care (Basel). 2021;16(5):475-83. https://doi.org/10.1159/000512416
- Frampton GM, Fichtenholtz A, Otto GA, Wang K, Downing SR, He J, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol. 2013;31(11):1023-31. https://doi. org/10.1038/nbt.2696
- Roychowdhury S, Iyer MK, Robinson DR, Lonigro RJ, Wu YM, Cao X, et al. Personalized oncology through integrative high-throughput sequencing: a pilot study. Sci Transl Med. 2011;3(111):111ra121. https://doi.org/10.1126/ scitranslmed.3003161
- National Comprehensive Cancer Network. NCCN Guidelines. Fort Washington: National Comprehensive Cancer Network; 2021 [cited on October 10, 2021]. Available at: https://www. nccn.org/guidelines/guidelines-detail?category=1&id=1419.



### Dermatitis neglecta in a patient with breast fibroadenoma: case report

Aline Cristina da Silva Lima<sup>1</sup> <sup>(D)</sup>, Juliana Pontes Farias<sup>1</sup> <sup>(D)</sup>, Renê Stéfano Costa Pontes<sup>1</sup> <sup>(D)</sup>, Isabelle Souza Medeiros Torres<sup>1</sup> <sup>(D)</sup>, Janislei Soares Dantas<sup>1</sup>\* <sup>(D)</sup>, Adriano de Lima Quirino<sup>1</sup> <sup>(D)</sup>, Ilzinalda dos Santos Ideão Farias<sup>1</sup> <sup>(D)</sup>, Joanne Elizabeth Ferraz da Costa<sup>1</sup> <sup>(D)</sup>

#### ABSTRACT

Dermatitis neglecta, a condition that results from inadequate skin cleansing, is still little reported in the literature and underreported. Although benign, it is aesthetically uncomfortable. It is associated with conditions that lead to fear of sanitizing a given region and may be related to psychiatric and neurological disorders. This observational study consisted of the case report of a patient followed up in a University Hospital in northeastern Brazil, with the objective of demonstrating the rare association between dermatitis neglecta and breast fibroadenoma. A young patient with a history of depressive disorder had crusted and hyperpigmented skin lesions covering the left breast and massive tumor in the same breast. The patient was oriented regarding the cleaning and removal of crusts, resulting in good clinical response. She underwent excision of the tumor, and the anatomopathological study was compatible with fibroadenoma. Interdisciplinary follow-up, including treatment for psychiatric disorder, was fundamental for the patient's recovery, considering the improvement of her mood after establishing the therapy and successful final breast reconstruction. Dermatitis neglecta can resemble other types of dermatitis, in such a way that it is essential to establish a differential diagnosis to avoid unnecessary evaluation procedures, interventions, and therapies. In this exuberant case of dermatitis neglecta, the importance of comprehensive health care is emphasized."

KEYWORDS: skin care; dermatitis; fibroadenoma; depression.

#### INTRODUCTION

Dermatitis neglecta is a condition related to inadequate skin cleansing, with accumulation of sebaceous secretion, sweat, corneocytes, and bacteria, forming a compact crust<sup>1</sup>. This benign skin alteration, although asymptomatic, is aesthetically uncomfortable. It is little reported in the literature, with underestimated prevalence and possibly underdiagnosed<sup>2.3</sup>.

As demonstrated in studies, it usually affects sites of hyperesthesia and previous traumas such as an area of previously excised skin neoplasia. It may also be related to neurological deficits, cognitive impairment, in which apathy and forgetfulness are typical, and psychiatric disorders, such as depression or other psychoses, i.e., it is a sign of self-neglect<sup>4,5</sup>.

It requires comprehensive clinical evaluation, including psychological and behavioral aspects, because the correlation between psychiatric and dermatological disorders is highly complex, considering the etiology, diagnostic procedures, and treatment<sup>3,4</sup>. Due to the low number of cases reported in the medical literature, the need for attention to differential diagnoses and the importance of recognizing the correlation between psychiatric and dermatological disorders, this study aimed to describe a case of exuberant dermatitis neglecta in the breast of a young patient with a previous history of fibroadenoma excision at the same site and depression, seen at the Dermatology Outpatient Clinic of a University Hospital located in the northeast region of Brazil.

#### **CASE REPORT**

A 19-year-old female patient, who had been followed up due to a nodule in the left breast for three years, with increased volume in the last year, reported the appearance of crusts in the same breast two years ago, but without pain or itching. Diagnosed with depressive disorder, she had been using Sertraline 50 mg a day for five months. Physical examination detected a significant increase

<sup>1</sup>Universidade Federal da Paraíba, Hospital Universitário Lauro Wanderley – João Pessoa (PB), Brazil.

\*Corresponding author: janisleisd@gmail.com Conflict of interests: nothing to declare. Funding: none.

Received on: 06/14/2022. Accepted on: 06/21/2022.

in the left breast, with thick hyperchromic crusts covering the entire areolar and periareolar region (Figure 1A). Breast ultrasonography showed a massive solid nodular formation of lobulated contours.

As diagnostic hypotheses for the dermatological condition, Paget's disease of the breast, hyperkeratosis of the nipple and areola, and eczema were suggested, and skin biopsy was scheduled. The patient was instructed to properly sanitize the area and apply oil with essential fatty acids to remove the crusts. A few days later, a reduction in crusts was observed, allowing the exposure of the nipple-areola complex, which was depigmented and deviated to the right side (Figure 1B).

The anatomopathological result showed, in a superficial fragment, keratin lamellae and, in a deep fragment, fibrous stroma permeated by mammary glands, suggestive of fibroadenoma. In view of the improvement with cleanliness alone, the diagnosis was then defined as dermatitis neglecta. When asked about her hygiene routine, the patient reported being afraid to sanitize the region. The importance of local asepsis and psychiatric follow-up was reinforced.

Subsequently, the patient was submitted to tumor removal and breast reconstruction, procedures performed by the mastology and plastic surgery team. The histopathological analysis of the surgical specimen showed, in the skin fragment, epidermis with hyperkeratosis, papillomatosis, orthokeratosis foci, and melanocytic hyperpigmentation of the basal layer (Figure 2A), and in the examination of the tumor fragment, the hypothesis of fibroadenoma was confirmed (Figure 2B).

During follow-up, we observed progressive improvement in the skin aspect as well as in the patient's mood (Figure 3).

#### DISCUSSION

Dermatitis neglecta is a condition related to inadequate hygiene of a certain region of the skin, which may be associated with psychiatric and neurological disorders<sup>6</sup>.

Also known as dermatosis neglecta, it was first described by Poskitt et al. in 1995. It affects people of both sexes and all ages.



Figure 1. (A) Breast asymmetry due to tumor in the left breast, with thick crusts covering the areolar and periareolar region. (B) Reduction of crusts, with exposure of the nipple-areola region, which is deviated to the right due to tumor.

Clinically, there are asymptomatic hyperkeratotic, hyperpigmented squamous plaques<sup>1,2</sup>.

Previously published studies<sup>1.3,7,8</sup> demonstrate varied historical antecedents, drawing attention to the multiplicity of forms adopted by dermatosis lesions. Most cases resulted from inadequate hygiene of surgical scar, previous dermatosis, sunburn, or trauma. There are also reports of patients with psychiatric conditions, including depression and schizophrenia, or related to religious beliefs. Lack of access to basic sanitation and cultural issues may also be factors associated with the pathology, whose higher prevalence is recorded in adults, but it may affect children<sup>9-11</sup>.

Considering the nonspecific anatomopathological findings of the skin fragment, the history of depression, the report of inadequate hygiene, and the improvement of the condition with



**Figure 2.** On the left, histological sections in hematoxylin-eosin staining visualized at 40x magnification: (A) skin fragment, noting hyperkeratosis and papillomatosis; (B) result from quadrantectomy with fibrous breast stroma permeated with glands without atypia, sometimes with reduced lumen, confirming the diagnosis of fibroadenoma; on the right (C), anatomical specimen corresponding to the giant fibroadenoma, measuring 11 cm.



**Figure 3.** Post-surgical follow-up, demonstrating partial repigmentation of the areolar and periareolar region.

cleanliness alone, we concluded that this was an exuberant case of dermatitis neglecta caused by the patient's fear of cleaning the breast that had a giant fibroadenoma.

Fibroadenomas are common benign lesions of the breast, usually found in patients under 20 years of age. Lesions measuring >5 cm, which are uncommon, representing less than 4% of cases, are defined as giant lesions<sup>12</sup>. They present themselves as a unilateral, circumscribed mass of rapid growth. Histologically, the tumor is composed of ducts and fibrous connective tissue, and can be treated with simple enucleation. Differential diagnosis of giant fibroadenoma includes *Phyllodes* tumor, inflammatory processes, and benign proliferative lesions<sup>13,14</sup>.

Dermatitis neglecta has as differential diagnosis the terra firma-forme dermatosis; however, in the latter, simply cleaning the site with soap and water does not improve the condition<sup>15</sup>.

Although the distinction of psychiatric conditions may represent a challenge, the diagnosis is still clinical. Patients should be properly instructed to maintain good personal hygiene, and keratolytic agents and emollients should be judiciously used when necessary<sup>16</sup>.

The patient's mood improvement after breast reconstruction is highlighted, positively impacting her self-esteem. With a view to the integrality of care, the therapeutic approach of psychodermatological disorders should be multidisciplinary, including primary care physicians, dermatologists, psychiatrists, psychologists, and nurses.

Despite being a relatively simple clinical condition with lowcost treatment, it is still underdiagnosed<sup>11</sup>.Therefore, the early recognition of clinical and psychosocial manifestations and the underlying cause is essential to avoid unnecessary diagnostic and therapeutic interventions.

#### CONCLUSIONS

A case of dermatitis neglecta in the breast of a young patient with breast fibroadenoma and depressive disorder was reported. The case is relevant due to the exuberant presentation, coexistence with psychiatric disorder, in addition to evidencing the need for comprehensive clinical examination, involving psychological, social, and behavioral aspects of the patient, which requires an interdisciplinary approach.

Better awareness of physicians and patients can avoid incorrect diagnoses and, consequently, unnecessary invasive examinations and procedures.

#### **AUTHOR'S CONTRIBUTION**

ACSL: Conceptualization, Methodology, Investigation, Writing – review & editing. JPF: Supervision, Visualization, Writing – original draft. RSCP: Methodology, Investigation, Writing – review & editing. ISMT: Methodology, Visualization, Writing – original draft. JSD: Conceptualization, Methodology, Investigation, Writing – review & editing. ALQ: Methodology, Visualization, Writing – original draft. ISIF: Methodology, Visualization, Writing – original draft. JEFC: Supervision, Methodology, Investigation, Writing – original draft.

#### REFERENCES

- Gutiérrez Fretes Lenny Gabriela, Rivelli de Oddone Victoria Beatriz. Dermatosis neglecta. Ver Virtual Soc Parag Med Int. 2022;9(1):126-9 https://doi.org/10.18004/ rvspmi/2312-3893/2022.09.01.126
- Mosena G, Bonkevitch F, Damiani L, Souza PRM. Dermatose neglecta – afecção de difícil suspeição diagnóstica. J Port Soc Dermatol Venereol. 2016;74(4):409-11. https://doi.org/10.29021/ SPDV.74.4.540
- Kumar PNS, Uvais NA, Gopalakrishnan A, Suresh R. Dermatitis neglecta: a case report in psychodermatology. Prim Care Companion CNS Disord. 2021;23(4):20102806. https://doi. org/10.4088/PCC.20102806
- Suresh PN, Uvais NA, Gopalakrishnan A, Suresh R. Dermatitis neglecta: a case report in psychodermatology. Prim Care Companion CNS Disord. 2021;23(4):20102806. https://doi. org/10.4088/PCC.20102806
- Brown TM. Dermatitis Neglecta, the cognitive assessment, and micronutrients. Psychosomatics. 2020;61(6):723-6. https:// doi.org/10.1016/j.psym.2020.08.006

- Lopes S, Vide J, Antunes I, Azevedo F. Dermatitis neglecta: a challenging diagnosis in psychodermatology. Acta Dermatovenerol Alp Pannonica Adriat. 2018;27:109-10. https:// doi.org/10.15570/actaapa.2018.22
- Bansod SH, Madke BS. A Case of Post Hair Transplant Dermatosis Neglecta: A Rare Entity. Int J Trichology. 2020;12(5):243-4. https://doi.org/10.4103/ijt.ijt\_78\_20
- Chen X, Zhang J, Zhou C. Dermatosis Neglecta of the Scalp Complicated with Alopecia Areata. Int J Trichology. 2020;12(3):138-9. https://doi.org/10.4103/ijt.ijt\_46\_19
- Taywade M, Panda PS, Sirka CS, Patro BK. Neonatal dermatitis neglecta – neglect by health system: a case report. J Family Med Prim Care. 2021;10(7):2718-9. https://doi.org/10.4103/ jfmpc.jfmpc\_2442\_20
- Venkatachalam K, Anila PS, A Bindu SS. Dermatosis Neglecta

   Report of a Case with Verrucous Plaque in a Child. Indian Dermatol Online J. 2019;10(5):609. https://doi.org/10.4103/idoj. IDOJ\_360\_18

- Saha A, Sengupta M, Ganguly N. Two Pediatric Cases of Dermatitis Neglecta - A Neglected Entity Needs Awareness. Indian J Dermatol. 2021;66(6):707. https://doi.org/10.4103/ijd.ijd\_981\_20
- 12. Meng X, Yamanouchi K, Kuba S, Sakimura C, Morita M, Matsuguma K, et al. Giant fibroadenoma of the breast: a rare case in a mature woman. Int J Surg Case Rep. 2019;63:36-9. https://doi.org/10.1016/j.ijscr.2019.09.015
- 13. Laporte BEP, Salgado HC, Monteze NM, Rangel JMC, Carvalho MAG, Esperança SD. Fibroadenoma in axillary accessory breast: a case report. Mastology. 2020;30:e20200055. https:// doi.org/10.29289/25945394202020200055
- 14. Kabuyaya MK, Mutombo FL, Moseka FM, Kihemba K, Wetzig N, Lussy JP. A giant fibroadenoma in a mature woman: diagnosis and treatment in a limited resource environment (a case report). Pan Afr Med J. 2021;38:19. https://doi.org/10.11604/pamj.2021.38.19.26200
- 15. Stiube A, Jenni D, Wiederkehr L, Anzengruber F, Nobbe S. Terra firme-forme dermatosis diagnostic sign and treatment: a case report. Case Rep Dermatol. 2019;11:108-12. https://doi. org/10.1159/000499897
- Šitum M, Kolić M, Buljan M. [Psychodermatology]. Acta Med Croatica. 2016;70(Suppl 1):35-8. PMID: 29087669.



# Stage IV invasive breast cancer in an indigenous villager: a case report and review of literature

Maillene Rodrigues Lisboa<sup>1</sup>\* <sup>(i)</sup>, Ana Lucia Escobar<sup>1</sup> <sup>(i)</sup>, Thamy Yamashita Shibayama<sup>1</sup> <sup>(i)</sup>, Raphael Lima de Assis Oliveira<sup>1</sup> <sup>(i)</sup>, Marcos Vinícius dos Santos<sup>1</sup> <sup>(i)</sup>

#### ABSTRACT

Breast cancer is one of the leading causes of death worldwide. Among the risk factors related to this disease, lifestyle and unhealthy diet have important relevance. In the present report, we describe the case of an indigenous villager who consumed processed foods, such as snacks, soft drinks, artificial juice and biscuits. Therefore, we were able to observe a transition in habits of the indigenous population with possible epidemiological repercussions.

KEYWORDS: breast cancer; risk factors; health services accessibility

#### INTRODUCTION

Breast cancer is among the most common cancer, being one of the main causes of mortality among American and Alaska native peoples. This population showed between the years 2012 and 2016 an incidence of 79.5 cases per 100 thousand individuals and a mortality rate of 14.3 deaths per 100 thousand individuals<sup>1</sup>.

In Brazil, there is a lack of information on the behavior of different types of cancer in the indigenous population. The Ministry of Health estimates, for the year 2020, 66,280 new cases of breast cancer for the general population, corresponding to 29.7% of all female cancers<sup>2</sup>.

The portrait of this cancer in the Brazilian population was clearly demonstrated by Rosa et al.<sup>3</sup>. The mean age at diagnosis was 53.9 years, and only 34% of the total number of diagnosed cases were performed through screening tests. Patients who used supplementary health plans were diagnosed at earlier stages, when compared to those in the public health service<sup>3</sup>.

This disease has very well-established risk factors: menstrualreproductive, environmental and lifestyle. Among these, the modifiable ones such as obesity and alcohol consumption, which can impact the incidence and mortality of various diseases<sup>4</sup>, stand out.

In the last census carried out in Brazil, in 2010, 817,963 people declared themselves as being indigenous, with the highest concentration in the northern region of the country<sup>5</sup>. This is where the Nambikwara people live, in an area that comprises the northwest of the state of Mato Grosso and the south of the state of Rondônia. They are composed of several subgroups, according to the place they occupy. In Vale do Guaporé (RO) live the Hahaintesu, who speak the

language of the Nambikwara linguistic family. There lies the west of the Nambikwara territory, with 85% of the area covered by forest<sup>6</sup>. Men have some degree of understanding of Portuguese, since they leave the villages more often, which allows for a closer contact with the habits of the surrounding national society, including processed foods. This is the scenario in which the patient featured in this report lived. She left the area in search of treatment at a state referral unit.

In the current scenario, according to the 1988 Constitution, health is a fundamental right. Inequalities determine the health standards faced by each population group, and indigenous peoples are exposed to a situation of greater vulnerability and less coverage of health programs and services<sup>7</sup>.

This aim of this study was to describe a case of ductal carcinoma in an indigenous woman who had never had contact with the surrounding national society and who had an unfavorable outcome as a consequence of the difficulty in accessing health services, a factor that compromises the prognosis.

The present report was obtained based on the care of an indigenous patient at the mastology outpatient clinic of the high complexity unit sector of the Hospital de Base Dr. Ary Pinheiro (RO), during 2015 and 2016. Data were collected by the first author himself, during seven meetings for consultations and returns.

#### **CASE REPORT**

Nambikwara Hahaintesu indigenous woman, 49 years old, with body mass index (BMI) of 28 kg/m² and normal vital signs, communicated

<sup>1</sup>Universidade Federal de Rondônia, Departament of Medicine – Porto Velho (RO), Brazil.

\*Corresponding author: maillenelisboa@unir.com

**Conflict of interests:** nothing to declare. **Funding:** none.

**Received on:** 02/17/2022. Accepted on: 08/04/2022.

through her partner, who understood some Portuguese, thus with some obstacles in communication. She reported swelling and intense pain in the left breast for a year and recent onset of redness and local swelling. Menarche was at age 18; the woman, G8P7A1, had all deliveries vaginal, the first at full term at age 22. She had no other complaints, past or present illnesses or medication use. She has always lived in the village, which has guided her life habits. She fed on products from collection, local agriculture, hunting and fishing, and also processed foods such as snack foods, soft drinks, artificial juices and cookies. On physical examination, she was in a regular general condition and lucid and oriented in time and space, with discolored mucous membranes. Static inspection revealed hyperchromic, crusted scars in the thoracic region and upper abdomen, edema, hyperemia and increased volume of the left breast, perception of a hardened mass occupying the entire left breast, coalescing lymph nodes in the ipsilateral axillary fossa and lymph node enlargement in the left cervical chain; and the right breast was flaccid and hanging, without palpable masses (Figure 1). Mammography showed fat-replaced breasts with skin thickening and a spiculated nodule measuring about 8.0 x 4.0 cm in the central region of the left breast; the lesion was Breast Image Reporting and Data System (BIRADS) 5. Histological examination was compatible with invasive ductal carcinoma, histological grade of Nottingham 2, reticular dermis infiltrate and subcutaneous cellular tissue, presence of lymphatic and perineural invasion, inflammatory infiltrate in the mild-tumor stroma, and epidermis and papillary dermis free of neoplasia (Figure 2). Immunohistochemistry indicated: estrogen receptor (ER)-positive at 70%; weak (focal) progesterone receptor (PR)- positive; Ki67 positive at 70%; and C-erb-B2 score 3+. Blood count was: red blood cells 3.06x10<sup>6</sup>/mm<sup>3</sup>, hematocrit 24.80%; hemoglobin 8.27 g/ dL; leukocytes 12,400/mm3 and platelets 124,000/mm3. Other blood tests showed glucose 85.50 g/dL; transaminases and urea nitrogen normal; and Venereal Disease Research Laboratory (VDRL), HBsAg,



**Figure 1.** Static inspection: Chest with multiple hyperchromic scars. Flaccid and pendulous left breast, the right breast increased in volume and firm due to the presence of the tumor – Front view.

anti-HCV and anti-HIV1e2 all negative. Computed tomography of the chest, abdomen and pelvis showed osteolytic and osteoblastic lesions affecting all bones of the rib cage, pelvis and lumbar vertebral bodies. Clinical stage IV (T4bN2M1) was evident.

She was referred to an outsourced oncology clinic, where she received 6 cycles of docetaxel and zoledronic acid. There was disease progression; she was referred for antialgic radiotherapy, and maintenance tamoxifen was started, while zoledronic acid was continued. She died 13 months after diagnosis.

#### DISCUSSION

In a review of medical records of adult patients from different ethnic groups and regions of the country diagnosed with solid cancer and treated at the Indigenous Patient Clinic of the Federal University of São Paulo, between 2005 and 2014, with 48 patients from 19 ethnic groups, represented mostly by women, there is no report of breast cancer. For cancer cases followed-up there, there was a mean time between the onset of symptoms and diagnosis of 9.0±8.8 months and between diagnosis and treatment of 3.4±4.6 months, a relatively long time. large, considering that most people came from the Southeast and Central-West regions of the country. This time resulted in diagnoses in more advanced stages of the disease<sup>8</sup>.

Indigenous people from the state of Pará were treated at the oncology hospital of reference in that state, with greater representation for females aged between 60 and 69 years. Among these, there was only one case of breast cancer, namely a 34-year-old indigenous woman of Wai Wai ethnicity<sup>9</sup>.

Reports in the literature on the incidence of breast cancer in indigenous Brazilians are scarce, either because they are rare or because they are underreported. It should be noted that a lower incidence of this cancer has been observed in minority ethnic groups<sup>10</sup>. Indigenous populations have a higher prevalence of cancer due to unfavorable socioeconomic conditions and infectious agents, as observed in the cancer mortality survey in the state of Acre. Thirty-three deaths were identified in indigenous women, whose main cause was cervical cancer and lower mortality from breast cancer<sup>11</sup>. The same was observed by Freitas-Junior et al., who, researching the number of deaths from breast cancer in Brazilian indigenous women of 0.25<sup>12</sup>.

A comparative study with Peruvian indigenous people living in the mountains and in the Amazon rainforest, with invasive breast cancer, found that those living in the jungle had an earlier age at diagnosis, almost five years earlier, triple negative tumors and shorter survival, and mortality was 1.7 times higher in these women. There was a probable association with the distance of this region to the treatment sites and with the strategies to address the disease, respecting the local culture<sup>13</sup>.

A survey of 269 breast cancer survivors among American Indians and Alaska Natives, to identify obstacles during treatment, observed



Figure 2. (A) Skin segment with infiltration by invasive breast carcinoma of no special type (NST)/invasive ductal carcinoma not otherwise specified (NOS) in subcutaneous tissue (hematoxylin and eosin, HE: 40x); (B) Cords and nests of atypical cells with prominent nucleoli and anisokaryosis, surrounded by desmoplastic stroma (HE, 250x); (C) Intermediate/grade 2 Nottingham histological grade (Scarrff-Bloom-Richardson modified by Elston and Ellis) invasive carcinoma (tubular formation score 3, nuclear grade score 2 and mitotic index 1) (HE 400x).

that the lower the level of education, the greater was the number of these, such as: difficulties in access, transportation and communication. It is noteworthy that most women had completed high school and were diagnosed in early clinical stages, which is probably why most of them had a survival rate of more than five years<sup>14</sup>. This reality differs greatly from the Brazilian Amazon. It is known that they have lifestyle habits and menstrual and reproductive characteristics that do not match the factors that promote breast cancer<sup>11</sup>. On the other hand, globalization and the facilities of modern life have reached the most distant corners of the country, with risk factors for cancer in general, especially modifiable factors, such as environmental ones. Types of food, active and/or passive tobacco smoke and nutritional factors, such as excessive alcohol consumption and obesity, are increasingly present<sup>4</sup>. In a comprehensive review of diabetes mellitus, metabolic syndrome and the relationship with breast cancer growth and progression, Kang et al. described changes in several compartments. In in vivo studies, hyperinsulinemia contributed to tumor growth rather than hyperglycemia alone, despite the tumor having increased glucose uptake. In adipose tissue, aromatization of estrogen results in the production of adipokines and inflammatory cytokines. And in the intestine, the enteric estrobolome, an aggregate of enteric bacterial genes whose product is able to metabolize estrogen, especially in bacteria that have  $\beta$ -glucuronidase and  $\beta$ -glucuronide, enzymes involved in estrogen deconjugation and conjugation<sup>15</sup>.

It is already established that the negative energy balance inhibits the progression of cancer, confirmed in a double-blind study, given the decrease in leptin and the increase in sex hormone binding globulin (SHBG), which would bind to sex hormones, thus reducing the risk<sup>16</sup>. More recently, a mouse and human breast tissue model of reduction mammaplasty observed that obesity promotes changes in the breast tissue microenvironment that may increase cancer risk by deregulating transforming growth factor beta-1 (TGF $\beta$ 1), which is an important regulator of mammary epithelial stem cells<sup>17</sup>.

This obesogenic environment is related to the type of food intake, and foods are classified according to the level of processing and treatment they undergo into four groups: raw or minimally processed foods, processed culinary ingredients, processed foods and ultra-processed foods (represented by soft drinks, snacks, sweets, snacks, breads, etc.). In the United Kingdom, it was observed that a 10% increase in the consumption of ultra-processed foods increased the prevalence of obesity in men and women by 18 and 17%, respectively<sup>18</sup>. In Brazil, in a survey with 32,898 people over 10 years old, there was an increase in consumption of minimally processed and ultra-processed foods to the detriment of those rich in protein and dietary fiber<sup>19</sup>. This change in eating habits was also observed in the indigenous population and documented in a study evaluating 113 villages with 5,305 families in five regions of the country, and it was concluded that non-pregnant women had a rate of 30.3% overweight and 15.8% obesity<sup>20</sup>. A proven fact in the patient's clinical history, dietary characteristics and BMI.

#### CONCLUSION

In the case presented, the late diagnosis was preponderant for the patient's death. It can be seen that only the indigenous people of North America seem to have a functioning health system. There are increasingly frequent reports of consumption of ultra-processed foods among indigenous populations in Brazil, showing a certain degree of nutritional transition they are going through. Government intervention is necessary to reduce avoidable morbidity and mortality.

#### **AUTHORS' CONTRIBUTION**

MRL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. ALE: Formal analysis, Writing – original draft, Writing – review & editing. TYS: Formal analysis, Writing – review & editing. RLAO: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. MVS: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

#### REFERENCES

- U.S. Department of Health and Human Services Office of Minority Health. Cancer and American Indian/Alaska Natives. 2021[cited on Feb 11, 2022]. Available from: https:// minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=31
- 2. Ministério da Saúde, Instituto Nacional de Câncer. Cuidado para todos é defendido em debate no INCA. 2022 [cited on Feb 11, 2022]. Available from: https://www.inca.gov.br/
- Rosa DD, Bines J, Werutsky G, Barrios CH, Cronemberger E, Queiroz GS, et al. The impact of sociodemographic factors and health insurance coverage in the diagnosis and clinicopathological characteristics of breast cancer in Brazil: AMAZONA III study (GBECAM 0115). Breast Cancer Res Treat. 2020;183(3):749-57. https://doi.org/10.1007/s10549-020-05831-y
- Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer (Dove Med Press). 2019;11:151-64. https:// doi.org/10.2147/BCTT.S176070
- Instituto Brasileiro de Geografia e Estatística. Indígenas. 2022 [cited on Feb 11, 2022]. Available from: https://www.indigenas. ibge.gov.br/
- Instituto Socioambiental. Povos Indígenas no Brasil. 2022 [cited on Feb 11, 2022]. Available from: https://pib.socioambiental.org/ pt/P%C3%A1gina\_principal
- Valle FAAL, Farah BF, Carneiro Jr N. Health-interfering streets experiences: homeless people's perspective. Saúde Debate (Rio de Janeiro). 2020;44(124):182-92. https://doi.org/10.1590/0103-1104202012413
- Aguiar Júnior PN, Stock GT, Lopes Júnior GL, Almeida MS, Tadokoro H, Gutierres BS, et al. Disparities in cancer epidemiology and care delivery among Brazilian indigenous populations. Einstein (São Paulo). 2016;14(3):330-7. https://doi. org/10.1590/S1679-45082016AO3754
- Nascimento ER, Wanderley AV, Chalu-Pacheco F, Almeida Júnior RC, Costa DF, Pereira GNL, et al. Perfil clínico e epidemiológico do câncer entre os índios do estado do Pará, Brasil. Rev Bras Oncol Clín (São Paulo). 2015;11(39):12-18.
- Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst. 2005;97(6):439-448. https://doi.org/10.1093/jnci/dji064
- 11. Borges MFSO, Koifman S, Koifman RJ, Silva IFD. Mortalidade por câncer em populações indígenas no Estado do Acre, Brasil

[Cancer mortality among indigenous population in Acre State, Brazil]. Cad Saúde Pública. 2019;35(5):e00143818. https://doi. org/10.1590/0102-311X00143818

- 12. Soares LR, Gonzaga CM, Branquinho LW, Sousa AL, Souza MR, Freitas-Júnior R. Mortalidade por câncer de mama feminino no Brasil de acordo com a cor [Female breast âncer mortality in Brazil according to color]. ver Bras Ginecol Obstet. 2015;37(8):388-392. https://doi.org/10.1590/SO100-720320150005319
- Tamayo LI, Vidaurre T, Navarro Vásquez J, Casavilca S, Aramburu Palomino JI, Calderon M, et al. Breast cancer subtype and survival among Indigenous American women in Peru. PLoS One. 2018;13(9):e0201287. https://doi.org/10.1371/journal.pone.0201287
- 14. Goodwin EA, Burhansstipanov L, Dignan M, Jones KL, Kaur JS. The experience of treatment barriers and their influence on quality of life in American Indian/Alaska Native breast cancer survivors. Cancer. 2017;123(5):861-8. https://doi.org/10.1002/cncr.30406
- Kang C, LeRoith D, Gallagher EJ. Diabetes, obesity, and breast cancer. Endocrinology. 2018;159(11):3801-12. https://doi. org/10.1210/en.2018-00574
- 16. Demark-Wahnefried W, Rogers LQ, Gibson JT, Harada S, Frugé AD, Oster RA, et al. Randomized trial of weight loss in primary breast cancer: Impact on body composition, circulating biomarkers and tumor characteristics. Int J Cancer. 2020;146(10):2784-96. https://doi.org/10.1002/ijc.32637
- 17. Chamberlin T, Thompson V, Hillers-Ziemer LE, Walton BN, Arendt LM. Obesity reduces mammary epithelial cell TGF $\beta$ 1 activity through macrophage-mediated extracellular matrix remodeling. FASEB J. 2020;34(6):8611-24. https://doi.org/10.1096/fj.202000228RR
- Rauber F, Steele EM, Louzada MLDC, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and indicators of obesity in the United Kingdom population (2008-2016). PLoS One. 2020;15(5):e0232676. https://doi.org/10.1371/journal.pone.0232676
- Louzada MLDC, Ricardo CZ, Steele EM, Levy RB, Cannon G, Monteiro CA. The share of ultra-processed foods determines the overall nutritional quality of diets in Brazil. Public Health Nutr. 2018;21(1):94-102. https://doi.org/10.1017/S1368980017001434
- 20. Coimbra Júnior CE, Santos RV, Welch JR, Cardoso AM, Souza MC, Garnelo L, et al. The first national survey of indigenous People's Health and nutrition in Brazil: rationale, methodology, and overview of results. BMC Public Health. 2013;13:52. https://doi.org/10.1186/1471-2458-13-52

© 2022 Brazilian Society of Mastology This is an open access article distributed under the terms of the Creative Commons license.



### Hematological ratios as prognostic indicators in patients with triple-negative breast cancer in southern Brazil

Camila Macedo Boaro<sup>1</sup>\* <sup>®</sup>, Laura Mendonça Diefenthäeler<sup>2</sup> <sup>®</sup>, Gabriela Krüger da Costa<sup>2</sup> <sup>®</sup>, Katsuki Arima Tiscoski<sup>2</sup> <sup>®</sup>, Rafael José Vargas Alves<sup>2</sup> <sup>®</sup>, Maiquidieli Dal Berto<sup>2</sup> <sup>®</sup>, Claudia Giuliano Bica<sup>1,2</sup> <sup>®</sup>

#### ABSTRACT

Introduction: The heterogeneous nature and intrinsically aggressive tumor pathology of the triple negative breast cancer subtype results in an unfavorable prognosis and limited clinical success. The use of hematological components of the systemic inflammatory response for patients with triple-negative breast cancer can add important prognostic information to the criteria traditionally used for cancer patients, since inflammation can promote tumor progression support by affecting the stages of tumorigenesis. Objectives: The aim of this study was to evaluate the hematological parameters neutrophil/lymphocyte, monocyte/lymphocyte and platelet/lymphocyte ratios as prognostic indicators in patients with triple-negative breast cancer. Methods: This was a single-center retrospective observational study in an oncology referral hospital in the South region of Brazil. Electronic medical records of patients diagnosed with triple-negative breast cancer from 2012 to 2016 were reviewed and analyzed using SPSS. Results: The low blood cell ratio groups had significantly higher overall survival than the high blood cell ratio groups. Univariate analysis also confirmed the correlation of patients in the high blood cell ratio groups with unfavorable results. Conclusions: Hematological components of the systemic inflammatory response are promising prognostic indicators. More studies on the subject should be carried out to assist in future medical decision-making so these parameters of easy assessment and low cost can be introduced in clinical practice.

KEYWORDS: breast cancer; triple negative breast neoplasms; prognosis; blood cell count.

#### INTRODUCTION

Breast cancer became in 2020 the leading cause of global cancer incidence — with around 2.3 million new cases — as well as the fifth leading cause of cancer mortality worldwide, with 685,000 deaths<sup>1</sup>. It is estimated that approximately 12% to 20% of breast cancer cases diagnosed annually are of the triple-negative histological subtype. Triple-negative breast cancer (TNBC) is characterized by the lack of expression of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER-2)<sup>2</sup>.

The heterogeneous nature and inherently aggressive tumor pathology of this breast cancer subtype result in an unfavorable prognosis, where clinical success is limited by the lack of targeted therapy and with a tendency for early recurrence<sup>3,4</sup>. Accordingly, this histological subtype requires new approaches, including assessment tools that complement conventional methods. More and more studies support the involvement of inflammation in cancer prognosis, as inflammation is related to the development, progression, metastasis and recurrence of the disease<sup>5-10</sup>.

Neutrophils, lymphocytes, monocytes and platelets, hematological components of the systemic inflammatory response, have been reported as prognostic factors in several types of tumors, including breast cancer, due to their influence on neoplastic processes. Neutrophil, monocyte, platelet, and lymphocyte counts, in the form of neutrophil/lymphocyte (NLR), monocyte/lymphocyte (MLR), and platelet/lymphocyte (PLR) ratios, are inflammatory biomarkers that serve as auxiliary tools to add prognostic information to the criteria. traditionally used in cases of cancer patients<sup>5-8</sup>.

<sup>1</sup>Universidade Federal de Ciências da Saúde de Porto Alegre – Porto Alegre (RS), Brazil. <sup>2</sup>Irmandade da Santa Casa de Misericórdia de Porto Alegre – Porto Alegre (RS), Brazil. **\*Corresponding author:** camila.boaro@hotmail.com **Conflicts of interest:** nothing to declare. **Funding:** none. **Received on:** 11/16/2021. **Accepted on:** 01/17/2021. Thus, the aim of this study was to evaluate NLR, MLR and PLR as prognostic indicators in patients with TNBC, to contribute information to assist in future clinical practice and medical decision-making.

#### METHODS

#### Patients

This was a single-center, retrospective observational study, in which we identified patients whose diagnosis and treatment for TNBC had been performed at a referral oncology hospital in southern Brazil, between 2012 and 2016. The study obtained the informed consent of patients and ethical approval from the Ethics Committee of the teaching hospital, in accordance with the Declaration of Helsinki (1964) and Resolution 466/2012 of the National Health Council/Ministry of Health of Brazil.

Eligible patients were female, aged 18 years or older, diagnosed with triple-negative breast cancer and registered in the electronic medical record system available at the referral hospital. Patients who did not sign an informed consent form and whose TNBC was not characterized as the primary tumor were excluded. Duplicate patients and those with missing clinical data or incomplete or absent pathological and laboratory results were also excluded.

#### **Clinicopathological characteristics**

According to pathology reports, we identified tumors lacking immunohistochemical expression of ER, PR and HER-2 receptors. We then reviewed the electronic medical records of these patients to check their age and medical history, occurrence of metastases, recurrence or death. Pathological characteristics were determined, including the classification of malignant tumors (TNM), involvement of lymphatic vessels, blood vessels and axillary and sentinel lymph nodes.

#### Laboratory data

A complete blood count was performed as part of the routine clinical evaluation before surgery. NLR, MLR and PLR were defined as the absolute count of neutrophils, monocytes and platelets divided by the absolute lymphocyte count, being calculated from the pretreatment complete blood count performed within six months before diagnosis. To investigate the association of blood cell ratios with death outcome, a graphical representation was performed based on the receiver operating characteristic curve (ROC curve).

#### Statistical analysis

Qualitative variables were provided as frequency and percentage, while the quantitative as mean and standard deviation. Through the ROC curve, the ratio cut-offs for the outcome of death were estimated according to the Youden index. The associations of the ratios with the clinicopathological characteristics were analyzed using the chi-square test or Fisher's exact test when appropriate, and age results were compared using Student's t-test. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Overall survival time was defined from the date of diagnosis to the date of death/last record, and progression-free time was defined from the date of diagnosis to the date of first relapse or death/last record. Hazard ratio (HR) was determined by Cox proportional hazard regression analysis, with 95%CI. We used the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) for the analyses, and a significance level of 0.05 was adopted.

#### RESULTS

#### Patients

A database consisting of 2890 records of patients with histopathologically confirmed breast cancer was reviewed, and 42 records of patients with histological subtype triple-negative were included after the screening process and checking eligibility criteria (Figure 1). In this study, 95.2% of the samples for anatomopathological analysis came from surgical samples and only 4.8% from biopsies. Baseline clinicopathological characteristics are shown in Table 1. The mean time between diagnosis and death or closure was 47.1 months (range 1-60 months) and death occurred in 13 (31%) of the 42 patients. The mean time between diagnosis and progression or closure was 37.7 months (range 0-60 months) and progression occurred in 21 (50%) of the 42 patients. The mean age of the patients was 54.8 years (range, 33.09-89.8 years) and 9 (21.4%) of the patients were 40 years old or younger. The NLR, MLR and PLR were determined for all patients and ranged from 0.44 to 9.71 (mean, 2.77; median, 2.05; SD, 1.81), 0.12 to 2.00 (mean, 0.44; median, 0.35; SD, 0.34) and 61.57 to 594.34 (mean, 204.54; median, 159.35; SD, 117.57), respectively.

#### Cut-off points for NLR, MLR and PLR

ROC curve analysis was performed to determine optimal cut-off values for pretreatment NLR, MLR and PLR (Figure 2). The cut-off values of NLR, MLR and PLR were 2.13, 0.55 and 203.55, respectively, indicating the highest Youden index (maximum point of sensitivity and specificity). Eligible patients were stratified into two groups (low and high) according to cut-offs. Twenty-two patients (52.4%) were classified in the low NLR group (NLR<2.13) and 20 (47.6%) in the high NLR group (NLR $\geq$ 2.13). Likewise, 32 (76.2%) of the patients were classified in the low MLR group (MLR<0.55), while 10 (23.8%) in the high MLR group (MLR $\geq$ 0.55). Regarding PLR, 25 (59.5%) of the patients were classified in the low group (PLR $\geq$ 203.5) and the other 17 (40.5%) in the high group (PLR $\geq$ 203.5).

#### Association of NLR, MLR and PLR with prognosis

There was no significant correlation between pretreatment NLR, MLR and PLR and clinicopathological indices such as age at diagnosis, histological grade, tumor size, lymph node status, invasion of skin, blood vessels or lymphatic vessels, molecular phenotype and locoregional recurrence (p>0.05) (Table 1). We found that the low NLR, MLR and PLR groups had significantly higher overall survival (OS) (NLR log rank p=0.010, MLR log rank p=0.003 and PLR log rank p=0.000) than the high NLR, MLR and PLR groups (Figure 3). In the analysis of progression-free survival (PFS) (Figure 4), there was no significant difference between the high and low NLR groups (log rank p=0.072). However, there was a significant difference in PFS for PLR (log rank p=0.003). Univariate analysis also confirmed the correlation of patients in the

high NLR, MLR and PLR groups with unfavorable outcomes. The chance of death at any time during follow-up increased 4.72-fold for NLR≥2.13 (95%CI 1.29–17.22, p=0.019), 4.56-fold for MLR≥0.55 (95%CI 1.52–13.72, p=0.007) and 11.02-fold for PLR≥203.5 (95%CI 2.42–50.05, p=0.002) in relation to low NLR, MLR and PLR.

#### DISCUSSION

In recent years, several studies in literature have demonstrated the important role of blood cell ratios as significant biomarkers for breast cancer and other solid tumors, such as colorectal cancer, gastric cancer, ovarian cancer, non-small cell lung cancer, and others<sup>9-18</sup>. Despite the technical-scientific advances on the subject, for breast cancer, studies on the predictive value of pretreatment hematological ratios in the Brazilian population



Figure 1. Records screened and included in the study.

are rare, especially for TNBC, known to be an aggressive cancer due to its high nuclear grade, high mitotic index and greater tendency for regional and distant metastases. The use of hematological components of the systemic inflammatory response for patients with TNBC can add important prognostic information to the criteria traditionally used in cases of cancer patients.

In the present study, we demonstrated that high PLR is a statistically significant predictor of worse OS and PFS (p=0.000, p=0.003, respectively) among women with TNBC. When compared to other pretreatment hematological ratios and factors associated with survival, such as the occurrence of recurrence, the high

PLR group again showed significantly unfavorable results. On the other hand, the NLR and MLR groups did not show statistically significant results in the PFS analysis (p=0.166, p=0.072, respectively). The prognostic effect of NLR, MLR and PLR was consistent with the clinicopathological findings, since the groups with high NLR, MLR and PLR values, which were associated with a worse OS, also had unfavorable clinicopathological results in relation to the low NLR, MLR and PLR groups.

Two recent meta-analyses corroborate the findings of this study, suggesting that breast cancer patients with a high level of PLR are associated with a significantly worse prognosis and shorter

Characteristics		NLR« (n=	<2.13 22)	NLR: (n=	NLR≥2.13 (n=20) p-value		MLR<0.55 MLR≥0.55 (n=32) (n=10)		PLR<203.5 p-value (n=25)		PLR≥203.5 (n=17)		p-value			
		n	%	n	%		n	%	n	%		n	%	n	%	
Age at diagnosis	Mean and SD	54.18	12.25	55.47	16.17	0.770	52.57	12.57	61.93	16.90	0.066	53.89	13.26	56.13	15.55	0.619
Histological	G1+G2	2	9.1	3	15.0	0.656	3	9.4	2	20.0	0 5 7 7	3	12.0	2	11.8	1 000
grade	G3	20	90.9	17	85.0	0.656	29	90.6	8	80.0	0.577	22	88.0	15	88.2	1.000
	T1	5	23.8	3	15.0		7	22.6	1	10.0		7	28.0	1	6.3	
Ŧ	T2	10	47.6	9	45.0	0.75.4	15	48.4	4	40.0	0.288	12	48.0	7	43.8	0.207
I	Т3	2	9.5	4	20.0	0.754	5	16.1	1	10.0		3	12.0	3	18.8	0.207
	T4	4	19.0	4	20.0		4	12.9	4	40.0		3	12.0	5	31.3	
	N0	12	57.1	9	45.0		19	61.3	2	20.0		16	64.0	5	31.3	
	N1	4	19.0	4	20.0		4	12.9	4	40.0		3	12.0	5	31.3	
Ν	N2	1	4.8	0	0.0	0.686	1	3.2	0	0.0	0.158	1	4.0	0	0.0	0.167
	N3	2	9.5	4	20.0		4	12.9	2	20.0		2	8.0	4	25.0	
	N4	2	9.5	3	15.0		3	9.7	2	20.0		3	12.0	2	12.5	
Invasion of skin	No	14	77.8	12	75.0	1.000	22	84.6	4	50.0	0.066	16	84.2	10	66.7	0.417
	Yes	4	22.2	4	25.0		4	15.4	4	50.0		3	15.8	5	33.3	
Invasion of blood vessels	No	20	90.9	17	94.4	1.000	28	90.3	9	100.0	1.000	22	88.0	15	100.0	0.279
	Yes	2	9.1	1	5.6		3	9.7	0	0.0		3	12.0	0	0.0	
Invasion of	No	9	40.9	8	40.0		14	43.8	3	30.0		12	48.0	5	29.4	
lymphatic vessels	Yes	13	59.1	12	60.0	0.952	18	56.3	7	70.0	0.490	13	52.0	12	70.6	0.228
Molecular phenotype	Basal-like	13	59.1	17	85.0	0.063	22	68.8	8	80.0	0.696	17	68.0	13	76.5	0.731
	Non-basal- like	9	40.9	3	15.0		10	31.3	2	20.0		8	32.0	4	23.5	
Chemotherapy	Neoadjuvant	8	40.0	10	58.8	0.054	14	46.7	4	57.1	0.600	7	30.4	11	78.6	0.004
	Adjuvant	12	60.0	7	41.2	0.254	16	53.3	3	42.9	0.693	16	69.6	3	21.4	
	No	13	59.1	9	45.0	0.044	19	59.4	3	30.0	0.450	17	68.0	5	29.4	
Recurrence	Yes	9	40.9	11	55.0	0.361	13	40.6	7	70.0	0.152	8	32.0	12	70.6	0.014
Locoregional recurrence	No	16	72.7	16	80.0	0.700	25	78.1	7	70.0	0.670	20	80.0	12	70.6	
	Yes	6	27.3	4	20.0	0.723	7	21.9	3	30.0	0.678	5 20.0 5	5	29.4	0.714	
Distant recurrence	No	16	72.7	10	50.0		21	65.6	5	50.0	0.445	19	76.0	7	41.2	0.023
	Yes	6	27.3	10	50.0	0130	11	34.4	5	50.0	0.465	6	24.0	10	58.8	
	No	19	86.4	10	50.0		26	81.3	3	30.0		23	92.0	6	35.3	0.000
Death	Yes	3	13.6	10	50.0	0.011	6	18.8	7	70.0	0.005	2	8.0	11	64.7	
	No	13	59.1	8	40.0		19	59.4	2	20.0		17	68.0	4	23.5	0.005
Progression	Yes	9	40.9	12	60.0	0.217	13	40.6	8	80.0	0.030	8	32.0	13	76.5	

NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SD: standard deviation; bold: with significant p.



The areas under the curve for each parameter were 0.70 (p=0.040), 0.71 (p=0.033) and 0.83 (p=0.001), respectively. NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

**Figure 2.** Receiver operating characteristic curve evaluating the cut-off points of the neutrophil/lymphocyte, lymphocyte/ monocyte and platelet/lymphocyte ratios to predict overall survival and progression-free survival in the study.



disease-free survival, as well as a higher risk of recurrence compared with the low PLR group<sup>14,19</sup>. These findings can be explained by the fact that platelets are associated with the inflammatory process. Inflammation, known as one of the hallmarks of cancer, can contribute to several factors, altering the microenvironment and possibly accelerating tumor progression by releasing growth factors that support proliferative signaling and survival factors that limit cell death, facilitating angiogenesis, invasion and metastasis<sup>20</sup>. Thus, platelets end up playing an important role in tumor progression, by releasing pro-angiogenic proteins and protecting tumor cells from cytotoxic natural killer (NK) cells, responsible for controlling the spread of neoplastic cells. As a consequence, platelets end up potentiating the metastatic capacity of tumor cells<sup>11,13,21</sup>. Therefore, PLR is an excellent indicator of tumor activity.

Systematic literature reviews and meta-analyses have reported that the high NLR group is associated with worse survival in patients diagnosed with multiple cancers<sup>12,22</sup>. The analysis conducted by Jia et al. revealed that high levels of NLR prior to neo-adjuvant therapy are associated with a worse prognosis, particularly TNBC<sup>6</sup>. In addition to being reported in breast cancer, the potential prognostic value of NLR has been reported in colorectal cancer, hepatocellular carcinoma, bladder cancer, lung cancer,



(A) Median overall survival was 54.95 months in the patients in the low neutrophil/lymphocyte ratio group and 38.55 months in the high neutrophil/ lymphocyte ratio group. (B) Median overall survival was 51.1 months in the patients in the low monocyte/lymphocyte ratio group and 34.6 months in the patients in the high monocyte/lymphocyte ratio group. (C) Median overall survival was 55.64 months in the low platelet/lymphocyte ratio group and 34.65 months in the high platelet/lymphocyte ratio group.

NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

Figure 3. Correlation between overall survival of patients with triple-negative breast cancer and pretreatment blood cell ratios.

pancreatic cancer, prostate cancer and renal cell cancer<sup>6,7,12</sup>. In this study, the NLR obtained a significant difference only in the analysis of OS (p=0.010). However, our findings corroborate with the literature, since high NLR increased the chance of death at any time during the follow-up by 4.7 times (95%CI 1.29-17.22, p=0.019) compared to low NLR. These findings can be explained by the ability of neutrophils to inhibit the immune system and promote tumor growth, suppressing lymphocyte activity and T cell response. Therefore, NLR is considered a negative prognostic factor, being associated with low survival of cancer patients<sup>6,7,12-14</sup>.

Huszno et al.7 did not identify prognostic value between MLR and OS in patients with breast cancer and with TNBC. In our study, although there was a significant difference only in the



analysis of OS (p=0.003), high MLR increased the chance of death by 4.56 times (HR: 4.56 95%CI 1.5-13.72, p=0.007). Therefore, more studies are needed to confirm our results.

To the best of our knowledge, this study was the first to evaluate the prognostic association of pretreatment blood cell ratios in patients with triple-negative subtype breast cancer for SG and PFS in patients from South Brazil. However, there are three important limitations that must be taken into account when interpreting our findings. Our main limitation refers to the sample size. Although we identified 324 patients with TNBC, as this was a retrospective, single-center study, there were several losses due to missing data and loss to follow-up, which resulted in only 42 eligible patients being included in the study. Unfortunately,



progression (months)

(A) Median progression-free survival was 43.8 months in the patients in the low neutrophil/lymphocyte ratio group and 30.6 months in the high neutrophil/lymphocyte ratio group. (B) Median progression-free survival was 41.5 months in the patients in the low monocyte/lymphocyte ratio group and 23.1 months in the high monocyte/lymphocyte ratio group. (C) Median progression-free survival was 47.2 months in the patients in the low platelet/lymphocyte ratio group and 22.5 months in the high platelet/lymphocyte ratio group.

60

NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

36

Time between the date of diagnosis and progression (months)

Log Rank = 8.67; p-value=0.003

48

Figure 4. Correlation between progression-free survival of patients with triple-negative breast cancer and pretreatment blood cell ratios.

0.0

0

12

24

it was not possible to perform more robust analyses to obtain detailed information on the prognostic association of pretreatment hematologic ratios in patients with TNBC due to the sample size. In addition, it should be borne in mind that markers of the systemic inflammatory response may be influenced by factors such as acute and/or chronic infections and drug use.

#### **CONCLUSIONS**

In conclusion, the hematological components of the systemic inflammatory response are promising prognostic indicators, as they allow determining the specific needs of a patient through minimally invasive tests such as the blood cell count, helping to choose individualized approaches, and possibly helping to optimize the results for the patients. However, our findings need to be validated in larger retrospective, cohort or prospective studies. More studies on the subject should be carried out with the aim of introducing these parameters of easy assessment and low cost of performance in clinical practice in Brazil.

#### ACKNOWLEDGMENTS

To Cristiane Bündchen (Research Support Center, Universidade Federal de Ciências da Saúde de Porto Alegre) for statistical advice, and to all the students and researchers indirectly involved in this study for their technical-scientific assistance.

#### **AUTHORS' CONTRIBUTION**

CMB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MDB: Conceptualization, Data curation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CGB: Conceptualization, Data curation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RJVA: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing. LMD: Methodology. GKC: Methodology. KAT: Methodology.

#### REFERENCES

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi. org/10.3322/caac.21660
- Wahba HA, El-Hadaad HA. Current approaches in treatment of triple-negative breast cancer. Cancer Biol Med. 2015;12(2):106-16. https://doi.org/10.7497/j.issn.2095-3941.2015.0030
- 3. Stival RA, Martins LRA, Paganini J, Caixeta GN, Manoel WJ, Paula EC, et al. Impacto do fenótipo triplo-negativo no prognóstico de pacientes com câncer de mama de uma unidade de referência no Brasil central. Rev Bras Mastologia. 2012;22(1):6-12.
- Silva JL, Nunes NCC, Izetti P, Mesquita GG, Melo AC. Triple negative breast cancer: a thorough review of biomarkers. Crit Rev Oncol Hematol. 2020;145:102855. https://doi.org/10.1016/j. critrevonc.2019.102855
- Pistelli M, Lisa M, Ballatore Z, Caramanti M, Pagliacci A, Battelli N, et al. Pre-treatment neutrophil to lymphocyte ratio may be a useful tool in predicting survival in early triple negative breast cancer patients. BMC Cancer. 2015;15:195. https://doi. org/10.1186/s12885-015-1204-2
- JiaW,WuJ,JiaH,YangY,ZhangX,ChenK,etal. The peripheral blood neutrophil-to-lymphocyte ratio is superior to the lymphocyte-tomonocyte ratio for predicting the long-term survival of triplenegative breast cancer patients. PLoS One. 2015;10(11):e0143061. https://doi.org/10.1371/journal.pone.0143061
- HusznoJ,KoloszaZ.Prognosticvalueoftheneutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratio in breast cancer patients. Oncol Lett. 2019;18(6):6275-83. https://doi. org/10.3892/ol.2019.10966

- Rubio ÂDS. Razão entre células sanguíneas como indicadores de prognóstico em pacientes com câncer de mama luminal [dissertação]. Porto Alegre: Universidade Federal de Ciências da Saúde de Porto Alegre, 2020.
- 9. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, et al. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer. 2014;110(10):2524-30. https://doi.org/10.1038/bjc.2014.163
- Romero-CordobaS, MeneghiniE, Sant M, Iorio MV, SfondriniL, Paolini B, et al. Decoding immune heterogeneity of triple negative breast cancer and its association with systemic inflammation. Cancers (Basel). 2019;11(7):911. https://doi.org/10.3390/cancers11070911
- 11. Asano Y, Kashiwagi S, Onoda N, Noda S, Kawajirir H, Takashima T, et al. Platelet-lymphocyte ratio as a useful predictor of the therapeutic effect of neoadjuvant chemotherapy in breast cancer. PLoS One. 2016;11(7):e0153459. https://doi.org/10.1371/journal.pone.0153459
- Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju124. https://doi.org/10.1093/ jnci/dju124
- Wariss BR, Abrahão KS, Aguiar SS, Bergmann A, Thuler LCS. Effectiveness of four inflammatory markers in predicting prognosis in 2374 women with breast cancer. Maturitas. 2017;101:51-6. https://doi.org/10.1016/j.maturitas.2017.04.015
- 14. Guo W, Lu X, Liu Q, Zhang T, Li P, Qiao W, et al. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-tolymphocyte ratio for breast cancer patients: an updated metaanalysis of 17079 individuals. Cancer Med. 2019;8(9):4135-48. https://doi.org/10.1002/cam4.2281

- 15. Tan D, Fu Y, Su Q, Wang H. Prognostic role of plateletlymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(24):e3837. https://doi.org/10.1097/MD.00000000003837
- 16. Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer. 2013;13:350. https://doi.org/10.1186/1471-2407-13-350
- Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol. 2011;13(7):499-503. https:// doi.org/10.1007/s12094-011-0687-9
- Zhao QT, Yuan Z, Zhang H, Zhang XP, Wang HE, Wang ZK, et al. Prognostic role of platelet to lymphocyte ratio in non-small cell lung cancers: a meta-analysis including 3,720 patients. Int J Cancer. 2016;139(1):164-70. https://doi. org/10.1002/ijc.30060

- Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High platelet-to-lymphocyte ratio predicts poor prognosis and clinicopathological characteristics in patients with breast cancer: a meta-analysis. Biomed Res Int. 2017;2017:9503025. https://doi.org/10.1155/2017/9503025
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74. https://doi.org/10.1016/j. cell.2011.02.013
- 21. Takeuchi H, Abe M, Takumi Y, Hashimoto T, Kobayashi K, Osoegawa A, et al. The prognostic impact of the platelet distribution width-to-platelet count ratio in patients with breast cancer. PLoS One. 2017;12(12):e0189166. https://doi.org/10.1371/journal.pone.0189166
- 22. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res. 2017;19(1):2. https://doi.org/10.1186/s13058-016-0794-1



#### ORIGINAL ARTICLE https://doi.org/10.29289/2594539420220010

# Real-world data on metastatic breast cancer in Goiânia, Brazil: a 17-year analysis (1995–2011)

Leonardo Ribeiro Soares<sup>1</sup> <sup>(b)</sup>, Ruffo Freitas-Junior<sup>1,2</sup>\* <sup>(b)</sup>, Rodrigo Disconzi Nunes<sup>3</sup> <sup>(b)</sup>, Edesio Martins<sup>1</sup> <sup>(b)</sup>, José Carlos Oliveira<sup>2,4</sup> <sup>(b)</sup>, Maria Paula Curado<sup>5</sup> <sup>(b)</sup>

#### ABSTRACT

Introduction: Most of the data on metastatic breast cancer (MBC) originate from hospital-based studies or controlled trials involving specific populations and controlled treatments. In this respect, few population-based studies have analyzed the profile of MBC in low- and middle-income countries. Objective: To describe the epidemiological profile of women with de novo MBC using data from a population-based cancer registry (PBCR). Methods: An ecological study conducted in a PBCR in Goiânia, Brazil, for the 1995–2011 period. Women with MBC at diagnosis were included and the standardized incidence rate and annual percent change (APC) over the period were calculated. The women's clinical and demographic characteristics and data on diagnosis and treatment were analyzed. Results: Overall, 5,289 cases of breast cancer were registered in the Goiânia PBCR, 277 (5.2%) at metastatic stage. The adjusted incidence was 8.9/100,000 in 1995 and 6.04/100,000 in 2011 (APC: 1.1; p=0.6). Most of the patients (70.3%) were receiving care within the public healthcare system and the mean age at diagnosis was 54.7±14.5 years. Additional data for a subpopulation of 156 patients were identified at the city's two main treatment centers. According to immunohistochemistry, 53 women (67.1%) had hormone receptor-positive cancer. Of these, 14.0% (6/43) received endocrine therapy as first-line systemic treatment and 48.5% (17/35) as second-line treatment. A comparison of clinical data between the 1995–2003 and 2004–2011 periods revealed no significant differences in age, histological grade, locoregional staging, the presence of symptoms at diagnosis, or in treatment. Conclusion: This study population of women with MBC consisted predominantly of locally advanced tumors and the luminal-like subtype. The incidence rate of MBC in Goiânia did not change over the 17-year period. Most cases received chemotherapy as firstline systemic treatment irrespective of the tumor phenotype.

KEYWORDS: breast neoplasms; neoplasm metastasis; incidence; epidemiology.

#### INTRODUCTION

Breast cancer is a heterogenous pathology involving different patterns of tumor biology that are reflected in individualized clinical behavior and response to treatment<sup>1-4</sup>. As a result of population screening, there has been an increase in the number of incident cases diagnosed at the initial stages in various countries<sup>5-7</sup>; however, no reduction has been seen in the number of women diagnosed with de novo metastatic carcinoma<sup>4,6,7</sup>.

Patients with metastatic breast cancer (MBC) receive a continuous regime of palliative treatment, resulting in elevated financial costs due to the high cost of the medications and the need to frequently undergo tests and hospitalization for clinical support<sup>8.9</sup>. The median 5-year survival of these women, however, remains poor, ranging from 15% to 35%<sup>10-12</sup>.

In recent years, increased knowledge of tumor biology, advances in disease diagnosis, and access to new therapeutic agents have increased the overall survival of patients with MBC<sup>13,14</sup>. Although these advances have resulted in more personalized management of the metastatic disease, they have also introduced new challenges associated with controlling adverse events<sup>8,15</sup>. Therefore, epidemiological and population-based evaluations of women with MBC can contribute towards elaborating and implementing measures for more effective management of these patients.

<sup>&</sup>lt;sup>1</sup>Universidade Federal de Goiás – Goiânia (GO), Brazil.

<sup>&</sup>lt;sup>2</sup>Hospital Araújo Jorge, Associação de Combate ao Câncer de Goiás – Goiânia (GO), Brazil.

<sup>&</sup>lt;sup>3</sup>Universidade de Gurupi, School of Medicine – Gurupi (TO), Brazil.

<sup>&</sup>lt;sup>4</sup>Associação de Combate ao Câncer de Goiás, Registro de Câncer de Base Populacional de Goiânia – Goiânia (GO), Brazil.

<sup>&</sup>lt;sup>5</sup>A.C. Camargo Cancer Center, Fundação Antônio Prudente – São Paulo (SP), Brazil.

<sup>\*</sup>Corresponding author: ruffojr@terra.com.br

Conflict of interests: nothing to declare. Funding: none.

Received on: 03/22/2022. Accepted on: 04/16/2022.

Currently, most of the data on MBC originate from retrospective hospital-based studies or controlled trials involving specific populations and controlled treatments<sup>13,14,16</sup>. In this respect, few population-based studies have analyzed the profile of MBC in low- and middle-income countries<sup>10-12,16-18</sup>.

Since population-based cancer registries record incident cases of cancer in a defined population over a period of time, their use in real-world studies allows a wider exploratory analysis to be conducted and confers the possibility of external validation. Therefore, the objective of this study was to describe the patient profiles and patterns of care in MBC in the city of Goiânia, Brazil.

#### **METHODS**

An ecological, population-based clinical study was conducted with women with MBC in the city of Goiânia, Brazil. The cases were extracted from the Goiânia population-based cancer registry database for the period between 1995 and 2011<sup>10</sup>.

#### Goiânia cancer registry, Goiás

The Goiânia population-based cancer registry was created in 1986 and has been recording all new cases of cancer in residents of the city of Goiânia uninterruptedly since its creation to the present day<sup>4,10,19</sup>.

#### Criteria for the selection of cases

All incident cases for which the variable "extent of the disease" was described as "metastatic" or "unknown" were potentially eligible for inclusion in the study.

#### Cases

The cases registered as metastatic at diagnosis were classified as de novo metastatic disease. This classification is based on the clinical report, imaging tests, and/or a histology report showing the presence of metastatic disease at sites other than the breast and axillae<sup>8,15</sup>.

All the cases of breast cancer for which the variable "extent of the disease" was registered as "unknown" in the cancer registry were reviewed by performing an active search in the patient's medical records at the Araújo Jorge Hospital of the Association for the Combat of Cancer in Goiás and at the Universidade Federal de Goiás Teaching Hospital, two reference centers for cancer treatment in the city of Goiânia. The medical records of patients with a diagnosis of metastatic disease were then reviewed and constituted the subsample of the populationbased registry.

Cases of breast carcinoma in situ were excluded from the study, as were those without histological confirmation and cases in which diagnosis had only been recorded on the death certificate.

#### Variables selected for analysis

The demographic variables *age at diagnosis, age at menarche, family history of breast or ovarian cancer*, and *type of access to treatment* (public or private healthcare system) were retrieved from the medical records at the city's treatment centers.

The site and morphology of the tumor were coded in accordance with the International Classification of Diseases for Oncology, third edition (ICD-O-3). The cases included the morphological codes 8500/3, 8520/3, and 8521/3<sup>20,21</sup>. Sarcomas (8800/3) and other morphological types (anaplastic carcinoma and spindle-cell neoplasms) were classified as "other subtypes".

Histological grade was classified as G1, G2, or G3 according to the Bloom-Richardson grading system<sup>22</sup>. Locoregional staging was classified according to the tumor-node-metastasis (TNM) staging system, as defined in the American Joint Committee on Cancer's (AJCC) cancer staging manual, 8th edition<sup>23,24</sup>.

Immunohistochemical estrogen and progesterone receptor expression was considered positive or negative according to the report from each laboratory. Human Epidermal growth factor Receptor-type 2 (HER2) expression was considered positive when reported as three crosses (3+) or when amplification was confirmed by immunofluorescence. Tumor phenotype classification was determined following the recommendations of the 2017 St. Gallen International Expert Consensus Conference<sup>25</sup>.

Data on the site of metastasis were collected from the medical records at the two participating institutes. The site of metastatic lesions and the presence of associated clinical symptoms were evaluated, as well as whether aspiration and/or biopsy of the lesions had been performed. Treatment data were collected on the type of surgery performed for the primary tumor and/or for metastasis and any systemic treatments given.

#### Statistical analysis

The database was constructed using Microsoft Office Excel®, version 2003 (Microsoft Corporation, Redmond, WA, USA). The frequency of all the variables was established and a central tendency analysis was conducted to determine the mean age.

The crude incidence rate was defined as the ratio between the number of new cases of MBC diagnosed annually and the number of women exposed to the risk of developing the disease at the mean point of the respective year, with the result being expressed as a coefficient per 100,000 women<sup>26</sup>. The number of women exposed to the risk of cancer was defined as the female population of the city of Goiânia in the respective year according to the census population count for the years 2000 and 2010 and the intercensal population counts for the other years<sup>27</sup>.

The standardized incidence rate was calculated based on Segi's world standard population and expressed per 100,000 inhabitants<sup>28,29</sup>. Due to the rarity of this event, the rates were smoothed to a three-year mean.

The temporal analysis of the clinical and therapeutic characteristics was performed by comparing the 1995–2003 period with the 2004–2011 period. Statistical analysis was performed using MedCalc for Windows (MedCalc Software, Ostend, Belgium), version 18.11. The chi-square test was used to compare two proportions (of independent samples), expressed as a percentage. P-values <0.05 were considered statistically significant.

The annual percent change (APC) and the average APC (AAPC) in the rate of MBC were calculated for the total sample and according to the age group ( $<50, 50-69, \text{ and } \geq 70 \text{ years}$ ), with age being the only variable for which data were available in all cases. The relevant 95% confidence intervals (95%CI) were calculated, with p-values <0.05 being considered statistically significant. The Poisson regression model was used for these calculations and the software program used was JoinPoint Regression, version 4.7.0.0, of February 2019 (National Cancer Institute, USA)<sup>30</sup>.

#### **Ethical aspects**

The Internal Review Board at the Araújo Jorge Hospital of the Goiás Association for the Combat of Cancer approved the study protocol under CAAE No. 61987716.0.0000.0031. All the recommendations for good clinical practice outlined in the Brazilian National Health Council's resolution 466/2012 and the Helsinki Declaration were followed.

#### RESULTS

Between 1995 and 2011, 5,289 cases of breast cancer were registered in Goiânia and 277 (5.2%) were diagnosed as de novo metastatic





**Figure 1.** Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, adjusted for age.

disease. The adjusted incidence rate was 8.9/100,000 in 1995 and 6.04/100,000 in 2011 (Figure 1). There was no difference in the proportion of metastatic cases between the 1995–2003 period (n=129; 46.6%) and the 2004–2011 period (n=148; 53.4%; p=0.2) or in the trend during the periods (APC: -1.1; -5.2–3.2; p=0.06).

In the subsample of 156 cases identified in the two treatment centers, the majority (70.3%) were patients receiving care in the public healthcare system. The mean age was  $54.7\pm14.5$  years (mean $\pm$ standard deviation [SD]). Eighty-eight women (88/129; 68.2%) had a single metastatic lesion and 65 (65/129; 50.4%) had a visceral disease at diagnosis (Table 1).

Ten patients were subjected to resection of the metastatic lesion (10/108; 9.2%). Four of these patients had lesions in the brain and three in distant lymph nodes (mediastinal, cervical, and contralateral axillary lymph nodes). A further twenty women were subjected to percutaneous biopsy (20/108; 18.5%) for confirmation by cytology or histology. Of the 50 women subjected to breast surgery, 40 underwent radical mastectomy and 10 conservative breast surgery.

Endocrine therapy was prescribed as first-line treatment for 14.0% (6/43) of the patients with hormone receptor-positive cancer, and for 48.5% (17/35) of the patients, as second-line therapy. Of the 24 women with HER2-positive breast cancer, three were given trastuzumab as first-line treatment (3/24; 12.5%) and two as second-line treatment for the metastatic disease (Tables 2 and 3).

There was no change in the distribution pattern of cases of MBC in the time periods analyzed here concerning histological grade, locoregional staging, the presence of symptoms at diagnosis, or the type of oncological treatment given. Between 2004 and 2011, there was a decrease in the number of luminal-HER2-positive cases and a reduction in the percentage of patients using the private healthcare system compared to the 1995-2003 period (Table 4). There was a reduction in the APC in women over 70 years of age (APC: -4.8; -9.3--0.1; p<0.001); however, there was no statistically significant difference for any of the other age groups. There were no statistically significant differences in the AAPC as a function of the age group (Figure 2).

#### DISCUSSION

This population-based study describes the profile of MBC in the city of Goiânia, Brazil. Around 5.0% of breast cancer cases were metastatic at diagnosis, a finding that is similar to that of other hospital-based studies conducted both in Brazil<sup>3,31</sup> and in countries with population-based mammography screening, including the United States, Denmark, and the Netherlands<sup>2,6,7,32</sup>. Therefore, genetic factors or exposure to risks may have made these women more susceptible to diagnosis at an advanced stage, not being detected through the screening policy adopted in Brazil<sup>5</sup>. Nevertheless, it was impossible to establish whether these women had undergone mammography screening. Likewise,

Toble in Sociodeniographic and enheat end deteriorites of Err women metabled ele breast editer between 1995 and Evri	Table	<ol> <li>Sociode</li> </ol>	emograpl	hic and	clinical	charact	eristics of	277	' women with	n metastatic	breast cancer	between	1995 and	2011.
--	-------	-----------------------------	----------	---------	----------	---------	-------------	-----	--------------	--------------	---------------	---------	----------	-------

Characteristics	Cases (n)	%	Characteristics	Cases (n)	%			
Age at diagnosis (years)			Total n*	89	100.0			
≤49	103	37.2	Estrogen receptor status					
50–59	75	27.1	Positive	53	67.1			
≥60	99	35.7	Negative	26	32.9			
Total n*	277	100.0	Total n*	79	100.0			
Skin color/ethnicity			Progesterone receptor status					
White	98	55.4	Positive	42	55.3			
Brown	69	39.0	Negative	34	44.7			
Black	5	2.8	Total n*	76	100.0			
Others	5	2.8	C-erb-B status	1				
Total n*	177	100.0	Positive	24	33.8			
Age at menarche (years)			Negative	47	66.2			
<11	10	21.8	Total n*	71	100.0			
12–13	18	39.1	Tumor phenotype					
>13	18	39.1	Luminal	34	47.9			
Total n*	46	100.0	Luminal-HER2	16	22.5			
Family history		·	Pure HER2	8	11.3			
Breast cancer, first-degree relatives	9	13.7	Triple-negative	13	18.3			
Breast cancer, second-degree relatives	6	9.1	Total n*	71	100.0			
Ovarian cancer, first-degree relatives	3	4.5	Staging (T)					
None	48	72.7	то	3	2.3			
Total n*	66	100.0	T1	12	9.3			
Presence of symptoms			Т2	22	17.1			
Yes	103	81.8	Т3	25	19.4			
No	23	18.2	T4	67	51.9			
Total n*	126	100.0	Total n*	129	100.0			
Histological type			Staging (N)					
Carcinoma, not otherwise specified	19	14.0	NO	31	25.2			
Ductal carcinoma	107	78.6	N1	40	32.5			
Lobular carcinoma	6	4.4	N2	37	30.1			
Sarcoma and others	4	3.0	N3	15	12.2			
Total n*	136	100.0	Total n*	123	100.0			
Histological grade			Type of healthcare					
G1	11	12.3	Public	90	70.3			
G2	51	57.3	Private	38	29.7			
G3	27	30.4	Total n*	128	100.0			

\*The number of individuals for whom data were available.

a more in-depth analysis of the respective risk factors could not be performed.

Over the 17-year period analyzed (1995–2011), no trend was found towards any changes in the incidence of MBC. This finding showed that the opportunistic screening carried out in the city of Goiânia has not been successful in reducing the incidence of advanced breast cancer. This fact is even more evident when comparing data with those of other Brazilian populations, for example, comparing data from the Goiânia population-based cancer registry with data from the city of Barretos and surrounding region where there is population-based mammography screening<sup>33</sup>. In the area covered by screening, there were significantly **Table 2.** Anatomical site of metastasis and treatment given to women with metastatic breast cancer at diagnosis in Goiânia, Brazil (n=277).

	Cases (n)	%					
Number of metastatic sites*							
1	88	68.2					
2	31	24.0					
≥3	10	7.8					
Total n†	129	100.0					
Site of metastasis							
Bone	36	27.9					
Visceral	41	31.8					
Visceral+bone	24	18.6					
Central nervous system	11	8.5					
Skin, subcutaneous tissue cells or distant lymph nodes	17	13.2					
Total n <sup>†</sup>	129	100.0					
First-line systemic treatment							
Chemotherapy (≥2 drugs)	94	86.2					
Chemotherapy (1 drug)	6	5.5					
Endocrine therapy	9	8.3					
Total n <sup>†</sup>	109	100.0					
Surgery for resection of the primary tumo	7						
Yes	50	40.6					
No	73	59.4					
Total n <sup>†</sup>	123	100.0					
Surgery for resection of metastases							
Yes	10	9.2					
No	98	90.8					
Total n <sup>†</sup>	108	100.0					

\*At the time of initial diagnosis; <sup>†</sup>Number of individuals for whom data were available.

fewer cases detected at stage III compared to Goiânia. However, for cases with a metastatic disease already at diagnosis, the incidence was similar<sup>33</sup>.

The subsample analyzed revealed a predominance of large tumors at diagnosis, with skin involvement and clinically compromised lymph nodes, reflecting difficulty to access disease diagnosis. This fact could probably be explained by the predominance of users of the public healthcare system in this study, since there are limitations to access within this system that are not found in the private healthcare system<sup>17,34,35</sup>. Nevertheless, the other clinical and demographic characteristics of the sample analyzed here were similar to those of the population with non-metastatic disease<sup>36</sup>.

Palliative endocrine therapy is the systemic treatment of choice for women with metastatic disease and hormone-positive

tumors in the absence of visceral crisis<sup>8,15,25</sup>. In itself, this is a more accessible and less expensive treatment than chemotherapy, a fact that is particularly important bearing in mind the progressive increase in the costs of cancer treatment<sup>9</sup>. In addition, endocrine therapy is associated with lower rates of adverse events and better quality of life, with no negative effect on progression-free survival or overall survival<sup>37,38</sup>. Therefore, the underutilization of endocrine therapy found in this study may reflect an inappropriate approach to treatment according to current recommendations and even according to the standard clinical practice within the time period studied<sup>8,15,37</sup>.

In the subgroup of women with HER2-positive tumors, the small number of patients who received anti-HER2 therapy is note-worthy. This finding could be explained by the predominance of patients receiving care within the public healthcare system where trastuzumab only became available for the treatment of meta-static HER2-positive breast cancer in 2017<sup>34,39</sup>. In years to come, with increased access to targeted therapy, a reduction should be seen in the rates of chemotherapy alone, with the introduction of CDK 4/6 inhibitors and anti-HER therapy<sup>8,14</sup>.

Data on the extent and the site of the metastatic lesions are crucial for planning treatment and evaluating individual prognosis<sup>12,40</sup>. In this study, despite the predominance of lesions at a single anatomical site, there was a high prevalence of visceral lesions and symptomatic disease at diagnosis. These data may partially explain the choice of chemotherapy as a first-line systemic treatment, even in cases of luminal tumors<sup>8,25</sup>.

Subjecting women with metastatic disease to breast surgery remains controversial and is usually reserved for selected cases<sup>8,41,42</sup>. However, scientific evidence at the time evaluated by this study was limited to retrospective, non-controlled studies showing better overall survival in patients subjected to breast surgery<sup>41</sup>. In this study, around 40% of the patients had been subjected to some type of breast surgery, a finding that could also be explained by the better local control that was achieved<sup>42</sup>. A population-based study conducted in the United States also found a similar rate of breast surgery in this population<sup>43</sup>. However, in the context of public health in low- and medium-income countries, the possibility of inadequate systemic staging at diagnosis and confirmation of the metastatic disease in the first months following breast surgery deserves special emphasis<sup>8,35,44</sup>.

The temporal analysis performed in this study failed to reveal any significant changes in the clinical characteristics or in the treatment provided despite the advances in diagnosis and treatment that have occurred in recent years<sup>8</sup>. This fact is probably due to the predominance of users of the public healthcare system in this study population. Nevertheless, a hospital-based study conducted in São Paulo included metastatic patients who received similar cancer treatment irrespective of whether they were clients of the private or public healthcare sector. In that series too, no statistically significant changes were found in the
	Systemic treatment	t Anthracycli	nes	Taxa	nes	Ta	amoxifen	Aromatase inhibitors
	Tumor subtype	n (%)		n ( <sup>4</sup>	%)		n (%)	n (%)
First- line	HR(+)/HER2(-) (n=34)*	25 (73.5)		16 (4	7.0)	3 (8.8)		3 (8.8)
	HR(+)/HER2(+) (n=9)*	7 (77.8)		4 (44	1.4)		-	1 (11.1)
	HR(-)/HER2(+) (n=7)*	7 (100.0)		4 (5	7.1)	-		-
	HR(-)/HER2(-) (n=11)*	10 (90.9)	10 (90.9)		7 (63.6)		-	-
<b>2</b> nd	HR(+)/HER2(-) (n=29)*	3 (10.3)		1 (3.4)		12 (41.4)		5 (17.2)
	HR(+)/HER2(+) (n=6)*	1 (16.6)		1 (16.6)		2 (33.3)		-
line	HR(-)/HER2(+) (n=4)*	-		-		-		-
	HR(-)/HER2(-) (n=5)*	-		-			-	-
	CMF	Platinum-based	Сар	ecitabine	Gemcital	bine	Vinorelbine	Trastuzumab
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)
	1 (3.0)	-		-				-
First-	1 (11.1)	-		-				1 (11.1)
line	-	1 (14.3)		-				2 (28.5)
	1 (9.1)	-		-				-
	-	4 (13.8)	3	(10.3)	4 (13.8	3)	1 (3.4)	-
2 <sup>nd</sup>	-	1 (16.6)	1	(16.6)	1 (16.6	5)	-	1 (16.6)
line	-	2 (50.0)	1	(25.0)	2 (50.0	))	1 (25.0)	1 (25.0)
	-	4 (80.0)	1	(20.0)	0.0) 3 (60.0		1 (20.0)	-

**Table 3.** Description of the systemic treatment given as first- or second-line treatment according to the immunohistochemical characterization of tumor subtype.

\*Total number of individuals for whom data were available for the respective line of systemic treatment. Each patient could have received more than one drug per line of treatment. CMF: Cyclophosphamide, methotrexate, 5-fluorouracil; HR: hormone receptor.

frequency distribution of the treatments carried out between 2000 and 2012<sup>45</sup>. Taken together, these data may reflect the progress of breast cancer treatment in the period, with a qualitative improvement in treatments already in use rather than the implementation of new treatment modalities.

Over the 17 years of analysis, a statistically significant alteration was found in only two variables. The reduction in the luminal-HER2 cases identified in immunohistochemistry is due to the small sample size. On the other hand, the increase in the proportion of public healthcare system users probably reflects the local socio-economic conditions<sup>17,35</sup>. Nevertheless, despite the difficulties of the Brazilian healthcare model<sup>10,16,34</sup>, the data found in this series are in agreement with international population samples and reinforce the concept of cancer treatment globalization<sup>11-14,16</sup>.

Limitations of this study include data missing from the population-based cancer registry database and from the medical records. These limitations are inherent to retrospective studies and do not affect the credibility or relevance of the results obtained<sup>46</sup>. The intersection of the population-based data made it possible to increase the robustness of this study by adding information on clinical, pathological, and treatment variables in patients with MBC. In theory, this real-world study, conducted in a city located in Brazil's Midwest, may reflect several other populations in low- and middle-income countries.

### **CONCLUSIONS**

Around 5% of the women with breast cancer in Goiânia between 1995 and 2011 had MBC, of which the most common subtype was luminal breast cancer. There was no change in the incidence trends over the 17 years of the study. Almost 90% of the patients received chemotherapy as first-line treatment and, of the patients with hormone receptor-positive tumors, only 14% received endocrine therapy as first-line treatment. The use of anti-HER2 treatment was also remarkably low. Therefore, further studies are required to identify the biomarkers that could anticipate the diagnosis of

	1995–200	)3 (n=129)	2004–201	1 (n=148)	Absolute	95%CL(%)	p-value†	
	Cases (n)	%	Cases (n)	%	difference (%)	55 /0CT (70)	p value	
Age at diagnosis (year:	s)							
≤49	50	38.8	53	35.8	3.0	-8.2 to 14.2	0.6	
50-59	37	28.7	38	25.7	3.0	-7.4 to 13.4	0.5	
≥60	42	32.5	57	38.5	6.0	-5.3 to 16.9	0.2	
Total n*	129	100.0	148	100.0				
Presence of symptoms	5							
Yes	40	75.5	63	86.3	10.8	-2.85 to 25.19	0.1	
No	13	24.5	10	13.7	+	+	+	
Total n*	53	100.0	73	100.0				
Histological grade								
G1/G2	31	72.1	31	67.4	4.7	-14.18 to 22.94	0.6	
G3	12	27.9	15	32.6	+	+	+	
Total n*	43	100.0	46	100.0				
Tumor phenotype								
Luminal	10	41.6	24	51.1	9.5	-14.41 to 31.45	0.4	
Luminal-HER2	9	37.5	7	14.9	22.6	1.85 to 43.76	0.03	
Pure HER2	2	8.4	6	12.7	4.3	-14.49 to 18.09	0.5	
Triple-negative	3	12.5	10	21.3	8.8	-11.91 to 24.68	0.3	
Total n*	24	100.0	47	100.0				
Staging (T)								
T0-2	19	31.7	18	26.1	5.6	-9.83 to 21	0.4	
Т3-4	41	68.3	51	73.9	+	+	+	
Total n*	60	100.0	69	100.0				
Staging (N)								
N0	19	32.8	12	18.5	14.3	-1.1 to 29.19	0.06	
N1	19	32.8	21	32.3	0.5	-15.62 to 16.82	0.9	
N2-3	20	34.4	32	49.2	14.8	-2.62 to 30.91	0.09	
Total n*	58	100.0	65	100.0				
Access to treatment								
Public healthcare	32	60.4	58	77.3	16.9	0.82 to 32.54	0.04	
Private healthcare	21	39.6	17	22.7	+	+	+	
Total n*	53	100.0	75	100.0				
First-line systemic trea	itment							
Chemotherapy (≥2 drugs)	41	89.1	53	84.2	4.9	-9.14 to 17.44	0.4	
Chemotherapy (1 drug)	1	2.2	5	7.9	5.7	-4.51 to 15.2	0.1	
Endocrine therapy	4	8.7	5	7.9	0.8	-9.91 to 13.26	0.8	
Total n*	46	100.0	63	100.0				
Surgery for primary tu	mor							
Yes	22	44.0	28	38.3	5.7	-11.52 to 22.84	0.5	
No	28	56.0	45	61.7	+	ŧ	+	
Total n*	50	100.0	73	100.0				
Surgery for metastasis	5				`			
Yes	2	4.5	8	12.5	8.0	-4.17 to 18.78	0.1	
No	42	95.5	56	87.5	+	ŧ	+	
Total n*	44	100.0	64	100.0				

Table 4. Temporal distribution of clinical and therapeutic variables in the 1995–2003 and 2004–2011 periods in women with metastatic breast cancer at diagnosis in the city of Goiânia, Brazil.

\*Number of individuals for whom data were available for each variable. <sup>†</sup>Chi-square test. <sup>‡</sup>For the dichotomous variables, the same proportion of difference and the same significance level values were maintained.



**Figure 2.** Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, by age group.

breast cancer before it becomes metastatic. Finally, appropriate health policies need to be implemented to ensure the availability of new agents for use in systemic rescue therapy, including anti-HER2 agents and cyclin-dependent kinase inhibitors.

# **AUTHORS' CONTRIBUTION**

LRS: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. RDN: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – review & editing. JCO: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. MPC: Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

#### REFERENCES

- Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52. https://doi.org/10.1038/35021093
- Hou L, Qiu M, Chen M, Li F, Li J, Deng S, et al. The association between molecular type and prognosis of patients with stage IV breast cancer: an observational study based on SEER database. Gland Surg. 2021;10(6):1889-98. https://doi.org/10.21037/gs-21-32
- Andrade ACM, Ferreira Júnior CA, Guimarães BD, Barros AWP, Almeida GS, Weller M. Molecular breast cancer subtypes and therapies in a public hospital of northeastern Brazil. BMC Womens Health. 2014;14:110. https://doi.org/10.1186/1472-6874-14-110
- Freitas Junior R, Nunes RD, Martins E, Curado MP, Freitas NMA, Soares LR, et al. Prognostic factors and overall survival of breast cancer in the city of Goiania, Brazil: a populationbased study. Rev Col Bras Cir. 2017;44(5):435-43. https://doi. org/10.1590/0100-69912017005003
- Dos-Santos-Silva I, De Stavola BL, Renna Junior NL, Nogueira MC, Aquino EML, Bustamante-Teixeira MT, et al. Ethnoracial and social trends in breast cancer staging at diagnosis in Brazil, 2001-14: a case only analysis. Lancet Glob Health. 2019;7(6):e784-e797. https://doi.org/10.1016/S2214-109X(19)30151-2

- Jørgensen KJ, Gøtzsche PC, Kalager M, Zahl PH. Breast cancer screening in Denmark: a cohort study of tumor size and overdiagnosis. Ann Intern Med. 2017;166(5):313-23. https://doi. org/10.7326/M16-0270
- National Cancer Institute. Surveillance Epidemiology and End Results Program. Cancer stat facts: female breast cancer. Bethesda: National Cancer Institute, 2019. [cited on 2022 Jun 23]. Available from: https://seer.cancer.gov/statfacts/html/breast.html.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Washington: NCCN; 2022.2. [cited on 2022 Feb 30]. Available from: https:// www.nccn.org/professionals/physician\_gls/pdf/breast.pdf
- Dvortsin E, Gout-Zwart J, Eijssen ELM, van Brussel J, Postma MJ. Comparative cost-effectiveness of drugs in early versus late stages of cancer; review of the literature and a case study in breast cancer. PLoS One. 2016;11(1):e0146551. https://doi. org/10.1371/journal.pone.0146551
- Soares LR, Freitas-Junior R, Curado MP, Paulinelli RR, Martins E, Oliveira JC. Low overall survival in women with de novo metastatic breast cancer: does this reflect tumor biology or a lack of access to health care? JCO Glob Oncol. 2020;6:679-87. https://doi.org/10.1200/JGO.19.00408

- den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK, Lohrisch CA. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat. 2017;161(3):549-56. https://doi.org/10.1007/s10549-016-4080-9
- 12. Rogoz B, de l'Aulnoit AH, Duhamel A, de l'Aulnoit DH. Thirtyyear trends of survival and time-varying effects of prognostic factors in patients with metastatic breast cancer-a single institution experience. Clin Breast Cancer. 2018;18(3):246-53. https://doi.org/10.1016/j.clbc.2017.08.012
- 13. De Placido S, Giuliano M, Schettini F, Von Arx C, Buono G, Riccardi F, et al. Human epidermal growth factor receptor 2 dual blockade with trastuzumab and pertuzumab in real life: Italian clinical practice versus the CLEOPATRA trial results. Breast. 2018;38:86-91. https://doi.org/10.1016/j. breast.2017.12.012
- 14. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al; ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95. https://doi. org/10.1016/j.annonc.2021.09.019
- 15. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-49. https://doi.org/10.1016/j. annonc.2020.09.010
- Renna Junior NL, Silva GA. Late-stage diagnosis of breast cancer in Brazil: analysis of data from hospital-based cancer registries (2000-2012). Rev Bras Ginecol Obstet. 2018;40(3):127-36. https://doi.org/10.1055/s-0038-1624580
- Barrios CH, Uema D, Cronenberger E, Lima V, Bines J, de Sant'ana RO, et al. Real World data and patterns of care of metastatic breast cancer (MBC) in Brazil: first results of LACOG 0312 retrospective study [abstract]. Cancer Res. 2017;77(Suppl. 4):P6-16-04. https://doi.org/10.1158/1538-7445. SABCS16-P6-16-04
- Renna Junior NL, Lima CA, Laporte CA, Coleman MP, Silva GA. Ethnic, racial and socioeconomic disparities in breast cancer survival in two Brazilian capitals between 1996 and 2012. Cancer Epidemiol. 2021;75:102048. https://doi.org/10.1016/j. canep.2021.102048
- Moura L, Curado MP, Simões EJ, Cezário AC, Urdaneta M. Avaliação do registro de câncer de base populacional do município de Goiânia, estado de Goiás, Brasil. Epidemiol Serv Saúde. 2006;15(4):7-17. https://doi.org/10.5123/S1679-49742006000400002
- 20. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. International classification of diseases for oncology. 3<sup>rd</sup> ed. Geneva: World Health Organization; 2000. [cited on 2022 Jun 22]. Available from: https://apps.who. int/iris/bitstream/handle/10665/42344/9241545348\_eng. pdf?sequence=1&isAllowed=y
- 21. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. International classification of diseases for oncology. First revision. 3<sup>rd</sup> ed. Geneva: World Health Organization; 2013. [cited on 2022 Jun 22]. Available from: https://apps.who. int/iris/bitstream/handle/10665/96612/9789241548496\_eng. pdf?sequence=1&isAllowed=y

- 22. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer. 1957;11(3):359-77. https://doi. org/10.1038/bjc.1957.43
- 23. Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA, Rugo HS, et al. Breast. In: Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8<sup>th</sup> ed. New York: Springer International Publishing; 2016. p. 589-636.
- 24. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 2018;25(7):1783-5. https://doi.org/10.1245/s10434-018-6486-6
- 25. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol. 2021;32(10):1216-35. https://doi.org/10.1016/j.annonc.2021.06.023.
- 26. Boniol M, Heanue M. Age-standardisation and denominators. In: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al., eds. Cancer Incidence in Five Continents, Vol. IX. Lyon: IARC; 2009. p. 99-101.
- Instituto Brasileiro de Geografia e Estatística. Diretoria e Pesquisa. Departamento de População e Indicadores Sociais. [cited on 2019 Mar 9]. Available from: https://www.ibge.gov.br/ estatisticas-novoportal/sociais/populacao.html
- 28. Segi M. Cancer mortality for selected sites in 24 countries (1950-57). Sendai: Tohoku University of Medicine; 1960.
- 29. Boyle P, Parkin DM. Cancer registration: principles and methods. Statistical methods for registries. IARC Sci Publ. 1991;(95):126-58. PMID: 1894318
- 30. National Cancer Institute. Division of Cancer Control & Population Sciences. Surveillance Research Program. Jointpoint trend analysus software. Joinpoint regression program. version 4.7.0.0. Bethesda [Internet]; 2019. [cited on 2019 Mar 4]. Available from: http://surveillance.cancer.gov/ joinpoint/
- 31. Liedke PER, Finkelstein DM, Szymonifka J, Barrios CH, Chavarri-Guerra Y, Bines J, et al. Outcomes of breast cancer in Brazil related to health care coverage: a retrospective cohort study. Cancer Epidemiol Biomarkers Prev. 2014;23(1):126-33. https://doi.org/10.1158/1055-9965.EPI-13-0693
- 32. Autier P, Boniol M, Koechlin A, Pizot C, Boniol M. Effectiveness of and overdiagnosis from mammography screening in the Netherlands: population based study. BMJ. 2017;359:j5224. https://doi.org/10.1136/bmj.j5224
- 33. Costa AM, Hashim D, Fregnani JHTG, Weiderpass E. Overall survival and time trends in breast and cervical cancer incidence and mortality in the Regional Health District (RHD) of Barretos, São Paulo, Brazil. BMC Cancer. 2018;18(1):1079. https://doi.org/10.1186/s12885-018-4956-7
- 34. Barrios CH, Reinert T, Werutsky G. Access to high-cost drugs for advanced breast cancer in Latin America, particularly trastuzumab. Ecancermedicalscience. 2019;13:898. https:// doi.org/10.3332/ecancer.2019.898

- 35. Rosa DD, Bines J, Werutsky G, Barrios CH, Cronemberger E, Queiroz GS, et al. The impact of sociodemographic factors and health insurance coverage in the diagnosis and clinicopathological characteristics of breast cancer in Brazil: AMAZONA III study (GBECAM 0115). Breast Cancer Res Treat. 2020;183(3):749-57. https://doi.org/10.1007/s10549-020-05831-y
- 36. Simon SD, Bines J, Werutsky G, Nunes JS, Pacheco FC, Segalla JG, et al. Characteristics and prognosis of stage I-III breast cancer subtypes in Brazil: the AMAZONA retrospective cohort study. Breast. 2019;44:113-9. https://doi.org/10.1016/j. breast.2019.01.008
- 37. Tian Q, Gao H, Zhou Y, Yang J. Overall survival and progression-free survival with cyclin-dependent kinase 4/6 inhibitors plus endocrine therapy in breast cancer: an updated meta-analysis of randomized controlled trials. Eur Rev Med Pharmacol Sci. 2021;25(23):7252-67. https://doi.org/10.26355/ eurrev\_202112\_27418
- 38. Werutsky G, Reinert T, Rosa ML, Barrios CH. Real-world data on first-line systemic therapy for hormone receptor-positive HER2-negative metastatic breast cancer: a trend shift in the Era of CDK 4/6 inhibitors. Clin Breast Cancer. 2021;21(6):e688-e692. https://doi.org/10.1016/j.clbc.2021.04.003
- 39. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Portaria nº 29, de 2 de agosto de 2017. Torna pública a decisão de incorporar o trastuzumabe para o tratamento do câncer de mama HER2-positivo metastático em primeira linha de tratamento, conforme Protocolo Clínico e Diretrizes Terapêuticas do Ministério da Saúde, no âmbito do Sistema Único de Saúde - SUS. Diário Oficial da União. Brasília, 3 de agosto de 2017. Seção 1, pag. 114. [Internet]. [cited on 2022 Jun 23]. Available from: https://www.jusbrasil.com.br/ diarios/155554002/dou-secao-1-03-08-2017-pg-114

- 40. Zeichner SB, Ambros T, Zaravinos J, Montero AJ, Mahtani RL, Ahn ER, et al. Defining the survival benchmark for breast cancer patients with systemic relapse. Breast Cancer (Auckl). 2015;9:9-17. https://doi.org/10.4137/BCBCR.S23794
- 41. Xiao W, Zou Y, Zheng S, Hu X, Liu P, Xie X, et al. Primary tumor resection in stage IV breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2018;44(10):1504-12. https:// doi.org/10.1016/j.ejso.2018.08.002
- 42. Tosello G, Torloni MR, Mota BS, Neeman T, Riera R. Breast surgery for metastatic breast cancer. Cochrane Database Syst Rev. 2018;3(3):CD011276. https://doi.org/10.1002/14651858. CD011276.pub2
- 43. Lane WO, Thomas SM, Blitzblau RC, Plichta JK, Rosenberger LH, Fayanju OM, et al. Surgical resection of the primary tumor in women with de novo stage IV breast cancer: contemporary practice patterns and survival analysis. Ann Surg. 2019;269(3):537-44. https://doi.org/10.1097/ SLA.00000000002621
- 44. Soares LR, Curado MP, Freitas-Junior R. Breast cancer staging in population-based registries: an alert to the quality of information. Mastology 2021;31:e20200067. https://doi. org/10.29289/2594539420200067
- 45. Makdissi FB, Leite FPM, Peres SV, Silva DRM, Oliveira MM, Lopez RVM, et al. Breast cancer survival in a Brazilian cancer center: a cohort study of 5,095 patients. Mastology. 2019;29(1):37-46. https://doi.org/10.29289/25945394201900 00437
- 46. Oliveira PPV, Silva GA, Curado MP, Malta DC, Moura L. Reliability of cancer as the underlying cause of death according to the Mortality Information System and Population-Based Cancer Registry in Goiânia, Goiás State, Brazil. Cad Saude Publica. 2014;30(2):296-304. https://doi.org/10.1590/0102-311X00024813



#### ORIGINAL ARTICLE https://doi.org/10.29289/2594539420210066

# Repercussions of the COVID-19 pandemic on breast cancer treatment in a referral hospital in Santos-SP, Brazil

Emily Brenda de Lima Sousa<sup>1</sup> <sup>(D)</sup>, Marina Antunes Kasa<sup>1</sup> <sup>(D)</sup>, Rafaela Cristina Trigueiro Rosado<sup>1</sup> <sup>(D)</sup>, Tatiana Carvalho Marques<sup>1</sup> <sup>(D)</sup>, Marina Filié Haddad Piccinalli<sup>1\*</sup> <sup>(D)</sup>

# ABSTRACT

Objective: Considering that breast cancer has the fifth highest mortality rate in the world, this study aims to evaluate the repercussions of the COVID-19 pandemic on the treatment, both surgical and systemic, of patients with cancer in general and those with breast cancer at Hospital Guilherme Álvaro (Santos, Brazil), between March 1st, 2019 and February 28, 2021. Methods: For this purpose, data were collected from both the hospital's surgery record book and electronic medical records of patients who were followed up in the Mastology and Oncology sectors at Hospital Guilherme Álvaro. This information was tabulated, estimating the total number of surgeries, whether: benign elective surgeries, diagnostic surgeries, surgeries of cancer in general, surgeries exclusive to mastology, of cancer in mastology, benign surgery in mastology, and plastic reconstructive surgery. The percentage ratio between these numbers was calculated. Results: A 49% reduction in total surgeries was observed, comparing the period prior to the pandemic (2019–2020) with the pandemic period (2020–2021), with a decrease of 24.6% in the number of general cancer surgeries except for mastology, and 19.6% of surgeries exclusive to mastology. In other words, there was a total reduction of 22.9% in all oncological surgeries. Moreover, there was a decrease of 11.5% in the total number of patients treated with chemotherapy. In 2020, of the 214 new cases, 116 (54.2%) were mastology patients, being 45.8% of other oncology clinics. Conclusion: Thus, it is concluded that the reduction in the number of aesthetic, benign, and reconstructive surgeries was expected, as observed in the decrease in the number of chemotherapies, which could be due to a limitation on medical appointments. The number of diagnostic surgeries remained stable, which could lead to positive outcomes for oncology patients. It is not possible to predict the next repercussions of the COVID-19 pandemic on breast cancer treatment while the pandemic endures, requiring more studies on this topic.

KEYWORDS: COVID-19; breast neoplasms; neoadjuvant therapy.

# **INTRODUCTION**

Breast cancer is the fifth with the highest mortality rate worldwide and has a high incidence among young women in Brazil<sup>1,2</sup>. Recently, it became the most diagnosed type of cancer, surpassing lung cancer<sup>1</sup>. Its early diagnosis, in addition to advances in treatment, has shown better results and greater survival for patients<sup>3</sup>. However, in December 2019, a new disease called COVID-19, caused by the SARS-CoV-2 virus, was detected in Wuhan, China. A pandemic was declared by the World Health Organization (WHO) in March 2020. Faced with this new situation, breast cancer screening and treatment were hampered  $^{4,5}$ .

Although breast surgery is of great importance in the treatment, as it aims to remove the entire tumor with free margins, neoadjuvant chemotherapy (NC) has gained prominence during the pandemic, and there is a decrease in the probability of recurrence and increase in the survival of patients who undergo this procedure<sup>6.7</sup>. The purpose of NC is to reduce mass in locallyadvanced tumors and to allow the use of efficient surgical and radiotherapy treatments<sup>7</sup>.

<sup>1</sup>Centro Universitário Lusíada – Santos (SP), Brazil. \*Corresponding author: amarinahaddad@hotmail.com Conflict of interests: nothing to declare. Funding: none. Received on: 01/13/2022. Accepted on: 02/24/2022. Until recently, the indication for NC was based on inoperable T3-T4/N2-N3 tumors (inflammatory breast cancer; inoperable tumor due to invasion of the skin or thoracic structures; clinically coalesced and/or fixed axillary lymph nodes; lymph node metastases beyond the axillary chain) or operable tumors in need of reduction to perform conservative surgery (tumor greater than 5 cm or between 2 and 5 cm with an unfavorable tumor/breast ratio for conservative surgery)<sup>689</sup>.

However, after the beginning of the pandemic, the recommendation for breast cancer treatment has changed. For new cases diagnosed after this period, it has been recommended to start systemic treatment with neoadjuvant endocrine therapy or neoadjuvant chemotherapy with anti-HER2 blockade, if the disease was positive for HER2<sup>10</sup>. As HER2 and triple negative tumors are more aggressive molecular subtypes, there are discussions for starting the treatment with chemotherapy and target therapy (HER2 subtype) before surgery in tumors larger than 1 cm, whereas in tumors smaller than 1 cm, surgery should not be postponed<sup>11</sup>. In addition, this should be considered in three situations: if the disease progresses during NC; if it is a malignant phyllodes tumor; or breast sarcoma<sup>10</sup>. It should be noted that, according to a systematic literature review and meta-analysis published in July 2021, the ideal time to perform breast surgery after the completion of the NC is four to eight weeks<sup>12</sup>.

Both the chemotherapy and radiotherapy used in the treatment and the cancer itself have immunosuppressive effects, making cancer patients vulnerable to infections<sup>13</sup>. Therefore, the recommendations for such patients also include limiting their exposure to SARS-CoV-2, encouraging telemedicine appointments whenever possible and restricting visits to wards with immunocompromised patients<sup>4,13</sup>.

Another important measure implemented to contain the advance of the new coronavirus was to consider many of the breast cancer treatment surgeries as elective<sup>8</sup>. Nevertheless, the choice to postpone such therapy is only possible when the patient is not at risk of life, or when it is possible to use less invasive methods such as chemotherapy and radiotherapy<sup>14</sup>. Thus, as in other services, the Mastology Department of Hospital Guilherme Álvaro, located in Santos (state of São Paulo, Brazil), expanded the indications for neoadjuvant care, restricted surgeries, and maintained outpatient care only for emergencies<sup>15</sup>.

Even though it is proven that these noninvasive methods can delay definitive surgical treatment for a period of time, the duration of restrictive measures during the pandemic remains indetermined<sup>14</sup>. The impact of postponing tumor resection and the administration of invasive therapies for an extended period of time on the outcome and survival of these patients is still uncertain<sup>13</sup>. Furthermore, in this context, the impact that cancer illness has on the physical and mental health of patients can have psychological effects such as anxiety, depression, anguish, and acute stress<sup>16</sup>. This situation, in addition to the fear of infection with the new coronavirus or the waste of health resources, would favor the reduction of diagnoses and the quality of cancer treatment<sup>16</sup>.

Hence, this study aims to assess the repercussion of the COVID-19 pandemic on the number of elective and oncological surgeries and chemotherapy treatments performed at Hospital Guilherme Álvaro, a major oncology reference center in Baixada Santista, state of São Paulo, Brazil.

#### **METHODS**

This is a cross-sectional and retrospective study, based on surgeries performed at Hospital Guilherme Álvaro, a public tertiary hospital located in the city of Santos, Brazil, from March 1<sup>st</sup>, 2019 to February 28, 2021. Data were obtained from the hospital's surgery record book, whose content was based on information such as date of surgery, patient's name, age, anesthetic risk, underlying pathology, surgical procedure, type of anesthesia, name of anesthesiologist, name of surgery resident, name of surgeon, time of the surgery, and destination of the patient after the surgical procedure; and electronic medical records of patients who were followed up in the Mastology and Oncology Departments of the institution.

These data were transcribed into a table on the computer, using the Microsoft Excel Office 2016 program, and the statistical analysis was later performed in the same program.

The analyzed variables were: benign elective surgeries, diagnostic surgeries, general cancer surgeries, and surgeries exclusive to mastology. In the latter group, it was observed which surgeries were related to breast cancer and whether adjuvant or neoadjuvant chemotherapy were administered.

Among the inclusion criteria, it is worth highlighting patients treated by the mastology team during the period stipulated by the research; patients treated by the surgical team of Hospital Guilherme Álvaro during the same period; and patients with breast diseases treated by the Oncology Clinics of *Rede Hebe Camargo de Combate ao Câncer* [Hebe Camargo Network for Combating Cancer], at Hospital Guilherme Álvaro. Patients whose data in the medical records were incomplete for the study, or patients treated outside the stipulated period, were not evaluated.

Data were monthly tabulated, estimating the total number of surgeries, as well as how many of them were benign, diagnostic, of cancer in general, exclusive to mastology, of cancer in mastology, benign surgeries in mastology, and plastic reconstructive. In addition, it was verified how many patients underwent chemotherapy, considering the patients who were already being treated prior to the pandemic and the new cases that emerged during that period. The percentage ratio between these numbers was estimated and the Z-test, a null hypothesis statistical calculation based on the Z statistics, was applied, which establishes whether the difference between the sample mean and that of the population is large enough to be statistically significant.

The pre-pandemic period was considered to be that between March 1st, 2019 and February 28, 2020; and the pandemic period, as that between March 1st, 2020 and February 28, 2021.

This study was submitted and approved by the Research Ethics Committee of Hospital Guilherme Álvaro and Fundação Lusíada (UNILUS), approved by Plataforma Brasil (Certificate of Presentation for Ethical Consideration — CAAE: 51960121.6.0000.5436), and complied with the code of ethics of the 1964 Declaration of Helsinki and all its subsequent updates. Furthermore, the study has own funding and the authors have no conflicts of interest to declare.

### RESULTS

After data collection, tables were monthly compiled to obtain the results. During the analyzed period, from March 1<sup>st</sup>, 2019 to February 28, 2020, 3,118 general surgeries were performed; and from March 1<sup>st</sup>, 2020 to February 28, 2021, 1,591 general surgeries, totaling a sample of 4,709 (Table 1).

By analyzing the data on general surgery, an association with statistical significance can be observed in the number of surgeries performed for benign pathologies, cancer in general, and plastic reconstructive procedures when comparing the pre-pandemic period with the pandemic period (p<0.01). Meanwhile, with regard to surgeries performed by the mastology sector, there was an association with statistical significance for surgeries performed for breast cancer and breast reconstructions when correlating the pre-pandemic and the pandemic periods (p<0.01) (Table 1).

According to data obtained from the Hebe Camargo Network, the number of cases undergoing treatment and new cases of chemotherapy, before and during the pandemic, can be verified. However, it was not possible to establish an association with statistical significance between the obtained results (Table 2).

#### DISCUSSION

After the beginning of the COVID-19 pandemic, the recommendation for breast cancer treatment has changed. The new indication is based on initiating neoadjuvant systemic or endocrine therapy whenever possible, in addition to having medical appointments via telemedicine, thus restricting visits to wards with immunocompromised patients. Elective surgical treatment would only be indicated again if there was a decrease in infection rates for at least two consecutive weeks in the hospital region<sup>17</sup>. A problem faced by the patients treated at Hospital Guilherme Álvaro was the lack of structure for some of these changes such as the impossibility of arranging medical appointments via telemedicine.

Thus, a 49% reduction in total surgeries at the hospital was observed when comparing the pre-pandemic period (2019– 2020) with the pandemic period (2020–2021), with a 24.6% drop in the number of oncological surgeries except for mastology and 19.6% in the number of oncological surgeries in mastology. Therefore, there was a total reduction of 22.9% in all oncological surgeries. Likewise, a study conducted in England also observed a 16.4% decrease in the number of patients receiving

	55 5	1 1				
	Pre-pandemic	During the pandemic	Z-test Difference between		Confidence Interval	
	Surgery of	cancer in general	(p-value)	proportions	-95%	+95%
Total surgeries	3,118	1,591				
Benign	2,471 (79.25%)	1,143 (71.84%)	<0.01	7.41%	4.90	10.00
General diagnostic	131 (4.20%)	93 (5.85%)	0.01	-1.64%	-2.90	-0.40
Cancer in general	272 (8.72%)	205 (12.88%)	<0.01	-4.16%	-6.00	-2.30
Plastic reconstructive	24 (0.77%)	0 (0.00%)	<0.01	0.77%	0.30	1.20
	Ma	astology				
Cancer	138 (4.43%)	113 (7.10%)	<0.01	-2.68%	-4.00	-1.30
Benign	19 (0.61%)	4 (0.25%)	0.09	0.36%	-0.10	0.80
Diagnostic	35 (1.12%)	28 (1.76%)	0.07	-0.64%	-1.30	0.10
Reconstructive	19 (0.61%)	1 (0.06%)	<0.01	0.55%	0.20	0.90
Cancer + immediate reconstructive	5 (0.16%)	3 (0.19%)	0.8241	-0.03%	-0.30	0.20
Non-oncological aesthetic	4 (0.13%)	1 (0.06%)	0.5143	0.07%	-0.10	0.30

#### Table 1. Total number of general and mastology surgeries in periods prior to and during the pandemic.

Source: Prepared by the authors.

	Pre-pandemic	During the pandemic	Z-test	Difference	Confidence Interval	
	Chen	notherapy	(p-value)	between proportions	-95%	+95%
Undergoing treatment	3,719 (94.1%)	3,283 (94%)	0.8555	0.10%	-0.98	1.18
New cases	233 (5.9%)	214 (6%)	0.8555	-0.10%	-0.98	1.18

#### Table 2. Total number of chemotherapies in periods prior to and during the pandemic.

Source: Prepared by the authors.

treatment in the first half of 2020 after breast cancer diagnosis compared with 2019, and the authors expected an even greater reduction<sup>18</sup>. This scenario had repercussions on the treatment of cancer patients during the pandemic, mainly because cancer is a progressive chronic disease and, in its initial phase, it can be controlled or even cured by surgical treatment<sup>17</sup>.

When analyzing the surgeries performed by the mastology team of Hospital Guilherme Álvaro, there was a decrease in their absolute number during the pandemic period (31.8%). However, if only oncological surgeries are considered, there is an increase of 2.67% (p<0.01). This is probably due to the fact that surgeries performed for aesthetic and benign purposes are not being prioritized during the pandemic period, after considering their risks and benefits<sup>4</sup>.

Another relevant finding was the sharp decrease of 94.7% of reconstructive surgeries in the 2020–2021 period compared with 2019–2020, a decrease proportional to the number of total surgeries, 0.55% (p<0.01). As in Brazil, Walter et al. found, in a study conducted in the United States of America, that 19% of physicians reported the suspension of immediate breast reconstruction surgeries during the pandemic at their institutions<sup>19</sup>. This situation reflects the recommendations of medical entities and societies, which indicate the careful selection of patients eligible for surgical treatment during this pandemic period<sup>18</sup>.

Consequently, not performing this procedure can be harmful to patients, as it is proven that immediate reconstruction has benefits both in improving self-image and in the quality of life and mental health in the long term. Another advantage would be not to subject the patient to more than one procedure, given the anesthetic risks inherent in the surgical process itself<sup>20,21</sup>.

Furthermore, in a research conducted in Londrina (state of Paraná, Brazil), the authors observed that women diagnosed during the pandemic had lower emotional and physical scores when compared with previously diagnosed patients<sup>22</sup>. We must also consider the effects of the psychological factor on those who have had treatment suspended due to fear of the progression of the disease while awaiting a new date for their definitive treatment.

As the recommendation of health agencies was to perform neoadjuvant therapy to reduce tumor size and postpone surgery during the peak of the pandemic, an increase in the number of this procedure was expected<sup>7,15</sup>. Nevertheless, there was a decrease of 11.5% in the total number of patients treated with chemotherapy during the pandemic<sup>13,15</sup>. One factor that may have contributed to this finding is that, although the indications and protocols for NC are well-established in the literature, in Brazil there are some barriers, especially in the public sector, related to the delay in diagnosis, the difficulty of infrastructure, and the incorporation of medicines<sup>23</sup>. Nonetheless, as the data were not statistically significant (p=0.85), further studies are necessary for a reliable and accurate interpretation.

In 2020, of the 214 new cases, 116 (54.2%) were from mastology patients, whereas 45.8% were from other oncology clinics. This predominance of new mastology cases in the chemotherapy sector could constitute a good prognostic factor, considering that it would reduce the likelihood of recurrence of the disease and increase survival<sup>7</sup>. One of the limitations found for the analysis of this information was the fact that the Instituto Hebe Camargo did not divide chemotherapy data by sector, which began to be done in 2020. Thus, it became difficult to compare the number of breast cancer chemotherapies from the periods prior to and during the pandemic. In addition, medical records were unavailable and could not be computed.

In comparison, a study conducted at Hospital Central da Aeronáutica in Rio de Janeiro (state of Rio de Janeiro, Brazil) evaluated surgeries in mastology during the pandemic period compared with the pre-pandemic period. The authors verified a decrease in the number of surgeries in mastology (28.6%) and an increase in the indications for neoadjuvant care (133%) in the same period<sup>15,24</sup>. These results can be compared with our findings, as both studies showed a total decrease in the number of surgical interventions. While in the present study it was not possible to obtain statistically significant results with regard to neoadjuvant chemotherapy, the research carried out in Rio de Janeiro reached a result that confirms the hypothesis of a possible increase in the number of NC<sup>15,24</sup>.

In view of these results, we can assess that the reduction in the number of aesthetic, benign, and reconstructive (elective) surgeries was expected due to the orientation to patients to avoid unnecessary visits to the hospital, once the risks and benefits were analyzed. Nevertheless, we also observed a decrease in the number of chemotherapies, which may be due to the limitation of outpatient care. Meanwhile, the number of diagnostic surgeries remained stable and may bring positive results to the prognosis of cancer patients.

Another beneficial aspect is due to the fact that the Hospital Guilherme Álvaro maintained a number of breast cancer surgeries, during the pandemic period, similar to that of the analyzed pre-pandemic period. However, it is worth mentioning that at the end of March 2021 the elective surgeries at the institution were suspended, and only those deemed urgent and emergency cases were performed, in exceptional situations. This change can be explained by the fact that, so far, March was the month with the worst repercussions of the pandemic in the State of São Paulo, with a mortality of 9.1 thousand people until March  $23^{25}$ .

The psychological factor of patients who had treatment suspended and were unable to undergo reconstructive surgery must also be considered, as they remain anxious and afraid of the disease while waiting for a new date for their definitive treatment. Therefore, even though it is proven that these noninvasive methods can delay definitive surgical treatment for a period of time, the duration of restrictive measures during the pandemic remains indetermined<sup>14</sup>. The impact of postponing tumor resection and the administration of invasive therapies over an extended period of time on the outcome and survival of these patients is still uncertain, in such a way that further studies on this topic are necessary<sup>13</sup>.

# CONCLUSIONS

We verified a reduction in the number of aesthetic, benign, and reconstructive surgeries, as well as in the number of chemotherapies, which may be due to the limitation of outpatient care. Moreover, the number of diagnostic surgeries remained stable and may bring positive results to the prognosis of cancer patients. As long as the pandemic continues, it will not be possible to fully predict the next repercussions of COVID-19 on the treatment of breast cancer, which indicates the need for more long-term research on this topic.

## ACKNOWLEDGEMENTS

The authors would like to thank all the professionals who worked on the COVID-19 front line, directly or indirectly.

# **AUTHORS' CONTRIBUTION**

MAK, EBLS, TCM, RCTR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing — original draft, Writing — review & editing. MFHP: Data curation, Formal analysis, Investigation, Supervision, Writing — review & editing.

# REFERENCES

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https:// doi.org/10.3322/caac.21660
- 2. Orlandini LF, Antonio MVN, Espreafico CR, Bosquesi PL, Poli-Neto OB, Andrade JM, et al. Epidemiological Analyses reveal a high incidence of breast cancer in young women in Brazil. JCO Glob Oncol. 2021;7:81-8. https://doi.org/10.1200/GO.20.00440
- 3. Organização Pan-Americana da Saúde. Câncer de mama é a 2ª principal causa de morte entre mulheres nas Américas; diagnóstico precoce e tratamento podem salvar vidas [Internet]. Brasília, DF: OPASBrasil; 2016 [cited on 2021 Feb 22]. Available from: https://www3.paho.org/bra/index.php?option=com\_content& view=article&id=5273:cancer-de-mama-e-a-2a-principal-causade-morte-entre-mulheres-nas-americas-diagnostico-precoce-etratamento-podem-salvar-vidas&Itemid=839#:~:text=do%20.
- 4. Instituto Nacional de Câncer José Alencar Gomes da Silva. Nota Técnica: detecção precoce do câncer de mama durante a pandemia de COVID-19. Rio de Janeiro: INCA; 2020. [cited on 2021 Feb 22]. Available from: https://saude.rs.gov.br/upload/ arquivos/202004/03141003-covid-19-nota-tecnica-deteccaoprecoce.pdf.
- Facina G, Oliveira VM. Breast cancer care during the coronavirus pandemic. Mastology. 2020;30:e20200014. https:// doi.org/10.29289/25945394202020200014

- 6. Ministério da Saúde. Protocolos clínicos e diretrizes terapêuticas em oncologia [Internet]. Brasília, DF: Ministério da Saúde; 2014 [cited on 2021 Feb 22]. Available from: https:// bvsms.saude.gov.br/bvs/publicacoes/protocolos\_clinicos\_ diretrizes\_terapeuticas\_oncologia.pdf.
- Barbosa EM, Donoso NF, Osório CABT, Alves EMF, Waldvogel FC, Oliveira CT, et al. Tumor residual pós-quimioterapia neoadjuvante para câncer de mama: impacto sobre o tratamento cirúrgico conservador. Rev Bras Ginecol Obstet. 1999;21(4):187-92. https://doi.org/10.1590/S0100-72031999000400002
- Costa MADL, Chagas SRP. Quimioterapia neoadjuvante no câncer de mama operável: Revisão da Literatura. Rev Bras Cancerol. 2013;59(2):261-9. https://doi.org/10.32635/2176-9745. rbc.2013v59n2.534
- Ferreira R, Kneubil MC, Brollo J, Tiago LHBL, Goulart KB, Litvin IE, et al. Evaluation of clinical and pathological response factors to neoadjuvant chemotherapy in breast cancer patients. Mastology. 2021;31:e20210005. https://doi.org /10.29289/10.29289/2594539420210005
- Amorim GLS, Assad DX, Ferrari BL, Rosa DD, Pereira BP, Clara RO, et al. Breast oncology and the COVID-19 pandemic: recommendations from the Brazilian Society of Clinical Oncology (SBOC). BJOncology. 2019;16:e-20190024. https://doi. org/10.5935/2526-8732.20190024

- Câncer de Mama Brasil. Cirurgia do câncer de mama em tempos de coronavírus. [cited on 2021 Feb 22]. Available from: https://www.cancerdemamabrasil.com.br/cirurgia-docancer-de-mama-em-tempos-de-coronavirus/.
- 12. Cullinane C, Shrestha A, Al Maksoud A, Rothwell J, Evoy D, Geraghty J, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: a systematic review and meta-analysis. European Journal of Surgical Oncology. 2021;47(7):1507-13. https://doi.org/10.1016/j.ejso.2021.01.025
- El-Shakankery KH, Kefas J, Crusz SM. Caring for our cancer patients in the wake of COVID-19. Br J Cancer. 2020;123:3-4. https://doi.org/10.1038/s41416-020-0843-5
- 14. Dietz JR, Moran MS, Isakoff SJ, Kurtzman SH, Willey SC, Burstein HJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. Breast Cancer Res Treat. 2020;181(3):487-97. https://doi.org/10.1007/s10549-020-05644-z
- 15. Lacerda P, Alves LJB, Silveira CC, Santos TN, Dias SB. A experiência do serviço de mastologia do Hospital Central da Aeronáutica durante a pandemia mundial de coronavírus [Internet]. In: XXIII Congresso Brasileiro de Mastologia. Florianópolis; 2021 [cited on 2021 Dec 22]. Available from: https://sbm.iweventos.com.br/evento/mastologia2021/ trabalhosaprovados/naintegra/44.
- 16. Cirilo SSV, Silva PHS, Cruz VT, Correia RS, Maia JPC, Silva FBF. Necessidade de assistência psicossocial em tempos de pandemia causada pelo novo coronavírus: um olhar atento aos pacientes oncológicos e aos profissionais da área da oncologia. Rev Bras Cancerol. 2020;66(TemaAtual):e-1071. https://doi. org/10.32635/2176-9745.RBC.2020v66nTemaAtual.1071
- 17. American College of Surgeons. American Society of Anesthesiologists. Association of periOperative Registered Nurses. American Hospital Association. Joint statement: roadmap for resuming elective surgery after COVID-19 pandemic [Internet]. Chicago: ACS; 2020 [cited on 2021 Apr 5]. Available from: https://www.facs.org/covid-19/clinicalguidance/roadmap-elective-surgery.

- Gathani T, Clayton G, MacInnes E, Horgan K. The COVID-19 pandemic and impact on breast cancer diagnoses: what happened in England in the first half of 2020. Br J Cancer. 2021;124:710-2. https://doi.org/10.1038/s41416-020-01182-z
- Joseph WJ, Bustos SS, Losee JE, Rubin JP, Cruz C. The Impact of the COVID-19 Pandemic on Breast Reconstruction Practices in the United States. Anticancer Res. 2021;41(4):1903-8. https:// doi.org/10.21873/anticanres.14956
- 20. Ministério da Saúde (BR). Tratamento do câncer [Internet]. Rio de Janeiro: INCA; 2021 [cited on 2021 Apr 5]. Available from: https://www.inca.gov.br/tratamento/cirurgia.
- 21. Lucas F, Bergmann A, Bello M, Tonellotto F, Neto BC. Reconstrução mamária em pacientes oncológicos durante a pandemia da COVID-19. Rev Bras Cancerol. 2020;66(TemaAtual):e-1004. https://doi.org/10.32635/2176-9745.RBC.2020v66nTemaAtual.1004
- 22. Atisha D, Alderman AK, Lowery JC, Kuhn LE, Davis J, Wilkins EG. Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the michigan breast reconstruction outcomes study. Annals of Surgery. 2008;247(6):1019-28. https://doi.org/10.1097/SLA.0b013e3181728a5c
- 23. Pinholato LA, Pupim MCS, Herrera ACSA, Oliveira CEC. Comparative analysis: QOL in breast cancer patients before and during the COVID-19 pandemic. Mastology. 2021;31: e20200084. https://doi.org/10.29289/2594539420200084
- 24. Amendola LCB, Gaui MFD, Carneiro AHPC, Canedo NHS. Clinicopathologic profile of breast cancer patients treated with neoadjuvant chemotherapy at HUCFF/ UFRJ. Mastology. 2021;31:e20200076. https://doi. org/10.29289/2594539420200076
- 25. Pinheiro L, Figueiredo P. Março de 2021 é o pior mês da pandemia em SP antes de terminar; 9,1 mil pessoas morreram por COVID-19 até dia 23. Globo; 2021 [cited on 2021 Feb 22]. Available from: https://gl.globo.com/sp/saopaulo/noticia/2021/03/23/marco-de-2021-e-o-pior-mesda-pandemia-em-sp-antes-de-terminar-91-mil-pessoasmorreram-por-covid-19-ate-dia-23.ghtml.



#### ORIGINAL ARTICLE https://doi.org/10.29289/2594539420210052

# Population-based study: breast cancer mortality trend in women in the state of Paraná from 2000 to 2017

Gabriel Zardo Ferreira<sup>1\*</sup> <sup>©</sup>, Lucas Roskamp Budel<sup>2</sup> <sup>©</sup>, Victor Setti Campelo<sup>1</sup> <sup>©</sup>, Vinicius Milani Budel<sup>1</sup> <sup>©</sup>

# ABSTRACT

**Objective:** Breast cancer is one of the main challenges in Brazilian public health due to the high associated mortality. Mortality has different patterns according to age group, usually increasing with age. The demographic stability in Paraná, with the growth of the elderly population, has a direct impact on the epidemiology of this disease. This study aimed to assess, on a population-based basis, the rates and trends of mortality from breast cancer among the age groups of women in the state of Paraná from 2000 to 2017. **Methods:** A statistical descriptive retrospective series study was carried out to analyze, on a population-based basis, the trend in breast cancer mortality rates among the age groups of women in the state of Paraná, from 2000 to 2017. The trend analysis of annual mortality rates was carried out through the software and simple linear regression models. **Results:** The population-based analysis showed that women aged 45–54 and 55–64 years had the highest number of deaths during the study period. However, when calculating the mortality rates by age group, it was observed that the mortality pattern increases proportionally to the longevity of the female population in the state. Trend analyses indicated an upward trend in mortality among women aged 25–34 years throughout the study period. The same trend was observed in women aged 35–44 years, but in a shorter period, from 2005 to 2017. **Conclusion:** Mortality rates, per 100,000 women, were directly proportional to age, increasing with age, indicative of greater mortality from the disease in elderly women. There was a trend of increasing mortality, with statistical significance, in the age groups from 25 to 34 and 35 to 44. The others were considered stable trends.

KEYWORDS: age distributions; age-specific death rates; mortality rates; breast tumor.

## INTRODUCTION

Breast cancer is the largest cause of cancer death in Brazil and worldwide and is the most frequent type, except for non-melanoma skin tumors. One in four diagnosed cases of cancer in women is breast cancer, and the global incidence progressive increasing in both developed and developing countries<sup>1-3</sup>. In Brazil, there were estimated 59,700 new cases of the disease in 2018, representing 29.5% of the total incidence of cancer, with an associated mortality rate of 14%<sup>4</sup>. In the Brazilian regions, the South has the second highest incidence of breast cancer, with a rate of 65 cases per 100,000 women, behind only Southeast Region<sup>3,5,6</sup>.

It is a heterogeneous disease, with multiple factorial etiologies and a complex relationship of hormonal, genetic, and environmental factors, and is closely related to the aging process. Postmenopausal women have considerably higher incidence and mortality rates than women of reproductive age; the peak occurs from 65 to 80 years<sup>7-10</sup>. Exposure to carcinogenic agents for long periods, mutations by failure in cellular DNA repair, and prolonged latency period could explain the higher frequency of neoplasia<sup>9</sup>. However, breast tumors tend to have a faster developmental profile and are biologically more aggressive in younger patients<sup>9,11</sup>.

<sup>1</sup>Mackenzie Evangelical College of Paraná – Curitiba (PR), Brazil.

<sup>2</sup>Universidade Federal do Paraná, Hospital of Clinics Complex – Curitiba (PR), Brazil.

\*Corresponding author: gabri.z.ferreira@gmail.com

Conflicts of interest: nothing to declare. Funding: none.

**Received on:** 07/12/2021. Accepted on: 04/24/2022.

The current demographic scenario in Brazil has had a rapid growth of the elderly population. The estimate is that in 2030 we will have an age pyramid similar to that of developed countries, and by 2060 the number of Brazilians over 65 years old could quadruple. Paraná follows the same accelerated pattern of population aging. The elderly population in the state, in 2021, represents 16% of the population of Paraná (1.8 million inhabitants), which represents an increase of 4.8 percentage points in relation to the 2010 IBGE Census<sup>12</sup>.

The aging process Brazilian population goes through and the natural history of breast cancer have a direct impact on the epidemiological health profile of the female population, which justifies the importance of a population-based study in epidemiological evaluations of breast cancer mortality, as well as on the assessments of the target population for public policies to screen the disease.

Our study aimed to analyze, on a population basis, the rates and trends mortality from breast cancer among the age groups of women in the state of Paraná, from 2000 to 2017.

#### METHODS

A retrospective time series study was carry out to analyze, on a population basis, the trend of breast cancer mortality rates in the age groups of women in the state of Paraná, from 2000 to 2017.

Data on all deaths were extracted from records in the Mortality Information System of Paraná/DATASUS (SIM/DATASUS), from the tabulation from 1999, which had breast cancer as their base cause (CID10 code: C50). Information on the female population of Paraná was collected from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* — IBGE) based on the 2000 and 2010 demographic censuses and intercensus population projections for non-census years. Work performed with public domain data in accordance to item III, sole paragraph, article 1st, of Brazilian resolution nº 510 of the National Health Council, Ministry of Health, of April 7, 2016: Will not be registered or evaluated by the CEP/CONEP system, research that uses information in the public domain.

With this information, mortality rates per 100,000 women were calculated for each age group during all years of the study. For this calculation, Excel version 2007 was used.

Analyses were performed in six age groups (i.e., from 25 to 34 years; from 35 to 44 years; from 45 to 54 years; from 55 to 64 years; and 75+ years), using the age stratification criteria of the World Health Organization (WHO), every 10 years. Women aged 15–24 years were excluded from the analysis due to insufficient data during the study period.

For the trend analyses, annual mortality rates were calculated, considering as dependent variable "y" and the years of the period studied as the independent variable "x"; mortality rates were standardized by the direct method. Initially, trend analysis was carried using the Joinpoint program version 4.8.0.1, provided by the National Cancer Institute of the United States, with free access (http://surveillance.cancer. gov/joinpoint/). This program estimates the annual percentage variation (APV), translation of annual percent chance (APC) in English, from a segmented linear regression (Joinpoint regression) and identifies inflection points by intensive statistical methods.

This program provides a 95% confidence interval (95%CI) around APC to determine whether the APC for each segment differs significantly from zero.

The U.S. National Cancer Institute establishes a systematic methodology to characterize trends in studies on cancer incidence and mortality. This methodology is applied globally in research on the disease and is contained in a public document called Cancer Trends Progress Report<sup>13</sup> that, based on the values of the APC, characterizes the trends of the series object of the study, taking into account the following criteria:

- If the absolute value of APC is less than or equal to 0.5% per year (-0.5≤APC≤0.5) and the APC is not statistically significant, the series trend is considered stable.
- When the APC value is greater than 0.5% per year in absolute value (APC<-0.5 or APC>0.5) and the APC is not statistically significant, the series trend is considered to vary and not significant.
- If APC is statistically significant and significantly positive, it is characterized as an increase trend.
- Variations with statistically significant and significantly negative APC are characterized as a decreasing trend.

In general, APC is significantly different from zero if APC<-0.5 or APC>0.5. It is also established that APC is statistically significant if p<0.05 using Student's t-test.

Although somewhat arbitrary, these categorizations provide a consistent and standardized method for characterizing trends in disparate measures. Statistical significance and the absolute value of change for incidence and mortality trends were used to ensure consistency with all major publications on national cancer trends.

Each inflection point reflects changes in the increase or decline in death rates. The Bayesian information criterion was used to find the inflection points, and for the choice of models, trend variations with a level of statistical significance of 5% were considered.

To complement the trend analyses, simple linear regression models were performed. In the equations (y=a+bx) of the model lines, "x" received the minimum value of zero in 2000 and the maximum of 17 in 2017. The value (b), which multiplies "x" in each equation, is the slope coefficient of the line, that is, the greater the module of "b," the more inclined up, from left to right, is the line. Negative value of "b" indicates downward slope, which is equivalent to the decline in the rate trend over that period. Positive value of "b" indicates an upward slope, which is equivalent to the increase in the rate trend over that period. The probability (p) of "b" being statistically equal to zero is equivalent to the fact that there was no change in rates over time.

The linear trend equations and model adjustment statistics ( $R^2$  value and the p-value of the model adequacy test) were obtained using the SPSS program, version 19.0. The level of significance adopted was 5%.

## RESULTS

The results of the analysis of the historical series of breast cancer mortality in the state of Paraná, between 2000 and 2017, indicated inequalities between the patterns observed for older and younger women.

Initially, with data analysis, it was possible to observe the gross number of deaths per age group over the period studied. The women aged 45–54 and 55–64 years had the highest number of registered deaths. Then, mortality rates were calculated for every 100,000 women, by age group, to observe the behavior of deaths in the population.

Figure 1 shows the behavior of mortality rates per group of 100,000 women in each age group. It is noted that in all years,



Source: Research database (2020). Figure 1. Behavior of breast cancer mortality rates.

the younger the younger, the lower the mortality rates, while the mortality of those over 75 years is higher compared to the other rates. This age stratum also showed an atypical variation from 2000 to 2002.

The trend in mortality rates for each series formed by age groups in the period was analyzed using Joinpoint. The results are shown in Table 1, which contains the values of the APC, as well as the CI for each age group.

These models only presented inflection for the second age group (from 35 to 44 years), which did not occur in the other.

The analyses of the last four age groups (45–54, 55–64, 65–74, and 75+ years) did not present statistical significance in the APC value, so the trend of the series in these age groups is considered stable.

Regarding the results observed in the age groups in which the APC value presented statistical significance, it was possible to identify an increase in mortality rates of women over 25 and less than 34 years between 2000 and 2017 (APC=1.86; 95%CI 0.1–3.7).

For women aged over 35 and under 44 years, from 2005 to 2017, there was a trend of the series in these age groups (APC=2.71; 95%CI 0.6–4.8).

To expand the information obtained with the Joinpoint system on the trend of the series of the four age groups, whose APC value resulted without statistical significance, the information generated by the linear regression models was used. The results of the equations of the models found values of R<sup>2</sup> and the respective p-values of the F-test are presented by age group in Table 2.

In the analyses of the constructed models, results similar to those obtained by the *Joinpoint* system were obtained. The coefficient of the variable "x" in each constructed model indicates the variation of the mortality rate in the series that corresponds to the respective age group.

The equation of the first line (y=0.282+0.006x) represents that, since the year 2000 (x=0), for each year from 2001 to 2017, the mortality rate for breast cancer in Paraná, in the age group representing women over the age of 25 and less than 34 years,

Mariable	A = = = = = = = =	laissaist	4.0.0	95%CI			
variable	Agegroup	Joinpoint	APC	LL	UL	p-value	
	25-34	0	1.86*	0.1	3.7	0.0	
	25 44	1 (2004)	-6.44 (2000–2004)	-18.3	7.1	0.3	
Crude mortality rate	55-44		2.71* (2004–2017)	0.6	4.8	0.0	
from breast cancer	45-54	0	0.1	-0.7	1.0	0.8	
	55-64	0	0.3	-0.7	1.3	0.5	
	65-74	0	0.4	-0.3	1.1	0.2	
	75 +	0	0.4	-0.5	1.3	0.4	

Table 1. Average percentage change values according to Joinpoint setting. Paraná, 2000–2017.

APC: average percentage change; CI: confidence interval; LL: lower limit; UL: upper limit. \*p<0.05.

increased by 0.006 units on average, from the value 0.282. Similar interpretations can be made with the values obtained in each of the lines constructed for each age group.

The  $R^2$  value of the model for the first age group is low, indicating a regular adjustment. The significance of the coefficient of the variable "x" (p=0.04), which represents the year of the study period, and "y" the positive value, suggests an increase in mortality rates in the age group in this period. A result similar to that obtained with the *Joinpoint* system, which shows a tendency to increase in this age group for the study period. When the model was adjusted for the series of the second age group, the  $R^2$  value was low and the coefficient of the variable "x" was not significant.

Two models were created, the first for the period from 2000 to 2003, which did not improve the adjustment made at the beginning, and the second, from 2004 to 2017, achieving substantial improvement in the adjustment and significance of the variable. Again, the model indicated an increase in mortality rates in the second age group, but only from 2004 to 2017, a result similar to that obtained with the *Joinpoint* system, which adjusted an inflection point, indicating an increase trend at the end of the period considered.

Regarding the models of the series of the third and fourth age groups, the  $R^2$  value of each adjusted model was low and the coefficient of the variable "x" was not significant. This result indicates that there was no change in mortality rates in these age groups over time.

In the series of the fifth age group, a situation similar to that occurred in the second was presented: the R<sup>2</sup> value of the adjusted model was low and the coefficient of the variable "x" was non-significant. Two models were soon made, one for the period from

 Table 2. Result of trend analysis and adjusted model of breast

 cancer mortality rate, according to age group, in the state of Paraná, from 2000 to 2017.

Variable	Аде дгоир	Model	R²	p-value
	25-34	y=0.282+0.006x (*)	0.229	0.044
	35–44 (period 2000–2007)	y=2.859+0.002x	0.191	0.893
	35–44 (period 2000–2003)	y=1.451-0.052x	0.106	0.674
Age	35–44 (period 2004–2017)	y=0.962+0.039x (*)	0.539	0.003
group	45-54	y=2.859+0.002x	0.001	0.893
	55-64	y=3.189+0.006x	0.012	0.670
	65–74 (period 2000–2017)	y=2.638+0.090x	0.065	0.307
	65–74 (period 2009–2017)	y=2.075+0.051x	0.370	0.081
	75+	y=1.685+0.008x	0.063	0.316

\*Significant at 5%.

Source: Research database (2020).

2000 to 2008 and another from 2009 to 2017. With this division of the original period, a substantial improvement was achieved in the adjustment and significance of the variable for the second period. Even so, it was not enough to say that there was a rising trend in the 65–74 years age group.

## DISCUSSION

As in the whole world, Brazil will see an increase in the number of people affected with some type of cancer in the coming years, as a consequence of the greater population aging and exposure to a considerable number of new carcinogenic agents.

According to data from the SIM, in the Southern states of Brazil, the pathology is very close to cardiovascular diseases as the main cause of death<sup>14</sup>.

Early diagnosis and timely treatment in the most at-risk populations can reduce these numbers, making cancer a chronic disease, prolonging the patient's life by many years.

This study made it possible to know the temporal patterns of mortality from breast cancer in women in the state of Paraná, from 2000 to 2017. In the first analysis, the results showed that women aged 45–54 and 55–64 years registered the highest number of deaths in the period studied. However, when the crude mortality rates were calculated by age group, it was observed that the mortality pattern increased directly proportional to the increase in age.

The higher number of deaths in lower age groups, in the first analysis, is explained by the larger population in these strata. This result, however, does not show that mortality affects younger women more. When calculating the mortality rate and standardization per 100,000 women, it can be seem that the behavior of mortality in Paraná remains proportional to the natural history of the disease, which has as its pattern higher mortality in older age groups<sup>15</sup>.

There is evidence of higher mortality rates in older women also in other regions of the country. Evaluating data regarding older women from other states, such as the others in the South and Southeast, between 1980 and 2005, higher rates were found as the age group increased<sup>16</sup>.

After an initial study, the trend of mortality rates by age group over time was interpreted, applying the Joinpoint method and simple linear regression. This system, widely applied in time series analyses, has as main function to calculate changes in the trend according to the APC. However, a disadvantage of the use of this calculation formula is the uncertainty in estimating the number of inflection points, which may not correspond to the actual variation<sup>17</sup>.

Linear regression models have an advantage of high statistical power, although the nonlinearity of the data can be cited as a disadvantage, it is compensated by the centralization of the historical series<sup>18</sup>. The use of these two models allowed the analysis of the APC in rates to be complemented by the observation of discrete oscillations, verified only through the regression method<sup>19</sup>.

It was observed that breast cancer mortality tends to increase in women from two age groups: 25–34 and 35–44 years old, with an APC that varies between age groups, increasing with age.

A similar result was found by Martin et al. who, evaluating the mortality trend in Brazil comparing two age groups: women aged 50 years or less and over 50 years, found growing trend in mortality of younger women<sup>20,21</sup>.

Paraná exhibits high levels of industrialization and, according to the latest research published by the IBGE, has the fourth highest Human Development Index (0.749) of Brazilian states. This coincides with a greater life perspective and consequently greater aging of the population. According to the 2000 IBGE census, Paraná counted 428,326 women aged over 60 years, while the 2010 census indicated an increase to 635,627<sup>14</sup>.

Considering the demographic transition through which the state goes, which is an important factor in understanding the epidemiological profile of breast cancer, the results obtained in the present study showed, on a population basis, higher mortality in older women, but there was a trend of growth, with statistical significance, of mortality only in younger women in the age groups of 25–34 and 35–44 years.

Although our work is a descriptive analysis and not of an inferential nature, using statistics to support it, we can assume that the global increase in the longevity of women in Paraná was the factor responsible for raising the mortality rates of folder patients compared to those of younger patients.

In contrast, an increasing trend in women of younger age groups may be associated with coverage of the breast cancer screening plan in the state and the tumor development profile, which is faster and more aggressive in these patients<sup>9,11</sup>.

Mammography is the only screening test with proven efficacy to reduce breast cancer mortality; however Paraná, in 2012, registered a percentage of mammographic coverage (ratio between the number of tests performed and expected tests) of only 35.9%, well below 70% recommended by the WHO<sup>3,22-24</sup>.

We should also consider that there is a disproportion in the offer of mammography in different age groups, considering that our screening model is opportunistic and not organized. In the latter, women of more advanced age groups would be the most benefited, in compliance with the greater compulsory call of heath services<sup>23,24</sup>.

The Ministry of Health currently recommends biannual screening, from the age of 50 years, and excludes women between 40 and 49 years from screening programs, which can result in insufficient reach of the target population and uncontrolled growth of mortality from the disease in women of younger age groups<sup>3,25,26</sup>.

In Brazil, it is essential to expand the coverage of screening services in the state and adapt the target population of the services, in addition to offering an organized screening model (characterized by the active search for patients) to the detriment of the predominant screening method, which is opportunistic, performed at the time of a medical cosultation<sup>25</sup>.

### CONCLUSION

The results obtained in the present analysis allow us to conclude that breast cancer mortality rates in women in the state of Paraná are directly proportional to age groups, evidencing higher mortality in older women.

Analyzing the behavior of mortality trends by age group, there was growth, with statistical significance, only in women of younger age groups, from 25 to 34 and from 35 to 44 years, with an average increase that differs between them. Among these, the one that includes women aged between 35 and 44 years presented the highest average annual increase; however, for this group, the trend was not uniform throughout the period.

These data showed the need for public health models with organized screening programs associated with the active search of the target population.

# **AUTHORS' CONTRIBUTION**

GZF, VSC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. LRB, VMB: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

## REFERENCES

- Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJL, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet [internet]. 2011 [cited on 2020 Mar. 15];378(9801):1461-84. Available from: https://doi.org/10.1016/S0140-6736(11)61351-2.
- 2. Release P. International agency for research on cancer. Asian Pacific J Cancer Prev. 2003;4(1):3-4. ISSN: 2476762X.
- 3. Urban LABD, Chala LF, Bauab SP, Schaefer MB, Santos RP, Maranhão NMA, et al. Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira de Ginecologia e Obstetrícia para o rastreamento do câncer de mama. Rev Bras Ginecol e Obstet. 2017;39(10):569-75. https:// doi.org/10.1055/s-0037-1606348.

- Makdissi FB, Leite FPM, Peres SV, Silva DRM, Oliveira MM, Lopez RVM, et al. Breast cancer survival in a brazilian cancer center: a cohort study of 5,095 patients. Mastology. 2019;29(1):37-46. https://doi.org/10.29289/259453942019000 0437.
- 5. Oliveira Santos M. Estimativa/2020 incidência de câncer no Brasil. Revista Brasileira de Cancerologia. 2020; 66(1):e-00927. https://doi.org/10.32635/2176-9745.RBC.2020v66n1.927.
- Tab Net [internet]. 2019 [cited on 2020 Mar. 15]. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def.
- Silva S, Tennekoon KH, Karunanayake EH. Overview of the genetic basis toward early detection of breast cancer. Breast Cancer Targets Ther. 2019;11:71-80. https://doi.org/10.2147/ BCTT.S185870.
- Testa U, Castelli G, Pelosi E. Breast cancer: a molecularly heterogenous disease needing subtype-specific treatments. Med Sci. 2020;8(1):18. https://doi.org/10.3390/medsci8010018.
- Ferreira DB, Mattos IE. Tendência da mortalidade por câncer de mama em mulheres no estado do Rio de Janeiro, Brasil, 1996–2011. Cienc Saude Coletiva. 2015;20(3):895-904. https:// doi.org/10.1590/1413-81232015203.07982014.
- 10. Ministério da Saúde. Portaria conjunta nº 04, de 23 de janeiro de 2018. Diário Oficial da União, Brasília, DF; 2018.
- 11. Benz CC. Impact of aging on the biology of breast cancer. Crit Rev Oncol Hematol. 2008;66(1):65-74. https://doi.org/10.1016/j. critrevonc.2007.09.001.
- Idoso CED. O idoso no Paraná [internet]. [cited on 2020 June 25]. Available from: http://www.cedi.pr.gov.br/modules/ conteudo/conteudo.php?conteudo=2.
- Cancer Trends Progress Report National Cancer Institute, NIH, HHS, Bethesda, MD [internet]. 2020 Mar. [cited on 2020 May 5]. Available from: https://progressreport.cancer.gov.
- IBGE. Censo 2010 [internet]. [cited on 2022 Jan. 24]. Available from: https://cidades.ibge.gov.br/brasil/pr/pesquisa/23/25888 ?detalhes=true.
- Freitas-Junior R, Freitas NMA, Curado MP, Martins E, Silva CMB, Rahal RMS, et al. Incidence trend for breast cancer among young women in Goiânia, Brazil. Sao Paulo Medical Journal; 2010. 128(2):81-4. https://doi.org/10.1590/S1516-31802010000200007.
- Basílio DV, Mattos IE. Câncer em mulheres idosas das regiões Sul e Sudeste do Brasil: evolução da mortalidade no período 1980–2005. Rev Bras Epidemiol. 2008;11(2):204-14. https://doi. org/10.1590/S1415-790X2008000200003.

- 17. Tiwari RC, Cronin KA, Davis W, Feuer EJ, Yu B, Chib S. Bayesian model selection for join point regression with application to age-adjusted cancer rates. J R Stat Soc Ser C (Applied Stat [internet]. 2005 [cited on 2020 May 5];54(5):919-39. Available from: https://doi.org/10.1111/j.1467-9876.2005.00518.x.
- Latorre MRDO, Cardoso MRA. Análise de séries temporais em epidemiologia: uma introdução sobre os aspectos metodológicos. Rev Bras Epidemiol [internet]. 2001 [cited on 2020 May 5];4(3):145-52. Available from: https://doi. org/10.1590/S1415-790X2001000300002.
- Ferreira DB, Mattos IE. Tendência da mortalidade por câncer de mama em mulheres no estado do Rio de Janeiro, Brasil, 1996–2011. Cienc Saude Coletiva. 2015;20(3):895-904. https:// doi.org/10.1590/1413-81232015203.07982014.
- 20. Martins CA, Guimarães RM, Silva RLPD, Ferreira APS, Gomes FL, Sampaio JRC, et al. Evolução da mortalidade por câncer de mama em mulheres jovens: desafios para uma política de atenção oncológica. Rev Bras Cancerol. 2013;59(3):341-9. https://doi.org/10.32635/2176-9745.RBC.2013v59n3.499.
- 21. Gonçalves ATC, Jobim PFC, Vanacor R, Nunes LN, Albuquerque IM, Bozzetti MC. Câncer de mama: mortalidade crescente na Região Sul do Brasil entre 1980 e 2002. Cad Saude Publica. 2007;23(8):1785-90. https://doi.org/10.1590/S0102-311X2007000800005.
- 22. INCA. Detecção precoce do câncer de mama [internet]. 2018 [cited on 2020 Jun. 24]. Available from: https://www.inca. gov.br/controle-do-cancer-de-mama/acoes-de-controle/ deteccao-precoce.
- 23. Budel VM. Câncer de mama diagnóstico precoce mamografia [internet]. [cited on 2020 Sept. 17]. Available from: https:// www.saude.pr.gov.br/sites/default/arquivos\_restritos/files/ documento/2020-05/cancer\_mama.pdf.
- 24. Thornton H, Pillarisetti RR. "Breast awareness" and "breast self-examination" are not the same. What do these terms mean? Why are they confused? What can we do? Eur J Cancer. 2008;44(15):2118-21. https://doi.org/10.1016/j.ejca.2008.08.015.
- 25. Silva RCF, Hortale VA. Rastreamento do Câncer de Mama no Brasil: quem, como e por quê? Rev Bras Cancerol [internet]. 2012 [cited on 2020 Sept. 17];58(1):67-71. Available from: https:// doi.org/10.32635/2176-9745.RBC.2012v58n1.1429.
- 26. Socieadade Brasileira de Mastologia. Sociedades brasileiras recomendam mamografia a partir dos 40 anos [internet]. 2017 [cited on 2020 June 24]. Available from: sbmastologia.com. br/noticias/sociedades-medicas-brasileiras-recomendammamografia-anual-a-partir-dos-40-anos/.



#### ORIGINAL ARTICLE https://doi.org/10.29289/2594539420210065

# Prognostic factors and molecular subtypes in young women with breast cancer

Yasmin Shukair<sup>1</sup> 💿, Rafaela Veiga Monteiro<sup>2</sup>\* 💿

# ABSTRACT

Introduction: Because of its high incidence, breast cancer is the subject of numerous studies today. Despite being an uncommon disease in young women, when it affects this population, it tends to be more aggressive and has high mortality rates. Objective: The objective of this study was to evaluate the prognostic factors present in the immunohistochemical profile of young women with breast cancer, comparing the age groups of very young women (<35 years old — Group I) and young women (between 35 and 40 years old — Group II), to see if the data obtained match what is reported in the literature. Methods: A cross-sectional study was carried out, analyzing the immunohistochemical tests of 90 female patients with invasive breast carcinoma. The groups were classified on the basis of molecular subtype: luminal A, luminal B, hybrid luminal, human epidermal growth factor receptor 2 positive and triple-negative. Results: The histological type with the highest incidence was invasive breast carcinoma of no special type. The most frequent molecular subtypes were luminal B and triple-negative. With regard to estrogen and progesterone receptors, there was a slight predominance of positive receptors. Ki-67 levels showed that in the triple-negative and human epidermal growth factor receptor 2 positive subtypes, there was a predominance of high cell proliferation index. Conclusion: In the population of young women in this cohort of patients, there was agreement with literature data regarding the predominance of the invasive carcinoma of no special type histological type and the luminal B and triple-negative molecular subtypes, and the presence of high cell proliferation rates, attesting to the higher prevalence of more aggressive tumors in the younger population. There was also no statistically significant difference in all aspects analyzed when comparing Groups I and II. However, a higher frequency of negative hormone receptors or overexpressed human epidermal growth factor receptor 2 molecular subtypes was not detected, characteristics that are common to young women with breast cancer, which has been pointed out in several studies worldwide.

KEYWORDS: breast cancer; immunohistochemistry; prognosis; biomarker.

### INTRODUCTION

It is a well-documented fact that breast cancer is the malignant neoplasm with the highest incidence in the female population worldwide, excluding only non-melanoma types of skin cancer<sup>1</sup>. Despite being relatively uncommon in young women, breast cancer is the leading cause of death from malignant neoplasms in women under 45 years of age<sup>2</sup>. Data presented by the World Health Organization (WHO), referring to a population of 100,000 women evaluated in 2020, showed the following results: incidence of 58.5% for all ages and 10.3% for under 40 years<sup>3</sup>; and percentage of deaths of 17.7% for all ages and 1.8% for under 40<sup>3</sup>. According to the Brazil's National Cancer Institute (INCA), the estimate of breast cancer cases in Brazil for each year of the 2020-2022 triennium is 66,280<sup>4</sup>. Regarding mortality, 18,068 deaths were recorded in 2019, of which 1,246 were women under the age of  $40^5$ . Such incidence and mortality values demonstrate the need for extensive research on the subject, focusing on early diagnosis through screening programs and determination of its main prognostic factors.

Numerous studies indicate that the age group with the highest incidence of breast cancer is between 50 and 65 years old, which is nine times greater than in women under 40<sup>6</sup>, making this cancer an event of low incidence in younger women<sup>7</sup>.

\*Corresponding author: rafaelavmonteiro97@gmail.com Conflict of interests: nothing to declare. Funding: none.

**Received on:** 12/19/2021. Accepted on: 04/16/2022.

<sup>&</sup>lt;sup>1</sup>Hospital Regional do Vale do Paraíba, Department of Surgical Oncology – Taubaté (SP), Brazil.

<sup>&</sup>lt;sup>2</sup>Universidade de Taubaté, Department of Medicine – Taubaté (SP), Brazil.

Regarding the number of cases of the disease, 10% were in the 34-to-44-year age group, while 2% between 20 and 34 and 0.1% under 20<sup>7</sup>. That is, the younger the patient, the lower the chances of developing breast cancer. On the other hand, while the most prevalent age group (50–65) has tumors with a better prognosis and easier diagnosis, young women have the worst prognosis and significantly lower survival<sup>8</sup>. Although there is no consensus, a young female patient it is classified as being under 40 years<sup>9</sup>.

According to the Brazilian Society of Mastology, breast cancer screening should be done through an annual mammogram for women over 40 years old. The exclusion of young women from mass screening, justified by the low incidence of the disease, can delay early diagnosis. In this age group, cancers of the human epidermal growth factor receptor 2 (HER2) and triple-negative subtypes are common, which are usually detected clinically, precisely when they have already reached large dimensions. Therefore, it is assumed that the higher rates of invasive tumors in relation to *in situ* tumors, in the population under 40 years old, must be attributed to the fact that many cases are diagnosed at an advanced stage<sup>6</sup>.

The non-inclusion of young women in screening programs and the more aggressive tumor biology not only lead to delayed diagnosis, increasing mortality rates, but also determine that epidemiological studies of breast cancer are mostly composed of older women, underestimating thus the values referring to the young women, considering them not very representative<sup>9</sup>.

However, it is known that mammographic screening in young women loses part of its sensitivity and specificity because of high breast density. This can also lead to unnecessary radiation exposure, to high rates of false positives or a false sense of security. The ideal would be individualized screening programs, taking into account the risk factors of each patient, such as family history and genetic mutations<sup>10</sup>.

Of all the genetic mutations associated with breast cancer, those of the BRCA1 and BRCA2 genes are important negative prognostic factors<sup>9</sup>, more commonly found in young women, reaching 40% in familial breast cancers<sup>11</sup>. These mutations have a prevalence of 10% in women younger under 40 years old and 30% in those under 30<sup>7</sup> and are associated with the development of basal-like tumors (negative for ER, RP and HER2 and positive for CK5), characteristic of the younger population<sup>12</sup>. In light of this, it can be inferred that although the development of breast cancer in very young women (<35 years) is a rare event, when it occurs, the chances of involvement of the BRCA genes are greater, and consequently, the greater is the probability of more aggressive molecular subtypes developing.

Thus, women with a BRCA mutation (1 or 2) are considered high-risk patients and fall into another screening profile, where mammography interspersed with magnetic resonance imaging is recommended every six months, starting at age 30<sup>13</sup>.

Since breast cancer is a disease with heterogeneous characteristics, several studies approach the oncological profile of patients through the analysis of prognostic factors and molecular biology, so the stratification of tumors into different degrees of aggressiveness and risk of recurrence makes it possible to identify the behavior of the cancer and individualized treatments.

Immunohistochemistry is routinely used in clinical practice because of its lower cost and better accessibility for classifying molecular subtypes. The accuracy of this methodology has already been demonstrated as safe in previous studies, detecting 85% of agreement between the immunohistochemical and molecular subtypes<sup>14</sup>. However, comparing the molecular classifications determined by immunohistochemistry and by the microarray PAM50 test (molecular assay of nonroutine use, due to its low cost-benefit), important discrepancies were found<sup>15</sup>.

Characteristics found in pathological and immunohistochemical tests, such as a higher frequency of high histological and nuclear grade, positive angiolymphatic invasion, negative hormone receptors, high cell proliferation index (CPI) and higher incidence of triple-negative molecular subtypes and amplified HER2, contribute to a worse prognosis in young women<sup>13,16,17</sup>. This fact confirms what was previously inferred, verifying that the tumors found in young women tend to be more aggressive.

On the basis of the information presented, this study was developed with the objective of analyzing the molecular profiles of women under 40 years of age, according to immunohistochemistry, and comparing them with the data contained in the literature.

This study was approved by the Research Ethics Committee of the University of Taubaté (protocol CAAE-42804120.1.0000.5501) according to Resolution CNS/MS No. 466/12.

#### **METHODS**

A cross-sectional study was carried out with the evaluation of prognostic factors, obtained through the analysis of immunohistochemical tests, of 90 women between 21 and 39 years old, from 2015 to 2020. The reports were provided by a pathological anatomy laboratory in the city of Taubaté (SP). Tumors were evaluated according to estrogen and progesterone hormone receptors, CPI (Ki-67) and HER2 expression. Cases with indeterminate HER2 not submitted to FISH (fluorescence *in situ* hybridization) analysis were not included. Examinations with incomplete immunohistochemistry data were excluded.

The classification according to the immunohistochemical profile is based on the evaluation of estrogen and progesterone receptors, CPI (Ki-67, referring to a nuclear protein strictly related to cell proliferation) and the biomarker HER2<sup>18</sup>.

Tumors were classified into five subtypes: luminal A, luminal B, hybrid luminal, HER2 and triple-negative. This classification was performed according to the Table 1 below:

For Ki-67, a cutoff point of 14% was used for the differentiation of cancers into luminal A and luminal B, based on the criteria established by Cheang et al.<sup>18</sup>.

The histological type, determined according to the WHO classification, was obtained by anatomopathological examination, including invasive carcinoma of no special type (NST) and special carcinomas. Reports with a diagnosis of ductal carcinoma *in situ* and lobular carcinoma *in situ* or with another diagnosis of non-carcinoma malignant breast cancer were excluded.

Patients were divided into two subgroups: less than 35 years old (Group I) and from 35 to 39 years old (Group II), to compare the prognostic factors found in different age groups, as was done in other studies<sup>1</sup>.

To compare young and very young women, the G (Williams) and  $\chi 2$  tests were performed, where p<0.05 was considered significant. The database was analyzed using the BioEstat 5.3 program.

#### RESULTS

The number of patients included in the study, diagnosed with breast carcinoma, was 90, of which 33 were between 23 and 34 years (Group I) and 57 were aged 35 to 39 years (Group II).

Evaluating the histological types, the most prevalent was nonspecial invasive carcinoma, present in 85 women (94.44%), and five special subtypes: invasive metaplastic, invasive metaplastic with myogenic and rhabdomyoplastic differentiation, invasive cystic adenoid, invasive colloid and invasive lobular.

Regarding the 90 patients, the most prevalent molecular subtype was luminal B, present in 26 women (28.89%), and non-basal triple-negative, in 24 (26.67%), followed by luminal A, detected in 19 (21.11%), HER2 in 11 (12.22%) and hybrid luminal in 10 (11.11%). As for hormone receptors, 53 ER+ (58.89%), 37 ER- (41.11%), 49 PR+ (54.44%) and 41 PR- (45.56%) were found.

 Table 1. Classification of the molecular subtypes according to

 immunohistochemical profile<sup>13</sup>.

Molecular subtype	Immunohistochemical profile
Luminal A	ER+ and/or PR+, HER2- and Ki-67<14%
Luminal B	ER+ and/or PR+, HER2- and Ki-67≥14%
Hybrid luminal	ER+ and/or PR+, HER2+ and any Ki-67
HER2	ER-, PR- and HER2+
Non-basal triple-negative	ER-, PR- and HER2-

HER2+: Human Epidermal growth factor Receptor-type 2 positive; HER2-: Human Epidermal growth factor Receptor-type 2 negative; ER+: Estrogen receptor positive; ER-: Estrogen receptor negative; PR+: Progesterone receptor positive; PR-: Progesterone receptor negative. In evaluating cell proliferation rates in triple-negative and HER2 tumors, we obtained the following results: triple-negative, 4 (16.67%) with low CPI, 2 (8.33%) with moderate CPI and 18 (75%) with high CPI; in HER2 tumors, 3 cases (27.27%) with low CPI, 2 (18.18%) with moderate CPI and 6 (54.54%) with high CPI.

The pathologists classified the tumors according to the CPI and defined it as low, moderate and high, according to the Ki-67 values, that is, low (<15%), moderate (from  $\geq$ 15% to  $\leq$ 20%) and high (>20%). According to the manual for standardization of histopathological reports<sup>19</sup>, the Ki-67 value above 15 to 20% is considered high; however, the literature does not establish a specific cut-off point, recommending only that the percentage of stained nuclei be mentioned in the histopathological report<sup>19</sup>.

The comparative analyses of the two groups are described in the following Table 2 and there were no statistical differences in the parameters analyzed between the two groups:

Table 2. Results obtained in the sample and respective p-values.

Parameters		<35 years n (%)	35–39 years n (%)	p-value	
	Luminal A	6 (18.18)	13 (22.80)		
	Luminal B	11 (33.33)	15 (26.32)		
Molecular	Hybrid luminal	3 (9.09)	7 (12.28)	0.9257 *	
subtype	HER2+	5 (15.15)	6 (10.53)		
	Non-basal triple- negative	8 (24.24)	16 (28.07)		
Estrogen	ER+	19 (57.58)	34 (59.65)	0 0764 **	
receptor	ER-	14 (42.42)	23 (40.35)	0.9764 ***	
Progesterone	PR+	18 (54.55)	31 (54.38)	0 8376 **	
receptor	PR-	15 (45.45)	26 (45.62)	0.0370 ***	
НЕР2	HER2+	8 (24.24)	13 (22.80)	0 9176 **	
	HER2-	25 (75.76)	44 (77.19)	0.9170	
Non-basal	Low	1 (12.50)	3 (18.75)		
triple-negative	Moderate	0	2 (12.50)	0.6250*	
tumor (CPI)	High	7 (87.50)	11 (68.75)		
	Low	1 (20.00)	2 (33.33)		
HER2 tumor (CPI)	Moderate	1 (20.00)	1 (16.67)	0.9038*	
· · /	High	3 (60.00)	3 (50.00)		

HER2+: Human Epidermal growth factor Receptor-type 2 positive; HER2-: Human Epidermal growth factor Receptor-type 2 negative; ER+: Estrogen receptor positive; ER-: Estrogen receptor negative; PR+: Progesterone receptor positive; PR-: Progesterone receptor negative; \* G test (Williams); \*\*  $\chi^2$  test.

### DISCUSSION

Regarding the histological type, the results obtained in this study showed that invasive ductal carcinoma was the most common (94.18%). Similar data were found in a national study that evaluated 12,689 young women<sup>1</sup>, demonstrating a frequency of 90.7% of invasive ductal carcinoma, with no statistical difference between two age groups: younger than 35 years and 35 to 39 years.

The study conducted in the United Kingdom<sup>20</sup>, published in 2013, analyzed about 3,000 women under 40 years old, finding similar percentages as in the present study: 86.5% were diagnosed with invasive ductal carcinoma, 4.5% with lobular carcinoma and 0.4% with metaplastic. Regarding hormone receptors, the same study<sup>20</sup> found 65.9% ER+, while our study here found 58.89% ER+ in the total number of women analyzed. Another similarity of the studies was the proportion of HER2+ tumors, so that by adding the cases with hybrid luminal and those with overexpressed HER2, 24.3% were found in the British article and 23.3% in the present work.

A 2014 literature review<sup>17</sup> compared several studies of gene expression and immunohistochemistry in women of different ages affected by breast cancer, whose results confirmed the hypothesis that young women have more aggressive molecular profiles than postmenopausal women. Other studies reached the same conclusion: young women (20–39 years) had a higher proportion of triple-negative, luminal B HER2-positive (ER+PR+HER2+, ER+PR-HER2+) and overexpressed HER2<sup>21</sup> tumors, while luminal A tumors predominated in those aged 40 to 98 years<sup>21</sup>.

Analyzing the different prevalences in the two groups studied, the present study showed a higher frequency of triplenegative molecular subtypes followed by luminal B in Group I (very young women) and luminal B followed by triple-negative in Group II (young women). This result reaffirms the presence of more aggressive molecular subtypes in most young women.

Many studies show a predominance of negative hormone receptors and high rates of overexpressed HER2 tumors in young women<sup>13,16,17,22</sup>. In this study, we observed a slight predominance of hormone receptor-positive tumors (ER 58.89% and PR 54.44%) in the two groups analyzed and a lower percentage for overexpressed HER2 tumors (12.22%), compared to the other molecular subtypes. Perhaps the limited sample size of this study (n=90) was not enough to better assess the frequency of hormone receptors and molecular subtypes.

Regarding the CPI index, the current study demonstrated greater percentages of high CPI in triple-negative and HER2 subtype tumors in both groups, corroborating the data in the literature, which demonstrate that high Ki-67 levels are commonly associated with overexpression of HER2<sup>23</sup>. In addition, the literature demonstrates a correlation between hormone receptors and Ki-67, which are inversely proportional: the more positive the receptors, the lower the levels of Ki-67<sup>23</sup>, so that the triple-negative and overexpressed HER2 subtypes, because they

are hormone receptor-negative, would actually have higher levels of Ki-67.

A Norwegian study<sup>21</sup>, published in 2019, aimed to assess the mortality rates of each molecular subtype in different age groups. The results revealed higher mortality rates in young (20–39 years) and older (70–89 years) women than in the screening-age population (50–69 years), and that triple-negative tumors were associated with higher mortality rates at all ages. The study raised the possibility that the high mortality rate in the elderly population is due to the greater number of comorbidities and less invasive treatments. On the other hand, it attributed the high death rate of young women with advanced stages of the disease at the diagnosis and high rates of more aggressive tumors<sup>21</sup>.

Although statistical studies show that young women do not account for the highest mortality rate<sup>3</sup> because of the lower incidence, breast cancer in this age group is more aggressive and a reason for lower life expectancy<sup>22</sup>.

#### CONCLUSIONS

The results found in this study showed a higher incidence of aggressive molecular subtypes and with a high rate of cell proliferation in young women, supporting the hypothesis that in this age group, breast cancers have a worse prognosis. Several hypotheses explain this result, such as diagnosis at an advanced stage due to lack of screening, high rates of hereditary syndromes with a high prevalence of mutations, and low clinical suspicion on the part of patients and health professionals.

The lack of individualized screening methods not only compromises early diagnosis but also prevents the adequate representation of patients with breast cancer at a young age in world surveys. Therefore, it is necessary to educate the public about the severity of the disease in young age groups, noting that even if its incidence is not high, these women have high rates of invasive tumors and metastases, and they should seek medical help through a clinical suspect condition<sup>4</sup>.

# ACKNOWLEDGMENTS

We thank Dr. Luís Eduardo Zucca for all his assistance in writing and revising the manuscript, Dr. Marcos Furlan for technical assistance in data analysis and Dr. Marcos Roberto Martins for providing us with data from the immunohistochemical assays used in this study.

## **AUTHORS' CONTRIBUTION**

RVM: Data curation, Formal analysis, Investigation, Software, Validation, Writing – original draft. YS: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

# REFERENCES

- Pinheiro AB, Lauter DS, Medeiros GC, Cardozo IR, Menezes LM, Souza RMB, et al. Câncer de mama em mulheres jovens: análise de 12.689 casos. Rev Bras Cancerol. 2013;59(3):351-9. https://doi.org/10.32635/2176-9745.RBC.2013v59n3.500.
- 2. Partridge AH, Ruddy KJ, Kennedy J, Winer EP. Model program to improve care for a unique cancer population: young women with breast cancer. J Oncol Pract. 2012;8(5):e105-10. http://doi. org/10.1200/JOP.2011.000501.
- International Agency for Research on Cancer World Health Organization. [Base de dados online] [internet]. Lyon: IARC; 2020 [cited on 1996 Nov. 2]. Available from: https://gco.iarc.fr/ today/home.
- 4. Instituto Nacional do Câncer (BR). Estimativa 2020. Incidência do câncer no Brasil. Rio de Janeiro: INCA; 2019. p. 34.
- Instituto Nacional do Câncer (BR). Atlas da mortalidade. [Base de dados online] [internet]. Rio de Janeiro: INCA; 2019 [cited on 2021 May 2]. Available from: https://www.inca.gov.br/app/ mortalidade.
- Pessoa JM, Oliveira PS, Fernandes LLMN, Ribeiro MS, Rocha FS. Avaliação do seguimento oncológico de mulheres abaixo de 40 anos portadoras de câncer de mama em um hospital de referência da Amazônia. Rev Bras Mastologia. 2015; 25(1):8-15. http://doi.org/10.5327/Z201500010003RBM.
- Torresan R. Tratamento do câncer de mama em mulheres muito jovens (<35 anos). Boletim da Associação Brasileira de Mastologia Regional São Paulo – Boletim Especial JPM 2015; ano XVIII(123):31-2.
- Chen H-L, Zhou M-Q, Tian W, Meng K-X, He H-F. Effect of age on breast cancer patient prognoses: a population-based study using the SEER 18 database. PLoS One. 2016;11(10):e0165409. https://doi.org/10.1371/journal.pone.0165409.
- Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim Jr HA, Bianchi-Micheli G, et al. ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4). Annals of Oncology. 2020;31(6):P674-96. https://doi. org/10.1016/j.annonc.2020.03.284.
- DesreuxJAC.Breast cancer screening in young women.European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018;230:208-11. https://doi.org/10.1016/j.ejogrb.2018.05.018.
- Shuen AY, Foulkes WD. Inherited mutations in breast cancer genes – risk and response. J Mammary Gland Biol Neoplasia. 2011;16(1):3-15. https://doi.org/10.1007/s10911-011-9213-5.
- Azim Jr HA, Nguyen B, Brohée S, Zoppoli G, Sotiriou C. Genomic aberrations in young and elderly breast cancer patients. BMC Med. 2015;13:266. http://doi.org/10.1186/s12916-015-0504-3.

- Bagnolli F, Brenelli FP, Pedrini JL, Freitas Jr R, Oliveira VM. Mastologia: do diagnóstico ao tratamento. Goiânia: Conexão Propaganda e Editora; 2017; cap. 27:277-85.
- Tiezzi, D. Biologia molecular no câncer de mama. Boletim da Sociedade Brasileira de Mastologia Regional São Paulo – Edição Resumos das aulas JPM 2020; ano XXII.
- 15. Kim HK, Park KH, Kim Y, Park SE, Lee HS, Lim SW, et al. Discordance of the PAM50 intrinsic subtypes compared with immunohistochemistry-based surrogate in breast cancer patients: potential implication of genomic alterations of discordance. Cancer Res Treat. 2019;51(2):737-47. https://doi. org/10.4143/crt.2018.342.
- 16. Frasson A, Millen E, Brenelli F, Luzzatto F, Berrettini Jr A, Cavalcante FP, et al. Doenças da mama: guia de bolso baseado em evidências. 2nd ed. Rio de Janeiro: Atheneu; 2018. cap. 50:445-51.
- Azim Jr HA, Patridge AH. Biology of breast cancer in young women. Breast Cancer Res. 2014;16(4):427. https://doi. org/10.1186/s13058-014-0427-5.
- Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):756-50. https://doi.org/10.1093/jnci/djp082.
- Bacchi CE, Melo CRA, Franco MB, Neto RA. Manual de padronização de laudos histopatológicos. 4th ed. Barueri: Minha Editora; 2014. p. 336.
- 20. Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18–40 years at diagnosis: the POSH study. J Natl Cancer Inst. 2013; 105(13):978-88. https://doi.org/10.1093/jnci/djt134.
- 21. Johansson ALV, Trewin CB, Hjerkind KV, Ellingjord-Dale M, Johannesen TB, Ursin G. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. Int J Cancer. 2019;144(6):1251-61. https://doi.org/10.1002/ijc.31950.
- 22. Anastasiadi Z, Lianos GD, Ignatiadou E, Harissis HV, Mitsis M. Breast cancer in young women: an overview. Updates Surg. 2017;69(3):313-7. https://doi.org/10.1007/s13304-017-0424-1.
- 23. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, Zeman F, Koller M, Gerstenhauer M, et al. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Res Treat. 2013;139(2):539-52 https://doi.org/10.1007/s10549-013-2560-8.



# Patient satisfaction among patients who underwent mastectomy and immediate breast reconstruction with silicone implants in an oncology hospital

Lia Raquel de Alcântara Caldas<sup>1</sup>\* 💿, Ércio Ferreira Gomes<sup>1</sup> 💿

# ABSTRACT

**Objective:** Breast reconstruction after mastectomy has increased the expectations regarding aesthetic outcomes and increased quality of life for the patient. The survey is an important study tool to assess patient satisfaction among those undergoing cancer treatment. The study aims at identifying the level of satisfaction of patients who underwent mastectomy because of breast cancer, followed by immediate reconstruction with silicone implants. **Methods:** Retrospective cohort study with 42 patients who underwent mastectomy and immediate reconstruction with silicone prosthesis, who answered the BREAST-Q patient reported outcome questionnaire. **Results:** In general, 78.1% of the patients were satisfied or very satisfied with the reconstruction, and 64.3% were satisfied or very satisfied about their self-esteem. **Conclusion:** Reconstructive surgery after mastectomy should be provided for patients whenever possible since it leads to higher self-esteem and personal satisfaction.

KEYWORDS: mastectomy; breast reconstruction; implants; satisfaction.

# **INTRODUCTION**

Total breast resection, which is considered as a mutilating surgery, may reduce women's self-esteem, and cause negative effects on their personal and professional lives. Therefore, reconstructive surgery aims at reestablishing body shape and reducing the psychological trauma caused by the breast cancer treatment<sup>1</sup>.

The relevance of this study is owed to the fact that breast cancer has become a common condition, and its high incidence is associated with the increasing number of women undergoing treatment; therefore, there are some effects related to cancer treatment. This fact makes it important to raise awareness about the main sequelae related to the therapy and their impact on quality of life<sup>2</sup>.

Federal Law no. 13,770, from December 19, 2018, ensures reconstructive breast surgery after a cancer treatment, including

procedures for breast symmetry and reconstruction of the nipple-areola complex. The law also states that the reconstruction should be immediate in the presence of technical conditions<sup>3</sup>.

The rates of postmastectomy breast reconstruction surgeries reflect the patients' demand for this procedure, but there is still room for discussion about the safety of breast implants and the effects of reconstruction in the follow-up of these patients<sup>4</sup>. Regardless of the technique used for reconstruction, the objective is to provide satisfaction both in the psychological and physical scopes for the patient, individually, to recover self-image and reach better acceptance of the new condition<sup>5</sup>.

Validated questionnaires are considered as appropriate methods to study outcome satisfaction after a treatment. International analyses with questionnaires and platforms have been developed to assess the acceptance and level of satisfaction of breast

<sup>1</sup>Hospital Haroldo Juaçaba – Fortaleza (CE), Brazil. **\*Corresponding author:** liaracaldas@gmail.com **Conflict of interests:** nothing to declare. **Funding:** none. **Received on:** 02/06/2022. **Accepted on:** 05/02/2022. reconstructive surgeries, both from the functional and self-esteem points of view<sup>2,6</sup>.

Mastectomy patients who undergo reconstruction usually have high expectations of well-being in comparison to those who only undergo mastectomy. The perception of the patients themselves about breast reconstruction can be difficult to measure and report in a scientific study. Besides, a positive evaluation can simply mean acceptance and conformism towards the disease, and not exactly a good aesthetic outcome, let alone better quality of life. For that, it is important to consider the patients' opinions and translate them through questionnaires that have been developed and tested for this end<sup>7</sup>.

The evaluation of quality of life is a complex matter, and its perception can vary individually and throughout the experiences of life<sup>8</sup>. According to the World Health Organization, quality of life is the "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"<sup>9</sup>.

BREAST-Q is a questionnaire used for patients who underwent aesthetic and reconstructive breast surgery. It was translated to Portuguese. This assessment tool was created in 2009 to evaluate the level of patient satisfaction. It is used in independent modules for breast cancer to assess patients who underwent mastectomy with conservative surgery and breast reconstruction. Each module is composed of multiple independent functioning scales. It is based on two themes or main domains: quality of life and patient satisfaction. Each of these domains presents six sub-themes: psychosocial well-being; physical well-being; sexual well-being; satisfaction with breasts; satisfaction with the outcome; satisfaction with care<sup>10-12</sup>.

The purposes of this study were to verify the level of patient satisfaction among those who underwent mastectomy due to malignant breast neoplasm followed by immediate breast reconstruction with silicone implants using the BREAST-Q questionnaire, and to identify the risk factors that could interfere with the level of satisfaction.

### METHOD

A retrospective cohort study was carried out with data collection from medical records and qualitative analysis of the opinions of patients who answered the sociodemographic questionnaires, which contained the following explanatory variables: age, weight, height, schooling, profession, radiotherapy, axillary dissection, uni or bilateral mastectomy and reconstructive surgery of the other breast. The BREAST-Q questionnaire had nine questions related to satisfaction, answered in a scale from 1 to 5, in which 1 indicated "Very dissatisfied", 2 indicated "Dissatisfied", 3 indicated "Normal", 4 indicated "Satisfied", and 5 indicated "Very satisfied". The data consist of the answers to the nine questions in the BREAST-Q questionnaire related to satisfaction and nine other explanatory variables (sociodemographic questionnaire), resulting in a database with 42 answers and 18 variables.

The variables from the BREAST-Q questionnaire were interpreted as qualitative or categorical. Among the explanatory ones, there are six qualitative (schooling, profession, radiotherapy, axillary dissection, uni or bilateral mastectomy and reconstructive surgery of the other breast) and three quantitative variables (age, weight and height).

The selected patients underwent uni or bilateral mastectomy due to malignant breast neoplasm followed by immediate breast reconstruction with silicone implants at Instituto do Câncer do Ceará, reference center in cancer treatments in the city of Fortaleza (CE). An active search of digital and printed medical charts was carried out for analysis and selection of eligible patients. The study patients underwent treatment from March, 2013, to August, 2019, especially in the three last years because of the outdated record of older patients.

Patients who had not concluded adjuvant radiotherapy, the ones with local recurrence, patients with distant metastasis on palliative care and those who, due to any intercurrence, had to remove the silicone implants, were excluded from the study.

The patients were initially contacted by a telephone call to hear the explanation about the study and the questionnaires; after a verbal authorization, the Google Form questionnaires were sent through a message application, together with the Informed Consent Form.

The main ordinal and regression components of the tabulated data in the questionnaire were analyzed in order to present a summary and verify the level of patient satisfaction, as well as to investigate the main demographic or clinical factors that could significantly interfere in satisfaction<sup>13</sup>.

The collection began after the project was approved on April 22, 2021, by the Research Ethics Committee in Instituto do Câncer do Ceará, with an Ethical Appreciation Presentation Certificate: 45873121.8.0000.5528.

# RESULTS

Sixty-seven patients who fit the study profile were selected. Of this group, it was not possible to reach 17 patients, and eight did not accept to participate in the study. Therefore, 42 patients assisted at the mastology service of Instituto do Câncer do Ceará participated in the study and answered the BREAST-Q and the sociodemographic questionnaires.

Mean age was 49.17 years and ranged from 30 to 67 years. As to schooling, 14.3% had higher education; 40.5%, high school; 23.8%, incomplete elementary school; and 21.4%, complete elementary school. Radiotherapy was performed by 54.8%. Axillary dissection was performed in half of the patients. Mastectomy was unilateral in 92.9% of the patients, and bilateral mastectomy, in 7.1%. The reconstructive surgery in the other breast was performed in 33.3% of the patients.

There is relatively little information about the profession variable because there are 30 categories, and we dispose of 42 observations. We emphasize that eight interviewees are farmers. The bilateral mastectomy variable showed major imbalance between the unilateral and bilateral categories — only three patients underwent bilateral mastectomy. Therefore, both were excluded from the statistical analysis.

The questions in the questionnaire were associated to subthemes related to satisfaction with the reconstruction. Question 1 (Q1) informs about general satisfaction with the reconstruction, whereas questions 2 to 9 are related to each satisfaction sub-theme: regarding the breasts, psychosocial, pain-related and sexual aspects. The sub-themes and their questions are specified in Table 1.

Among the patients' answers, one was not declared: one patient did not mention her profession. Therefore, this observation was declared as missing.

Figure 1 shows a graph with the satisfaction level for each question inserted in the BREAST-Q questionnaire. It is possible to observe that the "Very dissatisfied" event only occurred twice for each question, at most.

Table 1. Questions about satisfaction related to the sub-themes.

Sub-themes	Questions
Satisfaction with breasts	Q2, Q3 and Q4
Psychosocial satisfaction	Q5 and Q8
Satisfaction regarding pain	Q6 e Q7
Sexual satisfaction	Q9



**Figure 1.** Level of satisfaction in each question related to satisfaction. Fortaleza, CE, Brazil, 2021.

In Figure 1, general satisfaction (Q1) indicates that 78.6% of the participants are at least satisfied with the result, using silicone implants after immediate breast reconstruction. Specifically regarding the breasts (Q2, Q3 and Q4), about 56.3% are at least satisfied, and 19% consider themselves as dissatisfied and very dissatisfied. About psychosocial (Q5 and Q8), about 73.8% of the patients are at least satisfied with the sensation of having their breasts reconstructed. Regarding the pain (Q6 and Q7), the pattern was patients feeling normal. About 52.4% of the patients reported feeling normal regarding sexual activity.

The BREAST-Q questionnaire brought information about patient satisfaction through questions that are implicitly related to one another. Questions 2 to 9 clearly have an impact on general satisfaction with the outcome (Q1).

The correlation matrix between each question about satisfaction and Q1 was analyzed (Figure 2). With the correlation matrix between the BREAST-Q questions, being  $\rho_{ij}$  the (ij)-th component of the R matrix for every i = 1, 2, ..., 9 and j = 1, 2, ..., 9. For the first line of the correlation matrix, it is possible to observe that only questions 3 and 6 (columns 3 and 6) are weakly correlated with general satisfaction, since the  $\rho_{13}$  and  $\rho_{16}$  coefficients are lower than 0.5. Therefore, there is evidence showing that satisfaction with size and pain have low correlation with general satisfaction and the other sub-themes, it is observed that correlations between questions 1, 2 and 4 are strong, with correlation coefficients  $\rho_{12} = 0.688$ ,  $\rho_{14} = 0.807$  and  $\rho_{24} = 0.820$ .

Correlation values close to 1 indicate that the questions are directly proportional. Therefore, when the satisfaction of the interviewees in Q1 is high, then Q2 is also high. Likewise, when patient dissatisfaction in Q1 is high, then in Q2 it is usually high too. The interpretation is the same for the other questions. Even if Q3 is weakly correlated to Q1, Q2 and Q4, the strong relationship between general satisfaction and satisfaction with the breasts is clear. The same is true for the relationship between general, psychosocial, and sexual activity satisfaction. Only the relationship between general satisfaction and pain was moderate, with coefficients from 0.3 and 0.6.

Table 2 summarizes the relationship between satisfaction and outcome and the other sub-themes. In any way, it is suggested that the relationship between the sub-themes and general

1.000	0.688	0.313	0.807	0.702	0.475	0.564	0.627	0.612
0.688	1.000	0.254	0.820	0.610	0.598	0.514	0.702	0.457
0.313	0.254	1.000	0.254	0.216	0.157	0.236	0.241	0.298
0.807	0.820	0.254	1.000	0.662	0.561	0.436	0.763	0.532
R = [0.702]	0.610	0.216	0.662	1.000	0.562	0.531	0.714	0.665]
0.475	0.598	0.157	0.561	0.562	1.000	0.398	0.493	0.390
0.564	0.514	0.236	0.436	0.531	0.398	1.000	0.499	0.369
0.627	0.702	0.241	0.763	0.714	0.493	0.499	1.000	0.469
0.612	0.457	0.298	0.532	0.665	0.390	0.369	0.469	1.000

**Figure 2.** Correlation between each question related to satisfaction. Fortaleza, CE, Brazil, 2021.

satisfaction have a positive impact, that is, for that sample there is no sub-theme with a negative effect in relation to the general satisfaction of the patients.

To quantify the contribution of each covariable for the satisfaction level of the patients, a global satisfaction index was used as a response variable in a regression model. This index was obtained by performing an analysis of the main categorical components in the variables related to satisfaction. Therefore, the global satisfaction index was defined as the first main component, for being the most representative one, since it has most of the variability of the original data. Therefore, the global satisfaction index represents a scale to measure the satisfaction level based on every question related to satisfaction, that is, every sub-theme and general satisfaction.

For the regression model, we considered the explanatory variables — age, weight, height, radiotherapy, axillary dissection, and surgery in the other breast —, and the response variable was the general satisfaction index. As previously mentioned, the profession and mastectomy variables were excluded due to the low number of interviewees for each level (for instance, only three patients with bilateral mastectomy).

The schooling variable was also excluded for not presenting evidence of relationship with the response variable in the descriptive analysis. Besides, the schooling variable has four levels, so including it in the model with the five selected covariables could lead to estimation problems due to the sample size. With the same objective, the information about weight and height of the patients was synthetized into one variable: Body Mass Index (BMI), since it is more reasonable that the relationship between height and weight be more informative for the response variable than only height or only weight.

When we considered the most relevant variables as independent, observing the descriptive analysis, the simple linear regression model was computed. The estimated value and the respective standard error of each model parameter are presented in Table 3. We also show the descriptive level, p value, for the significance test of each parameter.

The regression model parameters associated with dichotomous variables (radiotherapy, axillary dissection, and surgery in the other breast) represent the difference in the global satisfaction level at the presence of such practices. Therefore, there is no evidence showing there is a difference between global satisfaction for the interviewees who did or did not undergo radiotherapy.

 
 Table 2. Level of relationship between general satisfaction and the Other sub-themes.

Sub-themes	Level
Satisfaction with breasts	Strong
Psychosocial satisfaction	Strong
Satisfaction regarding pain	Moderate
Sexual satisfaction	Strong

Likewise, there is no evidence showing if the patients who performed axillary dissection present significantly different satisfaction than those who did not perform it. There is the same result for the other breast.

For quantitative variables, age and BMI, the parameters represent the expected increase in global satisfaction when the variable increases in one unit. However, the parameter values are too close to zero, which indicates that, in fact, the age and BMI variables do not have significant influence on global satisfaction of the patient.

### DISCUSSION

The mean of mastectomy followed by immediate breast reconstruction with implants at Instituto do Câncer do Ceará in 2016 and 2017 was of approximately 109.5 surgeries a year. The mean of 2018 and 2019 was 144.5 surgeries a year, a 31.9% increase. According to the Brazilian Society of Mastology, approximately 34% off the women who underwent a mastectomy in 2017 also had breast reconstruction<sup>14</sup>.

This increased can be partly justified by law no. 13770/18, according to which "breast reconstruction will be performed at the surgical time of the mutilation". This law changes law n. 9,656, from June 3, 1988, and law no. 9,797, from May 6, 1999, to dispose about the plastic breast reconstructive surgery in cases of mutilation caused by cancer treatment<sup>3</sup>.

It is necessary to know about the impact on the quality of life of patients who suffered from physical changes due to cancer treatments. This knowledge can be reached through validated surveys, such as BREAST- $Q^{15}$ .

BREAST-Q can be used for a study of the impact and efficiency of breast surgeries considering the perspective of the patient by quantifying satisfaction and major aspects of quality of life, and through an approach based on evidence for the surgical practice<sup>16</sup>.

An observational study with women who underwent mastectomy and reconstruction with implants assessed 75 patients regarding satisfaction and quality of life using the BREAST-Q questionnaire, comparing the period before and after the procedure, with 95.94% of immediate breast reconstruction. The

**Table 3.** Linear regression model for the first main categorical variable.

Variable	Parameter estimation	Standard error	p-value
Intercept	30.1241	10.0676	0.00498
Age	0.0824	0.1341	0.54277
BMI	-0.1172	0.3001	0.69847
Radiotherapy	2.8537	2.9081	0.33300
Axillary dissection	0.5130	3.0561	0.86762
Surgery in the Other breast	-1.5518	2.5412	0.54527

BMI: Body Mass Index.

authors obtained statistical significance both in the satisfaction with the breast and in the physical well-being domains, and concluded that the quality of life of the patients who underwent reconstruction with breast implants is higher in comparison to the period prior to the surgery<sup>1</sup>.

A study that assessed pain after breast surgery, including mastectomy with reconstruction, showed that the incidence of pain was higher among the women who underwent mastectomy with reconstruction (49%), only mastectomy (31%) and reduction mastopexy (22%). Breast reconstruction with implants had high incidence of pain compared to reconstruction without implants. The incidence of pain among women who underwent reconstruction without implants was identical to that of women who only underwent mastectomy. All efforts should be made to reach a better aesthetic outcome in reconstruction, which justifies the use of implants. But patients should be informed about the possibility of developing chronic pain after the procedure<sup>17</sup>.

In our study, in the assessment of pain in the reconstructed breast, the pattern was that patients feel normal, thus not having a negative influence on dissatisfaction. The questions related to size and pain had little correlation with general satisfaction.

A 12-month long prospective study with 303 patients who underwent breast cancer surgery in Canada used the BREAST-Q questionnaire and other types of evaluation surveys. The satisfaction level was higher among patients who underwent conservative surgery, followed by patients who underwent mastectomy with reconstruction, p<0.001. The patients who underwent mastectomy with immediate breast reconstruction felt psychosocial well-being just like those who underwent conservative surgery, only mastectomy and mastectomy with reconstruction, p>0.05. The authors concluded that the level of satisfaction was higher among patients with conservative surgery and mastectomy with reconstruction<sup>18</sup>.

The complaint of chronic pain after mastectomy is a known complication of breast surgery, with prevalence of 20 to 52%. A study using two pain scale questionnaires, visual analog scale and painDETECT, compared patients who underwent mastectomy with immediate reconstruction or mastectomy Only. There was no evidence of increasing acute or chronic pain among patients with immediate reconstruction and mastectomy only, which supports the possible benefit of immediate reconstruction<sup>19</sup>.

The quality of life of 633 patients who underwent breast reconstruction with implants, with and without radiotherapy, was assessed using BREAST-Q, in a multicenter study in the United States and Canada. There was more dissatisfaction with breasts among patients who underwent radiotherapy (58.3 versus 64.0). Through the multivariate analysis, the conclusion was that radiotherapy had a negative effect on quality of life and the satisfaction of patients who underwent reconstruction with prosthesis, in comparison to those who did not undergo radiotherapy<sup>20</sup>. In our study, there was no evidence showing there was a difference between general satisfaction for the interviewees who did or did not undergo radiotherapy. Likewise, there is no evidence showing if the satisfaction of patients who underwent axillary dissection is different than that for the ones who did not.

Patients with mastectomy and breast reconstruction with autologous tissue or immediate prosthesis were assessed as to quality of life using the BREAST-Q questionnaire, with a two-year followup. The researchers concluded that the patients who underwent reconstruction with autologous tissue were more satisfied with the breasts and their psychosocial and sexual well-being than those who underwent reconstruction with implants, indicating there are differences in the outcomes of satisfaction and quality of life; therefore, this decision should be discussed in clinical practice<sup>21</sup>.

The relationship between chemotherapy and complications in immediate breast reconstruction are little described. The influence of neoadjuvant and adjuvant chemotherapy was assessed in 1,881 mastectomy patients who underwent immediate reconstruction with breast implants or autologous tissue using the BREAST-Q questionnaire. Patients who underwent chemotherapy had radiotherapy more often, and adjuvant chemotherapy was the most common one. Among patients who chose reconstruction with prosthesis, the complication rates were higher, especially for adjuvant chemotherapy, in comparison to patients who did not have chemotherapy. But these differences were not statistically significant. In relation to the assessment of quality of life, there was no difference between the chemotherapy groups, except regarding sexual satisfaction among patients with breast implants, who had a lower score in the adjuvant chemotherapy group<sup>22</sup>.

#### CONCLUSION

Most patients are at least satisfied in the psychosocial scope after breast reconstruction with prosthesis. The regression model did not present statistical significance for any sociodemographic variable.

Breast reconstruction allows the woman submitted to mastectomy to incorporate definitions of quality of life, integrity, and preservation of self-image to the cancer treatment. This leads to a less traumatic process of rehabilitation, which provides physical, psychological, and social benefits. Breast reconstruction with implants is associated with a higher level of general patient satisfaction. However, breast reconstruction is not free of negative repercussions, and the patient should be aware as to the limitations of the procedure in order not to create false expectations.

#### **AUTHORS' CONTRIBUTION**

LRAC: Investigation, Methodology, Writing – original draft, Project Administration, Formal analysis, Validation. EFG: Conceptualization, Investigation, Supervision, Formal analysis, Writing – review & editing, Visualization, Validation.

# REFERENCES

- Cammarota MC, Campos AC, Faria CADC, Santos GC, Barcelos LDP, Dias RCS, et al. Quality of life and aesthetic results after mastectomy and mammary reconstruction. Revista Brasileira de Cirurgia Plástica (RBCP) – Brazilian Journal of Plastic Sugery. 2019;34(1):45-57. http://www.doi.org/10.5935/2177-1235.2019RBCP0008.
- Vieira RAC, Silva FCB, Biller G, Silva JJ, Paiva CE, Sarri AJ. Instrumentos de avaliação quantitativa e qualitativa das sequelas relacionadas ao tratamento do câncer de mama. Revista Brasileira de Mastologia. 2016 Sep;26(3):126-32. http:// www.doi.org/10.5327/Z201600030008RBM.
- Brasil. Lei nº. 13.770, de 19 de dezembro de 2018. Altera as leis nº 9.656, de 3 de junho de 1998, e 9.797, de 6 de maio de 1999, para dispor sobre a cirurgia plástica reconstrutiva da mama em casos de mutilação decorrente de tratamento de câncer. Brasília, DF: Casa Civil; 2018.
- Morrow M, Li Y, Alderman AK, Jagsi R, Hamilton AS, Graff JJ, et al. Access to breast reconstruction after mastectomy and patient perspectives on reconstruction decision making. JAMA Surgery [internet]. 2014 [cited on 2020 July 31];149(10):1015-21. Available from: http://www.doi.org/10.1001/jamasurg.2014.548.
- Garcia CP, Barazzetti DO, Rendón NB, Parente ELM, Vasconcellos ZAA, Ely JB. Avaliação da qualidade de vida em pacientes submetidas à reconstrução mamária no Mutirão Nacional da SBCP ano de 2016 em Santa Catarina. Rev Bras Cir Plást. 2018;33(0):172-5. http://www.doi.org/10.5935/2177-1235.2018rbcp0083.
- Bayeh HA, Paulinelli RR, Soares LR, Prates A-CL, Morais PC, Albuquerque ICS, et al. The cosmetic outcome of breast reconstruction: reproducibility of different methods assessed by different professionals. Mastology. 2019;29(4):173-9. http:// www.doi.org/10.29289/25945394201920190001.
- Lee CN, Pignone MP, Deal AM, Blizard L, Hunt C, Huh R, et al. Accuracy of predictions of patients with breast cancer of future well-being after immediate breast reconstruction. JAMA Surgery. 2018 Apr. 18;153(4):e176112. http://www.doi. org/10.1001/jamasurg.2017.6112.
- Paredes CG, Pessoa SGP, Peixoto DTT, Amorim DN, Araújo JS, Barreto PRA. Impacto da reconstrução mamária na qualidade de vida de pacientes mastectomizadas atendidas no Serviço de Cirurgia Plástica do Hospital Universitário Walter Cantídio. Revista Brasileira de Cirurgia Plástica [Internet]. 2013 Mar 1 [cited on 2021 Nov. 19];28(1):100-4. Available from: https://doi. org/10.1590/S1983-51752013000100017.
- The World Health Organization Quality of Life Group. The World Health Organization Quality of Life Assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-9. https://doi.org/10.1016/0277-9536(95)00112-k.
- BREAST-Q<sup>®</sup>. Breast-Q, Breast Câncer. EUA: Q-Portfolio, 2020 [cited on 2020 June 17]. Available from: https://qportfolio.org/ breast-q/breast-cancer/.
- 11. Kim JB, Kim DK, Lee JW, Choi KY, Chung HY, Cho BC, et al. The usefulness of pedicled perforator flap in partial breast reconstruction after breast conserving surgery in Korean

women. Arch Plas Surg. 2018 Jan. 15;45(1):29-36. https://doi. org/10.5999/aps.2017.01200.

- 12. Santos G, Urban C, Edelweiss MI, Kuroda F, Capp E. Avaliação dos resultados estéticos e de qualidade de vida após tratamento cirúrgico do câncer de mama. Rev Bras Mastologia. 2013 Sept. 1;23(3):60-8. https://doi.org/10.5327/ Z0104-8058201300030002.
- Sbalchiero JC, Cordanto-Nopoulos FR, Silva CHD, Caiado Neto BR, Derchain S. Tradução do Questionário Breast-Q para a língua portuguesa e sua aplicação em mulheres com câncer de mama. Rev Bras Cir Plást. 2013;28(4):549-52.
- 14. Sociedade Brasileira de Mastologia. Cai número de cirurgias de reconstrução mamária no SUS durante a pandemia. Brasil: SBM, 2021. [cited on 2021 Apr. 27]. Available from: https://www. sbmastologia.com.br/noticias/cai-numero-de-cirurgias-dereconstrucao-mamaria-no-sus-durante-a-pandemia/.
- 15. Tsangaris E, Pusic AL, Kaur MN, Voineskos S, Bordeleau L, Zhong T, et al. Development and psychometric validation of the BREAST-Q Animation deformity scale for women undergoing an implant-based breast reconstruction after mastectomy. Ann Surg Oncol. 2021;28(9):5183-93. https://doi.org/10.1245/ s10434-021-09619-2.
- 16. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. Plastic and Reconstructive Surgery [internet]. 2009 Aug 1 [cited on 2021 Jan. 12];124(2):345-53. Available from: https://doi.org/10.1097/ PRS.0b013e3181aee807.
- Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. Pain. 1996;66(2):195-205. https://doi.org/10.1016/0304-3959(96)03064-3.
- Retrouvey H, Kerrebijn I, Metcalfe KA, O'Neill AC, McCready DR, Hofer SOP, et al. Psychosocial Functioning in Women with Early Breast Cancer Treated with Breast Surgery With or Without Immediate Breast Reconstruction. Ann Surg Oncol. 2019;26(8):2444-51. https://doi.org/10.1245/s10434-019-07251-9.
- Henderson JR, Tao A, Kirwan CC, Barr L. Immediate Breast Reconstruction Does Not Increase Postmastectomy Pain. Ann Surg Oncol. 2014;21(1):113-7. https://doi.org/10.1245/s10434-013-3293-y.
- 20. Albornoz CR, Matros E, McCarthy CM, Klassen A, Cano SJ, Alderman AK, et al. Implant breast reconstruction and radiation: a multicenter analysis of long-term health-related quality of life and satisfaction. Ann Surg Oncol. 2014;21(7):2159-64. https://doi.org/10.1245/s10434-014-3483-2.
- 21. Santosa KB, Qi J, Kim HM, Hamill JB, Wilkins EG, Pusic AL. Long-term patient-reported outcomes in postmastectomy breast reconstruction. JAMA Surg. 2018;153(10):891-9. https:// doi.org/10.1001/jamasurg.2018.1677.
- HartSE, BrownDL, KimHM, QiJ, Hamill JB, WilkinsEG. Association of clinical complications of chemotherapy and patient-reported outcomes after immediate breast reconstruction. JAMA Surg. 2021;156(9):847-55. https://doi.org/10.1001/jamasurg.2021.2239.

<sup>© 2022</sup> Brazilian Society of Mastology This is an open access article distributed under the terms of the Creative Commons license.



# Evaluation of metabolic syndrome and obesity in breast cancer survivors undergoing interdisciplinary approach: a prospective cohort study

Vanildo Prado<sup>1</sup> ©, Daniel Buttros<sup>1</sup>\* ©, Eduardo Carvalho Pessoa<sup>1</sup> ©, Luciana de Araújo Brito Buttros<sup>1</sup> ©, Heloisa Maria de Lucca Vespoli<sup>1</sup> ©, Jorge Nahás Neto<sup>1</sup> ©, Eliana Aguiar Petri Nahas<sup>1</sup> ©

# ABSTRACT

Objective: The purpose of this study was to evaluate the occurrence of the metabolic syndrome and obesity during the first year after the diagnosis of breast cancer in women undergoing interdisciplinary approach. Methods: In this prospective study, 81 women  $(age \ge 45 years)$  with recent histological diagnosis of breast cancer, no established cardiovascular disease, who attended at a single specialized center with an interdisciplinary approach (medical, nutritionist, and psychological) were included. Results: Women with metabolic syndrome were considered to have three or more diagnostic criteria: waist circumference >88 cm, triglycerides  $\geq$ 150 mg/dL, high-density lipoprotein <50 mg/dL, blood pressure ≥130/85 mmHg, and glucose ≥100 mg/dL. Obesity was considered when body mass index >30 kg/m<sup>2</sup> and abdominal obesity with waist circumference >88 cm. The evaluations were carried out at three time points: first cancer visit (T0m), 6 months (T6m), and 12 months (T12m). For statistical analysis, the McNemar test was used to compare these time points and the chi-square test was used for trends. The mean age of the patients was 58.4±10.7 years, and 83.3% of them were in the postmenopausal stage. There were no differences in the metabolic syndrome, body mass index, and waist circumference assessments at the indicated time points. When comparing the individual quantitative criteria for metabolic syndrome, there was a statistically significant difference in the values of triglycerides and blood glucose. At times T0m, T6m, and T12m, an increase in the mean triglyceride values was observed, 121, 139.4, and 148.46 mg/dL (p=0.003) and a reduction in the mean glucose values, 106.6, 100.46, and 98.96 mg/dL (p=0.004), respectively. Conclusion: Women with breast cancer subjected to interdisciplinary evaluation did not show an increase in the occurrence of metabolic syndrome and obesity during the first year following their cancer diagnosis.

KEYWORDS: breast cancer; metabolic syndrome; obesity; interdisciplinary approach.

## INTRODUCTION

The concept of longevity in patients treated for breast cancer is well established, requiring strategies to improve the quality of life, control complications, and prevent death from general and oncological causes. Women with luminal tumors treated using endocrine therapy in the early stages of the disease have an excellent 20-year prognosis<sup>1</sup>. With increased survival, death from other causes becomes a reality, and cardiovascular disease (CVD) is relevant in this scenario<sup>2-4</sup>. A recent observational study evaluating cardiovascular outcomes in about half a million postmenopausal women with or without breast cancer found an increased risk of heart failure, pericarditis, and deep vein thrombosis, which persisted for up to 5 years after the diagnosis. The authors concluded

that women with a history of breast cancer were at increased risk for CVD compared to women without cancer<sup>3</sup>.

Metabolic syndrome (MetS) is defined by a set of metabolic risk factors that include abdominal obesity, dyslipidemia, systemic hypertension, and hyperglycemia and significantly increase the risk of acute myocardial infarction, stroke, and breast cancer<sup>4-7</sup>. Buttros et al.<sup>4</sup>, evaluating postmenopausal women treated for breast cancer compared to women without cancer, observed a significant increase in the risk of MetS, abdominal obesity, atherosclerotic disease, diabetes, and hypertriglyceridemia<sup>4</sup>. Women treated for breast cancer, who have MetS, have poorer overall and disease-free survival<sup>8.9</sup>. An observational study, evaluating approximately 9,000 women in the early stages of breast

<sup>1</sup>Universidade Estadual Paulista "Júlio de Mesquita Filho", School of Medicine – Botucatu (SP), Brazil. **\*Corresponding author:** danielbuttros@claretiano.edu.br **Conflicts of interest:** nothing to declare. **Funding:** none.

Received on: 03/14/2022. Accepted on: 05/29/2022.

cancer, demonstrated that all components of MetS were statistically correlated with deaths from CVD and that abdominal obesity was correlated with breast cancer-specific mortality<sup>2</sup>.

In this context, it is important to understand the importance of controlling body weight and improving metabolic health in women treated for breast cancer. A Cochrane Library meta-analysis evaluated body weight management in overweight and obese women treated for breast cancer. The authors concluded that interdisciplinary interventions (including physical, nutritional, and psychological support) had a significant impact on reducing body weight, with a consequent decrease in body mass index (BMI) and waist circumference (WC) and an improved quality of life9. The 2021 National Comprehensive Cancer Network (NCCN) suggests that all cancer patients should be encouraged to achieve and maintain an adequate BMI<sup>10</sup>. A study that evaluated the actions of the interdisciplinary team with respect to 13,722 women with breast cancer concluded that the introduction of team care was associated with improved patient survival<sup>11</sup>. Thus, interdisciplinary teamwork is essential for the success of cancer treatment.

The purpose of this study was to evaluate the occurrence of the MetS and obesity during the first year after the diagnosis of breast cancer in women undergoing interdisciplinary approach.

## METHODS

#### Study Design and Sample Selection

This is a prospective clinical study carried out between August 2019 and December 2020 at the Center for Specialties and Diagnostic Support (CEAD) of the Municipal Health Foundation in the city of Rio Claro/SP/Brazil. Nonprobabilistic voluntary sampling was used. All patients treated during the study period were enrolled if the following criteria were met:

- age  $\geq$ 45 years;
- · recent histological diagnosis of breast cancer;
- stage I, II, or III;
- no established CVD;
- treated in the Unified Health System; and
- patient's agreement to participate in the study.

The women were evaluated at three time points: at diagnosis/ first visit (T0m), after 6 months (T6m), and after 12 months (T12m). All evaluations were performed by the same researcher (Prado V.).

#### Interdisciplinary Approach

All women diagnosed with breast cancer were treated by the CEAD interdisciplinary team throughout the study follow-up, as per the service routine, without a specific intervention in this study. The team consisted of a mastologist (Prado V.), responsible for visits at the time of diagnosis and during cancer treatment; a nutritionist, who conducted a nutritional evaluation and provided

dietary guidelines; and a psychologist, who helped the patient absorb the impact of the diagnosis and understand the disease discovery process.

### **Clinical Data**

The following data were collected through individual interviews: age, age at and time since menopause, parity, smoking, previous use of menopausal hormone therapy (MHT), family history of CVD, personal history of systemic hypertension, diabetes, dyslipidemia, frequency of physical activity, and blood pressure. Patients with a daily smoking habit were defined as smokers, regardless of the number of cigarettes smoked. Women who performed aerobic physical exercise of moderate intensity, for at least 30 min, 3-5 times a week (90-150 min/week), or resistance exercises 3 days a week, were considered active. Women who met three or more of the diagnostic criteria proposed by the U.S. National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATPIII)<sup>12</sup> were considered positive for MetS: WC >88 cm, triglycerides (TG) ≥150 mg/dL, high-density lipoprotein (HDL) cholesterol <50 mg/dL, systemic blood pressure ≥130/85 mmHg, and blood glucose ≥100 mg/dL or under treatment. The following data were obtained for anthropometric evaluation: weight, height, BMI (=weight/height<sup>2</sup>), and WC. The 2002 World Health Organization criteria were used to classify patients, according to BMI: normal ( $\leq 24.9 \text{ kg/m}^2$ ), overweight  $(25-29.9 \text{ kg/m}^2)$ , and obese  $(\geq 30 \text{ kg/m}^2)$ . For the measurement of WC, the midpoint between the last rib and the iliac crest was used, with the patient in a standing position; values over 88 cm were considered elevated (abdominal obesity)<sup>12</sup>. All clinical evaluations were performed at the time of diagnosis (T0m) and repeated after 6 months (T6m) and 12 months (T12m).

#### **Biochemical Analysis**

The lipid and glucose profiles were evaluated by measuring total cholesterol (TC), HDL, low-density lipoprotein (LDL), TG, and glucose. Blood samples were collected from each participant after a 12-h fast. TC, HDL, TG, and glucose measurements were processed by the RAXT automatic biochemical analyzer (Technicon , USA) and quantified by the colorimetric method, using specific commercially available reagents (Sera-Pak , Bayer, USA). The method is linear up to 800 mg/dL for TG and up to 900 mg/dL for TC. LDL was calculated from the Friedewald formula, whose use has limitations when TG values exceed 400 mg/dL. LDL was obtained by subtracting the TC value from the sum of HDL plus TG divided by 5. The values considered optimal were TC <200 mg/dL, HDL >50 mg/dL, LDL <100 mg/dL, TG <15 mg/dL, and blood glucose <100 mg/dL<sup>12</sup>. All measurements were performed on the first visit and repeated after 6 and 12 months.

#### Pathology and Immunohistochemistry

From the analysis of medical records, the following data were obtained: histopathological diagnosis of breast cancer, histological

grade, hormone receptor (estrogen receptor [ER] and progesterone receptor [PR]), human epidermal growth factor receptor-2 (HER-2), epithelial proliferative activity (Ki67), tumor stage, and treatments performed (i.e., surgery, radiotherapy, chemotherapy, and endocrine therapy). The tumor diameter was obtained from histopathological reports, and the tumor was graded as grade I (well-differentiated), II (moderately differentiated), or III (undifferentiated). The pathological staging of the tumor was defined according to the Sixth edition of the American Joint Committee on Cancer (AJCC), TNM system (tumor size, lymph node status, metastasis)<sup>13</sup>.

#### **Statistical Analysis**

The variables were analyzed using the Shapiro-Wilk test for normality and the Levene's test for homogeneity. Quantitative variables were tested for normality using the Kolmogorov-Smirnov test, and as they did not conform to a normal distribution, the nonparametric Friedman test was applied. When the variable showed a statistically significant difference, Dunn's post-hoc test was used. For data analysis, the mean and standard deviation were calculated for quantitative variables and frequency and percentage for qualitative variables. For qualitative variables, analysis of variance in relation to the time point (diagnosis/T0, 6 months/T6m, and 1 year/T12m) was performed using the McNemar test. Regarding the association between frequencies of categorical characteristics, the chi-square test of trends was employed. In all tests, a significance level of 5% or the corresponding p-value was adopted. Statistical analyses were performed using the Statistical Analysis System (SAS), version 9.4.

#### **Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki. Ethical approval was awarded by the Research Ethics Committee of the Botucatu Medical School, *Universidade Estadual Paulista "Júlio de Mesquita Filho"* (UNESP). Informed consent was obtained from all individual participants included in this study.

#### RESULTS

During the study period, a total of 81 women with breast cancer were enrolled. Among these, 72 patients underwent sample collection at 6 and 12 months (Figure 1). The clinical and oncological characteristics of the women with a recent breast cancer diagnosis (n=72) are shown in Tables 1 and 2. The average age of the patients was  $58.4\pm10.7$  years, of which 83.3% were postmenopausal. The patients on average were overweight (BMI 25.0–29.9 kg/m<sup>2</sup>), with an elevated WC (>88 cm) and baseline values of TC, LDL, and glucose above optimal levels (Table 1). Only 23.6%



Figure 1. Flowchart for the women enrolled in the study.

Parameters	Mean	Standard deviation
Age years	58.4	10.7
Menopause age, years	48.6	3.8
Time since menopause, years	13.1	8.8
Weight, kg	72.9	15.4
Height, m	1.6	0.1
BMI, kg/m <sup>2</sup>	28.9	6.1
WC, cm	97.2	13.2
SBP, mmHg	132.7	15.4
DBP, mmHg	82.2	10.9
Total cholesterol, mg/dL	203.1	36.1
HDL, mg/dL	56.2	13.2
LDL, mg/dL	124.7	30.0
Triglycerides, mg/dL	121.0	50.7
Glucose, mg/dL	106.6	28.0

**Table 1.** Initial descriptive clinical characteristics of the 72 wo-men with breast cancer.

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

of the patients reported prior use of menopausal hormone therapy, 87.5% reported not performing regular physical activity, and 18% were smokers (data not shown).

There was a higher proportion of women with good oncological prognosis factors for breast cancer. The most prevalent profile was early-stage disease (94.4% in stages I and II), tumors  $\leq$ 2 cm (56.94%), axillary node negative (72.2%), hormone receptor positive (79.1% ER and 72.2% PR), and HER2 negative (86.1%). Regarding the treatments performed, 73.6% of the patients underwent conservative surgery, 58.3% underwent chemotherapy, and 78% received radiotherapy (Table 2). Also, 64% were undergoing endocrine therapy during the final evaluation (T12m).

Parameter	Frequency (n)	%				
Stage I	33	45.83				
Stage II	35	48.61				
Stage III	4	5.56				
Tumor size						
Up to 2 cm	45	56.94				
>2 cm and ≤5 cm	26	36.11				
>5 cm	5	6.94				
Axillary lymph node negative	52	72.22				
ER+	57	79.17				
PR+	52	72.22				
HER 2-	62	86.11				
Ki67 <14%	50	69.44				
Conservative surgery	53	73.61				
Mastectomy	19	26.39				
Chemotherapy	42	58.33				
Endocrine therapy	50	69.44				
Radiation	56	77.78				

Table 2. Descriptive oncological characteristics of the 72 wo-men with breast cancer.

ER+: estrogen receptor positive; PR+: progesterone receptor positive; HER 2-: human epidermal growth factor receptor-2 expression negative; Ki67: epithelial proliferative activity. In the evaluation of MetS, no differences were observed at the three time points; 37.5, 43, and 44.4% of the patients had MetS at the time of diagnosis, at 6 months, and at 12 months, respectively (p=0.332). Likewise, four of the components of MetS (i.e., WC, HDL, blood pressure, and glucose) did not differ at the three time points, with the exception of hypertriglyceridemia ( $\geq$ 150 mg/dL), which increased from 25% at T0 to 44.4% at T12m (p<0.05) (Table 3).

In the quantitative comparison of the clinical and laboratory criteria for MetS at the three time points evaluated, a statistical difference was observed in the TG and glucose (Table 4). In relation to TGs, there was a progressive increase in the mean values (121, 139.4, and 148.4 mg/dL) at the three time points (T0m, T6m, and T12m) (p=0.001) (Figure 2). Blood glucose analysis showed a progressive decrease in the mean values (106.6, 100.4, and 98.9 mg/dL) at the three time points (T0m, T6m, and T12) (p=0.005) (Figure 3). The other clinical and laboratory criteria were not statistically different (Table 4).

There was no significant association between oncological treatment (surgery, chemotherapy, endocrine therapy, and radio-therapy) and the metabolic outcomes (MetS and its components) evaluated (data not shown).

# DISCUSSION

From our analysis, women with a recent diagnosis of breast cancer, who received medical, nutritional, and psychological care during the first year of cancer treatment, showed major benefits in terms of metabolic health. In addition to the significant decrease in serum glucose levels, there was no increase in the

**Table 3.** Comparison of the incidence of metabolic syndrome and its components at the three evaluation time points for the 72 women with breast cancer.

Characteristic		T0m	T6m	T12m	Time points compared	Р
Metabolic syndrome	Yes	27 (37.5)	31 (43)	32 (44.4)	T0m–T12m	0.332
	No	45 (62.5)	41 (57)	40 (55.6)		
WC>88 cm	Yes	53 (73.6)	58 (80.5)	57 (79.1)	T0m-T12m	0.125
	No	19 (26.4)	14 (19.5)	15 (20.9)		
BP≥130×85 mmHg	Yes	47 (65.2)	40 (55.5)	47 (65.2)	T6m–T12m	0.167
	No	25 (34.8)	32 (44.5)	25 (34.8)		
TG≥150 mg/dL	Yes	18 (25.0)	26 (36.1)	32 (44.4)	T0m-T12m	0.003
	No	54 (75.0)	48 (63.8)	40 (55.6)		
Glucose≥100 mg/dL	Yes	33 (45.8)	29 (40.2)	28 (38.8)	T0m-T12m	0.302
	No	39 (54.2)	43 59.8	44 (61.2)		
HDL<50 mg/dL	Yes	29 (40.2)	29 (40.2)	26 (36.1)	T6m–T12m	0.648
	No	43 (59.8)	43 (59.8)	46 (63.9)		

Data are expressed as absolute numbers (%). T0m: time of diagnosis; T6m: 6 months; T12m: 12 months; WC: waist circumference; BP: blood pressure; TG: triglycerides; HDL: high-density lipoprotein cholesterol.

Significant difference at p<0.05 (bold) (chi-square test for trends).

**Table 4.** Comparison of clinical and laboratory characteristics at the three evaluation time points for the 72 women with breast cancer.

Features	T0m	T6m	T12m	Р
Weight, kg	72.9 (15)	72.6 (14.7)	73.0 (15.3)	0.728
BMI, kg/m²	28.9 (6.1)	28.8 (5.7)	28.8 (5.9)	0.842
WC, cm	97.2 (13.2)	97.1 (12.1)	96.6 (12.6)	0.683
TC, mg/dL	203.1 (36.1)	207.3 (39.9)	201.3 (40.4)	0.348
HDL, mg/dL	56.2 (13.1)	55.9 (18.1)	56.8 (14.5)	0.894
TRIG, mg/dL	121.0 (139.4)	139.4 (61.3)	148.4 (68.7)	0.001
GLUC, mg/dL	106.6 (28)	100.4 (22.8)	98.9 (18.6)	0.005
SBP, mmHg	132.7 (15.4)	130.6 (17.6)	132.2 (15.5)	0.432
DBP, mmHg	82.2 (10.8)	81.4 (9.9)	83.6 (9.54)	0.156

Data are expressed as mean (standard deviation). T0m: time of diagnosis; T6m: 6 months; T12m: 12 months; BMI: body mass index; WC: waist circumference; TC: total cholesterol; HDL: high-density lipoprotein; TRIG: triglycerides; GLUC: blood glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Significant difference at p<0.05 (bold) (McNemar test).



T0m: time of diagnosis; T6m: 6 months; T12m: 12 months. \*p=0.001 (McNemar test).

**Figure 2.** Comparison at the three evaluation time points of the 72 women with breast cancer, according to triglyceride variable.



TUM: time of diagnosis; T6m: 6 months; T12m: 12 months \*p=0.005 (McNemar test).

**Figure 3.** Comparison at the three evaluation time points of the 72 women with breast cancer, according to blood glucose variable.

incidence of MetS, weight gain, and abdominal obesity. On the other hand, increases in TG concentration and hypertriglyceridemia were observed during the first year.

MetS is considered a risk factor for a poor prognosis in women treated for breast cancer, with lower overall and specific survival<sup>8</sup>. In our study, 37.5% of the women had MetS at the time of breast cancer diagnosis, and after 12 months, the incidence of MS was 44.4%, no significant difference. Abdominal obesity and hypertension were the most prevalent components of MetS throughout the study period, having been observed at the initial and final time points in 73.6% and 65.2% of the subjects and 79.1% and 65.2% of the patients, respectively (p>0.05 in both cases). Our findings are in agreement with those presented by Simon et al.<sup>2</sup>, who, after evaluating 8641 women with breast cancer, found that abdominal obesity and arterial hypertension were the most prevalent criteria among participating women<sup>2</sup>.

Women treated for breast cancer did not experience weight gain or increased WC during the first year of followup. Obesity is correlated with a poorer prognosis in women with breast cancer. Chan et al.<sup>14</sup> evaluated the risk of mortality in 213,000 women with breast cancer, considering the BMI at the time of diagnosis. They demonstrated that women with a BMI >30 kg/m<sup>2</sup> (obese) have a higher risk of mortality when compared to women with a BMI between 20 and 25 kg/m<sup>2</sup> (nonobese) (OR 1.41, 95%CI 1.29–1.53). Regarding the menopausal status, when obesity was present at the time of breast cancer diagnosis, premenopausal women had a higher longterm risk of mortality than postmenopausal women (OR 1.75, 95%CI 1.26–2.41 vs. OR 1.34, 95%CI 1.18–1.53). The authors noted that the risk of death from any cause in obese women is cumulative over time<sup>14</sup>.

Among our patients, 83.3% of which were postmenopausal, the mean BMI during the period evaluated falls into the overweight classification, namely, 28.9 kg/m<sup>2</sup> at T0m and 28.8 kg/ m<sup>2</sup> after 1 year. Our data are in harmony with the report by Simon et al.<sup>2</sup>, who also observed that most women studied had a BMI between 25 and 30 kg/m<sup>2</sup>. Abdominal obesity, defined as a WC >88 cm, is also considered a risk factor for a poor prognosis in women with breast cancer. In a recent publication, Buono et al.8 followed 717 women with early-stage breast cancer for 10 years and demonstrated poorer overall survival (OR 2.34, 95%CI 1.32-4.14) and specific survival (OR 3.24, 95%CI 1.64-6.41) in women with breast cancer and abdominal obesity<sup>8</sup>. Our data demonstrate that the women did not show a significant increase in WC during follow-up, even though the majority had abdominal obesity at the time of diagnosis (73.6%) and at the end of the study (79.1%).

Another important factor related to metabolic health is diabetes. A meta-analysis evaluating the impact of diabetes on the prognosis of 49,000 women treated for breast cancer found that

a diagnosis of diabetes prior to breast cancer was a risk factor for lower overall survival and disease-free survival (OR 1.51, 95%CI 1.34–1.70 and OR 1.28, 95%CI 1.09–1.50, respectively)<sup>15.</sup> These results are similar to those presented by Spalutto et al.<sup>16</sup> at the San Antonio Breast Cancer Symposium 2020 (SABCS/2020). This population study of more than 86,000 participants, with 1347 treated for breast cancer, concluded that diabetes reduced the survival of women with breast cancer, who were primarily black and had a low income<sup>16</sup>.

Hyperglycemia is also correlated with a poorer oncological prognosis. Buono et al.<sup>8</sup> demonstrated lower overall survival and disease-free survival in women with breast cancer with blood glucose  $\geq 110 \text{ mg/dL}^8$ . Our data showed significant results regarding serum glucose concentration, which decreased over the course of 1 year of follow-up. At the initial time point, mean blood glucose was 106.6 mg/dL and at the end of 12 months, it was 98.9 mg/dL (p=0.005). With respect to the baseline value of  $\geq 100 \text{ mg/dL}$ , there was no statistical significance in the comparison at different time points. Although the present study did not perform a specific nutritional intervention, we believe that nutritional guidelines had an impact on the reduction in blood glucose, since the women also did not increase their body weight and WC during the same period.

Dyslipidemia is a feature of MetS found in obese and diabetic patients. Elevated TC, hypertriglyceridemia, and decreased HDL cholesterol were associated with an increased cancer risk of 18, 15, and 20%, respectively<sup>17</sup>. In women treated for breast cancer, dyslipidemia is also associated with a poorer prognosis. In breast cancer mortality studies, the use of statins for the treatment of dyslipidemia has shown survival benefits, suggesting that cholesterol may promote tumor progression<sup>18</sup>. The Women's Health Initiative study indicated that the administration of statins independently contributed to the reduction of advanced stage breast cancer, especially in patients with tumors that were positive for ER expression<sup>19</sup>. In our study, we assessed HDL cholesterol and TGs. HDL cholesterol averaged 56.2 mg/dL at the time of breast cancer diagnosis, with no differences during the follow-up period. Regarding HDL of <50 mg/dL (component of MetS), the incidence was 40.2% at baseline and 36.1% at 12 months, but the differences did not reach statistical significance. On the other hand, TGs showed significant changes in this study. Both the mean concentration and the values considered abnormal (≥150 mg/dL) increased significantly during follow-up. There was an increase in the occurrence of hypertriglyceridemia among the patients, from 25% at diagnosis to 44.4% at the end of 1 year.

A possible explanation for this increase in TGs is the oncological treatments performed, specifically endocrine therapy with tamoxifen or an aromatase inhibitor. Tamoxifen, which is a selective estrogen receptor modulator (SERM), has a favorable effect on the lipid profile, with reduction from 10 to 15% in total serum cholesterol and from 15 to 22% in LDL cholesterol<sup>20-23</sup>. In contrast, some studies have reported increases in TG values in patients treated with tamoxifen, a risk factor for hypertriglyceridemia<sup>24,25</sup>. Aromatase inhibitors (AIs), in turn, by bringing the patient into a state of excessive hypoestrogenism, have a direct correlation with increased cholesterol. The ATAC<sup>26</sup> and BIG I-98<sup>27</sup> studies reported a higher incidence of hypercholesterolemia in patients treated with anastrozole and letrozole, respectively, when compared to women treated with tamoxifen. Approximately 70% of the women in our study were treated with endocrine therapy, the majority (83.3%) with AI because they were postmenopausal. Anastrozole is the AI of choice to initiate endocrine therapy in postmenopausal women in our service, and tamoxifen, in premenopausal women. Although we did not find a significant relationship between endocrine therapy and the increase in TGs, we believe that our small sample size and the short evaluation period (1 year) influenced our results.

Another relevant piece of data in the present study are the factors that enter into a good oncological prognosis of the recruited women. Approximately 95% of the participants were in stage I or II at the time of diagnosis of breast cancer. Regarding predictive and prognostic factors, most of them were positive for ER and PR (79% and 72%, respectively) and 86% were HER-2 negative. The AMAZONA study was a retrospective cohort that evaluated approximately 2300 women with breast cancer from all regions of Brazil<sup>28</sup>. The proportion of women with early-stage (I and II) breast cancer was 76.8%, lower than that found in our study. Immunohistochemical factors were also discrepant, with 63.8% positivity for ER, 54.9% for PR, and 62.6% negativity for HER-2. Data such as BMI and MetS were not reported in the AMAZONA study<sup>28</sup>.

This study has some limitations, mainly due to the small number of patients, the fact that they were recruited from only one center and the short follow-up period of 1 year. However, all the women underwent interdisciplinary evaluation, including medical, nutritional, and psychological assessments. This approach was not interpreted as an intervention, as it is the routine at the service in question. Perhaps, this interdisciplinary routine is responsible for the good results obtained, such as a significant improvement in blood glucose and maintenance of MetS and BMI status. Although we do not have it in our service, we believe that the team would be more effective with the inclusion of physical education in the patients' routine. The interdisciplinary approach is essential for improvement in the survival and quality of life of women under treatment for breast cancer<sup>9,11</sup>.

# CONCLUSION

Women with breast cancer undergoing interdisciplinary approach did not show an increase in the incidence of MetS and obesity during the first year following cancer diagnosis. Among the components of MetS, there was a reduction in blood glucose values and an increase in TG values.

# **AUTHORS' CONTRIBUTIONS**

VP, DB, EPN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, ECP, LB, HV, JNN: Project administration.

## REFERENCES

- 1. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377(19):1836-46. https://doi.org/10.1056/NEJMoa1701830.
- Simon MS, Beebe-Dimmer JL, Hastert TA, Manson JE, Cespedes Feliciano EM, Neuhouser ML, et al. Cardiometabolic risk factors and survival after breast cancer in the Women's Health Initiative. Cancer. 2018;124(8):1798-07. https://doi. org/10.1002/cncr.31230.
- Matthews AA, Hinton SP, Stanway S, Lyon AR, Smeeth L, Bhaskaran K, et al. Risk of cardiovascular diseases among older breast cancer survivors in the United States: a matched cohort study. J Natl Compr Canc Netw. 2021;5:1-10. https://doi. org/10.6004/jnccn.2020.7629.
- Buttros DAB, Branco MT, Orsatti CL, Almeida-Filho BS, Nahas-Neto J, Nahas EAP. High risk for cardiovascular disease in postmenopausal breast cancer survivors. Menopause. 2019; 26(9):1024-30. https://doi.org/ https://doi.org/10.1097/ GME.0000000000001348.
- Schneider JG, Tompkins C, Blumenthal RS, Mora S. The metabolic syndrome in women. Cardiol Rev. 2006;14:286-91. https://doi.org/10.1097/01.crd.0000233757.15181.67.
- Ninomyia JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation. 2004 Jan 6;109(1):42-6. https://doi.org/10.1161/01. CIR.0000108926.04022.0C.
- Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, et al. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. Menopause. 2013;20(12):1301-9. https://doi. org/10.1097/GME.0b013e31828ce95d.
- Buono G, Crispo A, Giuliano M, Angelis C, Schettini F, Forestieri V, et al. Metabolic syndrome and early stage breast cancer outcome: results from a prospective observational study. Breast Cancer Res Treat. 2020;182(2):401-9. https://doi. org/10.1007/s10549-020-05701-7.
- Shaikh H, Bradhurst P, Ma LX, Tan SY, Egger SJ, Vardy JL. Body weight management in overweight and obese breast cancer survivors. Cochrane Database Syst Rev. 2020;12:CD012110. https://doi.org/10.1002/14651858.CD012110.pub2.
- Nccn.org [internet]. National Comprehensive Cancer Network, Inc.; NCCN Guidelines Version 1.2021 Survivorship [updated

2021 Feb. 24] [cited on 2021 Mar. 15]. Available from: https://www.nccn.org/survivorship.

- Kesson EM, Allardice G, George WD, Burns HJG, Morrison DS. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. BMJ. 2012;344:e2718. https://doi. org/10.1136/bmj.e2718.
- 12. NCEP Expert Panel on the Detection, Evaluation, and Treatment of High Blood Pressure in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP). Adult Treatment Panel III (ATP III). JAMA. 2001;285(19):2444-9.
- American Joint Committee on Cancer. Cancer Staging Manual. 6th ed. Chicago: American Joint Committee on Cancer; 2002. p. 227-8.
- 14. Chan DSM, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer-systematic literature review and metaanalysis of 82 follow-up studies. Ann Oncol. 2014;25(10):1901-14. https://doi.org/10.1093/annonc/mdu042.
- Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: a systematic review and metaanalysis. Medicine (Baltimore). 2016;95(49):e5602. https://doi. org/10.1097/MD.000000000005602.
- 16. Spalluto LB, Reid S, Haddad D, Pal T, Mayer IA, Shu X. Diabetes decreases overall survival in women with breast cancer in the southern community cohort study. San Antonio Breast Cancer Symposium, Spotlight Poster Discussion 11; 2020.
- Melvin JC, Holmberg L, Rohrmann S, Loda M, Van Hemelrijck M. Serum lipid profiles and cancer risk in the context of obesity: four meta-analyses. J Cancer Epidemiol. 2013;823-49. https://doi.org/10.1155/2013/823849.
- Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. J Support Oncol. 2012;10(5):171-7. https://doi.org/10.1016/j. suponc.2012.02.001.
- Desai P, Lehman A, Chlebowski RT, Kwan ML, Arun M, Manson JE, et al. Statins and breast cancer stage and mortality in the Women's Health Initiative. Cancer Causes Control. 2015;26(4):529-39. https://doi.org/10.1007/s10552-015-0530-7.
- 20. Dewar JA, Horobin JM, Preece PE, Tavendale R, Tunstall-Pedoe H, Wood RA. Long term effects of tamoxifen on blood lipid

values in breast cancer. BMJ. 1992;305(6847):225-6. https://doi. org/10.1136/bmj.305.6847.225.

- 21. Esteva FJ, Hortobagyi GN. Comparative assessment of lipid effects of en- docrine therapy for breast cancer: implications for cardiovascular disease prevention in postmenopausal women. Breast. 2006;15(3):301-12. https://doi.org/10.1016/j. breast.2005.08.033.
- 22. Grey AB, Stapleton JP, Evans MC, Reid IR. The effect of the anti-estro- gen tamoxifen on cardiovascular risk factors in normal postmenopausal women. J Clin Endocrinol Metab. 1995;80(11):3191-5. https://doi.org/10.1210/ jcem.80.11.7593425
- 23. Morales M, Santana N, Soria A, Mosquera A, Ordovás J, Nóvoa J, et al. Effects of tamoxifen on serum lipid and apolipoprotein levels in postmenopausal patients with breast cancer. Breast Cancer Res Treat. 1996;40(3):265-70. https://doi.org/10.1007/BF01806815.
- Hozumi Y, Kawano M, Saito T, Miyata M. Effect of tamoxifen on serum lipid metabolism. J Clin Endocrinol Metab. 1998;83(5):1633-5. https://doi.org/10.1210/jcem.83.5.4753.
- 25. Liu CL, Yang TL. Sequential changes in serum triglyceride levels during adjuvant tamoxifen therapy in breast cancer patients

and the effect of dose reduction. Breast Cancer Res Treat. 2003;79(1):11-6. https://doi.org/10.1023/a:1023348021773.

- 26. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adju- vant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol. 2006;7(8):633-43. https://doi.org/10.1016/S1470-2045(06)70767-7.
- 27. Coates AS, Keshaviah A, Thürlimann B, Mouridsen H, Mauriac L, Forbes JF, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007;25(5):486-92. https://doi. org/10.1200/JCO.2006.08.8617.
- 28. Simon DS, Bines J, Werutsky G, Nunes JS, Pacheco FC, Segalla JG, et al. Characteristics and prognosis of stage I-III breast cancer subtypes in Brazil: The AMAZONA retrospective cohort study. Breast. 2019 Apr;44:113-9. https://doi.org/10.1016/j. breast.2019.01.008.
- 29. Motoki AH, Buttros DAB, Gaspar ALC, Pessoa EC, Almeida-Filho BS, Nahas-Neto J, et al. Association between metabolic syndrome and immunohistochemical profile at breast cancer diagnosis in postmenopausal women. San Antonio Breast Cancer Symposium, Session Poster Session 7; 2020.


#### ORIGINAL ARTICLE https://doi.org/10.29289/2594539420220015

## Home exercise adherence after breast cancer surgery: incidence and risk factors

Clarice Gomes Chagas Teodózio<sup>1</sup> <sup>(i)</sup>, Vivian de Freitas Martins da Silva<sup>1</sup> <sup>(i)</sup>, Suzana Sales de Aguiar<sup>1</sup> <sup>(i)</sup>, Luiz Claudio Santos Thuler<sup>1</sup> <sup>(i)</sup>, Anke Bergmann<sup>1\*</sup> <sup>(i)</sup>

#### ABSTRACT

Introduction: Functional limitations in women undergoing breast cancer treatment are common and have negative impacts during patient treatment. Physical exercise after breast cancer surgery has been shown to be safe and beneficial, as well as necessary during all stages in order to minimize the negative impact of complications that compromise functionality. This study aims to assess adherence to home exercises and associated factors in women undergoing breast cancer surgery. **Methods:** A prospective cohort study with an inclusion of women with indication for curative breast cancer surgery and an axillary approach. During the postoperative period, patients were instructed to perform home exercises and received a home guide that should be completed daily for 30 days. Patient adherence and perception about exercise difficulty and discomfort, and the presence of pain, insecurity and fear were assessed. A descriptive analysis of socio-demographic and clinical variables was performed, and a simple logistic regression was carried out to identify whether symptoms interfered with exercise adherence. **Results:** A total of 465 women were included, of which 43.6% fully adhered to the exercises, 31.6% partially adhered, and 24.7% either did not deliver the home guide, delivered it blank or containing illegible information. Arm discomfort was the most frequent subjective symptom (63.1%), followed by pain (51.6%). No variables were associated to exercise adherence. **Conclusions:** Patients undergoing breast cancer surgery presented total (43.6%) or partial (31.6%) exercise adherence in the first thirty postoperative days. Subjective symptoms and patient perception did not interfere in exercise adherence rates.

KEYWORDS: breast neoplasms; surgery; exercise; patient compliance; treatment adherence and compliance.

#### INTRODUCTION

In Brazil, 66,280 new cases of breast cancer have been estimated for each year of the 2020-2022 triennium, with an estimated risk of 56.33 cases per 100,000 women<sup>1</sup>. Breast cancer treatment may involve radiation therapy, chemotherapy, hormone therapy, target therapy and surgery. The surgical approach is the standard treatment and the type of surgery varies according to cancer stage, being radical or conservative<sup>2</sup>.

Post-surgical breast cancer complications include early edema, pain, paraesthesias, axillary web syndrome, decreased muscle strength, and reduced range of motion (ROM) of the involved limb, directly affecting the return to daily living activities and quality of life<sup>3-7</sup>. In addition to functional limitations, women undergoing breast cancer treatment are exposed to impacts in the psychosocial realm, with the possibility of a state of emotional need deprivation, generating psychological stress, such as changes in self-image, fear of evolution and anxiety concerning the return to professional activities, with negative impacts during patient treatment<sup>8,9</sup>. Physical exercise in women undergoing breast cancer treatment has been shown to be safe and beneficial, as well as necessary during all stages in order to minimize the negative impact of complications that compromise functionality<sup>10-12</sup>. Upper limb mobilization, in addition to improving functionality, positively interferes with self-confidence, encouraging the patient to continue the exercises in order to maintain daily, work and leisure activities. Unfortunately, low adherence to interventions is constantly reported in studies that recommend exercise for cancer patients, reaching approximately 32-42% of the studied populations<sup>11,13-15</sup>.

Factors associated with good adherence to exercises are generally associated to the bond between therapist and patient, achieved through professional welcoming and commitment and the perception of the benefits obtained from therapy and family support. Factors that hinder adherence include lack of time, work commitment, lack of interest, health conditions, treatment side effects and discouragement<sup>16,17</sup>.

<sup>1</sup>Instituto Nacional de Câncer José Gomes de Alencar, Clinical Research Division – Rio de Janeiro (RJ), Brazil.

\*Corresponding author: abergmann@inca.gov.br

**Conflict of interests:** nothing to declare. Funding: none.

**Received on:** 05/25/2022. Accepted on: 07/11/2022.

Exercise adherence is an important indicator of health care effectiveness, but no consensus on its definition and measurement is available, especially since the exercises are carried out at home, with no direct professional presence and participation<sup>16,18-20</sup>. Adherence to an exercise program, proposed by controlled studies, such as clinical trials, is essential for adequate results<sup>21</sup>. A better understanding of which factors hinder or facilitate exercise adherence may serve as a guide for future interventions and facilitate the therapeutic response of home exercise programs, in order to assist in restored function and in the return to daily and professional activities, identifying whether any subgroups are more prone to non- or low adherence<sup>21</sup>.

In this scenario, the aim of the present study was to assess adherence to home exercises and associated factors in women undergoing breast cancer surgery.

#### METHODS

This study comprised a prospective cohort study including women aged between 18 and 79, with indication for curative surgery and an axillary approach, for breast cancer treatment at *Hospital do Câncer* III / the Brazilian National Cancer Institute (*HCIII-INCA*), from February 01, 2019 to December 20, 2019. This study was approved by the INCA Research Ethics Committee, under no. 2.462.767 on January 9, 2018, and is part of a clinical trial registered at the National Library of Medicine (ClinicalTrials.gov Identifier: NCT03796845). The details of the study protocol have been previously published<sup>22</sup>.

The following patients were excluded: patients presenting bilateral breast cancer; anyone who had undergone previous surgical and/or radiotherapeutic breast cancer treatment; with indication for immediate breast reconstruction surgery; with functional upper limb changes prior to breast cancer surgery; and those who were unable to read, understand and/or complete the home guide. Eligible patients who agreed to participate in the study signed a Free and Informed Consent Form.

Patients were evaluated in the preoperative period, in an individual and group care, as a routine of Physiotherapy in order to carry out functional diagnoses and provide guidance on the prevention of complications.

On the first postoperative day, the patients received an instructional booklet (Figure 1) related to post-operative exercises and guidance, and were instructed on the need to perform home exercises. Women were randomized in two interventions groups. One performed restricted shoulder exercises with amplitude of movement above 90°, and the other with free amplitude of movement over 90°. They were taught four shoulder exercises, which had to be performed daily, three times a day. Patients returned to the physiotherapy service 30 days after surgery for a new evaluation<sup>3</sup>.

In order to verify the performance of the proposed exercises, a home guide was delivered on the first day after surgery, which

should be filled out by the patient daily, and delivered in the physiotherapy appointment 30 days after the surgery, following the established institutional routine.

The women were informed of the need to carry out the guidelines and provide accurate and real information regarding the symptoms and effects caused by the exercises. The home guide contained questions regarding exercise, frequency and subjective symptoms, such as the presence of pain, discomfort, difficulty, fear and insecurity when performing home exercises. All subjective symptoms were strictly related to upper limb mobilization.

The analysis of the exercise adherence was performed by completing the home guide, which also allowed for assessments concerning the patient's perception of the exercises. The following outcomes were analyzed: total, partial, no information or non-adherence. Total adherence was defined as performing the exercises three times a day on all days during the intervention weeks (regular frequency); partial adherence was considered when the exercises were performed less than three times a day every day or performed only a few days during the intervention weeks (irregular frequency). Non-adherence was considered when patients inform that did not perform exercises any day. Patients who did not deliver the home guide, delivered it blank or containing illegible information were considered as no information because we cannot assume that patients were adherent or not.

Sociodemographic and clinical data were collected through interviews and complemented by physical and electronic medical records analyses. All patients were assessed by the same physiotherapy team, according to the established service routine.



Source: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//mastologia-2017.pdf

Figure 1. Instruction booklet for home exercises.

#### Statistical analyses

To calculate the sample size, an outcome (adherence) of 65% with an accuracy of 5% was considered, at a 95% confidence interval. With these parameters, 350 women would be required. However, all women who met the eligibility criteria during the study period were included, totaling 465 participants.

A descriptive analysis of the distribution of the continuous variables of the study was carried out from the collected information filed in a database, through central tendency and dispersion measures, while frequency distributions were used for categorical variables. A simple logistic regression was performed to identify the association between the presence of subjective symptoms and exercise adherence. The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 20.0.

#### RESULTS

A total of 465 women who were followed up for 30 days after surgery for breast cancer were included in this study. Of this total, a loss of follow-up was observed for four (0.8%) participants due to the following reasons: failure to return to the appointment (n=2) and hospitalization for reasons not related to the surgical approach (n=2).

The 461 women who completed the 30-day follow-up had a mean age of 54 ( $\pm$ 11.54), 56.8% had a Body Mass Index (BMI) <30kg/m<sup>2</sup> and were predominantly non-white (66.9%), living without a partner (52.7%) and undergoing some professional activity (53.5%). Regarding comorbidities, 43.9% had arterial hypertension. Concerning clinical and treatment characteristics, 53.3% presented initial clinical staging <IIB, 56.3% underwent neoadjuvant treatment, predominantly with chemotherapy. With regard to the type of surgery, 56.8% underwent mastectomies, with 46.5% undergoing axillary lymphadenectomy (Table 1).

With regard to adherence to home exercises in the thirty days after surgery, 43.6% exhibited total adherence, 31.6% presented partial adherence, 24.7% had missing data, and 0.0% exhibited non-adherence. No statistically significant difference was observed concerning adherence to exercises according to sociodemographic, clinical characteristics or interventions groups (Table 1).

Concerning the subjective symptoms reported in the period of 30 days after surgery, arm discomfort when performing the exercises was present in most patients (63.1%), followed by the presence of upper limb pain (51.6%), difficulty in performing the exercises (49.2%), insecurity (45.5%), and fear of upper limb mobilization (44.9%). The patients' symptoms and perceptions were not associated with home exercise adherence (Table 2).

#### DISCUSSION

In this study, adherence to home exercises was evaluated daily on the first 30 postoperative days through patient self-reports in a home guide covering exercise performance and the existence of subjective symptoms related to upper limb mobilization. At the end of the thirty-day period, 43.6% of the patients exhibited total adherence to the exercises, 31.6% presented partial adherence and 24.7% did not deliver the home guide, delivered it blank or containing illegible data. Among the evaluated symptoms, discomfort was the most reported (63.1%), followed by arm pain (51.6%), difficulty in performing the exercises (49.2%), insecurity (45.5%) and fear (44.9%).

This form of assessment is seldom mentioned in scientific studies and is commonly associated with attendance to appointments or prescription exercise parameters (series, number of repetitions and intensity). Care was taken so that the guidance provided on the performance /benefit of the proposed exercises and guide completion was reinforced for full understanding by the patients and their families.

Petito et al. included 64 women undergoing radical and conservative surgical treatment in a study to assess the effectiveness of an exercise program in recovering shoulder range of motion from the preoperative period, with reassessments from the 7–105<sup>th</sup> postoperative day, and with the specific purpose of evaluating patient adherence to the program. Self-reporting was used as a way of measuring adherence, considering satisfactory when carried out for five to seven days a week at least once a day, and unsatisfactory when performed equal to or less than four times a week. The authors observed that exercise adherence is greater in the initial postoperative periods, decreasing over the weeks<sup>23</sup>.

Cnossen et al. investigated adherence in 50 patients with head and neck cancer using a home exercise program during and after six weeks of chemotherapy. The adherence measurement was performed through diaries filled out daily by the patients, consisting of three levels of adherence: low adherence, when the exercises were performed once a day; moderate, when performed once or twice a day, and high, when performed two or more times a day. A total of 40% of the patients displayed low adherence, 34% exhibited moderate adherence, and 26%, high adherence<sup>14</sup>. The patients in the present study were evaluated for 30 days, which may have facilitated the high percentage of total exercise adherence (43.6%).

Gutiérrez et al. reported on patients adherence to an exercise program with follow-up between the immediate postoperative breast cancer period and the first outpatient return visit (7 or 10<sup>th</sup> day), assessed through self-reporting, where patients considering themselves as adhering to the intervention when practicing the exercises as recommended, daily, but also including those with less daily frequency, totaling 64.2%. Non-adherence was considered when patients reported not performing the exercises or performing them irregularly, at 35.8%. The high adherence reported

#### Table 1. Characterization of the total study population and among adherence groups

Characteristics	Total n (%) 465	Partial adhesion n (%) 147 (31.6)	Total adhesion n (%) 203 (43.7)	No information n (%) 115 (24.7)	p-value†
Age (Years)					
Means (SD)	54.53(±11.54)	54.63 (±11.33)	54.22 (±11.33)	54.97 (±11.64)	0.744
Body mass index					,
<30kg/m²	264 (56.8)	82(55.8)	117 (57.6)	65 (56.5)	
≥30kg/m²	201 (43.2)	65 (44.2)	86 (42.4)	50 (43.5)	0.730
Race/Skin color*					,
White	154 (33.1)	48 (32.7)	71 (35.0)	80 (69.6)	
Non-white	311 (66.9)	99 (67.3)	132 (65.0)	35 (30.4)	0.651
Marital status					
No partner	245 (52.7)	74 (50.3)	104 (51.2)	67 (58.3)	
With partner	220 (47.3)	73 (49.7)	99 (48.8)	48 (41.7)	0.869
Schooling					
<8 years	103 (22.2)	34 (23.1)	35 (17.2)	34 (29.6)	
>=8 years	362 (77.8)	113 (76.9)	168 (82.8)	81 (70.4)	0.172
Professional activity					
Yes	249 (53.5)	79 (54.1)	113 (55.9)	57 (49.6)	
 No	214 (46.0)	67 (45.9)	89 (44.1)	58 (50.4)	0.735
No information	2 (0.4)				-
Systemic Arterial Hypertension				<u> </u>	
Yes	204 (43.9)	60 (40.8)	88 (43.3)	56 (48.7)	
 No	261 (56.1)	87 (59.2)	115 (56.7)	59 (51.3)	0.636
Diabetes			- ( )	- ( /	
Yes	74 (15.9)	19 (12.9)	35 (17.2)	20 (17.4)	
No	391 (84.1)	128 (87.1)	168 (82.8)	95 (82.6)	0.270
Clinical staging					
Initial ( <iib)< td=""><td>248 (53.3)</td><td>86 (57.8)</td><td>100 (49.3)</td><td>63 (54.8)</td><td></td></iib)<>	248 (53.3)	86 (57.8)	100 (49.3)	63 (54.8)	
Advanced (>IIB)	217 (46.7)	62 (42.2)	103 (50.7)	52 (45.2)	0.113
Neoadiuvant treatment	2.17 (1011)	01 (111)	,	52 (1512)	
Yes	262 (56.3)	80 (54.4)	117 (57.6)	65 (56.5)	
	203 (43 7)	67 (45 6)	86 (42 4)	50 (43 5)	0.550
Neoadiuvant chemotherapy	200 (10.17)	01 (13.0)	00(12.1)	50 (15.5)	
Yes	257 (55 3)	78 (53 1)	116 (57 1)	63 (54.8)	
No	208 (44 7)	69 (46 9)	87 (42 9)	52 (45 2)	0.448
Neoadiuvant bormone therapy	200 (44.7)	05 (40.5)	01 (42.5)	52 (45.2)	
Ves	154 (33 1)	46 (31 3)	70 (34 5)	38 (33 0)	
	311 (66 9)	101 (68 7)	133 (65 5)	77 (67.0)	0.531
Neoadiuvant target therapy	511(00.5)	101 (00.17)	135 (05.5)	11 (01:0)	
Ves	61 (13 1)	19 (12 9)	26 (12.8)	16 (13 9)	
	404 (86.9)	128 (87 1)	177 (87 2)	99 (86.1)	0.974
	404 (00.9)	120 (01.1)	(01.2)	55 (00.1)	
Segmentectomy	201 (43 2)	69 (16 9)	79 (38 9)	53 (46 1)	
Mastertomy	264 (56.8)	78 (53 1)	124 (61 1)	62 (53 9)	0.134
Axillary Approach	204 (30.0)	10 (55.1)	124 (01.1)	02 (55.5)	
Avillary lymphadenectomy	216 (46 5)	71 (48 3)	93 (45 8)	52 (45 2)	
Sentinel Lymph Node Biopsy	2/0 (40.3)	76 (51 7)	110 (54 2)	52 (45.2) 63 (54 Q)	0.645
	247 (33.3)	10(31.1)	110 (34.2)	03 (34.0)	
Free amplitude of movement	251 (51 6)	85 (57 9)	112 (55 2)	57 (10 4)	
	234 (34.0) 211 (45 A)		01 (44 0)	50 (50 1)	0.622
Resultced amplitude of movement	211 (45.4)	٥८ (4८.८)	דו (44.8)	JØ (JU.4)	

\*Non-white=black (n=100), brown (n=210), indigenous (n=1). †Comparison between partial and total adherence groups. Q-square test.

#### Table 2. Distribution of factors associated with partial and total adherence groups

Symptoms	Total n (%) 461	Partial adhesion 147(42.0%)	Total adhesion 203 (58.0%)	OR (95%CI)	p-value†
Arm pain					
Yes	240 (51.6)	101 (71.6)	139 (68.8)		
No	103 (22.2)	40 (28.4)	63 (31.2)	1.14 (0.714–1.83)	0.575
No information	122 (26.2)				
Arm discomfort					
Yes	291 (63.1)	120 (84.5)	171 (84.7)		
No	53 (11.4)	22 (15.5)	31 (15.3)	0.98 (0.54–1.79)	0.970
No information	121 (26.0)				
Difficulty in performing the exercises					
Yes	229 (49.2)	96 (68.6)	133 (66.2)		
No	112 (24.1)	44 (31.4)	68 (33.8)	1.11 (0.70–1.76)	0.642
No information	124 (26.7)				
Fear of performing the exercises					
Yes	211 (44.9)	92 (65.7)	117 (57.9)		
No	133 (28.6)	137 (34.3)	85 (42.1)	1.39 (0.89–2.17)	0.146
No information	123 (26.5)				
Insecurity to perform the exercises			`		
Yes	211 (45.4)	90 (64.3)	121 (59.9)		
No	131 (28.2)	50 (35.7)	81 (40.1)	1.20 (0.77–1.88)	0.412
No information	123 (26.5)				

OR: odds ratio. †Comparison between partial and total adherence groups. Logistic regression.

by the authors may be related to the low time interval assessed (up to the 7 or 10<sup>th</sup> postoperative day), which seems to facilitate patient compliance. In addition, the authors also identified patient difficulties impacting exercise adherence. The reasons related to non-compliance or impossibility to perform the exercises included fear of feeling pain, fear of performing the exercise and affecting the surgical wound site, lack of courage when trying and/or performing the exercises, and pain when trying and/or performing the exercises, with the latter being the main symptom (35.8%)<sup>11</sup>. In the present study, 51.6% of the participants reported pain, but discomfort during the exercise was the most frequent symptom, reported by almost two-thirds of the population (63.1%).

Regarding the associated factors related to adherence, Cnossen et al. found that exercise performance levels were not associated with age, gender, tumor site, tumor stage, but were associated with symptoms related to difficulty opening the mouth. Petito et al. found no difference between the surgical approach and the impact on adherence groups. And Gutierrez et al. identified that fear of feeling pain, fear of affecting the site of the surgical wound and pain when performing exercise impact on exercise adherence. In the present study, no statistically significant difference was observed regarding adherence to exercises according to sociodemographic, clinical, intervention groups or symptoms and patient perception (p>0.005). Amaral et al. compared the effectiveness of a home program with a supervised exercise program, assessing 56 women who underwent breast cancer surgery constantly monitored and reassessed for two months. No difference in ROM recovery was noted between groups. In addition, both groups showed low adherence to the exercises. The authors indicate that the reasons impacting the low adherence of the home group included functional ROM gain and difficulty in understanding the booklet, while for the supervised group, difficult access to the place of care for economic reasons or climatic variations (high temperatures) were reported<sup>13</sup>.

Lokapavani et al. analyzed the influence of preoperative physical therapy on shoulder ROM in 30 women undergoing modified radical mastectomy, categorized into two groups, where the intervention group received education and preoperative exercises two weeks before surgery, and the control group received a standard education leaflet, and both groups were followed up for one month after surgery. Shoulder ROM was recovered in both groups, but the intervention group reached the functional ROM required to perform daily living activities. Preoperative evaluation provides greater understanding of the surgical procedure and related aspects, such as drains, wound healing complications, seroma and physical-functional complications. The authors conclude that this information availability physically and mentally prepare the patient for surgery<sup>24</sup>.

#### Strengths and limitations

The limitations of the present study include performance of exercises without direct supervision, which may have negatively interfered in patient adherence, since one of the factors related to exercise adherence is the therapist-patient bond<sup>17</sup>. In addition, home guide self-completion may be susceptible to information bias, in accordance to Cnossen et al.<sup>14</sup>.

However, some strengths of the present study should also be highlighted. Although the present study evaluates exercise adherence after breast cancer surgery, pre and postoperative assessments and guidance were carried out in order to reduce the incidence of dysfunction of the upper limb homolateral to the surgery, and to guide the patient on the surgery and its functional effects. Another positive aspect of this study is the short follow-up time, which may have facilitated patient commitment to home guide completion, in addition to the robust sample size that may have provided greater statistical power to the results. It is also noteworthy that the study was carried out in a service whose professionals have extensive experience with patient treatment during the postoperative breast cancer period, allowing for uniform procedures and guaranteeing the quality of the intervention.

#### CONCLUSIONS

Patients who underwent surgery for breast cancer treatment exhibited total adherence (43.6%) and partial adherence (31.6%) to home exercises during the first thirty postoperative days, with discomfort as the main reported symptom. No factors associated with adherence to home exercises for 30 days after surgery were observed.

#### ACKNOWLEDGEMENTS

We would like to thank all patients, the nursing and physiotherapy departments of *Hospital do Câncer III* of the Brazilian National Cancer Institute for their contribution to this study.

#### **AUTHORS' CONTRIBUTION**

CGCT: Conceptualization, Data curation, Formal Analysis, Project administration, Writing – original draft. VFMS: Data curation, Formal Analysis, Writing – original draft. SSA: Conceptualization, Formal Analysis. LCST: Conceptualization, Data curation, Formal Analysis, Writing – original draft. AB: Conceptualization, Data curation, Formal Analysis, Writing – original draft.

#### REFERENCES

- Instituto Nacional de Câncer José Gomes de Alencar. Estimativas da incidência e mortalidade por câncer. Rio de Janeiro: INCA; 2020.
- Instituto Nacional de Câncer José Gomes de Alencar. Ações e programas. Rio de Janeiro: INCA; 2016.
- Bergmann A, Ribeiro MJP, Pedrosa E, Nogueira EA, Oliveira ACG. Physical therapy in breast cancer: clinical protocol at the Cancer Hospital III/INCA. Rev Bras Cancerol. 2006;52(1):97-109.
- Pereira ACPR, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. Breast. 2017;36:67-73. https://doi.org/10.1016/j. breast.2017.09.006
- Macedo FO, Bergmann A, Koifman RJ, Torres DM, Costa RM, Silva IF. Axillary surgery in breast cancer: acute postoperative complications in a hospital cohort of women of Rio de Janeiro, Brazil. Mastology. 2018;28(2):80-6. https://doi.org/10.29289/25 94539420180000377
- Lee SA, Kang JY, Kim YD, An AR, Kim SW, Kim YS, et al. Effects of a scapula-oriented shoulder exercise programme on upper limb dysfunction in breast cancer survivors: a randomized controlled pilot trial. Clin Rehabil. 2010;24(7):600-13. https:// doi.org/10.1177/0269215510362324
- Yang EJ, Kang E, Kim SW, Lim JY. Discrepant trajectories of impairment, activity, and participation related to upper-limb function in patients with breast cancer. Arch Phys Med Rehabil. 2015;96(12):2161-8. https://doi.org/10.1016/j.apmr.2015.08.426

- Silva G, Santos MA. Stressors in breast cancer post-treatment: a qualitative approach. Rev Lat Am Enfermagem. 2010;18(4):688-95. https://doi.org/10.1590/s0104-11692010000400005
- Izydorczyk B, Kwapniewska A, Lizinczyk S, Sitnik-Warchulska K. Psychological resilience as a protective factor for the body image in post-mastectomy women with breast cancer. Int J Environ Res Public Health. 2018;15(6):1181. https://doi. org/10.3390/ijerph15061181
- Lee CE, Von Ah D, Szuck B, Lau YK. Determinants of Physical Activity Maintenance in Breast Cancer Survivors After a Community-Based Intervention. Oncol Nurs Forum. 2016;43(1):93-102. https://doi.org/10.1188/16.ONF.43-01AP
- Gutiérrez MGR, Bravo MM, Chanes DC, Vivo MCR, Souza GO, et al. Adherence to an early rehabilitation program among women who underwent mastecmoty. Acta Paul Enferm. 2007;20(3):249-54. https://doi.org/10.1590/S0103-21002007000300002
- Ribeiro IL, Moreira RFC, Ferrari AV, Alburquerque-Sendín F, Camargo PR, Salvini TF. Effectiveness of early rehabilitation on range of motion, muscle strength and arm function after breast cancer surgery: a systematic review of randomized controlled trials. Clin Rehabil. 2019;33(12):1876-86. https://doi. org/10.1177/0269215519873026
- 13. Amaral MTP, Teixeira LC, Derchain SFM, Nogueira MD, Pinto e Silva MP, Gonçalves AV. Orientação domiciliar: proposto de reabilitação física para mulheres submetidas à cirurgia por câncer de mama. Rev Ciênc Méd. 2012 [cited on Dec 8, 2020];14(5):405-13. Available from: https://seer.sis.puccampinas.edu.br/cienciasmedicas/article/view/1151

- 14. Cnossen IC, van Uden-Kraan CF, Witte BI, Aalders YJ, Goede CJ, Bree R, et al. Prophylactic exercises among head and neck cancer patients during and after swallowing sparing intensity modulated radiation: adherence and exercise performance levels of a 12week guided home-based program. Eur Arch Otorhinolaryngol. 2017;274(2):1129-38. https://doi.org/10.1007/s00405-016-4367-9
- 15. Sagen A, Kaaresen R, Sandvik L, Thune I, Risberg MA. Upper limb physical function and adverse effects after breast cancer surgery: a prospective 2.5-year follow-up study and preoperative measures. Arch Phys Med Rehabil. 2014;95(5):875-81. https://doi.org/10.1016/j.apmr.2013.12.015
- Essery R, Geraghty AW, Kirby S, Yardley L. Predictors of adherence to home-based physical therapies: a systematic review. Disabil Rehabil. 2017;39(6):519-34. https://doi.org/10.3 109/09638288.2016.1153160
- Telles TCB, Araruna LC, Almeida MS, Melo AK. Adhesion and adherence to exercise: a bibliographical study. Rev Bras Psicol Esporte. 2016;6(1):109-20. https://doi.org/10.31501/rbpe.v6i1.6725
- Sant'anna KD, Almeida V, Petito EL, Gutierrez MGR. Adherence to the practice of exercises for functional rehabilitation of women with breast cancer: a literature review. Cienc Enferm. 2010;16(1):97-104. http://doi.org/10.4067/S0717-95532010000100011
- Rafn BS, Hung S, Hoens AM, McNeely ML, Singh CA, Kwan W, et al. Prospective surveillance and targeted physiotherapy for arm morbidity after breast cancer surgery: a pilot randomized controlled trial. Clin Rehabil. 2018;32(6):811-26. http://doi. org/10.1177/0269215518757292

- 20. Matarán-Peñarrocha GA, Palomo ICL, Soler EA, Gil-Martínez E, Fernández-Sánchez M, Aguilar-Ferrándiz ME, et al. Comparison of efficacy of a supervised versus non-supervised physical therapy exercise program on the pain, functionality and quality of life of patients with non-specific chronic low-back pain: a randomized controlled trial. Clin Rehabil. 2020;34(7):948-59. http://doi.org/10.1177/0269215520927076
- Kampshoff CS, van Mechelen W, Schep G, Nijziel MR, Witlox L, Bosman L, et al. Participation in and adherence to physical exercise after completion of primary cancer treatment. Int J Behav Nutr Phys Act. 2016;13(1):100. http://doi.org/10.1186/ s12966-016-0425-3
- 22. Teodózio CGC, Marchito LO, Fabro EAN, Macedo FO, Aguiar SS, Thuler LCS, et al. Shoulder amplitude movement does not influence postoperative wound complications after breast cancer surgery: a randomized clinical trial. Breast Cancer Res Treat. 2020;184(1):97-105. http://doi.org/10.1007/s10549-020-05826-9
- 23. Petito EL, Nazário AC, Martinelli SE, Facina G, Gutiérrez MG. Application of a domicile-based exercise program for shoulder rehabilitation after breast cancer surgery. Rev Lat Am Enfermagem. 2012;20(1):35-43. http://doi.org/10.1590/ s0104-11692012000100006
- 24. Lokapavani Y, Krishna SR, Madhavi K. Influence of preoperative physical therapy education and exercise on post-operative shoulder ranger of motion and functional activities in subjects with modified radical mastectomy. Int J Physio. 2014[cited on Dec 8, 2020];1(4):170-7. https://doi.org/10.15621/ijphy/2014/v1i4/54556



#### **ORIGINAL ARTICLE**

https://doi.org/10.29289/2594539420210044

### Mastalgia in medical students: a prospective and multicentric study

Welington Lombardi<sup>1</sup> ©, Luciana Borges Lombardi<sup>1</sup> ©, Flávia Vicentin Silva<sup>1</sup>\* ©, Narhima Ahdlie Bou Abbas<sup>1</sup> ©, Eduardo Rogério Malaquias Chagas<sup>2</sup> ©, Daniel Guimarães Tiezzi<sup>3</sup> ©

#### ABSTRACT

**Introduction:** Mastalgia or breast pain affects most women, especially those of reproductive age. Of organic or nonorganic cause and variable intensity, it is related to factors such as hormonal, dietary, metabolic, and emotional changes, making it difficult to understand its pathophysiology and the definition of care conduct. It can influence the quality of life. The aim of this study was to identify, classify, and know the treatments and their effectiveness for breast pain in university students, relating their interference in the quality of life. **Methods:** A total of 1,064 students from two medical schools in the interior of São Paulo were interviewed and evaluated using a standardized and specific questionnaire with the aim of characterizing breast pain. **Results:** Mastalgia was reported in 1,034 students (p=0.0003), body mass index >25 increased breast tenderness by 4.3 times (RR=4.3; p=0.001; 95%CI 2.5–6.73), and sedentary lifestyle increased by 10.82 times (p=0.02). It was more common in the premenstrual cycle (p=0.002), and the greater the intensity, the smaller the number of students who performed the self-examination (p=0.02). The greater the pain, the greater the chance of being absent from classes (RR=15.82; p=0.0003; 95%CI 13.23–17.3). Drug treatment was applied in 15.54% of the cases, with satisfactory results in 92.16% of them (p=0.000004). **Conclusions:** The study showed a high incidence of breast pain in medical students, impairing their academic activities, making it clear the importance of investigating any symptom related to the hormonal axis and showing significant efficiency of the pharmacological treatment.

KEYWORDS: mastalgia; quality of life; activity, daily living; pharmacologic therapy.

#### INTRODUCTION

Mastalgia, also known as mastodinia, is the term used to define pain in female or male breasts, which may be related to increased sensitivity or even breast engorgement<sup>1,2</sup>. Despite cyclic or noncyclic mastalgia, it affects most women of reproductive age. When it is cyclic, i.e., associated with physiological processes and without an organic cause, it appears in the days before menstruation and disappears in the first days of the cycle. In the case of a non-cyclic character, the symptom is not related to the menstrual period<sup>3</sup>.

Its classification is based on non-cyclic mastalgia, cyclic mastalgia, and extramammary pain. In the cyclic case, it usually affects both breasts, with more prevalence in the lateral and upper regions of the breasts, radiating or not to the upper limbs. It is usually associated with breast thickening, constituting the group of benign alterations related to the functional response of

the organ. In this case, the pain usually decreases in the beginning of menstruation, which is the most common characteristic recorded in women aged 30–40 years, in a period close to premenopause. Acyclic pain, in turn, may result from specific breast disorders or anatomical changes resulting from conditions such as breast inflammation, previous trauma, fibrosis, neuralgia, joint pain, dermatitis, and phlebitis.

In this situation, it is more localized, unilateral, and continuous, generally affecting women aged between 30 and 50 years. The extramammary classification refers to pain originating from structures outside the anatomy of the female and male breasts, whether or not arising from the heart, lungs, and esophagus<sup>1.4</sup>.

Although the rates of breast cancer associated with mastodinia range from 0.5% to 3.3%, this differential diagnosis should be discarded since, in general, consultation with a specialist is

\*Corresponding author: flavia\_fvs@hotmail.com

<sup>&</sup>lt;sup>1</sup>Universidade de Araraquara, Faculty of Medicine – Araraquara (SP), Brazil.

<sup>&</sup>lt;sup>2</sup>Faculdade de Medicina de Catanduva – São Paulo (SP), Brazil.

<sup>&</sup>lt;sup>3</sup>Universidade de São Paulo, Faculty of Medicine – Ribeirão Preto (SP), Brazil.

Conflict of interests: nothing to declare. Funding: none.

Received on: 02/17/2022. Accepted on: 05/29/2022.

mainly due to concern about the suspicion of malignancy, a determining factor for suffering psychological condition of the affected women. Other differential diagnoses are inflammation of extramammary tissues, intercostal neuralgias, and chest pain related to cardiac conditions<sup>2</sup>.

The intensity of breast pain is characterized as mild when it does not change the patient's daily life, moderate when it bothers them but does not change their daily habits, and intense when it interferes with their tasks and prompts to use medication frequently. Its prognosis tends to be favorable with spontaneous resolution of the condition between 3 months and 3 years<sup>5</sup>.

Breast tenderness should be considered more as a symptom than a disease. It is, without a doubt, the most frequent complaint of patients in relation to the mammary glands and the most common cause of consultations in mastology outpatients. Although very frequent, the fact of not knowing well its pathophysiology, as well as where hormonal, dietary, metabolic, and emotional factors interact, has generated uncertainty as to the type of preferential care conduct to be offered to these women<sup>6</sup>.

Its correlation with psychological disorders, such as anxiety and depression, should also be taken into account in terms of quality of life. Thus, its early identification and treatment deserve special attention<sup>7</sup>.

Therefore, this study aims to identify the incidence of breast pain in university students, classify its intensity, survey the main treatments used and the response rates, and assess the degree of interference of this condition in the daily routine of these women.

#### METHODS

This is a prospective and observational study conducted in the period from 2010 to 2019, totaling 10 years of analysis. The research project was carried out jointly by two faculties of medicine in the interior of São Paulo and approved by the respective ethics committees, under the numbers PIC 149 and 35/08.

Medical students from both institutions answered a specific questionnaire with the aim of characterizing breast pain. Only academics who met the following criteria were selected: having menstruated at least once, 18 years of age or older, and who agreed to voluntarily answer the questionnaire, after providing detailed information and signing the free and informed consent form. The evaluation was applied in the classrooms of the respective courses throughout the period foreseen for the study. The questionnaire contained 24 questions on various topics, such as anthropometry, gynecological background, use of prostheses, smoking, characteristics and treatment of pain, physical activity, and ingestion of xanthines (e.g., coffee, tea, or refrigerant), so that standardized responses allowed for agility and speed in data collection and subsequent analysis. For statistical analysis, the JMP 9.0.2 software was used.

#### RESULTS

A total of 1,064 university students were interviewed, 580 from one institution and 484 from another, aged between 17 and 70 years, with an average of 22 years. Age at menarche ranged from 8 to 17 years, with a mean of 12 years. The body mass index (BMI) of the sample ranged from 15 to 44, with a mean of 22.

Of the 1,064 students, 107 were already pregnant (10.05%), 44 (4.13%) used silicone breast implants, and 55.02% wore a mediumsized bra. It was found that the size of the breasts did not show a direct relationship with the clinical presence or absence of mastalgia. Users of combined oral contraceptives had less breast pain compared to the other participants.

As for the intensity of the pain, 1,034 students reported bilateral mastalgia, in the majority, and in the lateral quadrants of the breast (p=0.0003) (Table 1).

It was observed that overweight and obesity (BMI>25) increased the relative risk (RR) for mastalgia by 4.3 times, compared to patients with adequate BMI (RR=4.3; p=0.001; 95%CI 2.5–6.73). A sedentary lifestyle was related to mastalgia in 65.81% patients who were at 10.82 times higher risk when compared to those who practiced physical activity at least once a week (p=0.02) (Table 2).

Breast pain was more common in the premenstrual period (60.46%) compared to the postmenstrual period (p=0.002). The greater the intensity of breast pain, the lower the number of students who performed breast self-examination (p=0.02) (Table 3), and the more intense the pain, the greater the chance of being absent from classes (RR=15.82; p=0.0003; 95%CI 13.23–17.3) (Table 4).

Of the total evaluated, 15.54% used nonsteroidal anti-inflammatory drugs (NSAIDs) for less than 3 months, with satisfactory results in 92.16% of cases (p=0.000004) (Table 5).

Table 1. Mastalgia intensity and the relationship between the breasts.

		Later	Tabal				
Intensity	Bila	teral	Unila	iteral	Totat		
	n (%)	n	n (%)	n	n	n (%)	
Severe	69.46	439	80.06	277	716	73	
Moderate	2.69	17	0.87	3	20	2	
Weak	27.85	176	19.08	66	242	25	
Total	100.00	632	100.00	346	978	100	

#### DISCUSSION

Mastalgia is predominantly a female symptom, and only 15% of affected women will need some therapeutic modality. The evolution of breast pain is important to determine its relationship with a natural process, such as hormonal or pathological changes. Usually, breast tenderness is linked to benign pathologies; however, the search for specialized care results from the concern with serious diseases, for example, breast cancer, even though it is a rare symptom of this disease<sup>1-3,6</sup>. Breast pain, in turn, is considered common, and about 70% of Western women will experience it at some point during menacme<sup>5.8</sup>. A study involving 1,700 women with a mean age of 34 years showed that about 52% had breast tenderness, especially those of advanced age, while 41% reported problems related to sexual health and another 35% to sleep<sup>9</sup>.

In general, the response of non-cyclic breast pain to drug treatment tends to be less positive than its cyclic form; however, its resolution tends to be spontaneous<sup>2</sup>. Cyclic breast pain

Physical activity						Tabal				
Intensity × Physical activity		None		1 × per week		2 × per week		TOLAL		
		n (%)	n	n (%)	n	n (%) n		n (%)	n	
	Severe	72.23	502	92.89	196	70.83	85	74	756	
Pain	Moderate	1.44	10	2.37	5	4.17	5	2	20	
	Weak	26.33	183	17.54	37	25.00	30	24	250	
Total		100.00	100.00	100.00	695	100.00	211	100.00	120	

#### Table 2. Intensity of pain related to physical activity.

#### Table 3. Link between pain intensity and self-examination.

	Self Exam									
Pain Intensity	Ye	25	N	o	Total					
	N (%)	Ν	N (%)	N	N (%)	N				
Severe	62.50	200	78.66	542	73.54	742				
Moderate	1.56	5	2.18	15	1.98	20				
Weak	29.69	95	22.06	152	24.48	247				
Total	100.00	320	100.00	689	100.00	1009				

RR: relative risk. RR 10.82; p=0.02; 95%CI 6.32–15.23.

#### Table 4. Link between absence in class and intensity of pain.

	Absence In Class									
Intensity	Ye	25	N	0	Grand total					
	n (%)	n	n (%)	n	n (%)	n				
Severe	73.77	748	33.33	1	73.65	749				
Moderate	1.87	19	33.33	1	1.97	20				
Weak	24.36	247	33.33	1	24.39	248				
Total	100.00	1.014	100.00	3	100.00	1.017				

RR: relative risk. RR 15.82; p=0.0003; 95%CI 13.23-17.3.

#### Table 5. Link between treatment time and pain intensity.

	Treatment Time										
Intensity	None		1 month		2 months		3 months		Grand total		
	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	
Severe	76	623	65	114	33	4	40	2	75	756	
Moderate	1	11	3	6	17	2	20	1	2	20	
Weak	21	171	32	56	50	6	40	2	23	235	
Total	100	818	100	176	100	12	100	5	100	1.011	

corresponds to 66% of all women consulted and is related to hormonal variation during the menstrual period. It is usually bilateral and has a premenstrual character, being more frequently referred to in the upper lateral quadrant of the breasts<sup>10</sup>. The acyclic type, in contrast, corresponds to the remaining 34% and is not related to the menstrual cycle, assuming a constant or intermittent character and, generally, unilateral and with a variable location. According to some studies, the etiologies are related to the volume of the enlarged breast, responsible for the distention of Cooper's ligaments, the diet rich in lipids, the lifestyle (sedentary lifestyle and smoking), and the presence of breast microcysts, mastitis, and hidradenitis suppurativa, but there is no consensus on the main etiology involved<sup>10,11</sup>.

Appropriate assessment and adequate exclusion of the possibility of malignancy already reduce about 78%–85% of complaints, as reported by some studies. For a group of 10%–22% of women who reported persistent breast pain, conservative measures would suffice. Breast cancer rarely presents breast pain as a single finding, and it is present in 0.5%–3.3% of the time. If present, it manifests as localized acyclic mastalgia with nodulation associated with the condition<sup>2.8</sup>.

The search for organic diseases in the context of breast pain is indicated when there is evidence of failure in behavioral therapy, which consists of changing the lifestyle and the patient's understanding of the symptom. The workup should be performed using screening mammography and breast ultrasound, when indicated. With benign findings and the persistence of symptoms, therapy should be initiated<sup>12,13</sup>.

Verbal guidance as a form of treatment for cyclic breast pain should always be the first recommended option, considering the vast array of possible therapies for these cases, including the prescription of several drugs that are often expensive, some of which have not always been proven to be effective and others with significant side effects<sup>7,14</sup>.

Treatment should only be proposed after the evaluation of each case, always followed by verbal guidance, thus avoiding drug treatment as a first approach. Only for persistent and unresponsive cases would drug therapy be indicated. Several drugs have been proposed, including placebos, whose response can reach 19%<sup>15</sup>.

Although other drugs can be used, the first choice, both in the case of cyclic and acyclic breast tenderness, should be considered for a minimum period of 6 months and include the use of a topical NSAID such as diclofenac. Studies show significant improvement in up to 90% of patients, with minimal side effects<sup>15</sup>.

The second line of treatment is indicated for patients with debilitating breast pain, resulting in significant impairment in their quality of life. The therapy consists of the use of tamoxifen 10 mg/day, an antiestrogen medication, with efficacy demonstrated in a meta-analysis, proving to be more effective than placebo, with statistical significance (from 71% to 96%). However, this medication is associated with numerous side effects, such

as exacerbation of menopausal symptoms such as hot flashes, vaginal dryness, joint pain, and cramping in the lower limbs, in addition to severe events such as cerebrovascular accident, endometrial cancer, and cataract; therefore, it has been little used. Thus, the medication is not routinely used in therapy, although it is recommended in some studies. In turn, gamma-linolenic acid, present in evening primrose oil, has shown positive results in the management of breast pain<sup>15,16</sup>.

As for the use of hormones in the treatment of patients with mastalgia, there are controversies, especially with regard to the cyclic nature, since it is not possible to know whether this breast pain is a consequence of the use of oral contraceptives<sup>16</sup>. The administration of isolated progesterone, especially medroxyprogesterone acetate, taken orally or topically, had a negative impact on the control of breast pain<sup>17</sup>. A double-blind study found that natural progesterone, in relation to placebo, administered vaginally, was proved to be beneficial, significantly reducing the pain and local sensitivity. After 6 months, sustained pain and tenderness suppression were observed, without relevant side effects, concluding the possibility of this being a safe alternative to hormonal treatment against breast pain<sup>18,19</sup>.

It would also be important to change lifestyle habits, such as quitting smoking, as tobacco users had high rates of breast pain, although there is no robust data to support this statement. Dietary reduction of foods with methylxanthine-like components, such as coffee, tea, and chocolates, can reduce mastalgia, as the biochemical characteristics of these components are capable of increasing cell proliferation, stimulating fibrocystic changes, and causing mastalgia. However, studies have shown that reducing its consumption does not significantly reduce breast tenderness in practice<sup>16,20</sup>.

#### CONCLUSIONS

We found that breast tenderness was a frequent symptom in medical students from the institutions studied and was related to a decrease in quality of life, work performance, and abstention from college classes. We observed that it was associated with a sedentary lifestyle, a fact that increased the risk of the symptom by 10 times compared to those who practiced physical exercise at least once a week. The risk of abstaining from classes was about 15 times higher in the group that reported breast pain compared to the group that did not have this symptom. Pharmacological treatment, for a period of less than 3 months, showed improvement in 92% of cases with this complaint.

#### **AUTHORS' CONTRIBUTION**

WL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LBL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft. FVS: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing – original draft. NABA: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing – original draft. ERMC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing-original draft, Writing – review & editing. DGT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

#### REFERENCES

- 1. Grullon S, Bechmann S. Mastodynia. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 32644675
- Ader DN, Shriver CD. Cyclical mastalgia: prevalence and impact in an outpatient breast clinic sample. J Am Coll Surg. 1997;185(5):466-70. https://doi.org/10.1016/s1072-7515(97)00095-1
- Scurr J, Hedger W, Morris P, Brown N. The prevalence, severity, and impact of breast pain in the general population. Breast J. 2014;20(5):508-13. https://doi.org/10.1111/tbj.12305
- 4. Tahir MT, Shamsudeen S. Mastalgia. Treasure Island (FL): StatPearls Publishing; 2021. PMID: 32965866.
- Iddon J, Dixon JM. Mastalgia. BMJ. 2013;347:f3288. https://doi. org/10.1136/bmj.f3288
- Minton JP, Foecking MK, Webster DJ, Matthews RH. Caffeine, cyclic nucleotides, and breast disease. Surgery. 1979;86(1):105-9. PMID: 222001
- Katar MK, Başer M. Relationship between mastalgia and anxiety-depression: an observational study. Cureus. 2021;13(1):e12734. https://doi.org/10.7759/cureus.12734
- Groen JW, Grosfeld S, Wilschut JA, Bramer WM, Ernst MF, Mullender MM. Cyclic and non-cyclic breast-pain: a systematic review on pain reduction, side effects, and quality of life for various treatments. Eur J Obstet Gynecol Reprod Biol. 2017;219:74-93. https://doi.org/10.1016/j.ejogrb.2017.10.018
- 9. Rosolowich V, Saettler E, Szuck B; BREAST DISEASE COMMITTEE. Mastalgia. J Obstet Gynaecol Can. 2006;28(1):49-57. https://doi.org/10.1016/S1701-2163(16)32027-8
- Davies EL, Gateley CA, Miers M, Mansel RE. The long-term course of mastalgia. J R Soc Med. 1998;91(9):462-4. https://doi. org/10.1177/014107689809100903
- 11. Wisbey JR, Kumar S, Mansel RE, Peece PE, Pye JK, Hughes LE. Natural history of breast pain. Lancet. 1983;2(8351):672-4. https://doi.org/10.1016/s0140-6736(83)92543-6

- 12. Leung JW, Kornguth PJ, Gotway MB. Utility of targeted sonography in the evaluation of focal breast pain. J Ultrasound Med. 2002;21(5):521-6;quiz528-9. https://doi.org/10.7863/jum.2002.21.5.521
- 13. Leddy R, Irshad A, Zerwas E, Mayes N, Armeson K, Abid M, et al. Role of breast ultrasound and mammography in evaluating patients presenting with focal breast pain in the absence of a palpable lump. Breast J. 2013;19(6):582-9. https://doi.org/10.1111/tbj.12178
- Preece PE, Mansel RE, Hughes LE. Mastalgia: psychoneurosis or organic disease? Br Med J. 1978;1(6104):29-30. https://doi. org/10.1136/bmj.1.6104.29
- Colak T, Ipek T, Kanik A, Ogetman Z, Aydin S. Efficacy of topical nonsteroidal antiinflammatory drugs in mastalgia treatment. J Am Coll Surg. 2003;196(4):525-30. https://doi. org/10.1016/S1072-7515(02)01893-8
- Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of Mastalgia: a meta-analysis of randomised trials. Breast. 2007;16(5):503-12. https://doi. org/10.1016/j.breast.2007.03.003
- Maddox PR, Harrison BJ, Horobin JM, Walker K, Mansel RE, Preece PE, et al. A randomised controlled trial of medroxyprogesterone acetate in mastalgia. Ann R Coll Surg Engl. 1990;72(2):71-6. PMID: 2139769
- McFadyen IJ, Raab GM, Macintyre CC, Forrest AP. Progesterone cream for cyclic breast pain. BMJ. 1989;298(6678):931. https:// doi.org/10.1136/bmj.298.6678.931
- Nappi C, Affinito P, Di Carlo C, Esposito G, Montemagno U. Double-blind controlled trial of progesterone vaginal cream treatment for cyclical mastodynia in women with benign breast disease. J Endocrinol Invest. 1992;15(11):801-6. https:// doi.org/10.1007/BF03348808
- Hafiz SP, Barnes NLP, Kirwan CC. Clinical management of idiopathic mastalgia: a systematic review. J Prim Health Care. 2018;10(4):312-23. https://doi.org/10.1071/HC18026



## Overview of germline variants in the BRCA2 gene in cohort of Brazilian women with a high risk of hereditary breast cancer

Renata Mendes de Freitas<sup>1,2\*</sup> <sup>(i)</sup>, Gilda Alves<sup>3</sup> <sup>(i)</sup>, Maximiliano Ribeiro Guerra<sup>1</sup> <sup>(i)</sup>, Angélica Atala Lombelo Campos<sup>1</sup> <sup>(i)</sup>, Lucas Delmonico<sup>4</sup> <sup>(i)</sup>, Pedro Henrique de Oliveira Medeiros<sup>1</sup> <sup>(i)</sup>, Rafaela Russi Ervilha<sup>1</sup> <sup>(i)</sup>, Jane Rocha Duarte Cintra<sup>5</sup> <sup>(i)</sup>, Maria Teresa Bustamante Teixeira<sup>1</sup> <sup>(i)</sup>

#### ABSTRACT

Introduction: Malignant breast cancer is the second most common type of cancer among women in the world, leaving behind nonmelanoma skin cancer. The aim of this study was to identify germline variants in the *BRCA1* and *BRCA2* genes in women diagnosed with breast cancer in the southeastern region of Brazil. Methods: This study is part of a retrospective study, performed from a hospital-based cohort, consisting of 522 women. 92 patients were excluded from the study because they had carcinoma in situ and did not present clinical information, totaling 430 patients. Of these, we performed molecular investigation in 46 patients. *BRCA2* variants were detected in 10/46 (22%) women. From 7 missense variants identified, 5 and 2 showed benign and uncertain significance, respectively. Two synonymous variants not previously reported were considered of uncertain significance (c.2622T>A; c.2721G>A), and one nonsense variant showed pathogenic clinical significance (c.2847T>A). **Results:** The results showed that gene sequencing in individuals with a high risk of hereditary cancer is necessary, as it may reveal new variants, or initially described with uncertain significance. **Conclusion:** Although this study was conducted with a small cohort of selected breast cancer patients, it reinforces the importance of investigating the Brazilian population due to the finding of the pathogenic variant and genetic counseling.

KEYWORDS: breast cancer; BRCA2 gene; hereditary breast and ovarian cancer syndrome; Cohort study.

#### INTRODUCTION

Malignant breast cancer is the second most common type of cancer among women in the world, leaving behind nonmelanoma skin cancer<sup>1,2</sup>, and it has a multifactorial etiology associated with environmental and genetic factors<sup>3</sup>. In Brazil, 66,280 new cases of breast cancer are identified each year, corresponding to an estimated risk of 62 new cases per 100,000 women<sup>1</sup>.

It is known that the risk factors for the development of breast cancer are those related to a woman's reproductive life. For example, early age at menarche, late menopause, never having been pregnant or giving birth, first pregnancy after 30 years of age, and use of oral contraceptives and hormone replacement therapies in menopause can contribute to carcinogenesis<sup>3</sup>. In addition to hormonal factors, studies also indicate lifestyle-related risk factors, which include alcohol intake, smoking, physical inactivity, and exposure to ionizing radiation<sup>4</sup>.

However, hereditary predisposition is considered an important etiological factor. Approximately 5–25% of cancers are due to hereditary factors related to the multiple stages of carcinogenesis and may involve numerous genes, through gene mutations, chromosomal instabilities, gene amplifications, and epigenetic mechanisms. Among the main tumor suppressor genes involved in this process are the *BRCA1* and *BRCA2* genes<sup>5.6</sup>.

The identification of genes related to the development of hereditary cancer provides a better understanding of the disease and contributes to the management of control and earlier diagnosis<sup>7</sup>.

Some mutations in *BRCA1* and *BRCA2* are more prevalent in individuals from specific ethnic or geographical groups such as

\*Corresponding author: renatafreitas.mendes@gmail.com

**Conflict of interests:** nothing to declare. **Funding:** CAPES/PNPD Agency for the Postdoctoral Research Funding (Number Process: 88882.316108/2019–01).

<sup>&</sup>lt;sup>1</sup>Universidade Federal de Juiz de Fora, Postgraduate Program in Public Health – Juiz de Fora (MG), Brazil.

<sup>&</sup>lt;sup>2</sup>Fundação Oswaldo Cruz, Laboratory of Congenital Malformations – Rio de Janeiro (RJ), Brazil.

<sup>&</sup>lt;sup>3</sup>Universidade do Estado do Rio de Janeiro, Postgraduate Program in Medical Sciences – Rio de Janeiro (RJ), Brazil.

<sup>&</sup>lt;sup>4</sup>Universidade Federal do Rio de Janeiro, Instituto de Biofísica Carlos Chagas – Rio de Janeiro (RJ), Brazil.

<sup>&</sup>lt;sup>5</sup>Instituto Oncológico, Hospital Nove de Julho – Juiz de Fora (MG), Brazil.

Received on: 02/10/2022. Accepted on: 06/29/2022.

Caucasians and Ashkenazi Jews. This is due to the presence of initiating mutations in this population, which probably appeared several generations  $ago^{8-10}$ . There is evidence that the founding mutations – which are strongly related to hereditary breast and ovarian cancers (HBOC) and are identified in high penetration genes, such as *BRCA1*, *BRCA2*, and others – are the most prevalent pathogenic genetic alterations in the Brazilian population, due to the immigration events of European peoples to our country<sup>11-13</sup>.

The state of Minas Gerais, located in the southeastern region of Brazil and initially inhabited by South American Amerindians, has an estimated population of 21,292,666 inhabitants<sup>14</sup>. Its history is determined by the exploration of gold. Consequently, with the great mineral wealth, the state attracted residents from neighboring states, such as Rio de Janeiro and São Paulo, in addition to immigrants, mainly from Portugal, and African slaves who were brought to Brazil. According to Pena et al.<sup>15</sup>, European ancestry is prevalent in all Brazilian regions.

In Brazil, in the public health system, the genetic counseling services are principally located in university hospitals. They are carried out based on the investigation of clinical and family history in order to estimate the risk of hereditary cancer and the probability of pathogenic variants in predisposing genes. Genetic testing is offered to patients and families who meet some National Comprehensive Cancer Network (NCCN) eligibility criteria for hereditary breast cancer<sup>7</sup>.

The aim of this study was to screen and verify the prevalence of variants in the *BRCA1* and *BRCA2* genes by Sanger DNA sequencing of blood samples of 46 selected and unrelated women, with clinical evidence of HBOC in the state of Minas Gerais<sup>15</sup>. The comprehensive interpretation of the identified *BRCA2* variants was challenging for the genetic counseling support team.

#### METHODS

#### Patients

This study is part of a retrospective study, performed from a hospital-based cohort, consisting of 522 women diagnosed with breast cancer between 2014 and 2016, and treated at an oncology referral center in the Zona da Mata of Minas Gerais, in the southeastern region of Brazil<sup>16</sup>. Through the criteria used to assess hereditary breast cancer risk, recommended by the NCCN<sup>17</sup>, women were classified into two categories: increased and usual risk for hereditary breast cancer. The group with an increased risk for hereditary breast cancer considered the presence of at least one of the clinical criteria for HBOC Syndrome, such as age at diagnosis  $\leq$ 45 years; triple-negative subtype diagnosed in women aged  $\leq$ 60 years; diagnosis of breast cancer between ages of 46 and 50 years, with at least one first- or second-degree relative with malignant neoplasm in the breast or ovary; and a personal history of breast cancer with the presence of secondary malignant tumor in the same organ. The study excluded women with in situ breast cancer (n=42) and those without information about at least one of the biomarkers of the tumor for estrogen, progesterone, and HER-2 (n=50). Among the 430 women diagnosed with invasive breast cancer who composed our study population, 127 (29.5%) were classified as at increased risk for HBOC Syndrome<sup>16</sup>, according to the criteria recommended by the NCCN<sup>17</sup> and 36.2% of women were users of the public health service.

Of the 522 women, 23 (4.41%) died and 2 (1.57%) were part of the increased risk group for HBOC.

The molecular investigations of *BRCA1* and *BRCA2* genes were performed in 46 of the 127 women diagnosed and were classified into the category of increased risk for hereditary breast cancer.

Clinical and pathological information was extracted from medical records, while the complementary information was obtained from contact with patients and the analysis of laboratory results, pathological anatomy<sup>18</sup>, and immunohistochemistry.

All procedures followed ethical recommendations and the study was approved by the Ethics Committee in Research of the Federal University of Juiz de Fora (protocol number 5342919.0.0000.5147). All subjects provided written consent for *BRCA* testing.

#### **DNA** isolation

Genomic DNA was extracted from buccal epithelial cells using organic solvents, according to Aidar and Line (2007). DNA concentration, purity, and integrity were assessed by spectrophotometry (Nanodrop 2000 – Thermo Fisher Scientific<sup>®</sup>, Waltham, MA)<sup>19</sup>.

#### Point mutation screening

The entire coding sequence and exon-intron boundaries of the *BRCA1* (NM\_007294.3) and *BRCA2* (NM\_000059.3) genes were evaluated and detected by polymerase chain reaction (PCR). PCR conditions and primer sequences are available (Supplementary Material). All PCR products were purified using Exo-SAP (Affymetrix<sup>®</sup>) and sequenced by the Sanger method with the BigDye Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher<sup>®</sup>), in ABI 3730 XL genetic analyzer. Copy number variations were not analyzed.

#### **Classification of variants**

The identified variants were consulted in reference databases (gnomAD, ExAC, BRCA Exchange, dbSNP, ClinVar, LOVD, and ABraOM – a Brazilian database). The new variants were registered in the LOVD (Leiden Open Variation Database). For the biological significance of all variants, the Mutation Taster software was used, and the variants were classified using the IARC-LOVD<sup>20</sup>.

#### RESULTS

#### **Germline variants**

Of the 46 samples evaluated for the presence of *BRCA* mutations, 10 genetic variants were identified as heterozygous in the

Proband	cDNA	Genomic localization (GRCh38)	Alteration	Mutation type	Clinical significance	dbSNP	ClinVar	GnomAD	ExAC	ALFA Project	ABRAOM
BC7	c.2622T>A	13: 32911114	p.Tre874Tre	Synonym	VUS	NF	NF	NF	NF	NF	NF
BC15	c.5744C>T	13: 32340099	p.Thr1915Met	Missense	Benign	rs4987117	T=0.008*	T=0.020*	T=0.018*	T=0.027*	T=0.017*
BC20	c.2847T>A	13: 32337202	p.Tyr949Ter	Nonsense	Pathogenic	rs886040449	NF	NF	NF	NF	NF
BC21	c.2721G>A	13: 32911213	p.Lys907Lys	Synonym	VUS	NF	NF	NF	NF	NF	NF
BC22	c.2813C>A c.2971A>G	13: 32337168 13: 32337326	p.Ala938Glu p.Asn991Asp	Missense	Benign	rs55773834 rs1799944	NF G=0.080	A=0.000 G=0.037*	A=0.000 G=0.053	A=0.000 G=0.038*	NF G=0.045*
BC25	c.2680G>A c.2971A>G	13: 32337035 13: 32337326	p.Val894Ile p.Asn991Asp	Missense	Benign	rs28897715 rs1799944	NF G=0.080	A=0.000* G=0.037*	A=0.000* G=0.053	A=0.000* G=0.038*	NF G=0.045*
BC28	c.2649C>A	13: 32911141	p.Phe883Leu	Missense	VUS	NF	NF	NF	NF	NF	NF
BC28	c.2641G>A	13: 32336996	p.Glu881Lys	Missense	VUS	NF	NF	NF	NF	NF	NF
BC41	c.3055C>G	13: 32337410	p.Leu1019Val	Missense	Benign	rs55638633	G=0.000*	G=0.000*	G=0.000*	G=0.000*	NF
BC45	c.2971A>G	13: 32337326	p.Asn991Asp	Missense	Benign	rs1799944	G=0.080	G=0.037*	G=0.053	G=0.038*	G=0.045*

Table 1. Variants identified in the BRC	A2 gene for the :	study population. Minas	Gerais State, Brazil, 2014–2016
	2		, ,

cDNA: Complementary DNA; GRCh38: Genome Reference Consortium Human Build 38; dbSNP: contains records of allele frequencies for specific population samples that are defined by each submitter and used in validating submitted variations. (O link para o site encontra-se no tópico Websites); ClinVar: ClinVar aggregates information about genomic variation and its relationship to human health. GnomAD: Genome Aggregation Database; ExAC: Exome Aggregation Consortium; ABRAOM: Arquivo brasileiro online de mutações; BC: Breast câncer; NF: not found; VUS: variants of uncertain significance. \*MAF: minor allele frequency (<1%).The gray shadings represent the new variants identified in the study population.

*BRCA2* gene (Table 1) in nine patients. The variant was considered benign, as the change generated in the nucleotide sequence did not impact the function of the protein or influence the phenotype (missense). However, some missense alterations of conflicting interpretation or unclassified variants and of the synonym type were considered "variants of uncertain significance" (VUS), that is, the variant is detected, but its effect on the function of the gene is unknown; and the variant that generated a premature stop codon (nonsense) was classified as pathogenic, since the alteration interrupts the function of the gene and, therefore, is highly likely to have clinical consequences<sup>21</sup>.

In this study, five missense variants identified as benign clinical impact; two missenses as VUS; two synonymous variants not previously reported with clinical impact of VUS; and a nonsense variant, with pathogenic clinical significance associated with HBOC were found.

All detected variants were investigated in the available databases (gnomAD, ExAC, BRCA Exchange, dbSNP, ClinVar, LOVD, and ABraOM). The identified VUS was classified in accordance with the American College of Medical Genetics and Genomics criteria<sup>21</sup>, and submitted to the LOVD database. The minor allele frequency (MAF) of the altered allele, shown in the databases in the South Latin American population, is listed in Table 1. Rare variants were defined as MAF <1% and common variants as MAF >5%<sup>22</sup>.

#### Clinicopathological characterization

Of the 46 Brazilian women analyzed, 9 patients had variants in the *BRCA2* gene, and the average age of breast cancer diagnosis was 47.3 years (35–75 years), among self-reported white and nonwhite ethnoracial groups, users of the public health system (SUS) or private health system. Only three patients reported a positive family history of breast cancer (CM7, CM15, and CMCM28). We also assessed the overall survival of each woman, from the period in which the diagnosis was made until 2019 (Table 2). All of the abovementioned information on 46 women is summarized in the Supplementary Material.

#### Pathogenic variant

The CM20 proband, with a molecular finding of pathogenic implication (Figure 1), a self-reported non-white user of the private health service, was diagnosed at 45 years old in 2016 when identifying a palpable retroareolar lesion on the left breast, confirmed by mammographic screening images. During anamnesis, she did not have comorbidities or use hormone replacement therapy. The clinical TNM estimate was at stage IIIB, which is considered an advanced stage in this study. In an interview with a geneticist, she reported having a positive family history of cancer, with limited information about her parents and relatives. The patient was the first case of breast carcinoma in the family. This information is illustrated in Figure 2.

The biopsy result indicated invasive ductal carcinoma of histological grade 3, tumor size  $\leq 2$  cm with areas of carcinoma in situ and invasive component, solid patterns and comedonecrosis, and the presence of committed lymph nodes and left axilla with carcinoma macrometastasis in one isolated lymph node. Furthermore, the biopsied material from the periareolar lesion of the left breast showed changes in columnar cells without atypia and ectasia, apocrine metaplasia, intraductal papillomas, and florid ductal hyperplasia with the pathological TNM staging pT1c.

The immunohistochemistry analysis demonstrated the positivity of estrogen and progesterone receptors, negative HER2 expression, positive p53 marker, and Ki-67 of 15%. Additionally, the tumor has been classified as luminal subtype B.

Proband	Age at diagnosis	Self- reported ethnoracial group	Health system	Tumor laterality	Tumor size	Lymph nodes committed	GН	Immunophenotype	Ki-67 (%)	рТММ	FH of breast cancer	HRT
CM7	43	White	Public	R	≥2 cm	No	3	Luminal B ER+, PR–, Her2–	≥25	T2N1M0	Yes	No
CM15	75	White	Private	L	≤2 cm	No	2	Triple-negative	≥25	T1N0M0	Yes PH: hysterectomy at 30 years old	NR
СМ20	45	Non-white	Private	L	≤2 cm	Yes	3	Luminal B ER+, PR+, Her2–	<25	T4N1M0	No	No
CM21	44	White	Private	R	≤2 cm	No	2	Luminal A ER+, PR+, Her2–	≤25	T1N0M0	No	NR
CM22	41	White	Private	L	≥2 cm	No	2	Luminal B ER+, PR+, Her2–	≥25	T1N0M0	No PH: fibroadenoma	No
CM25	44	Non-white	Public	R	≤2 cm	No	2	Luminal B ER+, PR+, Her2-	≥25	T1N0M0	No	No
CM28	61	Non-white	Private	L	≥2 cm	No	3	Overexpression Her2	≥25	TONOMO	Yes PH: bilateral oophorectomy, hysterectomy and salpingectomy.	Yes
CM41	35	White	Public	L	≥2 cm	No	3	Triple-negative	≥25	T2N0M0	No	No
CM45	38	Non-white	Public	L	≥2 cm	Yes	3	Luminal B ER+, PR+, Her2–	<25	T2N1M0	No	No

	<u> </u>				1 C 1	
Table 2	( linical	characteristics of	natients and histo	Inathologic	ral findings of	hreast carcinomas
TODIC L.	Cunica		putients and moti	putriologit	cut i munigo oi	

GH: histological grade (provided by the Nottingham classification system); pTNM: pathological TNM<sup>18</sup>: tumor, linfonodo, metástase; FH: familial history; PH: personal history; HRT: hormone replacement therapy; NR: not reported. Ki: Ki67 is a nuclear antigen that is an excellent marker of active cell proliferation in the normal and tumor cell populations; ER: estrogen receptors; PR: Progesterone receptor. Her2: human epidermal growth factor receptor 2.

There was no systemic metastasis at diagnosis as well as no locoregional recurrence or distant metastasis during the course of treatment or follow-up. Regarding the therapeutic approach, a radical mastectomy of the affected breast (left) was performed, followed by adjuvant chemotherapy and radiotherapy, along with hormone therapy, which was prescribed for 10 years.

#### DISCUSSION

The use of genomic sequencing techniques has been a fundamental tool in the establishment of genetic diseases, particularly in those where multiple genes can be affected<sup>23</sup>. In this sense, the cause of hereditary predisposition to cancer can be elucidated and help to develop new applications for both the clinic and scientific research<sup>24</sup>. The *BRCA2* gene, a tumor suppressor located on chromosome 13, encodes a protein of 3,428 amino acids and is responsible for repairing the breaks in the double strand of DNA, together with the RAD51 protein<sup>25.26</sup>.

Approximately, 1 in 800 women carry *BRCA2* mutations. Similar to the *BRCA1* gene, *BRCA2* is related to 10–15% of hereditary cancers; moreover, the *BRCA2* mutation confers up to 85 and 27% of the cumulative risk of developing breast and ovarian cancers, respectively, throughout life<sup>27,28</sup>.

There are some management options that seek to reduce the risk in patients with mutations in known genes that confer high and moderate risk of HBOC, including bilateral risk-reducing mastectomy, salpingo-oophorectomy, chemoprevention, and intensive surveillance with annual breast magnetic resonance imaging<sup>29</sup>. Studies seek to screen the most prevalent mutations







\*\*AD: Age of diagnosis (years)

Figure 2. Heredogram of breast cancer 20 proband.

in *BRCA* in order to reduce costs through a method that is faster and more efficient in detecting mutations in *BRCA1* and *BRCA2*. This strategy would make it possible to include a greater number of investigated patients and a more accurate treatment, offering greater benefits to them<sup>30</sup>.

After identifying carriers of *BRCA* mutations, genetic counseling and testing for individuals at increased risk results in control and allows the use of risk-reducing strategies, which often lead to the prevention of primary or secondary tumors and an increased survival rate of the carriers<sup>7</sup>. Regarding these benefits, a study by Palmero et al.<sup>7</sup> warns of the limited genetic testing in Brazil, caused by the reduced supply, since medical genetics services are predominantly located in university hospitals. Furthermore, genetic testing is only offered to those families that fulfill the NCCN criteria for a hereditary breast cancer syndrome through local, national, and/or international collaborative research studies, once genetic testing is not covered by the Brazilian Public Health System.

In this study, we did not find any genetic variants in the *BRCA1* gene. However, in the *BRCA2* gene, we identified 9 singlenucleotide variants in 10 women diagnosed with breast cancer, with an average age of 47.2 years (SD=12.71). Two missense variants, rs4987117 and rs1799944, have already been identified in two other Brazilian studies. The latter was present in three women with the luminal subtype B tumor<sup>31,32</sup>. The variant rs4987117 was identified in 4 of 30 (13.3%) probands with triple-negative breast cancer, corroborating our finding<sup>33</sup>; it was less frequent in a cohort of 117 cases with sporadic breast cancer (positive estrogen receptor), in Poland (OR=0.39; 95%CI 0.19–0.82; p=0.013)<sup>34</sup>. Therefore, Meyer et al.<sup>33</sup> classified the variant as a "probable risk" for triple-negative breast cancer.

The missense variants rs28897715 and rs55638633, also with a benign clinical effect, were not detected in any other Brazilian study. The study by Balia et al. (2011) [35] describes the rs55638633 variant in a 39-year-old metastatic case (4 compromised lymph nodes out of 18 analyzed) with invasive ductal breast carcinoma (luminal subtype B), and histological grade 3. In the referred work, this variant is reported in the BIC (http:// research.nhgri.nih.gov/bic/) 22 times. In our study, a 35-year-old patient presented the same variant with breast cancer, a triple-negative subtype, without any family history of cancer<sup>35</sup>.

Another missense variant rs55773834 is referred to as probably benign (1) and VUS (8) in ClinVar, but not reported in other Brazilian studies. In general, VUSs are missense substitutions that result in changes to a single nucleotide, but they may also include small deletions, insertions, or other effects that may be unknown<sup>25</sup>. Therefore, the VUSs and its variants with conflicting interpretations represent a challenge for genetic counseling, because more genetic information is necessary to elucidate the clinical impacts in relation to the predisposition to cancer<sup>36</sup>.

Four newly identified variants were found, two being missense and two being synonymous changes. It is known that synonymous substitutions can alter the splicing site, creating or destroying a donor or receptor site, which can modify the protein translation, the mRNA structure, and the protein folding<sup>29</sup>.

The nonsense variant rs886040449 with a pathogenic clinical effect, mentioned in ClinVar, has no previous identification references in Brazilian studies - not even in the largest multicenter Brazilian study, conducted by Palmero et al. to track mutations in BRCA<sup>29</sup>. The study by Li et al. identified a family in which the proband had breast cancer at the age of 21 years and a recurrence at the age of 36 years, with a family history of an older sister diagnosed with breast cancer at the age of 60 vears. However, this reference is from a single nucleotide (delT) deletion in amino acid 949 of exon 11 BRCA2 gene<sup>37</sup>. Our finding is related to a single nucleotide substitution in the same amino acid. Pathogenic variants in the BRCA1/BRCA2 genes are significantly associated with an increased risk of breast, ovarian, pancreatic, and prostate cancer<sup>38</sup>. Thus, carriers of mutations can become eligible for and, therefore, beneficiaries of treatments with polyADP-ribose-polymerase inhibitors in advanced and recurrent ovarian, breast, pancreatic, and prostate carcinomas.

According to the Brazilian Society of Medical Genetics and some studies on care in the field of genetics carried out in Brazil, there are few genetic professionals for the territorial dimension of our country, the concentration of services is in large urban centers, and there are difficulties in accessing specialized services in the public health service. We know the benefits of counseling and genetic testing in risk management. To minimize limitations on access to specialized services, Achatz et al.<sup>6</sup> recommended a series of strategies that can overcome barriers to adequate early diagnosis and management of identified cases of HBOC in Brazil.

The VUSs, which are routinely identified in genetic testing, are reclassified as benign in 90–95% of cases<sup>21</sup>. The VUS investigation of the Brazilian population, such as the ones described here, is essential for us to know the genetic variability of our population and, thus, for us to have more appropriate data to evaluate the phenotypes and genotypes of individuals.

#### CONCLUSION

Although this study was conducted with a small cohort of selected breast cancer patients, it reinforces the importance of investigating the Brazilian population due to the finding of the pathogenic variant, not yet reported in the country as well as the VUS. In patients in whom no pathogenic variant was identified, the screening of other hereditary breast cancer genes should be implemented in the future. Therefore, our study provides relevant information for the genetic counseling of hereditary Brazilian breast cancer patients.

#### Websites

GnoAD: https://gnomad.broadinstitute.org ClinVar: https://www.ncbi.nlm.nih.gov/clinvar dbSNP: https://www.ncbi.nlm.nih.gov/snp LOVD: https://databases.lovd.nl/shared/genes/BRCA2 ABraOM: http://abraom.ib.usp.br EXAC: http://exac.broadinstitute.org BRCA EXCHANGE: https://brcaexchange.org VARSOME: https://varsome.com/variant

#### ACKNOWLEDGMENTS

Our sincere thanks to Dr. Fernando Regla Vargas of FIOCRUZ's Laboratory of Epidemiology of Congenital Malformations, to all professionals at the 9 de Julho Hospital/Oncological Institute of Juiz de Fora, Minas Gerais, Brazil, and to the CAPES/ PNPD agency for the postdoctoral research (number process 88882.316108/2019-01).

#### **AUTHORS' CONTRIBUTIONS**

RMF: Conceptualization, Data Curation, Formal Analysis, Methodology, And Writing – Original Draft. GA: Project Administration, Visualization, Writing – Original Draft. MRG: Supervision, Writing – Review & Editing. AALC: Data Curation, Validation. LD: Investigation, Methodology, Writing – Original Draft. PH: Data Curation; Validation. OM: Data Curation; Validation. RRE: Methodology, Writing – Original Draft. JRDC: Supervision, Validation, Writing – Review & Editing. MTBT: Supervision, Writing – Review & Editing.

#### REFERENCES

- Instituto Nacional do Câncer José Alencar Gomes da Silva (INCA). Estimativa 2020 – incidência de câncer no Brasil. Rio de Janeiro: Ministério da Saúde; 2019.
- Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi. org/10.3322/caac.21492
- Paula BL, Santos RS, Lima PS, Paula NM, Reis AAS. Os genes BRCA1 e BRCA2 e suas relações genéticas na predisposição aos carcinomas mamários hereditários e esporádicos. Estudos, Goiânia. 2012;339(2):199-208. http://doi.org/10.18224/est. v37i6.1898
- Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk Factors and Preventions of Breast Cancer. Int J Biol Sci. 2017;13(11):1387-97. http://doi.org/10.7150/ijbs.21635
- Coelho A, Santos M, Caetano R, Piovesan C, Fiuza L, Machado R, et al. Predisposição hereditária ao câncer de mama e sua relação com os genes *BRCA1* e *BRCA2*: revisão de literatura. RBAC. 2018;50(1):17-21. http://doi.org/10.21877/2448-3877.201800615
- Achatz MI, Caleffi M, Guindalini R, Marques RM, Nogueira-Rodrigues A, Ashton-Prolla P. Recommendations for Advancing the Diagnosis and Management of Hereditary Breast and Ovarian Cancer in Brazil. JCO Glob Oncol. 2020;6:439-52. http://doi.org/10.1200/JGO.19.00170
- Palmero EI, Campacci N, Schüler-Faccini L, Giugliani R, Rocha JCCD, Vargas FR, et al. Cancer-related worry and risk perception in Brazilian individuals seeking genetic counseling for hereditary breast cancer. Genet Mol Biol. 2020;43(2):e20190097. http://doi.org/10.1590/1678-4685-GMB-2019-0097

- Neuhausen SL, Godwin AK, Gershoni-Baruch R, Schubert E, Garber J, Stoppa-Lyonnet D, et al. Haplotype and phenotype analysis of nine recurrent BRCA2 mutations in 111 families: results of an international study. Am J Hum Genet. 1998;62(6):1381-8. http://doi.org/10.1086/301885
- Sakorafas GH, Tsiotou AG. Genetic predisposition to breast cancer: a surgical perspective. Br J Surg. 2000;87(2):149-62. http://doi.org/10.1046/j.1365-2168.2000.01347.x
- Iau PT, Macmillan RD, Blamey RW. Germ line mutations associated with breast cancer susceptibility. Eur J Cancer. 2001;37(3):300-21. http://doi.org/10.1016/s0959-8049(00)00378-6
- Ewald IP, Izetti P, Vargas FR, Moreira MA, Moreira AS, Moreira-Filho CA, et al. Prevalence of the BRCA1 founder mutation c.5266dupin Brazilian individuals at-risk for the hereditary breast and ovarian cancer syndrome. Hered Cancer Clin Pract. 2011;9(1):12. http://doi.org/10.1186/1897-4287-9-12
- Ashton-Prolla P, Vargas FR. Prevalence and impact of founder mutations in hereditary breast cancer in Latin America. Genet Mol Biol. 2014;37(Suppl 1):234-40. http://doi.org/10.1590/s1415-47572014000200009
- Giacomazzi J, Graudenz M, Osorio C, Koehler-Santos P, Palmero E, Zagonel-Oliveira M, et al. Prevalence of the TP53 p.R337H mutation in breast cancer patients in Brazil. PLoS One. 2014;9(6):e99893. http://doi.org/10.1371/journal. pone.0099893
- Instituto Brasileiro de Geografia e Estatística (IBGE). Cidades e Estados. 2021[cited on Mar 2, 2021]. Available from: www. ibge.gov.br.
- Pena SDJ, Santos FR, Tarazona-Santos E. Genetic admixture in Brazil. Am J Med Genet C Semin Med Genet. 2020;184(4):928-38. http://doi.org/10.1002/ajmg.c.31853

- Freitas RM, Guerra MR, Fayer VA, Campos AAL, Cintra JRD, Warren J, et al. Histological and immunohistochemical characteristics for hereditary breast cancer risk in a cohort of Brazilian women. Rev Bras Ginecol Obstet. 2022. http://doi.org/10.1055/s-0042-1743103
- National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology – genetic/familial high-risk assessment: breast, ovarian and pancreas. NCCN Guidelines Version 1. 2020[cited on Jul 20, 2021]. Available from: https://www.nccn.org/
- Aidar M, Line SR. A simple and cost-effective protocol for DNA isolation from buccal epithelial cells. Braz Dent J. 2007;18(2):148-52. http://doi.org/10.1590/s0103-64402007000200012
- Vallée MP, Francy TC, Judkins MK, Babikyan D, Lesueur F, Gammon A, et al. Classification of missense substitutions in the BRCA genes: a database dedicated to Ex-UVs. Hum Mutat. 2012;33(1):22-8. http://doi.org/10.1002/humu.21629
- 20. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24. http:// doi.org/10.1038/gim.2015.30
- Bodian DL, McCutcheon JN, Kothiyal P, Huddleston KC, Iyer RK, Vockley JG, et al. Germline variation in cancersusceptibility genes in a healthy, ancestrally diverse cohort: implications for individual genome sequencing. PLoS One. 2014;9(4):e94554. http://doi.org/10.1371/journal.pone.0094554
- 22. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4. http:// doi.org/10.1245/s10434-010-0985-4
- 23. Trujillano D, Bertoli-Avella A, Kumar Kandaswamy K, Weiss M, Köster J, Marais A, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. Eur J Hum Genet. 2017;25(2):176-82. http://doi.org/10.1038/ejhg.2016.146
- 24. Torrezan GT, Almeida FGDSR, Figueiredo MCP, Barros BDF, Paula CAA, Valieris R, et al. Complex landscape of germline variants in Brazilian patients with hereditary and early onset breast cancer. Front Genet. 2018;9:161. http://doi.org/10.3389/fgene.2018.00161
- 25. Guidugli L, Carreira A, Caputo SM, Ehlen A, Galli A, Monteiro NA, et al. Functional assays for analysis of variants of uncertain significance in BRCA2. Hum Mutat. 2014;35(2):151-64. http:// doi.org/10.1002/humu.22478
- 26. Freitas RM, Medeiros P, Guerra MR, Bustamante-Teixeira MT. Hereditary breast cancer – what we have learned in the last decade. Mastology. 2021;31:e20210041. https://doi. org/10.29289/2594539420210041
- Walavalkar V, Khan A, Kandil D. Familial breast cancer and genetic predisposition in breast cancer. Precision Molecular Pathology of Breast Cancer. 2015;10:15-37. https://doi. org/10.1007/978-1-4939-2886-6\_2

- Yamauchi H, Takei J. Management of hereditary breast and ovarian cancer. Int J Clin Oncol. 2018;23(1):45-51. https://doi. org/10.1007/s10147-017-1208-9
- 29. Palmero EI, Carraro DM, Alemar B, Moreira MAM, Ribeiro-Dos-Santos Â, Abe-Sandes K, et al. The germline mutational landscape of BRCA1 and BRCA2 in Brazil. Sci Rep. 2018;8(1):9188. https://doi.org/10.1038/s41598-018-27315-2
- 30. Dąbrowski A, Ułaszewski S, Niedźwiecka K. Rapid and easy detection of the five most common mutations in BRCA1 and BRCA2 genes in the Polish population using CAPS and ACRS-PCR methods. Acta Biochim Pol. 2019;66(1):33-37. https://doi. org/10.18388/abp.2018\_2654
- 31. Palmero EI, Alemar B, Schüler-Faccini L, Hainaut P, Moreira-Filho CA, Ewald IP, et al. Screening for germline BRCA1, BRCA2, TP53 and CHEK2 mutations in families at-risk for hereditary breast cancer identified in a population-based study from Southern Brazil. Genet Mol Biol. 2016;39(2):210-22. https://doi.org/10.1590/1678-4685-GMB-2014-0363
- 32. Cipriano Júnior NM, Brito AM, Oliveira ES, Faria FC, Lemos S, Rodrigues NA, et al. Mutation screening of TP53, CHEK2 and BRCA genes in patients at high risk for hereditary breast and ovarian cancer (HBOC) in Brazil. Breast Cancer. 2019;26(3):397-405. https://doi.org/10.1007/s12282-018-00938-z
- 33. Meyer P, Landgraf K, Högel B, Eiermann W, Ataseven B. BRCA2 mutations and triple-negative breast cancer. PLoS One. 2012;7(5):e38361. https://doi.org/10.1371/journal. pone.0038361
- 34. Krupa R, Sliwinski T, Morawiec Z, Pawlowska E, Zadrozny M, Blasiak J. Association between polymorphisms of the BRCA2 gene and clinical parameters in breast cancer. Exp Oncol. 2009;31(4):250-1. PMID: 20010525
- 35. Balia C, Galli A, Caligo MA. Effect of the overexpression of BRCA2 unclassified missense variants on spontaneous homologous recombination in human cells. Breast Cancer Res Treat. 2011;129(3):1001-9. https://doi.org/10.1007/s10549-011-1607-y
- 36. Richardson M, Hu C, Lee K, LaDuca H, Fulk K, Durda K, et al. Strong functional data for pathogenicity or neutrality classify BRCA2 DNA-binding-domain variants of uncertain significance. Am J Hum Genet. 2021;108(3):458-68. https://doi. org/10.1016/j.ajhg.2021.02.005
- 37. Li S, Tseng H, Yang T, Liu C, Teng S, Huang H, et al. Molecular characterization of germline mutations in the BRCA1 and BRCA2 genes from breast cancer families in Taiwan. Hum Genet. 1999;104(3):201-4. https://doi.org/10.1007/ s004390050936
- 38. Kuchenbaecker K, Hopper J, Barnes D, Phillips K, Mooij T, Roos-Blom M, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-16. https://doi.org/10.1001/jama.2017.7112



## De novo gastric metastasis from invasive lobular carcinoma of the breast: report of three cases and literature review

Jessica Gonzalez Suerdieck<sup>1</sup> ©, Juliana Alves Souza<sup>1</sup> ©, Mateus Mattioni<sup>1</sup> ©, Almir Galvão Vieira Bitencourt<sup>1</sup>\* ©

#### ABSTRACT

Invasive lobular carcinoma is the second most common subtype of invasive breast cancer and presents with an unusual metastatic pattern. Its gastric metastasis mimics primary adenocarcinoma and the differentiation between them is difficult but primordial for proper treatment. The aim of this study is to report three cases of de novo Invasive lobular carcinoma of the breast, diagnosed with gastric metastasis at presentation. Neither of the patients complained about breast symptoms before the diagnosis. The final diagnosis was made only by comparing breast and gastric samples.

KEYWORDS: gastric metastasis; breast neoplasms; invasive lobular carcinoma; ultrasound; magnetic resonance imaging; 18F-FDG PET/CT.

#### INTRODUCTION

Invasive lobular carcinoma (ILC) is the second most common subtype of invasive breast cancer, accounting for about 5-15% of cases<sup>1-3</sup>. It has a typical histopathological appearance of poorly cohesive cells<sup>1</sup>.

ILC is associated with the absence of E-cadherin that influences the tendency to spread among collagen fibers with less desmoplastic response and becomes more likely to migrate to distant places of the primary tumor<sup>4,5</sup>. This increases the rates of multicentricity and bilaterality and results in an unusual metastatic<sup>3,6-8</sup>.

Although rare, metastatic spread to the stomach stands out by being highly related to ILC and very difficult to differentiate from primary adenocarcinoma<sup>2,3,5-12</sup>. For this reason, previous studies questioned the real frequency of gastric metastasis from breast cancer, which might be underestimated<sup>13</sup>.

The aim of this study is to report three cases of de novo ILC of the breast, diagnosed with gastric metastasis at presentation, and to review the literature about the pattern of metastasis.

#### **CASE REPORTS**

#### Case 1

A 70-year-old woman presented with gastrointestinal (GI) symptoms developed in a 2-month period. An upper GI (UGI) endoscopy demonstrated a diffuse infiltrative lesion with thickening and rigidity of the gastric walls (Figure 1A), suggestive of linitis plastica. An initial histopathological study revealed a poorly differentiated adenocarcinoma with poorly cohesive cells. 18F-FDG PET/CT showed diffuse uptake of the gastric wall thickening (Figure 1B) along with focal uptakes of multiple lymph nodes, irregular lesions in the right breast (Figure 1C), and bone lesions. Ultrasound showed a hypoechoic nodule with an irregular shape and indistinct margins in the upper-outer quadrant of the right breast (Figure 1D). A core biopsy was performed, and the histopathological study revealed a pleomorphic ILC. After comparing the samples, the final diagnosis was a metastasis of breast carcinoma.

<sup>1</sup>Hospital A.C. Camargo Cancer Center, Department of Imaging – São Paulo (SP), Brazil. **Corresponding author:** almirgvb@yahoo.com.br **Conflicts of interest:** nothing to declare. **Funding:** none. **Received on:** 06/01/2022. **Accepted on:** 06/21/2022.



**Figure 1.** (A) UGI endoscopy showing diffuse infiltrative lesion with thickening of the gastric walls. (B) 18F-FDG PET/CT with diffuse uptake of the gastric wall thickening. (C) 18F-FDG PET/CT with irregular lesion in the right breast. (D) Ultrasound revealing a hypoechoic nodule with irregular shape and indistinct margins in the upper-outer quadrant of the right breast.

#### Case 2

A 42-year-old woman presented with GI symptoms developed in 3 months. An UGI endoscopy showed diffuse thickening and rigidity of the gastric walls (Figure 2A). Abdominal magnetic resonance imaging (MRI) demonstrated concentric thickening of the antrum and gastric body along with mesenteric lymph nodes, liver lesions, and diffuse bone lesions, all of which showed an increased 18F-FDG uptake in PET/CT (Figure 2B). The gastric histopathological study demonstrated infiltration by carcinoma with discohesive cells with probable mammary origin. The patient denied any breast symptoms. Ultrasound showed a hypoechoic nodule with an irregular shape and an indistinct margin in the lower-inner quadrant (Figure 2C). A core biopsy was performed in the nodule of the right breast, and the histopathological study revealed classic ILC.



**Figure 2.** (A) UGI endoscopy showing diffuse thickening and rigidity of the gastric walls. (B) 18F-FDG PET/CT showing uptake along the concentric thickening of the antrum and gastric body. (C) Ultrasound revealing a hypoechoic nodule with irregular shape and indistinct margin in the right breast.

#### Case 3

A 53-year-old woman presented with epigastric pain developed in 3 months. An UGI endoscopy showed an elevated lesion in the distal body of the stomach that was biopsied, and the result was a poorly differentiated adenocarcinoma, but the immunohistochemical analysis suggested the possibility of metastasis from ILC. Breast MRI showed suspicious focal nonmass enhancements and osteoblastic lesions in both breasts (Figure 3A). PET/CT revealed focal uptakes in two areas in the left breast and ipsilateral lymph nodes. Second-look ultrasound showed discrete hypoechoic areas (Figure 3B), which corresponded to the PET/CT findings, and the core biopsy revealed classic ILC. The patient also had two ulcerated lesions in the caecum and descending colon seen on colonoscopy. After the diagnosis of ILC, a new evaluation of the previous biopsies of the GI tract was made and all of them were metastasis.

#### DISCUSSION

ILC is the second most common type of breast cancer<sup>1-3</sup> and shows a higher rate of multiplicity and bilaterality as presented by our patients.

The metastatic involvement of the GI tract by breast cancer is rare and usually not remembered in daily practice  $^{3,5,8\cdot12}$ . The most



**Figure 3.** (A) Breast MRI showing suspicious focal nonmass enhancements in both breasts. (B) Second-look ultrasound showing discrete hypoechoic areas in the left breast, which corresponded to PET/CT findings.

common spread is to the stomach with frequencies ranging from 0.3% to 35%, followed by the colon<sup>1-3,5,9,11</sup>. Considering metastatic breast involvement in the stomach, ILC accounts for 80% of the cases<sup>5,79-11,13</sup>.

Gastric metastasis of breast cancer usually appears years after the primary lesion treatment, i.e., between 2 and 7 years<sup>2,3,5,6,9-11</sup>. However, the patients in this study were diagnosed with gastric lesions at the same time as primary cancer. They were all initially considered to have primary gastric cancer and then investigated for breast lesions. Two of them did not even complain of breast symptoms.

This pattern of metastasis mimics the primary adenocarcinoma because it has similar symptoms, imaging and endoscopic features, and histopathological findings<sup>2,3,5-7,9-12</sup>. This implies that the correct diagnosis requires a high level of suspicion. Usually, when there is a metastatic gastric lesion from breast cancer, concurrent metastases are present, mainly in the skeleton, liver, and lungs<sup>3,6,9-11</sup>. In all of our cases, both bones and lymph nodes were involved.

The most common macroscopic appearance is linitis plastica<sup>3,5,6,8,11,12</sup>. Two of our cases manifested this form of tumor infiltration in the stomach, and all of them manifested nonspecific digestive symptoms.

The histopathological findings are similar between primary and metastatic lesions and, above all, the ILC may produce a signet ring morphology that is the most common pattern of primary adenocarcinoma<sup>3,5,9,10</sup>. For a definitive confirmation, a detailed immunohistochemical analysis may be needed<sup>3,4,6,8,11</sup>. Metastatic breast carcinoma is usually positive for CK7, GCDFP-15, and estrogen and progesterone receptors, and negative for CK20<sup>3,4,6,8,11</sup>. However, CK7 and hormonal receptors may be expressed in gastric adenocarcinomas<sup>9,11</sup>. The absence of E-cadherin is significantly related to metastatic breast carcinoma<sup>9,11</sup>.

Histologic comparison of the endoscopic biopsies with the breast carcinoma specimen is highly recommended<sup>11,13</sup>. All our patients first had a diagnosis of primary gastric adenocarcinoma and, after comparison, the diagnosis changed.

The importance of distinguishing primary gastric adenocarcinoma from metastatic breast ILC is that the two diagnoses lead to divergent treatments: while the metastasis is treated using systemic therapies (chemotherapy and/or hormonal therapy), the primary cancer is treated by surgery<sup>2,6,8,9,11</sup>.

#### CONCLUSIONS

Distinguishing primary gastric adenocarcinoma from metastatic breast ILC is essential, considering that the two diagnoses lead to divergent treatments. Therefore, this entity needs to be remembered as a differential diagnosis in clinical practice.

#### **AUTHORS' CONTRIBUTIONS**

JGS: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. JAS: Conceptualization, Methodology, Writing – review & editing. MM: Investigation, Methodology, Writing – review & editing. AGVB: Conceptualization, Methodology, Writing – review & editing.

#### REFERENCES

- Inoue M, Nakagomi H, Nakada H, Furuya K, Ikegame K, Watanabe H, et al. Specific sites of metastases in invasive lobular carcinoma: a retrospective cohort study of metastatic breast cancer. Breast Cancer. 2017;24(5):667-72. https://doi. org/10.1007/s12282-017-0753-4
- Clinton LK, Plesec T, Goldblum JR, Hajifathalian K, Downs-Kelly E, PatilDT.Specifichistopathologicfeaturesaidindistinguishing diffuse-type gastric adenocarcinoma from metastatic lobular breast carcinoma. Am J Surg Pathol. 2020;44(1):77-86. https:// doi.org/10.1097/PAS.00000000001341

- El-Hage A, Ruel C, Afif W, Wissanji H, Hogue JC, Desbiens C, et al. Metastatic Pattern of Invasive Lobular Carcinoma of the Breast — Emphasis on Gastric Metastases. Journal of Surgical Oncology. 2016;114(5):543-47. https://doi.org/10.1002/ jso.24362
- Reed AEM, Kutasovic JR, Lakhani SR, Simpson PT. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. Breast Cancer Research. 2015;17(1):12. https://doi. org/10.1186/s13058-015-0519-x
- 5. Eo WK. Breast cancer metastasis to the stomach resembling early gastric cancer. Cancer Res Treat. 2008;40(4):207-10. https://doi.org/10.4143/crt.2008.40.4.207
- Dória MT, Maesaka JY, Martins Filho SN, Silveira TP, Boufellia G, Siqueira SAC, et al. Gastric metastasis as the first manifestation of an invasive lobular carcinoma of the breast. Autopsy and Case Reports. 2015;5(3):49-53. https://doi. org/10.4322/acr.2015.018
- Hong J, Kim Y, Cho J, Lim SW, Park SE, Kim HK, et al. Clinical features and prognosis of breast cancer with gastric metastasis. Oncology letters. 2019;17(2):1833-41. https://doi. org/10.3892/ol.2018.9754
- 8. Yagi Y, Sasaki S, Yoshikaw A, Tsukioka Y, Fukushima W, Fujimura T, et al. Metastatic gastric carcinoma from breast cancer mimicking primary linitis plastica: a case report.

Oncology Letters. 2015;10:3483-7. https://doi.org/10.3892/ ol.2015.3788

- Pectasides D, Psyrri A, Pliarchopoulou K, Floros T, Papaxoinis G, Skondra M, et al. Gastric metastases originating from breast cancer: repost of 8 cases and review of the literature. Anticancer Research. 2009;29(11):4759-64. PMID 20032432.
- Taal B, Peterse H, Boot H. Clinical presentation, endoscopic features and treatment of gastric metastases from breast carcinoma. Cancer. 2000;89(11):2214-21. https://doi.org/ 10.1002/1097-0142(20001201)89:11<2214::AID-CNCR9>3.0.CO;2-D
- Jones GE, Strauss DC, Forshaw MJ, Deere H, Mahedeva U, Mason RC, et al. Breast cancer metastasis to the stomach may mimic primary gastric cancer: report of two cases and review of literature. World Journal of Surgical Oncology. 2007;5:75. https://doi.org/10.1186/1477-7819-5-75
- Wong YM, Jagmohan P, Goh YG, Putti TC, Ow SGW, Thian YL, et al. Infiltrative pattern of metastatic invasive lobular breast carcinoma in the abdomen: a pictorial review. Insights Imaging. 2021;12(1):181. https://doi.org/10.1186/s13244-021-01120-4
- Xu L, Liang S, Yan N, Zhang L, Gu H, Fei X, et al. Metastatic gastric cancer from breast carcinoma: a report of 78 cases. Oncology Letters. 2017;14:4069-77. https://doi.org/10.3892/ ol.2017.6703

Mastology 2022;32:e20220016

#### REVIEW ARTICLE https://doi.org/10.29289/2594539420210051

## Integrative review on breast cancer screening in the transgender population: what do we know?

Maria Julia Gregorio Calas<sup>1</sup> <sup>(i)</sup>, Rebeca Fernandes de Azevedo Dantas<sup>1</sup>\* <sup>(i)</sup>, Carolina Bantim Ciscotto<sup>1</sup> <sup>(i)</sup>, Bruna Galper<sup>1</sup> <sup>(i)</sup>, Ingrid Meira Lopes de Carvalho<sup>1</sup> <sup>(i)</sup>, Juliana Moreira Guerra<sup>1</sup> <sup>(i)</sup>

#### ABSTRACT

The lack of formal breast cancer screening guidelines for the transgender population and the unpreparedness of health professionals to provide adequate health care to this population are described in the literature. The objective of this integrative review was to present the proposals for breast cancer screening in the transgender population, based on the literature, being searched in the Medline, PubMed, SciELO, and Lilacs databases. The articles that addressed breast cancer screening in the female and/or male transgender population were selected, in addition to the associated studies with the use of hormone therapy and breast cancer in transgender people, using the terms such as "transgender people," "early cancer diagnosis," and "breast." Of the 38 articles selected, 24 address recommendations for breast cancer screening in the female and/or male transgender population. There is limited population-based information on mammography screening in transgender people, which ultimately affects the analysis of cancer incidence in this population. The literature supports screening in the male transgender profile (similar to the female cisgender). In transgender females, recommendations are implemented based on expert's opinions, such as mammographic screening after 5 years of hormone use. More studies on this subject are needed. KEYWORDS: transgender persons; early detection of cancer; breast.

#### INTRODUCTION

Breast cancer is recognized as the most common malignant disease in the female population, representing 13% of all cancer deaths in women worldwide<sup>1-3</sup>.

Mammography is still the best method for breast cancer screening and has been proven to reduce mortality due to this type of cancer<sup>L-3</sup>. In Brazil, according to the Guidelines for the Early Detection of Breast Cancer, from the Ministry of Health, mammographic screening is recommended for women aged 50–69 years for a period of every 2 years. On the one hand the Brazilian Society of Mastology, the Brazilian College of Radiology, and the Brazilian Federation of Gynecology and Obstetrics recommend mammographic screening in women aged 40–74 years, annually, who are at usual risk<sup>3</sup>.

Breast cancer affects not only women but also men in about 1% of cases<sup>1.3,4</sup>. As breast cancer in men is rare, there are no Brazilian guidelines for screening in men. Data from the American Society of Clinical Oncology suggest screening only in high-risk male patients, including the group of patients who have undergone breast cancer surgery and have proven genetic mutations<sup>4</sup>.

However, it is noteworthy that despite the guidelines for breast cancer screening in cisgender women and in special situations in high-risk cisgender men, breast cancer can also affect transgender men and women<sup>5-7</sup>.

Transgender is an umbrella term to describe a group of diverse individuals who cross or transcend culturally defined gender categories. This transgender population is composed of individuals who have gender incongruence with the biological sex assigned at birth and may be male, female, or non-binary (who are identified as neither male nor female sex, regardless of the biological sex at birth)<sup>5.8,9</sup>.

Gender diversity is an area in a society marked by stigmas, causing failure in health care due to the lack of access and interest in the medical services for this population<sup>5.8.9</sup>. Briefly, the topic can be understood as having two main aspects:

- 1) the need to know the impact of hormonal treatments on the development of breast cancer; and
- 2) the need to educate these people as far as the early detection of this disease is concerned.

<sup>1</sup>Universidade Estácio de Sá – Rio de Janeiro (RJ), Brazil. **\*Corresponding author:** rebecaf.dantas@gmail.com **Conflict of interests:** nothing to declare. **Funding:** none. **Received on:** 10/19/2021. **Accepted on:** 03/02/2022. Thus, gender identification has peculiarities that deserve medical attention. This population lacks satisfactory studies and statistical significance regarding both the incidence of breast cancer and the possible ways of screening<sup>8-11</sup>.

The main data recently published by Spizzirri et al.<sup>5</sup> point out the fact that Brazilian individuals with gender diversity represent approximately 2% of the country's adult population (almost 3 million people) and are homogeneously located throughout the country, reiterating the urgency of public health policies for these individuals in the five Brazilian subregions<sup>5</sup>.

Given the relevance of the subject and the deficiency of research and studies on breast cancer screening in transgender people, the review aimed to present the main proposals for breast cancer screening in this population, described in the literature.

#### **METHODS**

This is an integrative review, in which the literature search was carried out in the search platforms PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE) databases, LILACS, and SciELO, using the following DECs and MeSH descriptors such as "transgender people," "early cancer diagnosis," and "breast."

The population included in this selection is female and/or male transgender people, in studies where the suggestion of different types of breast cancer screening was described (diagnostic intervention for breast cancer detection). As an outcome, it is expected that, in face of a standardized screening of this population, taking into account possible hormonal and surgical treatments, there will be an improvement in the quality of care provided to this population.

The extraction of data from the articles was carried out in a separate form, independently by two of the six authors. Duplicates (eight articles), abstracts, letters to journal editors, gray literature, and book chapters, as well as those that did not present in the title, abstract, or text the subject addressed in this review were excluded. It is worth mentioning that the studies repeated in the different databases were only excluded after being read in their entirety in order to avoid exclusion errors.

The main eligibility criteria articles were made available online in English, Portuguese, and Spanish, which addressed breast cancer screening in female and/or male transgender people. Articles that studied the encountered limitations by the transgender population in breast screening and studies that associated the use of hormone therapy and breast cancer in transgender people were also considered eligibility criteria.

For a better knowledge of important issues related to the transgender population, we complemented the review with the objective of identifying publications not captured by the electronic search, secondary references of articles, as well as additional searches of the literature on known and hypothesized cancer risk factors, the occurrence of cancer (incidence or prevalence) in a defined population of transgender persons, and the potential mechanisms by which exposure to these factors may affect cancer risk in this population.

Regarding the ethical issue of research by the National Health Council (Conselho Nacional de Saúde – CONEP), an evaluation was not necessary by an Ethical Research Committee (comitê de ética em pesquisa – CEP) according to Resolution No. 466/2012.

#### **RESULTS**

Of a total of the initially identified 76 articles, 38 were excluded. The flowchart about the selection of the articles is shown in Figure 1.

The articles that met all the selection criteria and made easier to answer the question of this review were selected (38 articles). Of this total, 24 were used to prepare the tables in this study. Of these 24 studies, 15 address the recommendation of screening in female and male transgender people, 8 articles address screening only in transgender males, and 1 article recommends screening only in transgender females.

The main results that were obtained by analyzing the articles from the bibliographic search and the proposed methodology are shown in Tables 1 and 2. The tables present the recommendations for breast cancer screening in the transgender population, which were divided into males<sup>12-34</sup> and females<sup>12-16,18,20-23,27,28,31,33-35</sup>. The tables also mention the references related to this review.

Regarding the proposed form of screening for the male transgender population, most articles suggest maintaining screening for transgender men with natal or residual breast tissue, in line with current guidelines for cisgender women<sup>12-25</sup>. Regarding the transgender female population, all studies indicate mammographic screening after 5 years of hormone (estrogen) use<sup>12-16,18,20-22,27,28,31,33,35</sup>.

To finalize the screening proposals, Table 3 summarizes the publication of the joint national position of the Brazilian College of Radiology and Imaging Diagnosis, the Brazilian Society of Endocrinology and Metabology, and the Brazilian Society of Clinical Pathology, coordinated by Vieira and collaborators, national reference in breast cancer screening recommendations for the transgender population<sup>6</sup>.

#### DISCUSSION

Transgender and nonbinary people have unique health care needs, which stems from gender-affirming hormone therapy and/or surgical interventions performed by this population<sup>11,13,16,21,26,31</sup>. The relationship between hormonal treatments in the sexual transition of female and male transgender people and the incidence of breast cancer is still discussed in the literature<sup>13,16,26,31</sup>.

As the transgender community gains visibility and recognition, health disparities become more apparent<sup>14,24,30</sup>. Despite the efforts to become more inclusive, access to health care for this population is a challenge because it is a system built on a binary model. Another major challenge in caring for the



Figure 1. Flowchart of the selection of articles for the integrative review identification.

Table 1	. Recommendatio	ns for breast	cancer screening	g in the tr	ansgender	male population	found in the review.
					2		

Breast cancer screening recommendation in transgender males	Number (and respective reference) of articles found with this recommendation
Screening for transgender men with natal or residual breast tissue, according to current guidelines for cisgender women	15 articles <sup>12-23,32-34</sup>
Biennial mammography in transgender men who used hormone therapy aged 50–69 years	6 articles <sup>24-29</sup>
Annual MRI and mammography for transgender men aged 25–30 years. Consideration of prophylactic bilateral mastectomy for patients with BRCA2	1 article <sup>30</sup>
Annual mammogram for transgender men aged 40 years and above	1 article <sup>31</sup>

Table 2. Recommendations for breast cancer screening in the transgender female population found in the review.

Breast cancer screening recommendation in transgender females	Number (and respective reference) of articles found with this recommendation
Annual mammogram for transgender women with more than 5 years of hormone therapy, BMI>35 kg/m <sup>2</sup> or a family history of breast cancer Breast ultrasound and magnet resonance imaging or mammography with displacement mammography for those with breast prostheses	2 articles <sup>13,34</sup>
Mammography for transgender women undergoing hormone therapy for more than 5 years	3 articles <sup>15,23,27</sup>
Mammography every 2 years for transgender women aged 50 years and above who have been on hormone therapy for more than 5 years	5 articles <sup>12,14,21,28,35</sup>
Annual or biennial mammography for transgender women aged 50 years or above who are undergoing hormone therapy for more than 5 years and with additional risk factors: BMI>35 kg/m²; family history of breast cancer	6 articles <sup>16,18,20,22,31,33</sup>

BMI: Body mass index.

**Table 3.** Recommendations for breast cancer screening in the male and female transgender population, according to the Joint Positioning of the Brazilian Society of Clinical Pathology, Brazilian Society of Endocrinology and Metabology, and Brazilian College of Radiology and Diagnostic Imaging.

Breast cancer screening recommendation in transgender males	Follows recommendations for cisgender women when bilateral mastectomy is not performed After bilateral mastectomy, mammographic screening is not recommended
Breast cancer screening recommendation in transgender females	Annual or biennial mammography, starting at age 50, in patients using hormone therapy for at least 5 years

transgender community is the scarcity of scientific and medical knowledge<sup>16,28,30-33</sup>.

Most health professionals receive less or no training to provide clinically and culturally appropriate health care to these patient groups<sup>7,14,34,35</sup>.

To date, no study is able to support a biological difference between transgender women and cisgender men, and between transgender men and cisgender women, since the incidence of breast cancer should be attributed to biological sex<sup>27,29</sup>.

#### Transgender men or male transgender people

Hormone therapy for transition helps this population to modify some physical or visual characteristics to become more phenotypically like a man. In this scenario, with the use of testosterone, the suppression of the period of breast development (depending on the age at the beginning of hormone therapy), an increase in lean muscle mass, and a male-standard body development<sup>13,16,20,36</sup> are expected. Such characteristics, which are potentially affected, are noticed in the first month of testosterone use, as well as an increase in skin oiliness and libido around 3 months after the start of therapy (directly related to testosterone levels in the blood and inversely proportional to the luteinizing hormone levels)<sup>13,16,20,36</sup>.

Concomitant with the external changes, histological evaluations of the endometrium of transgender men showed it to be atrophic and inactive, similar to the result observed in postmenopausal cisgender women without estrogen therapy. The menstrual period ceases approximately 2–6 months after initiation of testosterone hormone therapy. This process is faster when the therapy is used intramuscularly<sup>13,16,20,36</sup>.

As in the female transgender population, the relationship between hormone therapy and the onset of breast cancer is not well established<sup>14,20,36</sup>. One of the postulated pathways is peripheral aromatization in the breast and adipose tissue, which converted dehydroepiandrosterone into estradiol and estrone, in postmenopausal women. Another hypothetical mechanism is the direct stimulation of androgen receptors. Normal breast cells as well as breast cancer cells express androgen receptors in large numbers<sup>13,16</sup>. Chotai and colleagues<sup>20</sup>, in their study including 1,849 breast cancer patients, revealed that androgen receptor positivity was inversely related to clinical stage, histological tumor grade, and mitotic stage, suggesting an association of positivity between androgen receptors and less aggressive tumors<sup>20</sup>.

Regarding the published studies of breast cancer in male transgender people, Blok and colleagues<sup>29</sup>, with a sample of 1,229 men, identified four cases of invasive breast cancer, with a mean age of 46 years. Kiely<sup>27</sup>, in a cohort of 5,135 transgender people using cross-hormonal therapy, described 10 case reports of breast cancer: 7 cases in transgender men, 2 in transgender women, and 1 in a nonbinary patient. From this perspective, there are few cases of breast cancer in transgender described, proving to be an uncommon disease, but not absent<sup>24,28</sup>.

Gender-affirming mastectomy techniques vary significantly in relation to the amount of residual breast tissue, which has unknown implications for postoperative breast cancer incidence and the need for screening. Clinical examination remains the most commonly reported method of post-mastectomy malignancy detection<sup>21,36</sup>. For those who opted for a complete mastectomy, two authors recommend an annual clinical examination of the chest wall and armpits<sup>21,27,28</sup>. In the case of patients with a greater amount of residual breast tissue, they can be considered alternative imaging modalities, although the efficacy and cost-utility of these techniques have yet to be proven<sup>21,27,28,36-38</sup>.

Preoperative patient counseling about the risk of breast cancer after masculinizing mastectomy, in addition to the unknown implications of residual breast tissue and long-term exposure to androgens, is essential<sup>15,16,31,34</sup>.

There is still no established breast cancer screening guidelines for the transgender male population. However, some authors suggest screening based on the presence of breast tissue and risk factors<sup>15,24,26,27,30,34,35</sup>.

According to the study by Pivo and colleagues<sup>32</sup>, for transgender men, risk factors inherent to the female genotype should be considered, such as age, race, reproductive history, and family history of breast and ovarian cancers<sup>13</sup>. The study by Kiely<sup>27</sup> considered modifiable and non-modifiable factors for breast cancer risk, including family and personal history of breast and ovarian cancer, body mass index >35 kg/m<sup>2</sup> in menopausal women, early menarche, late menopause, and moderate or high alcohol consumption<sup>27</sup>.

Based on the guidelines of the Brazilian Society of Clinical Pathology, the Brazilian Society of Endocrinology and Metabology, and the Brazilian College of Radiology and Diagnostic Imaging, breast cancer screening for transgender men is limited to the type of examination, age, and periodicity. Mammography is recommended biennially for transgender men who are not having bilateral mastectomy and aged 50–69 years (as well as indicated for cisgender women at usual risk). For transgender men with bilateral mastectomy, screening is not indicated<sup>6</sup>.

#### Transgender women or female transgender people

Transgender women undergo hormone therapy with estrogen in conjunction with antiandrogen drugs, such as spironolactone, to inhibit the action of testosterone. The effects of hormone therapy include breast growth, decreased facial hairiness, increased capillary volume, altered body fat distribution, and decreased testicle size. Approximately from 3 to 6 months, it is possible to visualize the beginning of these phenotypic changes; however, it is only 2 or 3 years of hormone therapy in which the maximum growth of the breasts is evidenced<sup>26,31,33,34</sup>. The degree of breast development appears to be independent of the type and dose of hormone treatment used. Once the maximum development of female characteristics is reached, it is necessary to reduce the offered hormonal dose<sup>19,31</sup>.

After this process, the breast of the transgender woman has the same characteristics as the breast of a cisgender woman, with an exposure to develop benign tumors as well as malignant lesions. In addition, the potential increased risk of breast cancer with the use of exogenous hormones has not been completely elucidated, which makes it a challenge to assess the most appropriate screening recommendation in this population<sup>22,31</sup>. The potential risk goes beyond the increased risk of breast cancer in cisgender postmenopausal women undergoing estrogen hormone replacement therapy and is supported by the literature of case reports of breast cancer in transgender women<sup>29,33,34</sup>.

Regarding the studies that present case reports of breast cancer cases in transgender females, Hartley and colleagues<sup>31</sup> described 22 transgender women with breast cancer after a literature review including 18 articles. The average age was 51.5 years, where 7 of them reported a first-degree relative with breast cancer and 1 had a confirmed mutation in the BRCA2 gene. Among the types of cancer, most were represented by adenocarcinomas (13 cases, 59.3%); BIA-ALCL (breast implant-associated anaplastic large-cell lymphoma) (3 cases, 13.6%); ductal carcinoma in situ (1 case, 4.5%); secretory carcinoma (1 case, 4.5%), malignant phyllode tumor (1 case, 4.5%); and Paget's carcinoma associated with invasive ductal carcinoma (1 case, 4.5%) and without histological classification (2 cases, 9.1%)<sup>31</sup>.

Regarding the duration of hormone use, transgender women who presented with breast cancer used hormone therapy for an average of 18 years, with a predominance of luminal type tumors<sup>12,22,29,33,34</sup>.

In the Dutch study by Blok and colleagues<sup>29</sup>, in a group of 2,260 transgender women, 15 cases of invasive breast cancer were identified, with an average age of 52 years, which was comparatively lower than the average age (61 years) of involvement

of Dutch cisgender women<sup>29</sup>. The incidence of breast cancer in these women was considered higher than the risk in Dutch cisgender men (0.4 expected cases), but below the expected benchmark for Dutch women (72 expected cases)<sup>29</sup>.

The correlation of information obtained from the 15 articles selected in this review (Table 1) suggests mammographic screening in transgender women undergoing hormone therapy, after 5 years of use, although there is no consensus regarding its periodicity and age<sup>12-16,18,20-23,27,28,31,33</sup>. Screening mammography is not currently recommended for transgender women who are not using hormones, except in patients with other known risk factors, for example, those with Klinefelter syndrome<sup>4,11</sup>.

According to the Brazilian societies, breast cancer screening in transgender women should be performed if they have been using hormone therapy for more than 5 years, with intervals of 1 or 2 years, starting at the age of 50 years. If hormone therapy is not used, screening is not indicated<sup>6</sup>.

Some of these women opt for breast augmentation surgery with the use of breast implants. The surgery itself does not interfere with breast cancer risk, but it does affect the monitoring. In these cases, according to the studies by Schmidt and colleagues<sup>21</sup> and Hartley and colleagues<sup>31</sup>, the use of ultrasound and magnetic resonance imaging of the breasts or mammography with the displacement of the breast implants is suggested for screening.

Awareness and education of these patients play an important role in shared decision-making, but more research is needed to define standards of care and breast cancer screening in this population<sup>8,9,23</sup>.

#### **CONCLUSIONS**

Summarizing the main guidelines for breast cancer screening in transgender people, the literature describes the screening process for transgender men with natal or residual breast tissue, according to the current guidelines for cisgender women; and for the female transgender population, mammographic screening is indicated after 5 years of hormone use, but without consensus regarding the age of initiation and termination of this screening.

The severity and complexity of breast cancer, associated with the lack of robust data in the literature on the incidence and screening of this pathology in the group of transgender patients, indicate the need for further studies for a better understanding and applicability of the guidelines proposed in the literature.

#### **AUTHORS' CONTRIBUTION**

MJGC: Conceptualization, Data curation, Formal Analysis, Writing – original draft. RFAD: Conceptualization, Writing – review & editing. CBC: Conceptualization, Data curation, Writing – review & editing. BG: Visualization, Writing – original draft. IMLC: Methodology, Visualization. JMG: Writing – review & editing.

#### REFERENCES

- Brazil. Ministério da Saúde. Rastreamento. Série A. Normas e Manuais Técnicos Cadernos de Atenção Primária, n. 29. Brasília: Ministério da Saúde, 2010.
- 2. Urban LABDU, Schaefer MB, Duarte DL, Santos RP, Maranhão NMA, Kefalas AL, et al. Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para rastreamento do câncer de mama por métodos de imagem. Radiol Bras. 2017;50(4):244-9. https://doi.org/10.1590/S0100-39842012000600009
- Oliveira DAL. Políticas de saúde e diagnóstico precoce do câncer de mama no Brasil. Rev Enferm Digit Cuid Promoção Saúde. 2019;4(1):46-50. https://doi.org/10.5935/2446-5682.20190009
- Hasset MJ, Somerfield MR, Baker ER, Cardoso F, Kansal KJ, Kwait DC, et. al. Management of male breast cancer: ASCO Guideline. J Clin Oncol. 2020;38(16):1849-63. https://doi. org/10.1200/JCO.19.03120
- Spizzirri G, Eufrásio R, Lima MCP, Nunes HRCD, Kreukels BPC, Steensma TD, et al. Proportion of people identified as transgender and non-binary gender in Brazil. Sci Rep. 2021;11:2240. https://doi.org/10.1038/s41598-021-81411-4
- 6. Sociedade Brasileira de Endocrinologia e Metabologia (SBEM). Posicionamento Conjunto Medicina Diagnóstica inclusiva: cuidando de pacientes transgênero. Rio de Janeiro: Sociedade Brasileira de Patologia Clínica Medicina Laboratorial e Colégio Brasileiro de Radiologia e Diagnóstico por Imagem [Internet]. [cited on Jan 01, 2019]; 2019. Available from: https://www. endocrino.org.br/media/pdfs\_documentos/posicionamento\_ trangenero\_sbem\_sbpcml\_cbr.pdf
- Pratt-Chapman ML, Ward AR. Provider recommendations are associated with cancer screening of transgender and gender-nonconforming people: a cross-sectional urban survey. Transgend Health. 2020;5(2):80-5. https://doi.org/10.1089/ trgh.2019.0083
- Puechl AM, Russel K, Gray BA. Care and cancer screening of the transgender population. J Womens Health 2019;28(6):761-8. https://doi.org/10.1089/jwh.2018.6945
- Gibson AW, Radix AE, Maingi S, Patel S. Cancer care in lesbian, gay, bisexual, transgender and queer populations. Future Oncol. 2017;13(15):1333-44. https://doi.org/10.2217/fon-2017-0482
- Bazzi AR, Whorms DS, King DS, Potter J. Adherence to mammography screening guidelines among transgender persons and sexual minority women. Am J Public Health. 2015;105(11):2356-8. https://doi.org/10.2105/AJPH.2015.302851
- Phillips J, Fein-Zachary VJ, Mehta TS, Littlehale N, Venkataraman S, Slanetz PJ. Breast imaging in the transgender patient. AJR Am J Roentgenol. 2014;202:1149-56. https://doi. org/10.2214/AJR.13.10810
- Charkhchi P, Schabath MB, Carlos RC. Modifiers of cancer screening prevention among sexual and gender minorities in the behavioral risk factor surveillance system. J Am Coll Radiol. 2019;16(4 Pt B):607-20. https://doi.org/10.1016/j. jacr.2019.02.042

- 13. Eneros AA, Zamorano SJ, Salazar RR, Lagos MAC. Terapia Hormonal en la Transición Masculino a Femenino (MTF) ó transexual femenino o régimen de feminización: parte II. Rev Soc Chil Obstet Ginecol Infant Adolesc. 2017;24(1):18-27.
- 14. Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in transgender people: evidence and methodological considerations. Epidemiol Rev. 2017;39(1):93-107. https://doi.org/10.1093/epirev/mxw003
- Deutsch MB, Radix A, Wesp L. Breast Cancer screening, management, and a review of case study literature in transgender populations. Semin Reprod Med. 2017;35(5):434-41. https://doi.org/10.1055/s-0037-1606103
- 16. Stone JP, Hartley RL, Temple-Oberle C. Breast cancer in transgender patients: A systematic review. Part 2: Female to Male. Eur J Surg Oncol. 2018;44(10):1463-8. https://doi. org/10.1016/j.ejso.2018.06.021
- Price S, McManus J, Barrett J. The transgender population: improving awareness for gynaecologists and their role in the provision of care. Obstet Gynaecol. 2019;21(1):11-20. https:// doi.org/10.1111/tog.12521
- Nikolić D, Granić M, Ivanović N, Zdravković D, Nikolić A, Stanimirović V, et al. Breast cancer and its impact in male transsexuals. Breast Cancer Res Treat. 2018;171(3):565-9. https://doi.org/10.1007/s10549-018-4875-y
- Sonnenblick EB, Shah AD, Goldstein Z, Reisman T. Breast imaging of transgender individuals: a review. current radiology reports. 2018;6(1):1-12. https://doi.org/10.1007/s40134-018-0260-1
- 20. Chotai N, Tang S, Lim H, Lu S. Breast cancer in a female to male transgender patient 20 years post-mastectomy: issues to consider. Breast J. 2019;25(6):1066-70. https://doi.org/10.1111/ tbj.13417
- Schmidt M, Ditrio L, Shute B, Luciano D. Surgical management and gynecologic care of the transgender patient. Curr Opin Obstet. Ginecol. 2019;31(4):228-34. https://doi.org/10.1097/ GCO.000000000000553
- 22. Parikh U, Mausner E, Chhor CM, Gao Y, Karrington I, Heller SL. Breast imaging in transgender patients: what the radiologist should know. Radiographics. 2020;40(1):13-27. https://doi. org/10.1148/rg.2020190044
- Schmidt E, Rizzolo D. Disease screening and prevention for transgender and gender-diverse adults. JAAPA. 2017;30(10):11-6. https://doi.org/10.1097/01.JAA.0000524709.87224.57
- 24. Stewart T, Lee YA, Damiano EA. Do transgender and gender diverse individuals receive adequate gynecologic care? An analysis of a rural academic center. Transgend Health. 2020;5(1):50-8. https://doi.org/10.1089/trgh.2019.0037
- 25. Li JZ, Tu HYV, Avram R, Pinthus J, Bordeleau L, Hodgson N. Cancer prevention and screening in a BRCA2-positive male to female transgender patient. Breast J. 2018;24(6):1112-3. https:// doi.org/10.1111/tbj.13096
- 26. Eismann J, Heng YJ, Fleischmann-Rose K, Tobias AM, Phillips J, Wulf GM, et al. Interdisciplinary management of transgender individuals at risk for breast cancer: case reports and review of the literature. Clin Breast Cancer. 2019;19(1):e12-9. https://doi.org/10.1016/j.clbc.2018.11.007

- 27. Kiely D. Transgender patient screening: breast cancer risk assessment and screening recommendations. Clin J Oncol Nurs. 2017;21(3):E67-70. https://doi.org/10.1188/17.CJON.E67-E70
- Patel JM, Dolitsky S, Bachman GA, Meritens AB. Gynecologic cancer screening in the transgender male population and its current challenges. Maturitas. 2019;129:40-4. https://doi. org/10.1016/j.maturitas.2019.08.009
- 29. Blok CJ, Wiepjes CM, Nota NM, van Engelen K, Adank MA, Dreijerink KM, et. al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands British Medical Journal. BMJ. 2019; 365:11652. https://doi.org/10.1136/bmj.11652
- 30. Narayan A, Lebron-Zapata L, Morris E. Breast cancer screening in transgender patients: findings from the 2014 BRFSS survey. Breast Cancer Res Treat. 2017;166(3):875-9. https://doi.org/10.1007/s10549-017-4461-8
- Hartley RL, Stone JP, Temple-Oberle C. Breast cancer in transgender patients: a systematic review. Part 1: male to female. Eur J Surg Oncol. 2018;44(10):1455-62. https://doi. org/10.1016/j.ejso.2018.06.035
- 32. Pivo S, Montes J, Schwartz S, Chun J, Kiely D, Hazen A, et al. Breast cancer risk assessment and screening in transgender patients. Clin Breast Cancer. 2017;17(5):e225-7. https://doi. org/10.1016/j.clbc.2016.08.003

- 33. Kiran T, Davie S, Singh D, Hranilovic S, Pinto AD, Abramovich A, et al. Cancer screening rates among transgender adults: cross-sectional analysis of primary care data. Can Fam Physician. 2019;65(1):e30-7. PMID: 30674526
- 34. Sterling J, Garcia MM. Cancer screening in the transgender population: a review of current guidelines, best practices, and a proposed care model. Transl Androl Urol. 2020;9(6):2771-85. https://doi.org/10.21037/tau-20-954
- 35. Labanca T, Mañero I, Pannunzio M. Transgender patients: considerations for routine gynecologic care and cancer screening. Int J Gynecol Cancer. 2020;30(12):1990-6. https:// doi.org/10.1136/ijgc-2020-001860
- 36. Fledderus AC, Gout HA, Ogilvie AC, van Loenen DKG. Breast malignancy in female-to-male transsexuals: systematic review, case report, and recommendations for screening. Breast. 2020;53:92-100. https://doi.org/10.1016/j. breast.2020.06.008
- Brown GR. Breast cancer in transgender veterans: a ten-case series. LGBT Health. 2015;2(1):77-80. https://doi.org/10.1089/ lgbt.2014.0123
- Donati CA, Nagelberg A. Screening mamário em pacientes transgénero bajo tratamento hormonal cruzado (THC). Situación actual y controvérsias. Rev Argent Mastología. 2019;38(137):116-32.



# Free nipple graft: current indications and applications of a centenary breast surgery technique – an integrative review

Clécio Ênio Murta de Lucena<sup>1</sup> <sup>®</sup>, Rafael Araujo Ponce de Leon<sup>2</sup>\* <sup>®</sup>, Ana Carla Araújo Paiva<sup>2</sup> <sup>®</sup>, Carla Sobreira da Nóbrega<sup>2</sup> <sup>®</sup>, Isabela Ferreira Bahia<sup>2</sup> <sup>®</sup>

#### ABSTRACT

Introduction: Free nipple graft is a mammaplasty technique first described about 100 years ago. Its indication, restricted to reduction mammoplasty earlier, has been expanding into areas in mastology intervention, such as transgender and oncological surgery. Aim: The aim of this study was to evaluate the efficacy and outcomes of the technique. Methods: Electronic literature search was conducted, using PubMed and LILACS databases. The search strategy consisted of the keywords, MeSH terms, and free text words and variants for the free nipple graft and its application in reduction and mammaplasty, transgender, and oncoplastic surgery. Results: A total of 397 articles were found and, after inclusion and exclusion criteria, 15 were selected. Their outcomes have been shown, despite lack of standardized scores, as well as clinical trials to postulate better scientific evidence on its use and indications, that the technique, analyzed in over 1290 patients, achieved high safety rates and reproducibility. Conclusion: Aesthetics and patients satisfaction were found positive, as recommended by the authors in different studies discussed in this article.

KEYWORDS: free nipple graft; mammaplasty; transgender; breast neoplasms

#### INTRODUCTION

The surgical technique of free nipple graft (FNG), or areola autograft (Figures 1-3), was first described about 100 years ago by the Hungarian-American doctor named Max Thorek in 1922<sup>1,2</sup>. Its application was originally meant exclusively to reduction mammaplasty, but later expanded its role into areas of mastology intervention, such as oncoplastic surgery<sup>3</sup> and chest adjustment surgery in transgender males<sup>4,5</sup>. Despite the wide utilization and usefulness of FNG in mastology, this technique lacks reviews and secondary studies in literature that evaluate the efficiency and outcomes of its use. Thus, the importance of a single technique as FNG on interventional surgical treatment of multiple disorders related to breast such mammary hypertrophy, gender dysphoria, and even in potential life-threatening diseases, like cancer, is an emerging topic in mastology studies.

Symptomatic mammary hypertrophy is a medical condition that directly affects the physical and emotional health of the patients. Headache, cervical and back pain, as well as self-esteem problems are frequently related to this condition<sup>6</sup>. Randomized clinical trials (RCTs) have shown that conservative therapy is ineffective in improving symptoms and that reduction



**Figure 1.** Preoperative marks that guide the surgical approach and incision sites. The upper blue arrow indicates the position where replacement of the nipple graft should be implanted.

<sup>1</sup>Universidade Federal de Minas Gerais, Instituto Orizonti, Breast Center – Belo Horizonte (MG), Brazil.

<sup>2</sup>Universidade Federal de Minas Gerais – Belo Horizonte (MG), Brazil.

\*Corresponding author: rfapleon@hotmail.com

Conflict of interests: nothing to declare. Funding: none.

Received on: 11/03/2021. Accepted on: 02/21/2022.



**Figure 2.** The nipple areolar complex is de-epithelized, as a graft, that must be preserved in a saline solution while breast parenchyma is resected.



**Figure 3.** Reinsertion of the areola graft in the breast resected with sutures.

mammaplasty surgery remains the only intervention with the ability to reduce the patients<sup>7</sup> physical and psychological complaints, with approximately 129,000 surgeries being performed in 2017 with this purpose, according to the National Association of Plastic Surgeons<sup>8</sup>.

In this scenario, the technique first described by Thorek<sup>1,2</sup> in 1922, i.e., FNG, represented a mark in mammoplasty reduction at the time, due to its ability to maintain the nipple areolar complex (NAC), compared to underexplored by prior used techniques, such glandular and skin excision described by Frenchmen Morestin in 1908<sup>1</sup>. Despite its aesthetic functional limitations, related to insufficient breast projection and total loss of sensibility and lactation function of the nipple<sup>1,2,9-11</sup>, FNG remains the first choice technique in patients with gigantomastia weighing 1000 g and ptotic breasts<sup>11</sup>. Moreover, modifications of the original technique are providing new alternatives for indicating the use of FNG<sup>9-11</sup>.

In the past few years, sociocultural changes and a better understanding on gender dysphoria have been increasing the demand for masculinizing transgender procedures of the chest wall, in which mastectomy is one of the most efficient approaches on improving psychological outcomes of dissociation between body gender and biological sex experienced by these patients<sup>5</sup>. Literature reviews and comparative analysis on different surgical techniques have shown that double incision-free nipple graft (DIFNG), an adaptation of Thorek's technique, is the first choice in selected patients, as it promotes aesthetic satisfying outcomes and optimization of the relocation of the NAC, as well as lower rates of reoperations and anatomic limitations when compared to other chest wall masculinizing transgender techniques<sup>4,5</sup>.

Breast cancer is the most prevalent malignant neoplasia in women. According to the World Health Organizations (WHO), approximately 2.2 million women were diagnosed with the disease in 2020<sup>12</sup>. The progress in understanding and treatment of the disease made interventions possible, which, in addition to being curative, also provides a better aesthetic functional outcome in patients who undergo mastectomies and breast reconstruction. In this scenario, FNG has been indicated as an alternative option in the maintenance of the NAC in women who would be initially excluded from reconstructive surgery using the nipple-sparing mastectomy (NSM) due to anatomical limitations of the breasts, such as ptotic breasts and gigantomastia. Therefore, women who would be excluded from NSM can undergo FNG surgery and, in a two or a single surgical time, undergo NSM, maintaining the NAC and elevating their psychological and self-esteem.

#### **OBJECTIVES**

This literature review seeks to provide an updated synthesis of knowledge about the FNG technique and its outcomes related to aesthetics satisfaction, functionality, and safety profile, as well as to analyze its incorporation and applicability in several intervention areas involved in mastology and plastic surgery.

#### **METHODS**

A structured electronic literature search was conducted, using PubMed and LILACS databases. The search strategy consisted of the keywords, MeSH terms, and free text words and word variants for the FNG and its application in reduction mammaplasty, transgender, and oncoplastic surgery. In PubMed databases, a search was conducted using the keywords, such as "breast neoplasms" OR "transgender" OR "mammaplasty" AND "free nipple graft." The Mesh terms in PubMed were "Breast Neoplasms" [Mesh]) OR ("Transgender Persons" [Mesh]) OR ("Mammaplasty" [Mesh])) AND free nipple graft. In LILACS databases, the keywords were "breast neoplasms" OR "transgender" OR "mammaplasty" AND "nipple."

The PICO question was formulated: breast neoplasms, transgender, and mammaplasty as the problems in question; FNG as an intervention; other mammaries surgical techniques and noninterventional treatments as a control and aesthetics; and patients satisfaction, safety profile, and reproducibility as outcomes.

Date of publication was limited to the past 10 years. The following filter was applied: language (English). A hand search of bibliographies was conducted to identify any additional articles by two of the authors. All titles and abstracts were independently reviewed by two of the authors. All study types, such as RCTs, case-control, cohort, reviews, and case studies, were eligible for inclusion.

The different study designs and the heterogeneity of the outcomes reported in the studies precluded the possibility of pooling data across the studies. Therefore, a narrative synthesis was conducted.

#### RESULTS

A total of 397 articles were found (209 in PubMed and 188 in LILACS databases) and, after inclusion and exclusion criteria, 15 were selected according to PRISMA 2020 presentation in Figure 4. Results are summarized in Table 1.

From the selected articles, only four evaluated the traditional application of FNG in reduction mammaplasty, comparing it to other technique interventions and analyzing its current concepts and surgical complications<sup>13-16</sup>. A total of 824 patients and 1648 operated breasts were analyzed, with an average of 1250 g of resected parenchyma. The other six articles<sup>17-22</sup> refer to the applicability of FNG in oncoplastic surgery, in which a total of 123 patients and 238 mastectomies have been analyzed. Finally, five articles deal with FNG utility in masculinizing transgender surgery<sup>23-27</sup>, with 343 patients and 721 mastectomies analyzed.

Roje et al.<sup>13</sup> performed a retrospective study involving 59 patients, with a mean age of 48.5 years old (p=0.271) and 1050 g of parenchyma removed (p=0.009). The study compared the inferior pedicle, inverted T-scar, and FNG techniques based on aesthetic and functional outcomes and, therefore, determined

a more suitable technique for each patient. The authors emphasizes the importance of FNG technique for reduction mammaplasty, since it provides a possibility of parenchyma resection in patients at high surgical risk, such as smokers (OR=61.92; p=0.008). Moreover, it is able to be performed in reduced surgical time, aspect directly related to lower complication rates (OR=1.05; 95%CI 1.01–1.1; p=0.019). When compared to other techniques, it has been elected as first choice in patients with macromastia, those with ptotic breast, or those who are at high surgical risk.

Robert et al.<sup>14</sup>, in a retrospective analysis of 715 mammaplasty reduction surgeries, with a mean age of 38 years old, 27 kg/m<sup>2</sup> of body mass index (BMI) and suprasternal notch-nipple distance of 31.6 cm, when comparing the FNG technique to the superior pedicle technique, found that the FNG had lower overall surgical complication rates (OR=1.57; 95%CI 0.73–3.38 vs. OR=2.64; 95%CI 1.54–4.61). In addition, it allows a greater parenchyma resection (average 1100 g vs. 501 g; p<0.0001). However, authors narrow the FNG technique use only in patients with ptosis or macromasty<sup>14,15</sup> due to functional impairments involved in its application, such as total loss of NAC sensibility, nipple hypopigmentation, and insufficient breast projection, being preferable to use techniques with greater vascular safety profile in nonselected patients, since FNG has higher rates of areolar necrosis when compared to the inferior pedicle technique (61 vs. 4.7%; p<0.0045).

One of the major problems historically related to FNG is a partial loss of mammary projection 9-11,14. This aspect was approached by Karsidag et al.<sup>15</sup> who reported a better projection and aesthetic outcome through a modification of the original Thorek's technique, using a dermoglandular flap associated with a suture of pectoralis major within the parenchyma. It provided a satisfactory breast contour and projection in all 24 patients with severe macromastia over 1000 g and breast ptosis, with a mean distant suprasternal notch nipple of 48.5 cm. The outcomes were analyzed comparing preoperative and postoperative photographs, as well as a questionnaire filled out by the surgeon that considered patients' satisfaction and lasting breast projection for 1 year. Finally, the authors recommend the adoption of their modified technique for surgeons experienced in performing original FNG. Moreover, the authors highlight, as an advantage, the fact that the technique can be easily performed and exchanged intraoperatively, If an occlusion of nipple perfusion, such as ischemia, is identified, it can be converted into a pedicle technique, which may offer a higher vascular safety profile.

Firat et al.,<sup>16</sup> in their prospective study, in which 26 patients who underwent free nipple graft vertical mammaplasty using the Graf dermoglandular flap mastopexy as a novel autoprosthesis procedure with an average follow-up period of 22 months were evaluated for a conical breast shape with better projection and upper pole fullness after surgery. The average weight of removed breast tissue was 1634 g for the right breast and 1630 g for the left breast. The mean sternal notch-nipple distance was 37.1 cm,



Figure 4. Prisma flow diagram.

and the mean nipple-submammary fold distance was 20.7 cm. The authors concluded that novel autoprosthesis technique yields a conical breast shape with better projection and upper pole fullness, thereby providing a better long-term aesthetic outcome than previous procedures for treating patients with gigantomastia. The examinations performed 2 years postoperatively clearly show that the autoprosthesis increased breast projection and preserved breast shape in the long term. This technique is easy to perform and highly suitable for patients with gigantomastia.

The role of FNG in reduction mammaplasty for decades prospected new possibilities for its use. Kijima et al. $^{17}$  explored

FNG as a reconstructive plastic modified technique, associated with partial mastectomy in breast cancer conservative treatment. The authors reported a case of a 65-year-old woman who suffered from a bilateral ductal carcinoma in situ, who would have a compromised reconstruction surgery aesthetic result, in case of being submitted to the conventional pedicled technique, due to ptotic breasts. In this case, doctors opted to perform a partial bilateral mastectomy followed by a breast amputation with FNG. The modified technique was able to achieve a satisfactory oncological safety outcome in all quadrant areas, considering that the removal of the NAC from its original site

	Table 1. List of articles ac	cording to title,	author, year of is	ssue, procedures, i	number of patients	s, and results.
--	------------------------------	-------------------	--------------------	---------------------	--------------------	-----------------

Title/theme	Author and year of issue	Procedures and number of patients	Results
Mammaplasty			
Current trends in breast reduction	Roje et al. <sup>13</sup>	Retrospective cohort analysis of 59 patients who suffered from symptomatic macromasty and underwent surgical intervention from 1995–2011.	The free nipple graft technique is preferred for macromasty in smoker patients at high surgical risk.
Complications of breast reduction about 715 breasts	Robert et al. <sup>14</sup>	Retrospective cohort analysis of 715 patients who underwent a reduction mammaplasty in multiple techniques.	The free nipple graft has lower general rates of complications compared to the pedicle technique. Yet, its functional and aesthetic limitations as well as its high risk of mammillary necrosis restrict its use to severe macromasty and ptosis.
Reduction mammaplasty using the free-nipple-graft vertical technique for severe breast hypertrophy: improved outcomes with the superior dermaglandular flap	Karsidag et al. <sup>15</sup>	Prospective cohort study of 24 patients who suffered from severe mammary hypertrophy operated from 2003–2009.	The modified free nipple graft technique has shown to be effective in maintaining breast projection in all patients within the study. Experienced surgeons in superior pedicle technique used in reduction mammaplasty can adopt the suggested technique free nipple graft associated with superior dermoglandular flap.
An autoprosthesis technique for better breast projection in free nipple graft reduction mammaplasty	Fırat et al. <sup>16</sup>	26 patients who underwent free nipple graft vertical mammaplasty combined with the Graf dermoglandular flap mastopexy procedure were evaluated for a conical breast shape with better projection and upper pole fullness after surgery.	The novel autoprosthesis technique described yields a conical breast shape with better projection and upper pole fullness, thereby providing a better long-term aesthetic outcome than previous procedures for treating patients with gigantomastia.
Oncoplastic surgery		·	·
Oncoplastic surgery combining partial mastectomy with breast reconstruction using a free nipple-areola graft for ductal carcinoma in situ in a ptotic breast: report of a case.	Kijima et al. <sup>17</sup>	Case report of a 65-year-old patient with ductal carcinoma in situ associated with ptotic breast.	The free nipple graft technique can be performed with reduced surgical time when compared to the inferior pedicle technique and it is indicated for the treatment of carcinoma in situ in women with ptotic breast.
Free nipple grafting: an alternative for patients ineligible for nipple-sparing mastectomy?	Doren et al. <sup>18</sup>	Retrospective cohort analysis of 15 ineligible patients for nipple-sparing mastectomy who underwent free nipple graft free nipple graft in order to maintain the nipple areolar complex.	In case of anatomical incompatible criteria for nipple-sparing mastectomy, free nipple graft is a viable option. The graft success rates were 95%, and the complication rates including loss of projection and hypopigmentation were, respectively, 19% and 27%.
Free nipple grafting and nipple sharing in autologous breast reconstruction after mastectomy.	Egozi et al. <sup>19</sup>	A prospective analysis of 13 patients who underwent free nipple graft after mastectomy with autologous reconstruction.	The free nipple graft technique achieved high aesthetic satisfaction rates: 4.6 out of 5 in Nahabedian score, as well as low rates of complications. Only 1 out of 13 grafts did not succeed and 24% of the nipples did not maintain pigmentation.
Nipple-sparing mastectomy and ptosis: using a free nipple graft with tissue expander reconstruction	Ghidei et al. <sup>20</sup>	Retrospective cohort of 14 patients submitted to free nipple graft in an oncological center.	The proposed free nipple graft intervention allowed women with breast ptosis to undergo NSM with preservation of the nipple areolar complex. Graft-taking was 100%. Yet, complications such as mammillary necrosis, hypopigmentation, and loss of sensibility were observed, respectively, in 7, 14, and 100% of the cases.
Revisiting the free nipple graft: an opportunity for nipple-sparing mastectomy in women with breast ptosis.	Chidester et al. <sup>21</sup>	A series of case reports on three women with breast cancer who were ineligible for nipple-sparing mastectomy and underwent a free nipple graft procedure.	Women who were previously excluded for nipple-sparing mastectomy were able to maintain nipple areolar complex integrity with free nipple graft with no oncological harm.

Continue...

#### Table 1. Continuation.

Title/theme	Author and year of issue	Procedures and number of patients	Results
One-stage breast reconstruction using the inferior dermal flap, implant, and free nipple graft	King et al.22	A reconstruction using free nipple graft was performed following a wise pattern skin incision in 16 patients and 19 breasts. A prospective database was kept from it.	The inferior dermal flap with implant and free nipple graft is an excellent single- stage reconstruction option. This method offers a potentially safe, reliable, and aesthetically acceptable outcome for women with larger, ptotic breasts.
Transgender surgery			
Long-term changes in free nipple graft morphology and patient- reported outcomes in gender- affirming mastectomies	Timmerman et al. <sup>23</sup>	Data from two prospective cohorts were collected: 67 transgender men after a mastectomy with free nipple grafts and 150 cisgender men (reference sample). Both groups were compared to establish the long-term changes in nipple-sparing mastectomy morphology and compare these to cisgender male nipple-sparing mastectomy outcomes.	Satisfaction for size, shape, and flatness decreased significantly after postoperative day 30 in transgender men compared to cisgender men.
Our experience in mastectomy for transgenders female to male – A 90 cases cohort study	Wolf et al. <sup>24</sup>	Retrospective cohort of 180 mastectomies performed in 20 years in transgender men.	The two main techniques performed with the best indicators of satisfaction and complications were nipple-sparing mastectomy flap and nipple-sparing mastectomy graft.
The nipple split sharing vs. conventional nipple graft technique in chest wall masculinization surgery: can we improve patient satisfaction and aesthetic outcomes?	Bustos et al. <sup>25</sup>	Retrospective cohort analysis of 68 transgender patients who underwent free nipple graft or nipple split intervention.	The nipple split and the conventional free nipple graft techniques did not show statistically significant complication rates. Yet, the nipple split had higher satisfaction rates compared to conventional free nipple graft technique
Modified nipple flap with free areolar graft for component nipple-areola complex construction: outcomes with a novel technique for chest wall reconstruction in transgender men	Frey et al. <sup>26</sup>	Retrospective cohort analysis including 50 transgender patients who underwent free areolar graft technique.	The techniques allow nipple-sparing mastectomy reconstruction in an effective and safe way. General complication rates were 10%.
A review of 101 consecutive subcutaneous mastectomies and male chest contouring using the concentric circular and free nipple graft techniques in female-to- male transgender patients	Knox et al.27	Retrospective analysis of 101 transgender patients who underwent either free nipple graft or concentric circular surgical techniques.	The concentric circular technique showed better aesthetic results in a score proposed by the study. However, the free nipple graft technique showed lower rates of complications.

reduces recidivation, in addition to a shortened surgical time when compared to other techniques used in oncological surgeries such as the pedicle technique<sup>13,18</sup>. Besides, FNG provides a better outcome regarding breast symmetry, due to the possibility of positioning nipple intraoperatively according to surgeon metrics. Therefore, authors highly recommend FNG application in the conservative oncological treatment of women with ptotic breasts in early stages of cancer.

The use of FNG in oncological mastology continues to be explored by Doren et al.<sup>18</sup> and Egozi et al.<sup>19</sup>. The nipple-sparing mastectomy (NSM) is a consolidated technique to achieve aesthetic results in mammary reconstruction<sup>5,18,19</sup>. However, in some cases, due to anatomical limitations and exposition factors, there is a contraindication to surgery using NSM, being left to

perform a prior reconstruction followed by NSM in two surgical times. In retrospective cohort study by Doren et al.<sup>18</sup>, 15 patients who were previously excluded from NSM due to previous areolar incision (n=2), breast parenchyma weighing >700 g (n=2), ptosis (n=1), radiation therapy (n=5), and patient's desire for autologous reconstruction (n=5) underwent a modified technique NSM associated with FNG in a single surgical time. A total of 26 areolar grafts were analyzed with a mean age of 47 years old, and 518.5 g of breast parenchyma. The graft viability was 95%, and the complication rate for loss of projection and hypopigmentation were, respectively, 19% and 27%. Doren et al.<sup>18</sup> concluded that FNG is a viable option for patients who do not fit classic indications and, therefore, is initially excluded from nipple-sparing surgery. The complication rates of FNG in oncoplastic surgery are similar
to those of reduction mammaplasty surgeries performed with the technique. Moreover, it spares patients from a doubled surgical time and its complications. Egozi et al.<sup>19</sup> retrospectively studied 7 patients in whom 13 FNG surgeries were performed. Initially, those patients were not excluded from NSM, as they were at high risk of mammillary necrosis. The mean age of the patients was 39.7 years old, and the mean BMI was  $30.1 \text{ kg/m}^2$ . All of them suffered from ptotic breasts (Regnault's grade II or III), and the average of parenchyma resected was 953 g. Finally, the authors reported a taking of 12 (93%) out of 13 grafts, with only 3 (24%) had hypopigmentation, and regarding a rate scale, based on Nahabedian patient satisfaction score, the FNG intervention achieved 4.6 out of 5. Therefore, FNG use is highly recommended by the authors owing to its high aesthetic satisfaction and low complication rates, potentially sparing patients from mammillary necrosis18.

Ghiedei et al.<sup>20</sup> in their retrospective cohort study verified, as a primary outcome, the graft viability and postoperative complications in women who suffered from ptotic breasts. They underwent skin-sparing mastectomy, with oncoplastic purpose, followed by FNG in a single surgical time, aiming to maintain the integrity of NAC. In the retrospective study of 14 patients analyzed from 2014 to 2017, 10 suffered from invasive breast carcinoma and 4 underwent prophylactic mastectomy due to high-risk familiar history of breast cancer. The authors found that the use of FNG is able to maintain NAC integrity after mastectomy in women with ptosis, as well as achieved high rates of aesthetic satisfaction and free resection margins in an oncological perspective<sup>18,19</sup>. However, complications such as partial nipple necrosis, hypopigmentation, and loss of NAC sensibility were found, respectively, in 7, 14, and 100% of the patients observed in the study, reinforcing the need for a captious analysis on the indication and guidance of FNG due to complications which may impact the patient's self-esteem and quality of life.

The FNG intervention in breast oncology continues to be explored in the literature in the cases report by Childester et al.<sup>21</sup>, in which a series of cases of three different women suffering from breast ptosis and carcinoma in situ underwent five NSMs, followed by FNG in a single surgical time. Analysis found that 1 (20%) out of 5 areola grafts was not successful, though it did not require postoperative debridement. The authors concluded that FNG was able to maintain NAC and free oncological margin <sup>18-21</sup> when undergoing FNG and skin-sparing mastectomy in a single surgical time.

King et al.<sup>22</sup> conducted a prospective study on 16 patients with breast cancer who underwent reconstruction surgery, using an inferior dermal flap associated with free nipple graft in a onestage procedure and analyzed oncological safety and postoperative complications. Patient average age was 54 years, and average operative time was 165 min. There were no immediate complications requiring reoperation. All retroareolar biopsies were benign and no locoregional recurrences have occurred. Two nipples had partial necrosis of the lower pole but healed with conservative treatment. No patients required any subsequent procedures to their reconstructed breast. Although authors reinforce this type of procedure is proper for only a minority of patients who are suitable for immediate reconstruction, such as those who have a large ptotic breast and who have a low likelihood of disease involving the nipple, they concluded that FNG associated with dermal flap is a safe method of implant-based reconstruction, giving an excellent cosmetic result in a single procedure.

Society has experienced a paradigm shift concerning gender and sexuality in the past few years. This context expanded the areas of intervention in mastology and plastic surgery. The demand for transgender mammaplasty surgery has been rising in recent years, and FNG mastectomy is highlighted as one of the first choice techniques for chest wall masculinizing surgery in these patients <sup>4,5</sup>.

Timmerman et al.23 performed an observational, cross-sectional study, with data collected from two prospective cohorts transgender men (n=57) after a mastectomy with free nipple grafts and cisgender men (n=150) as a reference sample. Demographics and 3D images were collected for both groups. NAC measurements were performed on the 3D images at four time points (i.e., 7, 30, 90, and 365 days postoperative) in transgender men and once in cisgender men. NAC width and height in trans men changed from 21.5±2.7 to 23.8±3.9 mm (p<0.001) and 16.2±2.5 to 14.7±3.0 mm (p=0.01) within a year, respectively. The mean NAC width and height in cisgender men were 28.1±5 and 20.7±4 mm, being significantly larger than that in transgender men. Satisfaction for size, shape, and flatness decreased significantly after postoperative day 30 (p=<0.05) in transgender men. Therefore, authors conclude morphology and satisfaction with the NACs in transgender men significantly decreased over time. They enforce that understanding and incorporating these differences into preoperative counseling and surgical planning might help increase patient satisfaction in a long-term status and not only in an immediate postoperative analysis.

In retrospective cohort of 90 patients and 180 mastectomies by Wolf et al.<sup>24</sup>, two techniques NAC pedicle (41.1%) and NAC graft (41.1%), which is a modification of the original FNG technique, were the most used surgical procedures in transgender patients in the series of procedures performed by a single surgeon. A mean age of 22.4 years old and 467 g of resected breast parenchyma were analyzed, and the authors found that, although high satisfaction and low complication rates were found in total mastectomies, it is necessary to establish a clinical-surgical classification based on breast weight and symmetry, as well as clinical trials to define which technique is more suitable for transgender patients.

Bustos et al.<sup>25</sup> compared intraoperative and postoperative outcomes of two techniques, either based on FNG, used in chest wall transgender surgery, the DIFNG and the nipple split technique performed in a total of 34 transgender patients, with a mean age of 24 years old and BMI of  $32.2 \text{ kg/m}^2$ , retrospectively analyzed from 2017 to 2019. Both techniques did not have statistical difference concerning intraoperative and postoperative complication rates; however, the nipple split technique achieved a higher satisfaction rate according to patients (90.7 vs. 58.1%, p<0.05) calculated by a Likert scale questionnaire. Thus, the authors concluded that the nipple split FNG is able to achieve good aesthetic results with low complication rates and a high security profile and that it should be recommended as a first choice in transgender mastectomies instead of DIFNG.

Frey et al.<sup>26</sup> analyzed symmetry and plasticity of NAC, as a primary outcome, in 50 transgender patients who underwent DIFNG from March 2015 to October 2016. The mean age of patients was 30.6 years old, and the mean weight of resected breast parenchyma was 627.8 g. The authors concluded DIFNG has a satisfactory safety profile. General complication rates including seromas, cellulitis, and hematomas were about 10%, and specific aesthetic-related complications that needed reintervention to adjust size or symmetry of NAC were about 8%. Therefore, the authors recommend the adoption of the technique in transgender mastectomies due to its high aesthetic and success rates.

Knox et al.<sup>27</sup> reviewed 101 masculinizing mastectomies surgeries comparing two consolidated techniques in transgender patients: FNG and circular concentric. The authors found FNG had lower complication rates (12.7% vs. 37%; p<0.01). In addition, they found circular concentric technique achieved better aesthetic outcomes in the score proposed by the authors based on scar healing and breast shape ranging from 1 to 5 (circular concentric score 3.39 vs. 2.62 FNG; p<0.01). Therefore, the authors reduce the recommendation for the FNG technique in patients with BMI>27 kg/m<sup>2</sup> and distance nipple inframammary fold longer than 7 cm and patients who might be at a high surgical risk. Furthermore, the authors reinforce the need for standardized evaluation scores and clinical trials to define, with a higher evidence-based conduct, the most suitable technique for transgenders masculinizing mastectomies.

## DISCUSSION

A variety of surgical applications has been described for the free nipple graft technique. The data from the present literature and research have shown promising results that may provide plastic and mastology surgeons with an evidence-based incentive to adopt the FNG technique in its broad spectrum of intervention.

Moreover, the possibility to modify Thorek's original technique<sup>14,15</sup> was explored in this study as a viable way to improve aesthetic problems in reduction mammaplasty, such as insufficient breast projection. This possibility was already discussed in literature back to the 90s by Romano et al.<sup>9</sup> and Abramson et al.<sup>10</sup>

Some restrictions to the FNG use, described in the past decades, which limited its use to strict cases of reduction mammaplasty with

over 1 kg per breast to be resected, or sternal notch-nipple distance longer than 35 cm, were already questioned by Colen et al.<sup>11</sup> The authors suggest that FNG may achieve equal or better aesthetic and functional outcomes compared to traditional reduction mammaplasty techniques, such as inferior pedicle, not only in its classic indications for gigantomastia or breast weighing >1 kg but also in cases of preeminent ptosis, inverted nipple, and fatty breasts. Transgender individuals who underwent surgery using FNG had average breast parenchyma resection of 490 g in the studies<sup>24-26</sup>. That gives support to Colen et al.<sup>11</sup> questioning on limitations to FNG use in parenchyma weighing 1000 g to be resected and suggests misconception of those prior restrictions related to FNG indications.

As a subtype of free skin graft, FNG had already been studied in some references back to the 2000s when it was seen that inclusion criteria for breast conservative surgery continued to evolve, including lower quadrants mastectomy and large breasts. Spear et al.<sup>28</sup>. reviewed on 11 women with macromastia who underwent lumpectomy followed by mammaplasty reduction, using FNG in 8 out of 22. The authors have already determined the importance of this gathered oncoplastic procedure, in that the potential for disfigurement after breast conservative treatment would increase, especially in some risk patients, such as women with macromastia. Authors found similar results compared to some in this article<sup>17,22</sup> when it comes to recognize the importance of a coordinated oncoplastic program and the benefits in boosting self-esteem in those patients, but Spear et al.<sup>28</sup> also reinforced the need for better define and improve algorithms for selecting women who might benefit from this type of the procedure, since patients with macromastia are at higher surgical risk when compared to most patients. In the articles<sup>17-22</sup> found in this revision, none of them have proposed a standardized algorithm neither for macromastia nor for ptotic breasts in oncoplastic treatment.

Some limitations to this revision were also found. Except Robert et al.<sup>14</sup>, none of the studies analyzed a broad population with a standardized statistic score of outcomes, such as risk ratio and aesthetic results when it comes to compare various techniques used in reduction mammaplasty, oncoplastic, and transgender surgery. In this manner, a reduced sample limits a significant statistical analysis. Besides, a historical problem concerning difficulties in performing clinical trials related to surgical interventions<sup>29</sup> was also present in the literature concerning FNG as no RCT was found in the databases, which may reduce methodological and evidence strength of this study.

Another fact that must be considered is the lasting of the aesthetics results, especially in transgender surgeries. Timmerman et al.<sup>23</sup> were the only authors who approached a lasting satisfaction over 1 year in contrast of the other articles on transgender surgery<sup>24-27</sup>. This aspect could be more explored since nonlasting results may have impact on self-esteem and morbidity problems in those patients<sup>5</sup>.

Despite these considerations regarding methodological and articles limitations, it is important to emphasize a broad applicability of FNG technique and its limited dissemination and use in breast surgery. Notwithstanding inconveniences related to FNG technique, such total loss of nipple sensibility, areolar depigmentation, and flattening of the papilla over time, it is also necessary to reinforce the low rate of loss of graft as well as aesthetic result similar or better to those found using conventional mammaplasty techniques. Moreover, in cases of oncological surgeries, in which maintaining NAC would not be possible after mastectomy in ptotic or bulky breasts, FNG may be used for the maintenance of the NAC or correction of malposition of it after conservative or radical mastectomies<sup>17,18</sup>.

## CONCLUSIONS

The literature data analysis provides a broad view of possibilities in breast surgery using the FNG technique and its safety profile. This study represents a potential impact on both experienced and learner surgeons when providing the most complete and updated information about a technique with a large spectrum of intervention in mammaplasty, oncological, and transgender surgery. Furthermore, we reinforce the need for adequate interventional trials and standardized aesthetic functional scores in order to define with a better level of evidence the usefulness of FNG.

# **AUTHORS' CONTRIBUTION**

RP: Conceptualization, Methodology, Formal Analysis, Investigation, Writing – original draft. AA: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. CN: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. CE: Supervision, Project Administration, Formal Analysis, Writing – review & editing.

## REFERENCES

- 1. Wamalwa AO, Stasch T, Nangole FW, Khainga SO. Surgical anatomy of reduction mammaplasty: a historical perspective and current concepts. S Afr J Surg. 2017;55(1):22-28. PMID: 28876554.
- MattioliWM,PenazziJúniorSA,MeloDSF.Useoftheback-folded dermaglandular inferior pedicle in mammary amputation: improving results. Rev Bras Cir Plást. 2017;32(3):339-45. https://doi.org/10.5935/2177-1235.2017RBCP0057
- Kim EK, Cho JM, Lee JW. Skin-sparing mastectomy and immediate nipple graft for large, ptotic breast. J Breast Cancer. 2019;22(4):641-6. https://doi.org/10.4048/jbc.2019.22.e52
- Etemad SA, Furuyama WM, Winocour JS. Double Incision Mastectomy with Free Nipple Graft for Masculinizing Chest Wall Surgery. Plast Reconstr Surg Glob Open. 2020;8(11):e3184. https://doi.org/10.1097/GOX.00000000003189
- Wilson SC, Morrison SD, Anzai L, Massie JP, Poudrier G, Motosko CC, et al. Masculinizing Top Surgery: A Systematic Review of Techniques and Outcomes. Ann Plast Surg. 2018;80(6):679-83. https://doi.org/10.1097/SAP.000000000001354
- Santos GR, Araújo DC, Vasconcelos C, Chagas RA, Lopes GG, Setton L, et al. Impacto da mamoplastia estética na autoestima de mulheres de uma capital nordestina. Rev Bras Cir Plást. 2019;34(1):58-64. https://doi.org/10.5935/2177-1235.2019RBCP0009
- Saariniemi KM, Keranen UH, Salminen-Peltola PK, Kuokkanen HO. Reduction mammaplasty is effective treatment according to two quality of life instruments. A prospective randomised clinical trial. J Plast Reconstr Aesthet Surg. 2008;61(12):1472-8. https://doi.org/10.1016/j.bjps.2007.09.024

- American Society of Plastic Surgeons. Plastic surgery statistics report 2017. ASPS National clearinghouse of plastic surgery procedural statistics. 2018 [cited on Mar 01, 2022]. Available from: https://www.plasticsurgery.org/ documents/News/Statistics/2017/plastic-surgery-statisticsfull-report-2017.pdf.
- Romano JJ, Francel TJ, Hoopes JE. Free nipple graft reduction mammoplasty. Ann Plast Surg. 1992;28(3):271-6. https://doi. org/10.1097/0000637-199203000-00012
- Abramson DL. Increasing projection in patients undergoing free nipple graft reduction mammoplasty. Aesthetic Plast Surg. 1999;23(4):282-4. https://doi.org/10.1007/s002669900284
- Colen SR. Breast reduction with use of the free nipple graft technique. Aesthet Surg J. 2001;21(3):261-71. https://doi. org/10.1067/maj.2001.116439
- 12. World Health Organization. Breast cancer. 2021 [cited on May 25, 2021]. Available from: www.who.int/news-room/factsheets/detail/breast-cancer
- Roje Z, Roje Z, Milosević M, Varvodić J, Mance M. Current trends in breast reduction. Coll Antropol. 2012;36(2):657-68. PMID: 22856260
- 14. Robert G, Duhamel A, Alet JM, Pelissier P, Pinsolle V. Complications des réductions mammaires à propos de 715 seins [Complications of breast reduction about 715 breasts]. Ann Chir Plast Esthet. 2014;59(2):97-102. https://doi. org/10.1016/j.anplas.2014.01.003
- 15. Karsidag S, Akcal A, Karsidag T, Yesiloglu N, Yesilada AK, Ugurlu K. Reduction mammaplasty using the free-nipple-graft vertical technique for severe breast hypertrophy: improved outcomes with the superior dermaglandular flap. Aesthetic

Plast Surg. 2011;35(2):254-61. https://doi.org/10.1007/s00266-010-9592-9

- Fırat C, Gurlek A, Erbatur S, Aytekin AH. An autoprosthesis technique for better breast projection in free nipple graft reduction mammaplasty. Aesthetic Plast Surg. 2012;36(6):1340-6. https://doi.org/10.1007/s00266-012-9984-0
- 17. Kijima Y, Yoshinaka H, Hirata M, Mizoguchi T, Ishigami S, Arima H, et al. Oncoplastic surgery combining partial mastectomy with breast reconstruction using a free nipple-areola graft for ductal carcinoma in situ in a ptotic breast: report of a case. Surg Today. 2011;41(3):390-5. https://doi. org/10.1007/s00595-010-4294-0
- Doren EL, Kuykendall LE, Lopez JJ, Laronga C, Smith PD. Free nipple grafting: an alternative for patients ineligible for nipple-sparing mastectomy? Ann Plast Surg. 2014;72(6):S112-5. https://doi.org/10.1097/SAP.00000000000077
- Egozi D, Allwies TM, Fishel R, Jacobi E, Lemberger M. Free nipple grafting and nipple sharing in autologous breast reconstruction after mastectomy. Plast Reconstr Surg Glob Open. 2020;8(9):e3138. https://doi.org/10.1097/ GOX.000000000003138
- 20. Ghidei L, Bansil HA, Stuckey A, Pandya S, Edmonson D, Michaud P, et al. Nipple-sparing mastectomy and ptosis: using a free nipple graft with tissue expander reconstruction. Plast Reconstr Surg Glob Open. 2020;8(2):e2623. https://doi. org/10.1097/GOX.00000000002623
- 21. Chidester JR, Ray AO, Lum SS, Miles DC. Revisiting the free nipple graft: an opportunity for nipple sparing mastectomy in women with breast ptosis. Ann Surg Oncol. 2013;20(10):3350. https://doi.org/10.1245/s10434-013-3122-3
- 22. King IC, Harvey JR, Bhaskar P. One-stage breast reconstruction using the inferior dermal flap, implant, and free nipple graft. Aesthetic Plast Surg. 2014;38(2):358-64. https://doi.org/10.1007/ s00266-014-0276-8
- 23. Timmermans FW, Elfering L, Smit JM, van de Grift TC, Bouman MB, Mullender MG. Long-term changes in free nipple

graft morphology and patient-reported outcomes in genderaffirming mastectomies. Aesthetic Plast Surg. 2022. https:// doi.org/10.1007/s00266-021-02666-w

- Wolf Y, Kwartin S. [Our experience in mastectomy for transgenders female to male – a 90 cases cohort study]. Harefuah. 2020;159(8):595-9. PMID: 32852161
- 25. Bustos SS, Forte AJ, Ciudad P, Manrique OJ. The nipple split sharing vs. conventional nipple graft technique in chest wall masculinization surgery: can we improve patient satisfaction and aesthetic outcomes? Aesthetic Plast Surg. 2020;44(5):1478-86. https://doi.org/10.1007/s00266-020-01803-1
- 26. Frey JD, Yu JZ, Poudrier G, Motosko CC, Saia WV, Wilson SC, et al. Modified Nipple Flap with Free Areolar Graft for Component Nipple-Areola Complex Construction: Outcomes with a Novel Technique for Chest Wall Reconstruction in Transgender Men. Plast Reconstr Surg. 2018;142(2):331-6. https://doi.org/10.1097/PRS.00000000004551
- 27. Knox ADC, Ho AL, Leung L, Hynes S, Tashakkor AY, Park YS, et al. A review of 101 consecutive subcutaneous mastectomies and male chest contouring using the concentric circular and free nipple graft techniques in female-to-male transgender patients. Plast Reconstr Surg. 2017;139(6):1260e-72e. https://doi.org/10.1097/PRS.0000000003388
- McKissock PK. Reduction mammaplasty with a vertical dermal flap. Plast Reconstr Surg. 1972;49(3):245-52. https://doi. org/10.1097/00006534-197203000-00001
- 29. Spear SL, Pelletiere CV, Wolfe AJ, Tsangaris TN, Pennanen MF. Experience with reduction mammaplasty combined with breast conservation therapy in the treatment of breast cancer. Plast Reconstr Surg. 2003;111(3):1102-9. https://doi.org/10.1097/01.PRS.0000046491.87997.40
- McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. BMJ. 2002;324(7351):1448-51. https://doi.org/10.1136/ bmj.324.7351.1448

© 2022 Brazilian Society of Mastology

# Global impact of pandemic by SARS-CoV-2 on breast cancer diagnosis and screening

Amanda Dezordi Dall'Agnol<sup>1</sup> ©, Ana Katharina Dalbosco<sup>1</sup>\* ©, Giordana Vitória Bertozzo Suzin<sup>1</sup> ©, Mauricio Both<sup>1</sup> ©, Valentina Antonio Simonetti<sup>1</sup> ©, Emily Sanini Guimarães<sup>2</sup> ©, Luciano Luiz Alt<sup>1</sup> ©, Lia Mara Wibelinger<sup>3</sup> ©

## ABSTRACT

Introduction: The pandemic related to the new coronavirus is characterized by high rates of contamination, transmissibility, and mortality. The measures of social isolation adopted by the World Health Organization and corroborated by several countries, with a view to avoiding or minimizing the transmission of COVID-19, can lead to the reduction of the capacity of screening and diagnosis of diseases, such as breast cancer. **Objective:** This study aimed to analyze the diagnostic indexes and mamaria malignancy diagnosis test, such as mammogram, during the COVID-19 pandemic period. **Methodology:** Systematic review of the literature based on studies found in the PubMed, SciELO, LILACS, and ScienceDirect databases. **Results:** The six selected articles demonstrate a reduction in the diagnosis of breast cancer during the pandemic, although with discordant rates. Outcomes such as reduced number of mammograms and change in tumor stage were also analyzed. **Conclusion:** It is essential to maintain care with the screening, diagnosis, and treatment of breast cancer, in order to minimize the damage caused over more than 1 year of COVID-19 pandemic.

KEYWORDS: coronavirus; early detection of cancer; neoplasms; SARS-CoV-2.

### INTRODUCTION

The SARS-CoV-2 virus infections are first recorded in December 2019 in Wuhan, China. Spreading globally, due to the inherent characteristics of the virus, there was a need to implement measures to contain viral propagation, such as social distancing and the relocation of health services, in order to meet new global demands. Therefore, many countries have chosen to temporarily suspend their screening and diagnosis programs for breast cancer, which is the world's most common neoplasm among women<sup>1</sup>.

In Brazil, according to Bessa<sup>2</sup>, the National Health Agency recommended that non-urgent visits, examinations, or surgeries be postponed. The State has a screening program for the diagnosis of breast cancer through the Unified Health System in women aged between 50 and 69 years. Despite government efforts, even before the pandemic, it is estimated that, together with the search for private care, only 60% of screening coverage occurs in the country.

In this context of changes in the functionality of health systems resulting from the COVID-19 pandemic, the study aimed to analyze the overall impact on the number of diagnoses of breast neoplasms and on mammograms. Through a systematic review, pre-pandemic and pandemic comparative data are described.

#### **METHODS**

This study consists of a systematic literature review so that submission to the Ethics and Research Committee was not necessary. Articles indexed in the electronic databases PubMed, SciELO, LILACS, and ScienceDirect were manually collected from August 28 to 31, 2021. Cross-sectional and retrospective observational studies were selected using the following descriptors and keywords: (Diagnosis) AND (Breast Neoplasms) AND (COVID-19), which were obtained according to the Health Science Descriptors (DeCS).

The inclusion criteria for the selection of articles for systematic review were predetermined and include relationship between the number of breast cancer diagnoses before and during the COVID-19 pandemic; articles with real data presentation; and

<sup>2</sup>Universidade Federal Fronteira Sul, Faculty of Medicine – Chapecó (SC), Brazil.

\*Corresponding author: ana-kathi@hotmail.com

<sup>&</sup>lt;sup>1</sup>Universidade de Passo Fundo, Faculty of Medicine – Passo Fundo (RS), Brazil.

<sup>&</sup>lt;sup>3</sup>Universidade de Passo Fundo, Faculty of Physiotherapy – Passo Fundo (RS), Brazil.

Conflict of interests: nothing to declare. Funding: none.

**Received on:** 01/07/2022. Accepted on: 04/01/2022.

articles with translation into at least one of the following languages: English, Portuguese, or Spanish. The exclusion criteria were also predetermined for the search, being excluded: editorial articles; articles whose publication has been made in languages other than those mentioned above; and articles with speculative data.

In this search for the present study, 263 results were found on the PubMed platform, 174 articles on the ScienceDirect platform, and 5 articles on the LILACS platform, with no results on the SciELO platform. Only one of the articles was duplicated, so after reading the titles, 36 studies were selected to read the abstract and, after reading the respective abstracts, 21 articles remained. These 21 studies were read in full by three reviewers and selected independently so that they met the inclusion and exclusion criteria, leaving, at the end, 6 articles.

Of the 263 articles found on the PubMed platform, 262 remained after the exclusion of the duplicate, so that 229 of them were excluded after reading the title and 12 after reading the abstract for not meeting the pre-established requirements. Of the 19 articles read in full, 10 were excluded due to the absence of the outcome of the relationship between the number of breast cancer diagnoses during the pandemic, 4 were excluded because they were guidelines or editorial letters, and 1 was excluded because it referred to simulations with unrealistic data from population models. Of the 174 studies located on the ScienceDirect platform, 171 were excluded after reading the title and 2 were excluded after reading the abstract, so the article read in full was included in the review. Of the five articles found on the LILACS platform, four studies were excluded after reading the title and one was selected to integrate the systematic review. Finally, data were



Figure 1. Search strategy flowchart. Passo Fundo (RS), 2021.

extracted on the characteristics of the studies, results, and outcomes. The flowchart of the process of identification and selection of studies is presented in Figure 1.

#### RESULTS

All articles included were published in 2020 or 2021, written in English, with impact factors ranging from 4,018 to 11,059. Regarding origin, two studies are from the Netherlands<sup>3,4</sup>, one from Belgium<sup>5</sup>, one from Brazil<sup>6</sup>, one from Croatia<sup>1</sup>, and one from Italy<sup>7</sup>. The outcomes addressed by the studies were decreased in breast cancer diagnoses, reduction in the number of tests performed, and changes in the stage of cancer.

In the Brazilian article, coming from Fortaleza, Ceará, mammography and breast ultrasound examinations had the greatest impact due to the pandemic, with a decrease of 95% and 100%, respectively, which led to a reduction of up to 60% of diagnoses, since the number of new cases of breast cancer was 23 in May 2019 and 8 in May 2020<sup>6</sup>. When comparing two distinct periods, it was noted that, in northern Italy, between May 2019 and July 2019, 15,942 mammograms were performed and 223 individuals were diagnosed with breast cancer (221 women and 2 men), but in the same quarter of 2020, only 9,052 mammograms were performed and 177 patients were diagnosed (174 women and 3 men). In addition, in 2020, there was a statistically significant reduction in the diagnosis of breast cancer in situ (from 17% of breast cancer diagnoses in 2019 to 6.8% in 2020), but the rate of cT1, cT2, and cT3 tumors diagnosed in May to July 2020 did not differ significantly from the 2019 tumors. In contrast, cT4 tumors increased from 4 (1.8%) in 2019 to 14 (7.9%) in 2020 and the number of breast cancers with metastatic lymph nodes (cN+) at the time of diagnosis increased from 28 (12.5%) in 2019 to 42 (23.7%) in 20207.

In the Netherlands, the incidence of breast tumors detected at screening decreased during weeks 12–13 of 2020, almost zeroed during weeks 14–25, and increased during weeks 26–35. The decrease in incidence was observed in all age groups and occurred mainly for cTis, cT1, ductal carcinoma in situ, and stage I tumors. Due to the suspension of the breast cancer screening program and its restarting with reduced capacity, the incidence of tumors detected by screening decreased by 67% during weeks 9–35 of 2020, which equates to about 2,000 possibly delayed breast cancer diagnoses. Despite this, until August 2020, there was no evidence of a transition to breast cancer at higher stages after the restart of screening<sup>3</sup>.

A 24% reduction in newly diagnosed breast cancer cases in Croatia was seen during April, May, and June 2020 compared to the same period in 2019. However, during the whole of 2020, only 1% fewer new cases were reported than in 2019, 6% less than expected<sup>1</sup>. In Belgium, female breast cancer diagnoses in the screening population (50–69 years) decreased by 56% in April 2020, but it was possible to resume screening for these tumors, with only 6% of diagnoses missing by the end of  $2020^5$ .

### DISCUSSION

Breast cancer screening in the asymptomatic population leads to early diagnosis and treatment<sup>8</sup>. During the COVID-19 pandemic, there were problems in accessing cancer care services, which includes screening<sup>9</sup>, raising some concerns about the delay, and decreased diagnoses of the disease<sup>5</sup>. This context can have deleterious long-term effects, since it was estimated that the delay of each month in diagnosis is associated with a 1.8% higher probability of a more advanced stage of cancer<sup>1</sup>.

As can be seen in Table 1, the six articles selected for systematic review demonstrate a reduction in the diagnosis of breast cancer during the COVID-19 pandemic, although these rates present some disagreements. Lôbo et al.<sup>6</sup> reported a 60% reduction in diagnoses, the highest rate found, but these data are related to a restricted population, since they correspond to the city of Fortaleza (Ceará, Brazil). In addition, these rates also disagree with those presented by the National Cancer Institute<sup>10</sup> which demonstrates 59,700 new cases in 2019 and 66,280 in 2020, so that in Brazil, there was a 10% increase in new cases of the disease. Toss et al.<sup>7</sup>, Eijkelboom et al.<sup>3</sup>, Vrdoljak et al.<sup>1</sup>, and Eijkelboom et al.<sup>4</sup> demonstrated similar rates of diagnostic reduction in the first half of 2020, with 24, 37, 24, and 35% decrease, respectively. These values also disagree with those analyzed in the same studies by Vrdoljak et al.<sup>1</sup> and Peacock et al.<sup>5</sup>, which demonstrate a reduction of 1 and 6%, respectively, when compared to the whole year 2019 and 2020. The explanation for these data may lie in the fact that, as cancer care services returned to work, an increase in screening volumes may have reduced the deficit in accumulated mammograms, as demonstrated in the study by Miller et al.<sup>11</sup>, which brought up new diagnoses of the disease.

Regarding breast cancer screening tests, when analyzing the article by Lôbo et al.<sup>6</sup>, it was evidenced a 95% decrease in the rate of mammograms in the period from March to June 2020 compared to 2019 in Brazil, while in the study by Toss et al.<sup>7</sup>, in Italy, there was a 43% reduction in these rates from May to July 2020, compared to the previous year. The discrepancy of these data may occur due to the fact that the pandemic in Italy began earlier than in Brazil and had its peak waves of SARS-Cov-2 in different stages.

When comparing Brazilian studies, Lôbo et al.<sup>6</sup> with Bessa<sup>2</sup>, there is a difference in results, because Bessa<sup>12</sup>, based on DATASUS, showed a 42% drop in the rate of mammograms throughout the

Table 1. Outcomes found in the systematic s	earch.	

Reference	Analyzed site	Analyzed period	Breast cancer diagnostic reduction (%)	Mammography reduction (%)	Tumor stage (%)
1. Lôbo et al. <sup>6</sup>	Fortaleza, Ceará, Brazil	From March to June 2020, compared to the same period in 2019	60 of reduction in diagnostics	95	-
2. Toss et al.⁵	Province of Modena, northern Italy	From May to July 2020, compared to the same period in 2019	24 of reduction in diagnostics	43	IN SITU: decrease of 68 IIA: decrease of 12 Stage III: increase of 10 Stage I, IIB e IV no significant changes
3. Eijkelboom et al.²	Holland	From February to August 2020, compared with the same period in 2018 and 2019	37 of reduction in diagnostics	-	IN SITU: decrease of 57 Stage I: decrease of 43 Stage II: decrease of 25 Stage III: decrease of 16 Stage IV: decrease of 4
4. Vrdoljak et al.¹	Croatia	Year 2020 compared to 2019	24 of reduction in diagnostics from April to June 2020, if compared with the same period in 2019 1 of reduction in diagnostics for the whole of 2020	-	_
5. Eijkelboom et al.³	Holland	From February to April 2020, compared with the same period in 2018 e 2019	35 of reduction in diagnostics	_	IN SITU: decrease of 38 Stage I: decrease of 39 Stage II: decrease of 32,5 Stage III: decrease of 38 Stage IV: decrease of 15
6. Peacock et al⁴	Belgium	2020 compared to year 2019	6 of reduction in diagnostics	_	_

country and that the most affected state was Rondônia, with 67%. However, in the study by Lôbo et al.<sup>6</sup>, it is only in Fortaleza, Ceará, there was a 95% decrease, which is similar to the data demonstrated by Collado-Mesa et al.<sup>12</sup>, whose decrease in mammograms was 98% in Florida, USA. From March to June 2020, the same period as evidenced by Lôbo et al.<sup>6</sup>, the article by Song et al.<sup>16</sup> showed a 38% reduction in mammograms expected compared to 2019 in the United States. In another study conducted in the United States<sup>13</sup>, from March to May 2020, the absolute deficit in the American population in breast screening associated with the COVID-19 pandemic was estimated at 87.3% compared to the same time period in 2019.

In the analysis of the selected articles, a significant reduction of 68% of the tumor in situ is found in the study by Toss et al.<sup>7</sup> and of 57% is found in the study by Eijkelboom et al.3, demonstrating the proximity of the data. Already in the study by Eijkelboom et al.4, this rate is also decreased, but with a value of 38%. Stage I had similar results in the articles by Eijkelboom et al.<sup>3</sup> and by Eijkelboom et al.<sup>4</sup>, with a decrease of 43 and 39%, respectively. However, in the study by Toss et al.<sup>7</sup>, this stage does not present significant changes, as well as IIB and IV in the same article. Stage II demonstrates a decrease of 12, 25, and 32.5% in the studies by Toss et al.7, Eijkelboom et al.3, and Eijkelboom et al.4, in that order, in which the disparity of the data between the first and the other articles is perceived. Stage III shows decrease in the study by Eijkelboom et al.<sup>3</sup> of 16% and approximately double in the study by Eijkelboom et al.3, with 38%. However, Toss et al.7 presented a discrepancy in the data, with an increase of 10%. Stage IV showed a slight decrease of 4% in the study by Eijkelboom et al.3 and a more significant percentage of 15% in the study by Eijkelboom et al.<sup>4</sup>.

In relation to increased mortality due to delay and decrease in diagnoses, Yong et al.<sup>14</sup> estimated the long-term clinical impact of breast cancer screening interruptions in Canada, using a validated mathematical model, which demonstrated an increase of 110 deaths between 2020 and 2029 due to a 3-month break in the disease screening service. Another study<sup>15</sup> estimated the impact of COVID-19 on screening and treatment of breast cancer at Sharpless, using CISNET cancer simulation, which demonstrated an increase of more than 5,000 deaths in the next decade in the United States. This context of reduced diagnosis and screening tests demonstrated by systematic review occurs both due to the reduced operational status of imaging clinics and due to the fear of patients seeking health services<sup>16</sup>. However, even in the midst of the pandemic, other pathologies, such as breast cancer, have not stopped emerging and continue to cause high morbidity and mortality. In this sense, since the COVID-19 pandemic persists for more than 1 year, it is important that breast cancer care services continue to function, with due care, in order to perpetuate care for the pathology.

Although some studies present discordant rates, this review demonstrates the reduction in the number of tests performed for breast cancer screening, as well as the decrease in diagnoses of the disease in all sites studied by the analyzed articles. In addition, it is also suggested, as a consequence of the reduction in screening, changes in the staging of breast cancer. However, more studies are needed to confirm these findings. Even so, considering the data that indicate worsening in the stage of the disease, it is essential to maintain care with the screening, diagnosis, and treatment of breast cancer, aiming to minimize the damage caused over more than 1 year of COVID-19 pandemic.

## **AUTHORS' CONTRIBUTION**

ADDA: Conceptualization, Investigation, Methodology, Validation, Writing - original draft, Writing - review & editing. AKD: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing. GVBS: Conceptualization, Investigation, Methodology, Validation, Writing - original draft, Writing - review & editing. MB: Conceptualization, Investigation, Methodology, Validation, Writing - original draft, Writing - review & editing. VAS: Conceptualization, Investigation, Methodology, Validation, Writing - original draft, Writing - review & editing. ESG: Conceptualization, Investigation, Methodology, Validation, Writing - original draft. LLA: Conceptualization, Data curation, Investigation, Project administration, Supervision, Validation, Writing - review & editing. LMW: Conceptualization, Data curation, Investigation, Project administration, Supervision, Validation, Writing - review & editing

#### REFERENCES

- Vrdoljak E, Balja MP, Marušić Z, Avirović M, Blažičević V, Tomasović Č, et al. COVID-19 Pandemic Effects on Breast Cancer Diagnosis in Croatia: A Population- and Registry-Based Study. Oncologist. 2021;26(7):e1156-60. https://doi.org/10.1002/onco.13791
- Eijkelboom AH, de Munck L, Lobbes MBI, van Gils CH, Wesseling J, Westenend PJ, *et al.* Impact of the suspension and restart of the Dutch breast cancer screening program on breast cancer incidence and stage during the COVID-19 pandemic. Prev Med. 2021;151:106602. https://doi.org/10.1016/j. ypmed.2021.106602
- Eijkelboom AH, de Munck L, Peeters MJTFDV, Broeders MJM, Strobbe LJA, Bos MEMM *et al.* Impact of the COVID-19 pandemic on diagnosis, stage, and initial treatment of breast cancer in the Netherlands: a population-based study. J Hematol Oncol.2021;14:64. https://doi.org/10.1186/s13045-021-01073-7
- Peacock HM, Tambuyzer T, Verdoodt F, Calay F, Poirel HA, De Schutter H, *et al.* Decline and incomplete recovery in cancer diagnoses during the COVID-19 pandemic in Belgium: a yearlong, population-level analysis. ESMO Open. 2021;6(4):100197. https://doi.org/10.1016/j.esmoop.2021.100197

- Toss A, Isca C, Venturelli M, Nasso C, Ficarra G, Bellelli V, et al. Two-month stop in mammographic screening significantly impacts on breast cancer stage at diagnosis and upfront treatment in the COVID era. ESMO Open. 2021;6(2):100055. https://doi.org/10.1016/j.esmoop.2021.100055
- Lôbo CC, Pinhiero LGP, Vasques PHD. Impact of the COVID-19 pandemic on breast cancer diagnosis. Mastology. 2020;30:1-5. https://doi.org/10.29289/25945394202020200059
- Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. Breast-cancer screeningviewpoint of the IARC Working Group. N Engl J Med. 2015;372(24):2353-8. https://doi.org/10.1056/NEJMsr1504363
- Zadnik V, Mihor A, Tomsic S, Zagar T, Bric N, Lokar K, et al. Impact of COVID-19 on cancer diagnosis and management in Slovenia – preliminary results. Radiol Oncol. 2020;54(3):329-34. https://doi.org/10.2478/raon-2020-0048
- Chen RC, Haynes K, Du S, Barron J, Katz AJ. Association of cancer screening deficit in the United States with the COVID-19 pandemic. JAMA Oncol. 2021;7(6):878-84. https:// doi.org/10.1001/jamaoncol.2021.0884
- Sharpless NE. COVID-19 and cancer. Science. 2020;368(6497):1290. https://doi.org/10.1126/science.abd3377
- Nyante SJ, Benefield TS, Kuzmiak CM, Earnhardt K, Pritchard M, Henderson LM. Population-level impact of coronavirus disease 2019 on breast cancer screening and diagnostic procedures. Cancer. 2021;127(12):2111-21. https://doi.org/10.1002/cncr.33460

- Bessa JF. Breast imaging hindered during Covid-19 pandemic, in Brazil. Rev Saúde Publica. 2021;55:1-8. https://doi. org/10.11606/s1518-8787.2021055003375
- Instituto Nacional de Câncer. Estatísticas de câncer. Instituto Nacional de Câncer, Ministério da Saúde; 2020. [cited on Set. 08, 2021]. Available from: https://www.inca.gov.br/numerosde-cancer
- 14. Collado-Mesa F, Kaplan SS, Yepes MM, Thurber MJ, Behjatnia B, Kallos NPL. Impact of COVID-19 on breast imaging case volumes in South Florida: a multicenter study. Breast J. 2020;26(11):2316-9. https://doi.org/10.1111/ tbj.14011
- 15. Miller MM, Meneveau MO, Rochman CM, Schroen AT, Lattimore CM, Gaspard PA, et al. Impact of the COVID-19 pandemic on breast cancer screening volumes and patient screening behaviors. Breast Cancer Res Treat. 2021;189(1):237-46. https://doi.org/10.1007/s10549-021-06252-1
- 16. Song H, Bergman A, Chen AT, Ellis D, David G, Friedman AB, et al. Disruptions in preventive care: mammograms during the COVID-19 pandemic. Health Serv Res. 2021;56(1):95-101. https://doi.org/10.1111/1475-6773.13596
- Yong JH, Mainprize JG, Yaffe MJ, Ruan Y, Poirier AE, Coldman A, *et al.* The impact of episodic screening interruption: COVID-19 and population-based cancer screening in Canada. J Med Screen. 2021;28(2):100-7. https://doi. org/10.1177/0969141320974711

