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ABOUT

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

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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[1]. 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)[2].

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[3]. Breast cancer is the second type of cancer with the highest risk to develop brain metastases[4]. 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[5]. 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[6].

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

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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.

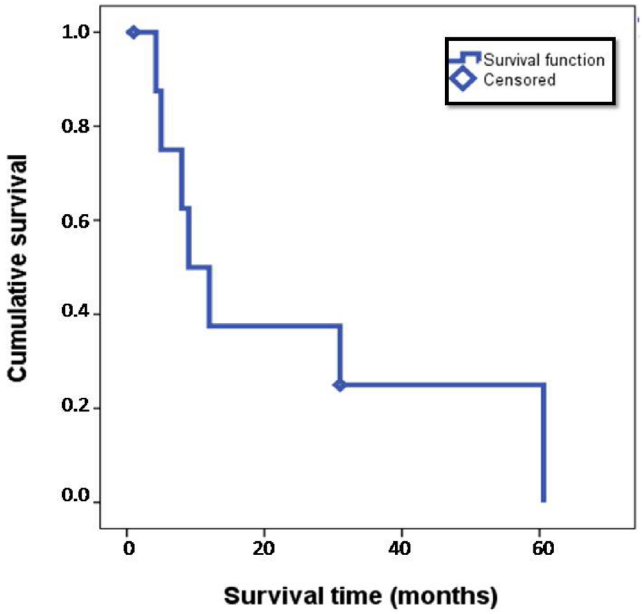
METHODS

The present study was conducted according to the STROBE statement for cross-sectional studies[8]. 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).

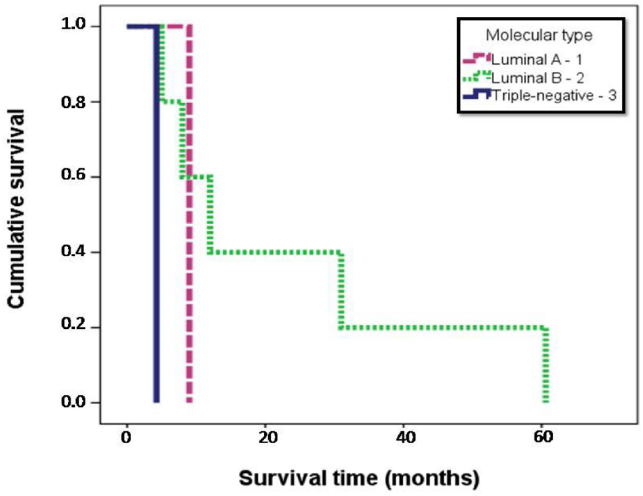
Molecular classification was possible in seven patients: five luminal B subtype, one luminal A case and one triple-negative case; patients with the luminal B subtype had a longer median survival – 23.3 months (95%CI 3.0–43.6; p=0.044<0.05). The triple-negative case had a lower median survival (4.25 months) (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).

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

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

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)[9]. 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)[9].

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%[9]. 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)[10]. 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[11].

According to the literature, the most common histological type is invasive carcinoma of no special type[11]; 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[12].

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[13]. 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[14].

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[15].

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[9].

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+)[13]. 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[15]. 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[16]. 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)[17] 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[17], 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)[17].

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[18]. 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[19]. 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[20]. In addition, there are associations in the literature between this alteration and evolution with triple-negative tumors[21].

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[9]. 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[22].

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[23]. 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[23].

Primary tumor resection can increase patient survival when performed at early stages, and it also impacts disease recurrence[24]. 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[23]. 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[25].

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.

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

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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[1]. According to international guidelines, breast cancer is uncommon in women under 40 years of age, representing less than 7% of all diagnosed cases[2]. Even rarer is the involvement of a second contralateral primary breast cancer, corresponding to a mean annual incidence rate of 0.5%[3,4]. 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[2,5]. 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[6]. 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%[7]. Those tumors that do not express the HER2 protein or hormone receptors are called triple-negative tumors, and they are more aggressive[8-10].

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

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divergent molecular profile between the initial breast tumor and the recurrent or[11] 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[11]. All this makes it often necessary to biopsy the new lesion, especially when the patient does not have a satisfactory therapeutic response[12].

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[11,13,14]. 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[11].

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[15,16]. 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[16].

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[17]. 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[18].

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 radiological 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[1]. According to international guidelines, breast cancer is uncommon in women under 40 years of age, accounting for less than 7% of all diagnosed cases[2]. The involvement of a second contralateral primary breast cancer is even rarer, corresponding to an average annual incidence rate of 0.5%[3].

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[4]. There are many risk factors for breast cancer; however, for contralateral disease, these factors are not well established[5].

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[2] index.

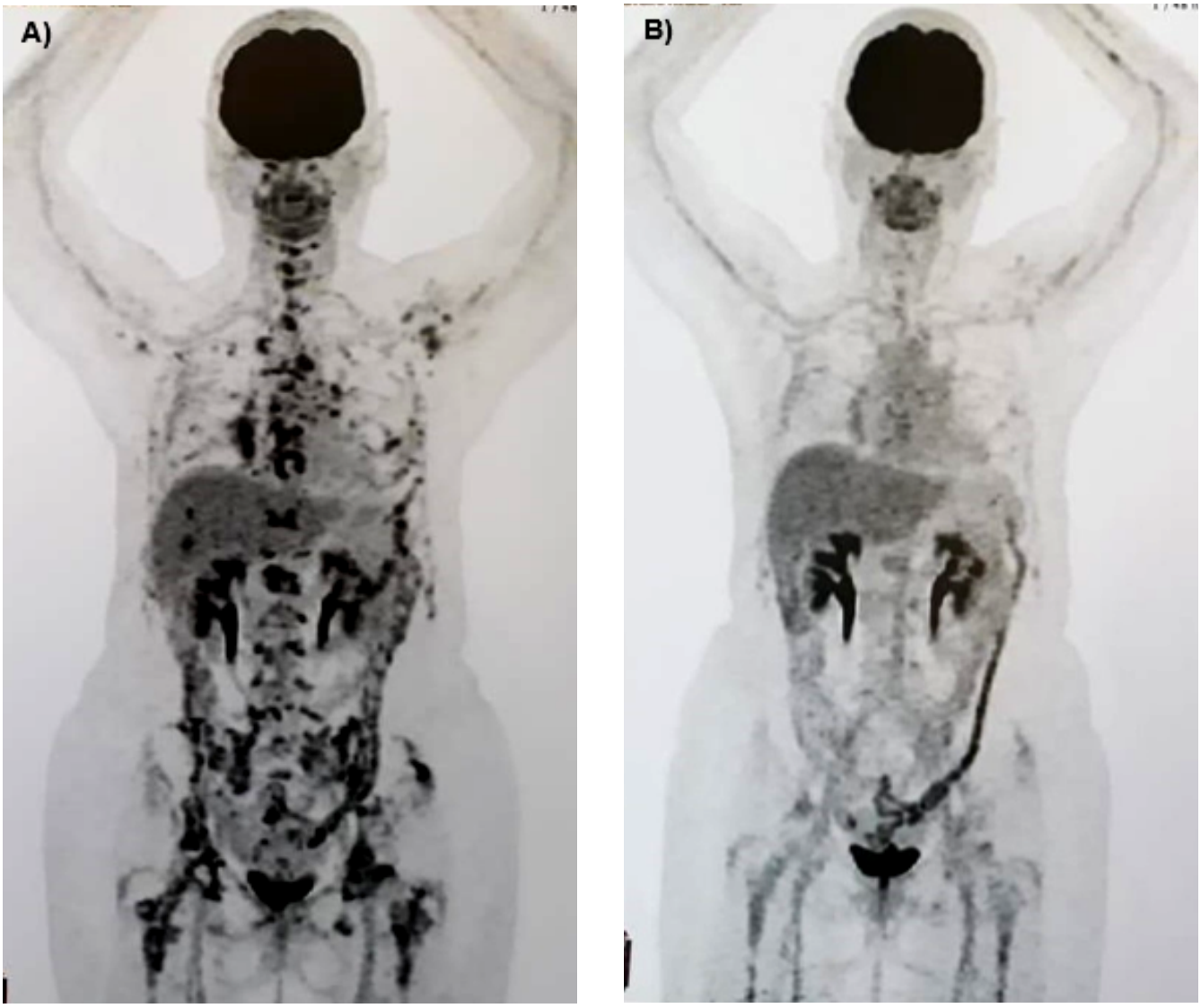

Figure 1. A) PETCT of the patient before starting treatment with trastuzumabe entansina combined with letrozol and denosumabe; B) PETCT of the patient at the end of treatment with trastuzumabe entansina combined with letrozol and denosumabe.

And it is according to each molecular subtype that survival rate is determined and therapeutic possibilities defined[6].

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 and HER2-positive or -negative with Ki67 index greater than 14%[7]. Those that do not express the HER2 protein and do not have hormone receptors are called triple-negative (TN) tumors and are more aggressive[8-10].

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[11].

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[15].

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[12].

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[13]. 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[14].

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[11]. 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[11]. 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[16].

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[17] 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[18]. 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[19].

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.

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CASE REPORT
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Dermatitis neglecta in a patient with breast fibroadenoma: case report

Aline Cristina da Silva Lima[1], Juliana Pontes Farias[1], Renê Stéfano Costa Pontes[1], Isabelle Souza Medeiros Torres[1], Janislei Soares Dantas[1]*, Adriano de Lima Quirino[1], Ilzinalda dos Santos Ideão Farias[1], Joanne Elizabeth Ferraz da Costa[1]

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[1]. This benign skin alteration, although asymptomatic, is aesthetically uncomfortable. It is little reported in the literature, with underestimated prevalence and possibly underdiagnosed[2,3].

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[4,5].

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[3,4].

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

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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[6].

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

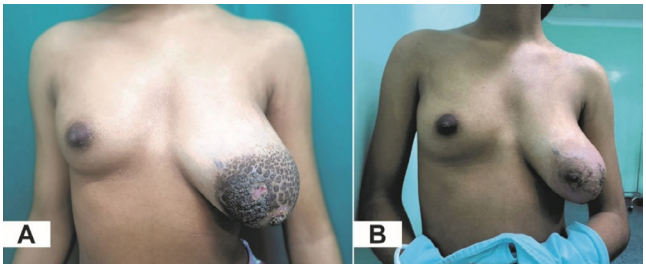

Figure 1. (A) Breast asymmetry due to tumor in the left breast, with thick crusts covering the areolar and periareolar region. (B) Reduction of crusts, with exposure of the nipple-areola region, which is deviated to the right due to tumor.

Clinically, there are asymptomatic hyperkeratotic, hyperpigmented squamous plaques[1,2].

Previously published studies[1,3,7,8] 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[9–11].

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

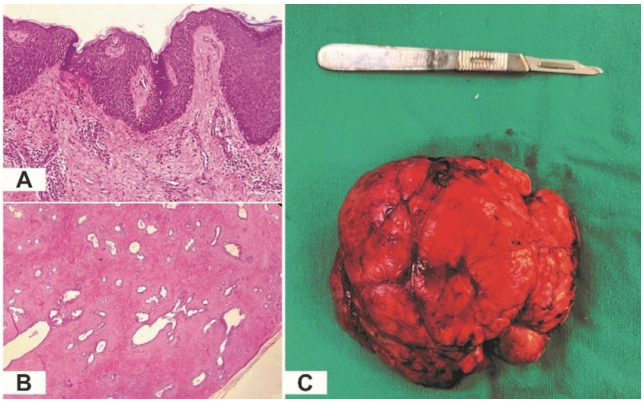

Figure 2. On the left, histological sections in hematoxylin-eosin staining visualized at 40x magnification: (A) skin fragment, noting hyperkeratosis and papillomatosis; (B) result from quadrantectomy with fibrous breast stroma permeated with glands without atypia, sometimes with reduced lumen, confirming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

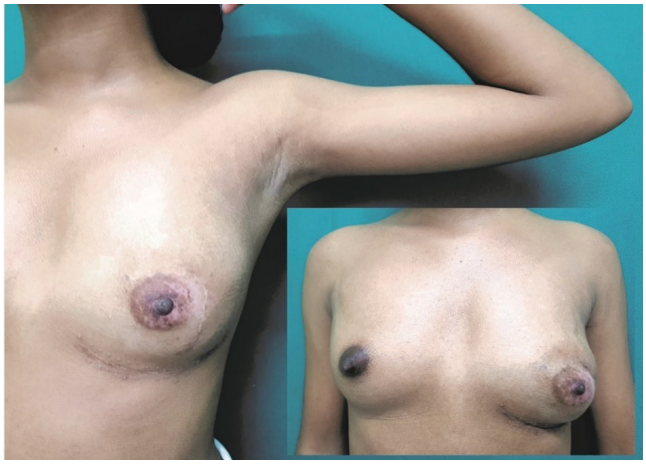

Figure 3. Post-surgical follow-up, demonstrating partial repigmentation of the areolar and periareolar region.

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[12]. 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[13,14].

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[15].

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[16].

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 low-cost treatment, it is still underdiagnosed[11].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.

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

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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[1].

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[2].

The portrait of this cancer in the Brazilian population was clearly demonstrated by Rosa et al.[3]. 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[3].

This disease has very well-established risk factors: menstrual-reproductive, environmental and lifestyle. Among these, the modifiable ones such as obesity and alcohol consumption, which can impact the incidence and mortality of various diseases[4], 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[5]. 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[6]. 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[7].

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/m^2 and normal vital signs, communicated

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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 $3.06x10^6/mm^3$, hematocrit 24.80%; hemoglobin 8.27 g/dL; leukocytes $12,400/mm^3$ and platelets $124,000/mm^3$. Other blood tests showed glucose 85.50 g/dL; transaminases and urea nitrogen normal; and Venereal Disease Research Laboratory (VDRL), HBsAg, 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.

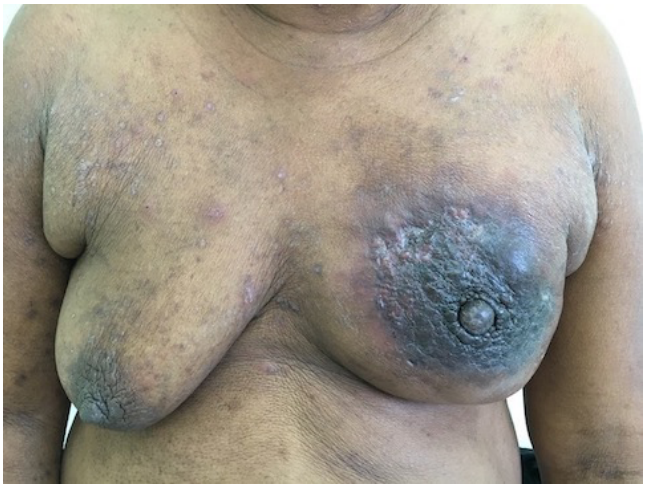

Figure 1. Static inspection: Chest with multiple hyperchromic scars. Flaccid and pendulous left breast, the right breast increased in volume and firm due to the presence of the tumor – Front view.

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[8].

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[9].

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[10]. 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[11]. The same was observed by Freitas-Junior et al., who, researching the number of deaths from breast cancer in Brazilian indigenous women between 2000 and 2010, observed a risk ratio for indigenous women of 0.25[12].

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[13].

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

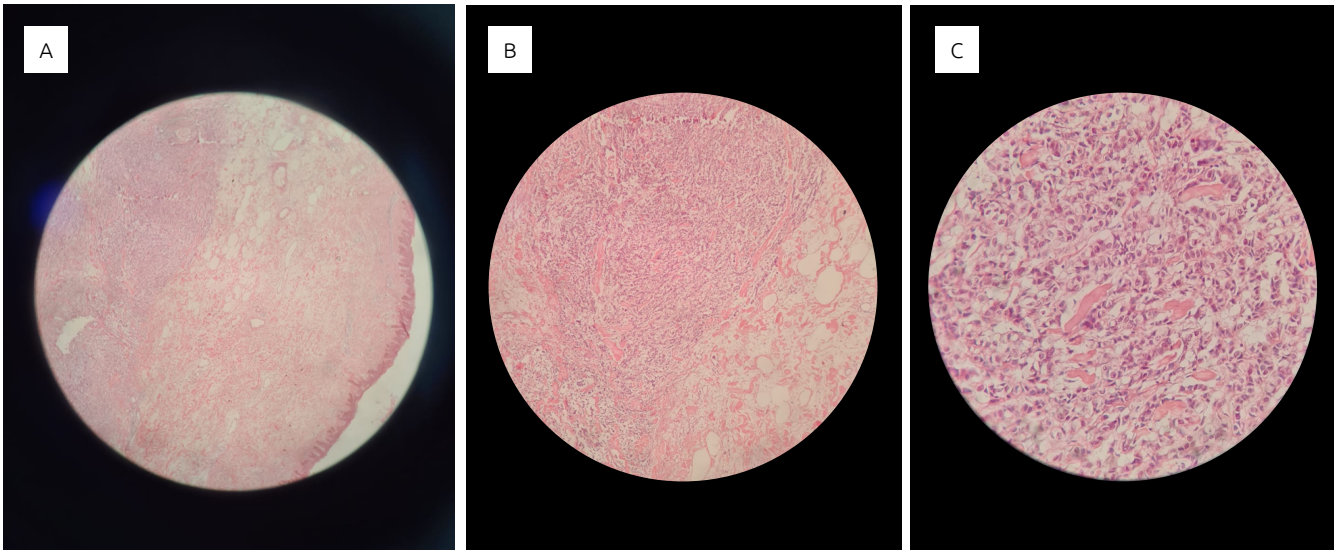

Figure 2. (A) Skin segment with infiltration by invasive breast carcinoma of no special type (NST)/invasive ductal carcinoma not otherwise specified (NOS) in subcutaneous tissue (hematoxylin and eosin, HE: 40x); (B) Cords and nests of atypical cells with prominent nucleoli and anisokaryosis, surrounded 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[14]. 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[11]. 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[4]. 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 β-glucuronidase and β-glucuronide, enzymes involved in estrogen deconjugation and conjugation[15].

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[16]. 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 (TGFβ1), which is an important regulator of mammary epithelial stem cells[17].

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[18]. 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[19]. 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[20]. 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.

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

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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[1]. 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)[2].

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[3,4]. 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[5-10].

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[5-8].

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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≥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≥0.55). Regarding PLR, 25 (59.5%) of the patients were classified in the low group (PLR<203.5) and the other 17 (40.5%) in the high group (PLR≥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=0.166), nor between the high and low MLR 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[9-18]. Despite the technical-scientific advances on the subject, for breast cancer, studies on the predictive value of pretreatment hematological ratios in the Brazilian population

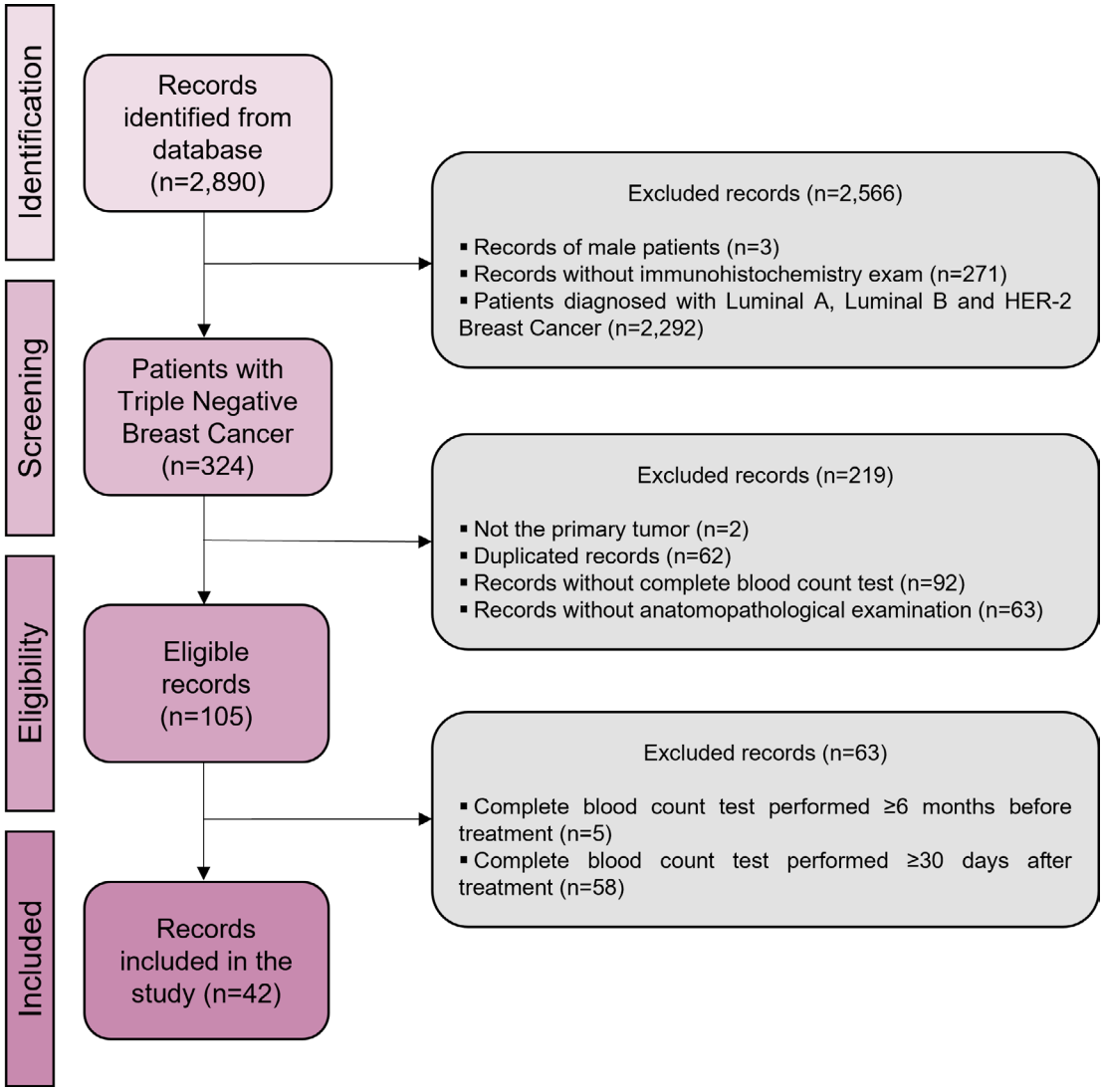


Figure 1. Records screened and included in the study.

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.

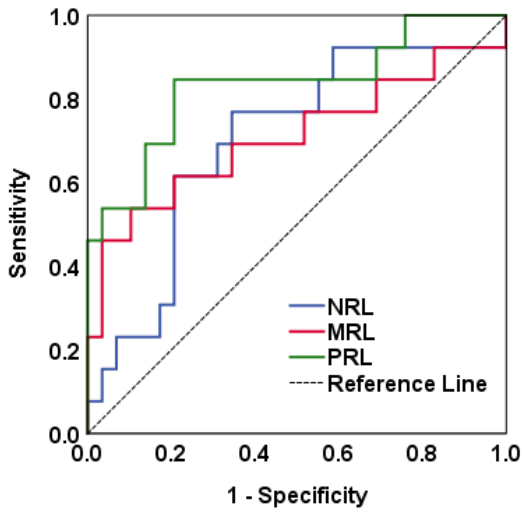
In the present study, we demonstrated that high PLR is a statistically significant predictor of worse OS and PFS (p=0.000, p=0.003, respectively) among women with TNBC. When compared to other pretreatment hematological ratios and factors associated with survival, such as the occurrence of recurrence,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

Table 1. Clinicopathological baseline characteristics of 42 patients with triple-negative breast cancer.

Characteristics		NLR<2.13 (n=22)		NLR≥2.13 (n=20)		p-value	MLR<0.55 (n=32)		MLR≥0.55 (n=10)		p-value	PLR<203.5 (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 grade	G1+G2	2	9.1	3	15.0	0.656	3	9.4	2	20.0	0.577	3	12.0	2	11.8	1.000
	G3	20	90.9	17	85.0		29	90.6	8	80.0		22	88.0	15	88.2	
T	T1	5	23.8	3	15.0	0.754	7	22.6	1	10.0	0.288	7	28.0	1	6.3	0.207
	T2	10	47.6	9	45.0		15	48.4	4	40.0		12	48.0	7	43.8	
	T3	2	9.5	4	20.0		5	16.1	1	10.0		3	12.0	3	18.8	
	T4	4	19.0	4	20.0		4	12.9	4	40.0		3	12.0	5	31.3	
N	N0	12	57.1	9	45.0	0.686	19	61.3	2	20.0	0.158	16	64.0	5	31.3	0.167
	N1	4	19.0	4	20.0		4	12.9	4	40.0		3	12.0	5	31.3	
	N2	1	4.8	0	0.0		1	3.2	0	0.0		1	4.0	0	0.0	
	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 lymphatic vessels	No	9	40.9	8	40.0	0.952	14	43.8	3	30.0	0.490	12	48.0	5	29.4	0.228
	Yes	13	59.1	12	60.0		18	56.3	7	70.0		13	52.0	12	70.6	
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	0.254	14	46.7	4	57.1	0.693	7	30.4	11	78.6	**0.004**
	Adjuvant	12	60.0	7	41.2		16	53.3	3	42.9		16	69.6	3	21.4	
Recurrence	No	13	59.1	9	45.0	0.361	19	59.4	3	30.0	0.152	17	68.0	5	29.4	**0.014**
	Yes	9	40.9	11	55.0		13	40.6	7	70.0		8	32.0	12	70.6	
Locoregional recurrence	No	16	72.7	16	80.0	0.723	25	78.1	7	70.0	0.678	20	80.0	12	70.6	0.714
	Yes	6	27.3	4	20.0		7	21.9	3	30.0		5	20.0	5	29.4	
Distant recurrence	No	16	72.7	10	50.0	0130	21	65.6	5	50.0	0.465	19	76.0	7	41.2	**0.023**
	Yes	6	27.3	10	50.0		11	34.4	5	50.0		6	24.0	10	58.8	
Death	No	19	86.4	10	50.0	**0.011**	26	81.3	3	30.0	**0.005**	23	92.0	6	35.3	**0.000**
	Yes	3	13.6	10	50.0		6	18.8	7	70.0		2	8.0	11	64.7	
Progression	No	13	59.1	8	40.0	0.217	19	59.4	2	20.0	**0.030**	17	68.0	4	23.5	**0.005**
	Yes	9	40.9	12	60.0		13	40.6	8	80.0		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.

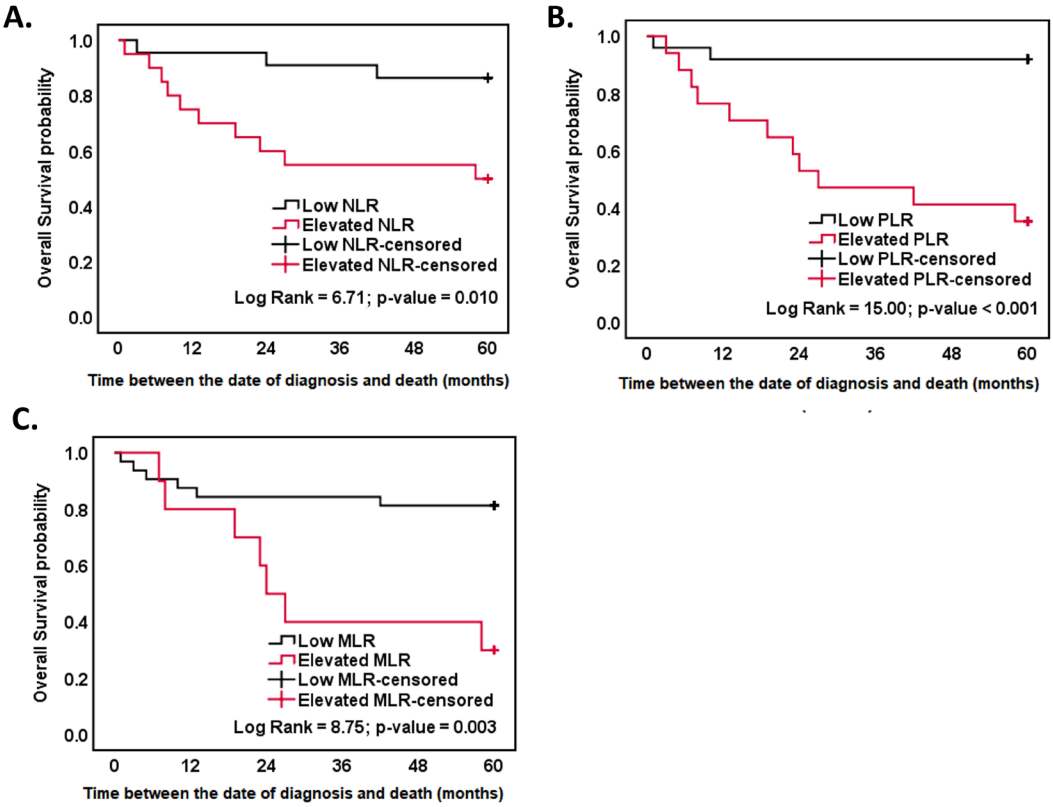


The areas under the curve for each parameter were 0.70 (p=0.040), 0.71 (p=0.033) and 0.83 (p=0.001), respectively.
NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

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[14,19]. 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[20]. 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[11,13,21]. 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[12,22]. The analysis conducted by Jia et al. revealed that high levels of NLR prior to neoadjuvant therapy are associated with a worse prognosis, particularly TNBC[6]. 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,



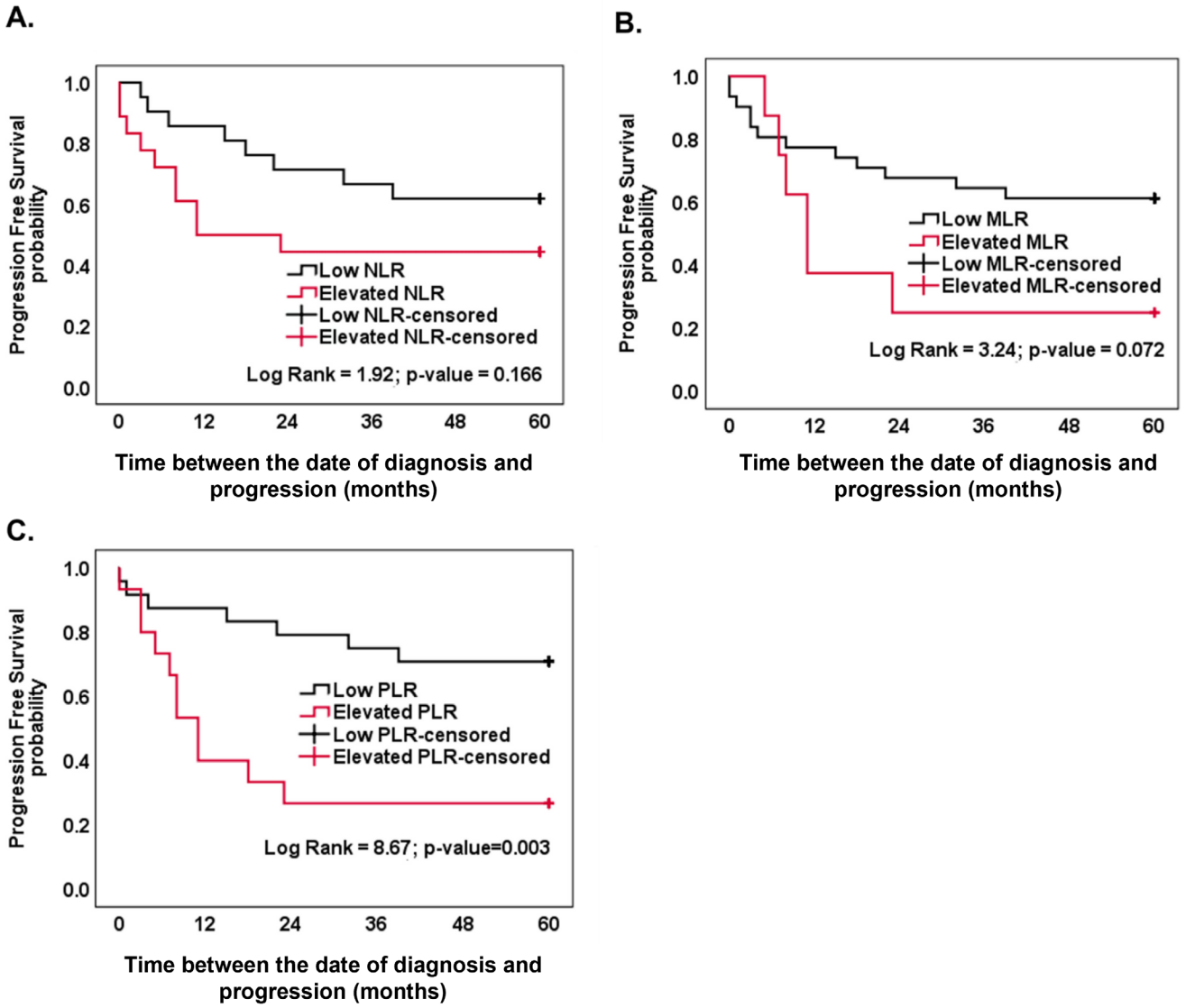
(A) Median overall survival was 54.95 months in the patients in the low neutrophil/lymphocyte ratio group and 38.55 months in the high neutrophil/lymphocyte ratio group. (B) Median overall survival was 51.1 months in the patients in the low monocyte/lymphocyte ratio group and 34.6 months in the patients 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[6,7,12]. 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[6,7,12-14].

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,



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

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

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.

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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.

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

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

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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 first-line 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[1-4]. 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[5-7]; however, no reduction has been seen in the number of women diagnosed with de novo metastatic carcinoma[4,6,7].

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[8,9]. The median 5-year survival of these women, however, remains poor, ranging from 15% to 35%[10-12].

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[13,14]. Although these advances have resulted in more personalized management of the metastatic disease, they have also introduced new challenges associated with controlling adverse events[8,15]. Therefore, epidemiological and population-based evaluations of women with MBC can contribute towards elaborating and implementing measures for more effective management of these patients.

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

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[10].

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[4,10,19].

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[8,15].

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 population-based 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[20,21]. 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[22]. 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[23,24].

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[25].

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[26]. 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[27].

The standardized incidence rate was calculated based on Segi's world standard population and expressed per 100,000 inhabitants[28,29]. 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.

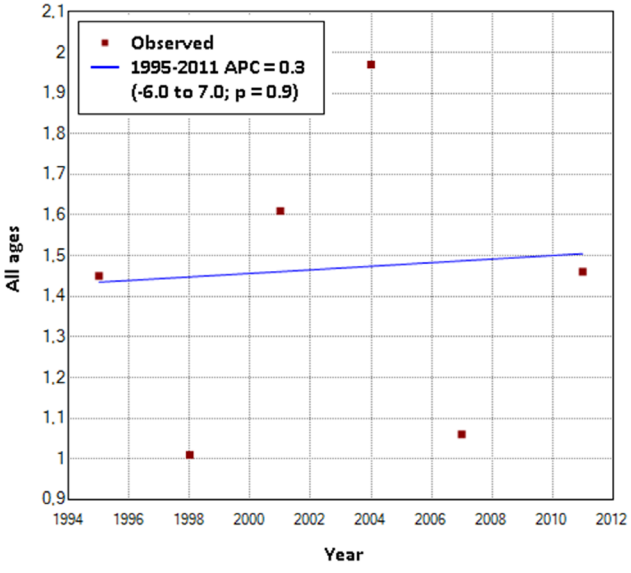
The annual percent change (APC) and the average APC (AAPC) in the rate of MBC were calculated for the total sample and according to the age group (<50, 50–69, and ≥70 years), with age being the only variable for which data were available in all cases. The relevant 95% confidence intervals (95%CI) were 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)[30].

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 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).



*Average APC (AAPC) 0.3; -6.0 to 7.0; p=0.9.

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.

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±14.5 years (mean±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[3,31] and in countries with population-based mammography screening, including the United States, Denmark, and the Netherlands[2,6,7,32]. 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[5]. Nevertheless, it was impossible to establish whether these women had undergone mammography screening. Likewise,

Table 1. Sociodemographic and clinical characteristics of 277 women with 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		
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	T0	3	2.3
Total n*	66	100.0	T1	12	9.3
Presence of symptoms			T2	22	17.1
Yes	103	81.8	T3	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	N0	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[33]. 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†	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†	109	100.0
Surgery for resection of the primary tumor		
Yes	50	40.6
No	73	59.4
Total n†	123	100.0
Surgery for resection of metastases		
Yes	10	9.2
No	98	90.8
Total n†	108	100.0

*At the time of initial diagnosis; †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[33].

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[17,34,35]. Nevertheless, the other clinical and demographic characteristics of the sample analyzed here were similar to those of the population with non-metastatic disease[36].

Palliative endocrine therapy is the systemic treatment of choice for women with metastatic disease and hormone-positive tumors in the absence of visceral crisis[8,15,25]. 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[9]. 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[37,38]. 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[8,15,37].

In the subgroup of women with HER2-positive tumors, the small number of patients who received anti-HER2 therapy is noteworthy. 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 metastatic HER2-positive breast cancer in 2017[34,39]. 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[8,14].

Data on the extent and the site of the metastatic lesions are crucial for planning treatment and evaluating individual prognosis[12,40]. 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[8,25].

Subjecting women with metastatic disease to breast surgery remains controversial and is usually reserved for selected cases[8,41,42]. 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[41]. 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[42]. A population-based study conducted in the United States also found a similar rate of breast surgery in this population[43]. 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[8,35,44].

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[8]. 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

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

	Systemic treatment	Anthracyclines	Taxanes	Tamoxifen	Aromatase inhibitors
	Tumor subtype	n (%)	n (%)	n (%)	n (%)
First-line	HR(+)/HER2(-) (n=34)*	25 (73.5)	16 (47.0)	3 (8.8)	3 (8.8)
	HR(+)/HER2(+) (n=9)*	7 (77.8)	4 (44.4)	-	1 (11.1)
	HR(-)/HER2(+) (n=7)*	7 (100.0)	4 (57.1)	-	-
	HR(-)/HER2(-) (n=11)*	10 (90.9)	7 (63.6)	-	-
2nd line	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)	-
	HR(-)/HER2(+) (n=4)*	-	-	-	-
	HR(-)/HER2(-) (n=5)*	-	-	-	-

	CMF	Platinum-based	Capecitabine	Gemcitabine	Vinorelbine	Trastuzumab
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
First-line	1 (3.0)	-	-			-
	1 (11.1)	-	-			1 (11.1)
	-	1 (14.3)	-			2 (28.5)
	1 (9.1)	-	-			-
2nd line	-	4 (13.8)	3 (10.3)	4 (13.8)	1 (3.4)	-
	-	1 (16.6)	1 (16.6)	1 (16.6)	-	1 (16.6)
	-	2 (50.0)	1 (25.0)	2 (50.0)	1 (25.0)	1 (25.0)
	-	4 (80.0)	1 (20.0)	3 (60.0)	1 (20.0)	-

*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[45]. 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[17,35]. Nevertheless, despite the difficulties of the Brazilian healthcare model[10,16,34], the data found in this series are in agreement with international population samples and reinforce the concept of cancer treatment globalization[11-14,16].

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[46]. 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

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.

	1995–2003 (n=129)		2004–2011 (n=148)		Absolute difference (%)	95%CI (%)	p-value†
	Cases (n)	%	Cases (n)	%			
Age at diagnosis (years)							
≤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							
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
T3–4	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 treatment							
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 tumor							
Yes	22	44.0	28	38.3	5.7	-11.52 to 22.84	0.5
No	28	56.0	45	61.7	‡	‡	‡
Total n*	50	100.0	73	100.0			
Surgery for metastasis							
Yes	2	4.5	8	12.5	8.0	-4.17 to 18.78	0.1
No	42	95.5	56	87.5	‡	‡	‡
Total n*	44	100.0	64	100.0			

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

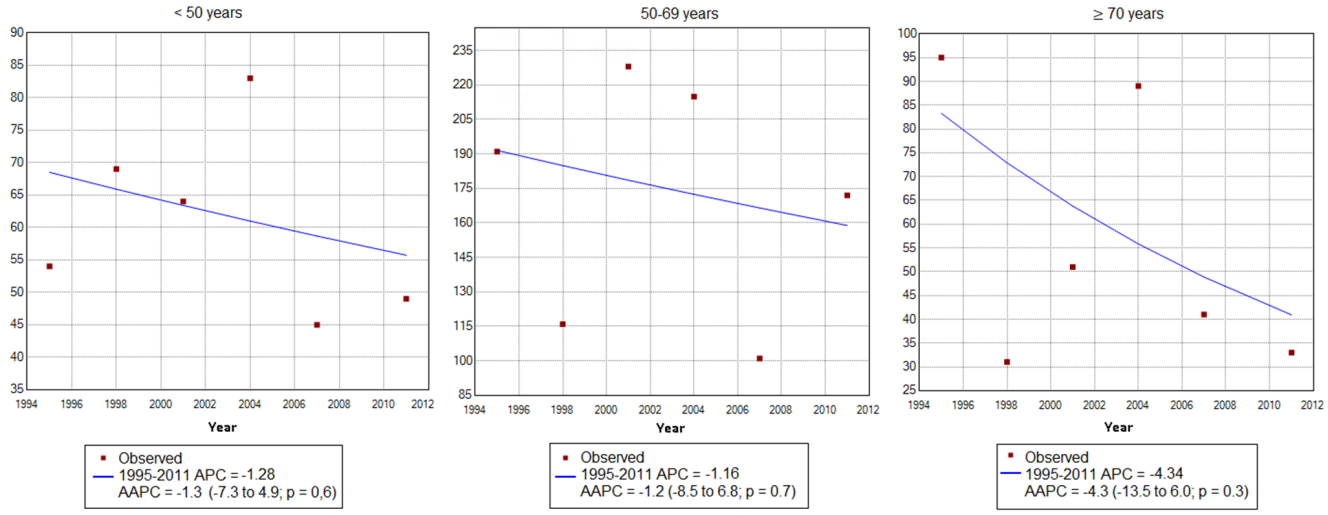


Figure 2. Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, by age group.

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.

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

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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[1,2]. Recently, it became the most diagnosed type of cancer, surpassing lung cancer[1]. Its early diagnosis, in addition to advances in treatment, has shown better results and greater survival for patients[3]. 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[6,7]. The purpose of NC is to reduce mass in locally-advanced tumors and to allow the use of efficient surgical and radiotherapy treatments[7].

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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)[6,8,9].

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[10]. 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[11]. 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[10]. 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[12].

Both the chemotherapy and radiotherapy used in the treatment and the cancer itself have immunosuppressive effects, making cancer patients vulnerable to infections[13]. 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[4,13].

Another important measure implemented to contain the advance of the new coronavirus was to consider many of the breast cancer treatment surgeries as elective[8]. 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[14]. 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[15].

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[14]. 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[13]. 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[16]. 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[16].

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 1st, 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 1st, 2019 to February 28, 2020, 3,118 general surgeries were performed; and from March 1st, 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[17]. 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

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

	Pre-pandemic	During the pandemic	Z-test (p-value)	Difference between proportions	Confidence Interval	
	Surgery of cancer in general				-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
	Mastology					
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

Source: Prepared by the authors.

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

	Pre-pandemic	During the pandemic	Z-test (p-value)	Difference between proportions	Confidence Interval	
	Chemotherapy				-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

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[18]. 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[17].

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[4].

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[19]. 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[18].

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[20,21].

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[22]. 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[7,15]. Nevertheless, there was a decrease of 11.5% in the total number of patients treated with chemotherapy during the pandemic[13,15]. 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[23]. 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[7]. 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[15,24]. 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[15,24].

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 non-invasive methods can delay definitive surgical treatment for a period of time, the duration of restrictive measures during the pandemic remains indetermined[14]. 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[13].

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.

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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.

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

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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[1-3]. 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%[4]. 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[3,5,6].

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[7-10]. 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[9]. However, breast tumors tend to have a faster developmental profile and are biologically more aggressive in younger patients[9,11].

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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[12].

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[13] 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 ($-0.5 \leq APC \leq 0.5$) 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.

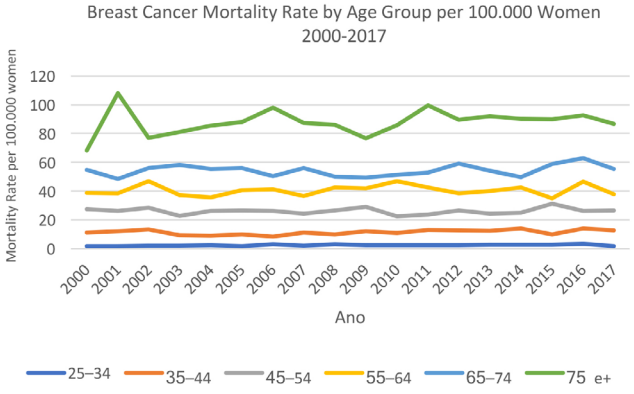
The linear trend equations and model adjustment statistics (R^2 value and the p-value of the model adequacy test) were obtained using the SPSS program, version 19.0. The level of significance adopted was 5%.

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, 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.



Source: Research database (2020).

Figure 1. Behavior of breast cancer mortality rates.

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^2 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,

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

Variable	Age group	*Joinpoint*	APC	95%CI – APC		p-value
				LL	UL	
Crude mortality rate from breast cancer	25–34	0	1.86*	0.1	3.7	0.0
	35–44	1 (2004)	-6.44 (2000–2004)	-18.3	7.1	0.3
			2.71* (2004–2017)	0.6	4.8	0.0
	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

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^2 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 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.

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	Age group	Model	R^2	p-value
Age group	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
	35–44 (period 2004–2017)	y=0.962+0.039x (*)	0.539	0.003
	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).

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[14].

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[15].

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[16].

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[17].

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[18].

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[19].

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[20,21].

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[14].

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[9,11].

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[3,22-24].

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[23,24].

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[3,25,26].

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[25].

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.

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Prognostic factors and molecular subtypes in young women with breast cancer

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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[1]. 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[2]. 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[3]; and percentage of deaths of 17.7% for all ages and 1.8% for under 40[3].

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[4]. 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[6], making this cancer an event of low incidence in younger women[7].

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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[7]. 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[8]. Although there is no consensus, a young female patient it is classified as being under 40 years[9].

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[6].

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[9].

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[10].

Of all the genetic mutations associated with breast cancer, those of the BRCA1 and BRCA2 genes are important negative prognostic factors[9], more commonly found in young women, reaching 40% in familial breast cancers[11]. These mutations have a prevalence of 10% in women younger under 40 years old and 30% in those under 30[7] 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[12]. 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[13].

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[14]. However, comparing the molecular classifications determined by immunohistochemistry and by the microarray PAM50 test (molecular assay of non-routine use, due to its low cost-benefit), important discrepancies were found[15].

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[13,16,17]. 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[18].

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.[18].

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[1].

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.

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 ≥15% to ≤20%) and high (>20%). According to the manual for standardization of histopathological reports[19], 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[19].

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:

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 non-special 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[13].

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.

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

Parameters		<35 years n (%)	35–39 years n (%)	p-value
Molecular subtype	Luminal A	6 (18.18)	13 (22.80)	0.9257 *
	Luminal B	11 (33.33)	15 (26.32)	
	Hybrid luminal	3 (9.09)	7 (12.28)	
	HER2+	5 (15.15)	6 (10.53)	
	Non-basal triple-negative	8 (24.24)	16 (28.07)	
Estrogen receptor	ER+	19 (57.58)	34 (59.65)	0.9764 **
	ER-	14 (42.42)	23 (40.35)	
Progesterone receptor	PR+	18 (54.55)	31 (54.38)	0.8376 **
	PR-	15 (45.45)	26 (45.62)	
HER2	HER2+	8 (24.24)	13 (22.80)	0.9176 **
	HER2-	25 (75.76)	44 (77.19)	
Non-basal triple-negative tumor (CPI)	Low	1 (12.50)	3 (18.75)	0.6250*
	Moderate	0	2 (12.50)	
	High	7 (87.50)	11 (68.75)	
HER2 tumor (CPI)	Low	1 (20.00)	2 (33.33)	0.9038*
	Moderate	1 (20.00)	1 (16.67)	
	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); ** χ^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[1], 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[20], 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[20] 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[17] 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[21] tumors, while luminal A tumors predominated in those aged 40 to 98 years[21].

Analyzing the different prevalences in the two groups studied, the present study showed a higher frequency of triple-negative 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[13,16,17,22]. 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[23]. 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[23], 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[21], 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[21].

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

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[4].

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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.

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

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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[1].

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[2].

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[3].

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[4]. 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[5].

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

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reconstructive surgeries, both from the functional and self-esteem points of view[2,6].

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[7].

The evaluation of quality of life is a complex matter, and its perception can vary individually and throughout the experiences of life[8]. 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"[9].

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[10-12].

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[13].

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 sub-themes 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

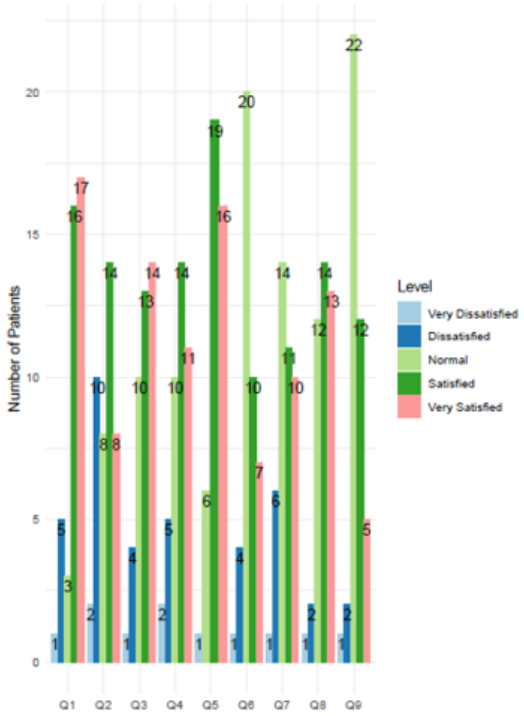

Figure 1. Level of satisfaction in each question related to satisfaction. Fortaleza, CE, Brazil, 2021.

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 ρ_{ij} the (ij)-th component of the R matrix for every $i = 1, 2, \ldots, 9$ and $j = 1, 2, \ldots, 9$. 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 ρ_{13} and ρ_{16} coefficients are lower than 0.5. Therefore, there is evidence showing that satisfaction with size and pain have low correlation with general satisfaction. To verify the relationship between 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

$$R = \begin{bmatrix} 1.000 & 0.688 & 0.313 & 0.807 & 0.702 & 0.475 & 0.564 & 0.627 & 0.612 \\ 0.688 & 1.000 & 0.254 & 0.820 & 0.610 & 0.598 & 0.514 & 0.702 & 0.457 \\ 0.313 & 0.254 & 1.000 & 0.254 & 0.216 & 0.157 & 0.236 & 0.241 & 0.298 \\ 0.807 & 0.820 & 0.254 & 1.000 & 0.662 & 0.561 & 0.436 & 0.763 & 0.532 \\ 0.702 & 0.610 & 0.216 & 0.662 & 1.000 & 0.562 & 0.531 & 0.714 & 0.665 \\ 0.475 & 0.598 & 0.157 & 0.561 & 0.562 & 1.000 & 0.398 & 0.493 & 0.390 \\ 0.564 & 0.514 & 0.236 & 0.436 & 0.531 & 0.398 & 1.000 & 0.499 & 0.369 \\ 0.627 & 0.702 & 0.241 & 0.763 & 0.714 & 0.493 & 0.499 & 1.000 & 0.469 \\ 0.612 & 0.457 & 0.298 & 0.532 & 0.665 & 0.390 & 0.369 & 0.469 & 1.000 \end{bmatrix}$$

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. 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.

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

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[14].

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[3].

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[16].

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[1].

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[17].

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 treatment, $p=0.07$. Sexual and physical well-being was similar for 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[18].

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[19].

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[20]. 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 follow-up. 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[21].

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[22].

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.

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

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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 ≥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 ≥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^2 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[1]. With increased survival, death from other causes becomes a reality, and cardiovascular disease (CVD) is relevant in this scenario[2-4]. 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[3].

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[4-7]. Buttros et al.[4], 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[4]. Women treated for breast cancer, who have MetS, have poorer overall and disease-free survival[8,9]. An observational study, evaluating approximately 9,000 women in the early stages of breast

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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[2].

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 life[9]. The 2021 *National Comprehensive Cancer Network* (NCCN) suggests that all cancer patients should be encouraged to achieve and maintain an adequate BMI[10]. 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[11]. 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 ≥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)[12] 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^2), and WC. *The 2002 World Health Organization* criteria were used to classify patients, according to BMI: normal (≤24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 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)[12]. 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[12]. 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)[13].

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±10.7 years, of which 83.3% were postmenopausal. The patients on average were overweight (BMI 25.0–29.9 kg/m^2), with an elevated WC (>88 cm) and baseline values of TC, LDL, and glucose above optimal levels (Table 1). Only 23.6% 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

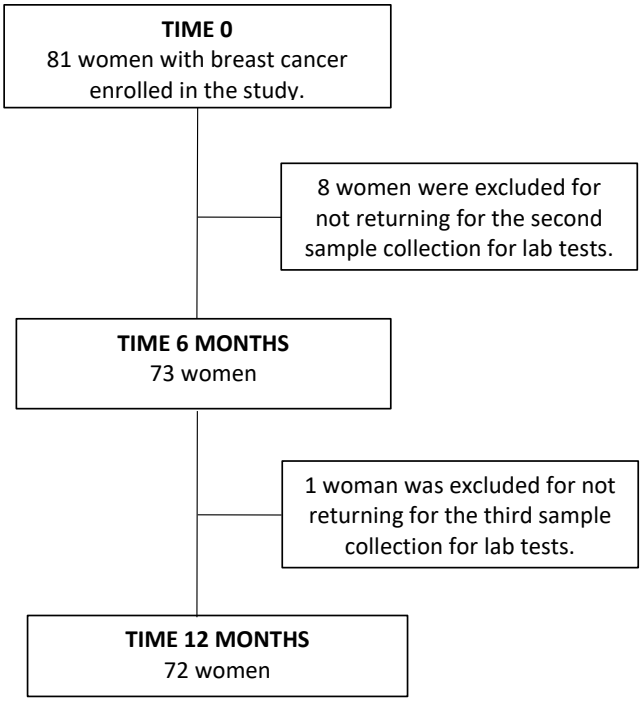


Figure 1. Flowchart for the women enrolled in the study.

Table 1. Initial descriptive clinical characteristics of the 72 women with breast cancer.

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^2	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

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

≤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).

Table 2. Descriptive oncological characteristics of the 72 women with breast cancer.

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

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 (≥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 radiotherapy) 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.

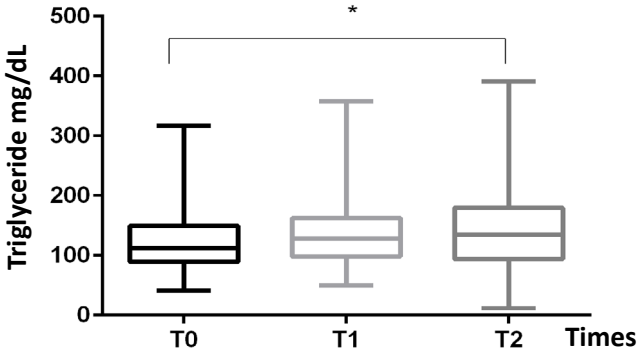
Characteristic		T0m	T6m	T12m	Time points compared	p
Metabolic syndrome	Yes	27 (37.5)	31 (43)	32 (44.4)	T0m–T12m	0.332
	No	45 (62.5)	41 (57)	40 (55.6)		
WC>88 cm	Yes	53 (73.6)	58 (80.5)	57 (79.1)	T0m–T12m	0.125
	No	19 (26.4)	14 (19.5)	15 (20.9)		
BP≥130×85 mmHg	Yes	47 (65.2)	40 (55.5)	47 (65.2)	T6m–T12m	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.

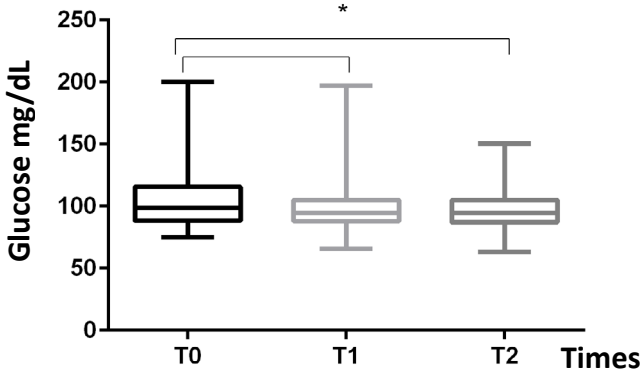
Features	T0m	T6m	T12m	p
Weight, kg	72.9 (15)	72.6 (14.7)	73.0 (15.3)	0.728
BMI, kg/m²	28.9 (6.1)	28.8 (5.7)	28.8 (5.9)	0.842
WC, cm	97.2 (13.2)	97.1 (12.1)	96.6 (12.6)	0.683
TC, mg/dL	203.1 (36.1)	207.3 (39.9)	201.3 (40.4)	0.348
HDL, mg/dL	56.2 (13.1)	55.9 (18.1)	56.8 (14.5)	0.894
TRIG, mg/dL	121.0 (139.4)	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.



T0m: 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[8]. 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.[2], who, after evaluating 8641 women with breast cancer, found that abdominal obesity and arterial hypertension were the most prevalent criteria among participating women[2].

Women treated for breast cancer did not experience weight gain or increased WC during the first year of follow-up. Obesity is correlated with a poorer prognosis in women with breast cancer. Chan et al.[14] 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/m² (obese) have a higher risk of mortality when compared to women with a BMI between 20 and 25 kg/m² (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 long-term 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[14].

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/m² at T0m and 28.8 kg/m² after 1 year. Our data are in harmony with the report by Simon et al.[2], who also observed that most women studied had a BMI between 25 and 30 kg/m². 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[8]. 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)[15]. These results are similar to those presented by Spalutto et al.[16] 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[16].

Hyperglycemia is also correlated with a poorer oncological prognosis. Buono et al.[8] demonstrated lower overall survival and disease-free survival in women with breast cancer with blood glucose ≥110 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 ≥100 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[17]. 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[18]. 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[19]. 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[20-23]. In contrast, some studies have reported increases in TG values in patients treated with tamoxifen, a risk factor for hypertriglyceridemia[24,25]. Aromatase inhibitors (AIs), in turn, by bringing the patient into a state of excessive hypoestrogenism, have a direct correlation with increased cholesterol. The ATAC[26] and BIG I-98[27] 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[28]. 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[28].

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[9,11].

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.

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

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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[1]. 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[2].

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[3-7]. 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[8,9].

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[10-12]. 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[11,13-15].

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[16,17].

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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[16,18-20]. Adherence to an exercise program, proposed by controlled studies, such as clinical trials, is essential for adequate results[21]. 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[21].

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[22].

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.

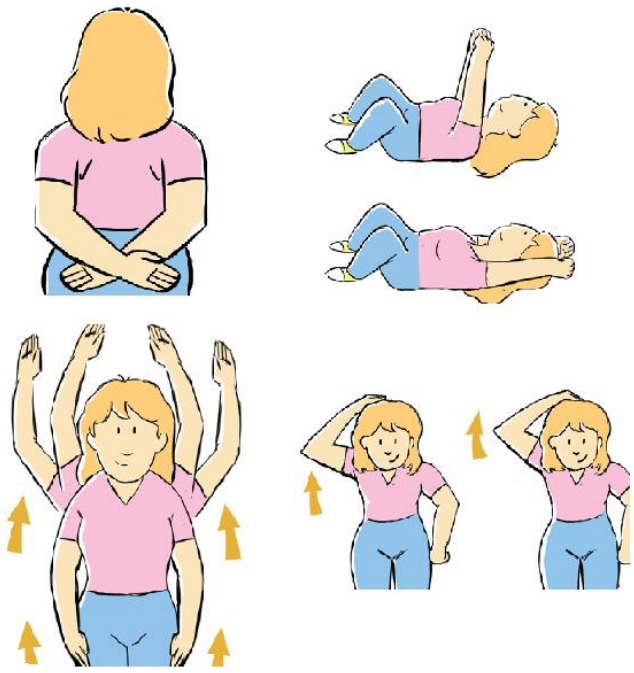
On the first postoperative day, the patients received an instructional booklet (Figure 1) related to post-operative exercises and guidance, and were instructed on the need to perform home exercises. Women were randomized in two interventions groups. One performed restricted shoulder exercises with amplitude of movement above 90º, and the other with free amplitude of movement over 90º. 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[3].

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 (±11.54), 56.8% had a Body Mass Index (BMI) <30kg/m^2 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 7–105th 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[23].

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[14]. 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 10th 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)	0.730
≥30kg/m²	201 (43.2)	65 (44.2)	86 (42.4)	50 (43.5)	
Race/Skin color*					
White	154 (33.1)	48 (32.7)	71 (35.0)	80 (69.6)	0.651
Non-white	311 (66.9)	99 (67.3)	132 (65.0)	35 (30.4)	
Marital status					
No partner	245 (52.7)	74 (50.3)	104 (51.2)	67 (58.3)	0.869
With partner	220 (47.3)	73 (49.7)	99 (48.8)	48 (41.7)	
Schooling					
<8 years	103 (22.2)	34 (23.1)	35 (17.2)	34 (29.6)	0.172
>=8 years	362 (77.8)	113 (76.9)	168 (82.8)	81 (70.4)	
Professional activity					
Yes	249 (53.5)	79 (54.1)	113 (55.9)	57 (49.6)	0.735
No	214 (46.0)	67 (45.9)	89 (44.1)	58 (50.4)	
No information	2 (0.4)				
Systemic Arterial Hypertension					
Yes	204 (43.9)	60 (40.8)	88 (43.3)	56 (48.7)	0.636
No	261 (56.1)	87 (59.2)	115 (56.7)	59 (51.3)	
Diabetes					
Yes	74 (15.9)	19 (12.9)	35 (17.2)	20 (17.4)	0.270
No	391 (84.1)	128 (87.1)	168 (82.8)	95 (82.6)	
Clinical staging					
Initial (<IIB)	248 (53.3)	86 (57.8)	100 (49.3)	63 (54.8)	0.113
Advanced (≥IIB)	217 (46.7)	62 (42.2)	103 (50.7)	52 (45.2)	
Neoadjuvant treatment					
Yes	262 (56.3)	80 (54.4)	117 (57.6)	65 (56.5)	0.550
No	203 (43.7)	67 (45.6)	86 (42.4)	50 (43.5)	
Neoadjuvant chemotherapy					
Yes	257 (55.3)	78 (53.1)	116 (57.1)	63 (54.8)	0.448
No	208 (44.7)	69 (46.9)	87 (42.9)	52 (45.2)	
Neoadjuvant hormone therapy					
Yes	154 (33.1)	46 (31.3)	70 (34.5)	38 (33.0)	0.531
No	311 (66.9)	101 (68.7)	133 (65.5)	77 (67.0)	
Neoadjuvant target therapy					
Yes	61 (13.1)	19 (12.9)	26 (12.8)	16 (13.9)	0.974
No	404 (86.9)	128 (87.1)	177 (87.2)	99 (86.1)	
Type of surgery					
Segmentectomy	201 (43.2)	69 (46.9)	79 (38.9)	53 (46.1)	0.134
Mastectomy	264 (56.8)	78 (53.1)	124 (61.1)	62 (53.9)	
Axillary Approach					
Axillary lymphadenectomy	216 (46.5)	71 (48.3)	93 (45.8)	52 (45.2)	0.645
Sentinel Lymph Node Biopsy	249 (53.5)	76 (51.7)	110 (54.2)	63 (54.8)	
Interventions group					
Free amplitude of movement	254 (54.6)	85 (57.8)	112 (55.2)	57 (49.6)	0.622
Restricted amplitude of movement	211 (45.4)	62 (42.2)	91 (44.8)	58 (50.4)	

*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)	1.14 (0.714–1.83)	0.575
No	103 (22.2)	40 (28.4)	63 (31.2)		
No information	122 (26.2)				
Arm discomfort					
Yes	291 (63.1)	120 (84.5)	171 (84.7)	0.98 (0.54–1.79)	0.970
No	53 (11.4)	22 (15.5)	31 (15.3)		
No information	121 (26.0)				
Difficulty in performing the exercises					
Yes	229 (49.2)	96 (68.6)	133 (66.2)	1.11 (0.70–1.76)	0.642
No	112 (24.1)	44 (31.4)	68 (33.8)		
No information	124 (26.7)				
Fear of performing the exercises					
Yes	211 (44.9)	92 (65.7)	117 (57.9)	1.39 (0.89–2.17)	0.146
No	133 (28.6)	137 (34.3)	85 (42.1)		
No information	123 (26.5)				
Insecurity to perform the exercises					
Yes	211 (45.4)	90 (64.3)	121 (59.9)	1.20 (0.77–1.88)	0.412
No	131 (28.2)	50 (35.7)	81 (40.1)		
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 10th 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%)[11]. 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[13].

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[24].

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[17]. In addition, home guide self-completion may be susceptible to information bias, in accordance to Cnossen et al.[14].

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.

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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.

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ORIGINAL ARTICLE
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Mastalgia in medical students: a prospective and multicentric study

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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[1,2]. Despite cyclic or non-cyclic 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[3].

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[1,4].

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

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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[2].

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[5].

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[6].

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[7].

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 medium-sized 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.

Intensity	Laterality				Total	
	Bilateral		Unilateral			
	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[1-3,6].

Breast pain, in turn, is considered common, and about 70% of Western women will experience it at some point during menacme[5,8]. 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[9].

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[2]. Cyclic breast pain

Table 2. Intensity of pain related to physical activity.

Intensity × Physical activity		Physical activity						Total	
		None		1 × per week		2 × per week			
		n (%)	n	n (%)	n	n (%)	n	n (%)	n
Pain	Severe	72.23	502	92.89	196	70.83	85	74	756
	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 3. Link between pain intensity and self-examination.

Pain Intensity	Self Exam					
	Yes		No		Total	
	N (%)	N	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.

Intensity	Absence In Class					
	Yes		No		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.

Intensity	Treatment Time									
	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[10]. 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[10,11].

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[2,8].

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[12,13].

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[7,14].

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%[15].

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[15].

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[15,16].

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[16]. The administration of isolated progesterone, especially medroxyprogesterone acetate, taken orally or topically, had a negative impact on the control of breast pain[17]. 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[18,19].

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[16,20].

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.

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

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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[1,2], and it has a multifactorial etiology associated with environmental and genetic factors[3]. 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[1].

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[3]. In addition to hormonal factors, studies also indicate lifestyle-related risk factors, which include alcohol intake, smoking, physical inactivity, and exposure to ionizing radiation[4].

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[5,6].

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[7].

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

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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[11-13].

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[14]. 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.[15], 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[7].

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[15]. 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[16]. Through the criteria used to assess hereditary breast cancer risk, recommended by the NCCN[17], 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 ≤45 years; triple-negative subtype diagnosed in women aged ≤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[16], according to the criteria recommended by the NCCN[17] 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[18], 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®, Waltham, MA)[19].

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®) and sequenced by the Sanger method with the BigDye Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher®), 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[20].

RESULTS

Germline variants

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

Table 1. Variants identified in the *BRCA2* gene for the study population. Minas Gerais State, Brazil, 2014–2016.

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*

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[21].

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[21], 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%[22].

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 non-white 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 ≤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.

Table 2. Clinical characteristics of patients and histopathological findings of breast carcinomas.

Proband	Age at diagnosis	Self-reported ethnoracial group	Health system	Tumor laterality	Tumor size	Lymph nodes committed	GH	Immunophenotype	Ki-67 (%)	pTNM	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
CM20	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	T0N0M0	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

GH: histological grade (provided by the Nottingham classification system); pTNM: pathological TNM[18]: 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.

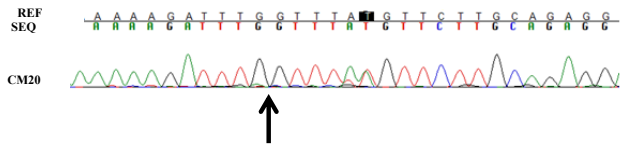


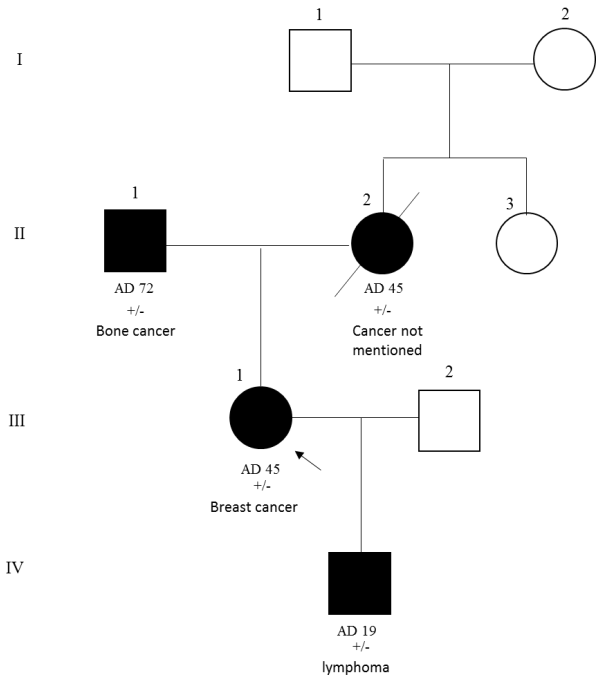
Figure 1. Sequencing of the *Breast Cancer 2* pathological variant c.2847T>A.

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[23]. 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[24]. 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[25,26].

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[27,28].

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[29]. 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[30].

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[7]. Regarding these benefits, a study by Palmero et al.[7] 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 single-nucleotide 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[31,32]. The variant rs4987117 was identified in 4 of 30 (13.3%) probands with triple-negative breast cancer, corroborating our finding[33]; 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)[34]. Therefore, Meyer et al.[33] 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[35].

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[25]. 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[36].

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[29].

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*[29]. 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 years. However, this reference is from a single nucleotide (delT) deletion in amino acid 949 of exon 11 *BRCA2* gene[37]. 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[38]. 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.[6] 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[21]. 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

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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.

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ORIGINAL ARTICLE
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Prevalence of obesity in patients with breast cancer followed-up at an oncology service in Goiania

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ABSTRACT

Objective: To verify the prevalence of obesity in patients undergoing cancer follow-up at Hospital das Clínicas in Universidade Federal de Goiás, analyzing the epidemiological and laboratory profile. **Methods:** Retrospective, analytical and observational study. The final sample consisted of 498 medical records of patients under regular follow-up with indication for chemotherapy between June 2018 and 2020. Anthropometric data, gestational history, personal and family history, menopausal status, comorbidities, staging, and laboratory tests were observed. **Results:** A mean body mass index of 28.3 kg/m² was found among the patients, and 26.51% were obese. Mean age at diagnosis was 52.79 years, and 51.81% were in menopause. Also, 26.23% had a personal history of breast cancer, and 44.76% had family history. Regarding comorbidities, 51.15% had them, being the most frequent one systemic arterial hypertension, more prevalent in the obese group compared to the normal body mass index. Also, 11.96% of the patients were nulliparous. Regarding staging, most were in T2N0M0 at diagnosis. In laboratory tests, it was found that among patients with breast cancer who had information on lipid profile, low-density lipoprotein and total cholesterol were above the reference limit. **Conclusion:** 57.63% were obese or overweight, demonstrating body mass index as a risk factor for breast cancer. It was observed that the group of patients with obesity had a statistically significant relationship with the presence of concomitant comorbidities; however, no statistically significant results were found regarding the relationship between body mass index and menopausal status.

KEYWORDS: breast cancer; obesity; body mass index; menopause; comorbidities.

INTRODUCTION

Breast cancer is the most prevalent type of cancer among women around the world, being responsible for the highest number of deaths by cancer in this population. According to the International Agency for Research on Cancer, in 2020 there were 2.3 million new cases, representing 24.5% of new cases among women. In the same year in Brazil, new cases of breast cancer represented 30.3% in the female population[1]. Regarding the epidemiological profile of patients undergoing breast cancer treatment, there was high prevalence in the age group of 51 to 60 years, with no previous and family history of breast cancer, stage IIa according to the TNM classification[2].

Likewise, the incidence of obesity in Brazil has also been increasing, following a global tendency[3]. In 2016, the prevalence of this disease among people aged more than 18 years was 18.9%[4]. The map made by the Brazilian Society of Obesity for the Study of Obesity and Metabolic Syndrome shows that, in Goiânia (GO), 17% of the women present with obesity. According to the World Health Organization (WHO), the estimation is that in 2025 2.5 billion adults will be overweight around the world, and, of these, 700 million will be obese[5].

Obesity is a known risk factor for several noncommunicable chronic diseases, such as cancer, and lifestyle plays a determinant role in this condition. The body mass index (BMI) is the main anthropometric indicator of generalized adiposity, whose ratio higher than 30 kg/m² characterizes obesity[6,7].

There seems to be an association between obesity, risk of breast cancer and its prognosis. Among the possible variables

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related to worse outcome for obese patients, some are: more advanced stage at diagnosis, other associated comorbidities, faster tumor growth and hormonal influence[8].

In postmenopausal women, obesity influences the risk for the onset of this type of cancer, because for these patients the conversion of androstenedione to estrone in the fat tissue is higher; this leads to higher concentration of free estrogen, besides lower levels of sex hormone-binding globulin, which also leads to higher availability of estrone. Besides, hyperinsulinemia can be generated and IGH-I can increase; the latter is responsible for stimulating cell proliferation, for regulating anabolic processes and for apoptosis[9].

The presence of comorbidities, considering the most common ones such as obesity, systemic arterial hypertension (SAH) and diabetes mellitus, is considered as a prognostic and determinant factor in the choice of cancer treatment, since this treatment may compromise the health of these patients even more[10].

Besides the fact that obesity is a risk factor for cancer, it can also interfere in the action of chemotherapy, once this condition can affect the metabolism of cytotoxic drugs, considering that its distribution in the fat and muscular tissue may interfere in its pharmacokinetics[11].

Regarding lipid profile, it was observed that some chemotherapy drugs used to treat breast cancer may increase plasma lipoproteins, such as LDL-cholesterol and hypertriglyceridemia, or reduce HDL-cholesterol, thus worsening the patient's condition[10,11]. Besides, there seems to be a relationship between a worsen prognosis related to the increase of LDL-cholesterol and a reduction of HDL-cholesterol in the diagnosis[12,13].

In this sense, there is a mutual relationship between weight and breast cancer; on the one hand, weight gain during the treatment of breast cancer is justified by several factors, such as chemotherapy, radiotherapy and decreased general status, leading to sedentary lifestyle, fatigue and indisposition; on the other hand, obesity is a risk factor for the onset of this type of cancer[6].

Therefore, the knowledge of anthropometric parameters, comorbidities and nutritional profile of oncologic patients at different stages is a way to characterize the metabolic profile, to estimate the survival rate and the impact of obesity on cancer treatment, to predict the chances of aggravation, besides allowing the early intervention in the treatment of obesity, which would result in better chemotherapy and clinical response among patients with breast cancer. Facing the exposed, the objective of this study was to verify the prevalence of obesity in patients undergoing cancer treatment at Hospital das Clínicas of Universidade Federal de Goiás, analyzing their epidemiological and laboratory profile.

METHODS

This is an observational, analytic, retrospective study. The data were collected between January and April 2021. The initial sample was constituted of 606 charts; however, 108 were excluded for not being available for study at the time of analysis. The final sample was constituted of 498 charts of patients who were regularly assisted at the oncology service of Hospital das Clínicas in Universidade Federal de Goiás, with indication for chemotherapy between June 2018 and June 2020. The patients were found through authorizations of outpatient procedures and analyzed based on anthropometric data of weight and height, gestational history, recurrence, presence of another tumor, family history of breast cancer, menopausal status, comorbidities, cancer staging and laboratory exams.

Concerning menopausal status, we considered the fact that patients were in menopause (post-menopause) or not (pre-menopause) when receiving the diagnosis of neoplasm. In gestational history, the number of pregnancies was assessed, and nulliparous women were those who had never been pregnant. The positive personal history for breast cancer includes the presence of diagnosis of previous biopsy for this type of tumor; family history of breast cancer was collected through the first appointment file. Weight and height were collected from the charts in kilograms and meters, respectively, and based on that BMI was calculated per square meter. The history of comorbidities was collected in the first appointment chart regarding its absence or presence at the time of diagnosis.

Breast cancer staging was collected from the charts, and the classification used was the one defined by the Union for International Cancer Control[14], which uses three definition criteria: breast tumor size (T), presence of damaged lymph nodes (N) and presence or absence of distant metastasis (M).

The laboratory data we used were not present in all sample charts. Therefore, the calculations were made according to the availability of data in each variable, forming an independent sample. Total cholesterol was found in 102 charts and classified as higher or lower than 190 mg/dL. HDL-cholesterol was present in 89 charts and classified as higher or lower than 40 mg/dL. LDL-cholesterol was found in 87 charts and categorized as higher or lower than 100 mg/dL. The values of triglycerides was present in 90 charts and were grouped as higher or lower than 150 mg/dL; fasting blood glucose was present in 282 cases and divided in higher or lower than 126 mg/dL[15].

The project was approved by the Research Ethics Committee of Universidade Federal de Goiás (number 4.431.837). The research did not cause the participants any risk, and the data were handled in secrecy. The collected data were tabled and analyzed using Microsoft Excel, version 2016, GraphPd prism, version 7, and Epi info 7.2.4.0. For quantitative variables, we determined measurements of central tendency, such as mean, median, absolute and percentage frequency, standard deviation, minimum and maximum values. Qualitative variables were presented in absolute numbers and percentage. To verify the statistic relation between menopausal status and BMI, we used the chi-square

test, considering a 5% significance level. The chi-square test was also used to verify the statistic relation between BMI and the presence of comorbidities, positive family history for cancer and lymph node damage. Both analyses of statistical association were made by excluding the patients who did not present one of the parameters available for analysis in the chart.

RESULTS

The study sample was comprised of a total of 498 participants, being 496 (99.60%) female and two (0.40%) male. Regarding the quantitative characterization of the population, we identified that the mean height of the individuals in the sample was 1.57 m, with minimum of 1.36 m and maximum of 1.76 m, median of 1.60 and mode of 1.60 m; standard deviation was 0.06 m. About weight, the mean was 68.66 kg, with minimum of 35 kg, maximum of 121.05 kg, median of 67 kg, mode of 70 kg; standard deviation was 14.57%. The mean BMI was 28.3 kg/m^2, and numbers ranged between 16.67 and 50.22 kg/m^2, with median and mode of 26 kg/m^2 and standard deviation of 6.88 kg/m^2. By classifying the BMI of the studied population in groups, 132 (26.51%) patients presented with BMI≥30 kg/m^2; 155 (31.12%) between 25 and 29.9 kg/m^2; 107 (21.49%) between 18.5 and 24.9 kg/m^2, and 6 (1.20%) lower than 18,5 kg/m^2.

The mean age at the diagnosis of cancer in the group was 52.79 years, being the youngest age of 25 years, and the oldest age of 92 years; median was 52 years of age, mode of 48 years of age, and standard deviation of 13.31. It was observed that, of the 496 women, 257 (51.81%) were in menopause at the time of diagnosis, and the mean age of the beginning of menopause was 45.6 years, ranging between 26 and 71 years; median was 44 years, mode was 42 years, and standard deviation, 8.08 years (Table 1).

As to the qualitative characterization of the population, it was found that 117 (26.23%) participants reported the recurrence of a cancer in the past at the time, or being with a second tumor at the time of analysis; 201 (44.76%) had family history of breast cancer. Regarding comorbidities, 245 (51.15%) patients had some at the time when cancer was diagnosed. The most frequent ones were diabetes and SAH. About gestational history, 56 (11.95%) women were nulliparous (Table 1).

The study about breast cancer staging was conducted using the Union for International Cancer Control (UICC) classification (14), TNM. However, 55 (11.04%) participants did not have this information in their charts. By analyzing the tumor size at the time of diagnosis, it was observed that primary tumor could not be evaluated (Tx) in only one case (0.20%), whereas 94 (18.88%) participants were classified as T1; 179 (35.94%) were T2; 74 (14.86%) were T3; 95 (19.08%), T4. The presence of lymph node damage was observed in 213 cases, being 151 (30.32%) classified in N1; 57 (11.45%), N2; 5 (1%), N3. However, lymph node damage was not assessed at diagnoses for three (0.60%) patients, and 227 (45.58%) did not present with any lymph node damage. The presence of distant metastasis was also analyzed, and 337 (67.67%) did not present with it, classified as M0; 25 (5.02%) were at M1; 1 (0.20%), at M2; and 80 (16.06%) did not have this type of evaluation or it was not clear in the chart (Mx) (Figure 1).

We analyzed laboratory examinations, observing that in most charts with this information total cholesterol was higher than 190 mg/dL (58.86%); o LDL was higher than 100 mg/dL (72.41%); HDL was higher than 40 mg/dL (74.16%); triglycerides were lower than 150 mg/dL (56.67%); and fasting glucose, in most charts, was lower than 126 mg/dL (88.30%) (Table 2).

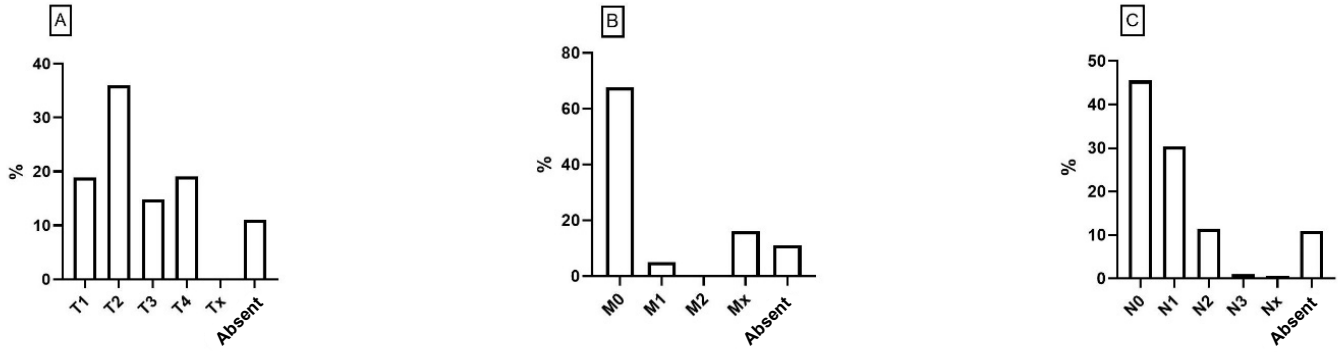
The analysis of the association between BMI and menopausal status showed that, among postmenopausal women, the BMI of 48 of them was normal; 74 were overweight; and 75 were obese. Among pre-menopausal women, the BMI of 57 of them was normal; 74 were overweight; and 57 were obese (Table 3). In this study, we did not find a statistically significant result about the relationship between BMI and menopausal status in the sample (p=0.220).

Table 1. Characterization of patients with breast cancer undergoing na oncology service in Goiania-GO.

	Minimum	Maximum	Mean	Median	Mode	Standard deviation
Height (m)	1.36	1.76	1.57	1.60	1.60	0.063
Weight (kg)	35	121.05	68.66	67	70	14.59
BMI (kg/m²)	16.67	50.22	28.3	26	26	6.88
Age at diagnosis (years)	25	92	52.79	52	48	13.31
Age at menopause (years)	26	71	45.68	44	42	8.08

	Present	Absent
Recurrence or other tumors (%)	117 (26.23)	329 (73.76)
Family history of breast cancer (%)	201 (44.76)	248 (55.23)
History of comorbidities (%)	245 (51.15)	234 (48.85)
Nulliparity (%)	56 (11.96)	412 (88.03)

BMI: body mass index; m: meters; kg: kilograms; kg/m²: kilograms per square meter. Amounts expressed in absolute numbers and percentage rates (%).



Quantification of breast cancer staging based on the TNM classification. (A) Tumor size; (B) distant metastasis; (C) regional lymph node damage. Being T: tumor size; N: lymph node damage; M: distant metastasis. Amounts expressed as percentage rates.

Figure 1. Quantification of breast cancer staging at the diagnosis of patients being followed-up at an oncology service in Goiania.

Table 2. Laboratory examinations of patients undergoing cancer treatment (except patients whose information was not in the medical chart)

Laboratory examinations	Absolute frequency	Percentage (%)
Total Cholesterol		
>190 mg/dL	58	56.86
<190 mg/dL	44	43.14
HDL-c		
>40 mg/dL	66	74.16
<40 mg/dL	23	25.84
LDL-c		
>100 mg/dL	63	72.41
<100 mg/dL	24	27.58
Triglycerides		
>150 mg/dL	39	43.33
<150 mg/dL	51	56.67
Fasting glucose		
≥126 mg/dL	33	11.70
<126 mg/dL	249	88.30

HDL-c: high density lipoprotein; LDL: low density lipoprotein; mg: milligrams; dL: deciliters.

Table 3. Association between body mass index and menopausal status of patients with breast cancer being followed-up at an oncology service in Goiania.

BMI	Post-menopause	Pre-menopause	p-value
Normal	48	57	
Overweight	74	74	0.22
Obesity	75	57	

BMI: body mass index. Amounts expressed in absolute numbers.

Finally, we analyzed the relationship between BMI and the presence of comorbidities, positive family history for cancer and the presence of lymph node damage. We found that comorbidities were present in 36.27% of the patients with normal BMI; in 45.70% of those overweight; and 64.62% of those with obesity. As to family history of cancer, it was observed in 44.33% of patients with normal weight; 46.48% for those overweight; and 49.56% for those with obesity. About lymph node damage, 48.95% of the patients with normal weight were N0; 34.37%, N1; 13.54%, N2; and 3.12%, N3. Among overweight patients, 48,96% were N0; 36.55%, N1; 13.10%, N2; none in N3, and 1.37% were not assessed (Nx). Among those with obesity, 43.69% were N0; 38.65%, N1; 15,96%, N2; 0,84%, N3; and 0.84% did not have this parameter analyzed (Nx). The analysis of such data showed a statistically significant association ($p<0.001$) only between the presence or absence of comorbidities and BMI (Table 4).

DISCUSSION

BMI is a good anthropometric indicator, and it is the most used on in the world. It is simple, practical and has no cost. However, there are some limitations for not considering differences in body composition due to gender, age, ethnicity, not distinguishing fat and lean body mass, and not reflecting the distribution of body fat. Therefore, the ideal is that BMI be used together with other methods to determine body fat, such as the association with the abdominal circumference measurement. This combined way to assess the risk helps to reduce the limitations of each one of the evaluations alone; but, in the initial screening, BMI can be used alone in a satisfactory manner[14]. This study found the fact that the abdominal circumference measurement was not present in the charts as a limitation.

Nowadays, the incidence of obesity has been increasing in Brazil, and 20.7% of the women present with BMI≥30 kg/m^2. Evidence suggests that high BMI is associated with increased risk of breast cancer, which can be explained by physical and

Table 4. Relation between the body mass index and the presence of comorbidities, family history of breast cancer and lymph node damage.

	Normal (%)	Overweight (%)	Obesity (%)	p-value
Comorbidity	37 (36.27)	69 (45.70)	84 (64.62)	
No comorbidity	65 (63.73)	82 (54.30)	46 (35.38)	p<0.0001
FH +	43 (44.33)	66 (46.48)	59 (49.58)	p=0.74
FH -	54 (55.67)	76 (53.52)	60 (50.42)	
Lymph node damage				
Nx	0 (0)	02 (1.37)	01 (0.84)	
N0	47 (48.95)	71 (48.96)	52 (43.69)	p=0.46
N1	33 (34.37)	53 (36.55)	46 (38.65)	
N2	13 (13.54)	19 (13.10)	19 (15.96)	
N3	03 (3.12)	0 (0)	01 (0.84)	

FH+: Family history positive for cancer; FH-: Family history negative for cancer. Amounts expressed in absolute numbers and percentage rate (%).

pathological changes in the insulin IGF-1 axis, sexual hormones and adipokines, leading to the poor adjustment of endocrine and paracrine functions, which can promote metabolic changes and contribute with the increased risk of cancer and worse outcomes[15,16]. Besides, studies showed that obesity is related to the increased prevalence of triple negative breast cancer, the most aggressive subtype; when associated with the menopausal status, it is a predictor for sensitivity to neoadjuvant chemotherapy[17]. In this study, we observed that 132 women (26.51%) were obese (BMI higher than 30 kg/m^2) during chemotherapy, and 155 (31.12%) were in pre-obesity (BMI between 25 and 29.9 kg/m^2). There was a large number of obese patients, but there was no comparison with a second cohort of cancer-free patients to define if the BMI in fact increased the risk in this group of women. In other studies, obesity was present in 34.4% of the patients undergoing breast cancer treatment[18], and pre-obesity affected 35.3%[19] of them; besides, obese patients had twice as many chances of being diagnosed with breast cancer at advanced stages when compared to patients with normal weight[20].

Obesity seems to influence the development of breast cancer, especially after menopause, and that is justified by the fact that circulating estrogen deriving from the fat tissue is associated with the increased risk and progression of estrogen receptor positive breast cancer. This study did not find a statistically significant association between the presence or absence of obesity and menopausal status in patients with breast cancer. However, past studies showed that 75% of the patients who had breast cancer after menopause presented worse outcomes when they were obese in comparison to women with normal BMI. Obesity is associated with worse prognosis, leading to higher levels of lymph node and distant metastasis, increasing tumor load and risk of recurrence[15,21]. In this study, 197 women were menopausal; 74 were overweight and 75 were obese. A similar result was found in another research, which showed an increasing risk of breast cancer together with an increase in BMI after 25 kg/m^2[22]. This study did not assess the use of hormone blockers in patients with a history of cancer because this information was not in the chart, which would be an important additional data.

Concerning the epidemiological profile of the study population, we observed that most did not present with recurrence or family history of breast cancer and had history of comorbidity, being SAH the most frequent one; the minority was nulliparous. Such data are in accordance with the study carried out with women undergoing breast cancer treatment in other states, such as Minas Gerais and Paraná, demonstrating a similar profile[23,24]. Regarding the age at diagnosis, the mean age was 52 years, similar to other studies that point out that the mean age of women diagnosed with breast cancer was between 50 and 69 years, thus leading to the need for programs of prevention and early diagnosis of breast cancer[24-26].

Regarding the analysis of staging at the time of diagnosis, based on the TNM system, most presented with a tumor classified as T2 (35.94%), lymph node damage classified as N0 (45.56%), metastatic involvement as M0 (67.67%); and 55 (11.04%) participants of the studied population did not present the TNM classification in the chart, showing a flaw in the follow-up of these patients, considering that this parameter is important to monitor the disease. However, it was not possible to clinically classify the population and correlate it with the presence of obesity, since other information, such as the type of receptor and protein of the tumor and histological level, was not analyzed. However, a direct relationship between the presence of obesity and more advanced stage and the presence of higher lymph node damage at diagnosis has been observed in another study[20].

About the laboratory profile of the patients, we observed that, in most charts, TC and LDL-c were above the reference value,

whereas fasting glucose, HDL-c e triglycerides were within normal limits[26,27]. In the literature, studies show that no direct associations were found between the lipid profile and the occurrence of breast cancer. On the other hand, the increasing lipoproteins can be a result of the disease itself, drugs used during chemotherapy and the lifestyle of the patients[12].

We found that, in the group of patients with normal BMI, 36.27% had some comorbidity, whereas in the group of overweight and obese patients, 45.70% and 64.62%, respectively, presented with associated comorbidities, leading to a statistically significant relationship between the increase of BMI and the prevalence of other comorbidities together with breast cancer in the sample ($p<0.001$). This information is verified by studies that show that the higher the BMI of a patient, the higher the risk of developing diseases, such as SAH and diabetes. This can be explained by physical and pathological changes that occur in obesity, leading to a pro-inflammatory state and reducing the quality of life of patients. According to the WHO, in 2010 obesity and excess weight caused 3.4 million deaths in the world, reinforcing the severity of the problem, the impact on the follow-up of patients and the need for attention addressed to weight control, since the incidence of obesity has been increasing around the world[28,29].

Observing the family history of cancer in obese and non-obese patients, we can notice that 49.58% of the group with obesity and 46.48% of the group with excess weight were positive, and 44.43% of the group with normal BMI was also positive. In this study, there was no statistically significant relationship ($p=0.74$) between family history of cancer and obesity; however, the literature reports that women with family history of breast cancer (first-degree relatives) present higher influence of BMI on the risk of developing cancer, which can be 2.9 times higher than when BMI is higher than 30 kg/m^2[30]; however, this study did not analyze the level of kinship, only the presence or absence of cases of cancer in the Family. By analyzing the relationship between obesity and lymph node damage in breast cancer, it is possible to notice that the level of damage increases in the group in which patients were overweight or obese, when compared to the group with normal weight; however, there was no statistically significant difference ($p=0.46$).

CONCLUSIONS

The results of the study in women undergoing regular breast cancer treatment at Hospital das Clínicas of Universidade Federal de Goiás characterized the percentage of participants who were overweight or with obesity as 57.63%, showing BMI as a relevant factor for the physician to assess. Besides, we found that the group with obesity presented a higher percentage of concomitant comorbidities when compared to the normal BMI group, pointing to a direct influence on the prognosis and quality of life of the patients. There was no statistically significant association between the presence or absence of obesity and menopausal status in patients with cancer; however, there may be a correlation between cancer and obesity based on the percentage found.

Therefore, due to the impact of breast cancer on the quality of life of the patients, we observed that the association with obesity or other comorbidities may worsen the status and lead to worse outcomes. So, it is possible to notice the importance of the analyses about implicated factors in the etiology and progression of breast cancer, thus leading to new possibilities of prevention and better prognosis. Thus, it is necessary to establish public health measures for the female population, in order to reduce the incidence of obesity/overweight and stimulate the early diagnosis of breast cancer.

AUTHORS' CONTRIBUTION

ACJFS: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. VBS: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. LLB: Data curation, Formal Analysis, Writing – review & editing. DGSTS: Writing – review & editing. EJFT: Writing – review & editing. CMG: Formal Analysis, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Comparative analysis between screening mammography performed in patients at usual risk and at high risk for breast cancer

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ABSTRACT

Introduction: Breast cancer is currently considered as a public health issue. To avoid late diagnosis, there is an attempt to use appropriate screening programs addressed to the early detection by testing the asymptomatic population in order to identify preclinical stage lesions. **Methods:** This is a retrospective, analytical, cross-sectional study of the notifications available in the cancer information system. The incidence of notifications from the reports of the BI-RADS™ notification system (Breast Imaging Reporting Data System) was compared between women at high and usual risk for breast cancer. **Results:** In the analyzed period, from 2013 to 2021, 16,065,383 screening mammographies were performed and notified in Brazil. Of these, 13,167,259 were performed in usual-risk women, whereas 2,898,124 were performed in high-risk women. To analyze the difference between reports of women at usual and high risk, the relative risk between them was calculated, as well as the necessary number to causa damage; the relative risk we found was of 0.5412 (95%CI 0.5341–0.5483) in B4 and relative risk of 0,433 (95%CI 0.4203–0.4462). As to the necessary number to cause damage, we observed 203 (95%CI 198–209) for B4 and 788 (95%CI 754–825) for B5. Despite the well-established need for breast cancer screening programs to reduce mortality, some aspects of screening do not have such a consensus. In this study, the incidence of reports that are suggestive of malignant breast lesions was higher among women at high risk. **Conclusions:** The study showed an increased prevalence of reports suggestive of malignancy in high-risk patients when compared to those at usual risk.

KEYWORDS: mammography; breast cancer; screening.

INTRODUCTION

Breast cancer is currently considered as a public health issue. Apart from non-melanoma skin cancer, it is the most common cancer among women in Brazil, in the South, Southeast, Midwest and Northeast regions. Besides, it represents the highest incidence and mortality rates among women all over the world, both in developing and developed countries[1-3].

Despite being the most common cancer affecting women (except for non-melanoma skin cancer), it is the fifth cause of death by cancer in general, reaching about 500 thousand deaths per year[4,5].

Breast cancer screening allows the early diagnosis and enables a more conservative and curative treatment. In Brazil, the death risk ratio is 17.1 times higher among patients diagnosed at advanced stages when compared to those who were diagnosed early, so that early diagnosis reduces mortality rates and increases survival rates, reaching 83.1% in 10 years[6,7].

Tumor size and lymph node involvement are currently considered the main prognostic factors in the analysis of breast cancer. That is, the larger the tumor, the higher the chances of lymph node metastasis and distant metastasis, as well as the lower survival and chances of healing for the patient[7-9].

To prevent the late diagnosis, there is an attempt to execute a strategy of appropriate screening programs, which can lead to the early detection by examining the asymptomatic population and identifying preclinical stage lesions[10]. The Ministry of Health recommends screening mammography in women aged from 50–69 years old every two years[11].

As to high-risk patients, individualized clinical follow-up is recommended and there is not a well-established consensus that is accepted by experts as to what should be done about them[9,10].

Nowadays, the breast self-exam is not recommended as a screening technique due to its low effectiveness and possible damage associated to this practice, since the studies did not

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show reduction in mortality rates and seem to cause a false sensation of safety among patients, which leads them to not look for screening[10,11].

In this context, it is necessary to analyze the impact of screening in the usual and high-risk population by assessing the incidence of suspicious mammography (BI-RADS™ 4 and 5) in patients submitted to screening mammography between 2013 and 2021 in Brazil. Only after understanding the magnitude of the problem can there be actions to mitigate the damage that this disease represents in female public health.

METHODS

An ecological, observational and cross-sectional study was performed based on retrospective data about the mammography screening program in Brazil. The data source was a National Screening Database (Cancer Information System – Siscan/Datasus), which is publicly available for download[12]. The selected interval of analysis was from 2013–2012, period when all the necessary variables for analysis are available.

The examinations performed from 2013–2021 with a screening purpose were selected. While usual-risk women were those without family history of personal history of breast neoplasm, high-risk women were those with family history of at least one first-degree relative diagnosed with breast cancer before the age of 50 years, bilateral breast cancer or ovarian cancer at any age; women with family history of male breast cancer; women with histopathological diagnosis of proliferative breast lesion with atypia or lobular carcinoma in situ; or women with personal history of breast cancer.

We excluded diagnostic examinations, those that did not present all of the information and those that were not in the stipulated age group.

Besides the information about the BI-RADS™ report, we analyzed the examinations comparing the epidemiological data between high-risk and usual-risk women. Other analyzed variables were the age group of the screened population and tumor size according to BI-RADS™.

The statistical analysis of the data was conducted using the SPSS software (Statistical Package for the Social Sciences), version 18.0, which calculated the mean and the confidence interval of the main variables.

RESULTS

In the analyzed period, from 2013–2021, 16.065.383 screening mammographies were performed and notified in Brazil. Of these, 13.167.259 mammographies were carried out in the target-population, while 2,898,124 mammographies were conducted in women classified as high risk. The report of each mammography performed in the target population and high-risk women can be observed in Table 1, which compared the relative risk of such populations using the SPSS software. To analyze the difference between reports in usual-risk and high-risk women, the relative risk between them and the necessary number to cause damage were calculated; we found relative risk of 0,5412 (95%CI 0,5341–0,5483) in B4 and relative risk of 0,433 (95%CI 0,4203–0,4462). As to the necessary number to cause damage, we observed (95%CI 198 – 209) for B4 and 788 (95%CI 754–825) for B5.

The age group of patients who underwent mammography can be observed in Table 2.

Finally, we calculated the comparison of proportion of tumor size found in the mammography and its relationship with the BI-RADS™ report between high-risk and usual-risk patients, according to the observations in Table 3. BI-RADS™ reports 1 and 2 were excluded from the analysis for not containing tumors[13].

Table 1. Mammography reports of examinations carried out in the target population and among high-risk women between 2013 and 2021 in Brazil.

	Usual-risk women (%)	High-risk women (%)	Relative risk (p-value)
B0	1,439,841–11	373,683–13	0,8481 (p<0.05)
B1	4,906,097–37	1,009,350–35	1,0698 (p<0.05)
B2	6,452,900–49	1,409,596–49	1,0076 (p<0.05)
B3	279,335–2.1	67,966–2.3	0,9046 (p<0.05)
B4	76,329–0.6	31,045–1.1	0,5412 (p<0.05)
B5	12,757–0.1	6,484–0.2	0,4330 (p<0.05)
Total	13,167,259–100	2,898,124–100	

Source: adapted by the authors of Siscan/Datasus. B: Breast Imaging Reporting Data System.

Table 2. Age group of the patients who underwent mammography from 2013 to 2021 in Brazil.

	Usual risk (%)	High risk (%)
Aged up to 14 years	2,901 (0.02)	529 (0.02)
Between 15 and 19 years old	2,230 (0.01)	801 (0.03)
Between 20 and 24 years old	5,378 (0.04)	2,733 (0.09)
Between 25 and 29 years old	10,533 (0.08)	7,407 (0.26)
Between 30 and 34 years old	32,058 (0.24)	25,243 (0.48)
Between 35 and 39 years old	267,999 (2.03)	141,936 (4.89)
Between 40 and 44 years old	1,612,354 (12.2)	392,689 (13.5)
Between 45 and 49 years old	2,010,696 (15.2)	443,187 (15.3)
Between 50 and 54 years old	2,869,991 (21.8)	514,746 (17.8)
Between 55 and 59 years old	2,490,346 (18.9)	458,261 (15.8)
Between 60 and 64 years old	1,934,049 (14.7)	364,576 (12.6)
Between 65 and 69 years old	1,241,975 (9.43)	244,425 (8.43)
Between 70 and 74 years old	439,439 (3.33)	119,015 (4.11)
Between 75 and 79 years old	179,337 (1.36)	53,946 (1.86)
Aged more than 79 years	67,973 (0.52)	26,456 (0.91)
Total	13,167,259 (100)	2,898,124 (100)

Source: adapted by the authors of Siscan/Datasus.

Table 3. Relative risk depending on tumor size and BI-RADS™ report between women at high and usual risk.

	<=10mm	11–20mm	21–50mm	>50mm
BI-RADS™ 0	0,8806 (95%CI 0,8562–0,9056)	0,8725 (95%CI 0,8423–0,9037)	0,8315 (95%CI 0,7729–0,8946)	1,0341 (95%CI 0,8816–1,2129)
BI-RADS™ 3	1,4464 (95%CI 1,2925–1,6186)	1,7870 (95%CI 1,5040–2,123)	1,2183 (95%CI 0,6933–2,1408)	0 usual risk patients>50mm and B3
BI-RADS™ 4	2,281 (95%CI 1,8479–2,8156)	1,9252 (95%CI 1,5848–2,3387)	1,5548 (95%CI 1,2454–1,9409)	1,1081 (95%CI 0,6290–1,9521)
BI-RADS™ 5	2,9962 (95%CI 1,9727–4,5506)	1,4758 (95%CI 1,0655–2,0442)	1,7349 (95%CI 1,3405–2,2453)	0 usual risk patients>50mm and B5

Source: adaptaed by the authors of Siscan/Datasus. BI-RADS™: Breast Imaging Reporting Data System.

DISCUSSION

Despite the fact that the need for breast cancer screening programs is well-established, some aspects of screening do not present such a consensus, such as the beginning and end of screening[14,15].

As established by the main societies specialized in mastology, patients with high risk for breast cancer were women with family history of at least one first-degree relative diagnosed with breast cancer before the age of 50 years, bilateral breast cancer or ovarian cancer at any age; women with family history of male breast cancer; women with histopathological diagnosis of proliferative breast lesion with atypia or lobular carcinoma in situ; or women with personal history of breast cancer[16-18].

In this study, as well as the findings in the literature, the incidence of suspicious reports for malignant breast lesions was higher among high-risk women. This finding can be compatible with the fact that women with risk factors have higher chances of developing breast cancer than those with usual risk[17,19].

In spite of that, it is important to be careful when analyzing this factor. Some studies show that examinations of high-risk patients tend to be analyzed in detail, so they present higher rates of false positive results than those of patients with low risk. Besides, examinations of low-risk patients present higher rates of false negative results[20].

Another aspect to be considered in the effectiveness of screening is the age group[21]. In this case, even though the Ministry of Health proposes the screening in patients aged between 50 and 64 years, it was observed that 44% of the mammographies carried out in low-risk patients were outside this age group[22]. Since this is a retrospective study including a database analysis, it is important to consider the possibility that the age group was filled out incorrectly.

The screening between the ages of 40 and 49 years and 64 and 69 years, despite not being recommended by the Ministry of Health, is recommended by the main mastology societies and by the Brazilian Federation of Gynecology and Obstetrics Associations, which can explain the lower incidence of mammography in these age groups, such as the fact that they were requested[23-25].

In this study, unlike another national study published in 2022, the higher incidence of tumors was found in high-risk patients, and, analyzing relative risk, we observed that the mere presence of a tumor in high-risk women, being the reports B3, B4 or B5, already meant a higher risk than that for usual-risk women, regardless of tumor size; that is because, in all sizes, the risk was higher among high-risk patients. On the other hand, when the report is B0, there seems to be higher incidence of tumors in usual-risk patients, which can be owed to the clinical influence at the time of classifying the patient's tumor[26].

CONCLUSION

The study showed an increased prevalence of reports suggestive of malignancy in high-risk patients when compared to those at usual risk. Such findings can mean that high-risk patients have higher prevalence of malignancy, but also that physicians analyze the examinations of high-risk patients more carefully, thus increasing the rates of reports that suggest malignancy among these patients.

Besides, further studies, with well-defined methodology and a sample that is representative of the population, are necessary to describe the main necessary characteristics for the screening program to succeed are.

AUTHORS' CONTRIBUTION

GDP: Investigation, Methodology, Writing – original draft. JMR: Supervision. MA: Conceptualization, Data curation, Methodology, Writing – review & editing. OF: Validation, Visualization. RGC: Supervision.

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Clinical quality assurance in breast cancer screening and diagnosis: a warning regarding mammographic positioning

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ABSTRACT

Objective: This study aimed to evaluate the clinical image quality of mammograms performed in users of the Brazilian Unified Health System (SUS) referred to a tertiary hospital. **Methods:** A prospective study assessed mammograms from women referred to a specialist breast center in Goiânia, Goiás, Brazil, between May and October 2017. Scans performed in the preceding 6 months, either screening or diagnostic, were included in the study. Clinical quality was determined from 40 variables related to patient identification, technical performance, the equipment, radiological findings, reporting of results, and breast positioning. Scans performed in the public and private healthcare networks were compared regarding mammographic positioning. **Results:** Overall, 4,560 variables associated with the clinical quality of the images were evaluated in scans from 114 women with a mean age of 50.6 years. A total of 660 (14.47%) inadequacies were found, 443 (67.12%) of which were related to breast positioning. The most common errors were as follows: pectoral muscle could not be seen in 86.8% of scans in the craniocaudal view and inframammary angle could not be seen in 79.8% of scans in the mediolateral oblique view. Considering the breast-positioning criteria evaluated in the mediolateral oblique view, there was a greater risk of the breast not being centrally positioned with the nipple in profile (RR 4.66; 95%CI 1.05–20.62; p=0.02) and of nonvisualization of the retro-areolar area (RR 4.14; 95%CI 0.92–18.66; p=0.04) in the exams performed in the private compared to the public network. **Conclusion:** The clinical quality of the scans analyzed was found to be inadequate, with most of the nonconformities being related to breast positioning.

KEYWORDS: mammography; diagnostic imaging; mass screening; image enhancement; patient positioning.

INTRODUCTION

Quality assurance in mammography is essential if the high-contrast resolution required to adequately identify breast lesions is to be achieved[1,2]. Each component in the sequential formation of the image, from the quality of the equipment to the positioning of the patient, as well as the quality of reporting are of key importance. Therefore, to achieve the required quality standards, preestablished criteria have to be rigidly followed, ensuring that the professionals involved in obtaining the image are duly qualified and that the material and equipment used are adequate[1,2].

The quality of mammography is directly associated with the accuracy of the method. Sensitivity can be around 65% when the appropriate quality standards are lacking, whereas compliance with quality standards may increase diagnostic detection to around 85% of cases in women aged 50 years or older[3]. Nevertheless, despite initial efforts made to implement mammography quality assurance in Brazil[4-8], there is currently no effective nationwide assessment program in the country. With few clinical quality assurance programs having been implemented to date, there are few related Brazilian studies in the literature[9,10]. Conversely, technical quality control based on the use of specific tests to periodically evaluate equipment and processing has been common[8].

In the international scenario, the European Guidelines for Quality Assurance in Mammography Screening (EGQAMS)

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were drawn up in an effort to standardize protocols for the evaluation of mammograms and to reduce subjectivity in clinical quality control[11,12]. These guidelines establish rigid criteria insofar as the positioning of the patient and exposure to radiation are concerned, and they have been widely used in various population samples, both in Brazil and worldwide[10-12]. Nevertheless, in most of the Brazilian studies, the samples analyzed were restricted to screening mammograms[13], thus possibly constituting a selection bias in the mammography quality control process in this country.

The present study proposed to evaluate mammograms in the real-life setting of clinical practice, including patients with different indications for undergoing mammography. The objective of the study was to evaluate the clinical quality of mammograms performed on users of the Brazilian Unified Health System (SUS) referred to a tertiary hospital and to describe the distribution of inadequacies in the clinical evaluation of the images and in the mammography reports.

METHODS

This was a prospective, observational study conducted to evaluate mammograms from women referred for consultation at a specialist breast clinic in the city of Goiânia (GO), Brazil. The study was conducted with a convenience sample consisting of women receiving outpatient care, irrespective of any history of breast cancer or abnormalities detected at physical examination, and who had had a mammogram in the 6 months preceding their inclusion in the study. To minimize the possibility of selection bias, the women were approached in the waiting room of the referral center, just prior to their medical consultation.

Scans from patients with breast cancer who were undergoing neoadjuvant chemotherapy and those from patients who had previously been submitted to mastectomy of any type were excluded from the study. In addition, scans from women with conditions that could hamper the clinical evaluation of the scan, including acute inflammatory processes of the breast, were also excluded.

Data collection

An instrument based on the criteria described in the EGQAMS and the National Mammography Quality Program (PNQM) was constructed for the specific purpose of collecting data for this study[1,5,11]. The instrument was subdivided into image annotations regarding patient identification, technical performance, breast positioning, general observations on the image and equipment, and the mammography report of findings and additional comments. All the exams were analyzed by the same evaluator, with specific training in clinical quality control.

Image annotations included data on patient identification with the initials of the patient's name and registration number, the date of the exam, and the positional markers indicating either the craniocaudal (CC) or the mediolateral oblique (MLO) view. Regarding the technical performance, the scan was considered adequate if the image showed as much as possible of the lateral aspect of the breast, if there was effective compression of the breast, and if the position of the identification and other markers on the image were appropriate.

The items that were evaluated in relation to breast positioning, for both the CC and MLO views, were as follows: breast symmetry, image of the whole breast, position of the nipple, absence of obscuring skin folds, visualization of the pectoral muscle, demonstration of the inframammary angle, and visualization of the retro-areolar area. The position of the nipple was considered adequate when in profile, i.e., not projected onto the breast tissue, centralized in the CC view and parallel to the base of the film/detector in the MLO view[13]. The symmetry of the acquired images and whole breast inclusion were evaluated in each scan and classified as adequate or inadequate. The presence of skin folds obscuring the breasts or axillae in either view was considered a positioning error. The position of the pectoral muscle was considered adequate when visualized in the image in the CC view and when visualized down to nipple level in the MLO view[13]. Finally, visualization of the inframammary angle was evaluated in the MLO view.

General aspects of the image included adequate visualization of the skin, the vascular spaces, and Cooper's ligaments, when pertinent. Opacities and microcalcifications were classified as true or false lesions. The glandular component and the impact of this variable on the adequacy of the clinical evaluation of the scan were also evaluated. Reduced-scale images, irrespective of the percentage of this reduction, were considered inadequate.

The mammography report was analyzed regarding the appropriate description of the breast density pattern and mammography findings, the recommended management according to the Breast Imaging-Reporting and Data System (BI-RADS®)[14], and the identification of the examining physician. Additional comments evaluated included the effective reporting of breast implants, alterations that resulted in a need for additional images and artifacts[15], as well as the patient's history of any previous breast surgeries. Artifacts were classified as present or absent. Bearing in mind that some mammograms could have been performed at healthcare facilities not included in the SUS, evaluation took into account whether the scan had been performed within the public or private healthcare system.

Statistical Analysis

The data collected were included in a database using double data entry, tabulated, and then analyzed using the Microsoft Excel software program, version 2007 (Microsoft, Redmond, WA, USA). An exploratory analysis was performed using descriptive

statistics, with the calculation of means, absolute frequencies, and percentages. These data were presented to the team and are available for use in future projects, aimed at increasing the quality of mammography in the state of Goiás.

After the principal errors related to breast positioning had been identified, comparison was made as a function of the type of establishment in which the scan was performed (whether in the public or private healthcare network). The percentages (incidence) of each type of positioning error in both the CC and MLO views were measured and the relative risks (RR) between the types of establishment were then calculated for each type of error. The Pearson's χ^2 test and Fisher's exact test were used to verify statistical significance, considering a 95% confidence interval (CI). All the analyses were performed using the Stata software program, version 14.0 (Stata Corp., College Station, TX, USA).

Ethical Issues

This study is part of a line of research developed by the Brazilian Breast Research Network. The internal review board of the Hospital Universitário da Universidade Federal de Goiás approved the study protocol under reference CAAE 65644217.8.0000.5078. All the recommendations for good clinical practice were followed, as stipulated in Resolution 466/2012 of the Brazilian Ministry of Health's National Health Council and in the Helsinki Convention. All the women who agreed to participate in the study signed an informed consent form.

RESULTS

Overall, 4,560 items related to the quality of mammograms were evaluated, with 40 items being assessed in each scan. A total of 114 women with a mean age of 50.61±10.2 years (± standard deviation [SD]) were included in this study. Among them, 11 (9.64%) were under 40 years of age and were investigated for palpable lumps or monitored following a previous episode of breast cancer; 6 (5.26%) had breast implants; and 51 (44.73%) had undergone some type of breast surgery previously. Of the previous surgeries carried out, the most common was quadrantectomy associated with sentinel lymph node biopsy (n=24; 47.05%) (Table 1).

Evaluation of the healthcare system in which the scans were performed showed that 57 (50%) were carried out in the public healthcare system and 55 (48.25%) within the private healthcare network, while this information was missing in 2 (1.75%) cases. The distribution of the variables related to identification, the technique performed, and mammography reports is shown in Table 1, which also lists the general annotations on the scans.

A total of 660 errors were found in the scans included in this study, corresponding to 14.47% of all the items analyzed. There were 443 errors related to breast positioning, which corresponded to 67.12% of all nonconformities, with a mean of 3.9 breast-positioning errors in each scan. The distribution of the number of positioning failures for each view (CC or MLO) is shown in Table 2.

All the scans were considered adequate with respect to the sharpness and contrast of the image, which are variables related to the equipment used. In contrast, noise and artifacts were found to be present in 5 (4.39%) and 23 (20.17%) scans, respectively. The scale of the images was reduced in 9 (7.89%), with a mean reduction of 20.7%. Following thorough examination of each image, 7 (6.14%) scans were found to have abnormalities that required additional images to be taken.

In relation to the findings of the mammography scans included in this study, evaluations were incomplete in 29 (25.9%) cases, i.e., BI-RADS® category 0. Regarding the results considered benign, 14 (12.5%) cases were classified as BI-RADS® category 1 and 48 (42.86%) as BI-RADS® category 2. For the other cases, there were 12 (10.71%) of category 3, 8 (7.14%) of category 4, and 1 (0.89%) of category 6. None of the 112 scans evaluated according to the BI-RADS® was classified as category 5.

With respect to the positioning criteria evaluated in the MLO view, the number of errors related to the requirement that the breast be centrally positioned with the nipple in profile (RR 4.66; 95%CI 1.05–20.62; p=0.02) and to the demonstration of the retro-areolar area (RR 4.14; 95%CI 0.92–18.66; p=0.04) tended to be greater in the scans performed in the private healthcare network compared to those performed in the public system. There were no other statistically significant differences between the two healthcare systems for any of the other variables related to breast positioning (Table 3).

DISCUSSION

The quality of mammography is directly related to the accuracy of this breast cancer diagnostic method[1,3,13]. Nevertheless, few studies have evaluated the clinical quality of mammograms in Brazil and those studies are limited to women participating in breast cancer screening programs[9,10]. Therefore, the relevance of the present study lies in the fact that clinical quality was assessed in a real-life clinical practice setting and that the study also included diagnostic mammograms and women with a prior history of breast cancer.

Identification markers are crucial in imaging exams in order to prevent reports from being switched and scans from being charged in duplicate. In this respect, although some isolated recommendations do exist[1,14], there is no established protocol governing identification procedures for mammograms and other imaging exams. In the present study, 25.4% of all scans were found to contain some form of identification error, particularly missing data on patient registration. In addition, the registration number printed on the mammogram image generally

Table 1. Factors taken into consideration in the evaluation of the quality of mammograms.

	Present		Absent	
	n	%	n	%
Identification				
Patient identification information	112	98.25	2	1.75
Organization identifier	112	98.25	2	1.75
Patient registration number	86	75.44	28	24.56
Date of the scan	113	99.12	1	0.88
Positional/anatomical markers (CC or MLO)	114	100.00	0	0.00
Performance of the scan				
The lateral aspect of the breast is clearly shown*	110	96.49	4	3.51
The position of the identification/other markers on the image was appropriate	113	99.12	1	0.88
Appropriate compression of the breasts	110	96.49	4	3.51
General observations regarding the image				
Reduced-scale image	9	7.89	105	92.11
Adequate visualization of the breast skin (no creases or folds)	112	98.25	2	1.75
Visualization of the vascular spaces through dense tissue	84	73.68	30	26.32
Visualization of Cooper ligaments	105	92.11	9	7.89
Do microcalcifications, when present, represent a true lesion?	34	85.00	6	15.00
Does opacity, when present, represent a true lesion?	37	88.10	5	11.90
Obscured breast glandular tissue	22	19.30	92	80.70
Mammography Report				
Adequate patient identification	112	98.25	2	1.75
Number of films**	60	53.57	52	46.43
Type of scan (public or private healthcare network)**	105	93.75	7	6.25
Report includes BI-RADS® classification**	111	99.11	1	0.89
Report includes mammography findings**	111	99.11	1	0.89
Report includes recommended management**	93	83.04	19	16.96
Identification of the examining physician	112	98.25	2	1.75

CC: craniocaudal; MLO: mediolateral oblique; BI-RADS®: breast imaging-reporting and data system. *The scans clearly show the medial border and as much as possible of the lateral aspect of both breasts. **n=112 due to missing data in two cases.

corresponds to the patient's registration at the radiology facility, which is not the same as her registration at the healthcare clinic; hence, it does not ensure that the patient is correctly identified during her medical consultation. In contrast, the majority of the scans analyzed in this study did contain the initials of the patient's name, the date on which the scan was performed, and positional and anatomical markers of the corresponding imaging views, thus ensuring that each participant in the study was correctly identified.

Nonconformities related to breast positioning are the most common type of error found in mammograms[13]. Nevertheless, despite the heterogeneity of the sample in the present study, the percentage of errors found was almost twice that reported in a previous study conducted with 5,000 scans performed for breast cancer screening in the state of São Paulo, Brazil[10].

In the sample included in the present study, the pectoral muscle was visible in the CC view in only 13% of scans, a rate that is lower than the recommended rate of 30%.[1,5] In the MLO view, the inframammary angle could not be seen in 79.8% of scans. These facts together reflect breast-positioning issues in both views. Nevertheless, continued education and constant training of the radiology technicians is believed to reduce these errors and improve the final quality of mammograms[13].

Regarding correct criteria insofar as breast positioning is concerned, the factors for which the percentages of accuracy were greatest were the absence of obscuring skin folds in the breast and axillae in 84.21% of the CC and 80.70% of the MLO views. This rate of accuracy is lower than that reported in a previous study conducted at the Barretos Cancer Hospital in which accuracy rates of 97.2% and 95.4%, respectively, were found regarding

Table 2. Distribution of positioning failures in each incidence of mammography.

	Conformities		Nonconformities	
	n	%	n	%
Craniocaudal view				
Symmetrical radiography	91	79.82	23	20.18
Exams favoring a quadrant	89	78.07	25	21.93
Nipple in profile	95	83.33	19	16.67
Nipple centered	95	83.33	19	16.67
Skin folds	96	84.21	18	15.79
Presence of the pectoral muscle	15	13.16	99	86.84
Visualization of the retro-mammary fat	109	95.61	5	4.39
Adequate sampling of the medial and lateral portions	113	99.12	1	0.88
Mediolateral oblique view				
Symmetrical radiography	85	74.56	29	25.44
Nipple in profile	91	79.82	23	20.18
Nipple centered	103	90.35	11	9.65
Skin folds	92	80.70	22	19.30
Visualization of the retro-mammary fat	103	90.35	11	9.65
Visualization of pectoralis major muscle at or below the nipple	79	69.30	35	30.70
Anterior border of convex pectoral muscle	102	89.47	12	10.53
Inframammary angle	23	20.18	91	79.82

Table 3. Distribution of positioning failures between mammograms performed in the private and public network*.

	Private network (n=55)		Public network (n=57)		RR	95% CI		p-value
	Failures (n)	Failures (%)	Failures (n)	Failures (%)		LL	UL	
Craniocaudal view								
Symmetrical radiography	14	25.45	8	14.04	1.81	0.82	3.97	0.12
Exams favoring a quadrant	13	23.64	12	21.05	1.12	0.56	2.24	0.74
Nipple in profile	11	20.00	7	12.28	1.62	0.68	3.89	0.26
Nipple centered	12	21.82	7	12.28	1.77	0.75	4.17	0.17
Skin folds	8	14.55	10	17.54	0.82	0.35	1.94	0.66
Presence of the pectoral muscle	48	87.27	49	85.96	1.01	0.87	1.17	0.83
Visualization of the retro-mammary fat	3	5.45	1	1.75	3.1	0.33	28.99	0.29
Adequate sampling of the medial and lateral portions	1	1.82	0	0.00	.....**	.....	.....	.....
Mediolateral oblique view								
Symmetrical radiography	17	30.91	12	21.05	1.46	0.77	2.78	0.23
Nipple in profile	16	29.09	7	12.28	1.95	0.87	4.33	0.08
Nipple centered	9	16.36	2	3.51	4.66	1.05	20.62	0.02
Skin folds	13	23.64	9	15.79	1.49	0.69	3.21	0.29
Visualization of the retro-mammary fat	8	14.55	2	3.51	4.14	0.92	18.66	0.04
Visualization of pectoralis major muscle at or below the nipple	20	36.36	15	26.32	1.38	0.79	2.41	0.25
Anterior border of convex pectoral muscle	6	10.91	6	10.53	1.03	0.35	3.01	0.94
Inframammary angle	14	25.45	9	15.79	1.61	0.76	3.41	0.20

RR: relative risk; 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit. *n=112 due to missing data in two cases; **the relative risk could not be calculated because there were no failures in the public network.

the absence of skin folds[10,13]. Nevertheless, since the present study population included breast cancer survivors, scars from previous surgeries and sequelae resulting from radiotherapy could have increased the occurrence of obscuring skin folds, asymmetries, and other breast-positioning errors.

The distribution of the breast-positioning errors found in the MLO view showed that the quality of the scans performed in the public healthcare network was better than that of the scans carried out in the private healthcare network. However, no statistically significant differences were found between the two healthcare networks for any of the variables evaluated in the CC view. Moreover, on the one hand, the majority of the scans performed in the public healthcare network and included in the present study were carried out in a university hospital that is currently in the initial stages of implementing internal quality control. In contrast, the scans performed in the private network originated from various different radiology units with varying standards of quality control. Therefore, despite the absence of statistically significant differences, it is notable that almost all the different types of error were more prevalent in the private network, except for the occurrence of obscuring skin folds.

In relation to the general observations on the image, attention is drawn to the occurrence of reduced scale in 9 (7.89%) scans, which may compromise the evaluation of the images and their comparison with previous ones. Nevertheless, despite the 16 (14.04%) cases of artifacts and 22 (19.30%) cases of obscured breast glandular tissue, among other nonconformities, only 7 of the patients included in the study had to repeat the scan. In other cases, when selective compression or magnification was required, the patients already had the additional images when they arrived for consultation, since the radiologist had already requested them. An observational study, in which 5,000 mammograms were performed using screen-film mammography, computed radiography, and full-field digital mammography, found that 11% of the errors detected were related to the mammography used, with a predominance of the screen-film mammography machines[13]. Therefore, the gradual replacement of screen-film machines for full-field digital ones, that has been occurring over recent years, may contribute toward reducing the nonconformities associated with the mammography machine used.

Mammography reports are the interface between the radiologist and the attending physician and, therefore, must also meet preestablished quality criteria[4]. In the present study, cases were common in which information on the clinical indication for performing the exam and/or the number of films or images produced had been omitted from the mammography report. Nevertheless, these data can be acquired at the time of the medical consultation and such errors do not generally hamper the diagnostic investigation. In contrast, 19 (16.96%) of the reports failed to include the recommended management. In clinical practice, this type of error can delay the diagnosis of a clinically suspicious breast lesion and the patient's subsequent referral to an oncology center, indirectly contributing to a need for more radical treatment and reduced overall survival[16,17].

The BI-RADS® classification, developed by the American College of Radiology, standardizes mammography, ultrasonography, and magnetic resonance imaging of the breasts and allows the potential malignancy of the respective radiological findings to be predicted and the exams and services performed to be audited[14]. In the present study, 99.11% of the mammography reports analyzed contained the respective BI-RADS® classification, reflecting the extent to which this methodology has been consolidated in the description of mammography findings. In contrast, the predominance of scans considered inconclusive or abnormal is explained by the fact that the sample analyzed consists of patients attending a tertiary hospital that is a regional reference for the diagnosis of breast cancer.

The limitations of the present study include the small number of scans examined in relation to the number of medical consultations made during the same period. This could be explained by the centralized process of recruitment and image evaluation, the objective of which was to increase control over the study and reduce the possibility of a selection bias and of interobserver variations. Nevertheless, the patients were included in the study over a 6-month period, which minimizes the possibility of a time bias in the quality of the scans.

CONCLUSION

The quality of the mammograms analyzed was found to be inadequate, with a predominance of nonconformities related to breast positioning. This is probably typical of what happens in most such facilities around the country. However, continued education and constant training for radiology technicians should reduce breast-positioning errors and improve the overall quality of mammograms.

AUTHORS' CONTRIBUTION

LRS: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft. RMSR: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – review & editing. VCJQ: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft. ÉCA: Data curation, Formal Analysis, Investigation, Validation, Writing – original draft. RSC: Data curation, Investigation, Visualization, Writing – review & editing. DCNR: Data curation, Investigation, Visualization, Writing – review & editing. LSC: Data curation, Investigation, Visualization, Writing – review & editing. RFJ: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE
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Axillary surgical approach in T1-T2N0M0 clinical breast cancer staging: Survival in a women's hospital cohort in Rio de Janeiro

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ABSTRACT

Introduction: The concerns regarding the prognosis and quality of life of patients with early breast cancer staging without lymph node involvement have increased, especially with regard to the axillary surgical approach. The aim of the present study was to determine overall survival and disease-free survival according to the axillary surgical approach. **Methods:** Retrospective cohort study of 827 women with clinical T1-T2N0M0 diagnosis attended at the Cancer Hospital III of the Brazilian National Cancer Institute, from January 2007 to December 2009, with a follow-up period of 60 months. Data were obtained from the Hospital Registry of Cancer through the medical records. **Results:** 683 women underwent sentinel lymph node biopsy and 144 underwent sentinel lymph node biopsy followed by axillary lymphadenectomy. After 5 years of follow-up, considering adjustment, it was observed overall survival (96.2% vs 93.6%; HR 0.98; 95%CI 0.42–2.29) and disease-free survival (93.7% vs 91.2%; HR 0.78; 95%CI 0.39–1.48) similar among patients undergoing either one or the other approach. In patients with micrometastasis, both overall (93.3%) and disease-free survival (100%) were higher in women who underwent only sentinel lymph node biopsy compared to those who underwent this procedure followed by axillary lymphadenectomy (OS: 87.5%; DFS: 90,7%), albeit not statistically significant. **Conclusions:** No difference was observed in overall or disease-free survival in patients with T1-T2N0M0 breast cancer staging according to axillary treatment (sentinel lymph node biopsy followed or not by axillary lymphadenectomy) in 60-month. In addition, no statistically significant differences in overall and disease-free survival were observed in women with sentinel node micrometastasis submitted to any of the approaches within 60 months.

KEYWORDS: breast cancer; sentinel lymph node biopsy; lymph node excision; survival analysis; disease-free survival.

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related deaths among women worldwide, with an incidence ranging from 36.1/100.000 women in countries with low human development index (HDI) to 75.6/100,000 women in very high HDI countries in 2020[1].

Surgery is the main treatment for breast cancer and can be complemented with radiotherapy, chemotherapy, hormone therapy, and biological therapy[2]. The surgical approach may be more conservative in the early stage of this neoplasm, depending on the presence or absence of axillary procedure. Thus, for proper axillary staging, surgical breast cancer treatment involves an approach through sentinel lymph node biopsy (SLNB) and/or axillary lymphadenectomy (AL). The AL intervention aims to establish lymph node status and to indicate the best treatment in order to improve survival and local disease control. However, it is often associated with increased early and late postoperative morbidity in breast cancer patients[3,4]. The first randomized studies to validate SLNB in breast cancer confirmed that this technique provides better disease control, improved survival, and accurate axillary staging, indicating that if the identified sentinel lymph node is not positive for cancer, the remaining lymph nodes display a high probability of being disease-free, so the patient is spared of AL and its complications[5,6].

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Thus, to minimize the complications generated by AL, in the 1990s, SLNB was incorporated to the diagnosis and therapeutic determination of breast cancer, marking a major advance in surgical treatment[7]. Currently, SLNB is the preferred staging method for breast cancer in clinically negative axilla patients with T1 or T2 classification[8]. Previously, due to the strongly negative prognostic value of axillary lymph node metastasis, AL used to be performed in patients with clinical lymph node metastasis, as well as in the case of positive SLNB. But, in recent years, this has changed, and a smaller number of AL has been performed for T1-T2 size neoplasms[9].

The evolution in sentinel lymph node evaluation methods has resulted in the frequent discovery of micrometastatic foci (≤2 mm in diameter) and isolated tumor cells, whose prognostic significance is still uncertain[7]. The literature shows a frequency of 4% to 8% of sentinel node micrometastasis[10,11], which could result in greater locoregional and distant recurrence, and possibly lower overall survival (OS) and disease-free survival (DFS) among patients undergoing SLNB compared to patients who underwent AL, as the presence of sentinel lymph node micrometastasis may indicate non-sentinel lymph node involvement[12]. However, several randomized studies have indicated that patients with negative SLNB fewer than three positive axillary lymph nodes or sentinel micrometastasis do not need to undergo AL[5,13-16]. It is known that most studies evaluating AL and lymph node micrometastasis in the survival of women with breast cancer have been conducted in developed countries, but the extrapolation of their results was not allowed for developing countries.

In Rio de Janeiro, the Cancer Hospital III of the Brazilian National Cancer Institute (HC-III/INCA) is reference for the treatment of breast cancer in this city and treats most breast cancer cases registered in the metropolitan region of the state, offering a rich database for exploring the survival of these patients. Taking this into consideration, this study aims to determine the OS and DFS of breast cancer patients with T1-T2N0M0 clinical classification, diagnosed and treated in the HC-III/INCA) from 2007–2009, according to the axillary surgical approach.

METHODS

An observational study was conducted with a cohort of 1,417 women presenting T1-T2N0M0 clinical stage breast cancer and treated at the HC-III/INCA, from 2007 to 2009, with a follow-up of 60 months. The original project was approved by the INCA Research Ethics Committees (under number 154/14) and by the National School of Public Health of the Oswaldo Cruz Foundation (under protocol 836,278).

The identification of T1N0M0 and T2N0M0 clinical staging was based on the Hospital Cancer Registry (HCR). The patients' physical and electronic medical records were obtained to extract sociodemographic, clinical and lifestyle-related (tobacco and alcohol consumption) data, as well as implemented treatments and outcome variables (disease status and vital status). The case condition and disease characteristics were validated by histopathological reports, which are analyzed at a single central INCA laboratory.

After reviewing medical records and histopathological reports, 590 out of the 1,417 patients were excluded (Figure 1), leaving a total study population of 827 women with tumors of up to 5 cm, negative axilla condition and no distant metastasis.

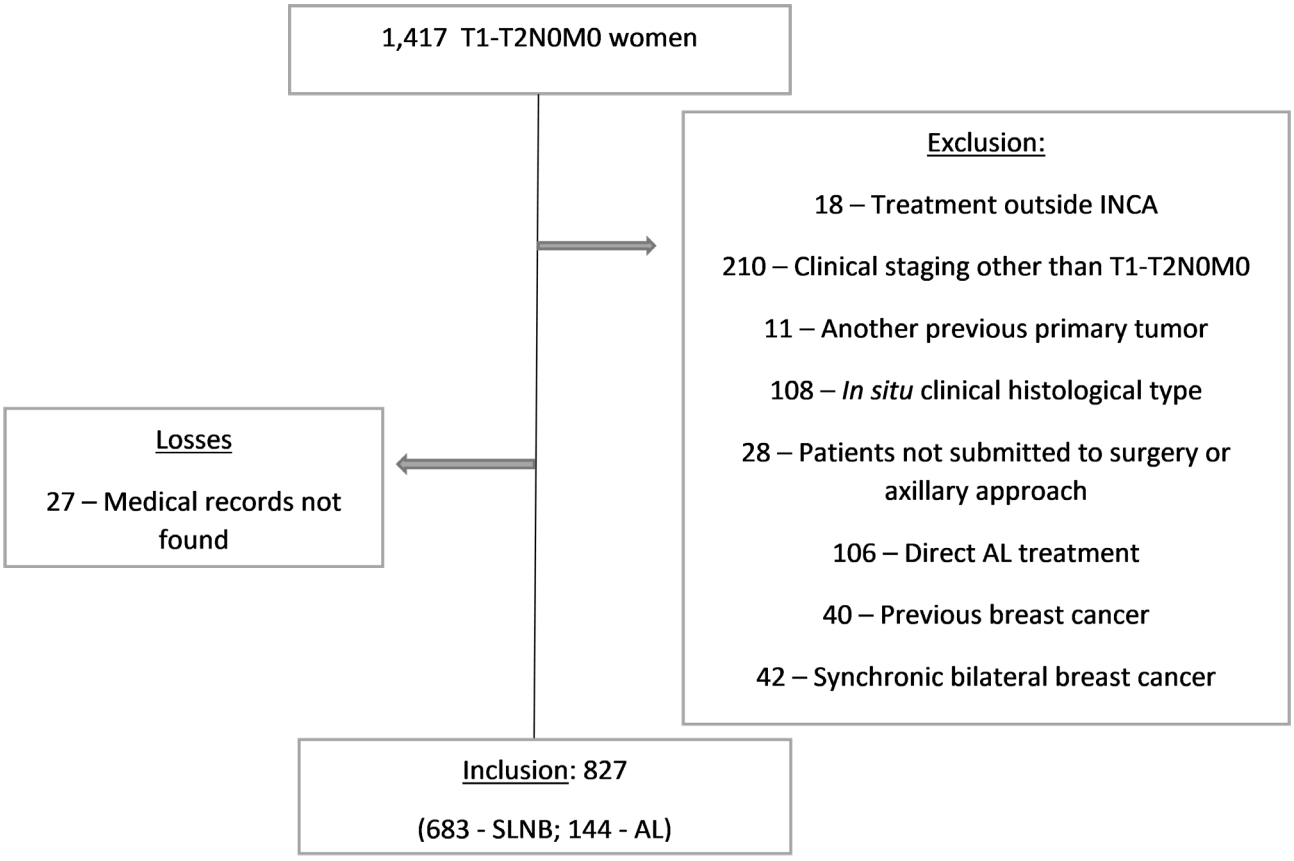
SLNB was defined as the removal of sentinel lymph nodes after identification, for histopathological examination[7]. AL was defined as the resection of at least one of the axillary levels. Lymph node metastases were classified according to the American Cancer Committee as metastases from 0.2 to 2.0 mm, while macrometastases were defined as those over 2.0 mm[17].

Regarding relapse, women with neoplastic cell proliferation in the operated region were considered as failures: skin, plastron, subcutaneous mesh, chest wall, lymphatic chains, and breast tissue in the case of conservative surgery; as well as those on which the disease spread to organs or tissues distant from the original tumor, confirmed by histopathological examination. Women who did not relapse were censored until the end of the study. Patients who were lost to follow-up were censored on the date of the last visit. DFS was characterized as the time elapsed between the date of surgery and the date of relapse diagnosis.

For the OS analysis, deaths from any cause occurring up to the end of 60 months were considered as a failure. Death information (date, cause, location) was obtained from physical medical records (death certificates) and electronic medical records. Women who were alive at the end of the study were censored, while those who were lost during follow-up were censored on the date of the last visit. OS was, then, characterized as the time elapsed between the date of breast cancer diagnosis and the date of death.

A descriptive analysis was performed using central tendency measures, as well as study cohort dispersion and frequency measures. Differences between means were assessed using Student's t-test for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Differences between proportions were evaluated using the Pearson's chi-square (χ^2) test for normally distributed variables and by the Fisher´s exact test for non-normally distributed variables. A significance level of 5% was considered for all assessments.

In addition, OS and DFS were estimated by the Kaplan-Meier analysis according to the axillary surgical approach. Differences between survival curves were assessed using the Log-rank test: 95%. The crude and adjusted relapse and death hazards ratios (HR), with their respective 95% confidence intervals (95%CI), were estimated using Cox proportional hazard regression analysis. Criteria for including variables in the final models were the statistical significance in the crude analyses (p-value≤0.20) and



SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; INCA: Brazilian National Cancer Institute.
Figure 1. Study sample selection flow.

biological importance; while for the model output, a significance level greater than 0.05 was considered. The fact that there were only 33 deaths limited the number of variables that could be used in a multivariate model without impacting model stability. Aiming to meet the criterion of a minimum number of failures in each axillary approach stratum for statistical modeling, a severity score was developed, consisting of six factors (0 to 6) for death outcome. This score included variables with statistically different distributions between the SLNB and SLNB+AL groups attributing weight to each variable category according to death risk, such as age (<40 years=0; 40–59 years=1; ≥60 years=2), clinical staging (T1N0M0=0; T2N0M0=1), histopathological grade (grade-1=0; grade-2=1; grade-3=2), and histopathological lymph node status (no metastasis=0; with metastasis=1). The total score was classified into three categories based on the mean, median and interquartile ranges. Thus, individuals who had a total severity score from 0 to 1 had characteristics that represented the lowest risk for death outcome, participants with scores from 2 to 4 had characteristics that conferred moderate risks of death, and those with scores from 5 to 6 had higher risks for death outcome.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) IBM software, version 20.0 for Windows.

RESULTS

The mean age of the women included in the study was 57 years old (±12.2). Most participants (65.7%) displayed clinical staging I (T1N0M0), 68.5% had tumors ≤2 cm, 40.1% presented histological grade 2, and 16.4% of the patients underwent removal of over 10 lymph nodes (Table 1). Regarding the axillary approach, 82.6% of women underwent just SLNB and 17.4% underwent SLNB+AL. Among the patients who underwent SLNB (n=683), most of them (61.9%) underwent conservative surgery, did not undergo chemotherapy (55.8%) but hormonal therapy (78%). Among those who underwent SLNB+AL (n=144), most underwent chemotherapy (80.6%), did mastectomy (57.6%), took hormonal therapy (86.8%), and presented distant recurrence (7.6%) (Table 1).

In patients who underwent SLNB alone, only two lymph nodes (±1.19) were removed on average, while those who underwent SLNB+AL removed an average of 17.8 lymph nodes (±5.35). No lymph node metastasis was observed in 699 (84.5%) patients, and 97.5% of these received only SLNB. In patients presenting lymph node metastasis (n=128), 2.5% underwent only SLNB, while 77.1% underwent SLNB+AL (Table 1). The median follow-up for both death and relapse in the cohort was of 60 months for both SLNB and SLNB+AL patients (Table 2). During this period, there were 33 deaths (SLNB: 24; SLNB+AL: 9) and 52 cases of relapse (SLNB: 40; SLNB+AL: 12).

Table 1. Distribution of sociodemographic and clinicopathologic status and treatment characteristics, according to axillary approach of the cohort of 827 women with breast cancer, treated at the Brazilian National Cancer Institute (2007–2009).

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Age				
<40	54 (6.5)	41 (6.0)	13 (9.0)	0.049
40–59	426 (51.5)	343 (50.2)	83 (57.6)	
≥60	347 (42.0)	299 (43.8)	48 (33.3)	
Skin color				
Non-White	267 (32.3)	229 (33.5)	38 (26.4)	0.096
White	560 (67.7)	454 (66.5)	106 (73.6)	
Marital status				
With a partner	431 (52.1)	346 (50.7)	85 (59.0)	0.068
No partner	396 (47.9)	337 (49.3)	59 (41.0)	
Schooling				
<8 years	350 (42.4)	296 (43.3)	54 (37.8)	0.220
≥8 years	476 (57.6)	387 (56.7)	89(62.2)	
Occupation				
Unemployed	32 (3.9)	28 (4.1)	4 (2.8)	0.482
External job	372 (45.3)	301 (44.5)	71 (49.3)	
At home	417 (50.8)	348 (51.4)	69 (47.9)	
Alcoholism				
No	597 (73.0)	487 (72.1)	110 (76.9)	0.243
Yes	221 (27.0)	188 (27.9)	33 (23.1)	
Smoking				
No	562 (68.2)	467 (68.6)	95 (66.4)	0.617
Yes	262 (31.8)	214 (31.4)	48 (33.6)	
BMI				
Low weight	35 (4.2)	30 (4.4)	5 (3.5)	0.583
Suitable weight	227 (27.4)	193 (28.3)	34 (23.6)	
Overweight	297 (35.9)	244 (35.7)	53 (36.8)	
Obesity	268 (32.4)	216 (31.6)	52 (36.1)	
Clinical staging				
T1N0M0 (I)	543 (65.7)	478 (70.0)	65 (45.1)	0.000
T2N0M0 (IIA)	284 (34.3)	205 (30.0)	79 (54.9)	
Tumor size				
T1	566 (68.5)	495 (72.6)	71 (49.3)	0.000
T2	253 (30.6)	184 (27.0)	69 (47.9)	
T3	7 (0.8)	3 (0.4)	4 (2.8)	
Histological type				
Lobular Invasive	52 (6.3)	40 (5.9)	12 (8.3)	0.249
Ductal Invasive	713 (86.2)	588 (86.1)	125 (86.8)	
Others	62 (7.5)	55 (8.1)	7 (4.9)	
Histological grade				
1	166 (22.7)	145 (24.2)	21 (16.0)	0.038
2	293 (40.1)	243 (40.6)	50 (38.2)	
3	271 (37.1)	211 (35.2)	60 (45.8)	
Number of lymph nodes removed				
1–3	619 (74.8)	619 (90.6)	0 (0.0)	0.000
4–10	72 (8.7)	64 (9.4)	8 (5.6)	
>10	136(16.4)	0 (0.0)	136 (94.4)	
Lymph node status				
No metastasis				
With metastasis				

Continue...

Table 1. Continuation.

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Sentinel lymph node metastasis				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
Micrometastasis	41 (5.0)	17 (2.5)	24 (16.7)	
Macrometastasis	87 (10.5)	0 (0.0)	87 (60.4)	
Status HER2[b]				
Negative	368 (74.8)	295 (75.4)	73 (72.3)	0.366
Positive	70 (14.2)	57 (14.6)	13 (12.9)	
Indeterminate	54 (11.0)	39 (10.0)	15 (14.9)	
Hormonal receptor				
Positive	694 (84.7)	564 (83.6)	130 (90.3)	0.042
Negative	125 (15.3)	111 (16.4)	14 (9.7)	
Triple negative[b]				
No	436 (90.8)	343 (89.8)	93 (94.9)	0.118
Yes	44 (9.2)	39 (10.2)	5 (5.1)	
Other primary cancer				
No	812 (98.2)	672 (98.4)	140 (97.2)	0.340
Yes	15 (1.8)	11 (1.6)	4 (2.8)	
Death				
No	794 (96.0)	659 (96.5)	135 (93.8)	0.127
Yes	33 (4.0)	24 (3.5)	9 (6.2)	
Lymph node status				
No metastasis	699 (84,5)	666 (97,5)	33 (22,9)	0,000
With metastasis	128(15,5)	17 (2,5)	111 (77,1)	
Locoregional recurrence				
No	808 (97.7)	665 (97.4)	143 (99.3)	0.158
Yes	19 (2.3)	18 (2.6)	1 (0.7)	
Distance recurrence				
No	790 (95.5)	657 (96.2)	133 (92.4)	0.043
Yes	37 (4.5)	26 (3.8)	11 (7.6)	
Breast surgery				
Conservative	484 (58.5)	423 (61.9)	61 (42.4)	0.000
Mastectomy	343 (41.5)	260 (38.1)	83 (57.6)	
Breast reconstruction				
No	681 (82.3)	557 (81.6)	124 (86.1)	0.192
Yes	146 (17.7)	126 (18.4)	20 (13.9)	
Chemotherapy				
No	409 (49.5)	381 (55.8)	28 (19.4)	0.000
Yes	418 (50.5)	302 (44.2)	116 (80.6)	
Radiotherapy				
No	328 (39.7)	265 (38.8)	63 (43.8)	0.270
Yes	499 (60.3)	418 (61.2)	81 (56.2)	
Hormonal therapy				
No	169 (20.4)	150 (22.0)	19 (13.2)	0.018
Yes	658 (79.6)	533 (78.0)	125 (86.8)	
Target therapy				
No	790 (95.5)	655 (95.9)	135 (93.8)	0.257
Yes	37 (4.5)	28 (4.1)	9 (6.2)	
Severity score[c]				
0–1	78 (9.4)	78 (11.4)	0 (0.0)	0.000
2–4	675 (81.6)	573 (83.9)	102 (70.8)	
5–6	74 (8.9)	32 (4.7)	42 (29.2)	

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; HER2: human epidermal growth factor receptor 2; χ^2: Pearson's χ^2 test; Non-white: black, brown. *The total value may change due to missing values. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy. [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests. [c]Severity score includes age, clinical staging, histological grade, and lymph node status.

Table 2. Follow-up time (death and recurrence), according to the axillary approach, of the cohort of 827 women with breast cancer treated at the Brazilian National Cancer Institute (2007–2009).

	Total	Axillary surgery	
		SLNB	SLNB+AL[a]
Follow-up time until death			
Mean (SD) n (%)	56.66 (9.93)	56.77 (9.61)	56.18 (11.33)
Median (months)	60.00	60.00	60.00
Minimum–Maximum (months)	1.7–60.0	1.7–60.0	6.8–60.0
Follow-up time until recurrence			
Mean (SD) n (%)	54.86 (12.17)	54.98 (11.82)	54.29 (13.72)
Median (months)	60.00	60.00	60.00
Minimum-Maximum (months)	0.8–60.0	0.8–60.0	2.1–60.0

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; SD: standard deviation. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy.

Among patients presenting only sentinel lymph node micrometastasis, it was observed higher survival rate in those undergoing SLNB alone (OS: 93.3%; DFS: 100%) compared to those who underwent SLNB+AL (OS=87.5%; DFS=90.7%), albeit without any statistical significance. All patients with sentinel node macrometastasis underwent AL after SLNB, hindering comparisons (Table 3).

The risk of relapse in women undergoing SLNB was not statistically different from those undergoing SLNB+AL (Figure 2). Disease-free 5-year survival did not differ significantly between the two approaches (SLNB: 93.7%; SLNB+AL: 91.2%; Log-Rank p=0.264). Thus, estimated risk of crude relapse (HR 0.69; 95%CI 0.36–1.32) and adjusted relapse (HR 0.78; 95%CI 0.39–1.48) comparing SLNB with SLNB+AL were not statistically significant, even when adjusted for age, clinical staging, grade, and hormone therapy (Figure 2).

Overall 5-year survival was 96.2% in SLNB and 93.6% in SLNB+AL patients (Log-Rank p=0.131) (Table 3). The crude HR of death between SLNB and SLNB+AL group was of 0.56 (95%CI 0.26–1.20; p=0.136). The severity score-adjusted death risk analysis, which included age, clinical staging, histopathological grade, and histopathological lymph node status, for the SLNB group compared to the SLNB+AL group was 0.98 (95%CI 0.42–2.29) (Figure 3).

DISCUSSION

Changes in breast cancer presentation and treatment, as well as the selection of systemic treatment based on tumor biology, have raised questions about the need for AL in some patients presenting sentinel node metastasis. Currently, the biology of breast cancer is much better understood than it was when AL was introduced. It has since been recognized that breast cancer biology, rather than the extent of surgery, is a major determinant of both systemic and locoregional metastasis risk, paving the way for new surgical approaches such as SLNB[18].

This study evaluated 827 women with clinical stage T1-T2N0M0 breast cancer who underwent SLNB and SLNB+AL, and no statistically significant differences were found after 60 months in the OS or DFS of women who underwent SLNB when compared to those who underwent SLNB+AL. Similar results were reported by Canavese et al.[19] in a randomized clinical trial conducted at the National Cancer Research Institute of Italy (Genoa, Italy), where the non-inferiority of SLNB relative to AL was noted for 2,570 patients with early breast cancer staging (<3 cm). The authors observed that the 5-year OS for both groups was of 97.2% (Log-Rank p=0.697). DFS was also not statistically different between SLNB and AL groups (AL: 89.8%; SLNB: 94.5%; Log-Rank p=0.715).

The benefits of SLNB on survival and postoperative complications in early stage breast cancer patients (T1-T2N0M0), including accuracy in predicting axillary status, have been demonstrated in several studies over time[14,15,19-22]. Based on the results, a negative SLNB outcome in these patients is considered sufficient to rule out the possibility of metastasis in other axillary lymph nodes and to prevent future AL, reducing short-term morbidity and improving quality of life[4,23,24]. However, information on the long-term effects of SLNB compared to routine AL is still considered limited.

On the other hand, an indication of AL has always been considered safe, as it removes all axilla disease, promoting greater locoregional control and providing important information for systemic and prognostic therapy. Nonetheless, this approach is associated with complications such as pain, reduced motion range, paresthesia, axillary web syndrome, winged scapula, and lymphedema[25,26]. Thus, SLNB has been rapidly integrated, as it avoids AL in a large number of patients with early breast cancer staging, while also providing important information to guide adjuvant treatment.

Randomized controlled trials have compared OS and DFS among patients who underwent SLNB or SLNB+AL approach in the presence of negative sentinel lymph nodes. The results of these studies showed no negative effect on OS and DFS for the

Table 3. Overall survival and crude hazard ratio according to sociodemographic, clinicopathologic and treatment characteristics in the cohort of 827 women with breast cancer treated at the Brazilian National Cancer Institute (2007–2009).

Overall (n=827)	Death n (%)	Overall Survival (%)			Crude HR (95%CI)
		SLNB	SLNB+AL[a]	LR p-value	
	33	96.2	93.6	0.131	
Age					
<40	2 (6.1)	97.4	92.3	0.396	1 (Ref.)
40–59	18 (54.5)	95.4	96.3	0.765	1.11 (0.26–4.77)
≥60	13 (39.4)	97.0	89.4	0.008	1.04 (0.23–4.62)
Skin color					
Non-White	12 (36.4)	95.3	94.4	0.721	1 (Ref.)
White	21 (63.6)	96.7	93.4	0.101	0.83 (0.41–1.69)
Marital status					
with a partner	18 (54.5)	95.7	95.2	0.783	1 (Ref.)
No partner	15 (45.5)	96.7	91.4	0.045	0.92 (0.46–1.82)
Schooling					
<8 years	16 (48.5)	95.6	92.4	0.264	1 (Ref.)
≥8 years	17 (51.5)	96.7	94.3	0.262	0.77 (0.39–1.52)
Occupation					
Unemployed	3 (9.5)	87.1	100.0	0.463	1 (Ref.)
External job	13 (39.4)	96.5	95.7	0.715	0.36 (0.10–1.27)
At home	17 (51.5)	96.6	91.2	0.032	0.44 (0.13–1.49)
Alcoholism					
No	19 (57.6)	97.2	94.5	0.137	1 (Ref.)
Yes	14 (42.4)	93.6	90.6	0.436	2.00 (1.00–3.99)
Smoking					
No	24 (72.7)	96.1	92.5	0.103	1 (Ref.)
Yes	9 (27.3)	96.4	95.7	0.761	0.80 (0.37–1.71)
BMI					
Low weight+Suitable weight	8 (24.2)	97.0	94.6	0.413	1 (Ref.)
Overweight+Obesity	25 (75.8)	95.8	93.3	0.220	1.41 (0.63–3.12)
Clinical staging					
T1N0M0 (I)	11 (33.3)	97.5	100.0	0.212	1 (Ref.)
T2N0M0 (IIA)	22 (66.7)	93.2	88.4	0.144	3.89 (1.89–8.03)
Tumor size					
T1 (≤2 cm)	14 (42.4)	97.2	98.6	0.518	1 (Ref.)
T2-T3 (>2–7,5cm)	19 (57.6)	93.5	88.7	0.139	3.00 (1.51–6.00)
Lymph node status					
No metastasis	26 (78.8)	96.3	90.5	0.073	1 (Ref.)
With metastasis	8 (21.2)	93.3	94.5	0.932	1.45 (0.63–3.33)
Sentinel lymph node metastasis					
No metastasis	26 (78.8)	96.3	90.5	0.073	1 (Ref.)
Micrometastasis	4 (12.1)	93.3	87.5	0.485	2.66 (0.93–7.63)
Macrometastasis	3 (9.1)	–	96.5	–	0.90 (0.27–2.97)
Number lymph nodes removed					
1–3	23 (69.7)	96.0	–	–	1 (Ref.)
4–10	2 (6.1)	98.4	87.5	0.075	0.75 (0.18-3.20)
>10	8 (24.2)	–	94.0	–	1.59 (0.71-3.56)
Histological grade					
1	1 (3.1)	100	95.2	0.011	1 (Ref.)
2–3	31 (96.9)	94.6	92.6	0.338	9.12 (1.24–66.81)

Continue...

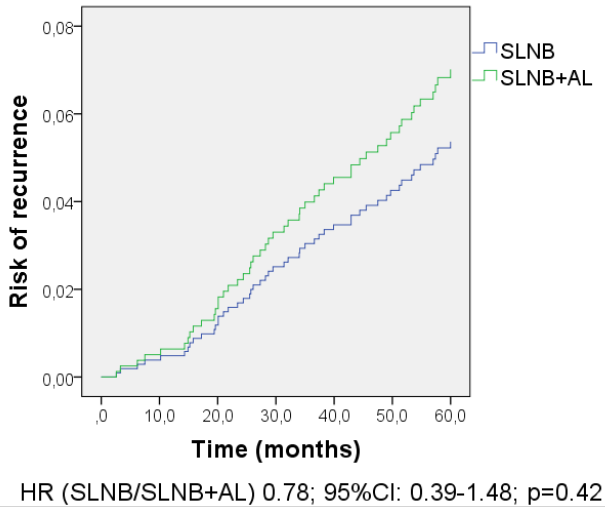
Table 3. Continuation.

Overall (n=827)	Death n (%)	Overall Survival (%)			Crude HR (95%CI)
		SLNB	SLNB+AL[a]	LR p-value	
	33	96.2	93.6	0.131	
Status HER2[b]					
Negative	14 (70.0)	96.8	93.0	0.117	1 (Ref.)
Positive	1 (5.0)	98.1	100	0.617	0.36 (0.05–2.76)
Indeterminate	5 (25.0)	85.4	100.0	0.138	2.61 (0.94–7.24)
Triple negative[b]					
No	18 (94.7)	96.0	94.6	0.497	1 (Ref.)
Yes	1 (5.3)	96.7	100.0	0.796	0.60 (0.08–4.51)
Hormonal receptor					
Positive	27 (81.8)	96.2	94.5	0.346	1 (Ref.)
Negative	6 (18.2)	96.0	84.6	0.049	1.28 (0.53–3.09)
Breast surgery					
Conservative	15 (45.5)	96.4	98.3	0.460	1 (Ref.)
Mastectomy	18 (54.5)	95.9	90.1	0.035	1.69 (0.85–3.36)
Histological type					
Lobular Invasive	1 (3,0)	97,4	100,0	0,591	1
Ductal Invasive	31 (93,9)	96,0	92,6	0,084	2,33 (0,32-17,10)
Others	1 (3,0)	98,0	100,0	0,708	0,89 (0,05-14,16)
Hormonal therapy					
No	10 (30.3)	96.2	72.7	0.000	1 (Ref.)
Yes	23 (69.7)	96.2	96.7	0.825	0.53 (0.25–1.11)
Chemotherapy					
No	13 (39.4)	96.8	92.9	0.225	1 (Ref.)
Yes	20 (60.6)	95.5	93.8	0.427	1.44 (0.72–2.89)
Radiotherapy					
No	16 (48.5)	96.4	88.8	0.011	1 (Ref.)
Yes	17 (51.5)	96.1	97.4	0.603	0.69 (0.35–1.36)
Target therapy					
No	33 (100)	96.0	93.2	0.114	1 (Ref.)
Yes	0 (0.0)	100.0	100.0	–	0.05 (0.00–54.54)
Other primary					
No	29 (87.9)	96.6	94.2	0.139	1 (Ref.)
Yes	4 (12.1)	72.7	75.0	0.964	8.16 (2.87–23.21)
Recurrence					
No	11 (33.3)	98.7	97.7	0.371	1 (Ref.)
Yes	22 (66.7)	55.2	50.0	0.445	37.43(18.10-77.40)
Severity score[c]					
0–1	1 (3.0)	98.7	-	-	1 (Ref.)
2–4	22 (66.7)	96.2	98.0	0.395	2. 60 (0.35–19.26)
5–6	10 (30.3)	90.0	82.9	0.329	11.79 (1.51–92.15)

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; Non-white: black, brown; LR: log-rank; HR: hazard ratio; 95%CI: confidence interval 95%. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy; [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests; [c]Severity score includes age, clinical staging, histological grade and lymph node status.

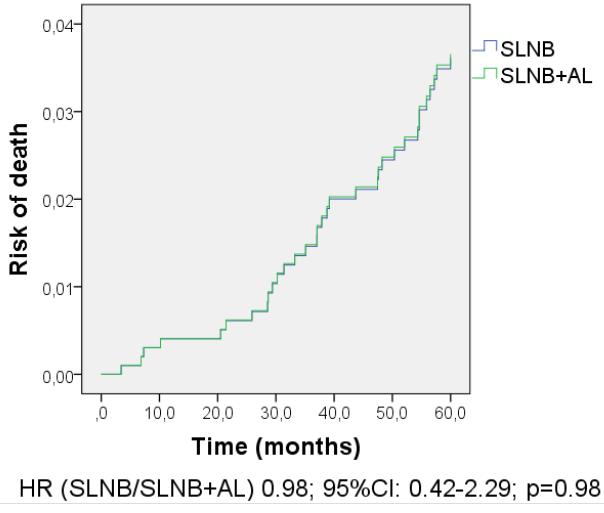
SLNB technique when compared to AL[6,19,26-28]. Two meta-analyses, which included all major randomized controlled trials evaluating the efficacy of SLNB in metastasis-free axilla (pN0), further reinforced the favorable effect of SLNB on survival and postoperative morbidity[29,30]. Thus, the results of this study corroborate previous studies, as it was observed no significant difference in overall and disease-free survival among patients who did not present lymph node metastasis (SLNB: 96.3; SLNB+AL: 90,7; p=0.073).

Although one of the inclusion criteria in this study was initial breast cancer staging (T1-T2N0M0) after the axillary approach, patients with lymph node involvement (micrometastasis: 41; macrometastasis: 87) were detected in the final histopathological examination. Of the women who presented micrometastasis, 17 underwent SLNB and 24 underwent SLNB+AL. On the other hand, all patients with macrometastasis received AL after SLNB. The OS among the 41 patients presenting micrometastasis was higher in those who underwent SLNB (93.3%) compared to those who underwent SLNB+AL (87.5%), but with no statistical significance (Log-Rank p=0.485). Similarly, no statistically significant differences in DFS were observed between both approaches (SLNB: 100%; SLNB+AL: 90.7%; Log-Rank p=0.241). These results corroborate previous studies, which reported that AL can be safely avoided in women with early breast cancer with sentinel lymph node micrometastasis[14,15,31]. The results of our study are worth considering (even though it is an observational research) since the multicenter clinical trials that compared the two types of approach in patients with micrometastasis did not include Brazilian or Latin American treatment centers.



SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; HR: hazard ratio; 95%CI: confidence interval 95%.

Figure 2. Adjusted hazard ratio model for recurrence according to axillary surgery approach (adjusted by age, clinical stage, grade, and hormonal therapy).



SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; HR: hazard ratio; 95%CI: confidence interval 95%.

Figure 3. Adjusted hazard ratio model for death according to axillary surgery approach (adjusted by severity score–age, clinical stage, grade, and lymph node status).

Several studies have shown that approximately 34.3% to 85.7% of patients with sentinel lymph node metastasis will not present additional nodal disease[32]. In the presence of micrometastasis or isolated tumor cells, the risk of additional lymph node involvement is even lower, of 20% and 12%, respectively[33,34]. Due to these findings, the performance of AL, even in the presence of positive sentinel nodes, becomes questionable, since most of them will not have additional nodal load.

According to the results obtained in this study, it was observed no significant difference among women undergoing SLNB and SLNB+AL concerning the frequency of locoregional recurrence. A low survival rate was observed in the OS analysis of patients who presented some type of relapse, but there was no significant difference between both axillary approaches (SLNB: 55.2%; SLNB+AL 50%; Log-rank p=0.445). Two large retrospective studies[35,36] observed no negative impact on OS and on axillary recurrence, even without AL, in the presence of positive sentinel lymph nodes.

The absence of significant differences between OS and DFS among the approaches observed in this study was confirmed by the analysis of gross and adjusted risks of death (crude HR 0.56; 95%CI 0.26–1.20; adjusted HR 0.98; 95%CI 0.42–2.29) and for relapse (crude HR 0.69; 95%CI 0.36–1.32; adjusted HR 0.78; 95%CI 0.39–1.48), indicating a lower risk for SLNB, but without statistical significance. These results corroborate the findings of two main randomized controlled trials that also compared the performance of SLNB and AL in patients with early staging and limited axillary disease. The American College of Surgeons Oncology Group (ACOSOG) Z0011 study concerning T1 and T2 patients who underwent conservative surgery, with one or two positive lymph nodes, observed an overall 5-year survival of 91.8% in the AL group and 92.5% in SLNB patients. Similarly, disease-free 5-year survival was of 82.2% in the AL group and 83.9% in those who underwent only SLNB. Regional recurrence was also

similar in both groups (AL: 0.5%; SLNB: 0.9%). The risk of death was similar for both approaches, even after age and adjuvant therapy adjustment (HR=0.87; 95%CI 0.62–1.23).) Also, the risk of recurrence was not statistically different between the axillary approaches, even after adjustment for age and adjuvant treatment (HR 0.88; 95%CI 0.62–1.25)[14]. Another clinical trial conducted by the International Breast Cancer Study Group (IBCSG), after an average follow-up of 5 years, also observed that AL could be safely omitted in patients with lymph node micrometastasis, with no inferiority compared to the SLNB technique[15].

Since the confirmation of non-inferiority of SLNB over AL, the conservative approach has been incorporated into the daily practice of cancer treatment centers, as breast surgeons' experience and confidence in the SLNB approach has increased[37-39]. A Dutch study assessing surgeon practice standards regarding SLNB and AL from January 1993 to July 2014 found that the number of patients undergoing SLNB without AL increased from 0% in 1993-1994 to 69% in 2013-2014. In the same period, the number of patients undergoing AL decreased from 88.8% to 18.7%[40].

One of the limitations of the present study includes such as those inherent to retrospective studies. Data collection based on medical records may introduce limitations concerning the quality of the data obtained from routine appointments. Another limitation is related to the small number of patients with micrometastasis in this sample, which does not allow for adjusted analyses concerning the effect of SLNB on death and relapse risks. Thus, further studies with a larger number of patients presenting micrometastasis are required. Finally, another limitation is the small number of death outcomes in the 5-year follow-up period, which limits the analysis of the independent effect of each of the variables such as age, clinical stage, histopathological degree and lymph node involvement. However, this limitation was addressed through the creation of the "severity score" variable, which was a combination of the effect of these variables. This strategy allowed the combined effect of these variables to be evaluated, without promoting overfitting of the model.

Nevertheless, this study comprises a high number of patients with T1-T2N0M0 staging, with a complete 60-month follow-up of almost 90% of the cohort, in favor of the consistency of our findings, so that estimates would not be distorted by selection biases. In addition, as these data are from the same institution, all procedures followed a standardized protocol and were less subject to professional conduct variations. Another important point of this study is that it presents the results of developing countries. As most of the studies that evaluated AL and lymph node micrometastases in the survival of women with breast cancer have been conducted in developed countries and they do not allow for results extrapolation to developing countries, this further reinforces the importance of this study.

Findings reported herein indicate that the axillary approach using the SLNB method is equivalent to AL for OS and DFS after five years, regardless of the adjustment variables.

In addition, no statistically significant differences in OS and DFS were observed after 60 months in women with axillary lymph node micrometastasis undergoing SLNB compared to those undergoing SLNB+AL. Due to the small number of micrometastasis cases observed in this study, further research, with larger sample sizes, are required to evaluate the non-inferiority of SLNB compared to AL in the overall DFS of patients with T1-T2N0M0 breast cancer.

AUTHORS' CONTRIBUTIONS

FOM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AB: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. RJK: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. DMT: Validation, Visualization, Writing – original draft, Writing – review & editing. EANF: Conceptualization, Investigation, Methodology, Writing – review & editing. RMC: Conceptualization, Investigation, Methodology, Writing – review & editing. FOF: Conceptualization, Investigation, Methodology, Writing – review & editing. IFS: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing

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ORIGINAL ARTICLE
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Germline genetic mutations in high-risk patients for breast cancer: profile of a group in the city of Florianopolis, Santa Catarina

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ABSTRACT

Introduction: To analyze the occurrence of genetic mutations in a sample of patients with high risk of breast cancer in Florianopolis/SC from December 1st, 2021, to January 31, 2022. **Methods:** An observational, descriptive and retrospective study carried out through data collection of a preexisting database. A total of 194 tests were analyzed. Of these, 192 met the inclusion criteria and composed the final sample of 205 genes. Data were classified and reported the frequency and percentage of the variables: gene and presence or absence of mutation. **Results:** Mean age of the analyzed patients was 52.3 years, and most underwent the test due to personal history of breast cancer (80%). Clinical significance classification showed that, of the 192 gene panels, 62% were variants of uncertain significance; 14% were pathogenic; and 24%, negative. Of the 205 mutations, the most prevalent genes were: *ATM* 8.7%, *MUTYH* 5.8%, *POLE* 5.8%, *BRCA2* 4.8%, *MSH6* 4.8% and *RECQL4* 4.8%. Of the pathogenic tests regarding genetic predisposition to cancer (n=38/14.1%), the most common mutations were *MUTYH* (23%) and *BRCA1* (15%), with mean age of 52 years (±14.3). In variants of uncertain significance panels (n=168/62%) the frequency rates were ATM (7.7%), *POLE* (7.1%) and *MSH6* (5.9%) genes. The high penetrance genes were present in 18% of the genetic predisposition to cancer panels. Of those with positive family history (n=40), 19% of the genes were pathogenic, 53% were variants of uncertain significance; and 26% were negative. Furthermore, in patients with pathogenic mutations and positive family history (n=11), the most common mutations were in *BRCA1* (27%) and *BRCA2* (27%). Of the patients who tested due to personal history (n=152), 64% of the genes presented variants of uncertain significance, 13% were pathogenic and 22% were negative. **Conclusion:** The results are consistent with those described in the literature, drawing attention to the frequency of genetic predisposition to cancer panels with variants of uncertain significance .

KEYWORDS: breast cancer; *BRCA1* protein; hereditary breast and ovarian cancer syndrome; gene expression; descriptive epidemiology.

INTRODUCTION

Breast cancer is the second most common malignant neoplasm among women in Brazil and around the world, losing only to non-melanoma skin cancer[1]. Even though it occurs mainly after the age of 50, in the past few years its incidence in younger age groups has been observed all over the world[2]. In Brazil, the highest rate of new cases of breast cancer is in the South and Southeast regions[3].

The incidence of malignant breast neoplasms presents a direct relationship with some risk factors, such as: being older than 50 years; early menarche and/or late menopause; first pregnancy after the age of 30; use of hormone replacement therapy; besides behavioral, environmental, genetic, and hereditary factors[3,4].

Knowing that ethnic differences in the incidence of breast cancer are the result of the interaction between genetic, epigenetic, and epidemiological risk factors, one of the methods related to primary prevention that has been gaining ground is genetic counseling to assess genetic predisposition to cancer[5-7]. Genetic testing aims at identifying germline mutations that lead to the onset of neoplasms at younger ages, when compared to the rest of the population[8-10]. Besides, the mutations found can

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be reclassified according to new discoveries, leading to changes in patient care[11].

In this context, many progresses have been taking place in gene sequencing in order to now the germline mutations associated with increased risk of breast cancer[12,13]. The development of the *Next Generation Sequence* (NGS) technology allowed the expansion of the number of analyzed genes and the inclusion of genes of high and moderate penetrance; 21 of them are associated with hereditary breast cancer[12,13].

Most cases of breast cancer heredity are attributed to germline mutations in high penetrance genes *BRCA1* and *BRCA2*, responsible for the Hereditary Breast and Ovarian Cancer Syndrome[14]. Several studies have identified other high-penetrance genes related to the susceptibility to breast cancer, such as: *TP53, PTEN, STK11* and *CDH1*, responsible for the Li-Fraumeni syndrome, Cowden's syndrome, Peutz-Jeghers syndrome, and hereditary diffuse gastric cancer, respectively[15].

The concept of gene penetrance for the predisposition to cancer refers to the relative risk (RR) of a mutation causing a specific type of cancer. High-penetrance genes are associated to RR higher than 5. On the other hand, the RR of low-penetrance genes is about 1.5[15] (Table 1).

The genetic predisposition to cancer panel can be used for patients who have high risk, both personally and due to their family, to develop breast cancer, being a useful tool to assess these patients[16]. This analysis is carried out more specifically, individualizing the screening process and providing adequate prevention measures for patients and their relatives (cascade testing), which are essential for this management[7].

Considering the clinical relevance related to genetic tests and their great implications in the appropriate care addressed to patients in the long term, it is possible to understand the importance of knowledge related to the theme, discussing profiles and patterns that are not yet determined.

METHODS

This is an observational, descriptive and retrospective study, with qualitative and quantitative approach and collection of secondary data. The study was conducted after the approval of the Research Ethics Committee, protocol 54851321.4.0000.0115.

The data were collected from the database of a private clinic in Florianópolis/SC, of patients who underwent genetic testing between December 1st, 2021, and January 31, 2022.

The study included female patients who underwent the genetic predisposition to cancer panel, with personal and/or family history of breast cancer and excluded male patients and those whose data were missing.

The analyzed variables included age, gene and presence or absence of the mutation. The statistical information was stored in Microsoft Excel tables, version 2017®, for further descriptive analysis.

The clinical variables found in genetic testing were classified according to the International Agency for Research on Cancer (IARC), being divided as benign and probably benign (classes 1 and 2), malignant and probably malignant (classes 4 and 5), and variant of uncertain significance (VUS), which apply to class 3.

The genetic test included DNA analysis through an oncologic panel by the laboratory INVITAE®. This test uses the NGS

Table 1. Main genes related to the onset of hereditary breast cancer regarding their penetrance.

Gene	Neoplasm	RR %
High-penetrance genes		
BRCA1	BC* and ovarian cancer	40–80
BRCA2	BC* and ovarian, prostate and pancreatic cancer	20–85
TP53	BC*, sarcoma, leukemia, brain and lung cancer	56–90
PTEN	BC* and thyroid and endometrial cancer	52
STK11	BC* and ovarian, endometrial, testicular and intestinal cancer	30–54
CDH1	BC* and hereditary gastric and colorectal cancer	30–60
MLH1, MSH2, MSH6 and *PMS2*	BC* and ovarian, endometrial and gastric cancer	15–80
Moderate and low-penetrance genes		
ATM	BC* and ovarian cancer	15–52
CHEK2	BC* and ovarian and pancreatic cancer	20–44
PALB2	BC* and ovarian and colorectal cancer	20–44
BRIP1	BC* and ovarian cancer	Variable
MUTYH	BC* and ovarian, endometrial, thyroid and colorectal cancer	4–100
RAD51D and *RAD51C*	Risk for BC* and ovarian cancer	Variable

*BC: Breast câncer. Fonte: Adapted from PIOMBINO et al.[28]

technique to examine genes related with predisposition to developing several types of cancer. The variants assessed in this study were analyzed according to their type and classified according to their pathogenicity. When the mutation is classified as benign, the test is negative (Table 2).

The collected data were analyzed using the IBM* software, Statistical Package for the Social Sciences (SPSS), version 20.0 and Minitab 16. Statistical tests were performed with α=0,05 significance level, therefore, 95% confidence level. The qualitative variables were expressed through frequency and percentage rates; besides, the existence of an association between them was investigated through the equality of two proportions, followed by a residue analysis, when statistical significance was observed. Age was expressed by mean and standard deviation (SD). The charts were elaborated in Microsoft Excel sheets, version 2010®.

RESULTS

One hundred and ninety-four genetic hereditary cancer panels of patients with personal and/or family history of breast cancer were analyzed. Two patients were excluded, one for being a man, and the other due to incomplete data, resulting in the final sample of 192 genetic hereditary cancer panels, accounting for 205 analyzed genes.

The age of the patients who underwent the test ranged between 26 and 89 years, with mean of 52.3 years (±14.2). Regarding the reason to undergo the test, 80% (n=152) of the patients did it because of personal history of breast cancer, and 20% (n=40) due to positive family history. The collection was performed using the saliva (94%; n=181) and blood samples (6%; n=11).

The classification regarding clinical significance of the 192 genetic panels (IARC classification, modified by the INVITAE laboratory) presented most tests as VUS. The other results are in Figure 1.

Regarding the 205 analyzed mutations, in genetic hereditary panels with pathogenic and VUS results, the most prevalent genes were: *ATM*, *MUTYH*, *POLE*, *BRCA2*, *MSH6, RECQL4* and *APC*, accounting for 80 mutations in only 7 genes (Table 3). The other 188 mutations were found in relation to 53 different genes (Table 3).

Of the 14.1% panels classified as pathogenic, the pathogenic mutation was present in 38 genes, and the frequencies of the presented mutations were *MUTYH* 23%, *BRCA1* 15%, *ATM* 13% and*BRCA2* 13%. Tem other mutations were found according to Figure 2. Mean age of the patients whose genetic panels had clinical and pathogenic significance was 52 years (±14.3).

In 62% of the genetic hereditary panels classified as VUS, 167 genes were analyzed, and those with the highest frequency were *ATM*, *POLE*, *MSH6*, *RECQL4* and *APC*.

Mentioning only high-penetrance genes, these were in 18% of the genetic hereditary panels, distributed as pathogenic and VUS. Mean age of the patients with high-penetrance genes was 52.4 years.

Of the patients with positive Family history (n=40), 56 genes were analyzed in total. Of these, 53% were VUS, 26% were negative, and 19% were pathogenic. Besides, in patients with pathogenic mutations associated with positive family history (n=11), the most common mutations were in *BRCA1* and *BRCA2* (n=3/each) and the others between *ATM* (n=2), *CHEK2, MUTYH* and *RAD51C* (n=1/each). In the 152 patients who got tested because of personal history of breast cancer, 211 genes were analyzed in total, and 64% of them presented with VUS classification; 22% were negative; and 13% were pathogenic.

About the relationship between prior morbid history and variant class, both patients with personal history and those with family history had similar percentage rates in the results of the genetic hereditary testing. However, there was no statistical relationship between the history of the disease and the variant test class (p>0.05), as shown in Table 4.

DISCUSSION

Breast cancer is the second most common malignant neoplasm among women in Brazil and in the world, related to the interaction between genetic, epigenetic and epidemiological risk factors[5,6]. The use of methods associated with primary care and the performance of genetic counseling (genetic hereditary panel) has

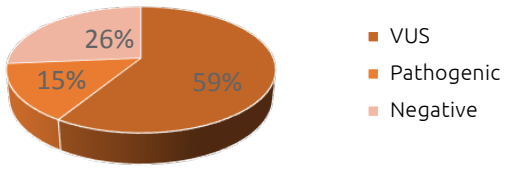

Figure 1. Classification of gene panels with clinical significance.

Table 2. Criterion of classification of variants according to the genetic panel INVITAE®.

Classification	Description
Pathogenic	Variant reported as having clinical pathogenic significance
VUS	Variant reported as having no consensus about clinical significance
Negative	Tests of benign clinical significance, not observing pathogenicity

Table 3. Genes according to classification, penetrance and frequency.

Gene	n	%	Genetic Hereditary classification		Breast penetrance
ATM	18	8.7	Pathogenic	5	**Moderate/Low**
			VUS	13	
MUTYH	12	5.8	Pathogenic	9	**Moderate/Low**
			VUS	3	
POLE	12	5.8	Pathogenic	–	Unrelated
			VUS	12	
BRCA2	10	4.8	Pathogenic	5	**High**
			VUS	5	
MSH6	10	4.8	Pathogenic	–	**High**
			VUS	10	
RECQL4	10	4.8	Pathogenic	1	Unrelated
			VUS	9	
APC	8	3.9	Pathogenic	–	Unrelated
			VUS	8	
BRCA1	7	3.4	Pathogenic	6	**High**
			VUS	1	
DICER1	6	2.9	Pathogenic	–	Unrelated
			VUS	6	
DIS3L2	6	2.9	Pathogenic	–	Unrelated
			VUS	6	
PTCH1	5	2.4	Pathogenic	–	Unrelated
			VUS	5	
CHEK2	5	2.4	Pathogenic	2	**Moderate/Low**
			VUS	3	
ALK	5	2.4	Pathogenic	–	Unrelated
			VUS	5	
NF1	5	2.4	Pathogenic	–	Unrelated
			VUS	5	
WRN	5	2.4	Pathogenic	1	Unrelated
			VUS	4	
AXIN2	4	1.9	Pathogenic	–	Unrelated
			VUS	4	
MET	4	1.9	Pathogenic	–	Unrelated
			VUS	4	
RET	3	1.4	Pathogenic	–	Unrelated
			VUS	3	
TERT	3	1.4	Pathogenic	–	Unrelated
			VUS	3	
MLH1	3	1.4	Pathogenic	–	**High**
			VUS	3	
BRIP1	3	1.4	Pathogenic	–	**Moderate/Low**
			VUS	3	
MEN1	3	1.4	Pathogenic	–	Unrelated
			VUS	3	
PALB2	3	1.4%	Pathogenic	–	Moderate/Low
			VUS	3	
VHL	3	1.4	Pathogenic	2	Unrelated
			VUS	1	
BRIPI1, CDKN2A, EGFR, HOXB13, KIT, NF2, NTHL, STK11, PDGFRA, SMARCA4, PMS2, POLD1, RAD50, RAD51C, RAD51D, TSC2 and BAP1.	2/each	0.9	Pathogenic *RAD51C RAD51D, NTHL e HOXB13*	2 1/each	**High** *STK11* and *PMS2* **Moderate/Low** *RAD51C* and *RAD51D*
			VUS	The others	
RB1, RECCQL4, RUNX, SDHD, SMARCB1, TP53, BARD1, OMS2, CARM, CASR, CDH1, CHECK, FLCN, GPC3, MAX, MITF, MSH2 e MSH3.	1/each	0.48	Pathogenic *MITF, TP53 and CDH1*	1/each	**High** *TP53, MSH2 and CDH1*
			VUS	The others	
TOTAL 205 mutations					

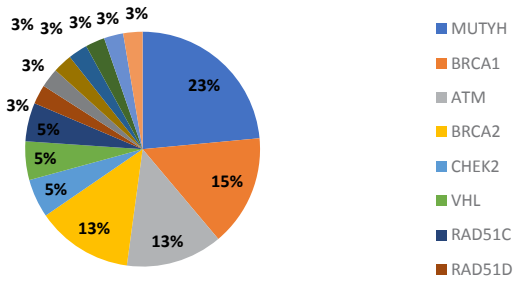

Figure 2. Distribution of pathogenic variants per gene.

Table 4. Relation between personal history and variant class.

	No History		History		Total	
	n	%	n	%	n	%
Negative	16	28.1	95	26.3	111	26.6
Pathogenic	11	19.3	51	14.1	62	14.8
VUS	30	52.6	215	59.6	245	58.6

p-value=0.510

been approached[7]. Genetic testing can identify mutations that enable the onset of some tumors[8,9].

The data obtained in our sample demonstrated women, mean age of 52 years. Most underwent the test due to personal (80%) and/or family history (26.3%). Similarly to our data, studies show that the mean age to undergo the test is around 50 years, and that 30-35% of the patients who take the genetic panel present with positive family history of breast cancer[7,13,17]. In the literature, a slightly lower percentage is observed in the search for testing due to personal history in comparison to our data[11]. This might be justified because the database belonged to a private clinic, where this test would be more likely to take place, and due to the higher prevalence of breast cancer after the age of 50 years.

The variants found in genetic hereditary panels are classified according to clinical significance[16]. Data in the literature show that VUS is present in about 40% of the examinations, which is similar to our data, in which 62% of the tests were classified as VUS[12]. Several approaches have been used to determine the pathogenicity of VUS, including frequency in healthy controls, lack of co-occurrence with pathogenic mutations, analysis of amino acid conservation and severity of the changes found[16]. However, nowadays, the best option in these results has been counseling according to Family history[12].

The presence of 14.1% of the genetic hereditary panels classified as pathogenic is similar to the proportion found in current publications[17,18]. Mean age of these patients was 52 years; however, the literature shows a younger age group with tests and the same outcome, mean of 40.7 years[19]. There is a possibility that such a discrepancy was found because the patients analyzed in the literature presented with breast cancer itself, not considering those with family history only. In the research data, 26.3% did not take the test because of family history, which increased our mean age. Besides, most guidelines recommend testing when the neoplasm occurs before the age of 50[19].

It is known that about 3.6% of the patients with high-penetrance genes present with tests with clinical and pathogenic significance, similar to the 5.8% found in this study[15]. The mean age of patients with high-penetrance genes was 52.4 years, which is expected, because breast cancer patients aged more than 60 years have lower frequency of mutations in high-penetrance genes[20].

The knowledge about some mutations found in the genetic panel has become popular, as was the case of the mutations in genes *BRCA1* e *BRCA2*[8]. Like in other studies, positive family history associated with pathogenic genetic panels characterizes 5.7% of the sample[15]. Mutations in genes *BRCA1* and *BRCA2* are responsible for most cases of early onset of breast cancer. Germline mutations in these two genes explain approximately 25% of the family breast cancer cases[17,18]. The risk that carriers of the gene BRCA have of developing breast cancer throughout their lives is of approximately 70%[8].

ATM is a highly susceptible gene for breast cancer (moderate penetrance), and it means three times more chances of developing the pathology[20]. Mutations in this gene are responsible for approximately half of the mutations identified in the tested patients when we disregard genes *BRCA1* and *BRCA2*[21]. In the current study, most mutations with clinical and pathogenic significance were found in the *ATM* gene, 8.7%. By not considering the pathogenic mutations coming from *BRCA1/2*, in this same study, changes in the ATM gene refer to 10% of the sample.

Breast cancer has been reported in families with syndromes of genetic hereditary panel for colorectal cancer, including Lynch syndrome and intestinal polyposis[22]. However, the mutation in the *MUTHY* gene is associated with low penetrance related to breast cancer[23]. In this study, 5.8% of all of the analyzed variants presented with a mutation in the *MUTHY* gene, and 75% of them, its majority, with clinical and pathogenic significance. Deletion in genes *MLH1*, *MSH2*, *MSH6* and *PMS2* is also associated with increased risk of this cancer and other syndromes. Mutation in *MSH6,* high-penetrance gene for breast cancer, was present in 4.8% of the results of genetic hereditary cancer panels. These data are different from those found in studies published recently, and this discrepancy cannot be explained based on our approach[24,25].

Many genes are associated with the predisposition to malignant breast neoplasm, such as *CHEK2* and *TP53*, which occur in about 0.6%–6% of genetic tests of patients with breast cancer[26,27]. This study showed mutations in these genes, present in up to 2.4% of the sample. Evidence shows that these variants with mutations offer a high risk for breast cancer, ranging from 4%–60% throughout life[9].

Three mutations were found in *BRIP1* genes, all classified as VUS. The variant was described in many studies that assessed

the gene as being susceptible to the development of breast cancer. However, it is observed that in families with mutations in the *BRIP1* gene and several cases of breast cancer, it is a low-penetrance gene due to the incomplete segregation of the mutation[28].

Mutations in the *PALB2* are important causes of hereditary breast cancer[20]. The data in a study published in 2014 by Antoniou AC et al. suggest that the risk of breast cancer for carriers of mutation in *PALB2* may overlap the risk for carriers of the mutation in *BRCA2*[29]. In a study by Fasching et al., which analyzed 2,595 patients with a total of 425 mutations, it was observed that the most common genetic mutations were found in genes *BRCA1/2,* besides 1.1% in *PALB2*[20]. In this study, the mutation *PALB2* had a similar frequency of mutation, in 1.4% of the genetic hereditary cancer panels.

The diversity of the studied population (ethnicity, environmental risk factors, access to investigation) can explain some of the differences between the findings of this study when compared to similar ones in the global literature. It is important to emphasize that the list of analyzed genes that have significant clinical validity is always evolving[8]. Therefore, all the variables found can be reclassified according to new discoveries, possibly leading to deep changes in patient care[9].

This study showed that counseling for genetic hereditary cancer panel still occurs mainly in the population that develops breast cancer, since only 40 tests were conducted based on family history of breast cancer. This demonstrates that strategies of awareness addressed to the population should be stimulated so that, in these cases, measures of risk reduction can take place, thus reducing the morbidity and mortality of cancer.

AUTHORS' CONTRIBUTIONS

NFR: Conceptualization, Investigation, Methodology, Project administration, Validation, Visualization, Writing – review & editing. RNH: Project administration, Validation, Visualization, Supervision, Writing – review & editing. GAOA: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. MAF: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. PCP: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. AMOF: Methodology, Validation, Writing – review & editing. MEM: Methodology, Validation, Writing – review & editing.

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ORIGINAL ARTICLE
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Evaluation of breast pathologies in puerperal women assisted at a philanthropic hospital in Presidente Prudente (SP), Brazil: longitudinal cohort.

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ABSTRACT

Introduction: Breast milk is the main source of nourishment for the healthy growth and development of newborns up do six months, and after that, it serves as a supplement up to two years. The act of breastfeeding, in addition to being an important means of forming an affective bond between the mother and infant, also promotes maternal, social and environmental benefits. Although its importance has been proven, it is known that there are several reasons that lead to the early interruption of breastfeeding, including breast complications. Our aim was to determine the incidence of complications related to breastfeeding in puerperal women seen at Hospital Regional, a philanthropic hospital in Presidente Prudente (SP) and the possible factors that led to their appearance as well. **Methods:** A quantitative-qualitative longitudinal study was carried out with puerperal women cared for at Hospital Regional of Presidente Prudente. A structured interview was administered in three stages: the first during the puerperal women's hospitalization and the others, through telephone contact at respectively 30 and 90 days after delivery, to monitor breastfeeding. **Results:** Of the total number of patients interviewed, 24.3% had some breast complications resulting from breastfeeding. Still in the immediate postpartum period at 30 days, this proportion reached 42.23%, decreasing at 90 days to 17.47%. Furthermore, of the puerperal women that showed any complication, 74% of them were single, 54% had brown skin color, 42.9% had completed high school and 52% were primiparous. Moreover, the patients who had a Cesarean section (53,8%) showed more complications than the ones who had natural childbirth (35,1%). **Conclusions:** The main breast complications found were nipple fissure, breast engorgement, milk retention nodules and mastitis.

KEYWORDS: breastfeeding; lactation disorders; weaning; risk factors; breast diseases.

INTRODUCTION

Breast milk is the main source of food for the healthy growth and development of infants. Thus, it should be the exclusive food of the child up to 6 months of age, and afterwards, it should help to complement the diet up to 2 years of age. Institutions such as the World Health Organization, the United Nations International Children's Emergency Fund (UNICEF) and Brazil's Ministry of Health (MS) recommend exclusive breastfeeding (EBF) for feeding the child, forming an affective bond between the mother and infant, in addition to being important from an immunological, nutritional and psychosocial point of view[1-3].

Breast milk contains substances that help the child's immune system to protect them against chronic and infectious diseases that can be causes of hospitalizations and mortality in the first year of life. In addition, it represents a source of energy and vitamin E, calcium, phosphorus and fatty acids, which help the formation of cell membranes, including the central nervous system, impacting children's cognitive sensor development[3-5].

While sucking, the baby also develops the functions performed by phonoarticulatory organs. Also, breastfeeding is linked to protection against obesity and the development of diabetes throughout life. In addition, EBF reduces the risk of cardiovascular diseases, neurological dysfunction and the development of cancer before the age of 15, as milk has an immunomodulatory action[1,3,6,7].

In addition to the benefits it provides to the baby, for the lactating woman, breastfeeding contributes to the delivery of the placenta, reduction of uterine size, reduction of the incidence of postpartum hemorrhages, amenorrhea and prevention of anemia. Furthermore, amenorrhea during breastfeeding increases

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the protection against a new pregnancy by 98% in the first six months in which it is practiced. That is, breastfeeding in the first six months protects the mother from a new pregnancy. In addition, breastfeeding reduces the risk of ovarian cancer, premenopausal breast cancer and the development of type II diabetes mellitus and mitigates the risk of endometrial cancer[3-5].

Although its biological importance has been proven, many mothers still hesitate to breastfeed exclusively, given its historical, social and psychological burden. Breastfeeding is culturally influenced, such as beliefs about milk being weak and not meeting the child's needs, corroborating the mothers' insecurity, who end up interrupting their breastfeeding. In addition, the baby's persistent cry after breastfeeding causes lactating women to associate it with hunger, making them feel unprepared or insufficient[4,5].

Early weaning is still related to the mother's age, her level of education, previous experience and knowledge on the subject, her socioeconomic and marital status, and the lack of follow-up in primary care that helps this mother to resolve her doubts and complications[4].

However, there are other reasons that lead these mothers to interrupt EBF; for example, breast complications, which are common in the postpartum period and are related to the shape of the nipple and the attachment or inadequate positioning of the child when breastfeeding. Among the complications, there is breast engorgement, nipple fissure, galactocele and puerperal mastitis[2,8].

Such complications cause specific symptoms and signs, generating discomfort and insecurity for breastfeeding. The higher frequency of breast complications is related to nipple trauma (fissure), which, at the beginning, causes pain when breastfeeding and erythema. Among the factors related to fissure, we highlight the difficulty of the newborn (NB) in terms of gripping the nipple and breast engorgement, which causes edema and stiffness in the entire breast, which when exposed to the baby's sucking, makes the nipple susceptible to cracking. Furthermore, the occurrence of a fissure generates a solution of continuity in the skin, predisposing to infection by microorganisms and its consequent inflammation, facilitating the occurrence of mastitis. That said, breast complications related to breastfeeding can be reversed with proper gripping techniques[9,10].

However, aggravations in the breasts should not make breastfeeding impossible. For this, it is necessary to offer guidance, support, encouragement and incentive, associated with teaching techniques for a more peaceful breastfeeding and prophylactic measures in case any complications occur[4,9].

METHODS

Therefore, the relevance of this study lies in the approach to breastfeeding and possible complications related to it, since EBF has been occupying a prominent place in public health, considering that the protection conferred by it on morbidity and mortality has been proven in several studies. Corroborating these studies, UNICEF believes that almost half of the deaths of children under 1 year old occur in the first week of life (49.4%), which points out that the introduction of breast milk soon after birth considerably reduces neonatal mortality (65.6%)[5-7].

In view of all the variables that remain associated with the interruption of breastfeeding, the most prominent are the social and economic ones, the lack of experience and transformation of the family structure, in addition to breast complications. Within the scope of the action of the global nutrition goals for 2025, the intention is that the EBF rate in the first 6 months of life is raised by 50%, which requires a great effort at a collective level, integrating governments, society and health systems[4,6,11].

Given the above, considering the relevance of breastfeeding and how it affects the nutritional status of the child, defense against infections, physiology and cognitive and emotional development, as well as having implications for the physical and mental health of the mother, it is essential to evaluate the main complications and problems that are involved with the interruption of breastfeeding, providing the mother and the infant with better conditions for this practice to take place[2,4,6,12].

Casuistics

This was a longitudinal cohort study carried out with puerperal women cared for at Hospital Regional (HR), a philanthropic hospital in Presidente Prudente (SP).

The sample size calculation for the incidence study considered a population of 268 postpartum women (n=268 – total estimate for four months), 98% confidence level, 4% error rate and p=0.43 (incidence obtained in a previous study), resulting in 203 samples (n=203). The interviewed mothers were selected in a probabilistic way, at random. A significance level of 5% was adopted (p<0.05).

In view of this, we expected to find an incidence of 43.4% of milk retention nodules, 28.3% of breast engorgement, 7.6% of nipple fissure and 2.8% of puerperal mastitis. We still estimated a higher occurrence of these complications in primiparous mothers (46.2%), in mothers with low education (53.1%) and in those who had no other experience with breastfeeding (54.5%).

Eligible for the study were hospitalized puerperal women who gave birth to live NBs, regardless of maternal age or type of delivery, who were breastfeeding and who gave permission to participate in the study, by signing an informed consent form, in accordance with Resolution No. 466/2012 of the National Health Council.

Excluded from the study were postpartum women who refused to participate, those with restriction or impediment to breastfeeding and those in which the pregnancy resulted in abortion, fetal death or stillbirth.

The instrument used for data collection was the structured interview (Appendix 1), through which the selected postpartum women were asked questions about their socioeconomic conditions, prenatal care and clinical obstetric and breast characteristics;

the mothers were also questioned about the NB. This interview consisted of three stages: the first, carried out while still in the hospital, during the immediate postpartum period; the others, by telephone, respectively at 30 and 90 days after delivery.

1st stage: carried out in the ward of the obstetrics sector, with the mothers hospitalized during the immediate puerperal period. The interview was composed of sociodemographic and clinical obstetric variables, such as: age, schooling, marital status, family structure, prenatal care, parity, type of delivery, preparation of the nipples during pregnancy and neonatal characteristics (weight at birth, hours of life, time of the first feeding) and whether breastfeeding was exclusively maternal or with the use of a supplement.

2nd and 3rd stages: telephone contact at 30 and 90 days after delivery to monitor breastfeeding. At those times, the interview focused on the changing questions related to breastfeeding and the possible breast complications that occurred.

RESULTS

Statistical analysis was performed in two stages. The first, there was a descriptive analysis of the data, through the calculation of absolute frequencies and percentages, numerical measures (mean, standard deviation and coefficient of variation) and construction of tables that characterized the sample.

In the second stage, statistical tests were performed to verify the association between socioeconomic, clinical obstetric conditions and prenatal care versus complications related to breastfeeding.

Data were tabulated using Microsoft Excel and RStudio software. In the analysis, the values were expressed as mean±standard deviation for continuous quantitative variables, median (minimum–maximum) for discrete quantitative variables and frequency and percentage for categorical variables.

For comparison between groups, the Student *t*-test was used for normal variables, Mann-Whitney test for non-normal variables and chi-square test for categorical variables. To compare the variables studied in the groups with and without complications resulting from breastfeeding, a logistic regression model was used. A significance level of 5% was considered in all cases.

Of the total number of patients interviewed, 24.3% had some breast complications resulting from breastfeeding, still in the immediate postpartum period. At 30 days, these findings reached 42.23%, decreasing at 90 days to 17.47% (Figure 1).

During the immediate puerperium, the following proportions were found: nipple fissure was present in 60% of the women, breast engorgement in 24%, milk retention nodules in 8%, non-latching in 4%, inverted nipple in 6%, pain in 4%, lack of milk in 4%, excoriation in 2% and bleeding in 2% of the interviewees.

At the second time, at 30 days, the following were found: nipple fissure in 73.5%, breast engorgement in 3.4%, mastitis in 3.4%, milk retention nodules in 17.2%, pain in 7.9%, little milk in 5.6%, dried milk in 4.5%, inverted nipple in 2.3%, bleeding in 3.4%, increased sensitivity in 1.1% and burning in 1.1% of mothers cared for.

At 90 days, the following were found: nipple fissure in 51.4% women, breast engorgement in 8.6%, mastitis in 2.8%, milk retention

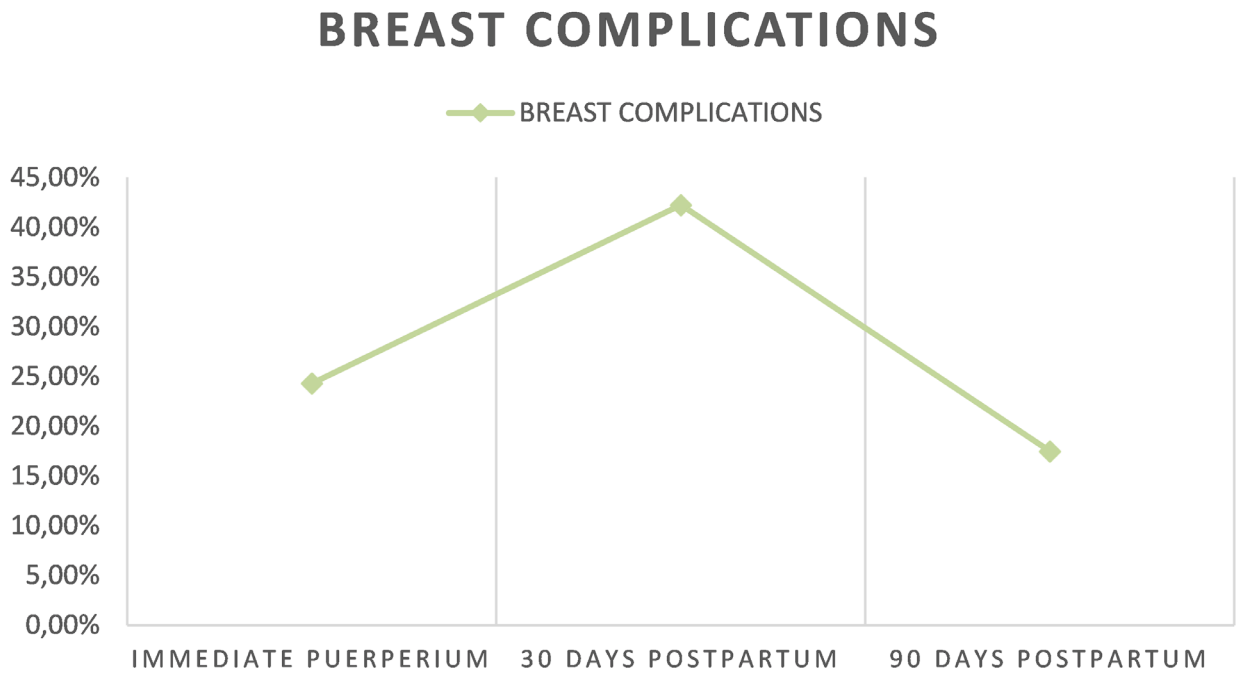

Figure 1. Incidence of breast complications in the population studied (n=206).

nodules in 14.3%, little milk in 2.8%, milk dried up in 17.1% and inverted nipple in 2.8%, while pain, bleeding, increased sensitivity and burning were not reported by any of the patients (0%) (Figure 2).

Regarding the socioeconomic data obtained, of the total number of interviewees (206), 41.4% of patients had an income less than or equal to one minimum wage and 66.5% were single. Also, we examined the association of the characteristics of the puerperal women with the complications resulting from breastfeeding. Those who displayed some complication, 74.0% were single, 54.0% were brown-skinned and 42.9% had completed high school.

With regard to clinical obstetric conditions, it was found that 62.1% of those cared for had natural childbirth, and 44.4% of mothers were instructed on breastfeeding during prenatal care, while 58.3% were educated at the maternity hospital (Figure 3). Regarding the type of delivery, mothers who had natural childbirth (25.1±5.8) were, on average, three years younger than those who had cesarean delivery (28.0±7.5) (p=0.002). In the contact made 30 days after delivery, there were more breast complications related to those who had a cesarean delivery (53.8%) compared to those who had a natural childbirth (35.1%) (p=0.013); nevertheless, in the contact made 90 days after delivery, this difference was no longer observed. As for parity, it was observed that 52% of the patients who showed breast complications were primiparous.

Regarding infant nutrition, 90.3% were exclusively breastfed in the joint accommodation, with a decline to 65.8% and 61.2% at 30 and 90 days, respectively. Furthermore, it was observed that not having used a supplement was a protective factor for breast complications resulting from breastfeeding (OR 0.3 (0.2–0.4); p<0.001).

Finally, regarding the use of contraceptives by mothers after childbirth at 30 days, 9.4% of mothers were already using this contraceptive method and, at 90 days, 52%.

DISCUSSION

Breast complications

Although this study was carried out in a tertiary hospital, where programs to encourage and promote breastfeeding are carried out, the data obtained indicate the existence of a considerable number of breast complications resulting from breastfeeding, the main ones being nipple fissure, milk retention nodules (galactocele), breast engorgement and mastitis.

Castro et al. (2009) carried out a study with 145 women and obtained the following proportions of breast complications: 43.4% had milk retention nodules, 28.3% breast engorgement, 7.6% nipple fissure and 2.8% puerperal mastitis. Still, according to Sales et al. (2022), in another study involving 70 women, the incidence of breast engorgement between 15 and 30 days was 46%, and nipple fissure occurred in 47% of women, while mastitis was seen in 79% of participants.

Fissures

Fissures are often found in puerperal women, being defined as erosions or cracks in the nipple skin that can cause the destruction of the epidermis layers to the lower layer of the dermis[13,14]. Our study revealed a rate of 60% of fissures in the patients studied during the immediate puerperium and corroborates the high incidence.

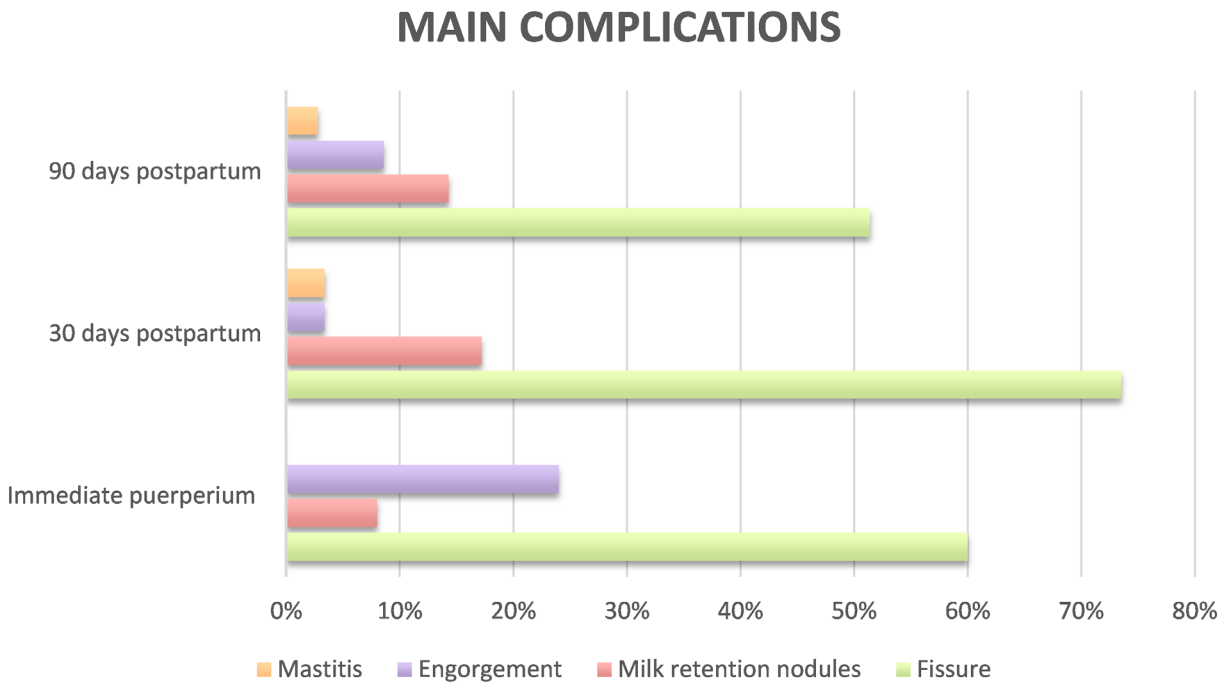

Figure 2. Main breast complications found at three different times.

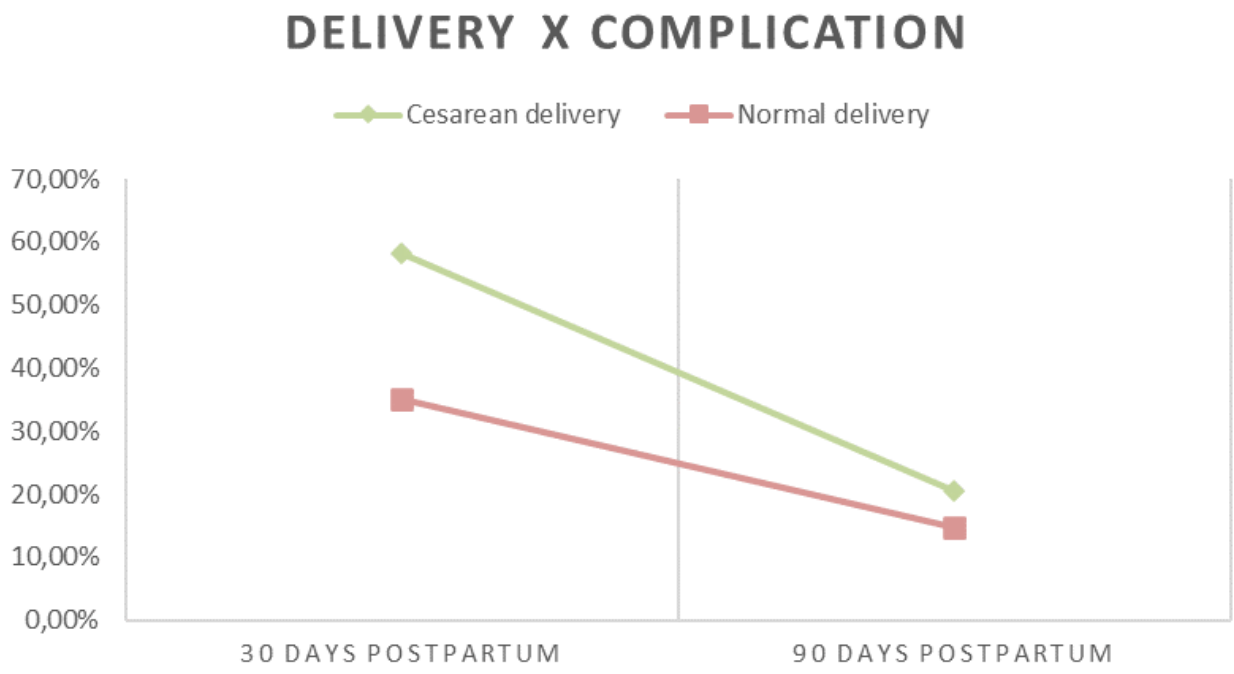

Figure 3. Relationship between the incidence of breast complications and the mode of delivery.

Fissures correspond to a sign that there is poor breastfeeding technique, and the pain resulting from this complication interferes with the maintenance of breastfeeding, which can lead to early weaning[15].

Among the factors associated with the occurrence of fissures, those that stand out are primiparity, absence of a partner, turgid and engorged breasts, and semi-protruding and/or malformed and depigmented nipples, along with inadequate grip and positioning of the neonate[14].

Mastitis

The incidence of mastitis affects, on average, 2% to 10% of lactating women. It is initially an inflammatory process resulting from milk stasis, areolar distension and obstruction of milk flow, and which may evolve later to bacterial growth, especially when associated with the occurrence of nipple trauma. This condition can worsen and progress to breast abscesses and sepsis[8].

In our study, we obtained, on average, a 2% rate of mastitis, corroborating the findings of both Maia et al. (2020) and Castro et al. (2009), in which the rates were 2% to 10% and 2.8%, respectively[8].

Mastitis can be suspected through clinical examination of the breasts, due to the presence of classic signs of inflammation: warmth, redness, mass, edema and pain. Other signs include: nipple retraction and changes in the color of the milky discharge[8].

Breast engorgement

It is characterized by excessive tissue distension, with consequent increase in breast size, presence of phlogistic signs and flattened nipples. This complication is usually more frequent in the first postpartum week, and can occur throughout the breastfeeding period, making it difficult and preventing the baby from properly emptying the breast, which worsens engorgement and pain[12,15].

The risk factors for the occurrence of this complication are related to late initiation of breastfeeding, infrequent and short-term breastfeeding, use of supplements, ineffective sucking of the NB, sudden increase in milk production and nipple injury. Proper management and resolution of the condition are important, as it can progress to mastitis[12,15].

In this study, we observed a 24.0% rate of breast engorgement in the immediate puerperium; at 30 days, this rate dropped to 3.4%, and at 90 days, it remained at 8.6%, although still well below the rate in the initial postpartum period. This fact may be related to the acquisition of lactation experience by parturient women during the puerperium days.

Galactocele

According to Castro et al., the incidence of galactocele in puerperal women was 43.40%, a fact that differs from the present study, since the average incidence found was 13.16%. Galactocele is the name given to a benign lesion of the breast, which is caused by the cystic formation of milk content in the breast ducts. It can occur both late in pregnancy and during breastfeeding, and it is thought to be caused by a lactiferous duct blockage[10,12].

Socioeconomic variables

Regarding the variables race, income, education, number of pregnancies and age of the mother, age and weight of the baby at birth, type of delivery, having had guidance on breastfeeding,

both in prenatal and maternity, in addition to carrying out the breast preparation, did not represent a risk or protective factor for the development of breast complications (p>0.001).

Marital status

Although the results of the present study show that most of the interviewees reported being single, most of the puerperal women lived under the same roof as their partner as if they were married, albeit in a non-formal way, a fact documented by Abreu et al., who observed in their studies that stable union was the most reported by women[16].

According to the Brazilian Civil Code, a stable union is characterized as a cohabitating family unit, continuous and lasting coexistence between a man and a woman, established with the objective of constituting a family. That said, even if the interviewee initially identifies as single, the stable union is a de facto situation, representing 36.4% of the total relationships in the country. According to Viduedo et al., there is a predominance of the frequency of breast complications in single women, a finding also found in our studies[17-19].

Low income

When analyzing income, this study showed that most nursing mothers had an income less than or equal to one minimum wage. This fact can be explained considering that the institution chosen for research serves users of the Unified Health System (SUS), which is the reference and the only health resource for 71.1% of the Brazilian population, according to the Brazilian Institute of Geography and Statistics (IBGE)[19].

Clinical obstetric variables

Breastfeeding guidance

According to a study carried out in Bahia, only 53.2% of women received guidance on breastfeeding during prenatal care. In our study, this value was even lower (44.4%), an aspect that increases the risk of interruption of breastfeeding and the development of breast complications. Based on the Ministry of Health's Low-Risk Prenatal Care, guidance on breastfeeding is a requirement to be fulfilled by primary care[18,20].

Thus, there is a failure in primary care, as the percentage of patients who received guidance on breastfeeding in a tertiary service (58.3%) was higher than that received in primary care (44.4%). Therefore, it is important to take measures that prioritize the prevention of breast complications, able to reduce possible complications or hospitalizations that overload the tertiary service[20,21].

Relation between age and delivery mode

In accordance with the literature studied, we found that the number of cesarean sections increased in a direct and proportional manner with the age of the mother, so that the higher the maternal age, the higher the values were for this type of delivery. Among adolescents, the percentages of cesarean section were lower when compared to adult women of advanced age, who ended their pregnancy by operative delivery in greater proportion[22,23].

On the other hand, even though natural childbirth is predominant among parturient women, from 2010 onwards, the number of cesarean deliveries increased among women aged 20 to 29 years, being the most common type of delivery. This fact is related to the evolution of technology in the field of obstetrics, the illusion that cesarean delivery would be better than vaginal delivery for the mother and infant, and the sensation of decreased pain and obstetric and fetal complications, in addition to influence from the community where it is available[22,24].

Primiparity

It was observed that most of the women interviewed were primiparous, and according to Cirilo et al., primiparous women have a higher frequency of nipple trauma (60.2%), which is explained by inexperience or exposure of nipple-areolar tissue for the first time to the NB[25].

Castro et al. observed that nipple trauma began in the first two weeks after delivery, when breastfeeding and the rhythm of breastfeeding are unstable. Furthermore, it is recognized that the anxiety experienced in the first postpartum days can interfere with the lactation process and generate such complications[10,20].

Cesarean delivery

Although, in the present study, the most prevalent route of delivery was vaginal, it was observed that most women who had breast complications gave birth by cesarean section, a result that is consistent with the literature. In addition, the study by Dias et al. argues that the pain experienced by parturient women, given the surgical incision, can affect the correct positioning of the child on the mother's breast, impairing the baby's latching onto the breast and contributing to the occurrence of nipple trauma[26].

Other factors

Nutrition

In this study, we found that not having used a complement was a protective factor for the development of breast lesions. The use of bottles and/or pacifiers imprints a different suction pattern compared to that performed during breastfeeding, resulting in "nipple confusion"[26-28].

When comparing the sucking patterns of the breast and the bottle nipple, it is noted that the oral postures adopted by the baby, the differences in pressure and the activated musculature are completely different. The first sucks performed by the baby quickly become a difficult habit to change; therefore, the more frequent and uniform the sucking pattern adopted by the infant, the greater the chances will be that the latching is done correctly, with a lower incidence of breast complications[7].

Contraceptive

Although we found a significant percentage of puerperal women who started contraception up to 30 days after delivery, it should only be restarted after the puerperium, a period that ranges from delivery of the placenta to six weeks after delivery (42 days)[27].

In our study, the contraceptives used were those composed only of estrogen or progesterone, mixed (estrogen and progesterone) and others (among those who could not specify). The most suitable and safe contraceptive pill for use during breastfeeding is the one that contains only progesterone, as it does not seem to have an impact on breastfeeding. In addition, the use of mixed contraceptives during breastfeeding is not recommended for the first six months after delivery[26,29,30].

Limitations

Among the limitations of the present study are: the difficulty in contacting the patients by telephone and the lack of knowledge and ability of the interviewees to recognize the different breast complications.

CONCLUSIONS

We conclude that the main breast complications were: nipple fissure, breast engorgement, milk retention nodules and mastitis, which were more prevalent in those who were single, primiparous, brown-skinned, with high school education and with family income less than or equal to one minimum salary and those who delivered by cesarean section and used a supplement in the nutrition of the NB. Although most patients were instructed about breastfeeding during their stay in the joint accommodation, there was still a high incidence of breastfeeding-related complications.

AUTHORS' CONTRIBUTION

LES: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. LS: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. TMF: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. RSS: Conceptualization, Supervision. MRA: Data curation. SUS: Formal Analysis.

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Appendix 1. Structured interview applied to puerperal women.

Evaluation of lactation and breast conditions in puerperal women.

A structured interview with puerperal women about
breast intercurrences and the possible factors that coincide for their onset.

1. Day of the interview

_____

Example: January 7, 2019

Questions regarding the puerperal women

2. Name

_____

3. Age

_____

4. Telephone number

_____

5. Self-reported skin color

Mark only one oval.

- ◯ White
- ◯ Black
- ◯ Brown
- ◯ Yellow

6. Family income (in minimum wages)*

*current minimum wage = R$ 1.100,00.

Mark only one oval.

- ◯ ≤ 1
- ◯ 1 - 2
- ◯ ≥ 3

7. Marital status

Mark only one oval.

- ◯ Single
- ◯ Married
- ◯ Divorced
- ◯ Other: _____

8. Schooling

Mark only one oval.

- ◯ No schooling
- ◯ Incomplete elementary school
- ◯ Complete elementary school
- ◯ Incomplete high school
- ◯ Complete high school
- ◯ Incomplete higher education
- ◯ Complete higher education

9. How many people live in the house

Mark only one oval.

- ◯ ≤2
- ◯ ≤4
- ◯ 5 - 8
- ◯ ≥ 9

10. Number of pregnancies

Mark only one oval.

- ◯ 1
- ◯ 2 - 3
- ◯ ≥ 4

11. Type of delivery

Mark only one oval.

- ◯ Natural
- ◯ Cesarean section

12. Were you advised about breastfeeding during prenatal care?

Mark only one oval.

- ◯ Yes
- ◯ No

13. Were you advised about breastfeeding in the maternity hospital?

Mark only one oval.

- ◯ Yes
- ◯ No

14. Medication used by the patient

_____

Questions about the breast

15. Did you prepare your breast for breastfeeding?

Mark only one oval.

- ◯ Yes
- ◯ No

16. If so, what did you do?

_____

17. Are there complications resulting from breastfeeding?

Mark only one oval.

- ◯ Yes
- ◯ No

Continue...

Appendix 1. Continuation.

18. If so, which ones?

Mark only one oval.

- ◯ Nipple fissures
- ◯ mammary ingurgitation
- ◯ Mastitis
- ◯ Milk retention nodules
- ◯ Other: _____

Questions about the newborn

19. Age at birth

_____

20. Weight at birth

_____

21. Time of the first feeding

_____

22. Is the breastfeeding exclusive?

Mark only one oval.

- ◯ Yes
- ◯ No

23. Is any complement used?

Mark only one oval.

- ◯ Yes
- ◯ No

24. If so, when did it start?

_____

CASE REPORT
https://doi.org/10.29289/2594539420220016

De novo gastric metastasis from invasive lobular carcinoma of the breast: report of three cases and literature review

Jessica Gonzalez Suerdieck[1], Juliana Alves Souza[1], Mateus Mattioni[1], Almir Galvão Vieira Bitencourt[1]*

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[1-3]. It has a typical histopathological appearance of poorly cohesive cells[1].

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[4,5]. This increases the rates of multicentricity and bilaterality and results in an unusual metastatic[3,6-8].

Although rare, metastatic spread to the stomach stands out by being highly related to ILC and very difficult to differentiate from primary adenocarcinoma[2,3,5-12]. For this reason, previous studies questioned the real frequency of gastric metastasis from breast cancer, which might be underestimated[13].

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.

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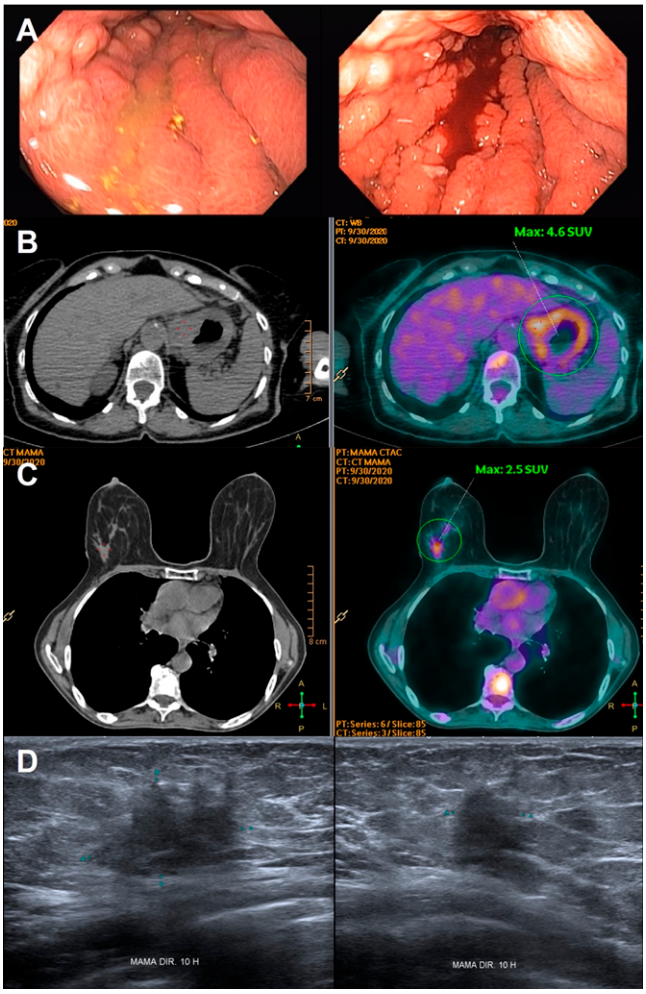

Figure 1. (A) UGI endoscopy showing diffuse infiltrative lesion with thickening of the gastric walls. (B) 18F-FDG PET/CT with diffuse uptake of the gastric wall thickening. (C) 18F-FDG PET/CT with irregular lesion in the right breast. (D) Ultrasound revealing a hypoechoic nodule with irregular shape 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.

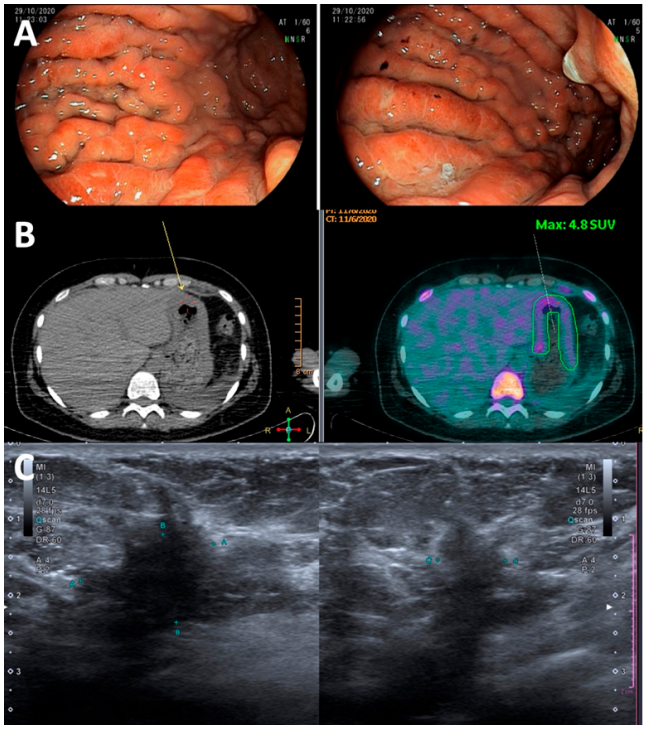

Figure 2. (A) UGI endoscopy showing diffuse thickening and rigidity of the gastric walls. (B) 18F-FDG PET/CT showing uptake along the concentric thickening of the antrum and gastric body. (C) Ultrasound revealing a hypoechoic nodule with irregular shape and indistinct margin in the right breast.

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[1-3] 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[3,5,8-12]. The most

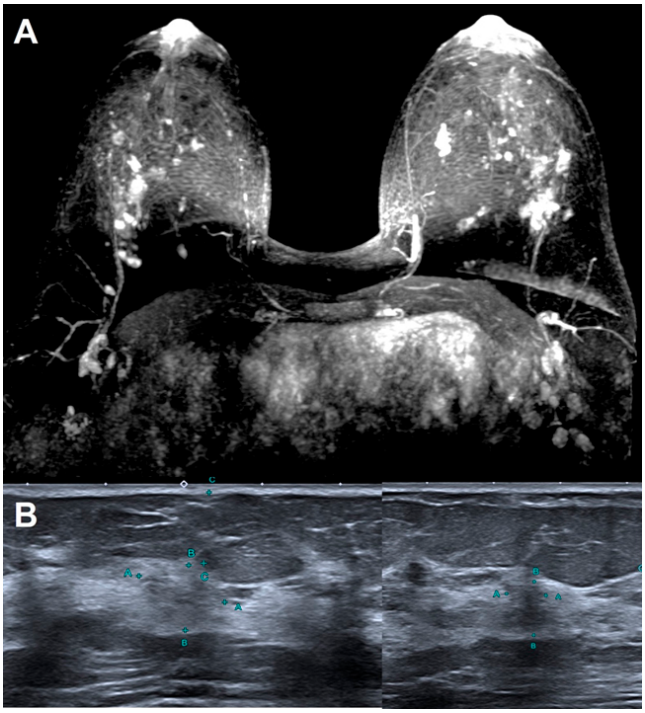

Figure 3. (A) Breast MRI showing suspicious focal nonmass enhancements in both breasts. (B) Second-look ultrasound showing discrete hypoechoic areas in the left breast, which corresponded to PET/CT findings.

common spread is to the stomach with frequencies ranging from 0.3% to 35%, followed by the colon[1-3,5,9,11]. Considering metastatic breast involvement in the stomach, ILC accounts for 80% of the cases[5,7,9-11,13].

Gastric metastasis of breast cancer usually appears years after the primary lesion treatment, i.e., between 2 and 7 years[2,3,5,6,9-11]. 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[2,3,5-7,9-12]. 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[3,6,9-11]. In all of our cases, both bones and lymph nodes were involved.

The most common macroscopic appearance is linitis plastica[3,5,6,8,11,12]. 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[3,5,9,10]. For a definitive confirmation, a detailed immunohistochemical analysis may be needed[3,4,6,8,11]. Metastatic breast carcinoma is usually positive for CK7, GCDFP-15, and estrogen and progesterone receptors, and negative for CK20[3,4,6,8,11]. However, CK7 and hormonal receptors may be expressed in gastric adenocarcinomas[9,11]. The absence of E-cadherin is significantly related to metastatic breast carcinoma[9,11].

Histologic comparison of the endoscopic biopsies with the breast carcinoma specimen is highly recommended[11,13]. 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[2,6,8,9,11].

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.

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CASE REPORT
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Invasive ductal carcinoma of the breast in a pregnant woman: case report

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ABSTRACT

Gestational breast cancer is the most common cause of cancer in pregnant women. It is a challenging condition for the medical team, since the physiological changes in the breast during this period increase the density of the breast parenchyma, which makes it difficult to detect the nodule on physical and imaging examination, causing delay in diagnosis. We present here a case report of a woman with breast cancer diagnosed during pregnancy. This was a 28-year-old female patient who arrived at the service at 14 weeks' gestation, diagnosed with invasive ductal carcinoma in the left breast, with T4dN2M0 staging. Neoadjuvant chemotherapy treatment was started with a pause for the cesarean section at 36 weeks' gestation. After delivery, chemotherapy was restarted, followed by radical mastectomy, radiotherapy and hormone therapy. Two years after the initial diagnosis and still being treated with hormone therapy, the patient presented with musculoskeletal pain, detected on magnetic resonance imaging and bone scintigraphy, as well as several points of metastasis in the spine with pathological fracture of L2-L3, where she was then submitted to decompressive laminectomy. After surgery, radiotherapy of the thoracic and lumbar spine was started, in addition to chemotherapy. Currently, the patient is asymptomatic, being on paclitaxel and transtuzumab, with stable bone scintigraphy and radiography and ultrasound showing no metastases, and the child is healthy after three years of follow-up.

KEYWORDS: pregnant woman; breast cancer; invasive ductal carcinoma; pregnancy.

INTRODUCTION

Gestational breast cancer is diagnosed during pregnancy or up to one year after delivery, where it is the most common cause of cancer in pregnant women, followed by cervical cancer, leukemia, melanoma and lymphomas[1]. The incidence varies between 0.02% and 3.8% of pregnancies, with a frequency of one case in every thousand pregnancies. Women over 35 years of age are at greater risk, and with the current lifestyle of postponing pregnancy to the third and fourth decades, the number of cases tends to increase[2].

No histological differences in breast cancer have been identified between pregnant and non-pregnant women. Therefore, the most common type is ductal, followed by lobular, while the mucinous, papillary, medullary and tubular types are less frequently found. However, among pregnant women, the tumors are usually larger and are associated with high lymph node involvement[3].

Some reported studies on the subject point to the breast lump as the main complaint of the patient, with the exception of the work published in BMC Women's Health, which presents a case of breast cancer in a pregnant woman whose only symptom was low back pain, where bone metastasis was later revealed. Another similarity between the studies already published concerns the delay in the diagnosis of this cancer in this specific group of patients, due to the difficulties encountered in performing imaging tests that emit radiation during pregnancy and the physiological changes in the breast during this period[4-8].

Breast cancer occurs rarely during the pregnancy-puerperal cycle, even though it is the most common malignancy in pregnant women. However, studies show that its incidence has increased in recent years. In this context, as it is an uncommon disease, there are few studies on the subject, with little known about its etiology, and treatment decisions are mostly derived from large trials in non-pregnant women[2].

Therefore, with the identification of a confirmed case, its documentation is considered of great importance to identify possible correlated risk factors, develop more specific therapeutic strategies and even design future prevention measures. Therefore, the aim of the present study was to report

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the case of a pregnant patient diagnosed with breast cancer, including her clinical history, histological subtype and course of treatment.

CASE REPORT

A female patient, 28 years old, 14 weeks pregnant, was seen at the cancer hospital of a city in the countryside of São Paulo State, Brazil in March 2018, complaining of a lump in the left breast. After core needle biopsy, the patient was diagnosed as having invasive ductal carcinoma of the left breast. On physical examination, she had an extensive area of *peau d'orange* skin edema on the left breast, globally indurated with a 12.5-cm nodular mass predominantly in the upper inner and upper outer quadrants and an axillary mass on the left compatible with coalescing lymph nodes. Core biopsy was performed, which showed grade III invasive ductal carcinoma (SBR) with vascular and lymphatic invasion. The immunohistochemical study demonstrated estrogen and progesterone receptors in 90% of cells, human epidermal receptor (HER2) positive (3+) and 80% Ki67 staining. Screening tests for metastases were requested, namely chest X-ray and abdominal ultrasound, which did not demonstrate expansive lesions in the evaluated areas or any changes. Thus, the initial clinical staging as T4dN2M0 was completed.

The therapeutic plan applied consisted of weekly neoadjuvant chemotherapy with paclitaxel (12 sessions), followed by four cycles of doxorubicin (A) and cyclophosphamide (C), interruption of preterm pregnancy with discontinuation of breastfeeding, surgical treatment, transtuzumab, radiotherapy and hormone therapy.

In August 2018, after 12 sessions of paclitaxel and three cycles of AC, with the last one at the end of July, the patient, with a gestational age of 36 weeks, underwent cesarean section, resulting in a live newborn without abnormalities. Cabergoline was prescribed for lactation inhibition, and breastfeeding was prohibited from the first postpartum moment. The patient was discharged with the newborn.

Twenty-five days after delivery, the patient underwent the last AC cycle. She then returned for preoperative evaluation, where a radical mastectomy with left axillary dissection was proposed. On physical examination, she showed clinical remission of the cancer, so preoperative tests were requested. After a few days, the patient came to the outpatient clinic with the results of these tests showing normal parameters. On clinical examination, she had an enlarged left breast, with bulging in the upper outer quadrant, diffuse nodular mass reaching almost all quadrants of the breast and an axillary lymph node on the left with fibroelastic consistency. On that day, the patient was referred for the proposed surgery, which was performed after six days. The histopathological examination showed the presence of invasive ductal carcinoma grade III SBR (architectural grade 3, nuclear 3, mitotic 3), measuring 13.5 cm in the longest axis and with vascular and lymphatic invasions present, skin and nipple infiltrated by the neoplasm, anterior surgical margin exiguous, cutaneous lymphatic emboli close to the margin, deep margin 2.5 mm apart, other margins free, metastases to 4 of 25 dissected lymph nodes, and pathological staging pT4B, pN2a. She was referred for follow-up with clinical oncology and physical therapy. In the same month, the use of leuprolide acetate combined with anastrozole and radiotherapy was started, followed by transtuzumab.

The patient remained asymptomatic until June 2020, when she was admitted to the emergency department reporting migratory and additive polyarthralgia for three months, with significant worsening in the previous two weeks, starting in the cervical spine joints and progressing to hand arthralgia and, soon after, hip arthralgia. The patient denied fever and joint swelling and reported loss of strength in the lower limbs, accompanied by persistent low back pain of severe intensity. Magnetic resonance imaging of the lumbar spine was performed, which showed a pathological fracture of L2-L3, with spinal cord compression and paravertebral extension, in addition to a fracture of L5, with a marked reduction in the height of the vertebral body, possibly indicating a lumbar metastasis. Also in June 2020, the patient underwent L1-L5 decompressive laminectomy, with subtotal removal of the neoplastic lesion and spinal canal decompression, in addition to pedicle fixation T11- L4 -L5.

After surgery, radiotherapy of the thoracic and lumbar spine was started, as well as treatment with capecitabine 500 mg, zoledronic acid and transtuzumab. In November, bone scintigraphy was requested, which showed progression of the bone lesion. Capecitabine was then discontinued, while zoledronic acid and transtuzumab were maintained, and paclitaxel was started.

Currently, the patient is asymptomatic on paclitaxel and transtuzumab, with stable bone scintigraphy and radiography and ultrasound without metastases. The child is healthy, now three years old.

DISCUSSION

In this article, we present a patient diagnosed with breast cancer detected during pregnancy, whose treatment was difficult and thus progressing to bone metastasis.

Gestational breast cancer has a clinical history similar to that of non-gestational breast cancer. There may be skin changes, hemorrhagic nipple discharge, enlargement of the affected breast, and most often the presence of a painless lump[2,9].

The diagnosis is made with the detection of the nodule in the physical examination of the breasts or in the ultrasound examinations of the breasts and mammography, and it should be confirmed preferably by core biopsy[10]. However, the detection of the nodule during pregnancy is hampered by the physiological

changes of pregnancy, which respond to the increase in the level of circulating hormones, causing intense ductal proliferation, lobular growth, fibroglandular enlargement of the parenchyma and glandular vascularization. These changes generate an increase in the density of the breast parenchyma, making it difficult to identify changes both in the physical examination and in the imaging tests, which can be difficult to interpret. As a result, there is an average delay of two months in the diagnosis of breast cancer in pregnant women[2].

For additional investigation of a palpable mass on physical examination in a patient who is pregnant or not, the main tests used are breast ultrasound and mammography, which are sensitive in the identification and characterization of nodules and lymph nodes, both being safe during pregnancy. After diagnosis, it is important to perform disease staging tests. The main classification used is the Classification of Malignant Tumors (TNM), which is based on the size of the nodule (T), the number of affected lymph nodes (N) and the presence of metastases (M). In turn, for the definition of T and N, the tests mentioned above are used. In the investigation of metastases, in general, computed tomography of the chest and abdomen and bone scintigraphy are used, tests that can be replaced by PET-Scan (PET/CT). In pregnant women, however, cumulative fetal exposure to radiation above 100 mGy should be avoided, given the risk of congenital malformations and miscarriages. Thus, examinations with greater radiation, such as tomography, scintigraphy and PET-Scan, should be replaced by those that do not expose the fetus to radiation, such as abdominal ultrasound and spinal magnetic resonance, the latter used only if the patient complains of back pain. Chest X-ray is also safe in the investigation of metastases during pregnancy, because despite using ionizing radiation, it has low levels, so it is not harmful to the fetus if used with caution[11].

First-line treatment remains radical mastectomy, and its indications follow the same criteria for performing it outside the pregnancy period[10]. Adjuvant chemotherapy is usually necessary in these cases, as they are young patients and, consequently, have greater tumor aggressiveness[2]. The therapeutic regimen most commonly used in pregnant women is based on doxorubicin, cyclophosphamide and paclitaxel (AC-T) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). Both regimens can be performed in the second and third trimesters of pregnancy and should be avoided during the first trimester and in the three to four weeks before delivery, as they are associated with fetal malformations and transient fetal myelosuppression, respectively[1,2]. Neoadjuvant treatment is reserved for cases of local recurrence and locally advanced or metastatic carcinoma[6].

Anti-HER2 therapy is indicated for patients with overexpression of this receptor, with trastuzumab being one of the drugs used. However, all drugs in this class, if administered during pregnancy, can cause complications such as oligohydramnios, fetal pulmonary hypoplasia and developmental abnormalities, so their use should be postponed to the postpartum period, which was performed in the study patient[8]. Another adjuvant therapy widely used to prevent recurrence of hormone-sensitive breast cancer is tamoxifen, but it is also a contraindicated drug during pregnancy because it presents a high risk of congenital abnormalities, miscarriages and stillbirth[12]. Although reports regarding the use of tamoxifen during pregnancy are scarce, in a study with pregnant mice injected with tamoxifen, morphological defects were observed in most of the evaluated animals, including pericardial edema, cleft palate, neural tube defects, necrotic embryos and ophthalmic defects. In addition, the mother displayed deleterious effects, the most common being uterine bleeding[13].

Furthermore, the patient should not breastfeed while being treated with these drugs[6]. Radiotherapy is also contraindicated during pregnancy because of fetal exposure to radiation, and should, if necessary, be performed in the postpartum period[14].

In the case reported, the patient was given paclitaxel, doxorubicin and cyclophosphamide as neoadjuvant therapy, as she had a locally advanced tumor. After delivery, the treatment was continued with the planning of the mastectomy and the use of radiotherapy and hormone therapy.

Prognosis depends on factors such as: patient age, tumor staging, histological grade and HER2 status. In addition, breast cancer during pregnancy is associated with worse survival[15].

CONCLUSIONS

The incidence of breast cancer during pregnancy shows an increasing trend for numerous reasons, the main one being the postponement of pregnancy. Despite this increase in cases, the difference in time of diagnosis between pregnant and non-pregnant women is still divergent, being earlier in non-pregnant women[16]. To reduce this difference and diagnose breast cancer earlier during pregnancy, it is critical that clinical breast examination be performed in every prenatal visit, in a routine way, with the aim of detecting possible gland changes.

The hormonal changes of pregnancy, as mentioned above, lead to greater difficulty in diagnosis by clinical examination, and in doubtful cases, investment in breast ultrasound can be useful, contributing to a diagnostic advance in this group of patients.

AUTHORS' CONTRIBUTION

MPPB: Data curation, Funding, Investigation, Methodology, Visualization, Writing – original draft. MBC: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. ELD: Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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CASE REPORT
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Lymphedema secondary to bartonellosis as a differential diagnosis of breast cancer

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ABSTRACT

In the presence of unilateral axillary lymphadenopathy associated with a breast radiological finding, breast cancer should constitute the main differential diagnosis. This fact is intensified when there is associated lymphedema. We present a case of a patient in these conditions, for whom breast cancer was not confirmed, and a subsequent evaluation showed that it was cat-scratch disease. This report constitutes the second case of association between lymphedema and bartollenosis.

KEYWORDS: bartonella henselae; cat-scratch disease; lymphedema; breast neoplasms; lymphadenopathy.

INTRODUCTION

When axillary lymphadenopathy is the first clinical finding, a wide range of etiologies must be considered – both benign and malignant[1-3]. Malignant etiologies should be ruled out and, when excluded, the etiological diagnosis is not always easy, often being one of exclusion.

Lymphedema is a chronic condition resulting from lymphatic obstruction, usually associated with a malignant condition[4], or being associated with a rare benign condition. The main diagnostic problem is how to approach a patient with unilateral axillary lymphadenopathy associated with lymphedema whose breast and axillary cancer evaluation was negative.

CASE REPORT

A female, 47-year-old patient was referred to an oncology service due to a suspicious lesion in the upper exterior quadrant of the right breast, seen in the mammography and ultrasound (BI-RADS V). At the same time, serological tests were made for toxoplasmosis, with negative IgM and reactive positive IgG.

The patient denied having previous comorbidities and autoimmune diseases, and no family history of neoplasm. The physical examination showed absence of palpable breast mass, presence of a 49 mm axillary adenopathy to the right, associated with lymphedema (2 cm difference in the diameter of the forearm, assessed 10 and 20 cm below the elbow). There were no other peripheral adenopathies. At first, neoplasia was considered the main differential diagnosis, because of the highly frequent association of adenopathy/lymphedema with breast neoplasia.

Mammography detected a nodule in the left breast, and right axillary lymph node enlargement (Figure 1A). An ultrasound showed a cyst in the left breast and confirmed the presence of an expansive formation in the right axilla, with approximate volume of 23 cm^3, irregular shape, lobulated margins and roughly heterogeneous echotexture, with asymmetric cortical thickening, BI-RADS IV (Figures 1B and C). A venous doppler of the upper right limb (URL) did not show history of thrombosis. Chest computed tomography showed parenchymal enhancement in the upper side of the right breast, associated with heterogeneous axillary lymph node enhancement to the cost of necrotic degeneration, measuring up to 2.4 cm (Figure 1D). Abdominal and pelvic computed tomography showed no changes. The results of the blood test and serology for the human immunodeficiency virus (HIV) were normal.

Fine needle aspiration indicated chronic granulomatous inflammation associated with acute inflammation in the

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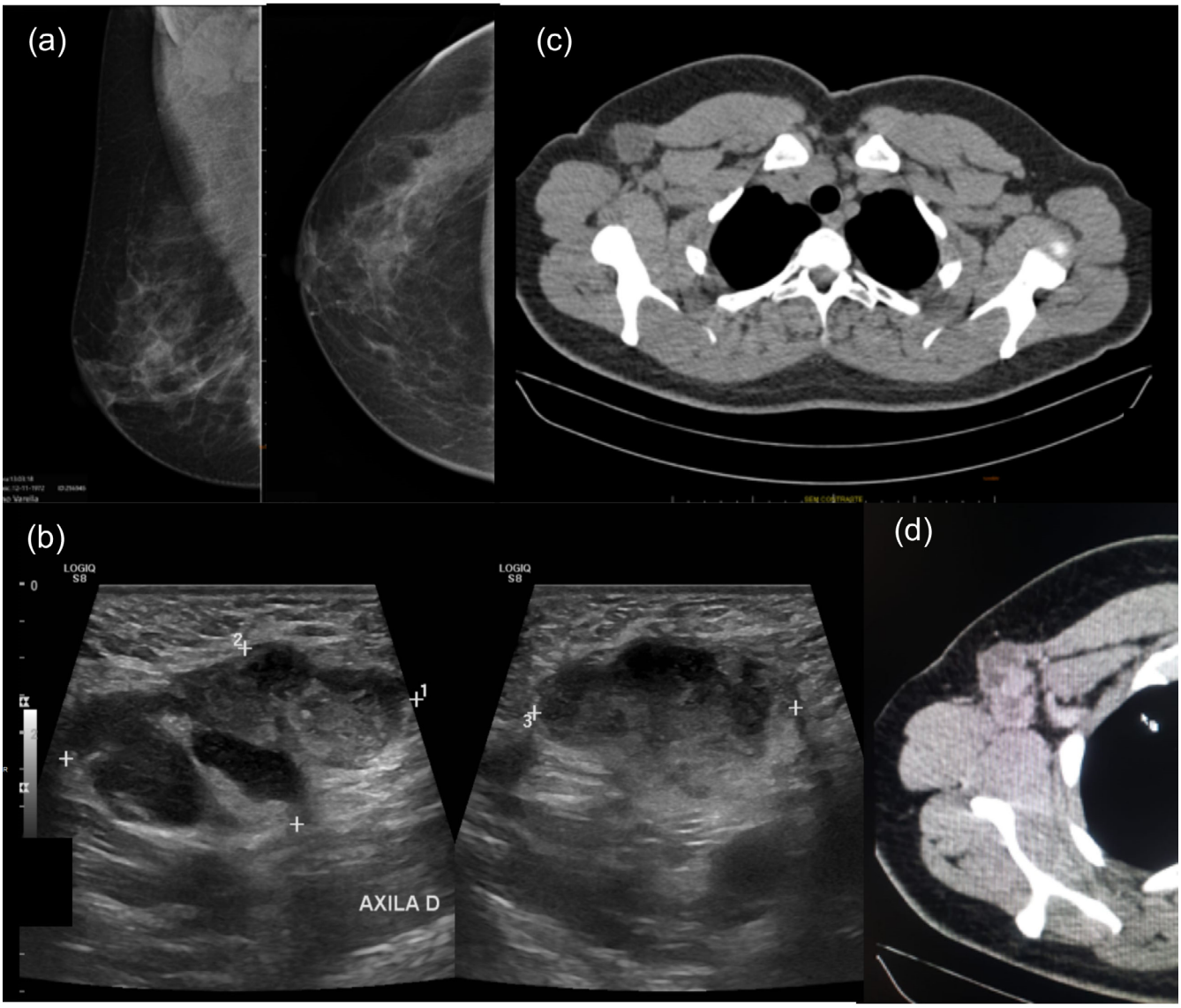
right axillary region, and core biopsy brought a diagnosis compatible with necrotizing granulomatous lymphadenopathy. The search for Acid-alcohol-resistant bacilli (BAAR) was negative. Due to the conflicting radiological and clinical findings, the choice was to perform an open biopsy, aiming at increasing the sample. Right axillary lymphadenectomy was performed. The anatomopathological examination of the surgical piece identified non-caseating granulomatous lymphadenitis, besides the absence of microorganisms according to the methods used for evaluation (Figures 2a and 2b). The hypothesis of neoplasm had been excluded, so it was necessary to assess other differential diagnoses, as well as to conduct an etiological evaluation aiming at a specific treatment.

In a new appointment, the patient reported working with sick animals (dogs and cats). Then, a test for cryptococcosis and angiotensin converting enzyme was requested to investigate sarcoidosis; the tests were negative. Then, a serology for *Bartonella hensalae* was conducted, and showed negative IgM and reactive IgG (1:640). The gene expression analysis using the PCR technique (Polymerase Chain Reaction) in the lymph node was positive[5] in segment of 138pb of the 16S-23S region, intergenic region of the ribosomal ribonucleic acid (rRNA) coding genes of the bacteria, fact that corroborates the lymph node infection by *Bartonella henselae* (Figures 2c and 2d). The treatment was carried out with azithromycin 500 mg (oral administration) for five days. After 12 months, the patients no longer presents with lymphadenopathy, IgG serology 1:320; however, with persistent lymphedema.



(a) Mammography – increased lymph nodes to the right; (b) Ultrasound – heterogeneous axillary adenopathy, with solid and cystic areas, hypervascularization (c,d) axillary lymphadenopathy to the cost of necrotic degeneration.

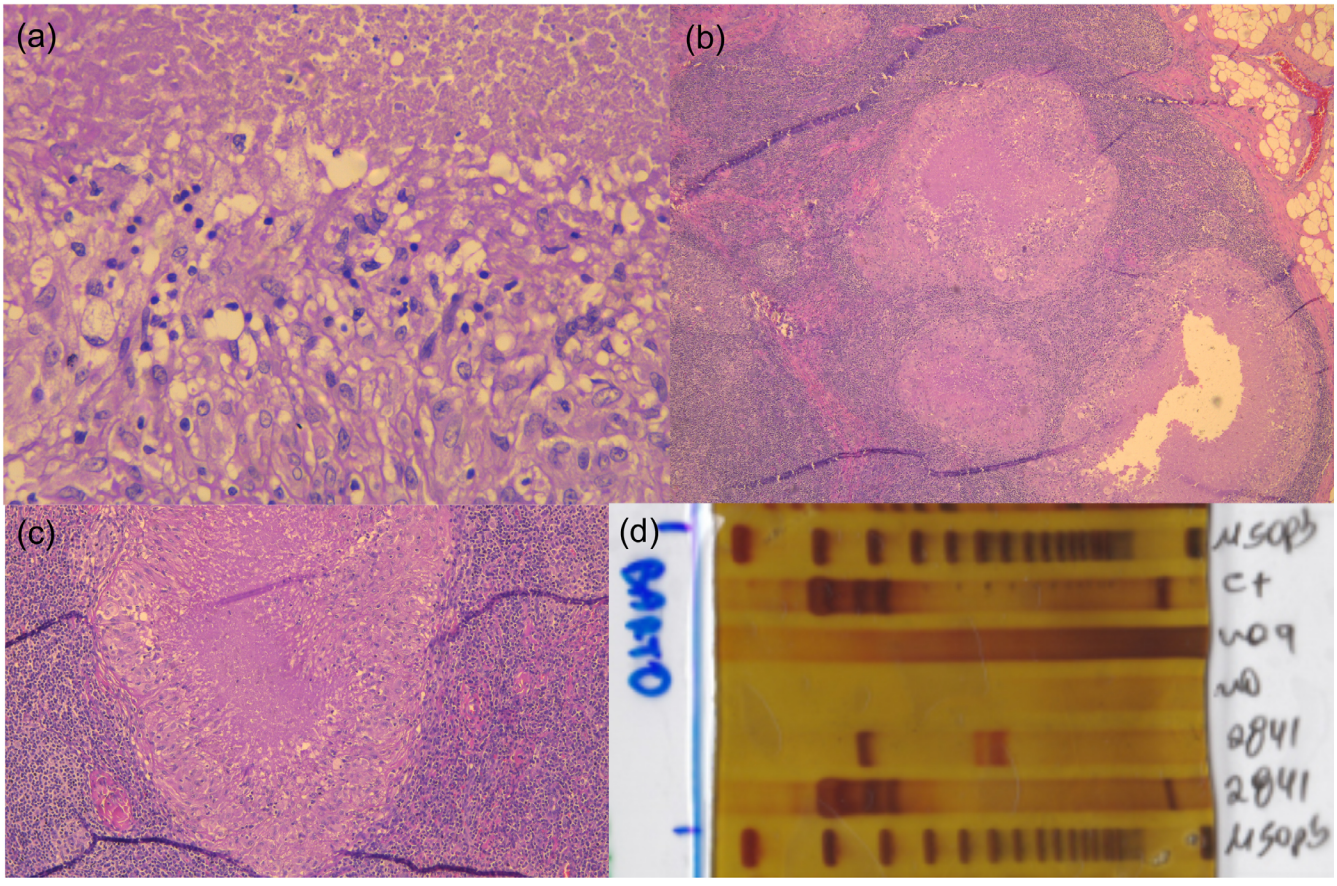
Figure 1. Radiological finding.

DISCUSSION

In patients with unilateral lymphadenopathy, when considering the evaluation of unilateral axillary lymphadenectomy, it is important to observe the age, usually associated with inflammatory pathologies in younger patients, and neoplasm[2,6] among the older ones[7,8]. The patient was 47 years old, and at that age the first differential diagnosis to be considered is breast neoplasm[6,7,9,10]. The first image showed a radiological change in the breast, which, due to the adenopathy, was classified as BI-RADS V, fact that is also observed in other studies[7,8], which led the patient to see a mastologist.

At the presence of neoplasm, immunohistochemistry will often define the primary site, and at the presentation of a possible unknown primary breast disease, associated with axillary metastasis, breast nuclear magnetic resonance becomes an essential test[3,11]. This case has a peculiar characteristic, which is the lymphedema, frequent cause in advanced breast carcinoma and rare in infectious/inflammatory pathologies. The presence of a lymphedema mimics the existence of a carcinoma; however, the data showed an infectious etiology. Such a fact was influenced by the infrequency of lymphedema associated with benign infectious pathologies; the last known case of bartonellosis associated with unilateral axillary lymphadenopathy and lymphedema was described in the 1960s[12].

At the presence of non-caseating granulomatous lymphadenitis, tuberculosis should be considered; however, the assessment of the material using the BAAR analysis (Ziehl-Neelsen staining) was negative. Therefore, the possibility of cryptococcosis and Bartonella was considered since serology was positive in the second case. The main manifestation of the cat scratch disease is regional lymphadenopathy, often affecting the axilla and the neck. This lymphadenopathy appears approximately two weeks after the cat scratch and can persist for a few months[13]. *Bartonella henselae* is a gram-negative rod that causes the cat scratch disease. Cats are natural reservoirs for this microorganism, developing bacteremia when infected. This bacteria can stay in the host's blood for long periods without causing them any symptom, due to its intraerythrocytic parasitism[14,15]. Even though the patient was treated with antibiotics, the lymphedema remained present after the physical therapy treatment and glove application,



(a) 400XX increase: palisade of histiocytes surrounding necrosis; (b) 40XX increase: microabscesses adjacent to the capsule; (c) 100XX increase: microabscess with histiocytes surrounding necrosis; (d) RT-PCR primer of the study of _*Bartonella henselae*. M — molecular marker (50pb); C+ — positive control (DNA extracted from the culture of _B. henselae_); No — negative control (without DNA); T — tested sample. The tested sample (T) presents an amplification 138 pb, suggestive of infection by _B. henselae_.

Figure 2. Pathological findings.

potentially associated with lymph node tissue damage. Since the presence of lymphedema was verified at diagnosis, it is possible to say that this is the second report of this type of case published in the literature, thus justifying its exposure[12].

CONCLUSION

Although it is a rare condition, bartonellossis may mimicking breast cancer. It must be considered in the differential diagnosis of a benign condition associated with unilateral axilary lymphadenopathy and lymphedema. IgG serology suggest the association, but PCR reaction is necessary to prove this condition.

AUTHORS' CONTRIBUTION

ACMMF: Data curation, Formal analysis, Methodology, Visualization, Writing – review & editing. BLGM: Data curation, Investigation, Resources, Visualization, Writing – review & editing. PCFJ: Investigation, Resources, Visualization, Writing – review & editing. LCNOF: Investigation, Visualization, Writing – review & editing. HCS: Investigation, Resources, Visualization, Writing – review & editing. LCNO: Data curation, Visualization, Writing – review & editing. CEB: Investigation, Resources, Visualization, Writing – review & editing. RACV: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing.

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REVIEW ARTICLE
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Integrative review on breast cancer screening in the transgender population: what do we know?

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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[1-3].

Mammography is still the best method for breast cancer screening and has been proven to reduce mortality due to this type of cancer[1-3]. 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[3].

Breast cancer affects not only women but also men in about 1% of cases[1,3,4]. 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[4].

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[5-7].

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)[5,8,9].

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[5,8,9]. 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.

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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[8-11].

The main data recently published by Spizzirri et al.[5] 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[5].

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[12-34] and females[12-16,18,20-23,27,28,31,33-35]. 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[12-25]. Regarding the transgender female population, all studies indicate mammographic screening after 5 years of hormone (estrogen) use[12-16,18,20-22,27,28,31,33,35].

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[6].

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[11,13,16,21,26,31]. 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[13,16,26,31].

As the transgender community gains visibility and recognition, health disparities become more apparent[14,24,30]. 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

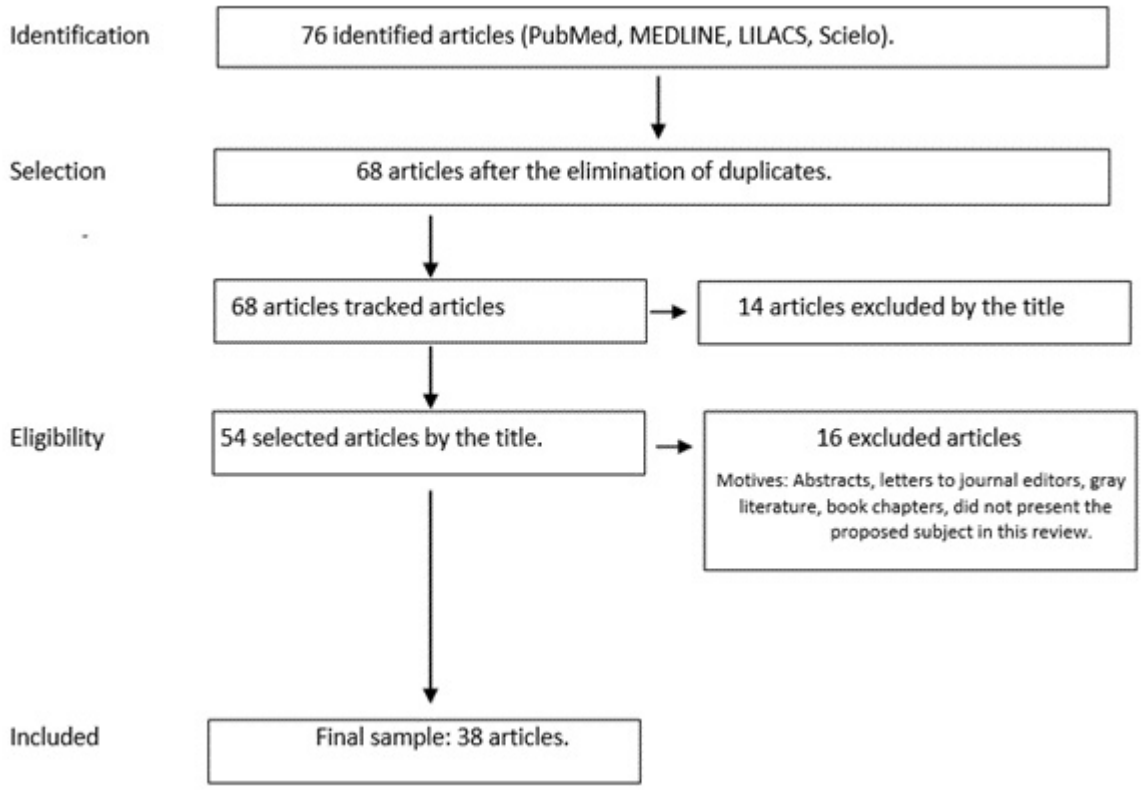

Figure 1. Flowchart of the selection of articles for the integrative review identification.

Table 1. Recommendations for breast cancer screening in the transgender male population found in the review.

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[12-23,32-34]
Biennial mammography in transgender men who used hormone therapy aged 50–69 years	6 articles[24-29]
Annual MRI and mammography for transgender men aged 25–30 years. Consideration of prophylactic bilateral mastectomy for patients with BRCA2	1 article[30]
Annual mammogram for transgender men aged 40 years and above	1 article[31]

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^2 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[13,34]
Mammography for transgender women undergoing hormone therapy for more than 5 years	3 articles[15,23,27]
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[12,14,21,28,35]
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/m^2; family history of breast cancer	6 articles[16,18,20,22,31,33]

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[16,28,30-33].

Most health professionals receive less or no training to provide clinically and culturally appropriate health care to these patient groups[7,14,34,35].

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[27,29].

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[13,16,20,36] 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)[13,16,20,36].

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[13,16,20,36].

As in the female transgender population, the relationship between hormone therapy and the onset of breast cancer is not well established[14,20,36]. 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[13,16]. Chotai and colleagues[20], 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[20].

Regarding the published studies of breast cancer in male transgender people, Blok and colleagues[29], with a sample of 1,229 men, identified four cases of invasive breast cancer, with a mean age of 46 years. Kiely[27], 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[24,28].

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[21,36]. For those who opted for a complete mastectomy, two authors recommend an annual clinical examination of the chest wall and armpits[21,27,28]. 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[21,27,28,36-38].

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[15,16,31,34].

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[15,24,26,27,30,34,35].

According to the study by Pivo and colleagues[32], 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[13]. The study by Kiely[27] 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^2 in menopausal women, early menarche, late menopause, and moderate or high alcohol consumption[27].

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[6].

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[26,31,33,34]. 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[19,31].

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[22,31]. 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[29,33,34].

Regarding the studies that present case reports of breast cancer cases in transgender females, Hartley and colleagues[31] 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%)[31].

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[12,22,29,33,34].

In the Dutch study by Blok and colleagues[29], 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[29]. 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)[29].

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[12-16,18,20-23,27,28,31,33]. 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[4,11].

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[6].

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[21] and Hartley and colleagues[31], 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[8,9,23].

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.

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REVIEW ARTICLE
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Free nipple graft: current indications and applications of a centenary breast surgery technique – an integrative review

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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[1,2]. Its application was originally meant exclusively to reduction mammaplasty, but later expanded its role into areas of mastology intervention, such as oncoplastic surgery[3] and chest adjustment surgery in transgender males[4,5]. 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[6]. Randomized clinical trials (RCTs) have shown that conservative therapy is ineffective in improving symptoms and that reduction

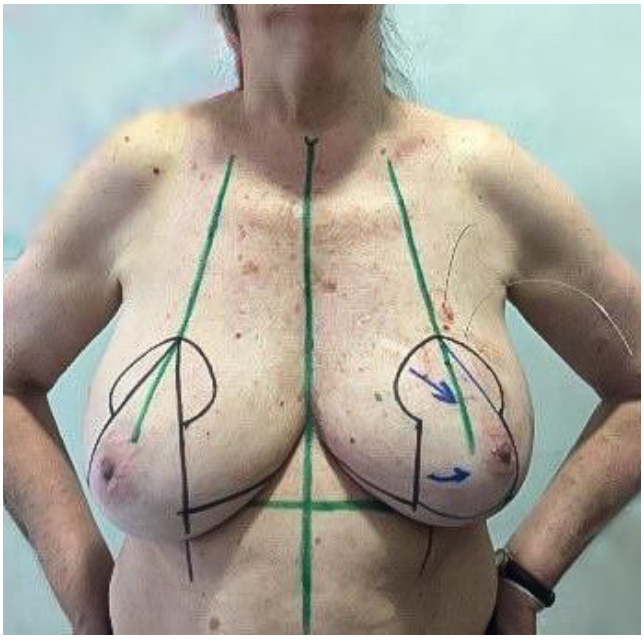

Figure 1. Preoperative marks that guide the surgical approach and incision sites. The upper blue arrow indicates the position where replacement of the nipple graft should be implanted.

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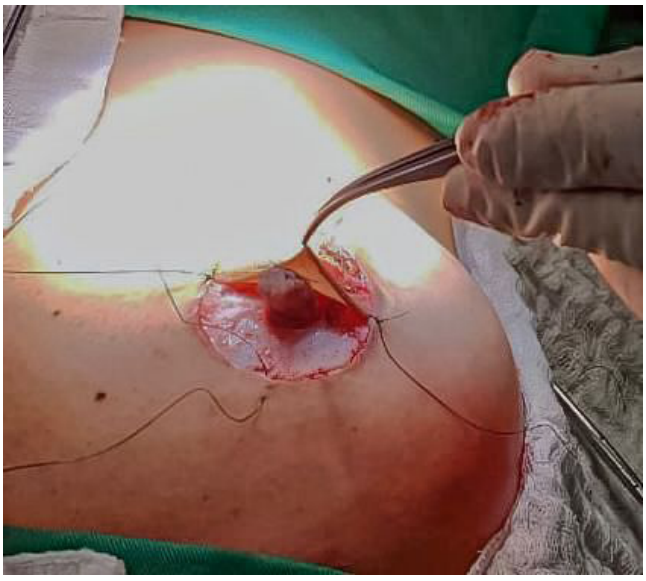

Figure 2. The nipple areolar complex is de-epithelized, as a graft, that must be preserved in a saline solution while breast parenchyma is resected.

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'[7] physical and psychological complaints, with approximately 129,000 surgeries being performed in 2017 with this purpose, according to the National Association of Plastic Surgeons[8].

In this scenario, the technique first described by Thorek[1,2] 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[1]. Despite its aesthetic functional limitations, related to insufficient breast projection and total loss of sensibility and lactation function of the nipple[1,2,9-11], FNG remains the first choice technique in patients with gigantomastia weighing 1000 g and ptotic breasts[11]. Moreover, modifications of the original technique are providing new alternatives for indicating the use of FNG[9-11].

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[5]. 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[4,5].

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[12]. 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[13-16]. A total of 824 patients and 1648 operated breasts were analyzed, with an average of 1250 g of resected parenchyma. The other six articles[17-22] 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[23-27], with 343 patients and 721 mastectomies analyzed.

Roje et al.[13] 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.[14], in a retrospective analysis of 715 mammaplasty reduction surgeries, with a mean age of 38 years old, 27 kg/m^2 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[14,15] 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.[15] 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.

Fırat et al.,[16] 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,

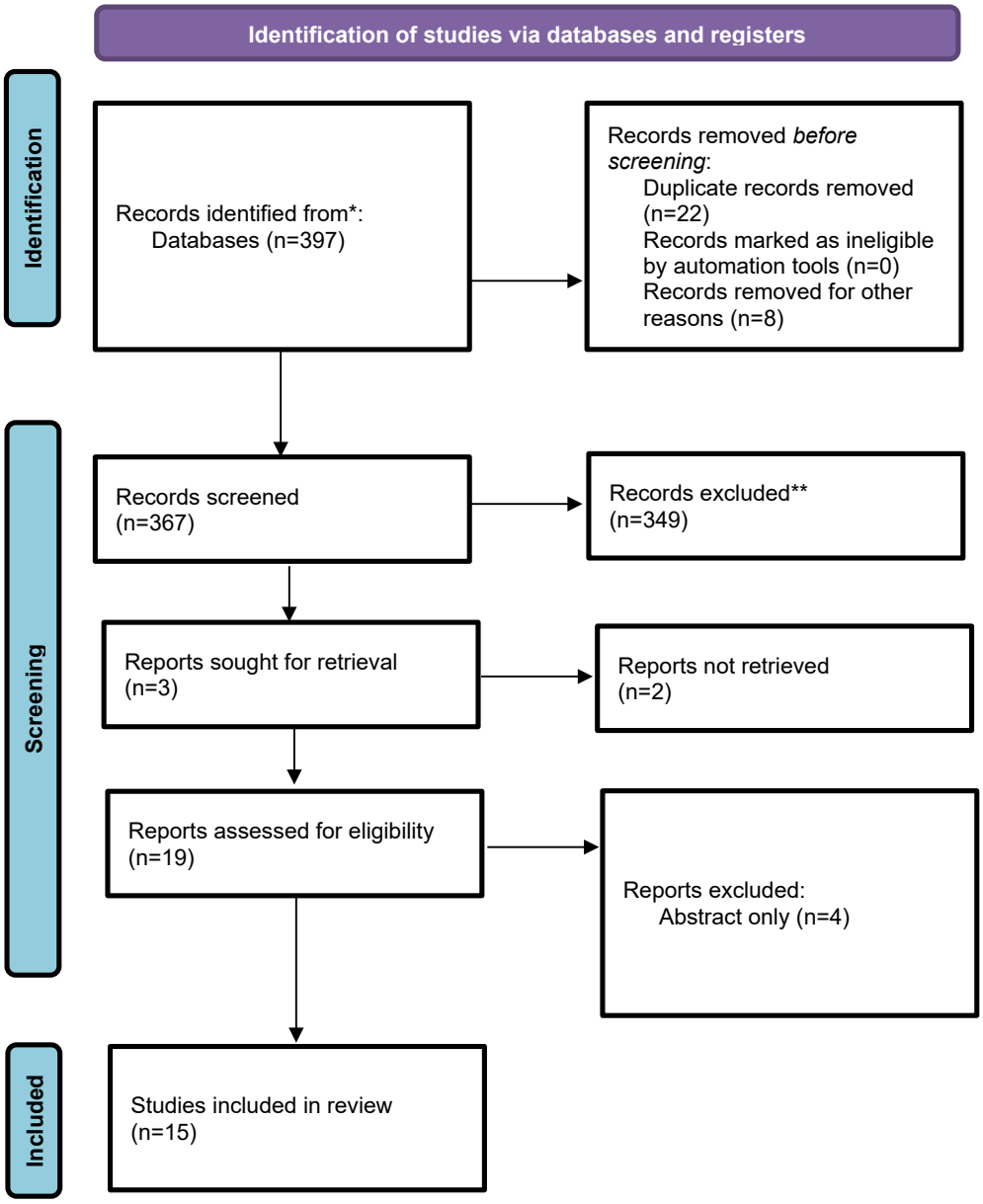

Figure 4. Prisma flow diagram.

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 according to title, author, year of issue, procedures, number of patients, and results.

Title/theme	Author and year of issue	Procedures and number of patients	Results
Mammaplasty			
Current trends in breast reduction	Roje et al.[13]	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.[14]	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.[15]	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.[16]	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.[17]	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.[18]	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.[19]	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.[20]	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.[21]	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.[23]	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.[24]	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.[25]	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.[26]	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[13,18]. 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.[18] and Egozi et al.[19]. The nipple-sparing mastectomy (NSM) is a consolidated technique to achieve aesthetic results in mammary reconstruction[5,18,19]. 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.[18], 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.[18] 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.[19] 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 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 necrosis[18].

Ghiedei et al.[20] 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[18,19]. 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.[21], 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 [18-21] when undergoing FNG and skin-sparing mastectomy in a single surgical time.

King et al.[22] 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 one-stage 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 [4,5].

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.[24], 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.[25] 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 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.[26] 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.[27] 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^2 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[14,15] 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.[9] and Abramson et al.[10]

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.[11] 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[24-26]. That gives support to Colen et al.[11] 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.[28]. 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[17,22] 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.[28] 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[17-22] 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.[14], 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[29] 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.[23] were the only authors who approached a lasting satisfaction over 1 year in contrast of the other articles on transgender surgery[24-27]. This aspect could be more explored since nonlasting results may have impact on self-esteem and morbidity problems in those patients[5].

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[17,18].

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.

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REVIEW ARTICLE
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Global impact of pandemic by SARS-CoV-2 on breast cancer diagnosis and screening

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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[1].

In Brazil, according to Bessa[2], 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

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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 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.

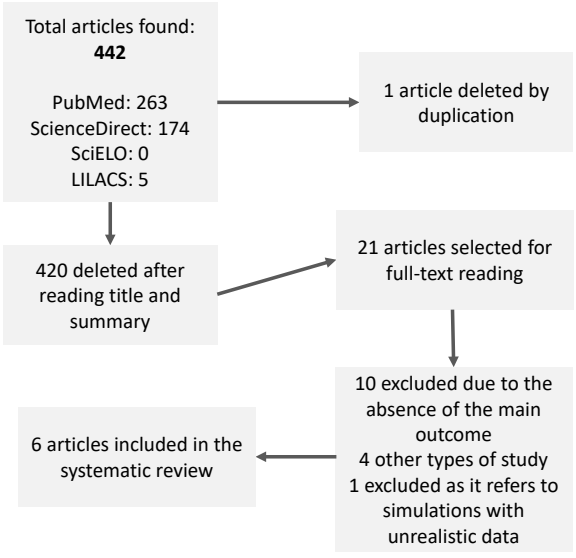

Figure 1. Search strategy flowchart. Passo Fundo (RS), 2021.

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[3,4], one from Belgium[5], one from Brazil[6], one from Croatia[1], and one from Italy[7]. 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[6]. 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 2020[7].

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[3].

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[1]. 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[8]. During the COVID-19 pandemic, there were problems in accessing cancer care services, which includes screening[9], raising some concerns about the delay, and decreased diagnoses of the disease[5]. 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[1].

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.[6] 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[10] 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.[7], Eijkelboom et al.[3], Vrdoljak et al.[1], and Eijkelboom et al.[4] 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.[1] and Peacock et al.[5], 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.[11], which brought up new diagnoses of the disease.

Regarding breast cancer screening tests, when analyzing the article by Lôbo et al.[6], 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.[7], 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.[6] with Bessa[2], there is a difference in results, because Bessa[12], based on DATASUS, showed a 42% drop in the rate of mammograms throughout the

Table 1. Outcomes found in the systematic search.

Reference	Analyzed site	Analyzed period	Breast cancer diagnostic reduction (%)	Mammography reduction (%)	Tumor stage (%)
1. Lôbo et al.[6]	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 al[4]	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.[6], it is only in Fortaleza, Ceará, there was a 95% decrease, which is similar to the data demonstrated by Collado-Mesa et al.[12], whose decrease in mammograms was 98% in Florida, USA. From March to June 2020, the same period as evidenced by Lôbo et al.[6], the article by Song et al.[16] showed a 38% reduction in mammograms expected compared to 2019 in the United States. In another study conducted in the United States[13], 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.[7] 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.[3] and by Eijkelboom et al.[4], with a decrease of 43 and 39%, respectively. However, in the study by Toss et al.[7], 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.[3] 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.[4].

In relation to increased mortality due to delay and decrease in diagnoses, Yong et al.[14] 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[15] 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[16]. 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

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REVIEW ARTICLE
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Optimizing pathological assessment of breast cancer in Brazil: recommendations from a multidisciplinary working group on the tumor-tissue journey

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ABSTRACT

Timely and correct assessment of histopathological, immunohistochemical and molecular features of biopsy and surgical specimens is of paramount importance in the provision of care to patients with breast cancer, particularly in the current era of precision oncology. In order to ensure that tissue samples are obtained, processed, analyzed and reported in an optimal way, a concerted effort is required by institutions and individuals, taking into account state-of-the-art scientific and technical knowledge and circumventing logistic and operational constraints. This may be particularly challenging in some settings due to several sources of economic, structural, organizational and communication inefficiencies. In the current article, we present a brief review of breast cancer epidemiology and challenges in the disease diagnosis, especially in Brazil, and report the results of a multidisciplinary working group convened in May 2020 in an expert panel to identify and discuss the barriers and challenges related to the journey of breast cancer samples in Brazil. Following the identification of the issues, the working group also discussed and proposed recommendations for improving the journey and quality of breast cancer samples based on their professional experience and the current scientific literature, including guidelines of national and international health organizations (e.g. World Health Organization), consensus of medical societies and other published literature on the topic. We outline the most salient issues related to that journey in Brazilian public and private medical institutions, based on the experts' clinical experience, since all of them are actively working at both sectors, and discuss current recommendations to address these issues aiming at mitigating and preventing preanalytical and analytical issues affecting diagnostic and therapeutic decisions. Such issues are grouped under four headings pertaining to education, communication, procedures in the operating room and sample transportation, and procedures in the pathology laboratory. Selected recommendations based on the current literature and discussed by the group of Brazilian experts are reviewed, which may mitigate the issues identified and optimize diagnostic and therapeutic decisions for patients with breast cancer, currently the most frequent malignant tumor worldwide and in Brazil. This paper has been submitted and published jointly, upon invitation and consent, in both the *Surgical and Experimental Pathology* and the *Mastology* journals.

KEYWORDS: breast neoplasms; specimen handling; pathology; interdisciplinary communication; treatment outcome; precision medicine.

INTRODUCTION

With an estimated 2.3 million new cases every year, breast cancer is currently the most frequent non-cutaneous malignant tumor worldwide[1]. Breast cancer currently accounts for one in four new cancer cases and one in six cancer deaths among women worldwide[1], and one in eight women born in developed countries are expected to develop the disease in their lifetime[2]. The burden of breast cancer continues to increase worldwide, particularly in developing countries, notwithstanding the great achievements of the past decades in terms of mammographic screening, increased understanding of genetic and environmental risk factors, and treatment[1,3,4]. Like many countries, Brazil

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faces an increasing challenge in providing health care to cancer patients; in this country, breast cancer is now the most frequent non-cutaneous malignant tumor in both sexes combined[5], but several barriers need to be overcome in the attempt to provide comprehensive diagnosis and treatment for our patients at the national level[6-8]. Moreover, Brazil has a dual health-care system, whereby nearly 75% of the population relies on medical care provided by a government-funded public system, and the remaining 25% has access to private health insurance[9]. Despite the attempts of the public system to provide full and comprehensive care to all citizens, access to health care in Brazil is very heterogeneous.

One of the greatest recent changes in our understanding of breast cancer has been the creation of a molecular taxonomy with diagnostic and therapeutic implications[4,10,11]. As a result, systemic treatment for molecularly defined subtypes of breast cancer has led to an increasingly complex decision tree for the management of patients with early-stage, locally advanced and metastatic disease[12-18]. This approach to treatment has paved the way to precision oncology, marked by the development of monoclonal antibodies and signal-transduction inhibitors of several relevant pathogenic alterations found in breast cancer and other tumor types. Thus, therapeutic decisions are now guided by comprehensive analysis of such alterations, and the molecular profile of each patient's tumor now routinely accompanies histopathological assessment[19,20]. Moreover, biological features (tumor grade, estrogen and progesterone receptors [ER and PR] and HER2 expression) and gene expression-based assays with prognostic relevance are now included in the 8th edition of the American Joint Committee on Cancer staging manual for breast cancer[21]. Finally, reliance on genotypic and molecular phenotypic features is only likely to increase in the future, as a result of the increasing role played by precision oncology in the treatment of patients with breast cancer[22-25].

For all these reasons, timely and correct assessment of histopathological, immunohistochemical (IHC) and molecular features of biopsy and surgical specimens is of paramount importance in the provision of care to patients with breast cancer. As a result, a concerted effort needs to be continuously undertaken by institutions and individuals in order to ensure that tissue samples are obtained, processed, analyzed and reported in an optimal way that takes into account state-of-the-art scientific and technical knowledge and circumvents logistic and operational constraints. This may be particularly challenging in some settings due to several sources of inefficiency in terms of economic, structural, organizational and communication features that preclude optimal pathological assessment of tumor specimens. In the current article, we present the issues related to the journey of breast cancer samples in Brazil that were identified and discussed by a working group convened in an expert panel and review important recommendations selected by the group based on the current literature and guidelines and also on their professional experience to address these issues. This paper is part of a larger initiative that aims to improve the health-care journey of breast cancer patients in Brazil[6]. The article was developed through a collaboration between members of the Brazilian Society of Pathology, Brazilian Society of Mastology, Brazilian Society of Histotechnology, and Brazilian Society of Operating-Room Nurses, and has been published jointly by invitation and consent in both, the *Surgical and Experimental Pathology* and *Mastology* journals

METHODS

Composition, objectives and funding of the working group

The multidisciplinary working group was composed of two pathologists (HG and FMC), one breast surgeon (RMSR), one oncology nurse (MIK), and one histotechnologist (DLP) from Brazil with experience or professional focus on breast cancer. The five members work in large hospitals/services located in four states of two different regions of the country. The working group convened in May 2021 in an expert panel upon invitation from Roche Produtos Químicos e Farmacêuticos, Brazil, who also had representatives attending the meeting with the aim of organizing it. The working group attempted to identify the most salient issues related to the breast cancer tumor-tissue journey in Brazilian public and private medical institutions, based on their experience, since all of them actively work at both sectors, and discussed the current scientific literature, with the main objective of selecting and reviewing recommendations that may mitigate and prevent preanalytical, analytical, and post-analytical issues that may affect diagnostic and therapeutic decisions. The financial sponsor had no influence on the discussions during the expert panel. Hence all the recommendations reviewed here and the writing of this article rest under the entire responsibility of the authors.

Issues identified and discussed by the working group

The preanalytical, analytical, and post-analytical issues discussed by the working group members were grouped under the four headings presented below and summarized in Table 1.

Professional education and awareness

Adequate knowledge on the part of the various individuals impacted by the tumor-tissue journey is a prerequisite for all the procedural steps required in this process. Each individual needs to understand the process as a whole and in its different steps, their own role, and the roles of others. Table 1 displays the specific issues identified by the experts based on their professional experience; the prevention or resolution of these issues

Table 1. Categories and issues identified as critical for optimizing the tumor-tissue journey.

Categories of issues	Specific issues
Education	• Lack of awareness of the problem • Insufficient knowledge of the various steps of the process • Lack of attribution of clear roles for each team member • Lack of standardization of procedures • Insufficient training
Communication	• Lack of communication among team members • Lack of communication among institutional sectors or departments • Lack of attribution of clear roles for each sector or department • Insufficient provision of information to, or lack of access to, the pathologist • Insufficient provision of feedback by the pathologist
Operating room and transport	• Unduly long time before the sample reaches the laboratory • Distance between laboratory and hospital • Insufficient basic infrastructure, leading to the use of improper containers for sample conditioning and inadequate fixation procedures • Insufficient technological infrastructure, e.g., for digitalizing information • Individual dynamics of operating rooms, e.g., with regard to time-out • Logistic bottlenecks in some institutions • Heterogeneity in organization systems • Incorrect or incomplete labeling of the specimen • Incorrect or incomplete forms accompanying the sample • Poorly designed forms • Lack of standardized identification packaging containing the specimen • Incorrect packaging of the specimen, including omission of buffered formalin • Unduly long-time outside formalin, and use of non-buffered formalin • Inadequate fixation or amount of formalin given sample dimensions • Delayed transportation of the sample to the laboratory
Pathology laboratory	• Insufficient information upon receipt of sample • Incomplete or unclear specification of procedures • Incomplete information regarding time of tissue collection and immersion in formalin • Delay in gross examination and sampling before fixation • Frequent change in provider in public hospitals outsourcing pathology services

can be accomplished with continued education, the creation of standardized operating procedures, and participation in external quality assurance programs. Moreover, institutional buy-in is paramount, because the process cannot rely simply on the goodwill of a few key persons. Institutions need to recognize their role in fostering professional education and awareness, as well as enforcing operating procedures.

Communication and integration within teams

In addition to awareness of their roles in the process, individuals must establish adequate communication with other team members; likewise, adequate communication among institutional sectors or departments is vital, and managers should work to ensure the necessary procedures and infrastructure. This may be particularly critical in publicly funded institutions, where the organization of roles and structures may depend on several layers of administration. Importantly, there must be a two-way communication between the pathologist and the rest of the team, in the sense that the relevant medical and practical information needs to be provided to the pathologist, who in turn must provide feedback to the team about sample quality and issues that may arise. There is often insufficient provision of relevant details, even on the part of surgeons, and this may preclude optimal interpretation of findings. Table 1 summarizes the communication issues identified by the task force members.

Procedures in the operating room and sample transportation

Table 1 also summarizes the key issues identified by the working group members regarding the procedures required in the operating room with the aim of optimizing the quality of the sample. A key issue in some institutions is the unduly long time taken before the sample reaches the laboratory, sometimes due to internal organization of the operating room or due to the physical distance between the hospital and the laboratory where samples will be processed and analyzed. In some cases, insufficient technology, e.g., lack of electronic medical records and barcode system for digitizing information, may increase that time. Other issues may also contribute to that increase, including individual institutional features that may create additional bottlenecks. Once again, institutional will is of paramount importance toward ensuring adequate and streamlined procedures that may ensure the minimum possible time between sample collection and delivery to the laboratory, and the best possible handling of the sample during that journey.

Issues related to sample identification, labeling, conditioning and transportation may occur from sample removal to its

delivery to the pathology laboratory (Table 1). Incorrect or incomplete labeling of the specimen or filling of forms accompanying the sample are unfortunately frequent occurrences. Individuals and the institution play an important role in devoting attention to the design of the forms and the choice of packaging and labeling materials. Of particular concern is the frequent lack of awareness about the importance of buffered formalin and of swift transportation of the sample to the pathology laboratory.

Procedures in the pathology laboratory

The pathology laboratory plays a central role in minimizing issues that may compromise correct and timely information required for diagnostic and therapeutic decisions (Table 1). In addition to standardization and proper implementation of techniques related to sample processing, including those involving conditioning, specimen cleavage and fixation, laboratory personnel must ensure that sufficient information has been provided upon receipt of samples. Very often, forms accompanying samples are incompletely filled. In publicly funded institutions, the practice of outsourcing pathology services is not uncommon, and frequent change in the providers of such services may represent an important hurdle for adequate patient management.

RESULTS

Recommendations to mitigate the identified issues and optimize pathological assessment of tumor specimens

Breast specimens obtained from outpatient procedures or from procedures performed in the operating room for the diagnosis of breast cancer require attention from collection to reporting of histological results. In this journey, several factors may interfere with the quality of the final diagnosis in terms of the disease definition, type, characteristics of greater or lesser biological aggressiveness, presence of hormone receptors, and HER2 expression. These factors guide the selection of the best therapeutic option for each case and, when incorrectly evaluated, may negatively affect patient prognosis.

The tumor-tissue journey of breast specimens involves the participation of physicians, nursing team members, biomedical professionals, biologists, lab technicians, and administrative personnel. As part of the task and based on the current guidelines and the published literature, the experts discussed the steps involved in each of the three phases of the tissue processing journey to review important recommendations. Figure 1 summarizes the steps comprising the pre-analytical, analytical, and post-analytical phases of the tissue journey, although variation may exist in how the steps are grouped[26].

Based on the issues identified (Table 1), the working group selected and discussed recommendations to address each aspect. The recommendations reviewed here were based on the current guidelines and orientations published by international organizations, such as World Health Organization (WHO)[26] and the College of American Pathologists (CAP)[27], and Brazilian Society of Pathology (SBP)[28], among other documents[29,30], as well as on the professional knowledge and experience of the multidisciplinary members of the working group, especially considering the local scenario.

Recommendations are summarized in Tables 2–4 and discussed below, according to the three phases, following the criteria adopted by the WHO guidelines[26].

General recommendations

In all the steps, samples must be identified with the name of the responsible person, the date and time, to ensure traceability. The experts recommend that the sample be accompanied throughout its journey, not only by the medical request form, but also by a document listing all the steps, with the name of the person responsible for each step, date and time, either on paper or electronically. Important information includes:

- Time of sample collection
- Time of sample placing in the fixative
- Cold ischemia time
- Time of sample delivery to the person responsible for transferring it to the pathology laboratory (intra- and inter hospital transport)
- Time of entry at the pathology laboratory
- Time of macroscopic evaluation

Pre-analytical phase

Table 2 displays actions and recommendations for the different steps of the pre-analytical phase[13,16,26,27,31-34].

Sample collection and conditioning

Sample collection is under the responsibility of the physician, surgeon, or radiologist, who is also responsible for filling in the exam request form with clinical information. Information about the time of specimen collection and the time of cold ischemia (defined as the time between removal of the tissue from patient until placement into the fixative) are under the responsibility of the nursing team (operating room) or the radiology assistant (radiology services). The cold ischemia time is an important variable to be emphasized as it can alter the gene expression and protein characteristics, thus interfering with the results of IHC and molecular tests[27]. Regarding this, a cold ischemia time of less than 1 hour is recommended.

The excised material must be clearly detailed in the request form and should be checked by the nursing team before placement in the containers with fixative. Regarding the handling of the specimens before placement in the fixative, there are specific recommendations for outpatient procedures and for surgical

Table 2. Summary of actions and recommendations for the pre-analytical phase.

	Recommendations (13, 16, 26, 27, 31-34)
Sample collection and conditioning	1) Personnel responsible for specimen collection and for completing the request form with clinical information: physician, surgeon, or radiologist 2) Personnel responsible for registering information regarding the time of specimen collection and the time of cold ischemia (defined as the time between tissue removal from patient until placement into the fixative): nursing team (operating room) or the radiology assistant/ technician (radiology services). 3) The excised material must be clearly specified in the request form and checked by the nursing team before placement in the containers with fixative. 4) Handling of specimens before fixation: • Outpatient procedures: keep in saline solution if fixation will not be performed immediately (for example, in cases that require radiography or photographic documentation of the specimen) • Surgical specimens: ◦ Small samples (nodulectomies, lymph nodes, lumpectomy), measuring less than 5.0 cm or at physician discretion, can be immediately placed in the fixative, fully submerged ◦ Larger samples, such as mastectomies and wide local excisions, should be sliced in case they are not immediately sent to the pathology laboratory (see below for details) ◦ Samples that had undergone an intraoperative frozen section should be sent fresh to the pathologist, who will be responsible for the specimen manipulation until the intraoperative diagnosis. After the test, the specimen will follow the same workflow described for samples that are not submitted to intraoperative procedures. 5) Preparation of larger specimens • Specimens with larger volume need to be properly prepared for adequate fixation. Although formalin is a good fixative, its action is slow, as it penetrates the tissue with a speed of 1 mm/hour at room temperature. This information can be used to support the choice of the thickness of the fragments (thinner thickness, in case delays in the specimen dispatch to the laboratory, for example, during the weekend or holidays). It is recommended that surgical specimens be cut in parallel slices performed from the deep fascia towards the skin, without transfixing the surgical piece so it can be recomposed in the laboratory. This procedure needs to be agreed between the pathology laboratory and the surgical team. • The pathologist is responsible for training the personnel involved in the procedure after the specimen excision, such as the surgical team members, technicians, paramedics etc., depending on the local conditions. • Ideally, before slicing, the resection margins should be identified and inked. In this case, it is necessary to dry the specimen using paper towel, apply the ink followed by acetic acid or vinegar so the ink can fix properly without dissolving in formalin and during the processing, thus allowing the proper assessment of the surgical margins. • Inadequate fixation impairs the histopathological diagnosis (differential diagnosis between benign and malignant, histological tumor typing and grading, and the immunoreactivity of target molecules. 6) Specimen labeling and identification (nursing team) • Labels for container or slide identification should be printed using computers or written in pencil in adhesive tape, and contain patient's name and information about the specimen • Ideal scenario: Bar-code or QR code • The label should be placed on the primary container, not in the lid. • Certify that the received specimen matches the description provided in the medical request 7) Placement in the containers • Containers should preferably be rigid, impermeable, break-resistant, and non-reactive to fixatives • Previously identified by the nursing team 8) Fixation • Register the time the specimen was placed in the fixative • Recommended cold ischemia time: less than 1 hour • Recommended type of fixative: 10% neutral phosphate buffered formalin (40% formaldehyde diluted to 10% - elevation of pH to ~7) • Fixative volume: 10 to 20 times the size of the specimen • Fixation time of tumor samples recommended for hormone receptors and HER2: 6-72 hours
Pathological exam request	• Responsibility of the medical team • The request form must accompany the specimen during the complete journey, from collection to the end of pathological exam. • Should specify: ◦ Laboratory of destination ◦ Patient identification ◦ Clinical diagnosis/diagnostic hypothesis ◦ Summary of the clinical history ◦ Procedure performed ◦ Date of procedure • The specimens should be preferably numerate and properly described regarding its type, laterality, and topography • Type of test to be performed (e.g., immunohistochemistry, molecular tests)

Continue...

Table 2. Continuation.

	Recommendations (13, 16, 26, 27, 31-34)

Transportation to the pathology laboratory	• Forms of sending the specimen/material
	  • Intra-hospital transfer (the pathology laboratory is located in the hospital or clinic itself)
	  • Laboratory outside the hospital (transportation using messenger service or mail):
	  ○ Adequate conditioning: primary container (container with the specimen properly identified), secondary (leak-proof) and tertiary (rigid, accompanied by the identification of the sender and the recipient, identification of the biological material, and phone number contact in case of accident).

Table 3. Summary of actions and recommendations for the analytical phase.

	Recommendations[26, 28-30,35,36]

Sample reception at the pathology laboratory	1) Responsible personnel: administrative or technical employee
	2) Verify the list of dates/times registered for the steps/procedures previously performed
	3) Register date and time of sample receipt
	4) Confirm the type of tissue (fresh or fixed) and the type of fixative, and register the date of entry at the laboratory
	5) The criteria for sample acceptance and rejection and the recommendations for exams to be performed in samples with restriction must be clearly specified in written instructions
	6) Reasons for samples rejection:
	  • Samples lacking patient identification or with doubtful or incorrect data
	  • Inconsistency between the type of sample mentioned in the exam request form and the type of material received
	  • Samples without a medical request form
	7) Factors that limit sample condition (notified at the registry of exam entry)
	  • Fixative is inadequate or absent
	  • Broken or cracked containers/slides with possible partial leakage of material
	  • Information about the dates/times of the previous steps is unavailable
	  • Inadequate proportion of fixative to specimen
	  • Large specimen not previously sectioned
	  • Inadequate containers
	  • Exam request form incomplete
	8) Specimen registration and transfer to macroscopy

Specimen registration in the laboratory	• Verify if specimens retrieved from the container used for transportation match the information provided in the labels and in the request form • If specimen and identification data match, a unique identification number is attributed for the sample to allow tracking during the process • When possible, use barcode labels to improve traceability of all materials of a single case (sample fragments, paraffin blocks, histological slides, routine and special staining, etc)
Macroscopic examination	• Manually performed by pathologist or laboratory technician • Verify the correspondence between the specimen/sample identification on the label and the request form, confirming the laterality and tumor location in breast quadrants • Follow the test and sampling protocols recommended by scientific societies of pathology and international institutions • Verify if fixation was properly performed • Measure the size and weight of the tissue surgical piece • Ink the surgical margins with different ink colors • Cut the specimen into thin, parallel, and cross-sectional slices, avoiding damaging or clamping the tissue • Describe the observed alterations in relation to the color, texture, consistency, delimitation of the adjacent tissue • Measure the lesions found in the macroscopic examination • Use clean cut surfaces and instruments to avoid cross-contamination with other samples • Special care is required for fine-needle biopsies to assure the inclusion of all fragments • Choose appropriate and labeled cassettes for each type of material, avoiding placing excess material • Describe and measure the lesions visualized in the macroscopic examination, registering information regarding the topography in relation to the anatomic position and distance from the nipple (when present) and surgical margins
Histological processing	• Performed by laboratory technicians using tissue processors • Use of adequate time of tissue processing for each type of specimen • Needle biopsies require shorter time in each reagent during processing than specimens from surgical resections

Continue...

Table 3. Continuation.

	Recommendations[26, 28-30,35,36]
Paraffin embedding technique	• Performed by laboratory technician • Manually (handling-processing) or with the use of a paraffin embedding machine • Avoid excessive heating of paraffin • Check the paraffin temperature regularly • Avoid overfilling of each mold/block • Samples should be carefully oriented, handled and positioned in the inclusion blocks
Microtomy	• Performed by a laboratory technician • Use high quality blades • Optimize the knife angle of inclination in the microtome • Slice the paraffin embedded tissue blocks carefully • Avoid freezing damages • Slice blocks in thin sections (3 to 5 micrometers), gently and slowly
Tissue floatation in water bath and placement of the paraffin embedded tissue sections on slides	• Use clean water • Certify that blades/knives are clean to avoid cross-contamination • Avoid simultaneous floating of various cuts in the water bath chamber • Check water bath temperature • Avoid excessive expansion and damage of tissue sections • Carefully choose tissue section with no folding or extensive distension • Avoid the formation of bubbles under the tissue sections that could lead to the detachment of the sections during histological staining
Dehydration of histological sections	• Dry the histological section before placing it in the histological incubator to dehydrate • Incubator temperature and dehydration time should be monitored
Routine staining	• Staining with hematoxylin and eosin are routinely performed manually by the histotechnician or using specific equipment (autostainer) • Histological sections must be completely deparaffinized before staining • Reagent should be regularly renewed • Use standardized conditions and protocols for staining, adopting precise times and quality constant monitoring
Coverage of tissue sections with coverslip	• Histological sections should completely dehydrate before mounting • Place the mounting medium and cover with cover slip • Avoid excessive drying, formation of crystals or bubbles.

Table 4. Summary of actions and recommendations for the post-analytical phase.

	Recommendations[13,16,26]
Slide reception by the pathologist	• Verify the clinical data provided in the pathological exam request form (age, clinical diagnosis, clinical information, imaging findings, neoadjuvant treatment, procedures performed) • Check the identification of the slides (name, number) • Review data from the macroscopic examination (type of specimen received, sampling, lesion features of the lesion(s), specimen dimension and localization)
Slide interpretation	• Follow the recommendations of standardized manuals and guidelines: o Manual for Standardization of Histopathological Reports of the Brazilian Society of Pathology: http://www.sbp.org.br/manual-de-laudos-histopatologicos/ o Protocols for Cancer and Biomarker reporting released by the College of American Pathologists (CAP): https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates o Guidelines on TIL-assessment developed by the International Immuno-Oncology Biomarker Working Group on Breast Cancer: https://www.tilsinbreastcancer.org/ o Residual Cancer Burden Calculator after neoadjuvant treatment http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3 o AJCC/TNM for anatomopathological staging and prognosis: https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%20Breast%20Cancer%20Staging%20System.pdf • Use standardized synoptic reports specifically designed for each type of specimen • Include in the report information regarding the sample quality (see description below) o adequate: no impact on histological, immuno-histochemical and molecular assessments o limited: can possibly impact on histological, immuno-histochemical and molecular assessments o inadequate: impairment of the histological, immuno-histochemical and molecular assessments

Continue...

Table 4. Continuation.

Sample quality	• Sample quality must be assessed • If sample quality is limited or inadequate, specify the causes: ( ) Cold ischemia time: o 1h-8h o 8h-12h o 12h-24h o >24h ( ) Fixative: o Non-buffered formalin o alcohol o no fixative o other: _____ ( ) Fixative volume is inadequate ( ) Fixation time: o <6h o 6-72h o 72-96h o >96h ( ) Histological sections with technical artifacts o thick sections o signs of excessive heat in paraffin o signs of excessive heat in water bath o excess of folding o clamping artifacts o thermal artifacts o loss of material during microtomy o inadequate staining (weak or strong) ( ) Immuno-histochemistry reaction o no internal control o no external control o presence of artifacts in the histological sections o abnormal staining
Suspected inconsistencies	• Notify if clinical, imaging, histological and immunohistochemical findings are consistent. • Examples of inconsistencies: • Radiologic image with extensive microcalcifications, invasive neoplasm with apocrine pattern, but HER2-negative • Low grade carcinoma, with low proliferative activity, but hormone receptor-negative or hormone receptor-low • HER2-positive carcinoma, but with low grade, low proliferative activity • High-grade carcinoma, high proliferative activity, but hormone receptor-positive/HER2-negative

specimens, as detailed in Table 2. Large tumor specimens require preparation for adequate fixation. Recommendations regarding sectioning before fixation, including the thickness of the sections, type of fixative and fixation time are provided in Table 2. This is an important topic, as inadequate fixation impairs the histological diagnosis (differential diagnosis between benign and malignant, histological typing and grading, and the immunoreactivity of target molecules, especially those of cytoplasm or membrane localization, such as programmed death 1 ligand [PD-L1], HER2, etc)[31-33].

Recommendations regarding sample identification, which is an attribution of the nursing team, characteristics and labeling of containers, fixation registry, duration, and fixative solutions are also detailed in Table 2. 10% neutral buffered formalin is the fixative solution most frequently preferred for routine histological preparations of surgical specimens. Monitoring the fixation time is critical. For hormone receptors and HER2, a fixation time of 6-72 hours is recommended[13,16].

Exam request

As previously mentioned, the medical team is responsible for completing the request form with clinical data and specimen information. The precise and complete filling of this form is of crucial importance to the tissue journey.

Transportation

The last step of the pre-analytical phase is the transportation of the sample to the pathology laboratory, which may be located at the same hospital/service involved in the specimen resection or may be in a different, distant location. Special care must be taken when transporting surgical specimens from the operating room to outside pathology laboratories. Specimens must be transported in rigid containers, with an adequate volume of buffered formalin[35]. Information regarding current recommendations in guidelines for specimen transportation is also detailed in Table 2.

Analytical phase

The analytical phase comprises the sample/specimen reception at the pathology laboratory, sample/specimen macroscopic examination, tissue processing, paraffin embedding, sectioning/microtomy of the paraffin blocks, routine staining, special staining, IHC, and other molecular techniques such as ***in situ*** hybridization (Figure 1)[26]. To be performed with safety and quality, this phase requires the establishment of standardized procedures and efficient channels of communication between the pathology laboratory and the clinical-surgical and imaging services where the samples were obtained. In the analytical phase, only a few steps are automated, with several steps in the process being manual, relying on the care and skill of the pathologist (gross examination, specimen cleavage and selection of samples for microscopy) and the laboratory technicians (inclusion and microtomy)[28].

Factors that are determinant to the analytical phase include the criteria adopted for sample acceptance or rejection, the thickness of tissue section into cassette, tissue processor fluid maintenance, paraffin type and temperature, and validity tests and controls[26].

A summary of the actions and recommendations for the main steps of the analytical phase is presented in Table 3 and briefly described below[26,28-30,35,36].

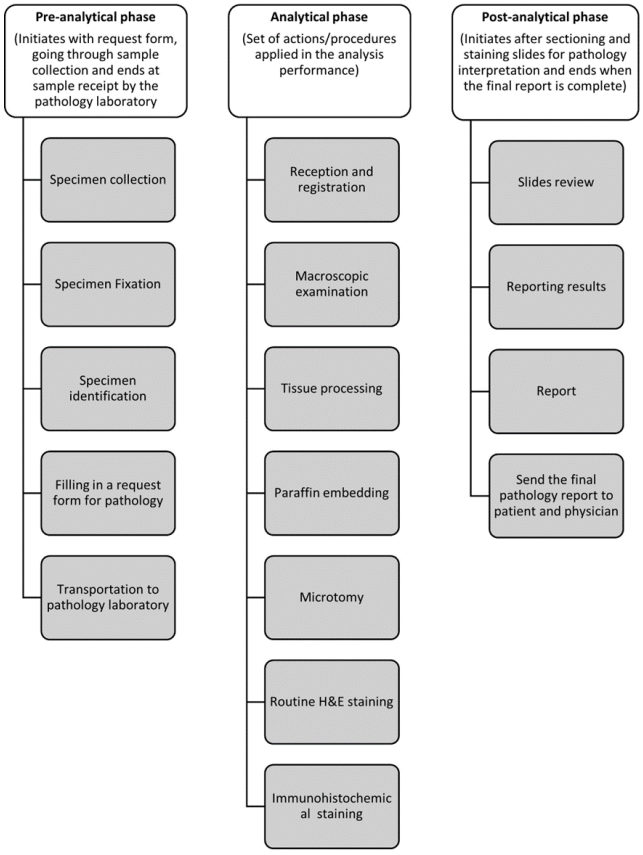

Figure 1. Flowchart of the main steps of the preanalytical, analytical, and post-analytical phases of the tissue-journey, adapted from the WHO document.

Sample reception

The reception of the pathology laboratory is where the samples are received. Upon receipt, it must be guaranteed that each specimen received is accurately labeled with the patient identification and accompanied by the examination request containing clinical information and previous laboratory tests, date and time of collection. The date and time of receipt of the material must be registered in the laboratory, confirming whether the tissue was received fresh or fixed and the type of fixative used. Predetermined rules previously established by the pathology laboratory receiving the samples should be followed for rejecting inadequate specimens whenever needed. These rules must be communicated to all physicians and healthcare professionals who send the materials. Situations in which specimens must be rejected include: unlabeled sample with no information regarding patient name and material identification; insufficient patient information; and information provided in the sample label not matching the patient name on the pathology request form[26,37]. Additionally, there are situations that do not imply rejection of material, but can interfere with the quality of the specimen, exam and results, including: damaged or leaking tube/container; inadequate volume of fixative for the amount of material; material partially dried up due to inadequate volume of fixative; and extended transportation time or other improper handling during transportation[26,28].

It is important that the laboratory communicates to the physician who requested the pathology exam any problem related to the rejection of the sample or the identification of situations that interfere with the quality of the exam.

Sample registration

Upon receipt, one important step is checking if the received specimens match the information and description provided for the case in the container labels and in the request form. Once the correspondence is confirmed, sample registration proceeds with the attribution of a unique identification number to facilitate sample tracking during the process. To improve traceability of materials (sample fragments, paraffin blocks, histological slides, routine and special staining, etc), the use of barcode labels is recommended wherever possible.

Macroscopic examination of specimens

Gross examination is performed by the pathologist or laboratory technicians. This step involves the description of the specimen in terms of shape, color, texture, consistency, and delimitation of the adjacent tissue, the measurement (size and weight) of the specimen, and its dissection. Lesions should be described and measured with information about their topography. More detailed recommendations are provided in Table 3. It is highly recommended to follow protocols and guidelines for testing and sampling established by pathology scientific societies and international institutions[29,30,36].

Histological processing

Tissue processing is performed using an automated tissue processor prior to microtomy. This equipment is maintained by lab technicians for the control of reagents used (formaldehyde, alcohols, xylene, paraffin). The time of tissue processing should be adequate to each type of specimen (Table 3).

Paraffin embedding

After processing, the tissue samples are embedded in paraffin wax. Monitoring paraffin temperature is crucial to avoid excessive heat. Samples should be carefully oriented, handled and positioned in the inclusion blocks. Specific recommendations selected by the working group based on the current guidelines and literature are listed in Table 3.

Microtomy

Sectioning the tissue block with the use of a microtome is the following step. Specific recommendations on sections thickness, quality and positioning of blades were reviewed and are provided (Table 3).

Tissue floatation in warm water bath, placement of the paraffin embedded tissue sections on slides, and dehydration of sections

As part of the process, the tissue slices are placed in a warm water bath. Precautions need to be taken to avoid cross contamination and damage of sections (Table 3). Tissue sections should be carefully selected and placed on slides. Before proceeding to staining, histological sections should be dehydrated. More detailed recommendations are displayed in Table 3 and in the original publication of the cited guidelines.

Routine and complementary stainings

Hematoxylin and eosin (H&E) are the stains routinely used in histopathology. Table 3 displays recommendations for this step. Special stainings (histochemistry) or, more often, IHC stainings, can be used to provide complementary information for diagnosis or for predictive tests for therapeutic response.

Immunohistochemical stain

It can be performed on specific equipments (autostainers) or manually using standardized procedures and specific reagents. Positive-charged or silane coated glass slides are recommended to ensure adherence of the histological sections and avoid loss of material during the different stages of the IHC technique. The choice of reagents (primary and secondary antibodies, detection system, and counterstaining) is of paramount importance and determines the quality of the reactions together with the standardization of procedures. The equipment used must be routinely calibrated. Antibodies should be chosen with care and used following the manufacturers' technical specifications, using antigen retrieval in the appropriate medium when necessary. Use an appropriate detection system, standardize washing steps and optimize counterstaining. An appropriate positive tissue external control should be included on all reactions. The WHO, the College of American Pathologists and the American Society of Clinical Oncology recommend that all primary breast tumors should be tested for hormone receptors (ER and PR) and HER2[13,16,38].

In situ hybridization

In situ hybridization should follow the same precautions recommended for the IHC method using properly fixed tissue and silane coated or positive-charged slides to avoid detachment problems and loss of material. Specific and standardized reaction protocols should be followed. Probes must be carefully chosen for each diagnostic indication, and appropriate controls used for all reactions.

Post-analytical phase

The post-analytical phase involves the interpretation of the slides and the preparation of pathology reports to describe the results. The use of synoptic reports is highly recommended to improve data reporting, as they provide a structured and standardized documentation[26].

As emphasized in the guide published by WHO in 2019, the post-analytical phase also includes the retention and disposal of all the materials containing patient tissues/samples (paraffin blocks and glass slides) and data archiving, with specific recommendations being attributed to these steps[26].

The quality of the sample must be assessed and the reasons for a sample to be considered of limited or inadequate quality must be notified, as described in the recommendations listed in Table 4[13,16,26]. Parameters used to attest the quality of a sample include the cold ischemia time, type and volume of fixative, fixation time, presence of technical artifacts, and factors affecting the IHC reaction/interpretation (e.g., the use of internal and external controls).

Recently, new categories of tumors, based on low expression of the traditional biomarkers ER and HER, have shown important prognostic and predictive differences[39]. HER2-negative 2018 ASCO/CAP group includes tumors with no staining (score 0), incomplete and faint/barely perceptible staining in up to 10% of tumor cells (score 0), incomplete and faint/barely perceptible staining in >10% of cells (score 1+), and those with weak/moderate complete membrane staining in more than 10% of cells (score 2+) with no amplification by in situ hybridization[16,40]. Breast cancer with low HER2 expression, particularly the group denominated HER2-low (score 1+ or 2+ without gene amplification), has shown response to new generation of antibody-drug conjugates, capable of delivering drug to tissues by binding to target cells[41]. However, reproducibility of the correct

classification among pathologists is suboptimal, with discordance of 35% of the cases, in part because of influence of preanalytical artifacts[42]. Pathologists should follow the specimen fixation, processing, and interpretation guidelines proposed by the 2018 ASCO/CAP HER2 test recommendations to ensure the reliability and reproducibility of classifying tumors into different expression categories of this biomarker.

DISCUSSION

The importance of pathological preanalytical and analytical issues to the adequate provision of contemporary cancer care cannot be overemphasized[6,13,16,43,44]. Most issues affecting timely and correct assessment of specimens occur in the preanalytical phase of processing[20,43,44]. Studies suggest that about 60–70% of laboratory errors are due to preanalytical factors[27]. Adequate handling of surgically removed specimens involves labeling, packaging, transportation, fixation and storage, as well as the collection and reporting of administrative, demographic and medical information. Attention to specimens at all these steps may mitigate errors and optimize histopathological, immunohistochemical, and molecular testing in breast cancer.

The relevance of the issues outlined here is only likely to increase, as a result of the increasing role played by precision oncology in the treatment of patients with breast cancer. The time from tissue removal to formalin fixation (cold ischemic time) and temperatures during fixation are crucial[13,16,45]. These parameters are particularly critical for the analysis of ER, PR, and HER2 expression[45]. Among other problems, antigen loss in formalin-fixed tissue sections is sufficient to preclude optimal diagnostic histopathology and IHC studies[44]. Even though we focus our attention on handling of samples for histopathological and IHC assessment, the problem is broader when one considers the increasing role of newer molecular-biology technologies that rely on the quality of tissue RNA in the assessment of gene expression[46]. Prognostic gene expression-based assays play an increasing role and have been increasingly used for decision-making regarding the indication of chemotherapy[47].

If the preanalytical phase is optimized, errors in the analysis or interpretation of results by the pathologist are minimized. Nevertheless, attention is needed to the frequent communication issues identified in Table 1, particularly with regard to insufficient provision of the relevant clinical information to the pathologist. Unfortunately, the pathology laboratory is also place for some of the preanalytical issues that can compromise correct and timely acquisition of information required for diagnostic and therapeutic decisions in oncology[19]. In Brazil, many hospitals do not have their own pathology laboratory, but rather outsource this service, which creates an additional layer of complexity in the attempt to minimize errors. Of note, there is frequent concern about the quality of the services provided by some of these laboratories, which are usually contracted on the basis of public procurement.

CONCLUSIONS

Ideally, patients with breast cancer should be under the care of a multidisciplinary team involving the various specialized professionals required for optimal results[6,12,19]. Although there is overlap between the function of individuals, departments and institutions in terms of their contribution to a seamless tumor-tissue journey, each participant in the process needs to be aware of their contribution and of the overall process. Education, communication, standardization of procedures, and creation of adequate infrastructure are the keys to success, and are ideally achieved in institutions motivated and with the required administrative will. These institutions are further embedded in larger publicly funded or private systems, which must recognize the importance and foster implementation of the issues highlighted here. We hope the recommendations reviewed here can play a role in that goal, and potentially inform public policy related to these issues.

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AUTHORS' CONTRIBUTIONS

HG: Conceptualization, Writing – original draft, Writing – review & editing. FMC: Conceptualization, Writing – original draft, Writing – review & editing. RMSR: Conceptualization, Writing – original draft, Writing – review & editing. MIK: Conceptualization, Writing – original draft, Writing – review & editing. DLP: Conceptualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE
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Integrative medicine and lifestyle in women survivors of breast cancer: an integrative review

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ABSTRACT

Breast cancer is the most frequent among women in the world and in Brazil. New treatment strategies are considerably increasing survival rates in the context of Breast cancer, making it important to study the physical, social, and emotional effects of the disease and its treatments. In this context, integrative medicine emerges as a strategy based on scientific evidence, along with conventional therapy, with a mind-body approach with the use of natural products and lifestyle changes. The aim of this study was to carry out a brief literature review on integrative medicine and lifestyle in women who survived Breast cancer. This is an integrative review carried out with studies indexed in PubMed. Eight search strategies were carried out using the keywords: "survivorship," "breast cancer," "lifestyle," "nutrition," "physical activity," "alcohol," "tobacco," "sleep," "distress," and "relationship," respecting the period between 2015 and 2021. In all, 166 articles were found. Studies that considered other types of cancer and did not focus on the lifestyle of cancer survivors were excluded from the analysis. The remaining 28 articles referring to the proposed theme were read and analyzed in full. The results were described according to the six pillars of a healthy lifestyle proposed by the American College of Lifestyle Medicine, being addressed as follows: (1) nutrition, (2) physical activity, (3) stress, (4) substance abuse (alcohol and tobacco), (5) sleep, and (6) healthy relationships (marital relationships and social support), showing the importance of training health services and professionals in cancer survival programs to provide better guidance to patients with Breast cancer on how to use integrative therapies properly and what lifestyle changes can help optimize various aspects of your health, reducing the risk of recurrence or a new cancer.

KEYWORDS: integrative medicine; lifestyle; cancer survivors; breast cancer.

INTRODUCTION

Breast cancer (BC) is the most common cancer in women worldwide, and its frequency is increasing in low- and middle-income countries[1]. In Brazil, it is not different. According to data from the National Cancer Institute, 66,280 new cases were estimated for each year of the 2020–2022 triennium[2].

With the evolution of treatments, BC survival is increasing, with almost 90% of patients surviving for more than 5 years after diagnosis[3]. Therefore, establishing a smooth post-treatment transition from a cancer patient to a BC survivor is an extremely important goal in the oncology care line[4].

Many BC survivors experience the physical, social, and emotional effects of the disease and its treatments for years after the initial diagnosis[5,6]. Long-term symptoms can include fatigue, pain, neuropathy, lymphedema, insomnia, weight gain, cognitive dysfunction, sexual dysfunction, and a constant fear of recurrence. These women often use integrative medicine (IM) to treat symptoms and long-term adverse effects, often without their doctors' knowledge[5].

The definition of IM and its use for the different treatment modalities vary from country to country and between the different cultures in which they are practiced. IM promotes a person's physical, emotional, and spiritual health by incorporating various modalities, based on scientific evidence, alongside conventional therapy[5].

Studies published around the world report increasing use of IM by people with cancer; it is estimated that 50%–60% use some form of complementary therapy[6]. In the main oncology centers in the United States, patients usually meet with the IM physician for an initial consultation, in which the physician and patient develop an individualized prescription that requests a mind-body approach, use of natural products, and lifestyle change. All

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of this is based on robust literature and guidelines published by the most recognized associations in the area[6,7].

In 2015, the American Cancer Society (ACS), together with the American Society of Clinical Oncology (ASCO), published a care guideline for BC survivors, covering five main areas: (1) surveillance for recurrence of BC; (2) screening for second primary cancers; (3) assessment and management of long-term physical and psychosocial effects and late effects of cancer and its treatments; (4) health promotion; and (5) care coordination and practical implications[8].

This review focuses on the topic related to health promotion and how a healthy lifestyle is essential to improve quality of life, reduce the risk of recurrence and emergence of a second cancer, prevent comorbidities, minimize symptoms secondary to cancer, and thus reduce the risk of overall mortality and specific cancer[4]. In this sense, the objective of this study was to carry out a brief literature review on the topic of IM and lifestyle in women who survived BC.

METHODS

This bibliographic review, of the integrative type, was carried out using the scientific production index PubMed. In the first search, the following search strategy was used: "survivorship" AND "breast cancer" AND "lifestyle," with the delimitation of studies for the period between 2015 and 2021. In all, 166 articles were found. Studies that considered other types of cancer and that did not focus on the lifestyle of cancer survivors were excluded from the analysis. Seven more searches were carried out; in them, the keyword "lifestyle" was replaced, individually, by keywords of the six pillars of a healthy lifestyle, such as "nutrition," "physical activity," "alcohol," "tobacco," "sleep," "distress," and "relationship," also respecting the period between 2015 and 2021. The same exclusion criteria were applied. In the end, there were 28 articles referring to the proposed theme. With the materials already selected for analysis, the exploratory and analytical reading of the articles that, in fact, were of interest to the research began.

RESULTS AND DISCUSSION

The management of BC survivors is now recognized as a new subspecialty[3]. Most individuals far exceed a 5-year disease-free survival rate. However, survivors are at increased risk of recurrence, even 20 years after the initial diagnosis. In addition, they are at increased risk of gaining weight and developing other comorbidities[9].

Studies have shown that an unfavorable lifestyle pre-diagnosis of BC was associated with an almost twofold increased risk of mortality[10] and that the adoption of a healthy lifestyle, after diagnosis, can improve the prognosis and decrease mortality rates in up to 50%[3]. These data were largely consistent across individuals from different socioeconomic backgrounds[10].

The results described below were divided according to the six pillars of a healthy lifestyle proposed by the ACLM[11].

Nutrition

Several risk factors are identified in the pathogenesis of breast tumors; among them, a large number are linked to nutrition and lifestyle[1]. The standard Western diet, high in sugar and fat and low in fiber, results in obesity, insulin resistance, dysbiosis, and inflammation[3].

Body weight is associated with a higher risk of postmenopausal BC. Each 5-unit increase in body mass index was associated with a 5%–50% increase in risk[10] and a 14%–29% increase in cancer-specific mortality[9,10]. Furthermore, patients with obesity have a 6%–10% higher risk of recurrence and a 41% relative increase in mortality compared to their normal weight counterparts[12,13].

The analysis of the correlation between diet and BC is a controversial issue. One of the main limitations in the field of nutrition science is that food and nutrients are not consumed in isolation and, from an epidemiological point of view, form a complex network of correlated influences[1].

Studies suggest that dietary fat increases the risk of hormone receptor-positive BC and the risk of recurrence or death in premenopausal women who survive BC[1,9].

Greater adherence to the Mediterranean diet in BC survivors, particularly rich in fruits, vegetables, whole grains, and foods rich in omega-3, significantly decreases fatigue and improves sleep quality, physical functioning, and general well-being, in addition to promote lower recurrence rate and reduce mortality from all causes[9,12,14].

As with the Mediterranean diet, other diets based on fruits and plants and limiting saturated fats, sugar, red meat, and processed products have shown a reduction in overall mortality and specific cancer[15].

Despite these findings, a large meta-analysis of 15 prospective studies found only a weak association between combined fruit and vegetable intake and BC. The evidence to date is still limited and no conclusions can be reached[8].

A recent meta-analysis of 17 prospective studies associated red meat consumption with a 6% higher risk of BC and a 9% higher risk with processed meat consumption. The 2018 World Cancer Research Found International (WCRF) and American Institute Cancer Research (AICR) recommendation is not to completely avoid eating meat, but to limit consumption so as not to extrapolate 350–500 g/week[9].

The available data on the association of consumption of dairy products with total carbohydrates or specific sugars and risk of BC are contradictory and inconclusive; however, control should be advised[9,14].

The use of green tea, omega-3 and omega-6 polyunsaturated fatty acids, consumption of soy-based foods in Western women,

intermittent fasting, antioxidant vitamin, and mineral supplements have recently been investigated in survivors; however, to date, the data are still immature, and the evidence is limited for a recommendation[9].

The ACS, World Health Organization (WHO), WCRF, AICR, European Society for Clinical Nutrition and Metabolism, and National Comprehensive Cancer Network (NCCN) guidelines guide a dietary pattern rich in vegetables, fruits, whole grains and legumes, low intake of dairy products, red meat, and little or no processed meat, as well as sugar, sweets, and alcohol[4,9,16].

Physical activity

The practice of physical activity (PA) was related to better quality of life after the end of adjuvant treatments in patients with BC, with a reduction in post-treatment side effects, including fatigue, lymphedema, peripheral neuropathy, symptoms of depression, and arthralgia related to aromatase inhibitors[12-14].

Survivors who undergo PA programs also show improvement in quality of life, cognitive function, cardiopulmonary performance, bone health, and the ability to maintain an adequate body weight, with a substantial reduction in the risk of death compared to sedentary survivors[4,13,15].

Studies also show that the intensity of PA has an influence on the degree of clinical benefit. A recent systematic review of 26 observational studies found that cancer survivors who exercise the most had a 37% lower risk of dying from cancer[13].

In line with these studies, patients who practiced high-intensity physical exercise during chemotherapy demonstrated a reduction in the burden of symptoms, less fatigue, better emotional well-being, shorter time to return to work, and lower rates of sick leave compared to the usual care group[17].

Additional studies demonstrate that regular PA after BC decreases recurrence by 24% of the risk of death from specific cancer and overall mortality by 41%[3]. Women who increased their PA after BC reduced the overall risk of death by 45%, while those who decreased it had a fourfold increased risk of death[5].

The ACS/ASCO and NCCN guidelines recommend returning to PA and exercise tailored to individual abilities and preferences as soon as possible. Women should strive to perform PA for at least 150 min/week, with an end goal of 300 min or more of moderate-intensity activity, or 75 min of vigorous activity, two to three sessions per week of strength training, and avoiding prolonged sedentary behavior[4,16].

Stress

Increasingly, clinicians are recognizing that for many survivors, the cancer experience does not end with the completion of therapy. Many problems persist and can affect all aspects of their lives, whether physical, psychological, social, existential, or financial concerns, among others[18].

Unfortunately, long-term survivors are not immune to stress and psychological distress. Not only the risk of a new or recurrent cancer, but also the appearance of comorbidities, such as heart disease, osteoporosis, diabetes, or health problems in general, affect physical and emotional well-being[18].

More than 50% of cancer survivors report ongoing difficulties with recovery and returning to "normal" after treatment. Some experience constant fear of recurrence, suffering, depression, and anxiety, representing enormous emotional, interpersonal, and financial costs for patients and their families, as well as economic consequences for the health system, when depressive and anxiety disorders are not treated[5,18].

Depression is a major public health problem and often goes undiagnosed and untreated in women with BC. If left untreated, depression can cause amplification of physical symptoms, poor adherence to cancer treatment, and increased functional impairment[5].

According to the NCCN, cancer-related fatigue (CRF) is defined as "a distressing, persistent and subjective feeling of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with normal functioning." CRF is a common complaint among cancer survivors and is graded on a scale of 1–10 as mild (0–3), moderate (4–6), and severe (7–10). It should always be addressed individually and based on patient reports and other clinical history data[16].

Treatment of these circumstances is based on well-founded guidelines, such as the ASCO published in 2014, which recommends, in addition to or in place of pharmacotherapy, psychotherapy, mindfulness approaches, expression of positive emotions, spiritual interventions, hope therapy, and interventions of creation of meaning, with a significant improvement in the quality of life and well-being[5].

Cognitive behavioral therapy (CBT) is a structured psychological approach to solving current problems, modifying behavior and useless thinking, promoting a reduction in symptoms of anxiety and depression, improving social life, and finding benefits in the cancer experience, with unquestionable improvement in quality of life[19,20].

Studies with interventions such as mindfulness, breathing exercises, and stretching have shown benefits in mental and physical health with reduced fatigue, anxiety, and symptoms of depression and greater resilience, as well as increased flexibility and psychological adaptation[19].

A Cochrane review concluded that yoga has a similar role in CBT and relaxation exercises for stress reduction, lower levels of fatigue, depression, and anxiety, as well as improved sleep quality, physical health, sex life, and consequent improvement in quality of life[20,21].

In addition to the above-mentioned therapies, the NCCN guidelines for stress management in cancer patients recommend PA, music therapy, dance, spiritual support, activities in support groups, and relaxation therapy as strategies with a level of evidence sufficiently adequate for their use and recommendation[16].

Substance abuse

Alcohol

The habit of drinking between 50 and 100 g of ethanol per day was associated with a 22%–91% increase in cancer incidence and a 31% increase in cancer mortality[14].

Bone loss and increased risk of fractures are clinical problems related to hormonal treatment of BC and excessive alcohol consumption (defined as greater than 2 units (U)/day – 3U/day [1 U equals 300 ml of beer, 1 glass of wine, and 25 mL of distilled beverage]), increasing the risk of osteoporotic fracture by up to 40% when compared to women who consume moderate or no alcohol[5].

The current recommendation for the use of alcohol in female survivors is no more than 1 drink per day[5,16].

Tobacco

Smoking is the most aggravating risk factor for cancer morbidity and mortality[14]. Numerous observational studies show that female smokers have significantly worse overall BC survival than former smokers and never-smokers at the time of diagnosis, with an increase of over 30% in mortality risk[4].

In addition to the negative effects of smoking on the outcome of BC, women who smoke have a very high risk of developing a new cancer in the lung, mouth, larynx, and upper digestive tract[13].

Passarelli et al. observed that patients who stopped smoking had a 33% reduction in the mortality rate from BC[22]. Like alcohol, tobacco use affects bone density and further increases the risk of fracture[5].

Consistent research shows that smoking cessation in BC patients is associated with a better survival status, making it essential for oncology services to prescribe and promote immediate smoking cessation for all survivors[23,24].

Sleep

Insomnia is defined as difficulty falling asleep, staying asleep, or waking up too early, at least three times a week, for at least 3 months. This is one of the problems most commonly described by patients with BC[15,25].

In oncology centers that screen for sleep disorders, up to 75% of patients report insomnia or sleep disturbance at some point after diagnosis; among them, patients with BC are the ones who experience this symptom chronically[25].

As sleep disorders are often multifactorial, it is difficult to define a single etiological factor for insomnia. However, emotional stress is cited by 87% of BC patients; 64% report hot flashes as a cause, and half of them associate difficulty sleeping with pain, discomfort at the surgery site, and treatment side effects[25,26].

Without adequate treatment, insomnia becomes chronic and has been associated with a series of physical and psychosocial consequences, including poor quality of life, fatigue, reduced daily functional activities, loss of productivity, lower rate of return to work, emotional stress, reduced cognitive capacity, lower rate of adherence to hormone therapy, and greater use of the health system[25,26].

Treatment options for sleep disorders include pharmacological and nonpharmacological therapies, used either separately or together, behavioral and psychosocial interventions, sleep hygiene protocols, and PA[15,25].

A range of drugs are described for the treatment of insomnia. Among the over-the-counter medications are diphenhydramine and melatonin, which have been studied in BC survivors with advantages compared to placebo[25].

Commonly prescribed for insomnia, benzodiazepines are associated with increased sleep duration and reduced sleep latency, and their use for short periods is safe, but chronic use can cause dependence and rebound insomnia[25,27].

Nonbenzodiazepine hypnotics such as zolpidem, eszopiclone, and zaleplon showed little benefit in polysomnography; trazodone has a solid benefit in interval insomnia. Quetiapine, gabapentin, mirtazapine, and ramelteon can be considered in selected patients[25,27].

Recently, cannabidiol has been studied for its potential impact on sleep disorders, but high-quality clinical trials are still needed for safe use in cancer patients[25].

Among nonpharmacological therapies, CBT is the most recognized intervention as a first-line therapy for chronic insomnia[27].

The use of mindfulness programs for stress reduction with a focus on meditation, acupuncture, PA, and yoga shows consistent results[25,26].

Healthy relationships

Two aspects of human life are relevant when talking about healthy relationships: marital relationships and social support.

Marital relationships

Epidemiological research highlights the importance of intimate relationships as a determinant of health, especially in times of stress. People with less secure and conflicting relationships have higher cortisol levels, higher levels of inflammation, and poorer immune functioning, increasing the chance of cancer recurrence and development of comorbidities, thus contributing to premature mortality[28].

The benefits of stress reduction associated with satisfying romantic relationships are also evident in BC survivors, helping them to cope with the emotional and physical consequences of receiving a potentially fatal diagnosis and undergoing treatment[28].

BC diagnosis and cancer treatment can negatively impact many facets of your relationships, including time with your partners, open and honest communication, and planning for the future. After survivors complete cancer treatment, it can be difficult to resume their pretreatment or "normal" lives with their partners. These changes in relationship satisfaction over the course of treatment may offer a new avenue for survivors' levels of stress and inflammation, ultimately affecting their long-term health[28].

Promoting survivor relationships and encouraging them to connect with their partners can help reduce inflammation and promote long-term health. The American College of Surgeons Cancer Commission and ASCO recommend that care services for BC survivors conduct

distress screening programs, screening for relationship satisfaction, and ultimately referral for couples counseling when appropriate[28,29].

Social support

Social support is understood as an individual's feeling of being loved and cared for by a social network, and this is a key factor in determining how women face the diagnosis of BC and subsequent treatment[30].

Studies in various parts of the world demonstrate a direct relationship between the quality of the social support network and outcomes during and after BC treatment. Women with adequate support have better health, fewer side effects from hormone therapy, fewer depressive symptoms, and an earlier return to what could be considered "normal life." Research has shown that the ability of survivors to reintegrate into a social structure, even on a new trajectory, is crucial for an extended quality of life[31].

Social support is also a key component of several theories of improving healthier behaviors. For example, higher levels of social support are associated with greater participation in PA among BC survivors and a reduced risk of all-cause mortality and BC-specific mortality[30].

Importantly, the completion of primary treatment coincides with a sudden decrease in health care visits from several times a month during treatment to once between 3 and 6 months during the follow-up phase. This reduction means that patients have fewer opportunities to get support from their health care teams. In addition, patients tend to underutilize their support networks and report receiving less social support from their friends and family within a year of primary treatment. Thus, for many women, the end of conventional treatment marks the beginning of a decline in social support, which can create unmet needs[32].

Paladin et al. evidenced that the presence of relatives and other allies to accompany the patients during medical consultations was a key factor in meeting the emotional and informational needs of the participants, as well as the fact that the support of formal groups with other survivors and the informal support of family and friends are essential for well-being during and after primary treatment[32].

Ultimately, oncology services must address these needs by facilitating connections between survivors, offering more avenues for receiving support from the health care team, and encouraging women to utilize their existing networks, inviting family and friends to be active contributors in their care[32].

CONCLUSION

IM and lifestyle medicine are modern medical disciplines that speak to and complement each other. BC survivors continue to experience adverse effects and sequelae of the disease for many years after diagnosis and use various techniques related to IM to help manage their symptoms, as well as having a keen interest in learning more about lifestyle improvements. After analyzing the available content on lifestyle in the context of BC and the solid scientific data presented, we concluded that it is essential that health services and professionals in cancer treatments be trained in cancer survival programs and educate patients about how to use appropriate integrative therapies and what changes in their lifestyle can help optimize various aspects of their health and reduce the risk of a recurrence or a new cancer.

AUTHORS' CONTRIBUTIONS

REARC: Data curation, Formal analysis, Investigation, Writing – original draft. RSN: Data curation, Formal analysis, Investigation, Writing – original draft. SFVV: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. RJVV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE
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Effects of clinical heterogeneity on Pregnancy-Associated Breast Cancer survival: a systematic review with meta-analysis

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ABSTRACT

Pregnancy-associated breast cancer is defined as a diagnosis of breast cancer during pregnancy or within 1 year of childbirth. Current evidence shows that Pregnancy-associated breast cancer is associated with poor prognosis; however, no systematic review has summarized and explored how baseline characteristics could impact survival. We aimed to explore the impact of breast cancer characteristics on death and disease relapse. A systematic review with meta-analyses was conducted by searching articles in the main databases (Medline, Embase, and Cochrane) and congress abstracts. Summarized death and disease-free survival hazard ratios were recalculated, and all meta-analyses used a random-effects model. Heterogeneity was reported using the I^2 method. A total of 7143 studies were identified and only 30 studies were included. Pregnancy-associated breast cancer is associated with a 96% (HR 1.96; 95%CI 1.58–2.35) higher risk of death and 82% (HR 1.82; 95%CI 1.45–2.20) risk of death or disease relapse in comparison to a population of non-pregnancy-associated breast cancer or nulliparous breast cancer. Through sensitivity analyses, we identified that clinical outcomes were impacted, possibly due to Ki-67 levels, poorly differentiated tumors, and triple-negative breast cancer frequency in the study. As relevant sources of inconsistencies, such clinical cancer-related characteristics should be better investigated as potential confounders for upcoming Pregnancy-associated breast cancer therapeutic strategies.

KEYWORDS: breast; cancer; pregnancy; breast neoplasm; systematic review.

INTRODUCTION

Pregnancy-associated breast cancer (PABC) is a rare type of cancer diagnosed during pregnancy or 1 year following delivery, impacting women of fertile age (23–47 years)[1].

Diagnosed in advanced stages[2-4], PABC is currently associated with the use of less aggressive treatments to address more safety to both mother and fetus[5]. However, poor prognosis persists even after adjustment for several clinicopathological factors, including age at diagnosis, year of diagnosis, stage, tumor grade, and hormone receptor status[6].

Previous systematic reviews attempted to review and pool the risk of death in PABC. Recently, Shao et al.[7] described that PABC patients had 45% more risk of death and a 39% chance of death or relapse compared to a non-PABC control. As an opportunity, we understood that this review did not explore how heterogeneity could affect their results. That is, we believe that by deepening how inconsistency (represented by I^2 in meta-analyses) affects outcomes, baseline differences in the study population could inform better if there is any subgroup of patients who could have a higher risk of disease relapse or death. In addition to those clinical characteristics, heterogeneity might be related to inclusion criteria, available data, and analyses performed. That said, through this review, we question if all PABC patients have the same survival and disease relapse rates and pool the effects of baseline characteristics on outcomes through meta-analyses.

Therefore, this systematic review with a meta-analytic approach focuses on closing this literature gap and explores

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the impact of heterogeneity on different risks of death and disease relapse, suggesting that clinical characteristics should be explored in further studies in order to improve clinical outcomes of patients with PABC.

METHODS

Protocol registration and rationale of review

Our review adheres to the PRISMA statement, and its protocol was registered at PROSPERO/University of York, and it can be accessed online (https://www.crd.york.ac.uk/prospero/ with protocol number: CRD42021272859).

The strategy for manuscript finding included the use of indexed keywords, such as: "pregnant*" OR "gestation*" OR "childbirth" OR "postpartum" OR "parity" AND "breast" AND "cancer" OR "neoplasia" OR "carcinoma."

In this review, we searched studies that could fulfill the following research question: Which clinical characteristics in PABC are associated with best/worst overall survival (OS) and disease-free survival (DFS) when compared with a population without PABC?

Data sources and searches

We reviewed four formal databases: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Lilacs. Other relevant databases were also studied:

1. The San Antonio Breast Cancer Symposium,
2. American Society of Clinical Oncology (ASCO) abstracts,
3. European Society for Medical Oncology (ESMO) abstracts, and
4. USP Digital Library of Theses and Dissertations.

Searches included published manuscripts from 2000 to August 30, 2021. No language restrictions limited our search strategy. For definition purposes, PABC was considered "the diagnosis of BC in women during pregnancy, or until 1 year of post-partum."

Eligibility criteria included

1. studies with a follow-up period longer than 6 months;
2. participants who were diagnosed with any TNM type of BC;
3. studies that had two groups comparing PABC versus non-PABC or nulliparous BC patients;
4. studies that contained information on OS and/or DFS; and
5. the risk point estimate was reported as a hazard ratio (HR) with 95%CI, or the data were presented such that an HR with 95%CI could be calculated.

Study selection and data extraction

Selection by title and abstract reading, inclusion by full-text reading, and data extraction were performed by two independent reviewers. In case of discrepancies between the two, a third reviewer was invited to make decision.

The following data were extracted:

1. general study information (country that the research was developed, PABC and non-PABC definition, and matching criteria);
2. PABC characteristics (age, stage, histologic grade, TNM, hormonal receptors, and HER2 status);
3. PABC treatment (chemotherapy, hormone therapy, radiotherapy, and type of surgery such as axillary lymph node dissection, breast-conserving surgery, sentinel lymph node dissection, and mastectomy); and
4. outcomes (OS and DFS).

Data synthesis and analysis

We performed a descriptive assessment of the included manuscripts by summarizing them in tables containing their clinical characteristics. Outcomes were meta-analyzed to determine the pooled HR of OS and DFS. To facilitate the interpretation of the results, OS and DFS were modified, so one would interpret them as deaths/mortality and disease relapse or death, respectively. Meta-analyses were conducted considering random-effects models and estimates were reported with their respective 95%CI. Heterogeneity was measured based on the I^2 method, where values >30% were considered heterogeneous. In the case of heterogeneity, sensitivity analyses were conducted by removing the outlier study. For these analyses, we used R-Studio (***meta*** and ***metaphor*** packages)[8] to summarize the occurrence of these events.

RESULTS

A total of 7143 studies were identified, of which 142 titles were screened and compatible with our preestablished inclusion criteria. During the eligibility phase (full-text reading), 30 studies[5,9-37] were included for completed text reading and 23 for meta-analysis (Figure 1). Overall, this systematic review comprised 4406 PABC and 130,860 non-PABC patients.

Pregnancy-associated breast cancer characteristics

Most of the included 30 studies were performed in the USA (20%), France (13.3%), and Korea (10%), among other nationalities: Taiwan, Spain, and Saudi Arabia (6.7%) and Belgium, Brazil, Canada, China, Czech Republic, Greece, Hungary, Israel, Italy, Mexico, and Pakistan (3.3% each). PABC population was commonly matched with non-PABC by age, stage, and year of diagnosis.

PABC patients had an average age of 34.4 years (range: 20–49), with tumors predominantly on stage II (41%) and histological grade 3 (30%) (Table 1). In the TNM classification, T2 (24%) and N0 (13%) were the most reported, and only 3% of the tumors were initially metastatic diseases. Most studies (54%) reported positive hormone receptors; while HER2 status (13%) and subtype of BC, such as TNBC (6%), were not commonly described.

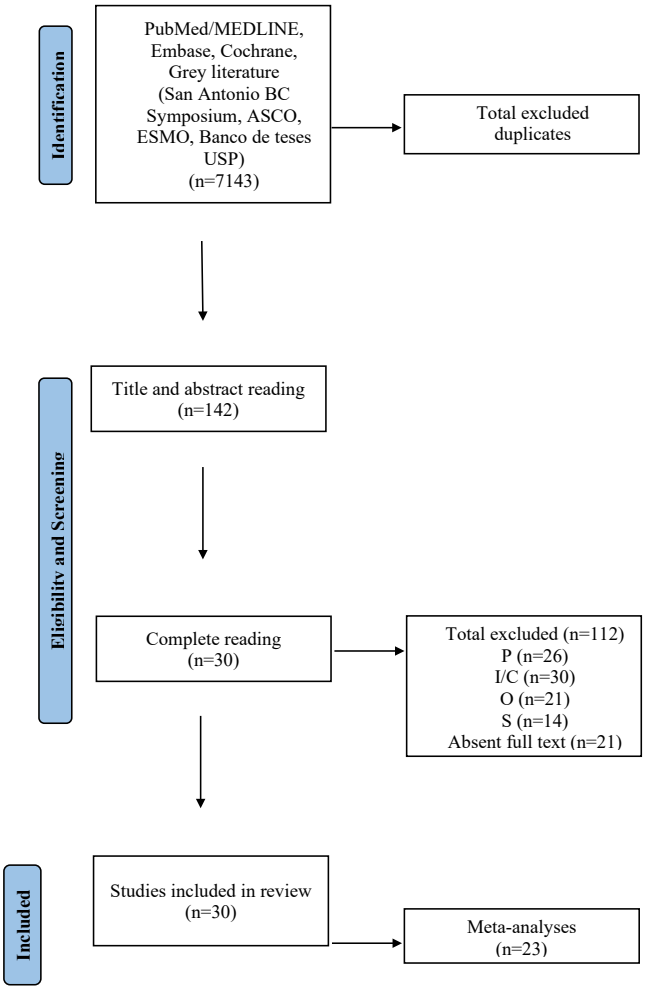

Figure 1. Flowchart of manuscript selection.

When described, 57% (±18%) of patients were hormone positive, 22% (±8%) were HER2+, and 32% (±7%) were TNBC subtype.

Exploring treatment options (Table 2), 72% of the PABC population received chemotherapy, of which only 10% underwent neoadjuvant/adjuvant schemes during pregnancy. Regarding surgical approach, 39% of patients received a mastectomy, 21% had breast-conservative surgery, 18% performed axillary lymph node dissection, and 11% had sentinel lymph node dissection.

Deaths

Overall, 21 studies involving 3383 PABC and 100966 non-PABC patients were included for meta-analysis. PABC patients were associated with a 96% higher risk of death (HR 1.96, 95%CI 1.58–2.35) in comparison to the non-PABC population (Figure 2a). The heterogeneity for this meta-analysis was considered high (I^2=95%).

Through sensitivity analysis (Figure 2b), when studies by *Madaras et al.* and *Mathelin et al.* were removed and a new pooled HR was calculated (HR 1.39, 95%CI 1.21–1.56), heterogeneity dropped down by 22% (I^2 was 95% before sensitivity analysis and 73% after sensitivity analysis). PABC-related death decreased by 56% in comparison to non-PABC. This suggests that studies by Madaras et al. and Mathelin et al. could be considered important sources of heterogeneity that increased the risk of PABC-associated deaths. Finally, through funnel plot analysis, it could be seen that there was publication bias (p=0.03) (Figure 2c).

Disease relapse or death

A total of 986 PABC and 3267 non-PABC patients enrolled in 11 studies were considered for DFS analysis. PABC patients have an 82% (HR 1.82, 95%CI 1.45–2.20) increased risk of death or disease relapse. Heterogeneity for this meta-analysis was also considered high (81%) (Figure 3a).

In sensitivity analysis (Figure 3b), by removing studies by *Siegelmann-danieli et al.* and *Mathelin et al.*, the heterogeneity was reduced by 30%, lowering the risk of disease relapse or death by 29% (pooled HR in sensitivity analysis=1.53, 95%CI 1.29–1.77). There was publication bias for this analysis (p<0.001) (Figure 3c).

DISCUSSION

In these recent meta-analyses about BC and pregnancy, we could identify that PABC, compared to the non-PABC population, has the worst prognosis in observational studies. PABC is associated with a 96% higher risk of death and an additional 82% risk of death or disease relapse in comparison to a population of non-PABC or nulliparous BC.

In addition, the present meta-analysis identified that studies by Madaras et al.[26], Mathelin et al.[27], and Sigelmann-Danielli et al.[35] were essential sources of heterogeneity for mortality and disease relapse outcomes.

Removing studies by Madaras et al. and Mathelin et al. from OS meta-analysis reduced heterogeneity by 22% and PABC-related mortality by 56%. In the meta-analysis of DFS, extracting studies by Sigelmann-Danielli et al. and Mathelin et al. improved heterogeneity by about 30% and minimized PABC-related relapse or death by 29%.

When PABC characteristics from the study by Madaras et al. are explored, it could be seen that all patients had Ki67 levels ≥14%, 84% were considered high histological grade, and almost half were classified as subtype triple negative. All these characteristics are considered predictors of poorer prognosis. Recently, Zhu et al. suggested that in a TNBC population, Ki67 levels were independent predictors of death[38]; however, they identified that the optimal cutoff score for predicting survival was 30% and the population was not specifically for PABC. On the other hand, Madaras et al. provided a lower cutoff point, suggesting that the most recent study by Zhu et al.[38] might provide relevant insights on clinical characteristics that might impact mortality in patients with BC, and possibly also in PABC. However, we found no study about the impact of different Ki67 levels was conducted in the PABC population.

Table 1. Pregnancy-associated breast cancer tumor characteristics

Author, year	Age (range)	Stage n (%)					Grade n (%)			T n (%)					N n (%)				M n (%)	HR n (%)	HER2 n (%)	TNBC n (%)
		0	I	II	III	IV	1	2	3	0	1	2	3	4	0	1	2	3				
Ali et al.[9]	33 (24–42)	NR	5 (12.5)	27 (67.5)	6 (15)	2 (5)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	22 (55)	NR	NR
Amant et al.[10]	33 (31–36)	NR	48 (15.4)	177 (56.9)	86 (27.6)	NR	7 (2.2)	67 (21.5)	237 (76.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	145 (46.6)	99 (31.8)	118 (37.9)
Aziz et al.[11]	32 (20–45)	NR	NR	NR	NR	NR	NR	NR	NR	NR	5 (20.8)	8 (33.3)	11 (45.8)	NR	NR	NR	NR	16 (66.6)	NR	NR	NR	
Bae et al.[12]	20–49	16 (3.9)	92 (22.3)	186 (45.2)	85 (20.7)	23 (5.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	272 (66.1)	91 (22.1)	NR
Baulies et al.[13]	35.3 (30.6–40)	NR	33 (58.9)	15 (26.8)	8 (14.2)	26 (46.4)	9 (16)	NR	22 (39.2)	14 (25)	5 (8.9)	7 (12.5)	NR	NR	NR	NR	NR	46 (82.1)	10 (17.8)	NR		
Beadle et al.[14]	33 (16–35)	NR	9 (8.6)	40 (68.4)	54 (51.9)	NR	2 (1.9)	32 (30.8)	62 (59.6)	NR	20 (19.2)	40 (38.4)	28 (26.9)	15 (14.4)	31 (29.8)	30 (28.8)	31 (29.8)	12 (11.5)	NR	66 (63.4)	NR	NR
Boudy et al.[15]	35 (30.5–39)	NR	NR	NR	NR	NR	1 (2)	20 (40.8)	27 (55.1)	1 (2)	20 (40.8)	13 (26.5)	8 (16.3)	7 (14.2)	NR	29 (59.1)	5 (10.2)	30 (61.2)	6 (12.2)	NR		
Choi et al.[16]	<35–≥35	NR	NR	NR	NR	NR	NR	NR	NR	1 (1.6)	21 (33.3)	25 (39.7)	11 (17.4)	5 (7.9)	29 (46)	16 (25.4)	11 (17.4)	7 (11.1)	2 (3.1)	53 (84.1)	13 (20.6)	NR
Chuang et al.[17a]	20–50	NR	24 (26.7)	51 (56.7)	15 (16.6)	NR	8 (8.9)	37 (41.1)	37 (41.1)	NR	26 (28.9)	44 (48.9)	19 (21.1)	NR	45 (50)	19 (21.1)	12 (13.3)	8 (8.9)	NR	64 (71.1)	12 (13.3)	NR
Chuang et al.[17b]	20–50	NR	86 (24.8)	197 (56.8)	64 (18.4)	NR	20 (5.8)	146 (42)	142 (40.9)	NR	127 (36.6)	145 (41.8)	64 (18.4)	NR	160 (46.1)	83 (23.9)	44 (12.7)	29 (8.3)	NR	245 (70.6)	31 (8.9)	NR
Dimitrakakis et al.[18]	34.3 (29.3–39.3)	NR	1 (2.6)	20 (51.3)	15 (38.5)	3 (7.7)	1 (2.6)	3 (7.7)	34 (87.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	33 (84.6)	NR	NR
Framarino--dei-Malatesta et al.[19]	37.2 (34–40.2)	NR	NR	NR	NR	NR	NR	10 (45.4)	11 (50)	NR	10 (45.4)	7 (31.8)	5 (22.7)	NR	11 (50)	8 (26.4)	3 (14.6)	NR	NR	12 (54.5)	NR	NR
Genin et al.[20]	35 (27–40)	NR	NR	NR	NR	NR	6 (6.9)	27 (31)	32 (36.8)	6 (6.9)	20 (23)	29 (33.3)	27 (31)	NR	31 (35.6)	5 (5.7)	42 (48.2)	17 (19.5)	NR			
Halaska et al.[21]	33.7 (25.9–41.6)	NR	NR	NR	NR	NR	2 (6.2)	15 (46.9)	15 (46.9)	NR	6 (18.7)	26 (81.3)	NR	18 (56.2)	6 (18.7)	22 (68.7)	10 (31.2)	NR				
Ibrahim et al.[22]	34 (28.9–39.1)	NR	2 (2.8)	22 (30.5)	29 (40.3)	19 (26.4)	0 (0)	23 (39.6)	35 (60.4)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iqbal et al.[23]	40 (20–44)	NR	111 (22.1)	237 (47.3)	128 (25.5)	25 (5)	NR	NR	NR	NR	79 (15.8)	127 (25.3)	42 (8.4)	NR	NR	124 (24.7)	NR	255 (50.9)	NR	NR		
Kim et al.[24]	33.7 (29.4–38)	13 (3.8)	62 (18)	154 (44.8)	95 (27.6)	20 (5.8)	10 (2.9)	94 (27.3)	170 (49.4)	13 (3.8)	83 (24.1)	155 (45)	66 (19.1)	25 (7.3)	165 (48)	97 (28.2)	45 (13)	31 (9)	NR	136 (39.5)	69 (20)	NR
Litton et al.[25]	24–45	NR	5 (6.7)	36 (48)	34 (45.3)	NR	0 (0)	12 (16)	63 (84)	NR	NR	NR	NR	NR	NR	NR	NR	NR	25 (33.3)	29 (38.7)	16 (21.3)	24 (32)

Continue...

Table 1. Continuation

Author, year	Age (range)	Stage n (%)					Grade n (%)			T n (%)					N n (%)				M n (%)	HR n (%)	HER2 n (%)	TNBC n (%)
		0	I	II	III	IV	1	2	3	0	1	2	3	4	0	1	2	3				
Madaras et al.[26]	34 (28–42)	NR	NR	NR	NR	NR	0 (0)	5 (16.1)	26 (83.9)	2 (6.4)	11 (35.5)	13 (41.9)	5 (16.1)	10 (32.2)	10 (32.2)	6 (19.3)	4 (12.9)	NR	NR	17 (54.8)	6 (19.3)	NR
Mathelin et al.[27a]	33.8 (28.4–39.2)	NR	NR	NR	NR	NR	2 (11)	2 (11)	13 (72)	NR	NR	NR	NR	NR	NR	7 (39)	2 (11)	7 (39)	13 (72)	NR	NR	
Mathelin et al.[27b]	33.3 (29.4–37.2)	NR	NR	NR	NR	NR	5 (23)	7 (32)	9 (41)	NR	NR	NR	NR	NR	NR	5 (23)	4 (18)	15 (68)	19 (86)	NR	NR	
Moreira et al.[28]	35 (31–39)	NR	NR	NR	NR	NR	20 (23)	22 (25.2)	NR	25 (28.8)	61 (70.1)	NR	78 (89.6)	29 (33.3)	39 (44.8)	NR	NR					
Muñoz-Montaño et al.[29a]	35 (21–44)	NR	25 (40.3)	30 (48.4)	7 (11.3)	5 (8)	23 (37)	34 (54.8)	NR	29 (46.8)	33 (53.2)	12 (19.4)	50 (80.6)	NR	31 (50)	14 (22.6)	17 (27.4)					
Muñoz-Montaño et al.[29b]	35 (23–47)	NR	13 (20.6)	31 (49.2)	19 (30.2)	5 (7.9)	19 (30.2)	39 (61.9)	NR	21 (33.3)	42 (66.7)	6 (9.5)	57 (90.6)	NR	20 (31.7)	19 (30.1)	24 (38.1)					
Murphy et al.[30]	NR	NR	NR	NR	NR	NR	2 (2)	11 (11.1)	83 (83.8)	40 (40.4)	48 (48.5)	10 (10.1)	0 (0)	40 (40.4)	29 (29.3)	19 (19.2)	11 (11.1)	NR	65 (65.6)	20 (20.2)	NR	
O'Sullivan et al.[31a]	34.5 (29.5–39.5)	3 (4.6)	10 (15.4)	26 (40)	14 (21.5)	7 (10.8)	1 (1.5)	14 (21.5)	49 (75.4)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29 (44.6)	13 (20)	NR
O'Sulliva et al.[31b]	34.7 (30.9–38.5)	3 (4)	11 (14.7)	25 (33.3)	16 (21.3)	20 (26.7)	2 (2.7)	11 (14.7)	57 (76)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	42 (56)	19 (25.3)	NR
Ploquin et al.[32]	33 (24–42)	NR	NR	NR	NR	NR	2 (1.8)	29 (26.1)	74 (66.7)	22 (19.8)	46 (41.4)	31 (27.9)	8 (7.2)	59 (53.1)	46 (41.4)	NR	56 (50.4)	24 (21.6)	45 (40.5)			
Reyes et al.[33]	37 (34–39)	NR	7 (16.7)	21 (50)	7 (16.7)	7 (16.7)	1 (2.4)	16 (38.1)	21 (50)	NR	12 (28.6)	16 (38.1)	5 (11.9)	7 (16.7)	21 (50)	14 (33.3)	3 (7.1)	4 (9.5)	7 (16.7)	26 (61.9)	11 (26.2)	9 (21.4)
Rodriguez et al.[34]	20–55	NR	139 (17.4)	415 (52)	130 (16.3)	39 (4.9)	NR	NR	NR	NR	235 (29.5)	332 (41.6)	127 (15.9)	27 (3.4)	NR	NR	NR	NR	NR	455 (57.1)	NR	NR
Siegelmann-Danieli et al.[35]	33 (25–37)	1 (4.3)	15 (65.2)	7 (30.4)	NR	NR	19 (82.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	2 (8.7)	9 (52.9)	NR	NR		
Strasser-Weippl et al.[36]	20–49	11 (10.1)	52 (47.7)	11 (10.1)	2 (1.8)	22 (20.2)	10 (9.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29 (26.6)	12 (11)	NR	
Suleman et al.[5]	34 (20–45)	NR	42 (38.2)	68 (61.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	15 (13.6)	41 (37.2)	29 (26.3)		
Yang et al.[37a]	34 (25–41)	0 (0)	2 (13.3)	8 (53.3)	3 (20)	2 (13.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	6 (40)	NR	14 (93.3)	6 (40)	NR		
Yang et al.[37b]	34 (25–41)	0 (0)	3 (27.2)	7 (63.6)	1 (0.9)	0 (0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	5 (45.4)	NR	11 (100)	4 (36.3)	NR		

HR: hormonal receptors (estrogen and progesterone); NR: not reported; TNBC: triple-negative breast cancer. [a]Patients diagnosed with PABC during the pregnancy; [b]Patients diagnosed with PABC until 1 year post-delivery.

Table 2. Pregnancy-associated breast cancer treatment characteristics.

Author, year	Chemotherapy n (%)	Chemotherapy during pregnancy n (%)	Hormone therapy n (%)	Radiotherapy n (%)	BCS n (%)	ALND n (%)	SLND n (%)	Mastectomy n (%)
Ali et al. [9]	NR	36 (90)	NR	32 (80)	3 (7.5)	30 (75)	2 (5)	3 (7.5)
Amant et al.[10]	307 (98.7)	200 (64.3)	117 (37.6)	205 (65.9)	140 (45)	NR	NR	147 (47.3)
Azizet et al[11]	21 (87.5)	NR	18 (75)	5 (20.8)	NR	NR	NR	NR
Bae et al.[12]	345 (83.9)	NR	NR	230 (56)	193 (47)	235 (57.2)	145 (35.2)	199 (48.4)
Baulies et al.[13]	42 (75)	7 (16.7)	NR	28 (50)	9 (16.1)	33 (58.9)	NR	34 (60.7)
Beadle et al.[14]	97 (93.3)	NR	29 (27.9)	NR	26 (25)	NR	NR	30 (28.8)
Boudy et al.[15]	49 (100)	49 (100)	29 (59.2)	41 (83.7)	26 (53)	36 (73.5)	13 (26.5)	22 (44.9)
Choi et al.[16]	NR	NR	NR	NR	NR	NR	NR	NR
Chuang et al.[17a]	67 (74.4)	11 (12.2)	45 (50)	42 (46.7)	31 (34.4)	NR	NR	52 (57.8)
Chuang et al.[17b]	283 (81.5)	NR	183 (52.7)	177 (51)	141 (40.6)	NR	NR	181 (52.2)
Dimitrakakis et al.[18]	39 (100)	NR	10 (25.6)	15 (38.5)	NR	NR	NR	NR
Framarino-dei-Malatesta et al.[19]	20 (90.9)	9 (40.9)	NR	NR	12 (54.5)	NR	12 (54.5)	10 (45.4)
Genin et al.[20]	63 (72.4)	NR	36 (41.4)	76 (87.3)	36 (41.4)	4 (4.6)	79 (90.8)	48 (55.2)
Halaska et al.[21]	31 (96.9)	NR	6 (18.7)	15 (46.9)	9 (28.1)	25 (78.1)	4 (12.5)	20 (62.5)
Ibrahim et al.[22]	52 (72.2)	NR	NR	NR	NR	NR	NR	NR
Iqbal et al.[23]	423 (84.4)	NR	NR	366 (73)	NR	NR	NR	NR
Kim et al.[24]	289 (84)	NR	123 (35.7)	178 (51.7)	144 (41.9)	276 (80.2)	41 (11.9)	180 (52.3)
Litton et al.[25]	44 (58.7)	NR	19 (25.3)	49 (65.3)	16 (21.3)	29 (38.7)	42 (56)	54 (72)
Madaras et al.[26]	24 (77.4)	NR	12 (38.7)	22 (71)	10 (32.2)	26 (83.9)	4 (12.9)	19 (61.3)
Mathelin et al.[27a]	NR	16 (89)	8 (44)	15 (83)	9 (50)	17 (94)	NR	9 (50)
Mathelin et al.[27b]	17 (94)	NR	10 (45)	16 (73)	7 (32)	22 (100)	NR	15 (68)
Moreira et al.[28]	NR	NR	NR	NR	NR	NR	NR	NR
Muñoz-Montaño et al.[29a]	NR	58 (93.5)	3 (4.8)	NR	NR	NR	NR	NR
Muñoz-Montaño et al.[29b]	63 (100)	NR	0 (0)	NR	NR	NR	NR	NR
Murphy et al.[30]	96 (97)	36 (36.4)	62 (62.6)	49 (49.5)	25 (25.2)	NR	NR	74 (74.7)
O'Sullivan et al.[31a]	40 (80)	NR	14 (28)	28 (56)	16 (32)	32 (64)	8 (16)	33 (66)
O'Sulliva et al.[31b]	40 (76.9)	NR	21 (40.4)	30 (57.7)	17 (32.7)	32 (61.5)	14 (26.9)	32 (61.5)
Ploquin et al.[32]	108 (97.2)	54 (48.6)	49 (44.1)	106 (95.5)	47 (43.1)	10 (9.5)	104 (99)	62 (56.9)
Reyes et al.[33]	22 (52.4)	NR	NR	NR	NR	NR	NR	NR
Rodriguez et al.[34]	556 (69.8)	NR	NR	310 (38.9)	NR	NR	NR	482 (60.5)
Siegelmann-danieli et al.[35]	23 (100)	NR	NR	NR	11 (47.8)	NR	NR	10 (43.5)
Strasser-Weippl et al.[36]	NR	NR	NR	NR	NR	NR	NR	NR
Suleman et al.[5]	NR	NR	NR	NR	NR	NR	NR	NR
Yang et al.[37a]	NR	5 (33.3)	NR	NR	NR	4 (26.7)	NR	10 (66.7)
Yang et al.[37b]	0 (0)	NR	NR	NR	NR	7 (63.6)	NR	4 (36.4)

ALND: axillary lymph node dissection; BCS: breast-conserving surgery; NR: not reported; SLND: sentinel lymph node dissection. [a]Patients diagnosed with Pregnancy-associated breast cancer during the pregnancy. [b]Patients diagnosed with PABC until 1 year post-delivery.

Importantly, Mathelin et al. reported the highest differences in survival in 5- (p=0.034) and 10-year (p=0.0001) follow-up, when comparing BC versus PABC. Differences in PABC and non-PABC populations might have impacted survival, such as low positive levels of estrogen (p=0.038) and progesterone (p=0.008) receptors between groups. In addition, threefold more patients with distant metastasis were included in the PABC group, compared to the control (p=0.0247). Such unbalanced groups not only depict that such clinical characteristics are important sources of clinical heterogeneity but also evidence that such PABC subgroups have the worst outcomes.

In sensitivity analysis, we also removed the study by Siegelmann-danieli et al. In their publication, the worst outcomes were closely

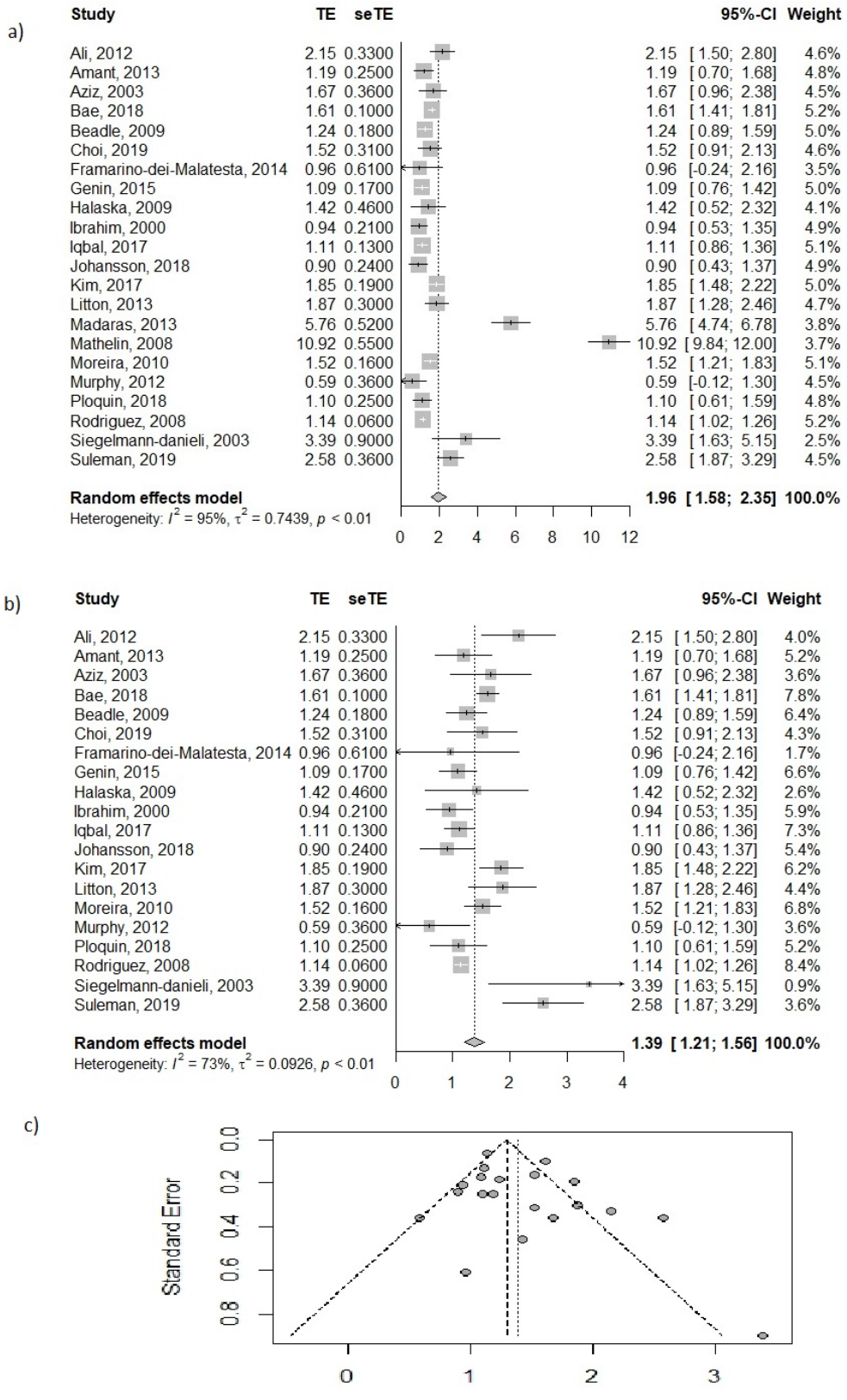

Figure 2. Pregnancy-associated breast cancer deaths compared to non-Pregnancy-associated breast cancer population. **(A)** A meta-analysis of Pregnancy-associated breast cancer vs. non-Pregnancy-associated breast cancer deaths, represented as hazard ratio; **(B)** sensitivity analysis for Pregnancy-associated breast cancer death, removing two outliers; and **(C)** funnel plot of Pregnancy-associated breast cancer death.

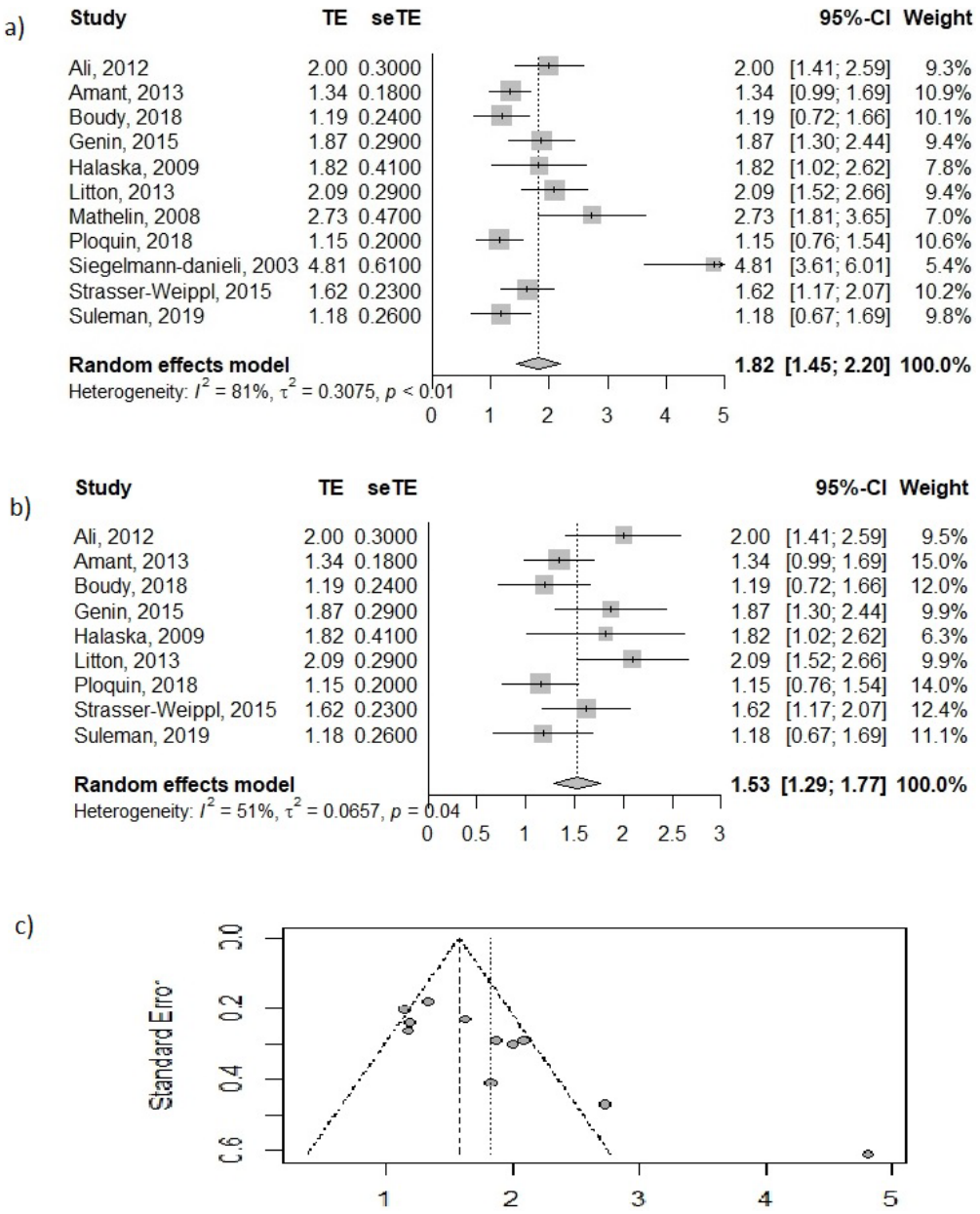

Figure 3. Pregnancy-associated breast cancer deaths or disease relapse compared to non-Pregnancy-associated breast cancer population. **(A)** A meta-analysis of Pregnancy-associated breast cancer vs. non-Pregnancy-associated breast cancer deaths or disease relapse, represented as hazard ratio; **(B)** sensitivity analysis for Pregnancy-associated breast cancer deaths or disease relapse, removing two outliers; and **(C)** funnel plot of Pregnancy-associated breast cancer deaths or disease relapse.

related to tumor staging. It is widely known that advanced disease is associated with higher mortality. Nevertheless, subtypes of BC, such as advanced triple-negative tumors were associated with 2–3 times more risk of mortality (p<0001) when compared to a cohort of non-triple-negative patients, as demonstrated by Saadatmand et al.[39].

Finally, considering the three studies removed for sensitivity analyses[26,27,35], another common feature between them was the high proportion (~70%) of patients with poorly undifferentiated tumors (grade 3 histological classification). As reported before, Rakha et al. showed that such histological subtypes are associated with 20% less chance of survival, in comparison to grade 1 and 2 diseases (chance of survival: 57.6, 61.4, and 81%, respectively, for grade 3, 2, and 1 histological subtypes)[40]. Poorly differentiated tumors are an independent prognostic factor, particularly in triple-negative molecular subtypes[41,42]. As a fact, besides the phenotypic expression of BC, nowadays, the poor prognosis can be attributed to a set of "poor prognostic genes," which include BRCA mutations (BRCAm), for example[43]. Unfortunately, none of the studies included the description of poor prognostic genes

for BC, suggesting that there might be unexplored subgroups of patients who might benefit from different treatment approaches, as nowadays, BRCAm BC might have a better prognosis if treated with recently approved drugs[44] addressed in future research.

Though this review adhered to PRISMA statement standards, it is not absent limitations. For example, as a systematic review with a meta-analytic approach, the study did not analyze patient-level data, which means that the relation between Ki67 and PABC outcomes requires further research specifically addressed for this hypothesis. On the other hand, this review quantitatively addressed this literature gap and might be useful for future studies.

CONCLUSIONS

PABC is correlated with a poorer prognosis, such as a 96% higher chance of dying and an 82% higher risk of disease relapse or death, compared to the non-PABC population. Through sensitivity analyses, we identified that clinical outcomes were impacted, possibly due to Ki67 levels, poorly differentiated tumors, and TNBC. No study addressed genetics profiling, such as BRCAm status, suggesting that besides early diagnosis, these clinical and genetic characteristics might be relevant sources of inconsistency. That is, such clinical sources of heterogeneity should be better investigated regarding the potential to evaluate alternative therapeutic strategies. Finally, further research could benefit from exploring the effect of the homologous recombination deficiency repair pathway on the survival of PABC patients, as it was poorly studied so far.

AUTHORS' CONTRIBUTIONS

MA: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. TTB: Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. JMR: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RGCL: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. OF: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LMO: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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