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EDITORIAL
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Peritumoral infiltration of local anesthetic before surgery in early breast cancer: a comment

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ABSTRACT

This is a comment on a study recently published about peritumoral infiltration of local anesthetic before surgery in early breast cancer. Previously, animal models and a randomized study for stage IV breast cancer patients inferred that the removal of the primary tumor resulted in increased growth factors and worse distant disease control. Therefore, breast cancer surgery might not be a strictly local intervention. In this new randomized study, the intervention was a peritumoral infiltration of local anesthetic — lidocaine 0.5% in the six tumor margins, as an attempt to limit the systemic repercussions of surgery. Although the adjuvant treatment available for the study seems outdated, leading us to question the external validation, limited resources may have increased the power of surgery. Unknown mechanisms during surgery can change the patient's journey, and it is our duty to look at surgical studies with due seriousness.

KEYWORDS: breast neoplasms; mastectomy; mastectomy, segmental; lidocaine.

EDITORIAL

This is a comment on a study recently published in the *Journal of Clinical Oncology* (JCO) about peritumoral infiltration of local anesthetic before surgery in early breast cancer[1]. The Indian group led by Dr. Rajendra Badwe is the same group that published, in 2014, a randomized study on primary site surgery for stage IV breast cancer[2]. In that study, patients in the upfront surgery group had worse distant disease-free survival (DFS). Similarly, in animal models, the removal of the primary tumor resulted in increased growth factors and worse distant disease control. It was then hypothesized that breast cancer surgery is not a strictly local intervention but has systemic consequences. This study, as well as studies on animal and experimental models, reinforces the need and interest in further well-designed studies to clarify the mechanism of lidocaine as a protective factor.

Badwe et al.[1] considered an intervention that could limit the systemic repercussions of surgery. The proposed intervention was a peritumoral infiltration of local anesthetic — lidocaine 0.5% in the six tumor margins. A total of 1,600 breast cancer patients with axillary staging N0 or N1 and eligible for upfront surgery were randomized 1:1 for peritumoral infiltration or conventional surgery.

The primary outcome was 5-year DFS. In the experimental and control groups, the 5-year DFS was 86.6% and 82.6%, respectively (hazard ratio (HR)=0.74, 95%CI 0.58–0.95, p=0.017). The secondary outcome was overall survival, with 90% in the lidocaine group and 86.4% in the control group (HR=0.71, 95%CI 0.53–0.94, p=0.019).

The absolute DFS difference found (4%) is below the minimum expected difference (7%) that was used for statistical design. The relative difference (HR) was also overestimated in the original protocol (estimated HR=0.68 and real HR=0.74). However, the number of events was also lower than expected (538 expected and 225 events found). Recruitment was slow and the protocol was amended to allow for an interim review. In any case, the DFS finding was positive with a significance below p=0.024, the alpha level established after the interim analysis.

By correspondence, Dr. Badwe stated that they did not systematically use ultrasound to guide the infiltration, as most of the tumors were palpable (mean size, 3 cm). The criterion for determining whether the infiltration was correct was the inability to use diathermy due to excess water content.

The study was open-label. The group did not consider the possibility of saline injection in the control group, for blinding

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purposes. Data on margins and weight of the specimens were not collected. Despite being defined as open-label, Dr. Badwe also stated that the team maintaining follow-up was not aware of the randomization.

Factors such as age, menopausal status, staging, molecular subtype, type of surgery, and adjuvant treatments were well balanced between groups. Approximately 36% of the patients underwent mastectomy, and 80% underwent adjuvant radiotherapy. Approximately 67% of patients underwent axillary dissection. Only 35% of all patients with overexpressed HER-2 received targeted therapy. This treatment seems outdated, leading us to question the external validation of the study for our population. However, limited adjuvant therapies may have increased the power of surgery.

A recent literature review by Zhang et al. summarizes clinical evidence and data from randomized trials that suggest the role of local anesthetics in inhibiting tumor progression[3]. This study by Badwe, as well as studies on animal and experimental models, reinforces the need and interest in further well-designed studies to clarify the mechanism of lidocaine as a protective factor.

It is too early to assess whether these findings will change our practice. Three factors can hinder surgeon adherence: infiltration impairs thermal dissection, infiltration has to be associated with intraoperative ultrasound for non-palpable tumors, and finally it was not tested after neoadjuvant therapy.

The JCO editorial that accompanied the article brings a reflection: "The administration of peritumoral lidocaine before surgery resulted in a 4% DFS benefit at 5 years which is not that dissimilar from benefit we see from many systemic therapies that carry potential toxicity risk"[4]. The editorial concludes by saying that "it seems reasonable to introduce this intervention as an easy, cost-effective intervention" and that "additional investigation will be required to elucidate the mechanism of this benefit."

Therefore, unknown mechanisms during surgery can change the patient's journey, and it is our duty to look at surgical studies with due seriousness. Finally, two lessons remain: surgery has power and the slightest thing can make a difference.

AUTHORS' CONTRIBUTION

JFB: Conceptualization, Methodoloy, Project administration, Writing – original draft. MMM: Conceptualization, Supervision, Validation, Writing – review & editing. JLBB: Conceptualization, Supervision, Validation, Writing – review & editing.

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ORIGINAL ARTICLE
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Use of artificial intelligence to predict response to neoadjuvant chemotherapy in breast cancer

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ABSTRACT

Introduction: Breast cancer is the object of thousands of studies worldwide. Nevertheless, few tools are available to corroborate prediction of response to neoadjuvant chemotherapy. Artificial intelligence is being researched for its potential utility in several fields of knowledge, including oncology. The development of a standardized Artificial intelligence-based predictive model for patients with breast cancer may help make clinical management more personalized and effective. We aimed to apply Artificial intelligence models to predict the response to neoadjuvant chemotherapy based solely on clinical and pathological data. **Methods:** Medical records of 130 patients treated with neoadjuvant chemotherapy were reviewed and divided into two groups: 90 samples to train the network and 40 samples to perform prospective testing and validate the results obtained by the Artificial intelligence method. **Results:** Using clinicopathologic data alone, the artificial neural network was able to correctly predict pathologic complete response in 83.3% of the cases. It also correctly predicted 95.6% of locoregional recurrence, as well as correctly determined whether patients were alive or dead at a given time point in 90% of the time. To date, no published research has used clinicopathologic data to predict the response to neoadjuvant chemotherapy in patients with breast cancer, thus highlighting the importance of the present study. **Conclusions:** Artificial neural network may become an interesting tool for predicting response to neoadjuvant chemotherapy, locoregional recurrence, systemic disease progression, and survival in patients with breast cancer.

KEYWORDS: artificial intelligence; breast; breast neoplasms; neoadjuvant therapy; neoplasms.

INTRODUCTION

Despite being the object of thousands of studies worldwide and having the largest body of evidence to explain its pathophysiology among all cancer types, breast cancer (BC) continues to claim thousands of lives each year[1]. Many different and customizable treatment options are available for the various types of BC. One treatment strategy widely used in clinical practice is neoadjuvant chemotherapy (NACT)[2].

NACT consists of the preoperative administration of chemotherapeutic drugs with a view to reducing tumor size before surgery. Its use has been associated with improved prognosis. Currently, response to NACT cannot be measured or predicted by the clinician, which restricts decision-making regarding the appropriateness of this treatment option in individual cases. Tools that can predict the response to NACT could be practice-changing by helping define the most appropriate clinical management strategy for each patient[2,3].

Nevertheless, few tools are available to corroborate prediction of response to NACT. Two prediction tools are currently on the market, the 21-gene Oncotype DX® panel and the 70-gene MammaPrint®[4,5] panel, both based on the quantification of the expression of different genes known to be involved in the pathophysiology of BC. Oncotype and MammaPrint are representative and very important on the world stage; however, their applicability is limited by the high cost inherent in the quantitative analysis of gene expression.

Artificial intelligence (AI) is being researched for its potential utility in several fields of knowledge, including oncology.

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The ability of a technology to receive information, process it, and make decisions based on that information can be very relevant in several aspects of the oncology practice, including the prediction of response to NACT. AI systems can currently receive and interpret clinical and pathological information about patients and predict possible outcomes based on cases from past examples, i.e., after learning about the subject[6-8].

The development of a standardized AI-based predictive model for patients with BC may help make clinical management more personalized and effective. In our study, we aimed to apply AI models to predict the response to NACT based solely on clinical and pathological data.

METHODS

a. Patients

All medical records of patients treated with NACT at the High Complexity Unit on Oncology (UNACON) of Hospital Geral de Caxias do Sul (RS), Brazil, and at an affiliated private clinic from March 2012 to June 2020 were reviewed. The records of 130 patients containing all clinicopathologic information of relevance to the study were analyzed and divided into two groups: 90 samples to train the neural network and 40 samples to perform prospective tests and validate the results obtained by the AI method.

b. Clinicopathologic criteria

The study included patients for whom the following information was available: age, body mass index, weight, height, menopausal status, histologic type, histologic grade, expression of estrogen (ER) and progesterone (PR) receptors, human epidermal growth factor receptor 2 (HER-2), expression of Ki-67, tumor size, axillary involvement, molecular subtype, clinical staging, chemotherapy protocol, progression during chemotherapy, targeted therapy, and pathologic staging.

Overall survival was analyzed from the date of diagnosis until the date of the last follow-up (for patients who remained alive) or date of death. Progression-free survival was analyzed from the date of diagnosis to the date of disease progression (for patients who experienced disease progression), date of death (for patients who died), or date of the last follow-up (for patients who remained alive). Pathologic complete response (PCR) was defined as absence of invasive carcinoma and/or carcinoma in situ in the breast, and ipsilateral axilla after NACT.

c. Expression of estrogen, progesterone, Ki-67 and HER-2 receptors

ER, PR, and HER expressions in breast biopsy specimens were evaluated by means of immunohistochemistry, with the following antibodies:

1. anti-ER MAb (Dako, Glostrup, Denmark, 1/100 dilution),
2. anti-PR MAb (Dako, 1/800 dilution), and
3. polyclonal anti-HER2 antibodies (Dako, 1/3200 dilution) for the HER-2-neu gene.

The scoring of ER and PR were based on the staining intensity (weak, moderate, intense). The evaluation criteria of HER2 status were based on immunostaining and the percentage of membrane positive cells, giving a score range of 1+, 2+, 3+. HER2 negative was categorical when no staining was observed or membrane staining was observed in 1–9% of tumor cells. HER2 was classified as score 2+ when there was a weak to moderate complete membrane staining in 10% to 49% of the tumor cells, while HER2 was positive score 3+ when there was a strong complete membrane staining in more than 50% of the tumor cells. In this study, HER2 scores 0 and 1+ were considered negative. HER2 3+ and the Amplified Fluorescence in situ Hybridization (FISH-amplified) tumors were considered positive. All HER2 2+ tumors and tumors for which immunohistochemistry (IHC) was not assessable were also tested for gene amplification by FISH.

Ki-67 labeling index was defined as the percentage of Ki-67 antigen positive cells, giving a score range low (<14%) and high (≥14%).

d. Analysis of tumor-infiltrating lymphocytes

The percentage of tumor-infiltrating lymphocytes (TILs) was assessed in paraffin-embedded tumor sections stained with hematoxylin and eosin (HE) and was defined as the percentage of lymphocytes in direct contact with tumor cells.

e. Artificial intelligence

AI is a growing science. Its core principle is the development of cognitive models that are capable of interpreting and forecasting data. This interpretation is based on the knowledge acquired by the model. Within AI science, "knowledge" is data[7].

Cognitive models are based on so-called artificial neural networks (ANNs), which simulate a biological neuron. Human neurons consist of several specific regions, as:

1. dendrites, which receive nerve impulses;
2. the cell body, or soma, in which information processing takes place; and
3. nerve endings, which are responsible for the output of nerve impulses.

An ANN has very similar regions, as seen in Figure 1 below. Its "dendrites" are represented by the letter *w*, which highlights the presence of more than one "nerve projection" (i.e., allowing receipt of more information), each differentially weighted to ensure a good data interpretation. In the "cell body" of the ANN, designated as *fa*, mathematical functions are applied to the data

obtained through *w*. Finally, "nerve endings" allow communication to take place between ANNs, simulating a neural synapse.

Clinicopathologic criteria were analyzed through the application of four ANNs composed of 200 neurons, each designed specifically for prediction of one of the following outcomes: PCR, locoregional recurrence, systemic disease progression, and death. The variables analyzed by the ANNs are described in Table 1.

Neural networks were created to analyze the outcomes of interest. These networks were trained on 90 samples and afterwards was prospectively tested on 40 additional samples.

f. Ethical aspects

As the present study consists of a retrospective analysis of data from medical records and does not involve direct intervention on human subjects, investigators were asked to sign a data use agreement and confidentiality form. Informed consent was waived.

g. Statistical analysis

After the identification of the core (indispensable) criteria, four supervised-learning ANNs were constructed using a pattern recognition tool. To ensure optimal fit, a backpropagation algorithm with feed-forward network topology was used to identify PCR, systemic disease progression, locoregional recurrence, and survival. To enhance ANN effectiveness, the number of neurons was tested with a variety of different settings. To evaluate whether the proposed system was effective, a prospective study was then carried out using the developed ANNs.

Descriptive analysis of clinicopathologic data was performed in SPSS 20.0 software (SPSS Inc. Chicago, IL, United States).

The Figure 1 illustrates the diagram with the methodologies used in this research.

Table 1. Variables used in the neural network.

	Values
Age (years)	Numeric
Body mass index	Numeric
Weight	Numeric
Height	Numeric
Menopausal status	Pre-menopausal or post-menopausal
Histologic type	Invasive lobular, invasive ductal, medullary, or other
Histologic grade	G1, G2, or G3
Estrogen receptor expression	Numeric
Progesterone receptor expression	Numeric
HER-2 expression	1+, 2+, 3+
Ki-67 expression	Low or high
Molecular subtype	Luminal A, luminal B, or HER2-enriched
Clinical staging	IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV
Chemotherapy protocol	Trastuzumab; lapatinib; pertuzumab; trastuzumab + pertuzumab; trastuzumab + lapatinib; other
Progression on chemotherapy	Yes or no
Neoadjuvant targeted therapy	None; trastuzumab; lapatinib; pertuzumab; trastuzumab +pertuzumab; trastuzumab+ lapatinib; other
Tumor size and location	Ductal carcinoma in situ, T1mi, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c, T4d
Lymph nodes staging	N0, N1, N2, N3
Number of affected lymph nodes	Numeric

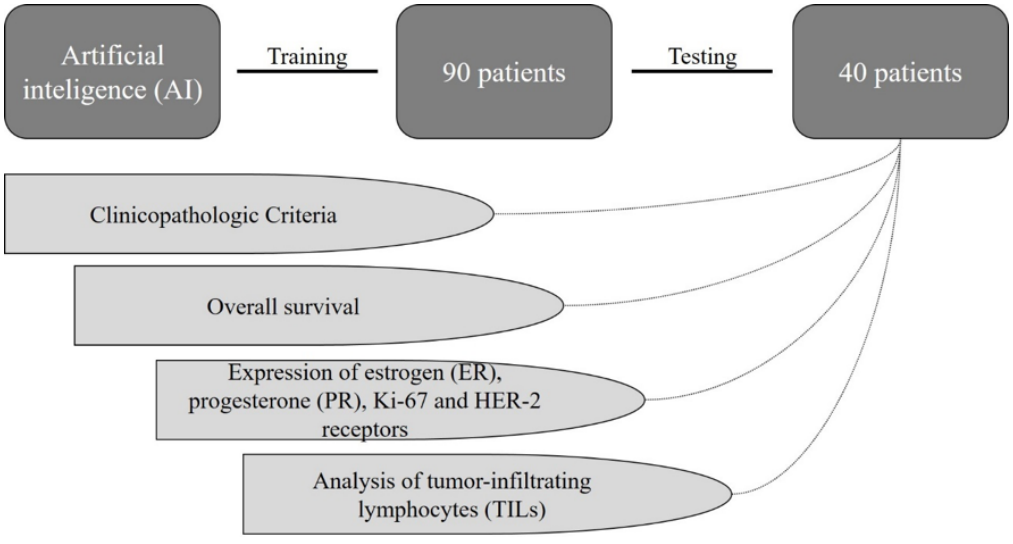

Figure 1. Diagram of methodologies used in this research.

RESULTS

Clinicopathologic data

A retrospective analysis of the medical records of 90 patients was carried out. The mean age at diagnosis was 46.3 years, and the mean body mass index was 27.0. Overall, 59 (65.6%) patients were pre-menopausal and 31 (34.4%) were post-menopausal. On histologic analysis, only 1 patient (1.1%) had invasive lobular BC, 73 patients (81.1%) had invasive ductal carcinoma, 5 (5.6%) had medullary carcinoma, and 11 (12.2%) had BC of other histological types. Most of the patients had histologic grade G3 tumors, totaling 48 (53.3%), 36 (40.0%) had grade G2, and only 6 (6.7%) had grade G1 (Table 2).

Regarding gene expression in biopsy specimens, 50 of 90 (55.6%) had biopsies strongly positive for ER, followed by 30 (33.3%) which were ER-negative. The rest of the biopsies showed low ER expression (2; 2.2%) and positive ER expression (8; 8.9%). As for PR expression, most biopsies were negative, being 39 (43.3%), followed by strongly positive expression in 31 (34.4%), positive expression in 18 (20.0%), and low expression in only 2 cases (2.3%) (Table 2).

Once HER2 expression was evaluated, 54 biopsies (60%) showed no expression and 36 (40.0%) showed 1+ expression. Furthermore, 87 biopsies (96.7%) showed high Ki67 expression. The molecular subtypes observed were: luminal B in 32 cases (35.6%), HER2-enriched in 24 (26.7%), triple-negative in 19 (21.1%), pure HER2 in 12 (13.3%), and luminal A in 3 (3.3%) (Table 2).

Of the 90 patients who received treatment, only 32 (35.6%) achieved PCR, while 58 (64.4%) did not. Fifteen patients (16.7%) experienced systemic disease progression, while 75 (83.3%) were progression-free (Table 2). This same analysis was performed in the prospective study (Table 2).

Artificial neural network performance evaluation

Clinicopathologic criteria were analyzed through application of an ANN composed of 200 neurons to predict the response to NACT. To assess predictive capacity, confusion matrices were generated. Sensitivity, specificity, false-positive rate, and false-negative rate were then derived.

With clinicopathologic data alone, the ANN was able to correctly predict PCR in 83.3% of cases, with 84.4% sensitivity, 82.8% specificity, a positive predictive value (PPV) of 73%, and a negative predictive value (NPV) of 90.6%. Tested prospectively, the ANN achieved an accuracy of 80.0%, sensitivity of 81.8%, specificity of 79.3%, and negative and positive predictive values of 92 and 60% respectively (Table 3).

When predictive capacity for systemic progression was assessed, the ANN exhibited 82.2% accuracy, with 0% sensitivity, and 98.7% specificity. The PPV was 0%, and the NPV, 83.1%. When prospectively tested, an accuracy of 77.5% was achieved, with sensitivity and specificity of 100% and 76.9%, respectively, and NPV of 100% and PPV of 10% (Table 3).

Table 2. Clinicopathologic data.

	n (%) retrospective	n (%) prospective
Age (years)	46.3	47.5
Body mass index	27.0	27.9
Weight	70.5	71.3
Height	1.6	1.6
Menopausal status		
Pre-menopausal	59 (65.6)	27 (67.5)
Post-menopausal	31 (34.4)	13 (32.5)
Histologic type		
Invasive lobular	1 (1.1)	0 (0)
Invasive ductal	73 (81.1)	37 (92.5)
Medullary	5 (5.6)	2 (5)
Other	11 (12.2)	1 (2.5)
Histological grade		
G1	6 (6.7)	5 (12.5)
G2	36 (40)	19 (47.5)
G3	48 (53.3)	16 (40)
Estrogen receptor expression		
None	30 (33.3)	17 (42.5)
Low	2 (2.2)	0 (0)
Positive	8 (8.9)	3 (7.5)
Strongly positive	50 (55.6)	20 (50)
Progesterone receptor expression		
None	39 (43.3)	19 (47.5)
Low	2 (2.3)	0 (0)
Positive	18 (20)	7 (17.5)
Strongly positive	31 (34.4)	14 (35)
HER2 expression		
0	54 (60)	33 (82.5)
1+	36 (40)	7 (17.5)
2+	0 (0)	0 (0)
Ki67 expression		
Low	3 (3.3)	7 (17.5)
High	87 (96.7)	33 (82.5)
Molecular subtype		
Luminal A	3 (3.3)	5 (12.5)
Luminal B / HER2-negative	32 (35.6)	15 (37.5)
Luminal B / HER2-enriched	24 (26.7)	3 (7.5)
Pure HER2	12 (13.3)	4 (10)
Triple negative	19 (21.1)	13 (32.5)
Pathologic complete response	32 (35.6)	15 (37.5)
No pathologic complete response	58 (64.4)	25 (62.5)
Systemic progression	15 (16.7)	10 (25)
No systemic progression	75 (83.3)	30 (75)

The same analysis was performed for locoregional recurrence. The ANN had 95.6% accuracy, with a sensitivity of 0% and specificity of 100%. Positive and negative predictive values were 0% and 95.6%, respectively. In the prospective test, the network accuracy was 95%, with sensitivity and specificity of 0% and 95%, respectively. The PPV was 0% and the NPV was 100% (Table 3). The sensitivity and PPV were 0% because no patient had disease progression or recurrence in the retrospective dataset.

When the ANN was used to predict whether patients would be alive or dead, it achieved 90% accuracy, with a sensitivity of 95.1%, and specificity of 44.4%. Positive and negative predictive values in this analysis were 93.9 and 50%, respectively. Tested prospectively, the ANN achieved an accuracy of 87.5%, sensitivity of 94.3%, specificity of 40%, NPV of 50%, and PPV of 91.7% (Table 3).

DISCUSSION

NACT is associated with PCR as well as with locoregional or systemic recurrence, and the response to NACT is the main determinant of each of these events. The present study demonstrated, for the first time, how the response to NACT can be predicted with AI methods. AI is a growing area of study, with an ever-increasing body of evidence demonstrating its applicability in various fields[6-8]. The possibility of using an AI tool to guide clinical management of BC, a life-threatening condition, is extremely relevant.

Neoadjuvant Chemotherapy and Pathologic complete response

PCR is associated with several factors. Understanding which are these factors and the relative importance of each one is essential. In this study, clinicopathologic data were used to train an ANN to predict response to NACT. Corroborating the present study, prior researches have described various clinical and pathologic factors that may be related to the response to NACT. Díaz-Casas et al.[9], in a study of 414 patients with BC, found that PCR was associated with tumor molecular type, observing higher rates of PCR in pure-HER2 and triple-negative tumors. They also found that larger tumors are associated with nonresponse to NACT.

When analyzing clinicopathologic predictors of recurrence in patients with BC who achieved PCR to NACT, advanced clinical staging, tumor size, presence of lymph node metastases, and HER2 positivity before NACT were identified as significantly predictive of disease recurrence. Conversely, residual ductal and nodal disease in situ after NACT were not significant predictors[10].

In a study of 117 patients, PCR was significantly associated with expression of ER and absence of HER2 expression (p=0.0006), as well as with stages T2 (p=0.043) and T3 (p=0.018)[11]. The same factors were assessed in our study and, corroborated as predictive of PCR. We used data to construct an ANN and predict the same outcome previously described in the literature, Thus, our results corroborate the data published in the literature, but with a significant difference: the use of AI to obtain them.

Neoadjuvant chemotherapy and locoregional recurrence

In our study, the ANN correctly predicted locoregional recurrence 95.6% of the time, with a NPV of 95.6%. These data were obtained through the use of an AI model based on clinicopathologic data only. This same correlation was described in a large study involving 3,088 patients over a 10-year follow-up period, which found that the clinical characteristics of a tumor can be used to predict the risk of locoregional recurrence[12]. The same association was observed by Gillon et al. in 1,553 patients; the authors reported that BC classification and PCR are important predictors of locoregional recurrence[13].

To date, there are no reports of the use of AI to predict locoregional recurrence in patients with BC after NACT. Therefore, this is the first study to demonstrate a new predictive model with the potential to change clinical management.

Neoadjuvant chemotherapy and systemic disease progression

Death after NACT is associated with progression of systemic disease. The ANN correctly predicted whether patients would be alive or dead after NACT 82.2% of the time, with a specificity of 98.7%; on subsequent prospective testing, 77.5% accuracy was achieved. Several factors have been described in the literature

Table 3. Predictive performance of an artificial neural network trained on clinicopathologic data alone to assess response to neoadjuvant chemotherapy in patients with breast cancer.

	Pathologic complete response		Systemic progression		Locoregional recurrence		Survival	
	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)
Accuracy	83.3	80	82.2	77.5	95.6	95	90	87.5
Sensitivity	84.4	81.8	0	100	0	0	95.1	94.3
Specificity	82.8	79.3	98.7	76.9	100	95	44.4	40
Positive predictive value	73	60	0	10	0	0	93.9	91.7
Negative predictive value	90.6	92	83.1	100	95.6	100	50	50

Retro: retrospective; Prosp: prospective.

as potential predictors of systemic progression. HER-2 expression and triple-negative status are two factors reported as such by Yiqun et al.[14].

A previous study evaluated the ability of an ANN to predict survival after BC without assessing the response to NACT. Based only on the Surveillance, Epidemiology, and End Results (SEER) Program[15] dataset, composed of 162,500 records with 16 main characteristics (the most informative ones being tumor size, number of affected lymph nodes, and age at diagnosis, all parameters which were also included in our model), this ANN achieved 65% accuracy[16].

Artificial intelligence-based forecasting

The use of AI in healthcare has been growing exponentially, with particular interest in the development of systems to guide clinical management. Specifically regarding BC, studies have focused on the ability of AI to interpret imaging findings[17-19]. There is very little published data on chemosensitivity and resistance[7,20], and, so far, no studies have demonstrated predictive ability based exclusively on clinicopathologic data. The present study is thus the first of its kind.

Some prior research has investigated the ability of ANNs and their learning models to predict risk in BC, including disease progression[21-25]. However, to date, no published research has used clinicopathologic data to predict the response to NACT in patients with BC, thus highlighting the importance of the present study in advancing science.

Limitations include the lack of validation of the model in a larger sample, which justifies the expansion of the present project. For this reason, we have requested this extension in an effort to minimize its limitations and hence contribute more significantly to the clinical management of patients with BC.

CONCLUSIONS

Breast cancer is a heterogeneous and complex disease. Considering their ability to adapt, learn from examples, organize data, and recognize patterns, ANNs may become an interesting tool for predicting response to NACT, locoregional recurrence, systemic disease progression, and survival in patients with BC.

AUTHORS' CONTRIBUTION

KOBG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MCK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. BC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. LLC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. MRE: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JAPH: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. JB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing

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CASE REPORT
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Salivary gland tumor: atypical presentation of breast cancer

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ABSTRACT

Breast cancer is a heterogeneous disease with various histological and molecular subtypes. Among them, salivary gland tumors are rare and can be divided into three groups: pure myoepithelial differentiation, pure epithelial differentiation and myoepithelial with mixed epithelial differentiation. In the last group, adenoid cystic carcinoma stands out, a rare entity with low malignant potential. It represents less than 0.1–3% of breast cancer cases and has the most frequent clinical presentation as a palpable mass. The diagnosis is confirmed by histology and immunohistochemistry. Classically, they are low-aggressive triple-negative tumors, with overall survival and specific cancer survival at five and ten years greater than 95%. However, there are rare reports of aggressive variants with a risk of distant metastasis and death. Treatment is based on surgical resection with margins. Lymphatic dissemination is rare, and there is no consensus regarding the indication of an axillary approach. Adjuvant radiotherapy is indicated in cases of conservative surgery and should be discussed in other cases. The benefit of chemotherapy remains uncertain, as most tumors are indolent. We report a case that required individualized decisions based on its peculiarities of presentation, diagnosed in an asymptomatic elderly patient during screening, in which mammography showed heterogeneous gross calcifications clustered covering 1.6 cm. Stereotactic-guided vacuum-assisted biopsy was performed, and the area was marked with a clip. The anatomopathological examination led to a diagnosis of salivary gland-type carcinoma, triple-negative. The patient underwent segmental resection of the right breast and sentinel lymph node biopsy. The final anatomopathological result was similar to that of the biopsy, with an immunohistochemical profile of the adenoid cystic type and two sentinel lymph nodes free of neoplasia. Considering age and histological subtype, adjuvant therapy was not indicated. Follow-up for three years showed no evidence of disease.

KEYWORDS: breast cancer; triple-negative breast cancer; adenoid cystic carcinoma.

INTRODUCTION

Breast cancer is the most common malignant disease in women[1], considered a heterogeneous disease with various clinical and pathological presentations[2], and among them, salivary gland tumors are rare. These can be divided into three groups: pure myoepithelial differentiation, pure epithelial differentiation and myoepithelial and mixed epithelial differentiation. In the last group, adenoid cystic carcinoma stands out, a rare entity with low malignant potential[3].

Adenoid cystic carcinoma (ACC) of the breast is a heterogeneous biphasic tumor composed of basaloid and epithelial cells. It represents approximately 0.1–3% of breast cancers[4,5]. Due to its rarity, there are few databases on this carcinoma, and most of the studies are case reports or with a small sample of patients. The management protocol remains unestablished. Therefore, to contribute to the formation of a database about the ACC, we report a case of an elderly patient diagnosed during screening, requiring individualized decisions based on their peculiarities of presentation.

CASE REPORT

A 74-year-old woman, menopausal, history of sister with breast cancer at age 58, presented to the outpatient clinic asymptomatic, and she was referred because of changes in the screening mammogram. Mammography (Figure 1) showed heterogeneous gross calcifications clustered in the superolateral quadrant of the right

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breast, measuring 1.6 cm, classified as BIRADS 4. A percutaneous vacuum-assisted biopsy guided by stereotaxis was performed, and the area was marked with a clip. The anatomopathological result showed a salivary gland-type carcinoma, histological and nuclear grade 2, with an immunohistochemical profile showing positive C-kit, CK5/6 and S-100 and negative hormone receptors and HER-2 (triple-negative).

Because of the favorable histology and extent of the disease, the patient was then submitted to segmental resection of the right breast and sentinel lymph node biopsy. The final anatomopathological result (Figure 2) confirmed that it was an invasive carcinoma of the salivary gland type, with a morphological and immunohistochemical pattern of the adenoid cystic type, histological and nuclear grade 2, measuring 2.2 x 1.5 cm, associated with flat and solid ductal carcinoma ***in situ,*** with deep and inferior margin compromised by the invasive neoplasia and two sentinel lymph nodes free of neoplasia. The patient then underwent enlargement of surgical margins, with multifocal residual invasive neoplasia, the largest focus measuring 0.81 cm, with free margins and the presence of angiolymphatic embolization. Considering age and histological subtype, adjuvant therapy was not indicated. She was followed up for three years and then had no evidence of disease.

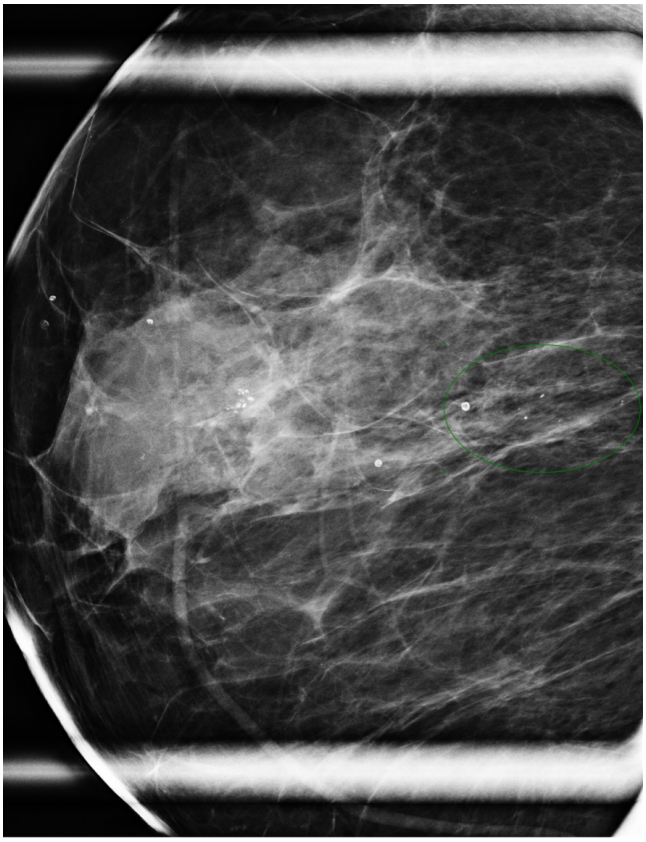

Figure 1. Calcification clustered in the superolateral quadrant of the right breast.

DISCUSSION

Clinico-pathological characteristics

ACC is a characteristically biphasic subtype of salivary gland tumor, composed of myoepithelial/basaloid and luminal/epithelial ductal cells, which can be arranged in tubular, cribriform or solid growth patterns[3,5,6]. Generally, there are these three patterns in the same tumor, present in heterogeneous proportions, the tumor being graded by the extent of the solid component[6]. Within this morphological spectrum of presentation, the basaloid predominant variants tend to have greater tumor aggressiveness[3,7].

On microscopic analysis, the cells of this tumor have scarce cytoplasm and a hyperchromic nucleus[6], but a variable spectrum of morphological aspects, similar to those seen in salivary glands, is reported, impacting the prognosis[3].

Genetically, ACC is characterized by a specific gene fusion, responsible for the development of its characteristic phenotype. The case in question had an infrequent presentation of adenoid cystic carcinoma (suspicious calcifications) on screening mammography[6].

This tumor is characterized by an insidious and continuous evolution[6], usually diagnosed in the early stages[4,5,8], as in the case of the patient in this report. The most common clinical presentation is a palpable mass/nodule, present in up to about 70% of cases[2,3,5]. The atypical presentation of the reported patient can be seen, who was asymptomatic, with a change in the screening examination.

Zhang et al. reported in a retrospective cohort and meta-analysis with a sample of 511 that more than half of diagnoses occur in patients between 50 and 69 years old[8], which is compatible with data from several other studies[2,4,5] and similar to that observed in American databases[9]. Our patient was slightly above this age range, as she was 74 years old at the time of diagnosis.

The rate of patients with a family history of breast cancer, suggesting a hereditary component, is similar to that usually described for invasive ductal carcinoma of no special type (IDC-NST).

The radiological findings are variable and may be difficult to interpret[2,3]. A suggestive sign on imaging is the presence of an isodense mass with internal septations on magnetic resonance imaging in the T2-weighted sequence[10]. The reported patient had a peculiar presentation, with a mammogram showing clustered heterogeneous coarse calcifications.

Preoperative diagnosis can be performed with fine-needle or core-needle biopsy, the latter being more accurate[3].

Immunohistochemistry helps in the diagnosis and explains the heterogeneity of the cells that make up the ACC: epithelial cells express CK7, CK8 and CD117(c-Kit); basaloids express CK14 and CK5/6; the myoepithelial ones express S-100[2-5]. As for the molecular classification, the vast majority are triple-negative[2-5,8]. However, there are controversies in the literature, with

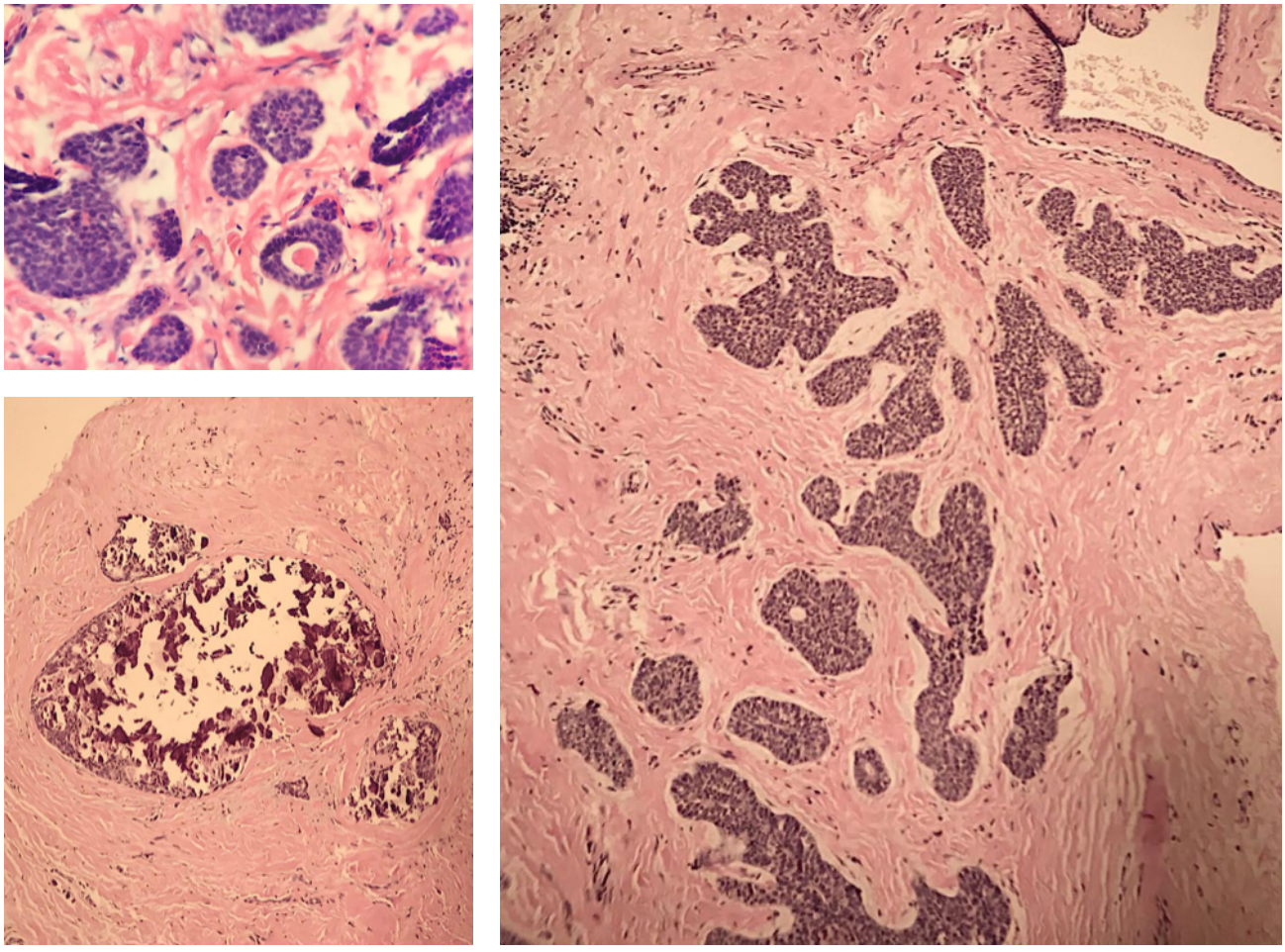

Figure 2. Histological pattern of the tumor.

the frequency of hormone receptor positive tumors ranging from 25%[11] to almost 50%[12]. The tumor in the reported case was triple-negative, fitting the most common form of molecular classification of this tumor subtype, and exhibited immunohistochemical expression of the markers mentioned in the literature, with c-Kit, CK5/6 and S-100 being positive.

Most triple-negative breast tumors are aggressive, with a high histological grade. However, ACC tends to have a favorable prognosis and low histological grade, even when it presents as triple-negative[2]. It is suggested that this is due to the lower Ki-67 rate, but there is still controversy in the literature[2]. Another study suggests that this association is due to the lower genomic instability of ACC[13].

Still, ACC may rarely undergo a process of dedifferentiation from the neoplastic clone, with the development of more aggressive high-grade carcinomas and with a greater risk of distant metastasis[3].

Treatment and prognosis

There are no well-established management protocols because of the sampling limitations of studies due to the rarity of this pathology[2,3]. Classically, treatment involves surgery with resection margins, with conservative surgery considered an adequate therapeutic option[14], always followed by adjuvant radiotherapy[2,6,14]. Zhang et al. reported a conservative surgery rate of 66%. The patient in the reported case underwent conservative surgery with assessment of intraoperative margins, which were compromised, leading to a reapproach for enlargement. Adjuvant radiotherapy followed[8].

Mastectomy may be indicated if the invasive lesion with tumor is affecting the breast in a proportion that makes an aesthetically satisfactory partial excision unfeasible[2]. In the literature, the percentage of patients undergoing mastectomy ranged from 33 to 72%[2-5,8].

An important consideration in therapeutic choice is the knowledge that there are tumor variants that can be more aggressive, such as those with a basaloid predominance. This graduation is given by the proportion of distribution of the histological components (tubular, cribriform and solid)[3]. In these aggressive basaloid variants, the rate of nodal involvement can reach 20% and that of distant metastasis, 16%[3,15].

In general, lymphatic dissemination is rare, ranging from 0 to 5% in the literature[2,4,6,8,14,16]. Khanfir et al. reported no nodal involvement in a sample of 51 patients[14]. Because of this low rate of nodal involvement, the role of axillary dissection remains

unclear[2,14]. Sentinel lymph node biopsy may be an option, with good identification rates. To decide on its use, factors such as tumor size, hormone receptor status, nuclear grade and lymphovascular invasion should be evaluated[16]. In recent studies, the rate of performance of this procedure varied between 50 and 100%[4,5]. In the present case, we opted for sentinel lymph node biopsy, whose anatomopathological examination identified two cancer-free lymph nodes.

The use of adjuvant chemotherapy is controversial but should be considered[7]. In the consensus of St. Gallen in 2011, indicating adjuvant chemotherapy was suggested for cases of high-grade tumors, tumors larger than 3 cm, lymph node involvement or distant metastasis[17]. However, this tumor is usually resistant to this therapy[6], which is why its indication is rarely described[4,8].

Wang et al. compared 36 cases of ACC with 108 cases of low-grade breast invasive ductal carcinoma, with standardized groups regarding clinical and tumor variables. These authors concluded that ACC has a lower rate of Ki-67 and tumor nodal involvement but larger-size tumor compared to low-grade IDC-NST[2].

Classically, ACC is described as being associated with a favorable prognosis, with a low rate of distant metastasis and local recurrence, with excellent survival rates[2,4,8,18]. It should be noted that some studies are controversial, perhaps because of the heterogeneity and rarity of ACC, reporting rates of local recurrence and distant metastasis varying between 8 and 14% and 8 and 21%, respectively[2,6,15]. The most common sites of distant metastasis are lung, bone and liver[2,5].

Overall survival at 10 and 15 years exceeds 90%[2], with no difference in overall or disease-free survival in relation to that described for low-grade IDC-NST[2,18]. In a study with 511 patients, Zhang et al. reported overall and cancer-specific survival at five and ten years of 95.7 and 100%, respectively[8].

Some predictive factors of recurrence-free survival are described, such as positive margin, neovascularization, basaloid variant, perineural invasion, lymphovascular invasion, >30% solid component, lymph node involvement and presence of necrosis[15].

CONCLUSIONS

ACC is a rare subtype of breast cancer, and knowledge about its peculiarities is important to guide the correct diagnosis and management. Although most triple-negative tumors are considered more aggressive, ACC is indolent and considered to have a good prognosis.

Because of its rarity, there are few and low-sample studies, subject to a higher risk of bias. Therefore, there is no consensus on the treatment to be followed, making it necessary to create management protocols. Individualized therapeutic choice is recommended, assessing the risk x benefit of each approach.

AUTHORS' CONTRIBUTIONS

MLN: Writing – original draft, Writing – review & editing. TFSD: Project administration, Supervision, Writing – original draft, Writing – review & editing. GAC: Data curation, Investigation, Methodology. FEMA: Project administration, Supervision.

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ORIGINAL ARTICLE
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Evaluation of clinical, pathological and epidemiological profile of patients with breast cancer in the microregion of Lavras – MG

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ABSTRACT

Introduction: Breast cancer is associated with high frequency and mortality in Brazilian women. There have been limited studies portraying the characteristics of breast cancer cases in the countryside of the state of Minas Gerais for a long period of time, a fact that will allow us to better understand the epidemiology of these tumors. This descriptive study aims to analyze the epidemiology and clinical features of patients with breast cancer treated at a public health service facility in Lavras, MG. **Methods:** This is a transversal study with 299 women diagnosed with breast cancer between 2002 and 2022, based on data collection from medical records and subsequent descriptive analysis. **Results:** There were a total of 317 cases, and 299 were eligible for the study. The mean age at diagnosis was 54.2 years, and 36.1% of the patients were under 50 years old at diagnosis. Positive family history was found in 17.0% of the patients. The diagnosis was made by clinical alteration detected on physical examination in 71.5% of cases, and lump was the most frequent type of lesion (89.0%). Invasive carcinoma was 93.1% of the cases, and the mean tumor size was 28.6 mm. The average time between first medical appointment and diagnosis was 63.2 days, and between diagnosis and beginning of treatment was 39.6 days. **Conclusions:** This study showed that a significant number of cases occurred in women outside the recommended age for screening in Brazil. Diagnosis was predominantly performed by clinical examination, with delays in obtaining the histological diagnosis, and the stage at diagnosis was high, and these facts were associated with the health system limitations.

KEYWORDS: breast neoplasm; age groups; cancer screening.

INTRODUCTION

Breast cancer (BC) is the most common malignant neoplasm among women in Brazil and in the rest of the globe, accounting for 23% of all cancer cases worldwide[1,2]. Several risk factors have already been established, including endogenous and environmental factors. It is the leading cause of death from cancer in the Brazilian female population[3].

In the United States, BC mortality rates showed a 40% decline from 1989 to 2017, meaning over 375,000 fewer deaths[4]. In contrast, as is the case in most low- and middle-income countries, Brazilian estimates indicate stable or increasing mortality rates, with more than 16,000 deaths in 2017[5].

Early diagnosis is closely related to imaging diagnosis and clinical recognition of small tumors, strongly influencing the prognosis of the disease. According to Records from the Cancer Hospital, in Brazil there were 40% of BC diagnoses in stage 3 and 4 in 2010[6], Advanced stage at diagnosis is difficult and costly to treat, and is associated with increased morbidity and poor survival[7,8].

Among the prognostic factors, besides the intrinsic tumor characteristics, such as the hormonal receptors status and the human epidermal growth factor receptor-type 2 (HER2) overexpression, associated with the tumor size, axillary status, and staging, the time between the clinical manifestation of the disease and its diagnosis and initiation of treatment may be included[9,10].

The state of Minas Gerais has few and short isolated studies that portray the profile of patients with BC, as well as stage at diagnosis, time to obtain the diagnosis and to start treatment. Faced with such an incident pathology that causes significant morbidity and mortality among the female population in Brazil, studies must be conducted to better elucidate epidemiology, disease presentation and behavior, and the best methods involved in the screening and diagnosis of this disease[9,10].

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The justification for carrying out the present study is based on the proposal to present the unprecedented results of a series of patients with BC in the microregion of Lavras, Minas Gerais.

The purpose of this article is to verify clinical and pathological characteristics, age distribution, as well as the time interval for the diagnosis and the beginning of treatment, of patients with breast cancer attended in the public service at a secondary reference center in the countryside of Minas Gerais (MG). Such knowledge may, thus, subsidize the planning, implementation, and evaluation of policies and actions of the Unified Health System (SUS) at the regional level, especially regarding the availability of methods that enable early detection and adequate treatment by the SUS.

METHODS

A descriptive, retrospective study was carried out based on the analysis of medical records of patients attended at the Mastology Service of the *Centro Estadual de Atenção Especializada* (CEAE) in the city of Lavras, in the south of the state of Minas Gerais, Brazil. The CEAE is a secondary care center, a reference in mastology care in the microregion of Lavras. It offers mastology appointments, imaging tests (mammography and ultrasound) and breast biopsies. Breast cancer surgeries are performed at *Santa Casa de Misericórdia de Lavras* – MG, and adjuvant treatments (chemo and radiotherapy) are provided in a reference center for the microregion in another city (Varginha, Minas Gerais).

People included in the study came from Lavras and its microregion, which comprises 10 other municipalities. Data were collected in a standardized form and, subsequently, tabulated and analyzed exposing quantitative variables and absolute and relative frequencies.

This study was approved by the Ethics Committee in Research with Human Beings of *Universidade Federal de Lavras* – MG (UFLA) – CAAE: 36285320.2.0000.5148.

All cases of breast carcinoma diagnosis between January 2002 and April 2022 were selected. The inclusion criterion was the histologic diagnosis of breast carcinoma in patients over 18 years of age. There were a total of 317 cases during the established period, 18 of which were excluded because there was no information in their records to obtain the necessary data and/or because they had undergone treatment at another health facility soon after diagnosis. Thus, the final sample of the study consisted of 299 patients.

Only cases of first-degree relatives with the disease, i.e., mother, sister and/or daughter, were considered as a positive family history. For the classification of the menopausal status, the definition of post-menopause was used, involving the classification of the patient into one of these four groups: women aged 60 years or older, women who underwent bilateral oophorectomy, women without their uterus and with laboratory tests showing increased follicle-stimulating hormone (FSH) levels, and women younger than 60 years of age, with uterus, non-users of hormonal therapy, in amenorrhea for at least 12 months before the diagnosis of breast cancer. Other than the situations described, the classification was premenopausal.

To obtain data for staging, classification of Tumor, Node, Metastasis (TNM), the 8th edition of the American Joint Committee on Cancer (AJCC) was used.

Molecular classification was based on luminal A (ER+/PR+/HER2-/low Ki-67: <20%), luminal B Her2-negative (ER+/PR+/HER2-/high Ki-67: ≥20%), luminal B Her2-positive (ER +/PR+/HER2+), Her 2 (ER-/PR-/ HER2+), and triple negative (ER-/PR-/HER2-) BC subtypes[11]. Positive ER or PR was considered when ≥1% of invasive malignant cells exhibited nuclear staining or immunoreactivity. The HER2 test was scored from 0 to 3+, where: score 0 or 1 was negative; 2+ was undefined; and 3+ was positive. When there was any undefined result, FISH (Fluorescence in situ hybridization) was performed for definition.

Database, analysis of variance and mean tests, as well as procedures for frequency analysis, were performed by the software Sisvar 5.3 Build 77.

RESULTS

In the final sample of the study, 299 patients with breast carcinoma were included; 204 of them were from the city of Lavras and the other 95 were from cities in the microregion.

The average age of the patients was 54.2 years (±12.3). The division into groups by age is shown in Figure 1.

The evaluation of the menopausal status showed that 40.5% of the patients were premenopausal at diagnosis. As for parity, 14.4% of the patients were nulliparous at the time of diagnosis. Positive family history was found in 17.0% of the cases. Clinical characteristics are listed in Table 1.

The diagnosis of breast cancer was given based on alterations in the clinical examination in 71.5% of the cases. Lump was the most common type of lesion found: 89.0% of the cases (Figure 2).

In this study, 93.1% of the patients had invasive breast carcinoma, and 6.9% were diagnosed with ductal carcinoma *in situ*. In cases of invasive carcinoma, the analysis of the histological type revealed the high prevalence of the ductal type: 84.5% of the cases (Figure 3).

The mean tumor size of invasive carcinomas was 28.6 mm (±19.5; 0.3–13.3 cm) and median of 25 mm. At the time of diagnosis, 56.9% of the patients had clinically negative axilla, and 43.1% had clinically positive axilla. Regarding the histologic grade, most patients had a lesion with histologic grade 2 (59.4%). Histopathological characteristics are listed in Table 2. The most common stages at the time of diagnosis were IIA and IA: 28.9 and 24.4%, respectively (Table 3).

The average time between the medical appointment that motivated the investigative process and the histologic diagnosis was

66.2 days (±48.0). The average time between the histologic diagnosis and the beginning of the treatment was 39.6 days (±29.8).

DISCUSSION

Breast cancer is a disease of global impact, high incidence, prevalence, and mortality. In Brazil, 66.280 new cases were estimated for 2022, which represents an adjusted incidence rate of 43.74 cases per 100,000 women[5]. For the same period, 8,250 new cases were estimated in Minas Gerais[5].

In this study, the mean age at diagnosis was 54.2 years. The highest frequency of cases occurred in women of the 50–59 age group (30.4%; n=91), but the high prevalence of cases among women aged 40–49 years stands out (25.4%; n=76). Combined with the cases of the 30-39 age group, they represent 34.8% of the total figure, a rather significant number of cases. The data evidenced

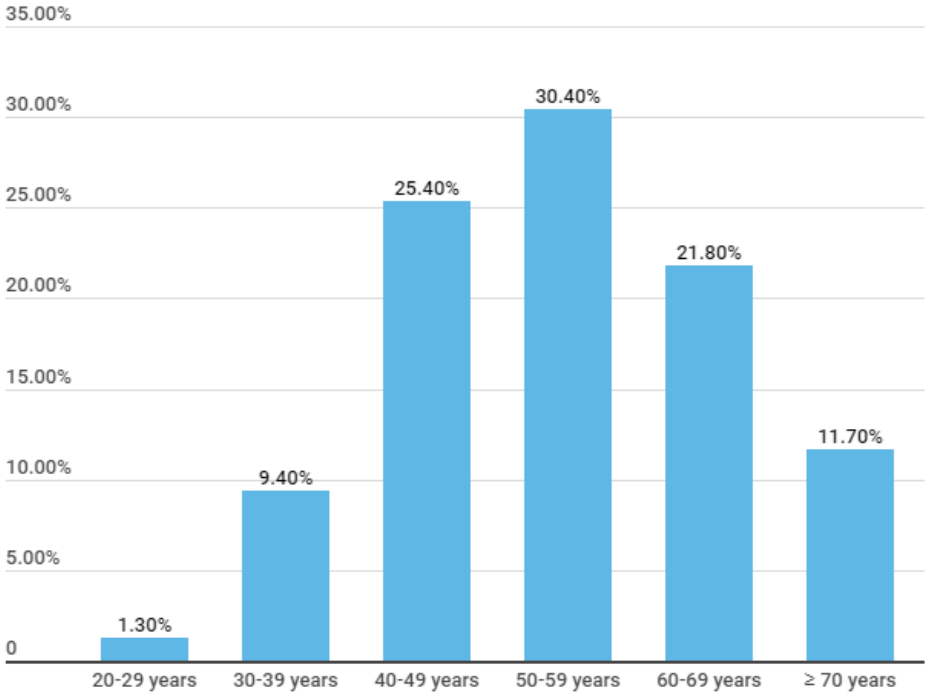

Figure 1. Distribution of breast cancer cases by age.

Table 1. Clinical characteristics of patients diagnosed with breast carcinoma.

	Category	Absolute frequency (n)	Percentage (%)
Parity	Nulliparous	43	14.4
	Primiparous	42	14.0
	Multiparous	214	71.6
Breastfeeding	Yes	231	77.3
	No	68	22.7
Menopausal status	Pre-menopause	121	40.5
	Post-menopause	178	59.5
Smoking	Yes	75	25.0
	No	224	75.0
Family History	Positive	51	17.0
	Negative	248	83.0
Type of Diagnosis	Clinical	214	71.5
	Imaging	77	28.5

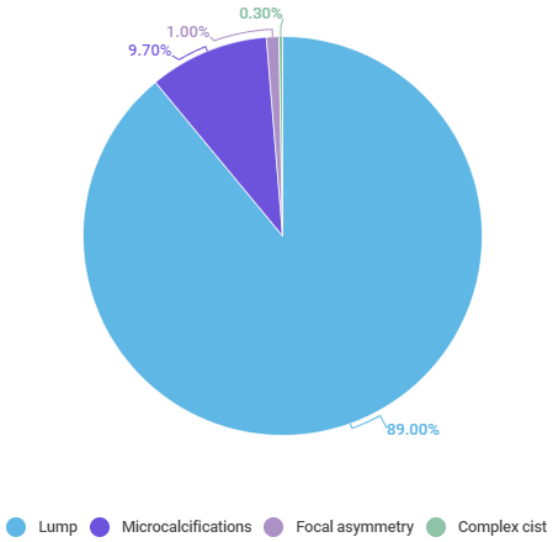

Figure 2. Type of lesion at disease presentation.

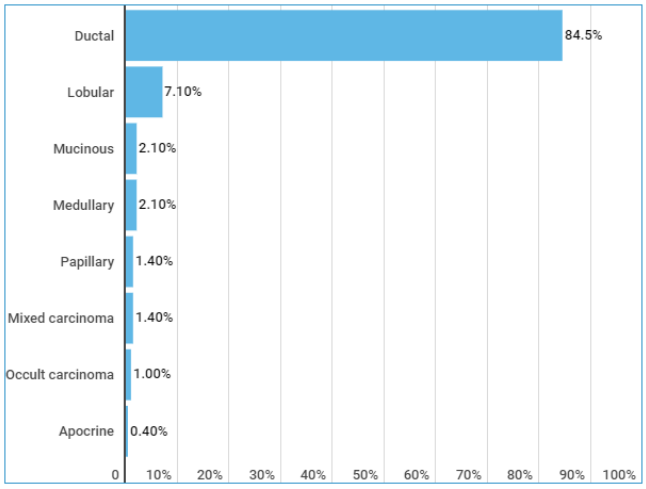

Figure 3. Distribution according to the invasive breast carcinoma histological type.

here are in agreement with other studies in the literature[12-14] Vale *et al.* found a prevalence of 34.4% in women under 50 years of age when surveying the number of breast cancer diagnoses given in the city of São Paulo between 2000 and 2015[15]. In the largest retrospective study on the breast cancer profile in the Brazilian population, called AMAZONA study, 41.1% of the patients were younger than 50 years old at the time of their diagnosis[16]. Such evidence raises the discussion regarding the need to expand the current screening program for breast cancer as adopted by the Ministry of Health in Brazil, which does not contemplate women between 40–49 years of age when they are at the usual risk. The high number of cases in women in this age group calls for greater attention for this public.

As for the histological type, it is known that the invasive ductal breast carcinoma, now called invasive carcinoma of no special type, is the most frequent subgroup, and the findings of this study are in line with the literature data[17]. The rate of ductal carcinoma *in situ* (DCIS) found was 6.9%. In Brazil, little information has been published on the epidemiology of carcinomas *in situ*. Its incidence is estimated to vary between 6.6 and 8.9%[12,18,19].

Table 3. Stage at diagnosis.

Stage	Absolute Frequency (n)	Percentage (%)
0	20	6.9
IA	71	24.4
IB	3	1.0
IIA	84	28.9
IIB	50	17.2
IIIA	33	11.3
IIIB	18	6.2
IIIC	5	1.7
IV	7	2.4

Table 2. Histopathological characteristics of the tumor.

Variable	Category	Absolute Frequency (n)	Percentage (%)
Estrogen receptor	Positive	234	81.5
	Negative	53	18.5
Progesterone receptor	Positive	215	74.9
	Negative	72	25.0
HER-2 Receptor	Positive	49	17.1
	Negative	237	82.9
Molecular Subtype	Luminal A	90	31.6
	Luminal B	114	40.0
	Luminal B-Her2	30	10.5
	HER-2	19	6.7
	Triple-negative	32	11.2

These numbers reflect the failure to establish an efficient mammography screening system. For the sake of comparison, internationally, DCIS now represents about 20% of all breast cancers diagnosed by screening[20,21].

Other data obtained in this study reveal that most patients (71.5%) had their diagnosis established when they already had palpable clinical lesions, which may have a direct relation to prognosis, type of treatment performed, and costs to the health system. The type of lesion most often found was lump (89.0%), which corroborates other studies that showed that the most associated sign of breast cancer is the breast nodule[12,22]. The presence of a nodule larger than or equal to 2 cm is related with increased risk of breast cancer[23]. In the present study, the average tumor size at diagnosis was 28.6 mm, which is not in line with a good early diagnosis strategy. The clinical examination of the breasts performed by trained health professionals associated with mammography remains the best strategy for diagnosis in women at usual risk. However, the low number of screening mammograms in Brazil reflects on the rates of diagnosis already with clinically identified lesions. It is also known that breast self-examination is not recommended as a cancer screening method and has not shown effectiveness in reducing mortality from BC, which further reinforces the need for organized screening programs in Brazil[24]. Recently, a large study carried out in Mumbai, India, has found that clinical breast examination conducted every two years by primary health workers significantly downstaged breast cancer at diagnosis, but with a non-significant 15% overall reduction in breast cancer mortality[25].

Nulliparity is recognized as a risk factor for the development of the disease. Nevertheless, in our study, only 14.4% of diagnosed patients had this condition. Pregnancy and lactation are considered important protective factors for breast cancer. In our analysis, most patients had such conditions: 71.6% of patients were multiparous and 77.2% had a history of breastfeeding. This information highlights the diversity of factors involved and their real weight in the development of a breast cancer.

A family history of breast cancer is also a crucial factor associated with an increased risk of BC. Approximately 16% of patients diagnosed with breast cancer report a first-degree relative affected by the same condition[17]. The data from our study showed a positive family history of breast cancer in 17.0% of the cases, numbers that are in agreement with other studies, such as Barboza ***et al***, in which 1,176 Brazilian patients were analyzed, and most had no cases of breast cancer in the family[26]. The positive family history of breast cancer in a minority of cases does not justify screening based on this circumstance by itself, requiring more careful risk assessment.

Data from the present study show that 25.0% of patients were smokers. It is noteworthy that carcinogens found in tobacco are transported to the breast tissue, increasing the likelihood of mutations in oncogenes and suppressor genes (p53 in particular). Moreover, a long smoking history and smoking before the first full-term pregnancy are additional risk factors, more pronounced in women with a family history of breast cancer[17]. Although it is controversial, the association between smoking and breast cancer is evidenced in several studies[3].

Axillary lymph node involvement is a prognostic marker in the management of BC, and sentinel lymph node biopsy is an important part of tumor staging[27]. Axillary lymph node clinical involvement was observed in 43.1% of cases (n=121), whereas 56.9% (n=160) of patients had no suspicious axillary lymph node at diagnosis. The National Surgical Adjuvant Breast and Bowel Project (NSABP) in B-32 trial reported 29% of sentinel lymph node positivity, while in specialized centers, and with effective screening, the positivity rate is dropping below 20%[28,29]. Such data reinforce the importance of the cyto/histological diagnosis of the axillary status, due to the considerable false positive and false negative results of the axilla clinical examination. In cases of histological lymph node involvement, late diagnosis negatively impacts survival, in addition to worsening quality of life when lymphadenectomy is performed.

The histological classification known as the Nottingham Classification System is a recommended grading system to help determine the prognosis of BC[30]. Several studies have shown that patients with histological grade 1 have the best prognosis, while grade 3 tumors have the worst prognosis[31]. In the present study, it was found that 13.0% (n=37) of the tumors diagnosed were histological grade 1, whereas most of the cases, 59.4% (n=170), were grade 2 and the other 27.6% (n=79) were classified as grade 3.

We observed that a smaller proportion of cases were diagnosed in early stages (stage 0 and I): 32,3%. Stage IIA was the most found, with 28.9% of cases (n=84), followed by IA with 24.4% (n=71), and IIB with 17.2% of diagnoses (n=50). These data are aligned with a previous descriptive study conducted in this same health center in the countryside of Minas Gerais, through the analysis of 112 cases of BC diagnosed between 2008 and 2013, which revealed stage II as the most common at diagnosis[12]. Dugno *et al.*, in a cross-sectional study with 273 patients in a hospital in southern Brazil, found that most patients had the disease diagnosed in stages I and II (70.8% of cases; 36.6%, and 34.2%, respectively)[32]. Similarly, Simon ***et al.*** observed in a retrospective cohort of 2,296 women with histologically proven breast cancer that more than half (53.5%) of cases were stage II at diagnosis[16]. On the other hand, such data also reflect the heterogeneity of BC in Brazil, given that another cohort of patients with BC treated surgically at *Hospital das Clínicas* in Belo Horizonte showed that the stage at diagnosis was higher among patients in the public health system compared with diagnoses made in the private system (58% of cases in the public health services were diagnosed in the initial stages and 42% in stage III, while in the private system 86.4% were detected in the initial stages and only 17.6% in stage III)[33]. We found a small number of cases in stages IIIB (6.2%), IIIC (1.7%) and IV (2.4%). These data

may reflect a possible bias related to the search or direct referral to a specialized oncology center, without the primary assessment in our service, in advanced cases. Possibly, the low rate of stage IV tumors is due to the fact that patients did not pass through our service. Our microregion has a reference center in oncology, located in another city, that offers surgeries, systemic treatment and radiotherapy, and some patients are referred directly to this center by their cities.

In Brazil, laws define the maximum period of 30 days between the diagnostic hypothesis of BC and the confirmation through exams necessary for elucidation, and of 60 days between diagnosis and the beginning of treatment[34]. In our study, it was found that the mean time between the first visit to the mastologist and the histological diagnosis of BC was 63.2 days, and the mean time between histological diagnosis and the beginning of treatment was 39.6 days. In a recent study conducted by Gioia *et al.* in Rio de Janeiro, Brazil, the mean time to start treatment was 39 days[35]. It can be perceived in our study that the beginning of the treatment is within what is recommended by law; however, as observed in other studies, a delay is identified concerning the time of diagnosis of BC, with reports of the average delay reaching 142.5 days in other Brazilian surveys[36]. We think that our delay in obtaining the diagnosis can be, in part, reduced with the adoption of a patient navigation process.

According to the World Health Organization, there are three main steps to early diagnosis: awareness of the cancer symptoms and getting medical care (access interval); clinical evaluation, diagnosis and staging (diagnostic interval); and transition to treatment (treatment interval)[37]. Strategies focused on reducing delays between the detection of the first sign or symptom and treatment initiation should address the delays in all these steps. Implementing a BC patient navigation program has great potential to alleviate the barriers faced by patients in the public sector, and improve the outcomes of patients with BC in Brazil.

It is important to note that the data found in the present study are limited by their retrospective methodology and the restricted number of participants. However, such data contribute to the discussion about the strategy of mammographic screening in a younger age range in comparison with the current recommendation of the Ministry of Health, considering the significant prevalence of cases in the 40–49-year-old age group, in addition to improving the coverage of mammography screening across the target population. Additionally, it was observed that there is still a delay between the first visit to a specialist and the histological diagnosis of the lesion, suggesting that the diagnostic strategy is not ideal, since a considerable portion of BC cases could have been diagnosed even earlier and faster.

CONCLUSION

This study showed an important number of cases of BC in women who have not reached the age range recommended for the beginning of screening. Although they do not correspond to the majority of cases, they deserve attention because of their significant observance in the total number of women affected in our microregion. There was a high number of diagnoses with palpable tumors, a considerable rate of disease with lymph node involvement and a longer time interval for obtaining the histological diagnosis, contributing to the rates of disease in advanced stages. The need for improvements in the performance of mammographic screening was demonstrated, aiming at early diagnosis, in addition to mechanisms that optimize patient navigation.

AUTHORS' CONTRIBUTION

CFH: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CMR: Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – original draft. ACOP: Investigation, Methodology, Validation, Visualization, Data curation. CACS: Data curation, Formal Analysis, Investigation, Validation, Writing – original draft. PHL: Data curation, Investigation, Visualization, Writing – review & editing. AOP: Data curation, Investigation, Visualization, Writing – review & editing. SMCR: Data curation, Investigation, Visualization, Writing – review & editing.

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Use of the serratus anterior fascia in immediate implant-based breast reconstruction

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ABSTRACT

Using the serratus anterior fascia may be a safe and effective option to recreate the lateral breast profile during subpectoral breast reconstruction, with minimal functional impact on the donor site. However, the literature is scarce when it comes to studies on this fascia flap in implant-based reconstruction. This article aimed to review the use of the serratus anterior fascia in immediate implant-based breast reconstruction, searching the electronic databases PubMed, Embase, Lilacs, and SciELO. The search was carried out by combining the following keywords: 'breast reconstruction' and 'serratus anterior fascia'. In the Pubmed and Embase databases, the search yielded a total of 12 and 15 articles, respectively, of which seven were selected according to the scope of this article. We found no studies on serratus anterior fascia and breast reconstruction in the Lilacs and SciELO databases. All works have results favorable for the use of the serratus anterior fascia flap and agree that this technique can be considered in the algorithm for the coverage of the inferolateral portion during subpectoral breast reconstruction.

KEYWORDS: serratus anterior fascia; breast reconstruction; breast implant; fascia; mastectomy.

INTRODUCTION

Breast cancer is the most commonly malignant neoplasm among women in most parts of the world, having 2.1 million new cases in 2018[1]. In Brazil, breast cancer is the most incident in women — after non-melanoma skin cancer —, with 74 thousand new cases estimated per year in the period from 2023 to 2025[2].

About 40% to 45% of patients diagnosed with breast cancer require mastectomy for local surgical control[3,4]. Breast reconstruction is part of the breast cancer treatment for patients undergoing mastectomy and minimizes mutilating sequelae, positively favoring their psychological health, sexuality, body image, and self-esteem[5].

Implant-based surgical techniques are the most used in immediate breast reconstruction in women with breast cancer undergoing mastectomy. The increased performance of skin and nipple-sparing mastectomies has favored single-stage reconstructions, without compromising oncological safety and providing better cosmetic results[6]. One of the benefits of immediate implant-based breast reconstruction is allowing rapid breast reshaping, preserving the patient's self-image, essential for their self-esteem and quality of life, in addition to helping reduce the number of surgical procedures and hospital visits[7,8].

Placing the implant below the pectoralis major muscle protects its integrity, reducing its visibility, palpability, and the occurrence of rippling[5,9]. In the subpectoral technique, the pectoralis major muscle covers about 2/3 of the implant. The options for complete prosthesis coverage, including the inferolateral portion, are total submuscular reconstruction, with the muscle flap and/or serratus anterior fascia, or the use of synthetic meshes and dermal matrices[10].

In breast surgery, the use of serratus fascia has been described in subfascial breast augmentation and in adipofascial tissue continuation with the pectoralis major muscle for coverage in breast reconstruction. However, few studies have reported its use in breast reconstruction[11]. The serratus anterior fascia flap in breast reconstruction can be a safe, effective, and fast option to recreate the lateral breast profile and prevent implant lateralization. The advantage of this flap is to be an autologous, well-vascularized tissue, which makes detaching the costal insertion of the serratus anterior muscle unnecessary, thus causing minimal impact on the morbidity and functionality of the donor site[11,12]. Despite its potential benefits, analytical studies evaluating the surgical results of using the serratus anterior fascia flap in breast reconstruction are scarce in the literature. This article aimed to review the use of the serratus anterior fascia in immediate implant-based breast reconstruction.

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METHODS

In order to systematize the search for articles in the literature, we used the PubMed, Embase, Lilacs, and SciELO electronic databases, combining the following keywords: 'breast reconstruction' and 'serratus anterior fascia'. The article selection sought to include the population of women undergoing implant-based breast reconstruction using the serratus anterior fascia in the reconstructive technique for implant coverage. The outcomes evaluated were postoperative results, surgical complications, and patient satisfaction.

We considered all types of articles published in English with the keywords present in the title, abstract, or both for the selection. Both authors reviewed the titles and abstracts independently. No time frame was set for the search. Based on this result, the articles were selected by title for abstract screening and subsequent inclusion in the bibliographic reference, after full-text screening. The articles chosen presented concepts and knowledge related to the use of the serratus anterior fascia in immediate implant-based breast reconstruction. We excluded abstract-only publications and duplicate articles.

In the Pubmed and Embase databases, the search yielded a total of 12 and 15 articles, respectively, of which seven were selected according to the scope of the review and eligibility criteria. Saint-Cyr et al.; Alani and Balalaa; Seth et al.; Bordoni et al.; Chan et al.; Cristofori et al.; and Tarallo et al.[11-17]. We found no studies on serratus fascia in the Lilacs and SciELO databases. Figure 1 shows the flowchart of article selection.

RESULTS AND DISCUSSION

Immediate implant-based breast reconstruction

Breast cancer is the most commonly malignant neoplasm among women in most parts of the world, having 2.1 million new cases in 2018[1]. In Brazil, breast cancer is the most incident in women — after non-melanoma skin cancer —, with 74 thousand new cases estimated per year in the period from 2023 to 2025[2]. Breast reconstruction is part of the breast cancer treatment for patients undergoing mastectomy and minimizes mutilating sequelae, positively favoring their psychological health, sexuality, body image, and self-esteem[5].

In 1963, Thomas Cronin and Frank Gerow were the first to report the use of silicone breast implants[18]. Historically, immediate implant-based reconstruction was performed with the placement of the implant in the subcutaneous plane; however, the technique was rejected due to the high rate of prosthesis displacement, flap necrosis, and capsular contracture[19]. In the 1980s, after Radovan's introduction to the use of tissue expanders, immediate breast reconstruction started to be performed; at first, in two stages[20]. The technological advancement of alloplastic materials and the introduction of conservative mastectomies contributed to single-stage breast reconstruction[21].

Currently, implant-based surgical techniques are the most used in immediate breast reconstruction among women with breast cancer[21]. Implant-based reconstructions show an upward trend of 11% per year. According to statistics from the American Society of Plastic Surgeons, 102,215 breast reconstructions were performed in 2016, of which, 83,149 used prostheses. This is due to the increasing performance of prophylactic mastectomies, as well as factors that improve the quality of reconstructions with prostheses, such as acellular dermal matrices, fat grafting, and nipple-sparing mastectomies[22]. The preference for prostheses is also related to the patient's choice for faster surgery with shorter recovery time, in addition to avoiding donor site morbidity, as occurs in autologous tissue reconstructions[23]. We emphasize that technological advances in prosthetic manufacturing and the current literature support the safety of breast implants[18].

In Brazil, women who undergo mutilating breast surgeries in the Brazilian public health system have the right to immediate breast reconstruction, as long as their medical condition allows its performance, as determined by Law 12,802/2013[24]. According to a study analyzing the pattern of surgeries performed in patients diagnosed with breast cancer in health facilities that are part of the Brazilian public health system from 2008 to 2014, Freitas-Júnior et al.[25] found an increased offer of breast reconstructions, both

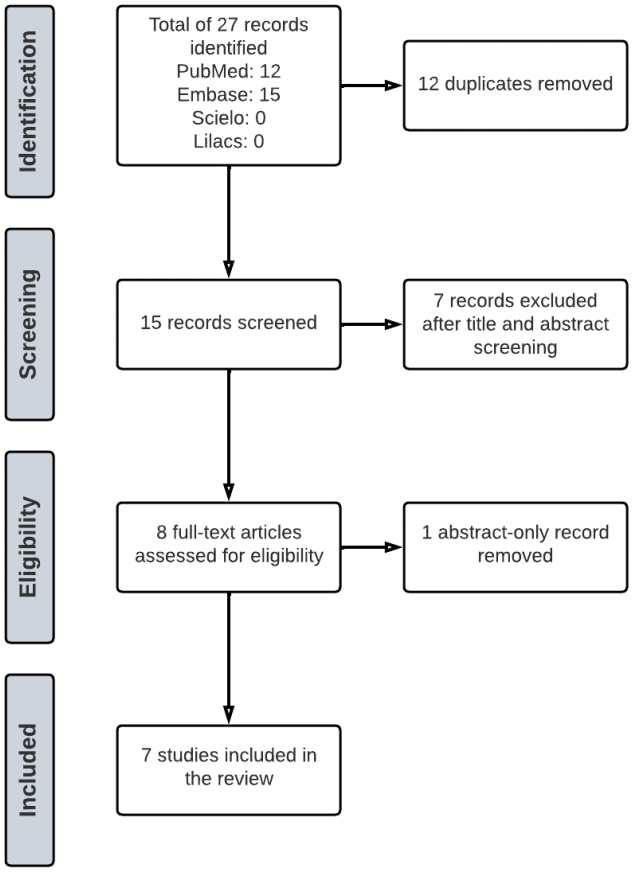

Figure 1. Flowchart of article selection.

flap- and implant-based. In 2008, women who underwent breast reconstructions represented 15% of mastectomized patients in the public health system, but this number increased significantly in 2013 and 2014 — 23.7% and 29.1%, respectively. Nevertheless, given the number of mastectomies performed, the offer of reconstructive surgery is still small[25].

The increased performance of skin and nipple-sparing mastectomies allowed the growing practice of single-stage direct-to-implant reconstructions, without compromising oncological safety and providing good cosmetic results[21]. The advantages of direct-to-implant reconstructions are lower number of surgeries; less exposure to anesthetic risk; fewer medical visits for expansion; in addition to immediate breast reshaping, which can reduce anxiety and improve self-image[8]. On the other hand, the disadvantage is that the quality of the flap or skin envelope available for coverage can limit the choice of implant volume. Yet, some findings indicate that the clinical results are comparable to two-stage reconstructions[26].

Conservative mastectomies

In 1894, Halsted revolutionized the treatment of breast cancer at the time by introducing radical mastectomy, considered the gold standard. Since then, the surgical approach has become less and less extensive. Subcutaneous mastectomy with preservation of the nipple-areola complex was first described by Freeman in the 1960s to treat a benign disease. However, the skin-sparing mastectomy technique became more popular after 1991, when Toth and Lappert described the technique as the use of minimal incisions and greater preservation of skin and inframammary fold, thus favoring the immediate reconstructive procedure[27].

Skin and nipple-sparing mastectomies are considered conservative mastectomies, defined by complete excision of breast tissue while preserving the skin envelope. The technique is safe for cancer treatment and comparable to conventional mastectomy and conservative surgery[28-30].

Moreover, preservation of the nipple-areola complex favors a better cosmetic result. Studies show that satisfaction with breast appearance and psychosocial well-being of patients undergoing nipple-sparing mastectomy and breast reconstruction is higher than preoperative satisfaction[9]. For women with large and ptotic breasts, pedicle and free nipple graft techniques can be used in nipple-sparing mastectomy[31].

Complications of conservative mastectomies with immediate reconstruction may include wound dehiscence, infection, implant loss, asymmetry, and capsular contracture, similar to conventional mastectomy. Nevertheless, the most common specific complications of the technique are flap and nipple necrosis. The rate of general complication is 22.3% and that of nipple necrosis is 5.9%. Among the factors associated with nipple necrosis, large breasts, ptosis, smoking, previous radiotherapy, periareolar incision, and comorbidities stand out[31].

Subpectoral implant placement

The prosthesis can be placed in the subpectoral or prepectoral position. Placing the implant below the pectoralis major muscle protects its integrity, reducing its visibility, palpability, and the occurrence of rippling. On the other hand, the disadvantage of subpectoral placement is related to muscle injuries, such as loss of strength and muscle spasms, causing animation deformity, in addition to being associated with greater postoperative pain compared to the prepectoral technique[5,9].

In order to create the total submuscular prosthesis pocket, the pectoralis major muscle is displaced until medially reaching the sternum insertions. Next, the pectoral muscle is sectioned at the nipple-areola complex level up to the lower extremity. Laterally, the serratus anterior muscle is detached from its costal insertions, allowing its displacement. These maneuvers allow the placement of the silicone prosthesis under the muscle flaps. The pocket with lateral coverage by the serratus muscle can result in flattening due to constant muscle pressure, interfering with the lateral breast profile[11].

In addition to the option of total submuscular reconstruction — a technique traditionally adopted for its low rate of complications, such as seroma, infection, and implant loss —, in which the implant is placed below the pectoralis major and serratus anterior muscles, subpectoral reconstruction can be performed using dermal matrices and synthetic meshes for inferolateral prosthesis coverage, helping delineate the inframammary profile[31].

Nonetheless, subpectoral reconstruction can be partial when the prosthesis is placed behind the pectoralis major muscle, thus leaving the inferolateral portion without coverage. Consequently, although it provides a better lateral outline, it has a risk of prosthesis lateralization. Preventing the skin suture from covering the prosthesis is also crucial to reduce the risk of implant exposure. Furthermore, the feasibility of this technique relies on having a viable dermal-fat flap[11].

Still, complete prosthesis coverage ensures greater implant protection and avoids its lateral migration. Alternatives to cover the inferolateral portion, besides the serratus anterior muscle, are synthetic meshes, acellular dermal matrices, dermal flaps, and serratus fascia. The problems of using mesh and dermal matrices are their high cost and complications such as seroma, while muscle flaps are associated with donor site morbidity. Therefore, using the serratus anterior fascia is a good option for covering the inferolateral portion, as it does not require detaching serratus muscle fibers and avoids additional costs with other alloplastic materials[9,11,32,33].

The serratus anterior fascia in breast reconstruction

In 1986, Wintsch and Helaly were the first to describe the use of the serratus fascia in a wrist reconstruction technique; later, its use was reported in the reconstruction of other body parts, such as wrist, forearm, leg, and back of the hand. In breast surgery,

the use of serratus fascia has been described in subfascial breast augmentation and in adipofascial tissue continuation of the pectoralis major muscle coverage in breast reconstruction. However, few studies have reported the use of the serratus anterior fascia flap in breast reconstruction[11]. Figure 2 illustrates the elevation of the serratus anterior muscle fascia.

The use of the serratus anterior fascia flap allows recreating the lateral breast profile and prevents the lateralization of the prosthesis or tissue expander, without needing to detach muscle fibers from the rib cage. The advantage of this flap is to be an autologous, well-vascularized tissue, in addition to making the costal detachment of the serratus anterior muscle unnecessary; it also has a low complication rate, with minimal donor site damage. Therefore, this technique provides safe, effective, technically easy, and fast inferolateral coverage of the submuscular prosthesis pocket with a high satisfaction rate[11,12,16].

In 2010, the use of serratus fascia in breast reconstruction was initially described by Saint-Cyr et al. after a retrospective study involving 22 patients with a mean follow-up time of 197 days. The authors concluded that the use of the serratus fascia is a safe, effective, and inexpensive method for lateral coverage of the tissue expander and reconstruction of the lateral breast profile, providing good cosmetic results with minimal complications. They also considered patients without comorbidities, history of radiotherapy, or axillary dissection, as well as those with a moderate body mass index, ideal for the technique. Yet, the authors reported some technical limitations when using serratus fascia, such as fascia damage by iatrogenesis, caused by axillary dissection, radiotherapy, or extensive oncologic resection of the lateral chest wall; anatomical variations, such as very small or thin fascias; and patient-inherent factors, such as smoking, diabetes, and low body mass index, which can be associated with attenuated fascias[11].

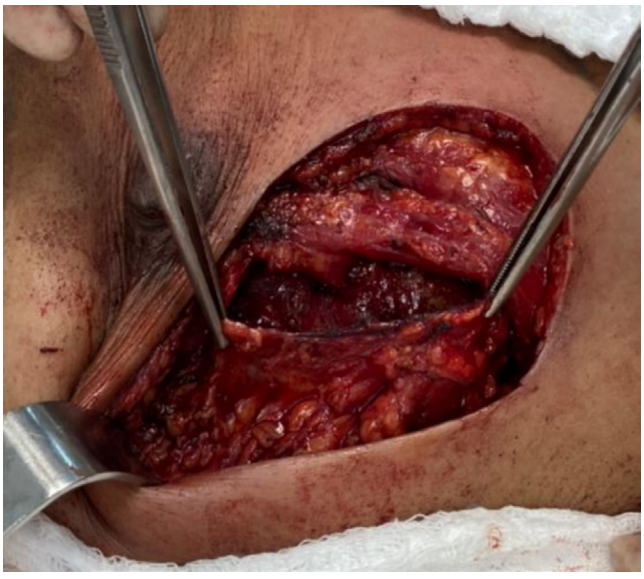

Figure 2. Image of the elevation of the serratus anterior muscle fascia.

Also, in a prospective study evaluating the musculofascial coverage — using the pectoralis major muscle, serratus anterior fascia, and superficial pectoralis major fascia — of the tissue expander in 59 patients who underwent immediate breast reconstruction, Alani et al. concluded that the fascia flap is an effective well-vascularized, autologous tissue option that prevents lateral displacement of the expander without needing to use another muscle flap or synthetic matrices[13].

The largest study on the use of serratus fascia in breast reconstruction was performed by Seth et al.[14]. It compared the use of serratus fascia (n=177) and serratus anterior muscle (n=375) for inferolateral coverage of the tissue expander. The authors revealed that elevation of the serratus fascia is a viable and safe alternative for inferolateral prosthesis coverage, with no differences in complication rates when compared to the serratus anterior muscle. In addition, they found that the fascia allowed for greater expander fill volumes and a lower number of expansions than the technique using the serratus muscle ($p<0.01$). The authors declared that fascial tissue is thinner and more pliable than muscle tissue, thus creating a larger potential space for expansion[14].

Bordoni et al.[12] analyzed 29 patients submitted to bilateral mastectomy and immediate breast reconstruction with placement of the tissue expander below the pectoralis major and serratus anterior muscle on one side and below the pectoralis major muscle and serratus fascia on the other, identifying lower postoperative pain levels and reduced seroma drainage on the fascia side, with statistical difference[12].

Chan et al.[15] evaluated 51 patients undergoing nipple-sparing mastectomy and direct-to-implant breast reconstruction, using only autologous flaps for coverage: pectoralis major muscle and serratus anterior fascia. They also reported that the serratus anterior fascia flap is a versatile, safe, and inexpensive option for inferolateral prosthesis coverage, especially in women with small and medium-sized breasts[15].

Cristofori et al. evidenced the effectiveness, safety, and lower complication rate, in addition to satisfaction with the result, of the serratus fascia flap (n=59) compared to the classical submuscular technique (n=64) in implant-based breast reconstructions[16]. Moreover, Tarallo et al. found good inferolateral coverage when evaluating soft tissue thickness by ultrasound in 20 breast reconstructions using the serratus fascia in the prosthesis coverage technique[17]. Table 1 summarizes the articles analyzed on serratus fascia and breast reconstruction.

CONCLUSIONS

Studies on immediate breast reconstruction involve heterogeneous populations and various surgical techniques.

Table 1. Summary of the articles.

Reference	Study design	Patients (n)	Population	Mean follow-up	Results	Level of evidence
Tarallo et al.[17]	P	18	Patients who underwent two-stage breast reconstruction with inferolateral coverage by serratus fascia from November/2018 to October/2019.	17.45 months	The serratus fascia provides good inferolateral coverage according to the thickness measurements of soft tissues over the prosthesis detected by ultrasound.	IV
Cristofori et al.[16]	R	123	Patients submitted to immediate implant-based breast reconstruction using the serratus anterior fascia flap or the classical technique between November/2012 and February/2015.	43.9 months	The modified serratus anterior fascia flap is a simple, safe, effective, and inexpensive autologous technique for immediate implant-based breast reconstruction.	III
Chan et al.[15]	R	51	Women with immediate implant-based breast reconstruction after nipple-sparing mastectomy from 2012 to 2016.	28.9 months	The serratus anterior fascia flap can provide autologous coverage in integrated mastectomy and implant-based breast reconstruction, especially in small and medium-sized breasts.	III
Seth et al.[14]	R	552	Women with serratus anterior fascia or muscle elevation in immediate reconstruction with tissue expander after mastectomy in a 10-year period in a single facility.	43.8 months	No differences in complications were found among patients with serratus muscle or serratus fascia. Serratus fascia elevation is a safe and viable alternative for inferolateral coverage during prosthetic breast reconstruction.	III
Bordoni et al.[12]	P	29	Women undergoing bilateral mastectomy and immediate two-stage implant-based breast reconstruction from January/2014 to January/2015.	20 months	The early postoperative pain score reported by patients was significantly lower with the fascial coverage.	III
Alani, Balalaa et al.[13]	P	59	Patients who had immediate breast reconstruction after mastectomy with the placement of a temporary tissue expander in the first stage, covered by a musculofascial layer composed of pectoralis major muscle, serratus anterior fascia, and superficial pectoral fascia for 3 years in a single center.	31 months	Serratus anterior fascia and superficial pectoral fascia flaps can be effectively used as a layer of autologous tissue to cover the inferolateral portion of the tissue expander in immediate breast reconstruction after mastectomy.	IV
Saint-Cyr et al.[11]	R	22	Patients who had immediate breast reconstruction with tissue expander after mastectomy using the serratus fascia.	197 days	The serratus anterior fascia flap is a versatile and safe option, providing vascularized coverage of the lateral prosthesis in expander-based breast reconstruction.	IV

P: prospective; R: retrospective; n: absolute number.

The literature is scarce when it comes to studies on the use of the serratus fascia in implant-based reconstruction. However, given the available data, the results of all studies agree that the serratus fascia flap technique can be considered in the algorithm for the coverage of the inferolateral portion in immediate implant-based breast reconstruction using the subpectoral technique. The evidence suggests that using the serratus fascia is simple, effective, and safe, in addition to favoring lower morbidity compared to the serratus anterior muscle flap.

AUTHORS' CONTRIBUTIONS

LSPR: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. JVB: Conceptualization, Methodology, Formal analysis, Supervision, Writing – review & editing.

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Most prevalent side effects of aromatase inhibitors in the treatment of hormone-positive breast cancer: a scoping review

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ABSTRACT

Hormone-positive breast cancer is the most commonly diagnosed breast neoplasm among postmenopausal women and is strongly associated with the effects of estrogens on hormone receptors of breast cells. Aromatase inhibitors are especially prescribed for treatment, and are effective to reduce mortality rates and the development of a new contralateral breast tumor. However, even with the proven efficacy and safety in use of these medications, approximately 50% of the patients abandon treatment before the prescribed period due to their side effects. The study was carried out with the objective of mapping what national and international literature declare about the most prevalent side effects caused by aromatase inhibitors in the treatment of women with hormone-positive breast cancer. We used the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review to elaborate this review. The methodology of choice was a scoping review aiming at synthetizing relevant information in an objective and clear manner about this drug class that is so common in breast cancer therapy, mainly benefitting women who are users of such drugs. According to the literature, reduced bone mineral density, arthralgia, hot flushes and dryness of the vaginal mucosa are the most reported symptoms, directly related with the absence of estrogen action on the body. These effects have a direct repercussion on the quality of life and on the discontinuation of treatment, leading to reduced functionality and high mortality rates.

KEYWORDS: Aromatase inhibitors; breast neoplasm; estrogen receptor; side effects.

INTRODUCTION

Breast cancer is the most frequently diagnosed neoplasm in women around the world, and represents the second main cause of death among women. In the diagnosed cases, about 75% are hormone-positive[1-4], associated with the proliferative effects of estrogens on estrogen receptors (ER) of breast cells.

The main source of estrogens among menopausal women comes from the action of the aromatase enzyme, responsible for converting androgens into estrogen in peripheral tissues, such as breast tissue. Its inhibition reduces the amount of circulating estrogen, thus decreasing the proliferation and growth of tumor cells[1,5,6]. Therefore, the drugs that are mostly used to treat this type of neoplasm in post-menopausal women are those included in the aromatase inhibitor class[2].

Drugs in this class are divided in non-steroidal, anastrozole and letrozole, which inhibit the aromatase enzyme competitively; and steroidal, exemestane, which irreversibly bonds with the binding site[1,2,7]. Despite its proven efficacy and safety in cancer treatment, about 50% of the women using aromatase inhibitors abandon treatment before the five years stipulated as time of general treatment. The main reasons for abandonment are the side effects caused by the class, especially musculoskeletal syndrome, fatigue and insomnia[6].

The scoping review was the methodology of choice for synthetizing information in a simple and objective manner, allowing the identification of research gaps. The objective of this review is to gather information about aromatase inhibitor drugs, in order to inform and understand their effects on the everyday life of women affected by breast cancer. It is important that health professionals be aware of the most prevalent side effects of this class, so that they can control the course of therapy and reassure and harbor these patients, communicating with them.

Therefore, the question is: which are the most prevalent side effects caused by aromatase inhibitors in hormone-positive breast cancer therapy?

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METHODOS

A study was conducted with the objective of mapping what national and international literature shows about the most prevalent side effects caused by aromatase inhibitors in treatments for women with hormone-positive breast cancer. Therefore, we used the PCC mnemonics to create the research question.

So, P (participants) refers to adult, post-menopausal women, with hormone-positive breast cancer; C (concept) includes the adverse effects of aromatase inhibitors; C (context) has not been defined, so it can be either the hospital or the household context, as long as there is treatment with the established drug class and determined type of neoplasm.

Quantitative studies, integrative reviews, case studies and clinical trials were considered. We also included grey literature (unconventional or unpublished publications).

As recommended by the methodology from Instituto Joanna Briggs (JBI), the search was carried out in three stages using the following databases: PubMed, VHL regional portal, CAPES, Brazilian Digital Library of Theses and Dissertations, and Scientific Electronic Library Online. We used the descriptors "woman", "breast cancer", "aromatase inhibitors", "hormone receptor positive", and "side effects" according to the vocabulary from Medical Subject Headings for the PubMed base, in different combinations, using synonyms and Booleans AND and OR. We did not use filters for period and language of the studies.

The initial analysis of the titles and abstracts was performed by two independent reviewers, and it was necessary to include a third reviewer when it was not possible to reach a consensus after discussion. Texts with potential were assessed in detail by each reviewer. For data selection, the identified studies had their information collected with the assistance of standardized Microsoft Excel® 2016 spreadsheets, and duplicates were removed.

This review was carried out according to JBI's methodology for scoping reviews, according to PRISMA-ScR guidelines. The previously elaborated research protocol was registered in the Open Science Framework platform, and its Digital Object Identifier was 10.17605/OSF.IO/J8UMV.

RESULTS

Among the five databases chosen for search, 238 studies were identified. After screening of titles and abstracts, 36 were selected for full reading and, from these, 22 met the inclusion criteria. Divergences between reviewers were solved by consensus.

The search results and selected studies are shown in a flowchart (Figure 1), as established by PRISMA-ScR.

The studies included different approaches of the several most prevalent adverse effects caused by aromatase inhibitors, and how these affect the lives of women undergoing breast cancer treatments. The general data are exposed in Table 1[1-22].

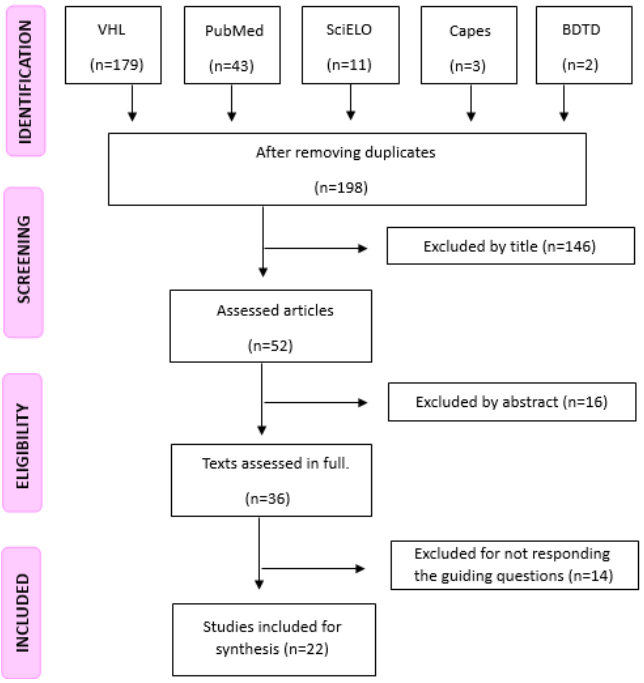

Figure 1. Study selection flowchart.

Of the 22 studies included in the synthesis, 15 mention musculoskeletal symptoms; 9, vasomotor symptoms; 8, gynecological/urogenital effects; 6, lipid profile; 6, cardiovascular effects; 3, ophthalmologic events; 3, effects on cognition; 3, mood swings; and 2, sleep and activities of daily living disorders. The selected productions are focused on the United Kingdom and the United States; 20 were published in English, 1 in French, 1 in Portuguese and 1 in Czech.

DISCUSSION

Breast cancer is the most common neoplasm among Brazilian women, and constitutes the second main cause of death by cancer in women[1-4]. The World Health Organization estimates there are more than one million new cases of breast cancer around the world per year[2] and, of these, more than 50% are hormone-positive, responding to hormone therapy with aromatase inhibitors[3].

The estrogen, chemical mediator produced by the ovaries from cholesterol, acts on different tissues during menacme due to the interaction with specific receptors to modulate essential functions in women's bodies[2]. Among the main functions of estrogen on women's bodies, we can mention the development of female characteristics, such as the increase of breasts and growth of pubic hair, and endometrial cell proliferation to allow the implantation of the embryo[6].

Besides, estrogen participates in the metabolism of calcium and the maintenance of bone mass, favors increasing fat deposition, promotes vaginal lubrication and increased libido[6]. Among premenopausal women, the main source of estrogen is the ovary.

Table 1. Year, type of study, authors, title, journal, country of publication and side effects.

Nº	Year	Type of study	Author	Title	Journal	Country	Side effects
01	2001	Clinical trial	Elisaf et al.[18]	Effect of letrozole on the lipid profile in postmenopausal women with breast cancer	European Journal of Cancer	United Kingdom	Increased serum LDL, total cholesterol and ApoB levels; increased atherogenic risk factor rates; reduced HDL and ApoA1 levels.
02	2006	Narrative review	Mouridsen,[17]	Incidence and management of side effects associated with aromatase inhibitors is the adjuvant treatment of breast cancer in postmenopausal women	Current Medical Research and Opinion	United Kingdom	Heat waves; arthralgia; myalgia; anorexia; alopecia; nausea; visual disorders; endometrial cancer; metrorrhagia; vaginal dryness; reduced bone mineral density; coronary artery disease; angina; acute myocardial infarction; venous thromboembolism; hypercholesterolemia; nausea; diarrhea; increasing levels of LDL and total cholesterol; reduced HDL levels.
03	2008	Case report	Nemitz et al.[9]	Intensification of a diffuse chronic pain syndrome by the introduction of an aromatase inhibitor	Praxis (Bern)	France	Fibromyalgia; diffuse chronic pain; arthralgia; myalgia; hot flushes; reduced bone mineral density; rigidity.
04	2008	Narrative review	Cella and Fallowfield[12]	Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy	Breast Cancer Research and Treatment	United States	Wave heats; vaginal discharge; dyspareunia; arthralgia; bone loss; venous thromboembolic events; cerebral ischemia; endometrial cancer; heart failure; hypercholesterolemia; night sweats; ostealgia; metrorrhagia; nausea; headache; irritability; mood swings; insomnia; weight gain; diarrhea; vaginal pruritus; reduced libido; mastalgia; uterine atrophy.
05	2009	Narrative review	Kwan and Chlebowski[19]	Sexual dysfunction and aromatase inhibitor use in survivors of breast cancer	Clinical Breast Cancer	United States	Sexual dysfunction; vaginal dryness; vaginal pruritus; dyspareunia; reduced libido.
06	2009	Narrative review	Bundred[11]	Aromatase inhibitors and bone health	Current Opinion in Obstetrics and Gynecology	United Kingdom	Reduced bone mineral density.
07	2011	Prospective cohort study	Gallicchio et al.[15]	Androgens and musculoskeletal symptoms among breast cancer patients on aromatase inhibitor therapy	Breast Cancer Research and Treatment	United States	Arthralgia; bone loss; arthritis; increased risk of fractures.
08	2011	Field survey	Scarpa et al.[14]	Rheumatic complaints women taking aromatase inhibitors for treatment of hormone-dependent breast cancer	Journal of Clinical Rheumatology	Italy	Spondyloarthritis; oligoarthritis; arthralgia; myalgia; sacroiliitis; arthritis; wave heats; night sweats; vaginal dryness; osteopenia; osteoporosis.
09	2011	Narrative review	Phillips et al.[21]	Do aromatase inhibitors have adverse effects on cognitive function?	Breast Cancer Research	Australia	No cognitive adverse effect was proven according to the available studies.

Continue...

Table 1. Continuation.

Nº	Year	Type of study	Author	Title	Journal	Country	Side effects
10	2012	Case report	Rocha-Cadman, et al.[22]	Aromatase inhibitors and mood disturbances	Palliative and Supportive Care	United Kingdom	Mood swings; suicidal ideas; anxiety; sadness; anger; hot flushes; irritability; difficulty to concentrate.
11	2014	Narrative review	Van-Asten et al.[8]	Aromatase inhibitors in the breast cancer clinic: focus on exemestane	Endocrine Related Cancer	United Kingdom	Hot flushes; bone loss; increased bone remodeling rate; carpal tunnel syndrome; morning stiffness; arthralgia; worsen lipid profile; increased risk of having coronary disease; myocardial infarction; stroke; transient ischemic attacks; atrial fibrillation; vaginal dryness; metrorrhagia; dyspareunia.
12	2014	Narrative review	Abubakar et al.[6]	The influence of genetic polymorphisms on the efficacy and side effects of anastrozole in postmenopausal breast cancer patients	Pharmacogenetics and Genomics	United States	Reduced bone mineral density; arthralgia; joint stiffness; myalgia.
13	2015	Prospective cohort study	Rodríguez-Sanz et al.[13]	CYP11A1 expression in bone is associated with aromatase inhibitor-related bone loss	Journal of Molecular Endocrinology	United States	Myalgia; arthralgia; reduced bone mineral density.
14	2015	Systematic review and meta-analysis	Artigalás[2]	Estudo farmacogenético e farmacoeconômico em pacientes brasileiras portadoras de câncer de mama tratadas com inibidores da aromatase		Brazil	ANASTROZOLE: vaginal bleeding; hot flushes; endometrial cancer; ischemic stroke; deep vein thrombosis; pulmonary embolism. LETROZOLE: hot flushes; nausea; hair changes (rarefaction and fine hair); arthralgia; myopathy; and arthritis. EXEMESTANE: increased appetite; hot flushes; excessive sweating; peripheral edema; nausea; arthralgia; diarrhea; visual changes; fractures.
15	2017	Narrative review	Borrie and Kim[1]	Molecular basis of aromatase inhibitor associated arthralgia: known and potential candidate genes and associated biomarkers	Expert Opinion on Drug Metabolism & Toxicology	United Kingdom	Arthralgia; myalgia; reduced bone mineral density; vaginal dryness; metrorrhagia; reduced libido.
16	2016	Narrative review	Krásenská[16]	Treatment with aromatase inhibitors in postmenopausal women with breast cancer and the possibility of influencing side effect	Klinická Onkologie	Czech Republic	Vaginal atrophy; dyspareunia; wave heats; redness; sweats; bone loss; arthralgia; myalgia; vaginal dryness; worsen lipid profile; urogenital atrophy; vaginal pruritus; polyuria; carpal tunnel syndrome; reduced prehension strength; morning stiffness.
17	2018	Clinical trial	Bhave et al.[7]	Effect of aromatase inhibitor therapy on sleep and activity patterns in early-stage breast cancer	Clinical Breast Cancer	United States	Reduced daily activity; fatigue; insomnia; musculoskeletal symptoms.

Continue...

Table 1. Continuation.

Nº	Year	Type of study	Author	Title	Journal	Country	Side effects
18	2019	Cross-sectional study	Gonzaga et al.[4]	Changes in cardiac autonomic modulation in women with breast cancer using aromatase inhibitors and the relation with biochemical variables	Arquivos Brasileiros de Cardiologia	Brazil	Worsen lipid profile; increased triglycerides; reduced variability in heart rate; higher risk of cardiovascular diseases; weight gain.
19	2019	Longitudinal study	Underwood et al.[3]	Cognitive effects of adjuvant endocrine therapy in older women treated for early-stage breast cancer: a 1-year longitudinal study	Supportive Care in Cancer	Germany	Changes in verbal memory.
20	2020	Case study	Bicer et al.[20]	The effects of adjuvant hormonotherapy on tear functions in patients with breast cancer	International Ophthalmology	Netherlands	Retinal hemorrhages; hemiretinal artery occlusion; keratoconjunctivitis sicca; blurry vision; foreign body sensation; redness; photosensitivity; Sjögren's syndrome.
21	2020	Narrative review	Tenti et al.[10]	Aromatase inhibitors-induced musculoskeletal disorders: current knowledge on clinical and molecular aspects	International Journal of Molecular Sciences	Switzerland	Reduced bone mineral density; arthralgia; myalgia; morning stiffness; carpal tunnel syndrome; reduced prehension strength; rheumatoid arthritis; spondyloarthropathy; Sjögren's syndrome; systemic lupus erythematosus; scleroderma; antisynthetase syndrome; antiphospholipid syndrome; hot flushes; night sweats; sleeping disorders; fatigue; anxiety; mild depression; vulvovaginal and urogenital atrophy; vaginal dryness; dyspareunia; metrorrhagia; dysuria; hypertension; venous thrombosis; arrhythmia; heart failure; peripheral arterial disease; embolism; myocardial infarction; atrial fibrillation; difficulty to concentrate; verbal memory deficit; paresthesia in extremities.
22	2021	Narrative review	Hyder et al.[5]	Aromatase inhibitor-associated musculoskeletal syndrome: understanding mechanisms and management	Frontiers in Endocrinology	Switzerland	Musculoskeletal syndrome associated with aromatase inhibitors; reduced bone mineral density; arthralgia; myalgia; joint stiffness; tenosynovitis; carpal tunnel syndrome; trigger finger.

Among post-menopausal women, it is especially produced in the fat tissue, breasts, brain, liver and muscles through the conversion of androgens by the aromatase enzyme (CYP19A1)[1-4].

The molecular action of estrogen begins in the cytoplasm, after bonding with estrogen receptors, represented by two subtypes, ERα (ESR1) and ERβ (ESR2)[6]. Most breast tumors express both receptor subtypes[6]. ERα is the main regulator of the estrogen proliferative action in the breast tissue, whereas ERβ has contrary effects by promoting antiproliferative and apoptotic functions[6].

Since hormone-positive breast cancer cells are modulated by the interaction between estrogen and its receptors, the most used therapy for this type of neoplasm include aromatase inhibitors. These drugs act by bonding, reversibly and irreversibly, to the heme group of the aromatase enzyme, thus preventing the aromatization of androgens, resulting in a state of estrogen deprivation (Figure 2)[1,2].

Aromatase inhibitors are classified as first, second or third generation, and these have been the most used ones recently[2,8]. The third generation is represented by anastrozole and letrozole, nonsteroidal competitive inhibitors, and exemestane, a steroidal non-competitive inhibitor that is irreversibly bonded with aromatase.

Anastrozole is administered in a 1 mg dose per day, being capable of reducing body aromatization in 97%. Letrozole reduces the biosynthesis of estrogens in 99% with a 25 mg daily dose, and exemestane reduces it in 98% with a 25 mg daily dose[9]. The three drugs are related with a range of side effects that affect the quality of life of patients, often leading to therapy discontinuation.

Most frequent side effects

Musculoskeletal effects

As presented in Table 1, most articles mention musculoskeletal effects as the most prevalent ones, present in about one third to half of the patients. Due to the repercussion of these symptoms on their quality of life, they are the main cause of treatment discontinuation[5,10] and medication change to estrogen receptor selective modulators, especially tamoxifen. Low adherence to treatment is associated with higher mortality rates related to breast cancer and higher recurrence rates[5].

Among these effects, reduced bone mineral density, which has a direct relation with increased risk of fractures due to fragility, mortality and loss of functionality, arthralgia and development of rheumatic autoimmune diseases are emphasized in 12 articles[10]. Effects on bones, especially the trabecular bone, begin in the first six months of use, mainly affecting lumbar vertebrae and the hip[11]. Ostealgia and myalgia can be associated with loss

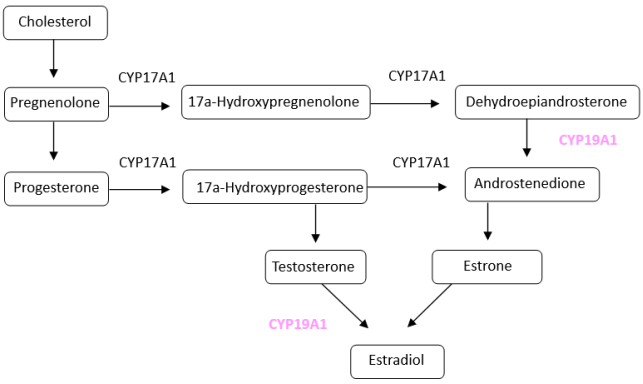

Figure 2. Estrogen metabolism[23].

in nociceptive estrogen modulation in the central nervous system and the increased process of bone resorption[12].

In physiological situations, estrogens modulate the balance between the activity of osteoblasts and osteoclasts, increasing the production of osteoprotegerin (OPG) and inhibiting the production of receptor activator of nuclear factor kappa B (RANKL) and of the macrophage colony-stimulating factor-1. Besides, estrogen inhibits the synthesis of pro-inflammatory cytokines by Th1 cells and monocytes, such as interleukin-1B, interleukin-6, interleukin-12, interferon gamma (IFN-y) and tumor necrosis factor alpha (TNF-a)[5], inducing the production of anti-inflammatory cytokines by Th2 cells, such as interleukin-2, interleukin-10, interleukin-4 and transforming growth factor beta (TGF-b)[10].

OPG prevents RANKL from bonding with the receptor of nuclear factor kappa B (RANK), resulting in the non-differentiation and activation of osteoclasts. This reduces bone resorption. Resorptive cytokines modulate the expression of these receptors, increasing their activity. Therefore, under the effect of estrogen deprivation caused by the use of aromatase inhibitors, the synthesis of these substances increases, as well as the dysregulation of Treg cell activity, and the production of anti-inflammatory cytokines and OPG decreases, with consequent increase of osteoclast activity[5,10].

The increased activity of osteoclasts causes higher bone resorption, leading to reduced bone mineral density and the development of osteopenia, osteoporosis and, consequently, fractures due to fragility. As brought up by 13.64% of the studies, increased bone resorption in some women may be associated with the existence of single nucleotide polymorphisms (SNPs), found in the genes that coordinate balance between the activity of osteoblasts and osteoclasts, as well as in estrogen receptors, vitamin-D receptor (VDR), RANK and OPG[10,13].

Three SNPs associated with higher risk of fractures were found in patients on aromatase inhibitors, in six genes regulated by estrogen action, CTSZ, SLMO2, ATP5E, TRAM2, TRAM14A, MAP4K4[5,10]. With the depletion of hormone levels, the genes are no longer inhibited and reduced bone mineral density is favored[5].

Arthralgia

Arthralgia affects about 74% of the patients and can range from mild to moderate, causing loss of functionality and impacting the patients' quality of life. Symptoms appear in the first six weeks of treatment, reaching is maximum at six months[5]. The most common ones are arthralgia, arthritis, morning stiffness, spondyloarthritis, sacroiliitis, carpal tunnel syndrome, trigger finger, tenosynovitis and reduced prehension strength. Figure 3 shows the main affected joints[1,12,14].

Risk factors for the development of arthralgia include hormone replacement therapy, chemotherapy with taxanes, obesity, vitamin D deficiency, arthralgia or previous osteoarthrosis,

perimenopause, joint and synovial fluid inflammation and previous use of tamoxifen[5,10]. For the diagnosis of arthralgia induced by aromatase inhibitors, it is necessary for patients to meet all of the major criteria, or at least three of the minor criteria[5], presented in Table 2.

Joint inflammation is related to the aromatase enzyme expression in synovial cells and chondrocytes of articular cartilage. Estrogen seems to have a chondroprotective effect, therefore, its deficiency has been reported with higher production of TNF-a, interleukin-6 and interleukin-1 in synovial fluid, causing pain and joint edema, besides causing damage to articular cartilage and degeneration of the subchondral bone[5,10].

Another estrogen action is to increase the activity of 1-α-hydroxylase enzyme, responsible for the hydroxylation of 5-hydroxy-cholecalciferol (calcidiol) to its active form, 1.25-dihydroxy-cholecalciferol (calcitriol). Therefore, according to Borrie and Kim, patients on aromatase inhibitors with musculoskeletal symptoms are more likely to have deficient baseline levels of vitamin D when compared to asymptomatic patients. Vitamin D levels are related to the intensity of arthralgia[1].

The activity of 1-α-hydroxylase enzyme, codified by CYP27B1, may be altered and result in reduced catalyzation of calcidiol to calcitriol due to the presence of two SNPs (rs4646536 and rs10877012) in the CYP27B1 gene[1]. Besides, the action of vitamin D on the body may be reduced by another SNP (rs1156882) found in the VDR gene, which codifies the calcitriol receptor, affecting its transcriptional activity and levels of gene expression[1].

Other SNPs were found in ESR1 (rs2234693 and rs9340799), in OPG (rs2073618), in VRD receptor, in CYP17A, in CYP19A1 and in gene HSD17B2, which codifies the enzyme that oxidizes oestradiol to estrone, which are associated with the onset of arthralgia 12 months after the beginning of treatment[10].

Main articulations affected by the use of aromatase inhibitors

- Sacroiliac;
- Talocrural;
- Radioulnar;
- Radiocarpal;
- Metacarpophalangeal;
- Distal interphalangeal;
- Proximal interphalangeal;
- Sternoclavicular joints;
- Metatarsophalangeal.

Figure 3. Main articulations affected by the use of aromatase inhibitors.[1,12,14]

Autoimmune rheumatic diseases

The main autoimmune diseases reported in three articles are rheumatoid arthritis, which is the most common, Sjögren's syndrome, systemic lupus erythematosus, fibromyalgia, antisynthetase syndrome and antiphospholipid syndrome[5,10]. These diseases are mostly related to the use of anastrozole and letrozole, and may manifest symptoms within three to six months. In the case of Sjögren's syndrome, observed by Tenti et al., there was reduction in arthralgia after exchanging letrozole for exemestane[10] after five years of treatment.

Nowadays, there are few studies about the pathogenesis of autoimmune diseases related to the use of aromatase inhibitors, but there is strong evidence that it is related with the effects of anastrozole in Th1/Th2 cellular balance, favoring the Th1 population (increase in interleukin-12 and IFN-y). Besides, the imbalance in the production of pro and anti-inflammatory cytokines and the inhibited differentiation of T *naive* to Treg cells[5,10], influenced by the low levels of estrogen, can also help to understand how these diseases are developed[15].

Vasomotor

Vasomotor effects, such as heat, redness and night sweats, are very common, reported in 36.4% of the included studies. They can be caused due to the activation of noradrenergic and serotonergic pathways in the central nervous system, resulting from the decreasing levels of estrogen[17]. This can cause anxiety, agitation, tachycardia, increased body temperature, sweating and chills[16]. Estrogen also modulates the thermoregulation center in the hypothalamus, which can change its activity when deficient[12].

Cardiovascular and lipid profile

According to Gonzaga et al., and Mouridsen, estrogen represents the main cardioprotective factor for women, responsible for increasing the synthesis of vasodilator enzymes and improving lipid profile. With the decrease of this hormone, there is an increase in serum levels of triglycerides, low-density lipoproteins (LDL), total cholesterol and apolipoprotein B (ApoB)[4,17,18].

Corroborating with a worsen lipid profile, there is reduction of high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1)[4,17,18]. Estrogen deficiency is also associated with increased sympathetic activity and reduced parasympathetic activity, which, added to a worse lipid profile, increases cardiovascular

Table 2. Definition of arthralgia induced by aromatase inhibitors according to Tenti et al.,[10].

Major criteria	Minor criteria
1. Using aromatase inhibitors; 2. Joint pain at the beginning or worsening since the beginning of therapy; 3. Improvement or resolution of joint pain two months after treatment discontinuation; 4. Joint pain reappears after returning to therapy.	1. Symmetrical joint pain; 2. Pain in fist and/or interphalangeal joints; 3. Carpal tunnel syndrome; 4. Reduced prehension strength; 5. Morning stiffness; 6. Improvement in joint discomfort with exercises.

risk. Therefore, there is increased risk of developing cardiovascular diseases, such as coronary disease, atrial fibrillation and systemic arterial hypertension[4].

Among aromatase inhibitors, exemestane was the only one without reports of effects on lipid profile; however, it was related to atrial fibrillation[10]. Meanwhile, anastrozole and letrozole were associated with venous thrombotic events, cerebral ischemia, heart failure, acute myocardial infarction and peripheral obstructive vascular disease[4,18].

Gynecological/urogenital

The gynecological effects related to the use of aromatase inhibitors work as an exacerbation of menopausal symptoms and repercuss on the relations with partners and female self-image[19]. Since estrogen acts by increasing lubrication in the vaginal canal and controls sexual behavior, especially in the follicular phase of the menstrual cycle, it is expected that its reduction leads to changes in desire and sexual performance[16,19].

Therefore, the main gynecological effects found in 41% of the articles include vaginal dryness, reduced libido, dyspareunia, vaginal pruritus, urogenital and vulvovaginal atrophy, metrorrhagia and mastalgia. Besides, reduced levels of estrogen increases the exposure to urinary tract infections (UTI), dysuria and polyuria[10,16,19].

Increased frequency of UTI happens because there is loss in the hormone protective action, which maintains a slightly acid pH in the vaginal canal. The bacteria that usually causes cystitis go up to the urethra of the periurethral region, vaginal introitus and perianal region[19].

Other side effects

Other side effects related with estrogen deficiency include retinal hemorrhage, hemiretinal artery occlusion, keratoconjunctivitis sicca, blurry vision, foreign body sensation, red eye, and photosensitivity. These effects are associated with the presence of estrogen receptors in the cornea, iris, crystalline, ciliary body, conjunctive, lacrimal and Meibomian glands[17,20].

The dry eye syndrome, or keratoconjunctivitis sicca, is the most common ophthalmologic effect and is prevalent among older women, resulting from the regulatory action of estrogens on lacrimal glands. When serum levels are low, they culminate in xerophthalmia with aqueous deficiency, rupture, apoptosis and necrosis of acinar cells[20]. Bicer et al. suggest that estrogen deprivation caused by the use of aromatase inhibitors can lead to the development of Sjögren's syndrome[20].

Due to the presence of estrogen receptors in areas of the central nervous system related to cognition, such as hippocampus, prefrontal cortex, amygdala and basal ganglia, the signs of difficulties in concentration and poor verbal memory can be explained by the reduced estrogen activity in these receptors. Estrogens also work in the promotion of neuroplasticity and regulation of learning and memory pathways, especially by the decreased synthesis of the n-methyl-d-aspartate receptor protein, involved in the glutamatergic activation of the hippocampus[3,9,21].

The evidence for mood swings are unusual. Patients may present with irritability, mild depression, suicidal ideas, anxiety, sadness and anger[22]. Users of these drugs can also have insomnia, fatigue, reduced daily activity, nausea, headache, weight gain, scleroderma, anorexia or more appetite, even though these effects are less frequent.

CONCLUSIONS

It was observed that decreased bone mineral density and arthralgia are the most reported effects by patients, followed by vasomotor and gynecological symptoms. Musculoskeletal effects are not only the most prevalent ones, but are also the main cause of treatment discontinuation, leading to the need to investigate its development during the years of therapy. The importance of handling the symptoms of these patients reflects on breast cancer mortality and recurrence rates, besides the relief and improvement in quality of life.

AUTHORS' CONTRIBUTION

GRZ: Conceptualization, Investigation, Methodology, Writing – review & editing. KAR: Conceptualization, Investigation, Methodology, Writing – review & editing. HC: Investigation, Methodology, Writing – review & editing. AISC: Conceptualization, Writing – review & editing.

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REVIEW ARTICLE
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Hormone therapy in the treatment of breast cancer and main outcomes in sexuality

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ABSTRACT

Hormone-dependent breast cancer has growth factors that respond positively to the hormones estrogen and progesterone. Thus, adjuvant endocrine therapy causes decreased or undetectable serum levels of these hormones. However, this treatment can have side effects that compromise the sexual health of patients, such as dyspareunia, vaginal dryness and decreased libido. In this scenario, the objective of this work was to document the main outcomes in sexuality in women after treatment for hormone-positive breast cancer. Thus, this is an integrative literature review, in which the following databases were used: U.S. National Library of Medicine (PubMed), Virtual Health Library (BVS), SCOPUS and Scientific Electronic Library Online (SCIELO), using the descriptors: "sexuality", "antineoplastic agents, hormonal" and "breast neoplasms", joined by the Boolean operator "AND". Full articles published in the last 5 years (2017-2022) were included; written in Portuguese or English. Articles dealing with non-hormone-dependent or metastatic breast cancer, or with patients younger than 18 years, or articles that did not answer the research question were excluded. In total, 26 articles were identified, of which 7 comprised the final sample of this review. A total of 3,850 women participated in the included studies. The main sexual dysfunctions found were: dyspareunia, hot flashes, decreased libido, vaginal dryness, breast tenderness, self-image concerns and hair loss. The symptom vaginal dryness was the most prevalent, mentioned in 71.4% of the articles included. In view of the adverse effects listed in this review, there is a need to carry out more studies on this topic, since the diagnosis of this comorbidity brings clinical, psychological, emotional, sociocultural and economic outcomes for the patient. Thus, a multidisciplinary team must assertively address these complaints to improve the overall quality of life of these women.

KEYWORDS: sexuality; antineoplastic agents, hormonal; breast neoplasms.

INTRODUCTION

Breast cancer is the most prevalent cancer among women — with the exception of non-melanoma skin tumors[1]. Treatment may include surgery, radiotherapy, chemotherapy, immunotherapy and/or hormone therapy. The use of the latter as a treatment strategy is based on immunohistochemical findings of positivity for female hormone receptors[2].

In this context, pharmaceutical options for hormone therapy include selective estrogen receptor modulators (SERM) and aromatase inhibitors (AI). Tamoxifen, belonging to the SERM class, competitively inhibits estrogen binding to breast hormone receptors. On the other hand, AI decrease estradiol concentration by inhibiting aromatase, the enzyme that converts androstenedione into estrone in peripheral tissues[3].

Therefore, the result of these medications is a decrease in the action of estrogen in breast cancers that respond positively to this hormone. This fact can interfere with the homeostasis of sex hormones, causing sexual dysfunctions that simulate menopause, the most prevalent of which are: hot flashes, vaginal dryness and dyspareunia[4].

Thus, hot flashes appear as a sensation of intense heat, where approximately 83.3% of patients undergoing hormone therapy reported having this symptom, according to Daldoul et al.[5]. The presence of vaginal dryness, in turn, was present in up to 50% of the patients evaluated in the same article.

Bui et al. observed several symptoms in premenopausal women undergoing hormone-responsive breast cancer treatment, including: vaginal dryness, decreased sexual interest, and day and night

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sweats, both for women with ovarian function suppression (OFS) and those on hormone therapy only. That is, the current literature shows that even in women only undergoing hormone therapy, there is already a considerable impact on their sexuality[6].

Symptoms of sexual dysfunction can occur with development of the cancer itself, but are more often associated with its treatment and follow-up. Thus, the study points out that sexual dysfunction is a common and a lasting complication for cancer survivors, affecting over 60% of women diagnosed with cancer[7].

Hormone therapy protocols recommend that patients receive 5 to 10 years of therapy. Thus, a significant number of patients discontinue treatment, which has a direct impact on mortality and relapses[8]. Therefore, sexual side effects can be significant in the quality of life and prognosis of these women[9].

OBJECTIVE

To review the current scientific literature to document key outcomes in sexuality in women undergoing treatment for hormone-positive breast cancer.

METHODS

This was an integrative literature review, allowing the critical evaluation of different methodological approaches, gathering and synthesizing knowledge, as well as drawing conclusions based on scientific evidence, applying its discoveries in clinical practice[10]. Inclusion criteria were: retrospective studies published up to 5 years ago, in Portuguese or English, with no location restriction, available online in full and with full or partial content approach.

Phase 1 began with the elaboration of the guiding question, formulated through the definition of the participants (women undergoing treatment for hormone-dependent breast cancer); interventions to be evaluated (use of hormone therapy) and results to be measured (impact on sexuality). Thus, the following question was formulated: "What does the current literature say about the main negative sexuality outcomes of hormone therapy in women with hormone-positive breast cancer?"

In turn, Phase 2 involved an extensive literature search, including searching through databases and manually searching the references of selected studies. The databases used were: U.S. National Library of Medicine (PubMed), Virtual Health Library, SCOPUS and Scientific Electronic Library Online (SCIELO). The keywords previously consulted in the medical subject headings (MeSH) were included, with the descriptors "Sexuality", "Antineoplastic Agents, Hormonal" and "Breast Neoplasms", joined by the Boolean operator "AND". Table 1, below, represents the complete description of the search keywords and filters used in the electronic databases.

Articles dealing with non-hormone-dependent breast cancer and with patients under 18 years of age were excluded, as well as news, editorials, comments and letters of introduction — where content is not based on the scientific method.

Table 1. Search key and filers by electronic database.

Database	Search key
SCOPUS	((("SEXUALITY") AND ("ANTINEOPLASTIC AGENTS, HORMONAL")) AND ("BREAST NEOPLASMS") (LIMIT-TO (PUBYEAR, 2022), (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017)) AND (LIMIT-TO (LANGUAGE, "English"))
SCIELO	((("SEXUALIDADE") AND ("ANTINEOPLÁSICOS HORMONAIS")) AND (NEOPLASIAS DE MAMA") Filters: Full text, English, Portuguese, 5 year
PUBMED	((SEXUALITY) AND (ANTINEOPLASTIC AGENTS, HORMONAL)) AND (BREAST NEOPLASMS)
BVS	((SEXUALITY) AND (ANTINEOPLASTIC AGENTS, HORMONAL)) AND (BREAST NEOPLASMS) (year cluster: [2017 TO 2022])

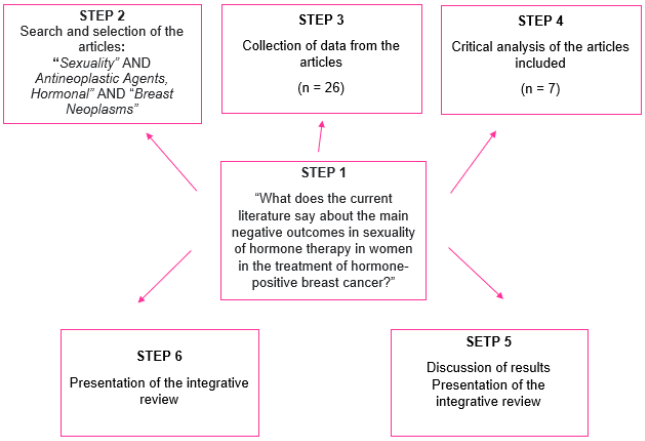
Therefore, the selection of articles was carried out in two stages: initially, with the reading of the titles, followed by the reading of the abstracts and, later, through the complete analysis of the studies. Screening was carried out independently by two researchers, inspired by predetermined criteria. A manual search was carried out in all references of the selected articles, having as eligibility criteria the articles most cited in the initial studies and that corroborate the primary objective of this work. Figure 1 shows the steps of the integrative review. In turn, Figure 2 illustrates the article selection flowchart.

In Phase 3, the following were removed from the articles: definition of subjects, methodology, sample size, measurement of variables, method of analysis and basic concepts employed. In step 4, a critical analysis of the included studies was therefore carried out, contemplating the information contained. Publication data were organized and synthesized to simplify the integration of findings, according to the following variables: database, title, journal, author, country/year and design/sample.

Finally, phases 5 and 6 were performed, corresponding to the discussion of results and presentation of the integrative review, respectively[11]. As for ethical aspects, all information extracted from the articles belongs to the public domain, and the ideas, concepts and definitions of the authors included in the review were respected.

RESULTS

In this study, 26 articles were identified. Of these, 1 article belongs to BVS, 20 to PUBMED and 5 to SCOPUS. Ten articles were excluded after reading the title. All articles selected by title were selected for reading in full, after reading the abstract. Of the 16 articles selected for reading in full, 4 were duplicates, resulting in 12 articles chosen for reading in full.



Source: Adapted from Mendes et al.[18]

Figure 1. Steps of the integrative review.

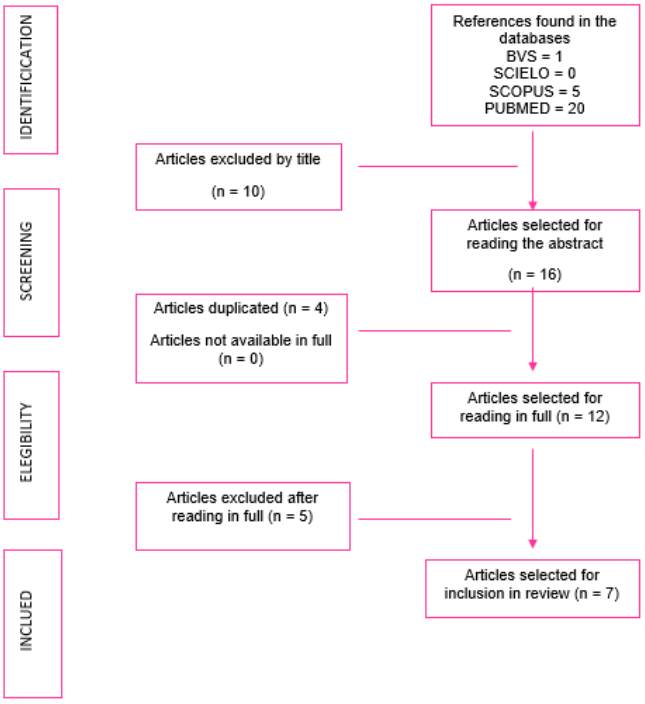


Figure 2. Flowchart of the selection process for articles included.

After the critical analysis of the pre-selected studies, 7 articles were listed as selected studies, since they presented aspects that answered the guiding question of this review. Regarding the year of publication of the articles included in this review, there were: 1 (14%) from 2017, 1 (14%) from 2018, 4 (57%) from 2019 and 1 (14%) from 2020.

Of the seven articles included, 2 (28%) were prospective studies, 1 (14%) randomized study, 1 (14%) a letter to the reader, 1 (14%) a cross-sectional observational study, 1 (14%) a case-control cohort study and 1 (14%) a multicenter prospective cohort study.

Still, regarding the countries of publication of the included articles: 1 (14%) was from the United Kingdom; 2 (28%) from England; 1 (14%) from Australia, 1 (14%) from New Zealand, 1 (14%) from the United States and 1 (14%) from Spain. Table 2 characterizes them using: number, title, total number of participants, main statistical results, main results and main limitations.

DISCUSSION

According to Table 2, a total of 3,850 women participated in the 7 studies included in this review. The main sexual dysfunctions found by these studies were: dyspareunia and hot flashes (discussed in 57% of the articles included); decreased libido (discussed in 28% of the articles included); vaginal dryness (discussed in 71% of the articles included); breast sensitivity (discussed in 28% of the articles included); concern with self-image (discussed in 42% of the articles included) and concern with hair loss (discussed in 14% of the articles included). Figure 3 shows in graphic form the main sexual dysfunctions found by the authors.

Dyspareunia

Dyspareunia is the term used to define pain during sexual intercourse whether due to lack of lubrication, vaginal irritation or vicinity diseases. Accordingly, Ribi et al.[12] evaluated the sexual dysfunctions and overall quality of life of 2287 women, divided into two distinct groups: 1260 in the SOFT trial and 1027 in the TEXT trial, over 6, 12 and 24 months. In SOFT (Suppression of Ovarian Function Trial), premenopausal women were randomly assigned to receive 5 years of tamoxifen; tamoxifen plus ovarian suppression or exemestane plus ovarian suppression. In turn, in the TEXT study (Tamoxifen and Exemestane Trial), women were also randomized to receive tamoxifen and exemestane, associated with ovarian suppression.

In that same study, participants were divided into five cohorts — cohort 1: tamoxifen alone; cohort 2: cytotoxic chemotherapy followed by tamoxifen alone; cohort 3: cytotoxic chemotherapy, followed by exemestane or tamoxifen combined with OFS; cohort 4: endocrine therapy alone, with exemestane or tamoxifen combined with OFS; and cohort 5: cytotoxic chemotherapy and OFS before the use of endocrine therapy. Thus, it was observed that the item "pain" or "discomfort during sexual intercourse" worsened over the first 6 months and remained constant until 24 months[12].

A cohort study published by Li et al.[13] revealed that adjuvant chemotherapy did not influence the severity of vasomotor and sexual symptoms in women with cancer, except for the symptom of pain with sexual intercourse. The authors reported that one of the reasons why some studies identify high rates of dyspareunia in patients undergoing chemotherapy is due to differences in samples in terms of menopausal status and therapies used.

Daldoul et al.[14], gathered results of dyspareunia in about 60% of patients on hormone therapy who were evaluated. Thus, according to the sample size of 30 women, 12 had dyspareunia with sexual dysfunction, versus 6 women who also had dyspareunia but without sexual dysfunction. The study also demonstrated that this symptom has already been reported in patients because of fear of infertility and loss of sexual perception.

Table 2. Main sexual dysfunctions encountered.

Nº	Title	n total	Sexual dysfunctions	Statistical results	Main results	Main limitations
1	*Female Sexuality in Premenopausal Patients with Breast Cancer on Endocrine Therapy*	30	Dyspareunia	n=12	Sexual dysfunction was present in over 63.3% of patients. Endocrine therapy and most of its side effects were not associated with sexual dysfunction.	Sexual function was not assessed before endocrine therapy was started (the observed dysfunction may have been caused by the breast cancer itself or even preceded the disease).
			Hot flashes	n=18		
			Vaginal dryness	n=14		
			FSFI	63.3% of participants with score of sexual dysfunction		
2	*Treatment-induced symptoms, depression and age as predictors of sexual problems in premenopausal women with early breast cancer receiving adjuvant endocrine therapy*	2287 (1260 SOFT, 1027 TEXT)	Dyspareunia	6 months: n=409 12 months: n=416 24 months: n=402	Sexual problems increased at six months and persisted at that level. In general. Patients with the most severe worsening of vaginal dryness, sleep disturbances and bone or joint pain at 6 months reported a greater increase in sexual problems at all checkpoints.	The study did not discriminate between the sexual side effects of tamoxifen and exemestane. Some of the patients may not have continued with the long-term treatment, and this influences the results.
			Hot flashes	6 months: n=6 12 months: n=3 24 months: n=2		
			Vaginal dryness	6 months: n=13 12 months: n=12 24 months: n=9		
			Decreased libido	6 months: n=647 12 months: n=737 24 months: n=700		
3	*Identifying distinct trajectories of change in young breast cancer survivors' sexual functioning*	896	Concern with body image	RRR=2.52 SD=0.53	Five distinct trajectories of sexual function were identified: one asymptomatic, one minimally symptomatic, two moderately symptomatic and one severely symptomatic. 12% of women were asymptomatic during the entire follow-up. Most patients had stable mild symptoms (42%). 11% had stable severe symptoms that did not improve over time.	Possible pre-diagnosis sexual dysfunctions were not determined. The severely symptomatic line suggests that symptoms were prior to diagnosis. One of the questionnaires (CARES SCALE) did not have the "sexual desire" item, in addition to not obtaining information about recently sexually inactive women.
4	*Partner status moderates the relationships between sexual problems and selfefficacy for managing sexual problems and psychosocial quality-of-life for postmenopausal breast cancer survivors taking adjuvant endocrine therapy*	125	Decreased libido	n=64	Women who reported greater sexual problems and lower sexual self-efficacy had worse quality of life and lower sexual satisfaction. Women without partners had worse psychosocial quality of life when compared to women with steady partners.	The sample was mostly Caucasian, with advanced education and with older women, limiting the generalizability of these data. Patients' sexual partners were not accessed during the studies.
			Vaginal dryness	n=63		

Continue...

Table 2. Continuation.

Nº	Title	n total	Sexual dysfunctions	Statistical results	Main results	Main limitations
5	*Quality of life in elderly breast cancer patients with localized disease receiving endocrine treatment: a prospective study*	148	Sexual function	Tamoxifen: Mean: 6.1 SD: 13.5 Anastrozole: Mean: 10.1 SD: 16.4 EORTC QLQ-BR-23 SCORE: First visit: 5.4 Second visit: 5.2 Third visit: 9.3	Better quality of life scores were found in women after using endocrine therapy for three years, which shows good adaptation of patients to the treatment. Differences in quality of life impact between aromatase inhibitors and tamoxifen were irrelevant.	More comprehensive results were found regarding aromatase inhibitors, since more patients used aromatase inhibitors when compared to tamoxifen. There may have been a follow-up bias, as only 79% of participants answered the questionnaire on the second visit, which could have led to erroneously optimistic results.
			Sexual pleasure	Tamoxifen: Mean: 33.3 SD: 38.4 Anastrozole: Mean: 30.8 SD: 29.1 EORTC QLQ-BR-23 SCORE: First visit: 29.6; Second visit: 21.5; Third visit: 31.1		
			Active sexual life	Tamoxifen: Mean: 6.1 SD: 13.2 Anastrozole: Mean: 11.6 SD: 19.7 EORTC QLQ-BR-23 SCORE: First visit: 5.3 Second visit: 4.8 Third visit: 10.6		
			Hot flashes	Tamoxifen: Mean: 5.9 SD: 13.1 Anastrozole: Mean: 17.5 SD: 24.1 EORTC QLQ-BR-23 SCORE: First visit: 13.9 Second visit: 21.2 Third visit: 16.4		
			Sexual interest	Tamoxifen: Mean: 6.1 SD: 13.5 Anastrozole: Mean: 8.5 SD: 15.7 EORTC QLQ-BR-23 SCORE: First visit: 5.5 Second visit: 5.6 Third visit: 8		

Continue...

Table 2. Continuation.

Nº	Title	n total	Sexual dysfunctions	Statistical results	Main results	Main limitations
5	*Quality of life in elderly breast cancer patients with localized disease receiving endocrine treatment: a prospective study*	148	Breast sensitivity	Tamoxifen: Mean: 11.7 SD: 9.3 Anastrozole: Mean: 9.3 SD: 12.2 EORTC QLQ-BR-23 SCORE: First visit: 13.6 Second visit: 12.5 Third visit: 9.6	Better quality of life scores were found in women after using endocrine therapy for three years, which shows good adaptation of patients to the treatment. Differences in quality of life impact between aromatase inhibitors and tamoxifen were irrelevant.	More comprehensive results were found regarding aromatase inhibitors, since more patients used aromatase inhibitors when compared to tamoxifen. There may have been a follow-up bias, as only 79% of participants answered the questionnaire on the second visit, which could have led to erroneously optimistic results.
			Concern with body image	Tamoxifen: Mean: 97.1 SD: 5.1 Anastrozole: Mean: 95.1 SD: 13.7 EORTC QLQ-BR-23 SCORE: First visit: 13.6 Second visit: 12.5 Third visit: 9.6		
			Concern about hair loss	EORTC QLQ-BR-23 SCORE: First visit: 24.2 Second visit: 20.2 Third visit: 18.7		
6	*Impact of chemotherapy on symptoms and symptom clusters in postmenopausal women with breast cancer prior to aromatase inhibitor therapy*	339	Dyspareunia	Mean: 0.731 - 11.1 (anastOnly - 228 women) 0.859 - 10.4 (***chemoanast*** - 111 women) TOTAL: 10.8 DP: 23.4 (anastOnly); 21.4 (***chemoanast***) TOTAL: 22.7	The most severe symptoms occurred in women on aromatase inhibitors. There were no differences in symptom severity between the two groups.	Other factors that may influence the symptomatology process of women undergoing treatment were not accounted for, such as broader demographic characteristics, personality, general health status, comorbidities, menopausal status and genetic differences, among others.
			Hot flashes	Anastrozole mean 20.9 (anastOnly) 23.2 (***chemoanast***) TOTAL: 21.7 General mean: 0.851 (anastOnly - 228 women) 0.833 (***chemoanast*** - 111 women) Anastrozole SD: 27.0 (anastOnly) 27.3 (***chemoanast***) TOTAL: 27.1		
			Vaginal dryness	Mean: 0.583 – 16.9 (anastOnly); 0.769 - 20.9 (***chemoanast***) TOTAL 18.2 SD: 23.5 (anastOnly); 28.5 (***chemoanast***) TOTAL 25.3		

Continue...

Table 2. Continuation.

Nº	Title	n total	Sexual dysfunctions	Statistical results	Main results	Main limitations
6	*Impact of chemotherapy on symptoms and symptom clusters in postmenopausal women with breast cancer prior to aromatase inhibitor therapy*	339	Breast sensitivity	Anastrozole mean: 37.1 (anastOnly); 23 (***chemoanast***) TOTAL: 32.5 Anastrozole SD: 30.2 (anastOnly) 27.6 (***chemoanast***) TOTAL: 30.1	The most severe symptoms occurred in women on aromatase inhibitors. There were no differences in symptom severity between the two groups.	Other factors that may influence the symptomatology process of women undergoing treatment were not accounted for, such as broader demographic characteristics, personality, general health status, comorbidities, menopausal status and genetic differences, among others.
			Concern with body image	Anastrozole mean 29.7 (anastOnly) 33.3 (***chemoanast***) TOTAL: 30.9 Anastrozole SD 28.7 (anastOnly) 31.1 (***chemoanast***) TOTAL: 29.5		
7	*The effects of fractional microablative CO 2 laser therapy on sexual function in postmenopausal women and women with a history of breast cancer treated with endocrine therapy* *FSFI SCORE improvement data	25	FSFI – Excitation IMPROVEMENT	0.52	There was a statistically significant improvement in all domains of FSFI, WBFS and FSDS-R when comparing baseline scores with the three post-treatment symptom scores for all patients.	Small sample size. Absence of control group. Because of the size of the groups, it was not possible to directly compare postmenopausal women with women treated with hormone therapy.
			FSFI – Sexual desire IMPROVEMENT	0.37		
			FSFI - Lubrification IMPROVEMENT	0.33		
			FSFI - Orgasms IMPROVEMENT	0.66		
			FSFI – Dyspareunia IMPROVEMENT	0.91		
		3850				

TEXT: Tamoxifen and Exemestane Trial; n: sample number; RRR: relative risk; SD: standard deviation; M: mean; FSFI SCORE: score for questionnaire female sexual function index; EORTC QLQ-BR-23 SCORE: score for quality of life specific for breast cancer; chemoanast: women previously treated with chemotherapy in addition to anastrozole; anastOnly: women treated only with anastrozole.

Dyspareunia: pain and/or discomfort during penetrative sexual intercourse; hot flashes: feeling of intense warmth over the chest, neck and face, which can be accompanied by chills; SOFT: Suppression of Ovarian Function Trial,

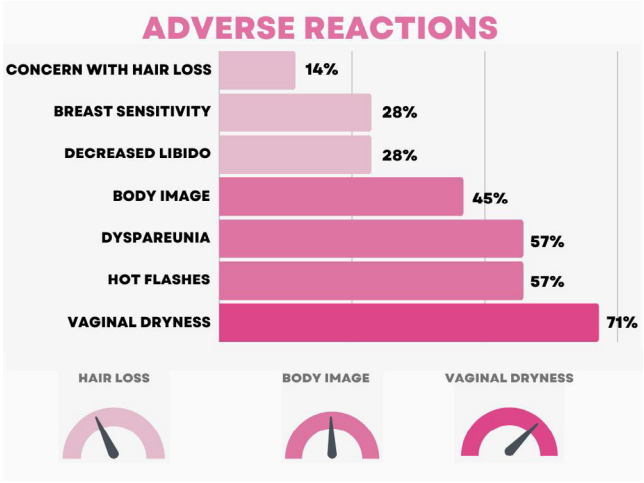


Figure 3. Main adverse effects found on sexuality.

Hot flashes

Hot flashes are defined as a feeling of intense heat in the chest, neck and face, and may be accompanied by chills, palpitations and anxiety attacks. Thus, women undergoing treatments that cause early menopause, such as endocrine therapy, may experience more severe and even longer hot flashes[15].

Among the articles read in full, Franzoi et al.[16] and Dos Santos et al.[17], 2021 are integrative reviews that discuss pharmacological and non-pharmacological interventions currently available to mitigate the negative side effects of adjuvant endocrine therapy.

Thus, they were not selected to be included in this review, as they did not directly answer the research question. Despite this, these studies are addressed in the present discussion to summarize these management options, since the authors consider

it essential to improve the sexual function of cancer patients to increase the quality of life of these women[16,17].

In the context of pharmacological interventions for this symptom, antidepressants such as SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-noradrenaline reuptake inhibitors) can be used, especially venlafaxine combined with tamoxifen[14,15].

Randomized clinical trials have shown the effectiveness of the anticonvulsants gabapentin and pregabalin in controlling hot flashes[13]. The alpha-adrenergic antihypertensive drug clonidine has also been shown to be effective, but it is rarely prescribed because of its side effects, which include dry mouth, constipation and drowsiness[14,15].

Vaginal dryness

Dorfman et al.[9], in their cross-sectional study, state that up to 93% of breast cancer patients using hormone therapy experience sexual side effects, including vaginal dryness. According to the study, particularly among postmenopausal women, endocrine therapy can exacerbate menopausal symptoms, and vaginal dryness is highlighted as one of the main symptoms.

Daldoul et al.[14]. conducted a cross-sectional observational study that gathered a sample of 30 patients on hormone therapy. With this, the fear of these patients in relation to vaginal dryness was observed. In this scenario, the authors indicated that, among this same sample, 14 women reported vaginal dryness with sexual dysfunction, versus 5 without dysfunction.

Thus, in the context of lack of vaginal lubrication, some measures can be taken to improve this side effect. Cancer patients can receive local estrogen hormone therapies, such as intravaginal pills, rings, inserts and creams[17].

As non-hormonal options, there are aqueous compresses of 4% lidocaine in the vulvar vestibule (between the glans of the clitoris and the beginning of the perineum). Vaginal CO_2 or erbium laser therapy has been shown to be effective in improving the symptoms of vaginal dryness, dyspareunia and itching and/or vaginal redness in these patients[11]. However, as it is a recent therapy on the market, the lack of well-designed safety studies, in addition to its high cost, limits its recommendation[16].

Decreased libido

In the study by Dorfman et al.[9], almost 70% of postmenopausal patients diagnosed with hormone-positive breast cancer who received endocrine therapy reported at least one sexual problem. Of these, more than half declared a decreased libido and/or vaginal dryness, and 40.2% of women said they avoided intimacy with their partners.

Ribi et al.[12] comment in their discussion that many studies have reported an association between depressive symptoms and sexual problems related to sexual inactivity or hypoactive sexual desire disorder in breast cancer survivors. However, in contrast to the hypothesis of this study, depression was associated with sexual problems in the first six months, but no longer influenced sexual dysfunction in the following two years, indicating that the analyzed decreased libido may be involved in factors that are no longer psychological, but to physical factors such as fatigue, joint and musculoskeletal pain and genitourinary symptoms.

When comparing the two main drugs of endocrine therapy, Arraras et al.[15] commented that patients using AI had a greater reduction in libido compared to patients on tamoxifen, during 3 years of treatment. Accordingly, it is stated that the discontinuation of endocrine therapy is associated with a worse doctor-patient relationship, in addition to the side effects of the treatment.

Breast sensitivity

With regard to breast sensitivity, von Hippel et al.[18], studied the trajectory of groups undergoing therapy with aromatase inhibitors alone and in combination with chemotherapy. In this sense, the authors state that the impact of breast pain was greater in younger women and in the group with endocrine therapy alone. In addition, this study affirmed the controversy in the current literature about the influence of chemotherapy on sexual symptoms, as well as the difficulty in differentiating the symptoms of physiological menopause from those caused by hormone therapy.

Also, Li et al.[13], when comparing a group of women using only anastrozole and a group that received chemotherapy combined with an AI, greater breast sensitivity was observed in the group being treated only with AI. The authors provide in their discussion a meta-analysis in which breast pain is related to younger women, in agreement with Li and collaborators, in which women using only anastrozole were younger than women undergoing chemotherapy combined with AI.

When analyzing patients using quality of life questionnaires, Arraras et al.[15], comment in their results that symptoms of breast sensitivity and having an active sex life improved on the third visit, 3 years after starting treatment, compared to the first two visits. Depending on the study, the authors reported that other studies, involving radiotherapy, show improvement in breast tenderness after 2 years of treatment.

Limitations

In addition to the limitations already mentioned in Table 2, the importance of continued research in this area of oncology is highlighted, especially in underdeveloped and developing countries. In addition, it is difficult to detail the impact of hormone therapy on sexuality alone, since most of the analyzed studies have a set of oncological therapies involving cancer surgery and/or cytotoxic therapy, in addition to the psychological and emotional impact of cancer diagnosis and treatment. The clinical relevance of a varied population sample is also highlighted, for a better generalization of the adverse reactions found.

CONCLUSIONS

Vaginal dryness was found to be the most prevalent symptom, and other symptoms were also found, such as dyspareunia,

decreased libido, hot flashes, concern with body image, breast pain or tenderness and concern with hair loss.

There is a need to carry out more studies on this topic, since the diagnosis of this comorbidity affects clinical, psychological, emotional, sociocultural and economic outcomes for the patient. Thus, a multidisciplinary team must assertively address these complaints to improve the overall quality of life of these women.

AUTHORS' CONTRIBUTION

ETC: Conceptualization, Investigation, Methodology, Project Administration, Visualization, Writing – review & editing. CCRM: Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing. DPA: Data curation, Formal Analysis. PNSM: Visualization, Review. ASIC: Investigation, Data curation, Methodology, Visualization, Supervision, Writing –original draft.

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REVIEW ARTICLE
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Integrative review of clinical trials and meta-analysis of the main studies of neoadjuvant chemotherapy in the treatment of breast cancer in the past 30 years

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ABSTRACT

Neoadjuvant chemotherapy (NAC) has become a common treatment strategy for early-stage breast cancer. In this study, we conducted a systematic research in the PubMed database using the following terms: breast cancer, neoadjuvant chemotherapy, randomized clinical trials, complete pathological response, overall survival, and disease-free survival. The research has been limited to articles published in the past 30 years (1993–2023). We included only randomized clinical trials that evaluated the use of NAC in breast cancer and data on PCR rates and survival outcomes. Our research resulted in a total of 13 randomized clinical trials and two meta-analyses. The PCR rates ranged from 13% to 58%, with higher rates observed in patients with triple-negative breast cancer (TNBC) and human epidermal growth factor 2 (HER-2+) disease. Several trials reveal a significant association between PCR and better survival results, including overall survival and disease-free survival. However, the impact of PCR on survival results was less consistent in patients with hormone receptor-positive breast cancer. The use of taxanes in combination with anthracyclines has been the most common NAC scheme evaluated in these trials. The PCR rates have been associated with better survival outcomes, in patients with TNBC and HER-2+ disease. However, the impact of PCR on survival outcomes in patients with hormone receptor-positive breast cancer is less clear. Additional studies are needed to determine the optimal NAC regimen for each subtype of breast cancer and to identify biomarkers that can predict the NAC response.

KEYWORDS: breast neoplasms; neoadjuvant therapy; chemotherapy.

INTRODUCTION

Breast cancer (CM) is the most common type of cancer and the leading cause of cancer death among women worldwide[1]. Treatment of breast cancer is complex and depends on several factors, such as stage, degree, status of hormone receptors, and human epidermal growth factor 2 (HER-2). Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer and is increasingly used for early-stage breast cancer[2]. It has been shown to improve the chances of conservative breast surgery, reduce the risk of involvement of lymph nodes, and increase the possibility of achieving a complete pathological response (PCR)[3].

The PCR is defined as the absence of any invasive or *in situ* cancer in the breast and axillary lymph nodes after completion of NAC[4]. The PCR has been suggested as a substitute outcome for long-term survival outcomes, such as global survival (SG) and disease-free survival (SLD)[5]. However, the relationship between the PCR and survival outcomes is still controversial, and many studies have conflicting results.

In recent years, several randomized clinical trials (ECRs) and meta-analyses have investigated the effectiveness of NAC in breast cancer and its relationship with PCR and survival outcomes. The aim of this integrative review is to synthesize the evidence of ECRs and meta-analysis published over the past 30 years on NAC in breast cancer, with a particular focus on the association between PCR, SG, and SLD.

METHODS

This is a non-systematic integrative review that aims to synthesize evidence on NAC for the treatment of breast cancer, specifically

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in relation to its impact on PCR and overall survival and disease-free survival. The search was carried out in the PubMed database using the following MeSH terms: "Breast Neoplasms"[Mesh] AND "Antineoplastic Combined Chemotherapy Protocols"(Mesh) AND "Neoadjuvant Therapy" (Mesh), AND "Randomized Controlled Trials as Topic"(Mesh), and "Meta-Analysis as Topics" (Mesh). The search was limited to studies published in the past 30 years (January 1993 to December 2022) in English. In addition, manual searches were carried out in the reference lists of relevant studies to identify additional articles.

The inclusion criteria were as follows:

1. Randomized clinical trials and meta-analyses that assessed the effectiveness of NAC in breast cancer;
2. Studies that reported the rates of PCR, SG, and/or SLD;
3. Studies that were published in English.

Exclusion criteria were as follows:

1. Studies that did not evaluate NAC;
2. Studies that did not report the rates of PCR, SG, and/or SLD;
3. Studies that were not published in English.

The data synthesis was carried out using a narrative approach, and a summary table was created to present the main features of the studies included. The results were summarized separately for subtypes and all subtypes. Studies that did not report PCR or survival outcomes were excluded from the synthesis.

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed throughout the review process. The initial search identified a total of 1,276 studies, of which 1,129 were found on PubMed, 127 on EMBASE, and 20 on ClinicalTrials.gov. After the removal of duplicate studies, the total number of studies was reduced to 1,116. The sorting of titles and summaries led to the exclusion of 1,077 studies. Full-text articles were obtained for the remaining 39 studies, of which 33 were clinical trials and 5 were meta-analyses. After the inclusion and exclusion criteria were applied, a total of 15 studies were included in the final synthesis (Figure 1).

Integrative review

Treatment of breast cancer

Treatments for non-metastatic CM are surgical resection, systemic therapy (chemotherapy, endocrinotherapy, and target therapies), and radiotherapy. Systemic treatment prior to definitive surgical treatment, called neoadjuvant treatment, is recommended for almost all patients diagnosed with locally advanced breast cancer. The primary objective of this approach is to reduce the volume of the tumor and allow the realization of surgical treatment with better aesthetic results not only in those patients considered inoperable to the diagnosis but also in those with operable tumors and who wish to be subjected to conservative surgery[2]. Moreover, neoadjuvant treatment allows direct observation of response to treatment, with the potential to provide data that can be used with predictive and prognostic intent[6]. From studies in adjuvant treatment (the one that is administered after surgery), we can obtain information regarding the outcomes of SLD and SG, but such studies require the inclusion of a large number of patients and that they are followed for a long period, which generates a high cost. On the contrary, studies in neoadjuvant treatment can be conducted with fewer patients and at a shorter time interval, as well as provide information on intermediate outcomes, such as PCR and clinical response, which could predict the benefit in terms of long-term outcomes at a lower cost. These advantages have stimulated the expansion of the number of studies in NAC in recent years, including those for the inclusion of new drugs[6,7].

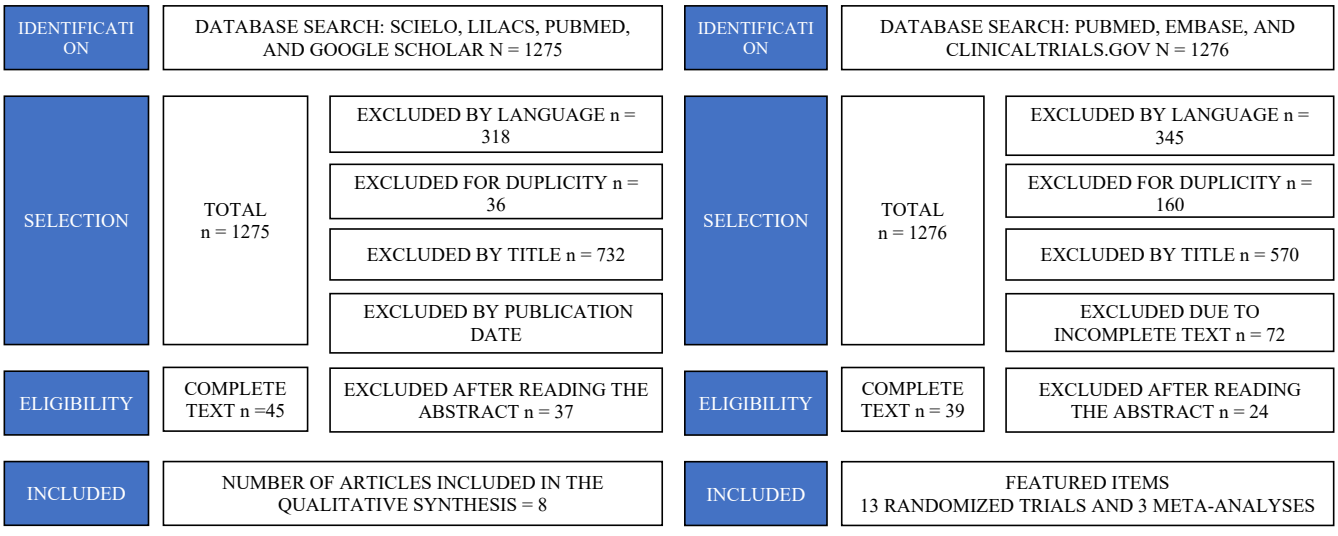

Figure 1. Database search flowchart.

While historically surgery followed by adjuvant chemotherapy has been considered the first and primary treatment, neoadjuvant chemotherapy (administration of chemotherapy before surgery) has emerged as the recommended approach in patients with locally advanced disease, or whose "tumor size/mother" ratio is unfavorable for conservative surgery, or for those with aggressive tumor biology (triple-negative breast cancer (TNBC) and HER-2 positive (HER-2+))[8]. The NAC approach offers multiple advantages as it offers the opportunity to reduce surgical management based on the response, provides response information that is prognostic and is used to guide adjuvant treatment recommendations, serves as a platform to advance in drug development, and enables time gains until the outcome of the genetic panel for hereditary breast cancer[9].

In Table 1, we find the main current schemes for NAC established by the National Comprehensive Cancer Network Guideline updated in February 2023[2].

Complete pathological response rates

One of the pioneering studies on NAC in breast cancer was conducted by Bonadonna et al. and published in 1976[10]. This study, conducted at the National Cancer Institute of Milan, evaluated the use of chemotherapy with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) before surgery in women with operable breast cancer. The results of this study showed that NAC reduced the size of the tumor and increased the rate of conservative resection of the breast[10].

After two decades of studies comparing adjuvant versus neoadjuvant strategies, such as the National Surgical Adjuvant Bowel and Breast Project (NSAPB) B-18[11], which randomized 1,523 women with operable CM for doxorubicin (Adriamycin) and cyclophosphamide (AC) in the neoadjuvant or adjuvant treatment, the rate of PCR in this initial study was only 13%, which is much lower than that currently seen. This study was carried out before the routine tests for RH or HER-2 to guide the selection of systemic therapy[11].

The NSABP B-27 study evaluated the addition of paclitaxel (T) to the combination of AC in the neoadjuvant or adjuvant scenario and clearly demonstrated the benefit of adding the taxane, with improved PCR rates (26.1%), thus indicating a factor of better prognosis[12].

The GeparDuo study was conducted to determine the rate of PCR between administrations of dense-dose AC chemotherapy (ACdd) every 14 days, compared with conventional scheme every 21 days. The PCR rate was significantly higher in the ACdd group (14.3% versus 7.0%)[13].

A meta-analysis that included nine randomized clinical trials (RC) with a total of 3,274 patients, who received dense-dose NAC schemes, did not observe an increase in PCR (OR 1.18) in all patients; however, when evaluating patients with low hormone receptor expression (HR), there was a significant increase in PCR (OR 1.36)[14].

Over the past few years, several studies have shown different rates of PCR, which vary, in a general way, from 3.3 to 40.9%, without assessing the molecular profile[15]. A meta-analysis with eight EC and eight retrospective studies (RS) showed a PCR of 22.4%. Thus, PCR rates are discordant between different subtypes, and the prognostic effects of PCR are not applicable to all molecular subtypes of CM[15].

The rate of PCR is higher in TNBC and HER-2-positive patients than in HR+/HER-2-negative patients[15]. According to the results of the CTNeoBC meta-analysis, which analyzed 12 EC on the association of PCR with long-term results, patients with highly aggressive subtypes, such as TNBC or HER2+, who achieved PCR, showed better results than patients with luminal subtypes A[16].

Spring et al.[17] conducted a meta-analysis of 52 studies and 27,895 patients, of whom 14,254 (51.1%) came from ECRs, 1,709 patients (6.1%) from non-randomized clinical trials, and 11,932

Table 1. Main current schemes for neoadjuvant chemotherapy of National Comprehensive Cancer Network version 4.2023[6].

Subtype of Breast Cancer	Main NAC Scheme	Associated Target Therapies	Main indications
RH+ HER-2 -	AC-T sequential		Conservative Surgery Wish T>5.0 cm or N+ <40 years, G3
	TC		Cardiotoxicity risk
HER-2 +	AC – T sequential	Trastuzumab + Pertuzumab (1 year)	T>2.0 cm or qqT N+
	T Carboplatin		
TNBC	AC + T Carboplatin	Pembrolizumab (T>2,0 cm)	T>1.0 cm qqN

NAC: neoadjuvant chemotherapy; HER-2+: human epidermal growth factor 2; TNBC: triple-negative breast cancer; AC: Adriblastine + Cyclophosphamide; T: Taxanes; TC: Taxane + Cyclophosphamide; ACdd: Adriblastine + Cyclophosphamide dose dense, qq: any, N+ - armpit with involved lymph nodes, G3 histological grade.

patients (42.8%) from retrospective cohort studies. CTNeoBC[16] meta-analysis data were included in a single study, showing that the PCR was 21% (range: 10.1%–74.2%), with the highest rate of PCR observed in HER2+ tumors at 36.4% (range: 17.5%–74.2%) and TN tumors at 32.6% (range: 20.3%–62.2%), while HR+/HER2-negative tumors had the lowest rate at 9.3% (interval: 5.5%–31.3%)[17].

Full pathological response rate in HER-2+ patients

In general, superexpression of the HER-2 protein and/or the amplified HER-2 gene is found in about 20%–25% of CM cases. It is known that CM HER-2+ has a more aggressive phenotype, with a higher rate of relapses and mortality when left untreated; however, HER-2 blockage with anti-HER therapies demonstrated a significantly better prognosis[18].

The first major study was conducted at the MD Anderson Cancer Center, comparing the effect of NAC with or without Trastuzumab in 42 patients with operable HER-2+ disease. They were randomly assigned to paclitaxel followed by 5-FU + Epirubicin + cyclophosphamide (FEC) for four cycles, or to the same Trastuzumab chemotherapy regimen. The rates of PCR were 25% in the chemotherapy-only group and 66.7% in the chemo + Trastuzumab group (p=0.02). Despite the small sample size, the study showed that adding Trastuzumab to chemotherapy improves PCR[18].

The TRYPHAENA study is an open phase II study, in which patients with operable, locally advanced, or inflammatory HER-2+ disease were randomized into three groups: FEC + trastuzumab + pertuzumab followed by taxane + trastuzumab + pertuzumab (arm A), FEC followed by taxane + trastuzumab + pertuzumab (arm B), and FEC followed by taxane and carboplatin + trastuzumab & pertuzumab (arm C). The PCR was 61.6% in arm A, 57.3% in arm B, and 66.2% in arm C[19].

The NeoSphere study also evaluated the effectiveness of pertuzumab use in neoadjuvant treatment. Patients were randomized to receive trastuzumab + taxane (group A), pertuzumab + trastuzumab + taxane (group B), pertuzumab + trastuzumab (group C), or pertuzumab + taxane (group D). Patients in group B had significantly higher response, with a PCR of 45.8% compared with patients in group A, with a PCR of 29.0%. The PCR in group C was 16.8%, and in group D, it was 24%. According to the study, the best option for NAC is the taxane scheme associated with double block HER-2[20].

The TRAIN-2 study assessed the effect of omitting the use of anthracyclines in patients with HER-2+ breast cancer. In the study, 438 patients were randomized to receive anthracyclines or not, and there was no difference in PCR rates between the groups. The group that received anthracyclines showed a PCR rate of 67%, while, in the group that did not receive them, the rate was 68% (p=0.95). These results suggest that omitting anthracyclines may be a viable treatment option in patients with HER-2+ breast cancer, without compromising the effectiveness of treatment[21].

Full pathological response rate in triple-negative patients

Patients with TNBC account for 13–20% of cases and respond significantly better to NAC compared with luminal subtype, probably because they are more proliferative. Three major studies, namely, BrighTNess[22], GeparSixto[23], and CALGB 40603[24], have shown that the addition of platinum to a NAC regimen leads to higher PCR rates. However, enthusiasm for increased PCR rates is accompanied by additional toxicity, often requiring dose reductions or cycle eliminations, with results that do not always improve long-term survival rates[22-24].

The addition of platinum derivatives to NAC in TNBC patients has shown an increase in PCR rates. A meta-analysis was performed with nine ECs, totaling 2,109 patients with a PCR in the group that received a platinum scheme of 52.1% compared with 37.0% in the non-platinum group[25].

Recent successes in immunotherapy have been able to incorporate it into NAC for CM. The interaction between the programmed cell death receptor 1 (PD-1) and the programmable cell death ligand 1 (DP-L1) constitutes a key immune control point that negatively regulates T-cell activity and is exploited by tumors to escape immunological surveillance. Inhibition of the interaction between PD-1 and PD-L1 has been successfully used in several tumors to restore or enhance the endogenous antitumoral immune response. The three most important studies evaluating the addition of immunotherapy to NAC are I-SPY2, KEYNOTE-522, and IMpassion031[26-28].

I-SPY2 is an open, multicenter, randomized neoadjuvant phase II clinical trial that evaluated the addition of Pembrolizumab with paclitaxel in NAC. The addition of Pembrolizumab tripled the estimated PCR rates in TNBC, 22% with placebo and 60% with Pembrolizumab[26].

KEYNOTE-522 was designed to determine whether Pembrolizumab added to standard NAC improved the PCR and SLD rates in patients with operable TNBC. This study was randomized, phase III, and placebo-controlled. The PCR rates were improved with Pembrolizumab: 64.8% in the study group and 51.2% in the placebo group. The positive subgroup for PD-L1 showed overall higher PCR rates, but the benefit was observed independently of the expression of PD-L1[27].

IMpassion031 is a minor phase III study with a design similar to KEYNOTE-522(28), but it evaluated Atezolizumab as the immunotherapy agent. The study PCR rates for the PD-L1 positive subgroup achieved overall higher PCR (68.8% with Atezolizumab versus 49.3% with placebo), but the benefit was observed independently of PD-L1 expression, with a PCR of 57.6% with Atezolizumab versus 41.1% with the placebo[28].

The addition of NAC-specific immunotherapy in patients is independent of PD-L1 expression and is currently the new treatment scheme for patients with NBC[2].

In Table 2, we find a summary of the main studies of NAC and its receptive rates of PCR and NAC scheme.

Causes of complete pathological response failures

Failure to PCR is related to unfavorable prognosis in TNBC and HER-2+ tumors, but not in most luminal patients[29]. In fact, studies have indicated that luminal patients tend to present a favorable prognosis, although they are less responsive to chemotherapy, with relatively lower chances of achieving PCR, thus reflecting the uncertain correlation between PCR and long-term outcomes in luminal patients[16].

Although estimated PCR rates have increased after the addition of new drugs to routine chemotherapy, many patients cannot PCR after NAC, and not all patients with PCR have a good prognosis[17].

Factors related to the highest probability of PCR include TNBC tumors, HER-2+, high rate of cell proliferation (Ki67), and high degree of nuclear and ductal histology. Usually, patients with positive hormone receptor (RH+) have worse rates of PCR[12,29,30].

Table 2. Pathological complete response rates in neoadjuvant treatment for breast cancer.

Study	Year	Subtype	NAC Scheme	PCR (%)
Fisher et al.[11] NSABP-B18	1997	All	AC	13.0
Bear et al.[12] NSABP B27	2003	All	AC + T	26.1
von Minckwitz et al.[13] GeparDuo	2005	All	ddAC AC	14.3 7.0
Spring et al.[17]	2020	All	Various schemes PCR vs. non-PCR	21.1
von Minckwitz et al.[23] GeparSixto	2014	TNBC	A+T Carboplatin + Bev A+T + Bev	53 43
Sikov et al.[24] CALGB 40603	2015	TNBC	TCarbo+AC + Bev T + AC + Bev	54 41
Geyer et al.[22] BrigTNess	2020	TNBC	T + Veliparib + Carbo T + Veliparib + AC	58 31
Poggio et al.[25]	2018	TNBC	Scheme with Platinum Non-Platinum Scheme	51 37
Mittendorf et al.[28] IMpassion031	2020	TNBC	Atezolizumab + Nab-P □ Atezolizumab + ddAC Nab-P □ ddAC	58 41
Nanda et al.[26] I-SPY2	2020	TNBC	Pembrolizumab +T + AC AC + T	60 22
Schmid et al.[27] KEYNOTE-522	2020	TNBC	PCarbo + AC ou EC + Pembrolizumab PCarbo + AC ou EC + Placebo	64.8 51.2
Spring et al.[17]	2020	TNBC	Various schemes PCR vs. non-PCR	32.6
Budzar et al.[18]	2005	HER-2+	AC -T + Placebo AC - T + Trastuzumab	25 66.7
Scheeweiss et al.[19] TRYPHAENA	2013	HER-2+	FECHP + THP FEC + THP TCHP	61.6 57.3 66.2
Gianni et al.[20] NeoSphere	2012	HER-2+	T+Trastuzumab T+Trastuzumab + Pertuzumab Trastuzumab + Pertuzumab Taxane + Pertuzumab	29.0 45.8 16.8 24
van Ramshorst et al.[21] TRAIN-2	2018	HER-2 +	3FEC + HP + 6TCarboHP 9TCarboHP	67 68
Spring et al.[17]	2020	HER-2 +	Various schemes PCR vs. non-PCR	36.4

AC: Adriblastine + Cyclophosphamide; T: Taxanes; TC: Taxane + Cyclophosphamide; ddAC: Adriblastin dose dense + Cyclophosphamide; Carb: Carboplatin; Bev: Bevacizumab; TNBC: triple-negative breast cancer; Nab-P: Nab-paclitaxel; P: Paclitaxel; EC: Epirubicin + Cyclophosphamide; FEC: 5FU + Epirubicin + Cyclophosphamide; H: Trastuzumab; HP: Trastuzumab + Pertuzumab; PCR: polymerase chain reaction.

Currently, the rates of PCR are higher in TNBC patients, reaching 64.8% due to the use of immunotherapy with Pembrolizumab combined with chemotherapy[27], and in HER-2+ due to double blockage with trastuzumab and pertuzumab associated with chemotherapy[20] (Table 3).

Complete pathological response relation and prognosis

Several studies have shown that NAC is an effective treatment option in patients with breast cancer. In addition to reducing the tumor size, NAC has been associated with a significant influence on the extent of surgery. In addition, PCR after NAC has been shown to be an important prognostic factor in patients with breast cancer. This observation highlights the relevance of PCR as a prognostic marker and reinforces the importance of the use of NAC in the treatment of patients with CM[16,31,32].

The initial study comparing adjuvant versus neoadjuvant treatment was NSAPB B-18[11]. The aim was only to assess the PCR rates. These patients continued to be followed in a new study to define the prognosis of the disease. Their follow-up showed that patients who performed NAC showed an SG of 81% and those who did in adjuvance showed an SG of 80%; the SLD was 55% versus 53%, respectively, with no significant difference for the two outcomes. Patients with PCR after NAC had an SLD of 75% versus 58%, while SG was 85% versus 73%, showing that PCR has an impact on long-term prognosis[33].

The NSABP B-27 study, which evaluated the addition of paclitaxel (T) to the combination of AC in the neoadjuvant or adjuvant scenario, demonstrated that there was no modification in GH with the addition of taxane. However, when patients were evaluated for PCR, there was an improvement in GHS (89% versus 74%), showing a reduction in rates of mastectomy and smaller local relapses. This study clearly demonstrates the benefit of adding the taxane with improved rates of PCR (26.1%) and thus a better prognosis[12,34].

The findings of NSABP B-18 were corroborated in a joint analysis of 12 ECs, including 12,000 patients, which showed that those who achieved PCR had improved survival, in TNBC and HER-2+[35].

In the TRYPHAENA study, in the evaluation of SLD over 3 years, the results were found to be 87%, 88%, and 90% in groups A to C, respectively. Progression-free survival rates were found to be 89%, 89%, and 87%. The risk rate for SLD was 0.27 in comparison between PCR and non-PCR[19].

In the NeoSphere study, the addition of Pertuzumab showed that PCR can be considered a long-term prognosis improvement factor. Patients were randomized to receive trastuzumab + taxane

Table 3. Main randomized clinical trials and meta-analysis of randomized clinical trials, in neoadjuvant chemotherapy and polymerase chain reaction relationship and prognosis.

Study	Year	Subtype	NAC Scheme	SLD (%)	SG (%)
Wolmark et al.[35] NSABP-B18	2001	All	AC	75 x 58	85 x 73
Rastogiet al.[34] NSABP B27	2008	All	AC + T		89 x 73
Spring et al.[17]	2020	All	Various schemes PCR vs. non-PCR	88 x 67	94 x 75
Poggio et al.[25]	2018	TNBC	Scheme with Platinum Non-Platinum Scheme	No difference	No difference
Nanda et al.[26] I-SPY2	2020	TNBC	Pembrolizumab +T + AC AC + T	95 81	
Spring et al.[17]	2020	TNBC	Various schemes PCR vs. non-PCR	90 x 47	84 x 57
Schneeweiss et al.[19] TRYPHAENA	2013	HER-2+	FECHP + TTP FEC + TTP TCTP	87 88 90	
Gianni et al.[20] NeoSphere	2012	HER-2+	T+Trastuzumab T + TP TP TP	81 84 80 75	
van der Voort et al.[36] TRAIN-2	2021	HER-2+	3FEC + HP + 6TCarboHP 9TCarboHP	92.7 93.6	97.7 98.2 42
Spring et al.[17]	2020	HER-2+	Various schemes PCR vs. non-PCR	86 x 63	95 x 76

AC: Adriblastine + Cyclophosphamide; T: Taxanes; PCR: polymerase chain reaction; TNBC: triple-negative breast cancer; HER-2+: human epidermal growth factor 2; FECHP: 5-fluorouracil, epirubicin, cyclophosphamide, trastuzumab, pertuzumab; TTP: docetaxel, docetaxel, pertuzumab; TCTP: docetaxel, cyclophosphamide, docetaxel, pertuzumab; TP: docetaxel, pertuzumab; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; 5FU + Epirubicin + Cyclophosphamide; HP: Trastuzumab + Pertuzumab.

(group A), pertuzumab + trastuzumab + taxane (group B), pertuzumab + trastuzumab (group C), or pertuzumab plus docetaxel (group D). Patients in group B had SLD of 84% in 5 years compared with 81% in patients in group A. Group C showed an SLD of 80%, and group D showed an SLD of 75%[20].

In the TRAIN-2 study, the 3-year follow-up analysis noted that the use of anthracyclines in the treatment of patients with HER-2+ CM showed no improvement in SLD (92.7% versus 93.6%) and SG (97.7% versus 98.2%). In the evaluation of patients with PCR alone, SG was 42% (p=0.006)[36].

The addition of platinum derivatives in NAC in TNBC patients was studied in a meta-analysis with nine ECs, totaling 2,109 patients, and an increase in PCR rates was found, but there was no significant improvement in SG and SLD (OR 1.17, 95%CI 0.51–2.67, p=0.711)[25].

In the publication of I-SPY2, EC for the use of Pembrolizumab in NAC, in the ratio of PCR and SLD, a 95% SLD was observed in patients with PCR, while, in patients without PCR, an 81.9% SLD was observed in 3 years of follow-up[37].

The meta-analysis of 52 studies by Spring et al., totaling 27,895 patients, showed that patients with PCR after NAC had significantly better SLD (88%×67%), TNBC (90%×47%), and HER-2+ (86%×63%). Similarly, PCR was associated with better SG (94%×75%), TNBC (84%×57%), and HER-2+ (95%×76%). The association of the improvement of SG and SLD occurred only when the retrospective studies and the EC were evaluated separately, and in retrospective studies, there was no such observation[17].

The association of the improvement of SG and SLD with PCR in HER-2+ patients was confirmed in a meta-analysis of 78 studies (retrospective and EC), totaling 25,150 patients, which showed that PCR improves SLD (91.6%×79.0%) and SG (93.8%×80.3%) as well[38].

A growing number of studies have investigated the prognostic value of PCR and whether there is a relationship with age. Although BC in young women tends to be more aggressive, with a relatively unfavorable prognosis, reports show that patients ≤40 years of age can also obtain significant survival benefits when achieving PCR after NAC. As a prognostic indicator, PCR has the advantage of reflecting chemo-sensitivity shortly after NAC, which highlights the need for subsequent adjuvant treatment after surgery[39].

Although several studies have suggested a correlation between PCR and better prognosis, a small group of people have recurrence of the disease and metastasis in the short term, even reaching PCR after NAC. Studies point out that factors such as HER-2+, axillary lymph nodal metastases, premenopausal patients, and advanced clinical stage (IIIA–C) may increase the rates of recurrence or metastasis in patients who have achieved PCR[34-40].

The presence of PCR has emerged as a powerful prognosis predictor for patients undergoing NAC, especially TNBC and HER-2+; thus, in these patients, it has been used as a prognostic outcome. As such, PCR has entered as a criterion to accelerate the approval of medicines by the Food and Drug Administration (FDA)[41,42].

In Table 3, we find the main EC and meta-analysis of EC, in NAC and PCR ratio and prognosis.

CONCLUSIONS

NAC has become a common treatment strategy for early-stage breast cancer, and several randomized clinical trials have evaluated its effectiveness over the past 30 years. The use of taxane in combination with anthracyclines has been the most common NAC scheme evaluated in these trials. The addition of HER blocking (preferably double – trastuzumab and pertuzumab) has been indicated in HER2+ patients, while the addition of immunotherapy has been preferential in triple-negative diseases. The PCR rates have been associated with better survival outcomes in patients with TNBC and HER-2+ disease. However, the impact of PCR on survival outcomes in patients with hormone receptor-positive breast cancer is less clear. Additional studies are needed to determine the optimal NAC regimen for each subtype of breast cancer and to identify biomarkers that can predict the NAC response.

AUTHORS' CONTRIBUTION

MA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. AM: Formal Analysis, Investigation, Methodology, Writing – original draft. GDP: Formal Analysis, Investigation, Methodology, Writing – original draft. LHG: Supervision, Validation, Visualization. OF: Supervision, Validation, Visualization. RGCL: Supervision, Validation, Visualization. JMR: Supervision, Validation, Visualization.

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REVIEW ARTICLE
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Advances in breast imaging: a review on where we are and where we are going

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ABSTRACT

Breast radiology has undergone significant advances in recent years, and, naturally, several possibilities open up for attending physicians. Concomitantly, it increases the responsibility to keep up to date and provide the best care for each patient. Aware of the complex implications that the implementation of some of the technological advances may bring, such as increased costs, limited availability of equipment, and a potential increase in examination time, the objective of this study is to carry out a narrative review and provide a collection of advances that, in our opinion, are already gaining ground and should be consolidated in clinical practice. We will discuss new breast imaging methods that can be used both for screening and for the diagnostic investigation of breast lesions and we will summarize the most relevant aspects of each of them, addressing the technique, applicability, positive aspects, and limitations of each modality in a standardized way.

KEYWORDS: breast; breast neoplasms; early cancer detection; breast ultrasonography; mammography; magnetic resonance imaging.

INTRODUCTION

The first uses of X-ray images for the diagnosis of breast cancer were made in 1927 and formed the basis for clinical trials that associated mammography with the reduction of breast cancer mortality[1]. In this historical context, it is worth highlighting the first randomized clinical trial, the 1961 Health Insurance Plan of Greater New York (HIP study), which showed a 22% reduction in breast cancer mortality, and also the "Breast Cancer Detection Demonstration Project," between 1973 and 1981, in which 39% of cancers were identified only on mammography, but not on clinical examination[2].

The era of breast radiology was then inaugurated. These first results boosted significant advances that allowed the dissemination of methods, such as ultrasound and magnetic resonance imaging (MRI), while others have emerged and continue to develop at a pace that challenges even great scholars to keep up to date.

In a dichotomous way, the speed of these advances is impressive, but at the same time, it raises questions about the viability of their applicability in clinical practice. Is there room for so much novelties? Will the promises of artificial intelligence (AI) ever be fulfilled?

Despite the impossibility of exhausting the topic, in the present article we aim to carry out a narrative review of the state of the art of breast imaging with an emphasis on the advances of different imaging methods that are gaining ground in clinical practice and should be progressively consolidated in the coming years.

METHODS

Data collection was based on bibliographic research in the PubMed, Scielo and LILACS databases between 2010 and 2023, including in the search the following terms: "breast imaging," "breast radiology," "contrast-enhanced mammography," "breast tomosynthesis," "automated whole-breast ultrasound," "abbreviated breast MRI," and "artificial intelligence breast imaging."

In view of the breadth resulting from the search for multiple subitems involved in this study, a narrative review of the literature was conducted, and the selection of studies was based on publications whose topics are most recurrent and with greater relevance in clinical practice. The vast topic of breast imaging was summarized with an emphasis on innovation in each of the techniques addressed. Historical data, properties of the method, sensitivity, specificity, advantages, and limitations were collected for each of the imaging techniques evaluated in this study. The main advances in breast imaging were summarized and presented in a standard way in the results section.

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RESULTS

Contrast-enhanced mammography

The only screening test proven to be associated with reduced breast cancer mortality in the population at regular risk is mammography, with a reduction of about 13–17% according to recent meta-analyses[2,3]. Since its inception, mammography has undergone significant advances, such as the conversion from analog to digital, in addition to the development of other imaging methods derived from mammography such as tomosynthesis (which will be discussed next) and contrast-enhanced mammography (CEM). Some highlights are worth making about the latter.

Contrast-enhanced mammography is an emerging technique consisting of obtaining dual-energy images after the administration of iodinated contrast, that is, a low-energy image, equivalent to the usual mammogram, and a high-energy image, which provides the recombination of the images and allows the identification of contrast enhancement. Since 2011, this technique has already had commercial application, and in 2022, a supplementary attachment to BI-RADS® was published, released by the American College of Radiology, with descriptions for CEM.

The rationale behind its creation is inspired by the success of MRI, the most sensitive imaging method for detecting breast cancer and whose performance is the result of an interpretation of anatomical and physiological findings. This is also the case with CEM. The physiopathological basis of this phenomenon is the greater vascular permeability of the blood vessels resulting from neoangiogenesis, which allows the extravasation of the contrasted material, which diffuses into the tumor tissue, culminating in the highlighted image[4]. This results in rapid local highlighting and allows the detection of neoplasms even in patients with dense breasts[4]. Simultaneously, arteriovenous shunts are formed, which also allow a rapid elimination of contrast.

The CEM can be used both as a diagnostic test, after an abnormal finding on a screening mammogram, and in the screening setting of high-risk women (lifetime risk for breast cancer >20%), especially those who cannot undergo MRI[4,5].

Advantages

The CEM has the advantage of demonstrating both anatomical changes and changes in breast perfusion, which, although not pathognomonic, may presumably result from neoplasms. This technique shows promising results in the first studies. Compared to conventional mammography, the CEM presents a significant gain in sensitivity, which can range from 48% in the case of dense breasts to 96%, while the specificity can range from 42% to 87%[6]. Studies have also demonstrated a better relationship between tumor size in CEM and histological size, making it a reliable test for preoperative planning[6].

When compared to MRI, CEM is an alternative in some situations because of the shorter execution time, around ten minutes, and reduced cost[7,8]. It is especially beneficial for patients who cannot perform MRI, such as claustrophobic patients, those using pacemakers and/or metal devices. Finally, the contrast-enhanced mammography also allows the detection of microcalcifications, and is therefore more sensitive than MRI in the diagnosis of ductal carcinoma *in situ*[6].

Disadvantages

Among the negative aspects of this new technique, we can first list the use of iodinated contrast, which brings with it the possibility of adverse effects. However, it should be noted that low osmolality contrast is used, which presents a lower risk of reaction when compared to conventional iodinated contrast.

The second negative aspect worth noting is the still limited availability of this examination. Due to the need for specific software, it cannot be performed on any mammography device.

Another consideration to be made is the increase in the radiation dose to which the patient is submitted, since a dual-energy mammogram is performed, with two mammogram purchases at the same compression, even though, of course, the radiation dose remains within safe limits.

With regard to sensitivity, even though it has a functional character, this technique is still based on morphological aspects and, therefore, it is affected by breast density. Lastly, it is worth considering that, when compared to conventional mammography, there is an increase in examination time, as images are obtained between 2 and 7 minutes after the intravenous administration of contrast[4,6].

Tomosynthesis

Digital breast tomosynthesis is an imaging method that is gaining ground in clinical practice and can be used both in breast cancer screening and in the diagnostic setting[9,10]. Resulting from the evolution of digital mammography, it is often mistakenly referred to as "3D mammography." In fact, the only technique that actually acquires three-dimensional X-ray images of the breast is computed tomography, which is not commonly used in breast radiology because it requires the acquisition of axial thoracic images, which would result in unnecessary radiation, especially to the intrathoracic organs. The tomosynthesis device acquires multiple two-dimensional images of the breast based on the rotation of the X-ray tube in an arc trajectory. The scanning amplitude comprises a limited range of angles, which can vary between 15º and 60º[9], obtaining images with a low radiation dose that are used for reconstruction and whose quality depends on the angle spectrum and the radiation dose used.

Advantages

The main objective of the tomosynthesis is to reduce the effect of tissue overlap, considering that a reconstruction of the breast is performed from multiple two-dimensional images from different

angles[11]. This provides one of the great benefits of tomosynthesis: the reduction of false positive results caused by the effect of overlap. Therefore, tomosynthesis allows for a better identification and characterization of the nodal margins and the reduction of the unnecessary recall rate for the screening of patients with dense breasts by about 16%[12,13].

Another significant advantage is the increase in the breast cancer detection rate of 29% when tomosynthesis was added to digital mammography screening[9]. At this point, it should be noted that the long-term benefit is still uncertain. The question arises because the increased detection rate is, for the most part, due to the detection of low-grade tumors. If, on the one hand, this detection allows, in theory, for a less aggressive treatment, on the other hand, there is no robust evidence about the impact on survival[9]. To assess the survival benefits of breast cancer, prospective, randomized studies with long-term follow-up are necessary.

The Verona study[14] demonstrated that, among the invasive neoplasms detected by tomosynthesis, there was a large proportion with histological characteristics associated with a good prognosis. Supporting this line of reasoning, the Oslo study[15] showed that cancers detected exclusively by tomosynthesis tend to have lower Ki-67 rates.

Thus, despite the higher detection rate of breast cancer in tomosynthesis, considering that a significant proportion is comprised of tumors with a tendency to better prognosis, it is not clear whether these lesions could not be identified in subsequent digital mammography examinations, and long-term follow-up studies are necessary to elucidate the impact on overall survival[9].

Disadvantages

It should be noted that tomosynthesis is still an exclusively anatomical method, and it is, therefore, affected by breast density, with limitations remaining in cases of extremely dense breasts. In addition, the tomosynthesis is associated with an increase in image acquisition time, as well as interpretation time, although it should be noted here that interpretation time tends to decrease with the increase in the physician's experience with the examination[9].

Another noteworthy aspect is the concern about the increase in the radiation dose promoted by tomosynthesis, especially when the examination is performed in conjunction with digital mammography. This fear motivated the development of synthesized mammography, in which two-dimensional images are reconstructed from tomosynthesis data, in order to eliminate the need for simultaneous digital mammography.

Finally, it is worth noting that, despite being a promising method, tomosynthesis is still a method with limited availability in Brazil, both in the Brazilian Unified Health System (SUS) and in the private system, as it has a high cost (about four times the price of digital mammography) and it does not yet have universal coverage by health insurance plans.

Automated whole-breast ultrasound

The use of ultrasound as a complementary method to mammography, especially in patients with dense breasts, is already well-established in clinical practice[16]. In order to save time and standardize the images to allow interobserver comparisons and the comparison with previous examinations, a technique was developed that uses ultrasound and is performed in an automated manner. Thus, the automated whole-breast ultrasound (ABUS) emerged. ABUS can be used as a supplementary screening, combined with mammography in patients with extremely and heterogeneously dense breasts[17], and its use has been approved by the Food and Drug Administration since 2012.

Advantages

The great advantage of the ABUS is that it allows the image to be acquired by a technical professional, while the reading can be performed remotely by the doctor, allowing the optimization of time and focus on detecting the lesion. In addition, it is possible to simultaneously visualize in a single image the entire volume of the breast, from the skin to the chest wall, producing images similar to those of conventional manual ultrasound[18]. Furthermore, the image can be stored in order to allow temporal comparisons with previous and future studies, an essential characteristic when considering a screening exam[19].

According to a German study conducted by Wojcinski et al.[20], the accuracy, sensitivity, and specificity of the ABUS for the diagnosis of breast cancer was, respectively, 79.0%, 83.3%, and 78.1%.

Disadvantages

The greatest limitation of this technique is the noninclusion of the armpit in the ABUS field of view, so that conventional manual ultrasound is necessary for the evaluation of axillary lymph nodes[17]. Moreover, the benefit of reading in real time, which allows better detailing of a given finding, is lost at the expense of the standardization of the technique and the absence of a doctor during the examination.

Other negative aspects are the impossibility of the ABUS to guide biopsies and the unavailability of the use of Doppler[17]. Finally, when used in addition to mammography to screen patients at regular risk, it presents a low positive predictive value (5.4%) of biopsies performed on lesions identified exclusively by the ABUS[17].

In short, ABUS is an incipient imaging method, which aims to combine the desirable priorities of ultrasound with standardization and interobserver agreement. Although promising, the indications for the systematic application of this test in clinical practice are not yet consolidated in the literature. Besides, the price of the device and the cost of examinations for large-scale screening are not yet determined. It is known, however, that it is considerably more expensive than a high-quality conventional ultrasound device[21] and is intended exclusively for breast examination. Its large-scale employability in Brazil still remains a question.

Abbreviated breast MRI

MRI is, without a doubt, the most sensitive imaging method for the diagnosis of invasive breast cancer, and has a very well-established application in the screening of high-risk patients (lifetime risk for breast cancer >20%)[22]. In this scenario, MRI increases cancer diagnosis rates at earlier stages and reduces the rate of interval tumors[23]. However, this test is not accessible to a large number of high-risk patients. Considering the importance of MRI in this population, and in order to increase the availability of the method, a shorter protocol for screening was developed.

The abbreviated protocol was initially introduced and demonstrated its viability by Dr. Christiane Kuhl in 2014, consisting of a pre-contrast sequence and a post-contrast sequence, in addition to post-processing images[24]. In this study, Kuhl et al. demonstrated a very impactful reduction in image acquisition time, from 17 to 3 minutes[24], as well as in exam reading time, while maintaining diagnostic accuracy equivalent to the full protocol[24]. The time taken to acquire images, however, has a variable duration between different institutions. A review published in 2019 in the *Journal of the American College of Radiology*[25] evaluated the acquisition time of 70 abbreviated protocols and 736 complete protocols and found an average imaging time, respectively, of 17.5 minutes and 28.8 minutes. These data still demonstrate a significant reduction in the time taken to obtain the images, but to a lesser extent than the original study by Kuhl et al.[24]

Currently, the most used application of abbreviated MRI is in the scenario of screening high-risk patients[26]. A systematic review published in 2021 in the *European Journal of Radiology*, however, reported recent studies that also used abbreviated MRI in the diagnostic setting, aimed at studying the recurrence, staging, and assessment of the extent of the disease[27].

Advantages

The objective of shortening the MRI protocol is to make the method simpler, faster, and to increase its availability, in addition, of course, to improve its tolerability by patients[28,29]. In Brazil, abbreviated protocols are already validated and in operation, and there are others that are undergoing validation processes for use in the screening of high-risk women.

It is worth highlighting that there is heterogeneity of protocols between different institutions. In our service, for example, there is currently an abbreviated protocol in the process of being validated.

The SUS can also greatly benefit from this innovation, which makes a great contribution to the optimization of resources such as time and cost. Currently, the MRI examination is not included in the SUS table of procedures, medications and orthoses, prostheses, and special materials (SIGTAP). The code authorizing the examination to evaluate breast implant complications was revoked in December 2016. The dissemination of the abbreviated protocol offers prospects for the inclusion of MRI in the SUS procedure table, considering that it allows the optimization of machine time and reading time by the examiner, reducing costs and allowing the filling of the vast gap in the suppressed demand for breast MRI that currently exists in the Brazilian public system.

Disadvantages

As aforementioned, breast magnetic resonance imaging has a high cost and low availability, factors that limit its use on a population scale in Brazil. Furthermore, another negative aspect is the discomfort of performing it, as it requires a high degree of collaboration on the part of the patient, who must remain immobile throughout the examination period, which lasts an average of approximately 29 minutes[25]. Claustrophobic patients have great difficulty performing the examination.

Artificial intelligence in breast imaging

AI applied to breast imaging brings with it two recurring and intertwined concepts: machine learning, which corresponds to the way in which computers can learn and build models based on multiple statistical data[30]; and deep learning, which also consists of a learning methodology in which a complex multilayer network is developed to learn data representations automatically[31]. It is, therefore, an automated way of optimizing learning that allows the analysis of millions of cases, which not even the most experienced professionals would be able to study and memorize throughout their lives. AI, therefore, can be very robust as long as there is enough broad and diverse data for its training[31]. In fact, several retrospective studies have demonstrated AI models that perform better than experienced radiologists[32-35].

In the current clinical practice, AI resources are already available. The computer-aided detection and the computer-aided diagnosis help doctors in interpreting the tests, pointing out alarm signals and directing the evaluation. In addition, some more recent AI systems, when used in screening mammograms, demonstrated performance comparable to or even better than that of radiologists in the autonomous diagnosis of breast cancer, achieving a sensitivity of 56.2% to 81.9%, with a specificity of 84.3% to 96.6%[32,35]. AI, however, requires great standardization of examinations so that the data can be used. There is no doubt, therefore, that this topic is complex and that there are some steps that must be followed by professionals, national agencies, and health systems before AI becomes widely incorporated into clinical practice.

DISCUSSION

Breast radiology has undergone significant advances in recent years. Naturally, several possibilities open up for attending physicians. This study was developed to assist the attending physician in updating new topics in breast imaging, and during its execution, the main limitation we found was the wide breadth of the subject, as each of the advances discussed may be the focus of an individualized systematic review. Aware of the impossibility of investigating in depth each of the imaging methods discussed, our proposal in the present review was to highlight the new features that are already gaining ground in clinical practice and to provide a collection of advances that should be progressively consolidated in the coming years, both in the screening and diagnosis of lesions.

The contrast-enhanced mammography, which has been used commercially for just over a decade, stands out for achieving high sensitivity and specificity even in dense breasts. Despite the aforementioned limitations, because it is a functional method, it has the prospect of gaining space, especially in those contexts in which MRI cannot be used. Therefore, we can state that it is a method that has been adopted as an alternative to the use of resonance and as a complement to digital mammography in selected cases.

Another method derived from mammography, tomosynthesis, is already gaining ground in Brazil in the context of screening, especially in the private system. Despite the increase in radiation dose and the cost about four times higher than that of digital mammography, patients with dense breasts benefit from this method due to the higher breast cancer detection rate and lower false positive rate. Long-term follow-up studies may elucidate the impact on overall survival of this new method.

The ABUS is, among the four methods discussed, the least used in clinical practice. The idea of documenting large breast volumes simultaneously to allow temporal comparisons and between different observers requires a standardization of images that deprives the real-time assessment of lesions, a great advantage of conventional ultrasound. Furthermore, the lack of inclusion of the armpit in the field of view is another important limitation and requires the use of conventional manual ultrasound for the evaluation of axillary lymph nodes. Hence, there is still no consensus in the literature regarding its indications, and its use remains restricted.

Abbreviated MRI, in turn, is a version of the method that is already widely known, with the adaptation of its protocol aimed at saving examination time, leading to reduced costs and greater tolerability on the part of patients. It is an advance that presents greater prospects of use for patients at high risk for breast cancer than for patients at usual risk.

Finally, the topic of AI, although not limited to a specific imaging exam, was included in this study because of its development potential and the large number of recent publications. This phenomenon is a reflection of the great speed with which advances are being made in the field of AI in different imaging methods and the emergence of algorithms that can exceed human performance, increasing diagnostic accuracy and potentially reducing costs. This topic requires great technical knowledge, and its thorough investigation may be the topic of new targeted review studies.

CONCLUSIONS

In this study we presented a narrative review of the state of the art of breast imaging with an emphasis on the advances that are already employed in clinical practice and that tend to be consolidated in the near future. This is especially important for professionals working in a country such as Brazil, where, as technologies emerge, new challenges are simultaneously presented to attending physicians, firstly to keep up to date, and secondly to seek information about the availability of these new advances in each situation.

Brazil is already facing difficulties resulting from the dissociation between demand and supply of diagnostic procedures, especially in the public system, and not all technological advances will prove to be cost-effective in the long term. As new technologies tend to incorporate expenditures, the debate must focus on the rational use of resources, which requires studies with more robust follow-ups for most of the novelties discussed in this article.

We, as mastologists, understand that discoveries must be inserted into the reality of each patient, from a perspective that meets the trend in current medicine according to which the conducts must become increasingly individualized. The exponential number of recent publications on advances in breast imaging is an invitation to deepen the studies, and it is the responsibility of the attending physician, taking into account technical rigor, to filter information. Research such as the present review can assist in determining the best applicability in each case and in decision-making.

AUTHORS' CONTRIBUTION

FMOC: Conceptualization, Data curation, Investigation, Methodology, Project administration, Visualization, Writing – original draft. MFSVG: Data curation, Investigation, Writing – review & editing. KPCL: Data curation, Investigation, Writing – review & editing. RCSF: Investigation, Validation, Visualization, Writing – review & editing. JTCA: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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CASE REPORT
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Erysipelas after surgery for breast cancer: a real-world cohort

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ABSTRACT

Erysipelas is often related to lymphedema, which can occur in up to 60% of cases, with advanced age, radiotherapy, tumor extension, surgical approach, and infections as risk factors. The aim of this study was to present and discuss a series of cases of erysipelas after breast cancer surgery treated in a private mastology clinic over the past ten years. This is a retrospective horizontal cohort study in which we selected all cases of erysipelas after breast cancer surgery from 2009 to 2019. The following were evaluated: number of patients treated with a diagnosis of breast carcinoma with axillary approach, age, surgery performed, adjuvant treatment and treatment of erysipelas, presence of lymphedema, and measurement of circumferences between both arms and associated diseases. A total of 12 cases of breast cancer were treated. In 66.66% of cases, a radical axillary lymphadenectomy was performed, and in 16.66% of cases, only a sentinel lymph node investigation was performed. The average age was 67.6 years. Erysipelas appeared, on average, 43 months after cancer diagnosis. Two deaths were reported due to severe erysipelas leading to sepsis. More studies are still needed on the subject. Of the 12 cases in this study, eight (66.66%) were associated with lymphedema. Only two (16.66%) of the patients in this group who developed erysipelas were not submitted to axillary dissection. The treatment for 50% of the participants in this research was with penicillin G benzathine. There were three relapses, and two patients died during the research period.

KEYWORDS: erysipelas; breast cancer; surgery.

INTRODUCTION

Erysipelas is an infectious cellulitis, which compromises the epithelial tissue with involvement of lymphatic vessels, mainly caused by group A beta hemolytic streptococci, rarely group C streptococcus and *S. aureus*[1,2]. In cancer patients who undergo breast and armpit surgery, this type of dermatitis is a significant postoperative complication, due to the impairment of the lymphatic microcirculation in the affected region[3].

This infection is often related to lymphedema, which can happen in up to 60% of cases, with advanced age, radiotherapy, tumor extension, surgical approach, and infections as risk factors[4,5].

Age and radiotherapy are risk factors for lymphedema as they cause fibrosis of the lymphatic vessels. The size of the tumor and the surgical trauma injure the lymphatic vessels and axillary lymph nodes, altering the lymphatic drainage of the upper limb and ipsilateral breast and, consequently, the patient's immune system. This becomes an essential vicious circle for the pathogenesis of erysipelas, as well as its recurrence[6,7].

Erysipelas is both a causal factor and a consequence of lymphedema, considering that the exudate from the infection can cause obstruction of the lymphatic vessels, as well as the imbalance of lymphatic drainage can lead to impaired immunity[8,9].

Currently, research performing a sentinel lymph node instead of an axillary lymphadenectomy in the treatment of breast cancer decreases the incidence of lymphedema and, consequently, the occurrence of erysipelas[2]. A series of cases of erysipelas after surgery for breast cancer treated at a private mastology clinic in the past 10 years is presented.

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CASE REPORT

This is a series of cases in a retrospective horizontal cohort format carried out in a private mastology clinic.

During the study period, approximately 1,200 cases of breast cancer were treated at the clinic, of which 12 cases evolved with a subsequent diagnosis of erysipelas on the ipsilateral upper limb. In 66.66% of cases, radical axillary lymphadenectomy was performed, and in 16.66% of cases, only sentinel lymph node research was performed.

The age of patients ranged from 38 to 82 years, with a mean age of 67.6 years. One case occurred in males (Figure 1). All patients underwent surgery for breast carcinoma, with eight (66.6%) cases of surgery with axillary dissection. Of note, 10 (81.8%) and 11 (90.9%) underwent chemotherapy and radiotherapy, respectively (Table 1).

In 50% of these patients, both arms were measured, and the difference between them ranged from 3 to 6.5 cm.

Erysipelas appeared, on average, 43 months after cancer diagnosis. The mean number of episodes was 1.75 per patient, with recurrence in three cases. Lymphedema was clinically present in eight (66.6%) of the patients, and the other reported symptoms were erythema, edema, heat, and pain, accompanied by fever, chills, general malaise, nausea, or vomiting. Two deaths were recorded due to severe erysipelas leading to sepsis. One patient sought the emergency department twice with a clinical picture of erysipelas, being medicated only with symptomatic drugs and analgesic, and when she returned for the third time, she was already in septic shock, being admitted to the intensive care unit, but evolving with multiple organ and system failure and death. The other patient had symptoms of erysipelas for several days at home, and when she sought the medical service, she was in septic shock, which led to her death.

DISCUSSION

In the present study, most patients with erysipelas had a history of axillary dissection. Of the patients who presented erysipelas, 66.6% had lymphedema and 75% had other associated diseases.

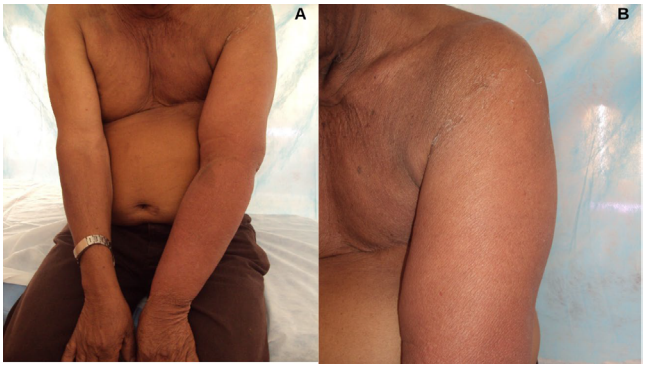

Figure 1. Male patient in the study. Six years after surgery, there were seven episodes of erysipelas in the left upper limb (A and B).

The clinical picture of erysipelas is characterized by erythema, edema, heat, and pain, accompanied by fever, chills, general malaise, nausea, or vomiting[1]. And the main risk factors are advanced age, surgeries, lymphedema, neoplasms, and chemotherapy.

These risk factors generate leukopenia and compromise cellular immunity, impairing chemotaxis and phagocytosis of polymorphonuclear cells, which facilitates the prevalence of skin infections. In addition to lymphedema, advanced age, radical mastectomy, chemotherapy, and radiotherapy are also risk factors, as observed in the present study[10].

In the results, the average age affected by post-mastectomy erysipelas is 67.6 years, which is in line with studies that claim a higher prevalence of infection from the fifth decade of life. The relationship with advanced age can be explained, as physiologically, from the age of 40 years, and there is fibrosis of the blood vessels, which generates imbalance in the lymphatic and immune systems, leading to exudate accumulation and bacterial proliferation[6,8].

It is noted that 90% of patients underwent complementary treatment with chemotherapy or radiotherapy, which are risk factors for erysipelas. Thus, it is important to instruct patients to detect early signs of redness, swelling, or pain in the upper limbs after regional therapies, in order for oral or parenteral therapy to be effective[2].

The main risk factor for erysipelas in patients who have undergone treatment is the occurrence of lymphedema, with the standardization of the sentinel lymph node technique for most patients with breast cancer. In the current scenario, the rate of lymphedema has greatly decreased, with a meta-analysis showing an incidence of only 6.3% compared to 22.3% after radical axillary lymphadenectomy[11,12].

Another technique that reduces the risk of lymphedema is the reverse search of the sentinel lymph node; however, this technique is not routinely used[13].

In patients with lymphedema, microsurgery and omentum lymph node transplantation have been used with encouraging results, but these procedures are performed by few surgeons and are therefore not widely available[14,15].

Post-mastectomy physiotherapy is essential, since the association of various therapies, such as manual lymphatic drainage, compressive bandaging, the use of bandages, complex decongestive physiotherapy, among others, results in an improvement in lymphedema or prophylaxis of this, by maintaining adequate lymphatic circulation, in addition to preventing relapses[6,7].

The recommended treatment for erysipelas is empirical antibiotic therapy, with intramuscular benzathine penicillin G being the reference antibiotic, but oral antibiotics such as amoxicillin or erythromycin can also be used[1]. In the present study, drugs of the cephalosporin class and benzathine penicillin G were used in three and six patients, respectively.

In our series, three patients had recurrence. One of the patients had seven cases of erysipelas; the last four episodes

Table 1. Erysipelas series after lymph node emptying.

Age (years)	Gender	Comorbidities	Appearance after cancer diagnosis	Staging	Surgery	Chemotherapy	Radiotherapy	Lymphedema	Number of episodes	Treatment	Follow-up time after erysipelas	Outcome
72	F	DM SAH	2 years	IIA	Mastectomy + axillary dissection + sentinel lymph node	✓	✓		1	Cephalexin and ciprofloxacin	7 years	No disease
64	F	SLE SAH	5 years		Mastectomy + sentinel lymph node	✓	✓		1	Cefadroxil	7 years	No disease
71	F	SAH	10 years		Mastectomy + axillary dissection + sentinel lymph node	✓	✓	✓	1	?	14 days	
66	F	Dyslipidemia	5 years		Centralectomy + axillary dissection + sentinela lymph node	✓	✓	✓	1	Penicillin G benzathine	1 year and 3 months	
75	M	SAH	6 years		Mastectomy + axillary dissection		✓	✓	7	Penicillin G benzathine	7 years	No disease
74	F		2 years	IIB	Mastectomy + axillary dissection + sentinel lymph node	✓	✓	✓	2	Penicillin G benzathine 2 doses	10 months	Death
79	F	SAH	1 year	IIA	Mastectomy + axillary dissection	✓	✓	✓	1	?	?	
40	F		1 year	IIIB	Segmental resection + axillary dissection + sentinel lymph node	✓	✓	✓	1	Penicillin G benzathine	1 year	
73	F		4 years		?				1	Penicillin G benzathine	1 year	
38	F	DM	4 years		Mastectomy + sentinel lymph node	✓	✓	✓	1	Penicillin G benzathine 1x/m/year	5 years	
82	F	SAH	3 years		Mastectomy	✓	✓	✓	2	Cefaclor	8 years	No disease
78	F	SAH	1 year	IIIA	Segmental resection + axillary dissection				1	?	?	Death

DM: Diabetes mellitus; SAH: Systemic arterial hypertension; SLE: Systemic lupus erythematosus.

were reported in the research time frame and were treated with penicillin G benzathine. Another patient used cefaclor in case of recurrence, thus not presenting erysipelas later. Finally, the third case of recurrent erysipelas in the study had been treated with penicillin G benzathine in the first episode, and after 10 months, he was hospitalized with severe erysipelas that progressed to sepsis and death.

According to the literature, only about 5% of blood cultures in the case of erysipelas are usually positive. Because bacteremia is rare in this type of infection, diagnosis and treatment are immediate without the need to wait for laboratory test results. Cultures can also be performed using needle aspiration, but the availability of this type of test is not the same in all health services, and its sensitivity is also low[1,16]. In none of the cases in the study was a culture performed to identify the infectious agent causing erysipelas.

However, when easily available, performing the culture should be prioritized, since there may be complications due to the ineffectiveness of treatment for infectious agents considered rarer. For this, two samples are punctured and collected from the site of infection and analyzed in the laboratory in order to isolate the causative agent, but the result takes at least 72 h.

Finally, erysipelas can cause death, as reported here. Physicians in the family health program and those working in emergency departments must be aware of this disease so that therapy with benzathine penicillin can be instituted as soon

as possible, determining control of the infection and avoiding unnecessary deaths.

The limitations of our study are the small number of cases, the lack of objective measurement of the presence of lymphedema, using only the difference in the measurements of the circumference between the arms, and the failure to perform a culture to identify the etiological agent in any of the cases.

CONCLUSIONS

Of the 12 cases of post-mastectomy erysipelas reported in this study, 8 (66.66%) were associated with lymphedema. Only two (16.66%) of the patients in this group who developed erysipelas did not undergo axillary dissection. The treatment for 50% of the participants in this research was done with penicillin G benzathine, of whom three had relapses and two patients died during the research period.

AUTHORS' CONTRIBUTIONS

SVSR: Formal Analysis, Investigation, Writing – original draft.
AVLM: Formal Analysis, Investigation, Writing – original draft.
DRSF: Formal Analysis, Investigation, Writing – original draft.
RSN: Data curation, Formal Analysis,Writing – review & editing.
SCV: Conceptualization, Data curation, Methodology, Resources, Writing – review & editing

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CASE REPORT
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The use of ReadyWrap® reduces the volume of the upper limb with lymphedema related to breast cancer: a case report

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ABSTRACT

Lymphedema secondary to breast cancer is a chronic condition that requires continuous care to control the volume of the affected limb, with compression therapy as the main treatment. The self-adjusting compressive wrap is a new option, whose main advantage is the fact that it is put on by the patient himself. The aim of this study was to describe the use of self-adjusting clothing as an alternative to reduce the volume of the upper limb of a patient with breast cancer-related lymphedema. This study was part of the study adjustable garment compression therapy (ReadyWrap®) in lymphedema secondary to breast cancer: a randomized clinical trial, approved by the CEP/INCA under opinion 4.611.711 and registered in the Clinical Trials under no. NCT04934098. The patient was evaluated before and after the 30-day intervention using physical examination (e.g., inspection, palpation, and perimetry). Skin tissue characteristics were collected using a thermographic camera, while the health-related quality of life (HRQoL) was assessed by answering the EORTC-QLQ C30 questionnaire. As an intervention, an adjustable garment (ReadyWrap®) was used for 30 days. An absolute reduction of 612.47 mL (61.1%) was observed, and at the end of this period, the difference of 21.5% in excess volume compared with the volume of the contralateral limb was maintained. Regarding the tissue characteristics of the skin, there was an increase in the minimum temperature in the affected upper limb, which reached 31.8°C, against 31.2°C in the contralateral limb, with ΔT=0.6°C. Compressive therapy by adjustable garment (ReadyWrap®) demonstrated a 61.1% reduction in the volume of the upper limb with breast cancer-related lymphedema in 30 days of use.

KEYWORDS: breast cancer; breast cancer-related lymphedema; compressive bandages; physiotherapy; case report.

INTRODUCTION

Breast cancer is the most common cancer in women in the world[1]. In Brazil, for 2023, 73,610 new cases of the disease were estimated, corresponding to an incidence rate of 41.89 new cases per 100,000 women[2].

Despite the improvement in access to screening methods for breast cancer, part of the population is still diagnosed with the disease in advanced stages, which requires more aggressive treatments, contributing to the increased incidence of complications[3], such as lymphedema, which represents an important public health problem due to its high incidence and chronic condition[4].

Breast cancer-related lymphedema is the result of the inability to drain the lymphatic system as a result of the surgical approach to axillary lymph nodes and/or postoperative radiotherapy[5]. Its occurrence may be responsible for physical changes, such as pain, heaviness, and discomfort of the affected upper limb, decreased range of motion, cellulite, as well as psychosocial changes, impacting the quality of life[6].

Complex decongestive therapy (PDT) remains the gold standard in the treatment of lymphedema. With the objective of reducing the volume of the limb as much as possible, the intensive phase includes skin care, compressive bandaging with multilayer bandages, manual lymphatic drainage, and exercises[7].

The use of a self-adjusting compression device is a new possibility to treat patients with lymphedema related to breast cancer, demonstrating to be safe, with mild and controlled adverse events, and efficacy similar to compressive therapy with multilayer bandages in reducing the volume of the limb with lymphedema[8].

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Thus, the objective of this case report was to describe how the use of self-adjusting clothing can reduce the volume of the upper limb of a patient with lymphedema.

CASE DESCRIPTION

This report is part of the study "Compressive therapy by self-adjusting clothing (Ready Wrap®) in lymphedema secondary to breast cancer: randomized clinical trial," approved by CEP/INCA under opinion 4,611,711 and registered in Clinical Trials under No. NCT04934098. The detailed study protocol has been previously published[9].

A 79-year-old female patient, brown-skinned, widowed, completed higher education, living in the city of Rio de Janeiro/RJ, Brazil, was diagnosed with left-sided breast cancer, micropapillary carcinoma-pT2pN1, G3, underwent segmental breast resection and sentinel lymph node biopsy, and subsequently, adjuvant treatment with chemotherapy, radiotherapy, and hormone therapy.

Following the physiotherapy service, the patient was evaluated on the first day of the postoperative period (1st POD) and by teleconsultation for 30 days. No feeling of heaviness, left upper limb edema (MSE), or surgical wound complications were reported. She had a complete shoulder range of motion and did not report any functional complications.

On physical examination, the volume of the limbs was calculated using the trunk cone formula $V=h^* (C^2+Cc+c^2)/(\pi*12)$, where V is the volume of the limb segment, C and c are the circumferences at each end, and h is the distance between the circumferences (C), representing the estimated volume of the limb[10]. The percentage reduction in limb volume was calculated by (VI – VF/VI)*100, where VI was the initial volume and VF was the final volume. An increase in arm volume greater than 10% in the postoperative period compared with the volume of the arm in the preoperative period is defined as lymphedema[11]. In the evaluation of the first POD, the patient presented a percentage difference in volume of 2.29%, which was not characterized as lymphedema.

After 26 months of surgery, the patient came to the physiotherapy outpatient clinic reporting swelling and a feeling of heaviness in the upper limb that had started about two months earlier. On physical examination, the volume of the upper limb on the side of the breast cancer was 2,922 mL and that of the contralateral limb was 1,920 mL, corresponding to an excess volume of 52.19%. On palpation, areas of fibrosis were also observed on the forearm.

Skin tissue characteristics and temperature were collected using a FlirOne pro/usb-c thermographic camera. The device has a temperature of -20 to -120°C and 0–400°C, a thermal sensitivity of 150 mK, and an image resolution of 160×120. Regarding the standardization of the collection, all images were taken in a dark room with a thermal scale of 22.0–32.7°C, with respect to the ambient temperature of 23°C.

The patient was instructed to remove her clothes, as well as all accessories, and to wait about 15 min at rest to avoid large temperature variations. The posterior position was chosen for the analysis to standardize the analysis of skin characteristics. The thermal images were analyzed using the comparative method, which consists of investigating things or facts and explaining them according to their similarities and differences[12]. Data analysis was performed in a descriptive and diagnostic manner, in order to investigate the cause-and-effect relationship in the object of the study, describing the findings in the calculations (TI (initial temperature) – TF (final temperature) = ΔT (temperature variation)), that is, the difference between the initial and final temperatures of a body[13].

In the thermographic evaluation, a lack of normal symmetry between the limbs was observed, indicating changes in functional behavior. Bilateral hyporadiation was observed in the triceps brachii and flexor carpi muscles. The temperature recorded in the affected upper limb was 28.2°C and in the contralateral limb was 28.1°C (Δt=0.1°C), as shown in Figure 1A and Table 1. After compression therapy, the minimum temperature of the upper limb (Tmin)=31.8°C and of the contralateral limb Tmin=31.2°C, with Δt=0.5 (Figure 1B; Table 1).

Health-related quality of life (HRQoL) was assessed using the EORTC QLQ C30 (*European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30*), which was validated for use in the Brazilian population[14].

After initial evaluations, the patient underwent lymphedema treatment, including skin care, daily upper limb therapeutic exercises, and the use of compression therapy with a self-adjusting garment (ReadyWrap®) (Figures 2A and 2B). She was instructed to wear the garment all day, especially during the exercises, and at night, to remove it only for bathing.

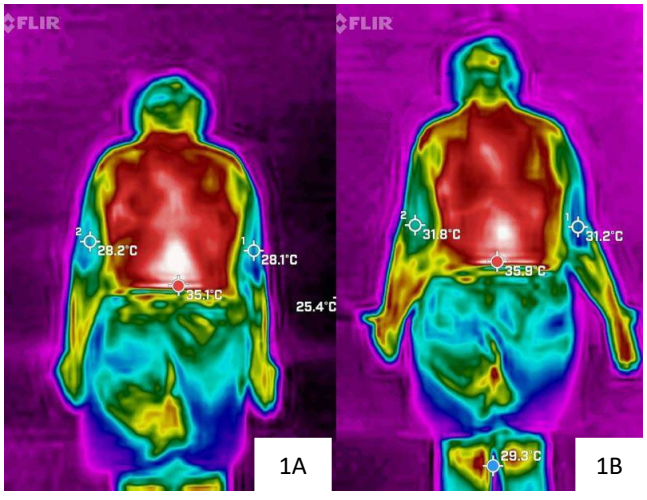

Figure 1. (A) Thermal image with a posterior view (initial evaluation). Point 1 (28.1°C) and point 2 (28.2°C) were selected near the olecranon region. (B) Thermal imaging with a posterior view (after 30 days). Point 1 (31.2°C) and Point 2 (31.8°C) were selected near the olecranon region.

Table 1. Parameters of the evaluations performed before and after 30 days of lymphedema treatment.

Evaluation	Lymphedema treatment		
	Initial	After 30 days	Δ Pre- and post-treatment
Limb volume			
ΔV Left upper limb (affected) (mL)	2922 mL	2201 mL	-721 mL
ΔV Right upper limb (contralateral) (mL)	1920 mL	1811 mL	-109 mL
ΔV absolute between upper limbs (mL)	1002 mL	389 mL	-612 mL
ΔV relative between upper limbs (%)	52.1%	21.5%	-30.6%
Thermography			
Minimum temperature of the left upper limb (affected) °C	28.2	31.8	+3.6
Minimum temperature of the right upper limb (contralateral) °C	28.1	31.2	+3.1
ΔT	0.1	0.6	+0.5
Quality of life (EORTC QLQ C30)			
Functional scales*			
Physical function	80.0	53.3	26.7
General function	66.7	50.0	16.7
Emotional function	83.3	100.0	16.7
Cognitive function	100.0	100.0	0
Social function	66.7	100.0	33.3
Overall quality of life	58.3	83.3	25
Symptom/item scales†			
Fatigue	11.1	0	11.1
Nausea and vomiting	0	0	0
Pain	0	0	0
Dyspnea	0	0	0
Insomnia	0	0	0
Lack of appetite	0	0	0
Constipation	0	0	0
Diarrhea	0	0	0
Financial difficulty	0	0	0

ΔV: volume difference; Δt: temperature difference; EORTC QLQ C30: *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30*. *Higher score is related to a better quality of life; †Higher score is related to a worse quality of life.

These devices are made of wide bands of inelastic material and consist of two pieces (arm and hand), which, adapted to the size and shape of the affected upper limb, extend to the metacarpophalangeal joint. The device is easy to handle—it can be applied and removed by the user himself—as it is closed by velcro straps. This is one of its main advantages, as it allows adjustment as the volume of the affected limb decreases. It also encourages patient autonomy.

Thermography is a safe and non-invasive imaging method that can aid in assessing the distribution of body temperatures. Skin tissue changes, such as inflammation, metabolic changes in the subcutaneous tissue, and blood supply, result in changes in the temperature gradient in the affected area, which can be observed with thermography, as well as the different stages of lymphedema[15].

An absolute reduction of 612.47 mL was observed, corresponding to a relative reduction of 61.13% compared with the

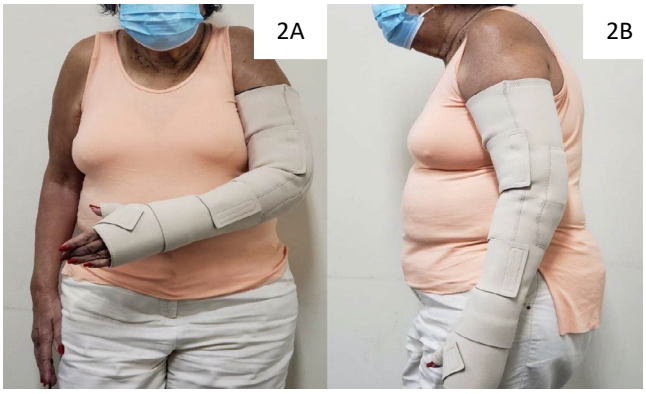

Figure 2. (A) Front image of compression therapy with ReadyWrap® adjustable garment. (B) Side image of compression therapy with ReadyWrap® adjustable garment.

contralateral limb, maintaining a volume difference of 21.52% from one limb to the other (Table 1). Regarding thermography, there was an increase in Tmin in the affected upper limb of 31.8 and 31.2°C in the contralateral limb, with ΔT= 0.6°C (Figure 1B; Table 1).

After 30 days of wearing the garment, the patient showed improvement in general quality of life and the scales of fatigue and emotional and cognitive functions and worsening in physical and general functions (Table 1).

DISCUSSION

In this case report, the use of the self-adjusting compression device (ReadyWrap®) for 30 days proved to be a therapeutic resource capable of helping to reduce the volume of the upper limb in the intensive phase of treatment for lymphedema related to breast cancer.

It can be an alternative in treatment, as clothing therapy can be easily adapted and self-managed, without the need for professional help, unlike conventional therapy with multilayer bandages, in which compressive bandaging is done in an outpatient setting at least twice a week, for approximately 30 days. After the maximum reduction in the volume of the limb, a compressive mesh (standard or custom-made size) is adapted and the patient is instructed on daily home exercises for the upper limbs, in addition to skin care and activities of daily living[16].

To date, we are aware of only one Spanish randomized clinical trial that confirmed that compression therapy with adjustable garments and multilayer compression bandages has similar efficacy in reducing excessive volume or symptoms of upper limb lymphedema in women with breast cancer[8].

Thermography can be used to evaluate patients with lymphedema, and it is possible to observe hot or cold spots in the affected limb compared with the unaffected limb, such as in women with secondary lymphedema related to breast cancer, in which the skin temperature tends to be lower, on average 1.3°C, an alteration caused by a decrease in blood flow in the affected limb[17].

To date, there are no studies on the change in limb temperature assessed by thermography during limb volume reduction treatment in patients with cancer-related lymphedema. In this case report, after compression therapy, the patient presented a Tmin of 31.8°C in the affected upper limb and 38.2°C in the contralateral one, and it was possible to observe Δt=0.6°C, demonstrating an increase in the temperature of the upper limb after treatment with adjustable clothing.

The use of thermography has proven to be a safe assessment method, capable of offering functional information associated with vasodilation, hyperperfusion, and hypoperfusion, measuring various patterns of temperature distribution, and can be a strong ally in the diagnosis of lymphedema[17].

In our study, the patient showed improvement in the functional domains of general quality of life and the scales of fatigue and emotional and cognitive functions after 30 days of PDT using adjustable clothing. In Poland, a randomized clinical trial evaluated the use of low-compression garments in the prevention of lymphedema and its impact on quality of life, demonstrating improvement in the self-reported functional, symptom, and general quality of life scales in the same instrument used in the present questionnaire[18].

On the contrary, physical and social functions presented lower scores, being related to a worse quality of life when evaluated in 30 days, which may lead to speculation, justifying the need to intensify home exercises and the continuous use of compression therapy in the phase of volume reduction of the affected limb[19]. This is the most intense moment of lymphedema treatment when limitations in carrying out some daily activities increase and social participation, in general, is reduced.

Compressive therapy by adjustable garment (ReadyWrap®) demonstrated a reduction of more than 50% in the volume of the upper limb with breast cancer-related lymphedema in just 30 days of its use. Self-application of compression can be a facilitator of independence and a sense of control in lymphedema treatment.

This is the first case report to evaluate an adjustable garment in the reduction phase of upper limb lymphedema related to breast cancer in Brazil. Although the results are encouraging, this is a case report, so there are methodological limitations to defining the real impact of this treatment on the alteration of limb volume with lymphedema and on the quality of life of women with lymphedema secondary to breast cancer. Thus, randomized clinical trials are needed to evaluate the efficacy and safety of these devices in this population.

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AUTHORS' CONTRIBUTIONS

RDDA: Formal analysis, Investigation, Writing – original draft. **JMPS:** Formal analysis, Investigation, Writing – original draft. **SSA:** Formal analysis, Data curation, Writing – review & editing. **MVMP:** Conceptualization, Data curation, Methodology, Resources, Writing – review & editing. **LCST:** Project administration, Supervision, Writing – original draft, Writing – review & editing. **AB:** Project administration, Supervision, Writing – original draft, Writing – review & editing.

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SHORT COMMUNICATION
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Sequels associated with breast cancer treatment: what is important to measure in a report

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ABSTRACT

Breast cancer treatment is associated with functional sequelae that limit patients in their daily activities or work, impacting their quality of life. This fact becomes more noticeable in the Public System, the tumors are more advanced, leading to more aggressive treatments. Women with low education generally perform menial activities, playing an important role in family income. After cancer treatment, many are unable to carry out their usual activities, having difficulties with their work activities, requiring rehabilitation. These dysfunctions make it difficult or unfeasible to return to work, limiting family income. Knowledge of the Laws, the main sequelae and evaluation methodologies facilitates a more accurate diagnosis of functional conditions, determining the need for rehabilitation. Social Security provides economic support, but to have access to the benefit, a good report is necessary. This, well directed, helps the social security expert and the patients, who are generally so fragile by the disease and the treatment. In this article we discuss the main functional sequelae, how to evaluate them, and how to make a good report to be sent to an expert.

KEYWORDS: breast neoplasms; diagnosis; diagnostic techniques and procedures; rehabilitation; quality of life.

Early diagnosis and multiple treatment modalities have increased the cure rate and survival of patients with breast cancer. The different therapeutic modalities can be associated with sequelae that can impact the quality of life, hence the need to diagnose these changes in order to provide treatment and/or physical therapy support[1-5].

The treatment implies changes in the patient's life, and in those who work, the consequences can impact the return to work, the need for rehabilitation and/or the need for retirement. A Brazilian study carried out in a hospital that treats women with breast cancer, exclusively attended by the Unified Health System (*Sistema Único de Saúde* – SUS), showed that 54.0% of women return to work after cancer treatment, and these are generally younger, with higher education, higher income, and with smaller tumors, and that the loss of shoulder mobility determines an increase in the risk of not returning to work[6]. Returning to work is a multifactorial matter, as it involves conditions related to the woman (age, race, education, physical activity), the context (marital status, family income, participation in the family income), the type of activity (remuneration, work activity, possibility of relocation, working conditions), the disease (stage, treatment impact, associated sequelae, recurrence, and quality of life), in addition to the laws that support cancer patients[6]. This fact is more important in patients from the public system, in which social security assistance is of fundamental importance.

We sought to analyze the issue in Brazil from the perspective of different professionals who deal with patients undergoing different breast cancer treatments, assessing the main functional sequelae, and, based on this condition, identifying points to be implemented in a report.

PATIENT ASSISTANCE LAWS

There are some laws created to help breast cancer patients, especially those with functional dysfunction, namely:

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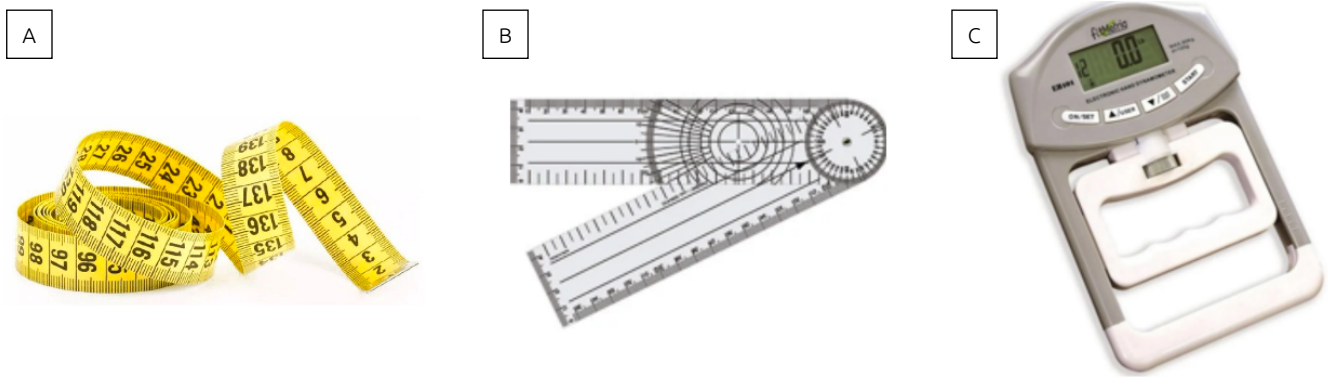
- Decree No. 3.048, of May 1999[7], which regulates the Social Security System. This legal instrument values the mandatory contributory nature, allowing contributors to cover temporary or permanent disability events, as well as the possibility of aid (temporary or permanent), temporary leave and rehabilitation, in addition to disability retirement associated with total and definitive disability, with the need for evaluation by an expert social security doctor. The definitive concession is made by two independent experts and separately. Subject to these conditions are patients who previously contributed to the disease — in the case of breast cancer, there is no waiting period.
- Organic Law of Social Assistance (*Lei Orgânica da Assistência Social* – LOAS), Federal Law No. 8.742, of December 7, 1993[8] — provides for the possibility of benefit for people with no social security system and family income of less than one quarter of the minimum wage for people with physical disabilities and inability to work.
- Law No. 8.036, of May 11, 1990 (art. 20, items XI, XIII, XIV, and XVIII)[9] — provides for withdrawal from the Severance Indemnity Fund (*Fundo de Garantia por Tempo de Serviço* – FGTS) for people with serious illnesses, including cancer. For this, the patient must be symptomatic, even with locoregional symptoms, and be under outpatient treatment/follow-up.
- Decree No. 9.580, of November 22, 2018 (art. 35, item II, items B and C)[10] — provides for exemption from income tax and the granting of disability benefits and pensions.

FUNCTIONAL SEQUELS

Knowledge about potential sequelae associated with treatment is of utmost importance[2], especially the functional ones[1]: lymphedema, changes in shoulder mobility, rotator cuff syndrome, changes in sensitivity, breast asymmetry, fibrosis, syndrome axillary, changes in muscle strength, pain, brachial plexopathy, hand-foot syndrome, and secondary heart disease. Table 1 presents the main dysfunctions[1,5]. Figure 1 presents the main instruments that can be used in diagnostic evaluation, and their acquisition is simple and inexpensive (R$ 200; US$ 50).

Table 1. Main sequelae associated with treatment[1,5]

Sequelae	Treatment	Rate (%)
Lymphedema	Reversible but incurable	9.5 to 49.0
Change in shoulder mobility	Reversible	mean 19.2; 18 to 49 associated with lymphedema
Rotator cuff syndrome	Reversible	–
Sensitivity change*	Irreversible	100 intercostobrachial injury
Brachial plexopathy*	Difficult treatment	Up to 13.6
Her2 heart disease Anthracycline (Taxol)	Reversible (Her2) Reversible or not	4
Hand-foot syndrome	Reversible	20 to 60
Breast asymmetry	Treatable	–
capsular contracture	Treatable	14.7
Fibrosis	Irreversible	29.1
Pain	Treatable	19.2



(A) Measuring tape; (B) goniometer; (C) dynamometer.

Figure 1. Simple instruments that improve clinical assessment.

Of the main complications associated with treatment, some have an important functional impact and can be assessed using simple methodologies[1,6,11], which improve our clinical examination, helping in the functional assessment of patients, namely:

- Lymphedema is one of the main sequelae. It has a chronic nature, usually irreversible. Evaluation of the perimeter of the upper limb, using a tape measure (Figure 1A), taking measurements from defined and symmetrical points, always comparing one limb with the other, is a simple way to measure it. Lymphedema is considered when there is a difference of ≥2 cm in the perimetry of the side ipsilateral to the treatment in relation to the other side.
- Shoulder mobility. Patients may present limitations in the mobility of the shoulder ipsilateral to the treatment. Evaluation is performed with the aid of a goniometer (Figure 1B), through which the angles of the active movements of flexion, extension, abduction, and internal and external rotation of the shoulder are analyzed. The instrument also assesses range of motion, with good references for bilateral assessment and the inclusion of data on abduction and flexion of the upper limb. A change in shoulder mobility is considered when there is active goniometry <150° for shoulder flexion and/or abduction.
- Muscle strength. A difference of 12%[12] between limbs is estimated in disease-free individuals. The easiest way to measure strength is by means of a handheld dynamometer (Figure 1C). The presence of brachial plexopathy will be an important functional diagnostic tool.
- Brachial plexopathy is associated with irradiation of the supraclavicular fossa and axilla; although infrequent, it is associated with neurogenic pain with progressive motor and sensory deficit in the ipsilateral limb to treatment[13]. The LENT/SOMA Scale (late effects of normal tissue/subjective-objective-management-analytic) can be used to define its gradation[1].
- Hand-foot syndrome[14], which is also infrequent, may occur after treatment with chemotherapy drugs such as taxol, anthracyclines, and carboplatin[15], causing peripheral neuropathy. The complaint should be valued, since the neuropathy is mainly sensitive, however, when associated with motor alteration (gait or strength), this must be reported. The etiological diagnosis is difficult[16]. It leads to therapeutic discontinuity, affecting the quality of life.
- Breast reconstruction using autologous flaps or implants is associated with changes in shoulder mobility[17]. In patients undergoing reconstruction with a retromuscular implant, there is thinning of the pectoral muscle, influencing mobility and local functionality.
- Shoulder functional assessment quality questionnaires[18]. The SPADI (Shoulder Pain and Disability Index) stands out, validated into Portuguese[11], a simple questionnaire that indirectly assesses the degree of disability and pain in the limb ipsilateral to the treatment. Although it can be considered subjective, it presents objective clinical responses. It becomes an important tool in the evaluation, as it is able to provide the physician and the physiotherapist with information about the patient's level of function, contributing to the clinical diagnosis and physiotherapeutic decision-making.

REPORT

There are four main ways to report (or assess) the patient's condition to another professional:

- Medical attending statement: document issued by the attending physician, which certifies a momentary condition.
- Medical report: represents the scenario of the patients' illness, and should contain information on diagnosis, treatment performed, evolution, etc.
- Physiotherapeutic technical report: document with technical-scientific opinion resulting from the physiotherapeutic evaluation. Information on the studied situation must be reported, analyzed, and integrated. It is important to contain the proposed objective, the therapeutic plan, the evolution of the treatment, and the International Classification of Functioning, Disability and Health (ICF)[19].
- Technical report or expert report: to be carried out by official experts/specialists, legally qualified professionals, who issue their report according to specific knowledge, data collected from patients and impressions they had about what or who evaluated it. The report is always conclusive and serves as technical support to the social security doctor.

According to the legislation, proving the allegation of incapacity is the duty of the insured person (patients). The presentation of a good certificate/report help social security experts to have subsidies with objective and solid data, so that they can make a conclusive report. The report will be forwarded to the social security expert, and the better and more detailed it is, the greater the possibility of successful removal of the patient who has sequelae associated with the treatment. It is the experts' job to:

- Establish the disease and the degree of functional limitation;
- Establish the functional requirements necessary for the exercise of one's usual work activity;
- Establish adaptive capacity (current and future perspective);
- Define the existence or not of labor incapacity;
- If there is incapacity, the professional will assess whether it is partial or total and whether it is temporary or permanent;
- Establish the onset dates of the illness and disability, as well as the benefit termination date;
- Grant the benefit, which can be aid or disability retirement. To this end, this will assess whether the disability is partial or total, irreversible or subject to rehabilitation, with the possibility of professional rehabilitation.

Aiming to support the experts, when preparing a medical report, it is appropriate to present the report with the code of the International Statistical Classification of Diseases and Related Health Problems (ICD) — or literal diagnosis —, pointing out the different treatments performed, the main complaints, and detailed clinical examination. Regarding physiotherapists, their report should contain the physiotherapy diagnosis or the functional kinetic diagnosis, obtained through the evaluation of complaints, physical examination and classification of functionality by ICF[19], having fundamental importance in the treatment, control, and rehabilitation. The main points to be included in a medical and physiotherapeutic report are found in Tables 2 and 3, respectively.

Patients may have temporary or permanent disabilities, being eligible for temporary social security benefits during personal and functional rehabilitation. Some, due to disease conditions, age, education/activity or type of sequelae, may be considered invalid, but this definition depends on the criteria of the social security expert.

A well-designed report depends on time and good will and can help both patients and experts in their evaluation. The report can only be prepared after the patients' request and authorization.

Some information can and should be included in the medical report, which may help the patient and the social security expert, namely:

- According to the Code of Medical Ethics[20], the patient's physician is prohibited from carrying out an expert report, and may only prepare a medical report;
- A summary of the treatment should be presented, pointing out the main conditions that can lead to a potential sequel. Some situations increase the risk of sequelae and, when present, should be scored, such as axillary lymphadenectomy and radiotherapy under the supraclavicular fossa[4,13];
- A record of complaints and clinical alterations can be presented, allowing to point out the clinical conditions associated with treatment sequelae, such as lymphedema, change in shoulder mobility, change in strength. It should include the LENT/SOMA Scale in the presence of brachial plexopathy. The SPADI questionnaire can help, as long as it is associated with a clinical condition of pain and disability;
- Notes such as:
  a. "The treatment can result in alterations/sequelae in the breast and in the limb ipsilateral to the treatment performed, a fact that can influence daily activities and quality of life. These changes are influenced by time, individual response and the type of treatment";

Table 3. Points to be approached in the physiotherapy report.

Item	Description
Diagnosis	ICD (or literal diagnosis) and ICF, ICF being optional
Physiotherapy diagnosis	Targeted complaints; painful symptom
	Physical therapy examination: associated skeletal alteration Diagnosis and degree of alteration
Care	Care to be taken with the manipulated limb
Diagnostic hypothesis	Neoplasm
	Pain complaint
	Functionality (SPADI can be used)
Conclusion	Treatment/treatment time Activity limitation

ICD: International Statistical Classification of Diseases and Related Health Problems; ICF: International Classification of Functioning, Disability and Health; SPADI: Shoulder Pain and Disability Index.

Table 2. Points to be approached in the detailed medical report.

Item	Description
Diagnosis	ICD (or Literal Diagnosis)
Treatment carried out	Start of treatment, clinical stage, molecular subtype
	Surgery, chemotherapy, radiotherapy, hormone therapy
	Current status of the disease
Clinical complaints	Systemic, local and locoregional (as long as they are associated with the underlying disease) SPADI can be added (determines a percentage of disability and pain)
Clinical examination	Locoregional
	Aimed at the main sequelae: perimetry, goniometry, dynamometry
Diagnostic hypothesis	Neoplasm and associated sequelae hypothesis
Conclusion	Time away from patients undergoing treatment Referral to other specialists Referral to a physiotherapist if sequelae that require evaluation/treatment are found

ICD: International Statistical Classification of Diseases and Related Health Problems; SPADI: Shoulder Pain and Disability Index.

b. "The treatments carried out followed current guidelines, aimed at controlling the disease";
- It may be suggested that patients undergoing oncological treatment or who have metastases be on temporary leave. However, outside of these conditions, only the social security expert will be able to determine the length of leave or retirement;
- The term "functional limitation" may be used, but the term disability cannot.

With regard to the physiotherapeutic report:
- It should present a summary of the physiotherapeutic treatment, pointing out the main conditions that can lead to a potential sequel.
- You may have complaints and clinical changes associated with treatment sequelae, such as lymphedema, change in shoulder mobility, change in strength, fibrosis. The SPADI questionnaire can help, as long as it is associated with a clinical condition of pain and disability.
- It must contain the physiotherapeutic diagnosis or functional kinetic diagnosis, obtained through the evaluation of complaints and physical alterations and classification of functionality by the ICF[19].
- It may suggest day-to-day care and limitation of some activities of daily living and work, due to the risk of progressing to lymphedema, if the patient has undergone axillary lymphadenectomy.
- The term "functional limitation" can be used, but the term disability cannot.

CONCLUSION

This discussion sought to present objective parameters that can help patients with functional disorders, improving the report to be presented to the expert. Its preparation demonstrates a new level of document, which depends on goodwill, attention and affection for patients, already weakened by the disease. In the context of SUS, this fact is accentuated by the financial condition, the advanced stage and the sequelae associated with the treatment.

AUTHORS' CONTRIBUTION

RACV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. RESC: Data curation, Formal analysis, Visualization, Writing – original draft Writing – review & editing. MAA: Data curation, Formal analysis, Visualization, Writing – original draft Writing – review & editing. ADS: Data curation, Formal analysis, Visualization, Writing – review & editing. LCNO: Data curation, Formal analysis, Visualization, Writing – review & editing. AJS: Data curation, Formal analysis, Visualization, Writing – original draft Writing – review & editing.

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ORIGINAL ARTICLE
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Clinicopathological characteristics and recurrence risk in patients with ductal carcinoma in situ of the breast

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ABSTRACT

Introduction: With the widespread adoption of mammographic screening for breast cancer, ductal carcinoma in situ (DCIS) has been detected more frequently. In developing countries, the prevalence of ductal carcinoma in situ is low due to the opportunistic nature of breast cancer screening. The aim of this study was to evaluate the clinicopathological characteristics and recurrence rate in a cohort of patients with ductal carcinoma in situ in Brazil. **Methods:** This study was an retrospective analysis of all 1,736 patients with non-metastatic breast cancer treated at a reference public hospital between 1999 and 2013. All data were collected from medical records and the descriptive statistics were performed to characterize the clinical and pathological features. **Results:** In the present cohort, we identified 102 (5.2%) patients with non-invasive breast neoplasms. Mean age at diagnosis was 54±12.7 years and most patients were treated with breast conserving surgery. There is a strong association between nuclear grade and the expression of estrogen and progesterone receptors in ductal carcinoma in situ. Ipsilateral and contralateral recurrence rates in 10 years were 7.2% and 2%, respectively. **Conclusion:** The pathological features of ductal carcinoma in situ diagnosed in Brazil are similar to those observed in patients diagnosed in countries following a systematic screening program, and the treatment in our patients achieves similar success compared with published data in high-income countries.

KEYWORDS: ductal carcinoma in situ; DCIS; local neoplasm recurrence; breast; prognoses.

INTRODUCTION

Ductal carcinoma in situ (DCIS) was rarely diagnosed before widespread adoption of breast cancer screening, but it currently accounts for 20%–25% of breast cancer detected in developed countries that have introduced an adequate population screening program[1].

DCIS is a proliferation of neoplastic luminal cells that are confined to the duct system of the breast[2]. The risk of developing metastasis or death in a patient with pure DCIS is rare[3]. However, DCIS can progress to invasive carcinoma and is currently considered a direct precursor to invasive breast malignancy. The key point of treatment is local excision of the lesion. Simple mastectomy and conservative surgery followed by radiation therapy are the standard options for local disease control[4]. Patients with positive hormone receptor tumors benefit from receiving endocrine therapy to reduce the risk of future invasive breast cancer[5].

The 10-year local recurrence rate is about 1%–2% in women undergoing mastectomy[6], while patients who undergo conservative surgery with adjuvant radiotherapy have a 10-year local recurrence rate of 13%, but no difference in breast cancer mortality was detected[7]. An invasive carcinoma is diagnosed in half of patients who experience a local recurrence[8]. Among all the risk factors, only the size of the margin is potentially modifiable by re-excision[9]. Although the involvement of margins is associated with a higher risk of recurrence after conservative surgery, there is still no consensus on the ideal size of the resection margin[10].

In Brazil, there is a lack of evidence-based data on recurrence rates of DCIS in the Brazilian population. Recent studies

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have demonstrated that DCIS detection rate is low due to the opportunistic nature of the breast cancer screening program[11]. This may interfere with the clinical and pathological presentation, the type of treatment, and the risk of recurrence. The aim of this study was to evaluate the clinicopathological characteristics and recurrence rate in a cohort of patients with DCIS treated in a public hospital in Brazil.

METHODS

This study is a retrospective cohort dataset including all 1,736 patients with non-metastatic breast cancer treated at the Breast Disease Division of the Hospital das Clínicas of Ribeirão Preto Medical School. The cohort was previously approved by the Research Ethics Committee (approval number 2.638.453/05/07/2018). The following attributes were used for data analysis: age, menopause status, histological grade, immunohistochemistry (IHC) for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), type of surgery, lesion size, adjuvant radiotherapy, adjuvant endocrine therapy, follow-up time, and presence of local recurrence.

The overexpression of HER2 and the expression of hormonal receptors (HR) were determined by IHC in accordance with specific guidelines[12,13]. HER2 positivity was established in accordance with the pathology report in the clinical chart. The subtype was considered luminal if ER or PR was positive and HER2 was negative; HER2/HR+ if ER and/or PR was positive and HER2 was positive; HER2 if ER and PR were negative and HER2 was positive; and triple negative (TNBC) when ER, PR, and HER2 were negative.

Statistical analysis

Descriptive statistics was performed to characterize the group of patients diagnosed with DCIS. Multiple hypothesis tests were applied to compare the clinical and pathological characteristics between the groups of patients with DCIS and invasive ductal carcinoma (IDC). The sample size was determined by convenience. Variables were classified as qualitative or quantitative. Quantitative variables were tested for normality using the Shapiro-Wilk test. Chi-square test was used to compare qualitative variables and the t-test or Wilcoxon test (depending on the normality test) was used to compare continuous variables. The local recurrence event was treated as a function of time using the Kaplan-Meier method. The recurrence time was the difference between the surgery date and the event. Cases were censored at the time of the last available clinical assessment. Univariate analysis for each potential risk factor was applied. All analyses were performed with the R software version 4.1.2 (R Core Team, Austria) and significance was determined for $P<0.05$.

RESULTS

Prevalence of non-invasive breast neoplasm and clinical characteristics of patients with ductal carcinoma in situ

We found 102 non-invasive breast neoplasms (5.2%). Most non-invasive neoplasms were pure DCIS (n=95) and two DCIS were associated with Paget disease. There were three pure Paget diseases and two papillary intracystic carcinomas that were not included in the subsequent analyses. We observed that the mean age of patients with DCIS and IDC was similar (54±12.7 and 55.9±13.8 years, p=0.1), and the DCIS/IDC prevalence ratio did not significantly change according to different age groups (p=0.2). The prevalence of DCIS diagnosis was 6.5%, 5.7%, and 3.5% in (18,50), (50,70), and (70,100) age groups, respectively. The types of local treatment between patients with DCIS and patients with IDC subjected to primary surgery were compared. The breast conserving surgery (BCS) ratio was 61.9% in DCIS patients and 67% in IDC patients (p=0.3). Adjuvant radiation therapy was delivered to 88.3% of DCIS patients and 95.6% of IDC patients subjected to breast conserving surgery (p=0.2).

Ductal carcinoma in situ pathological features

The pathological size was recorded in 58 DCIS lesions. The median size was 12 mm (interquartile range, IQR 18.9), and most DCIS are of high nuclear grade (55.2%) with the presence of comedonecrosis (55.7%). In terms of immunohistochemical analysis, 82.2% of DCIS lesions were ER positive, 75.5% were PR positive, and 29.9% were HER2 positive. According to molecular subtyping, luminal subtype was the most frequent (63.2%). Although the subtype distribution among DCIS lesions was similar to IDC (p=0.1), comparing the distribution of TNBC and non-TNBC, there is a high percentage of TNBC in IDC compared to DCIS (15.6% versus 6.9%, respectively, with p=0.04). Table 1 explains the clinical and pathological features of DCIS and IDC patients. There is a significant association between DCIS grade and the expression of ER, PR, and HER2 proteins. High-grade DCIS lesions are associated with the negative expression of ER (p=0.002) and PR (p=0.008) and there is a trend to have positive expression of HER2 (p=0.06). Table 2 shows the association of DCIS nuclear grade with ER, PR, and HER2 expression and the molecular subtypes. All HER2 positive and TNBC subtypes were of high-grade DCIS.

Ipsilateral and contralateral recurrence (Ipsilateral and contralateral recurrence, respectively)

We observed seven ILR (7.2%) and two invasive CLR (2%). Figure 1 shows the cumulative plot for ILR in DCIS patients. We analyzed the association of clinical and pathological features and the locoregional recurrence (LRR). Although we did not observe any significant predictive factor for LRR, all ILR occurred in patients

Table 1. Clinical and pathological features of patients with ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC)

	DCIS (97)	IDC (1639)	p-value
Age (years; SD)	54±12.7	55.9±13.8	0.1
Age groups (n; %)			
(18, 50)	41 (6.5)	592 (93.5)	
(50, 70)	46 (5.7)	768 (94.3)	
(70, 100)	10 (3.5)	277 (96.5)	0.2
Surgery (n; %)			
Mastectomy	37 (38.1)	293 (33)	
BCS	60 (61.9)	596 (67)	0.3
Radiation therapy (%)	88.3%	95.6%	0.2
ER positive (n; %)	74 (82.2)	1180 (72.8)	0.06
PR positive	68 (75.5)	976 (60.1)	0.005
HER2 positive	26 (29.9)	419 (25.9)	0.5
Subtype (n; %)			
Luminal	55 (63.2)	941 (58.4)	
HER2	8 (9.2)	168 (10.4)	
HER2/HR positive	18 (20.7)	251(15.6)	
TNBC	6 (6.9)	252 (15.6)	0.1

DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; SD: standard deviation; BCS: Breast-conserving surgery; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; HR: hormonal receptors; TNBC: triple negative breast cancer.

Table 2. Association of invasive ductal carcinoma (IDC) histological grade and ductal carcinoma in situ (DCIS) nuclear grade and immunohistochemical (IHC) features

	High Grade (%)	Non-high Grade (%)	p-value
DCIS – IHC			
ER positive	69.4	97.5	0.002
PR positive	63.3	90	0.008
HER2 positive	39.6	18.4	0.06
DCIS – subtypes			
Luminal	47.9	81.6	
HER2	16,6	0	
HER2/HR positive	22.9	18.4	
TNBC	12.5	0	0.0007*

IHC: immunohistochemistry; DCIS: ductal carcinoma in situ; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; TNBC: triple negative breast cancer. *Fisher's exact test.

with high-grade DCIS. ILR was observed in 15.4% of HER2 positive and 4.9% of HER2 negative (p=0.2). We observed only one disease-specific death during the follow-up after an invasive contralateral recurrence.

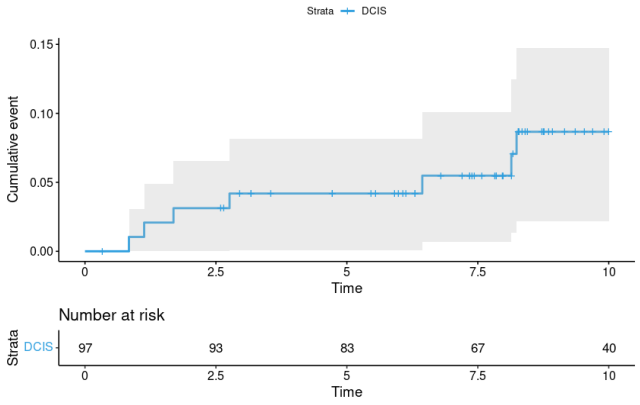

Figure 1. The 10 years cumulative plot for ipsilateral recurrence in 97 patients with ductal carcinoma in situ (DCIS).

DISCUSSION

DCIS is mainly diagnosed in asymptomatic women from breast cancer screening programs. Despite being highly curable, the major concern about the disease is the recurrence associated with invasive carcinoma and the increased risk of a new breast cancer throughout life. In Brazil, the reported DCIS detection rate is low due to the opportunistic nature of the breast cancer screening program[11,14]. In our study, we observed that about 5% of breast cancer patients were diagnosed with DCIS. The clinical and immunohistochemical features in DCIS are quite similar to the features in IDC. We observed only 7.2% of patients experienced ILR in a mean follow-up of 10 years, demonstrating the high effectiveness of the local treatment for DCIS.

The diagnosis of DCIS is a condition mainly associated with breast cancer screening nowadays. Thus, the rate of women diagnosed with DCIS in low- and middle-income countries, in general, is very low, ranging from 1% to 7%[15], compared to the rate in developed countries which is above 20%[16]. This discrepancy is due to the widespread adoption of a mammographic screening program and the efficient and rapid diagnosis and treatment onset in high-income countries. In Brazil, where 70% of women rely on the public health system (Sistema Único de Saúde, SUS), the 5% of DCIS found in our study exemplifies this scenario[17].

Although the number of women diagnosed with DCIS has increased substantially over the past decades in developed countries, the breast cancer-specific mortality in early-stage breast cancer did not significantly decrease, suggesting that the treatment of most patients with DCIS may be considered overtreatment[18,19]. Despite the fact that DCIS overtreatment is associated with emotional and physical damages and unnecessary cost, some studies have investigated the safety of low-risk DCIS active surveillance[20-22]. Low-risk DCIS may be characterized by the histological morphology, grade, size, margin width, and the expression of ER/PR and HER2 proteins[23,24].

In low-income countries, the current DCIS detection rate remains similar to the detection rate in European countries before the implementation of the breast cancer screening program[25]. A few studies characterizing the clinicopathological characteristics of DCIS in Brazil have been published, and none has investigated the efficacy of the treatment in a long-term follow-up[26-28]. Investigating the clinical and pathological features of women diagnosed with DCIS in developing countries is crucial to the management decision in the current and the near future scenario for DCIS treatment.

The incidence of DCIS is strongly related to older age and extremely uncommon before the age of 40 years, a subgroup of women not included in screening programs. The mean age of DCIS in our study was 54±12.7 years with no significant difference from women diagnosed with IDC, corroborating the mean age presented by Virnig et al., which reveals that the incidence of DCIS rises steadily to a peak of 96.7 per 100,000 at the ages of 65–69 years and then declines until the age of 79 years and abruptly after 79 years[29]. We observed the same trend with only 3.5% of cases diagnosed as DCIS in women after the age of 70 years.

Mastectomy is a reasonable option for DCIS treatment for women who do not meet the criteria for BCS. In Brazil, the opportunistic nature of the breast cancer screening program is associated with a low prevalence of DCIS[11,30]. To make inference how this may affect the local treatment decision in DCIS, we investigated the mastectomy ratio and compared it to the women diagnosed with IDC in our study population. The mastectomy ratio was 38.1% in DCIS patients compared to 33% in IDC patients subjected to primary surgery. Although our data demonstrated that the mastectomy ratio is similar when comparing patients with DCIS and early-stage IDC, the BCS ratio in our DCIS population is in accordance with other reports[31].

We analyzed the expression of ER, PR, and HER2 proteins and the breast cancer subtypes in DCIS and IDC. We observed that the distributions in luminal and HER positive subtypes are similar. The prevalence of TNBC lesions is significantly low in DCIS and the prevalence of ER and especially PR positive lesions are higher in DCIS. The IHC and subtypes distributions are highly associated with the nuclear grade in DCIS. High-grade DCIS are more likely to be ER negative compared with non-high-grade DCIS. All HER2 positive and TNBC subtypes are high-grade lesions in our cohort. This observation is in accordance with previous reports[28].

According to local recurrence, the unique randomized clinical trial specifically restricted to DCIS, published by McCormick et al., showed that unicentric disease, tumor size ≤2.5 cm, grade 1 or 2 and negative margins greater than 3 mm are factors of low risk of recurrence in patients treated with breast conserving surgery[32]. The current consensus guidelines for margins in DCIS recommend 2 mm to decrease local recurrence rates[33], and some studies include comedonecrosis as a pathological feature of high risk of recurrence[34]. In our study, none of the characteristics (mean size of 12 mm [IQR 18.9]), 55% of high-grade tumors, 55.7% of comedo DCIS, and 63.2% of luminal tumors) were correlated to local failure. Other studies demonstrated similar results[8,35]. The ipsilateral and contralateral local recurrence observed in our cohort (7.2% and 2%, respectively) was similar to an American study which included 2,759 DCIS patients, and the competing risk analysis demonstrated 7.8% and 2.9% rates for 5-year ILR and CLR, respectively[36].

The limitations of this study include those associated with observational and retrospective studies. This is a single-centered study cohort based on a convenience sampling. The tumor size measurements were missing in 40% cases. However, it is a common problem in DCIS studies. The frequent multifocal nature of DCIS makes it hard to accurately measure the lesion. Also, we could not explore the exact margin width because of unavailable data. After all, since we lack data of Brazilian DCIS patients, more studies are warranted to identify the clinicopathological features of DCIS and the risk factors for recurrence in our population.

CONCLUSION

Although the rate of patients diagnosed with DCIS is low and most of the patients with DCIS come from an opportunistic screening program in Brazil, our data suggest that the clinical and pathological features are similar to those observed in patients diagnosed in countries following a systematic screening program. Moreover, the DCIS treatment in our patients achieves similar success compared with published data in high-income countries.

AUTHORS' CONTRIBUTIONS

MHCNB: Conceptualization, Writing – original draft, Writing – review & editing. VHS: Conceptualization, Writing – original draft, Writing – review & editing. LFO: Writing – original draft, Writing – review & editing. HHAC: Conceptualization, Writing – review & editing. FJCR: Conceptualization, Writing – review & editing. JMA: Conceptualization, Writing – review & editing. PLB: Conceptualization, Writing – review & editing. DGT: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
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Temporary trend of breast cancer mortality in the state of Santa Catarina in the period from 1996 to 2019

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ABSTRACT

Introduction: Breast cancer is the most common female cancer and the leading cause of cancer death in women around the world. It has repercussions not only on human health, but also on health services due to the high incidence resulting in a large number of consultations and treatments. The disease is responsible for a large demand for hospitalizations throughout Brazil, where an increase in mortality rates is observed and Santa Catarina does not differ from the national scenario. The study aimed to analyze the temporal trend of the breast cancer mortality rate in the state of Santa Catarina from 1996 to 2019 **Methods:** This is an ecological epidemiological study of time series of breast cancer mortality in the population residing in the state according to age groups and health macro-regions. Data were obtained from the Mortality Information System and the Brazilian Institute of Geography and Statistics. Simple linear regression of standardized mortality rates according to the world standard population was performed. $p<0.05$ was considered significant. **Results:** Data showed 9,637 deaths in the period. There was a significant upward trend in mortality in the state (from 6.50 to 7.92/100,000 women). An upward trend was observed in the age groups of 30–39 years, 60–69 years, and over 80 years. All seven health macro-regions showed an upward trend in mortality. **Conclusion:** The overall mortality rate from breast cancer in Santa Catarina showed a significant upward trend. A significant increase was also observed in the age groups of 30–39 years, 60–69 years, and 80 years old or older and in all health macro-regions. Problems in public health infrastructure, lack of control of risk factors and deficiency in mammographic screening are revealed. The elaboration and strengthening of public policies to control the disease are fundamental.

KEYWORDS: breast neoplasms; mortality; time series.

INTRODUCTION

Breast cancer is the most common female cancer worldwide — except for non-melanoma skin cancer — and represents a serious public health problem. It is a disease that does not recognize borders, ethnicities, or social classes, which affects women all over the world and is the main cause of cancer mortality in the female universe[1-3]. It has a higher incidence and mortality in underdeveloped countries, mainly due to difficult access to health care and late diagnosis[1-3]. These rates show an international upward trend, especially in underdeveloped countries[3], being very different between regions depending on the lifestyle of each population and exposure to risk factors such as age, long menstrual history (early menarche and late menopause), nulliparity, late primigravidae, sedentary lifestyle, alcoholism, obesity, and use of hormone replacement therapy[2-4]. Its impact is observed not only on human health, but also on economy due to its high incidence resulting in high morbidity and mortality and high therapeutic cost[5].

In Brazil, there is also an increase in these rates[5], mainly in the North and Northeast regions[6]. Likewise, there was an increase in the mortality rate in the South of the country, mainly in the state of Rio Grande do Sul[7]. The disease is responsible for a large demand for hospitalizations, thus increasing the cost of treatment[6]. Santa Catarina does not differ from the national and international scene; the rates tend to increase, mainly due to the longevity of the state's population[8].

Early diagnosis and treatment stages are important for a favorable prognosis[2,3], therefore, prevention strategies and investment in public health are essential[2,5].

Therefore, the analysis of the behavior of breast cancer in Santa Catarina, in order to identify the epidemiological profile and establish projections, may help in providing subsidies for the

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planning of public health policies, prevention, implementation and elaboration of health promotion actions and early diagnosis or palliation of the disease, to be carried out by public and private entities.

Based on these assumptions, the objective of this research was to analyze the temporal trend of the breast cancer mortality rate in the state of Santa Catarina from 1996 to 2019.

METHODS

An epidemiological study with an ecological time series design was carried out. Cases of female deaths from breast cancer in individuals residing in Santa Catarina were included from the Mortality Information System database, made available by the Department of Informatics of the Unified Health System, according to age groups and macro-regions in the period of 1996 to 2019. All cases of deaths due to malignant neoplasm of the breast, CID 10–C50, of women residing in the state of Santa Catarina during the study period were included. Population data were obtained from the Brazilian Institute of Geography and Statistics through the 1991, 2000 and 2010 censuses and intercensal estimates for the other years.

Dependent variables were general mortality rates from breast cancer and specific ones according to age range (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80 years old or older) and health macro-regions (South, North and Northeast Plateau, Center-West and Serra Catarinense, Expanded West, Expanded Florianópolis, Foz do Rio Itajaí, and Alto Vale do Itajaí). The independent variable was the study period (1996 to 2019).

Data were tabulated in Windows Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) 18.0 program. For each year of the period studied, overall mortality rates from breast cancer and by age groups and macro-regions per 100,000 women were calculated. The rates were standardized according to the world population for the general rate of Santa Catarina. For the analysis of temporal trends, mortality rates calculated using the simple linear regression method were used. Using the dependent variables and the years, the models estimated by equation (1) were obtained:

$$Y=b0+b1X \quad (1)$$

Where
Y=rate;
b0=average rate for the period;
b1=mean annual increment; and
X=year.

For the behavior of increase, decrease or stability and the mean annual variation in the mortality rate, the positive or negative value and the statistical significance of the regression coefficient, β, were evaluated. It was considered increasing when β was positive and decreasing when β was negative. Values of $p<0.05$ were considered statistically significant.

The research project was submitted and approved by the Research Ethics Committee of Universidade do Sul de Santa Catarina, with CAAE number 51129621.9.0000.5369. The resources used were from the researchers themselves, without external funding. There are no conflicts of interest on the part of the researchers.

RESULTS

In the analyzed period, there were 9,637 female deaths in Santa Catarina due to malignant neoplasms of the breast. Of the total deaths that occurred in the period, 76 occurred between 20–29 years old (0.78%), 681 between 30–39 years old (7.00%), 1,782 between 40–49 years old (18.50%), 2,442 between 50–59 years old (25.33%), 2,069 between 60–69 years old (21.46%), 1,506 between 70–79 years old (15.62%), and 1,080 over 80 years old (11.20%).

An upward trend was observed in the standardized mortality rate, from 6.50/100,000 women in 1996 to 7.92/100,000 women in 2019, with an increase of 0.0506 in the rate per year ($p=0.007$) (Figure 1 and Table 1).

The highest mortality rates occurred in the age groups over 60 years. Significant upward trends were observed in the age groups of 30–39 years, 60–69 years, and over 80 years ($p=0.041$, $p=0.003$, and $p<0.001$, respectively). In the 30–39 years old range, mortality rate varied, between 1996 and 2019, from 0.29/100,000 women to 0.54/100,000 women — an increase of 0.006 in the rate per year. In the 60–69 age group, it increased from 1.26 to 1.78/100,000 women between 1996 and 2019, an increase of 0.017 per year. In the age group over 80 years old, it went from 1.05 to 1.67/100,000 women, increasing by 0.024 per year. The other age groups tended toward stable rates but did not show a significant trend ($p>0.05$) (Table 2).

All health macro-regions showed significant upward trends in crude breast cancer mortality rates in the state of Santa Catarina (Figure 2). The biggest increase occurred in the region of Foz do Rio Itajaí, with an increase of 0.524 per year in the period from 1996 to 2019, increasing from 4.15 to 22.27/100,000 women. The North and Northeast Plateau region increased by 0.493 per year in the period, from 7.30 to 18.83/100,000 women. The South region at the beginning of the period had a rate of 0.75/100,000 women, increasing to 17.86/100,000 women at the end of the period, an annual increase of 0.482. In Alto Vale do Itajaí, the mortality rate increased from 9.23/100,000 women in 1996 to 19.15/100,000 women in 2019, an increase of 0.388 per year. In the Center-West and Serra region, the annual increase was 0.384, going from 7.87/100,000 women to 13.21/100,000 women in the period. In Expanded Florianópolis, the mortality rate was 13.08/100,000 women to 21.85/100,000 women, an increase of 0.351 between 1996 and 2019. The Expanded West region was the one with the lowest annual increase — 0.029 per year, from 6.04/100,000 women in 1996 to 14.82/100,000 women in 2019 (Table 3).

In 1996, the lowest mortality rate was found in the Foz do Rio Itajaí region (4.15/100,000 women) and the highest in Expanded Florianópolis (13.08/100,000 women). In 2019, the lowest rate was found in the Center-West and Serra (13.21/100,000 women) and the highest mortality rate in Foz do Rio Itajaí (22.27/100,000 women).

DISCUSSION

This is a research that sought to analyze the temporal trend of the breast cancer mortality rate in the state of Santa Catarina from 1996 to 2019. The results showed an upward trend with an average annual increase of 0.05 in the rate (p=0.007).

According to the World Health Organization, countries in Asia and Latin America have shown an increasing trend in mortality from breast cancer in the last three decades[4].

A study by Silva et al.[9] showed an increase of 1% in annual mortality from breast cancer in Brazil between 2004-2017 (p<0.001). Couto et al.[10] also showed an increasing trend in breast cancer mortality in Brazil between 1990 and 2010. They also revealed a significant difference in regional mortality; mortality was higher in the South region and lower in the North.

A study carried out by Rodrigues et al.[11], in the period from 2000 to 2015, pointed to an increase in the coefficients of mortality from breast cancer in Brazil, with a standardized rate of 30.15/100,000 women. The South region had the highest rate (38.55/100,000 women) and the North had the lowest (23.22/100,000 women). Lôbo et al.[12] showed an increase in mortality from breast cancer in the state of Alagoas between 2001 and 2016; the rate went from 6.4/100,000 women to 11.1/100,000 women, an increase of 4.30% per year over the period studied.

Table 1. Breast cancer mortality rates (per 100,000 women) in Santa Catarina, from 1996 to 2019.

Year	Number of deaths	Crude mortality rate	Standardized mortality rate
1996	204	8.37	6.50
1997	239	9.64	7.74
1998	260	10.34	8.45
1999	244	9.57	7.98
2000	278	10.35	7.85
2001	264	9.66	7.44
2002	293	10.56	7.43
2003	296	10.52	7.81
2004	283	9.92	7.49
2005	324	11.00	8.47
2006	320	10.70	8.01
2007	344	11.31	7.12
2008	346	11.36	6.98
2009	400	12.99	7.81
2010	435	13.82	8.10
2011	470	14.77	8.89
2012	491	15.27	9.16
2013	518	15.53	8.02
2014	532	15.74	8.48
2015	567	16.55	8.81
2016	585	16.84	8.52
2017	617	17.53	9.11
2018	661	18.54	8.12
2019	666	18.45	7.92

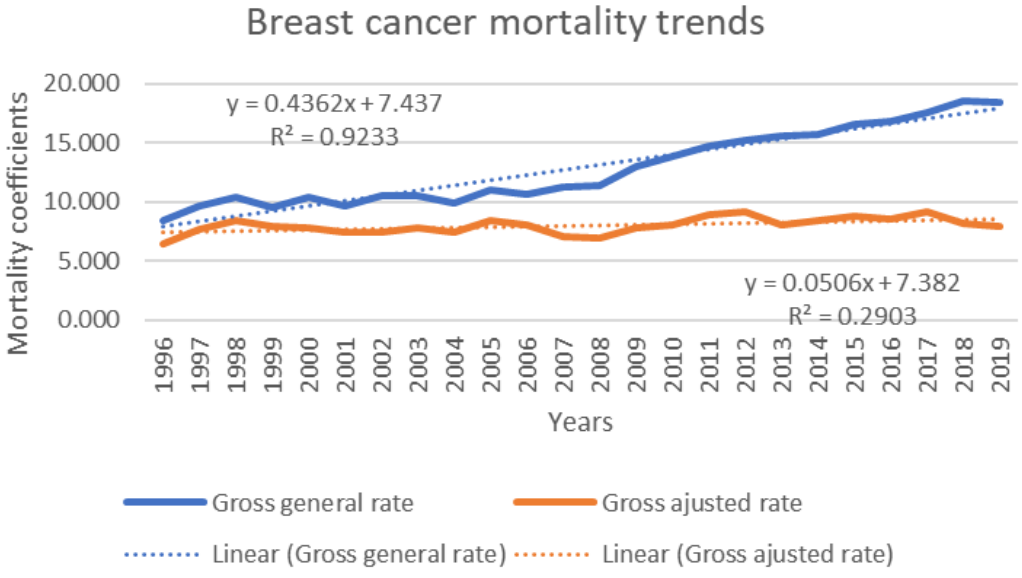

Figure 1. Trend in the crude and standardized mortality rate due to breast cancer (per 100,000 women) in Santa Catarina, from 1996 to 2019.

A study carried out by Silva et al.[13] in Santa Catarina also revealed an increase in the mortality trend; mortality rates increased from 3.78/100,000 women in 2000 to 8.38/100,000 women in 2017.

The present research brought data compatible with the literature when compared with national and regional studies, as it presents an increase in mortality. The state of Santa Catarina has the highest life expectancy in the country, so an increase in breast cancer numbers is already expected due to the simple aging of women in Santa Catarina[12,14]. A change in the demographic pyramid with a decrease in the fertility rate, postponement of the first pregnancy, and income growth contribute to the increase in the rates[4,10,15]. It is also worth considering the improvement in the recording of mortality data, in addition to population growth[16].

Diverging from this study, Siegel et al.[17] found a downward trend in mortality from the disease in the United States of America (USA) in the period from 2010 to 2019. This drop was associated with early diagnosis, mammographic screening, and treatment evolution. Wojtyla et al.[18] observed a decreasing trend in mortality across the European continent between 1980 and 2017.

The international literature reveals that European countries, as well as the USA, have shown a decrease in mortality rates for years. Epidemiological data differ from those found in this research, but corroborate the fact that the state of Santa Catarina, despite its development compared to other states, is part of a developing country.

This work revealed a stationary trend in mortality in each of the age groups 0–19, 20–29, 40–49, 50–59, and 70–79 years. A significant tendency toward an increase in the rate was observed in the age groups between 30–39 years, 60–69 years, and ≥80 years. The concentration of deaths occurred between 50–69 years (46.79%).

A study carried out by Basílio et al.[15] pointed to an increase in mortality from breast cancer in the South and Southeast regions, between 1980 and 2005, in the age groups of 60–69 years, 70–79 years, and ≥80 years, corroborating the findings of this study. Carvalho et al.[19] pointed to an increase in mortality from breast cancer in women over 60 years of age in the Northeast between 2010 and 2015. The research by Rodrigues et al.[11] showed an increase in mortality rates with advancing age between 2000 and 2015 in state capitals.

Lôbo et al.[12], in a study carried out in the state of Alagoas between 2001 and 2016, showed a stationary trend in mortality from breast cancer in women aged between 20 and 39 years and an increase in mortality in other age groups, highlighting the significant increase in 9.2% per year in women over 80 years of age.

Barros et al.[16] showed that between 2005 and 2015, in Ceará, the number of deaths from breast cancer increased considerably from the age of 40, with the highest mortality rates observed in the age groups of 50–59 years and 60-69 years.

In disagreement with the present study, Silva et al.[13] observed a decreasing trend in the mortality of women from Santa Catarina in the age groups of 20–39 years, 60–69 years, and 70–79 years in the period from 2000 to 2017.

The increase in mortality with aging was already expected due to the behavior of the disease[12] and to socioeconomic development[19]; however, with the greater longevity of women from

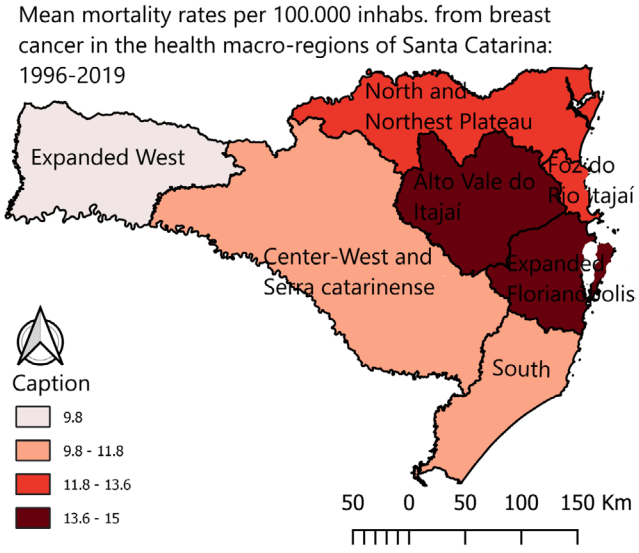

Figure 2. Mean mortality rates from breast cancer in the health macro-regions of Santa Catarina, from 1996 to 2019.

Table 2. Regression coefficients and statistical significance of the standardized breast cancer mortality trend, according to age range, in Santa Catarina, from 1996 to 2019.

Age range	Regression coefficient	95%CI	p-value	R^2	Correlation coefficient
20–29 years	0.002	-0.001; 0.003	0.055	0.159	0.39
30–39 years	0.006	0.000; 0.011	0.041	0.176	0.42
40–49 years	0.000	-0.009; 0.009	0.995	0.000	0.00
50–59 years	0.001	-0.011; 0.013	0.884	0.001	0.00
60–69 years	0.017	0.007; 0.028	0.003	0.341	0.58
70–79 years	-0.001	-0.025; 0.022	0.906	0.000	0.00
≥80 years	0.024	0.012; 0.036	<0.001	0.432	0.66

Table 3. Regression coefficients and statistical significance of crude mortality trends from breast cancer, according to health macro-regions in Santa Catarina, from 1996 to 2019.

Health macro-region	Regression coefficient	95%CI	p-value	R^2	Correlation coefficient
Expanded West	0.029	0.129; 0.462	0.001	0.381	0.62
Center-West and Serra	0.384	0.267; 0.501	<0.001	0.679	0.82
Alto Vale do Itajaí	0.388	0.280; 0.490	<0.001	0.738	0.86
Foz do Rio Itajaí	0.524	0.360; 0.680	<0.001	0.670	0.82
Expanded Florianópolis	0.351	0.200; 0.490	<0.001	0.528	0.73
South	0.482	0.380; 0.570	<0.001	0.828	0.91
North and Northeast Plateau	0.493	0.380; 0.590	<0.001	0.814	0.90

Santa Catarina, a higher concentration of deaths was observed from the age of 50, and 46,79% of deaths in the studied period occurred between 50 and 69 years. 26.28% of deaths occurred between 20–49 years of age, and 26.82% over 70 years of age. These data draw attention to the fact that 53.10% of the deaths shown in this study occurred outside the screening age expected by the Ministry of Health[20].

With regard to breast cancer mortality rates in the health macro-regions of Santa Catarina, all seven macro-regions showed an increasing trend in the mortality rate during the study period. The highest crude mortality rates, at the end of the period, were observed in the coastal regions: Foz do Rio Itajaí (22.27/100,000 women), Expanded Florianópolis (21.85/100,000 women), and Alto Vale do Itajaí (19.15/100,000 women). The highest annual increases during the study period were observed in the regions of Foz do Rio Itajaí (0.524), North and Northeast Plateau (0.493), and South (0.482).

In this context, Silva et al.[9] observed a greater increase in mortality from breast cancer in the capitals of the South region than in other regions between 1980 and 2017. Couto et al.[10], in turn, showed higher mortality rates from breast cancer in Brazilian municipalities with a population greater than 500,000 inhabitants or smaller than 5,000 inhabitants, associating the fact with less access to health in small municipalities and displacement to large urban centers for medical care.

The results of this study should be interpreted with caution. All research carried out using secondary data is subject to bias arising from possible delays and errors in recording deaths and population estimates, despite the fact that the research was carried out based on available official data. Another important limitation lies in the fact that the standardization of mortality rates by health macro-region was not possible due to the difficulty in obtaining population data by region. Thus, the upward trends in gross rates in the macro-regions can, in part, be attributed to demographic dynamics with an aging population in the period studied.

The upward trend in mortality from breast cancer in the state suggests the need to review public policies for coping with the disease. Considering the severity of the disease, the impact generated for the woman and her family, and the social and economic cost, it is necessary to review and strengthen public policies for prevention and early diagnosis — behavioral measures to control exposure to risk factors such as smoking, alcoholism, and obesity, for example. In addition, it is important to improve access to mammographic screening and to carry out studies on the suitability of expanding the screening age, since its positive predictive value depends on the prevalence of the disease and a significant portion of deaths occur outside the current screening range recommended by the Ministry of Health. All of these are essential measures for controlling breast cancer.

CONCLUSIONS

The overall mortality rate from breast cancer in Santa Catarina showed a significant upward trend. There was also a significant increase in the age groups 30–39 years, 60–69 years, and 80 years or more and in the seven health macro-regions of the state.

Based on the results presented, it is possible to determine the importance of breast cancer in the state of Santa Catarina and the damage caused to women in this region. The results contribute to the knowledge of the general panorama of female mortality and help to provide knowledge for the elaboration of public policies, whether for prevention or diagnosis.

It is extremely important to monitor the disease, as it causes damage to women's health in the state of Santa Catarina. Despite the high numbers of mortality, with the improvement of indicators and investments in the health area, it is expected that mortality will be controlled and that, in the future, the rates will begin to decrease.

AUTHORS' CONTRIBUTION

GAOA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. ESAT: Formal analysis, Methodology, Supervision, Writing – review & editing. GOCP: Formal analysis, Software.

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REVIEW ARTICLE
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Lifestyle and breast cancer: review article

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ABSTRACT

The aim of this study was to improve our knowledge about carcinogenesis and lifestyle, given their impact on the occurrence of breast cancer, emphasizing the importance of lifestyle changes as a preventive factor in the development of the disease. We conducted a bibliographic review with the analysis of 31 articles in English and Portuguese. As a result, the articles selected for study showed that factors such as diet, alcohol intake, smoking, obesity, physical activity, occupational exposure, hormonal factors (hormone therapy, contraceptives) and reproductive factors (menarche, menopause, nulliparity, pregnancy, breastfeeding) have a protective or risk effect on breast cancer. We conclude that eating healthy, with fruits, vegetables and greens, practicing moderate physical activity, avoiding alcoholic beverages and breastfeeding exclusively reduce the risk of developing breast cancer by 28%. Therefore, it is necessary to make the public aware of these modifiable risk factors.

KEYWORDS: breast cancer; lifestyle; carcinogenesis.

INTRODUCTION

Currently, breast cancer (BC) is the most prevalent cancer in the world, followed by lung and colorectal cancer, while BC mortality ranks fifth among cancer-related deaths, representing a major global public health problem. In Brazil, it is the most frequent neoplasm in all regions, with 66,280 new cases and an adjusted incidence rate of 43.74 cases/100,000 women in 2021[1].

The diagnosis of BC occurs mainly in women over 40 years old, and it is one of the most feared types of cancer for them, because of its high frequency and its psychological effects, such as changes in sexuality and body image, low self-esteem, fear of relapse, anxiety and depression.

Lifestyle, in turn, is the result of choices and priorities listed by each person. This can be the result of habits learned from the family culture, the environment or the place where one lives, but it can also be learned and modified at any time in life. Knowing the life habits that are modifiable risk factors for BC is the first step towards a healthier life, with a reduction in the possibility of the disease occurring. The physician's role is to motivate their patients regarding these choices and also to encourage discipline to maintain acquired good habits.

The causes of BC are multifactorial with interaction between genetic and environmental factors. According to data from the Brazilian National Cancer Institute (INCA), genetic factors account for 10% to 20% and other factors account for 80% to 90% of cases, including random cases (with no related cause). It is therefore understood that factors related to lifestyle (diet, physical activity, sleep, stress management) and also environmental factors (exposure to pesticides and other xenoestrogens, for example) play a significant role in the pathogenesis of BC. Considering the percentage related to non-genetic factors in BC, it is important to know these factors to try to minimize the risks. Nowadays, the population is increasingly exposed to environmental risk factors such as inadequate diet, sedentary lifestyle, excessive alcohol consumption, smoking, alteration of the circadian cycle and high levels of stress. Several studies claim that these are risk factors for BC, and it is necessary to know these factors to better guide the public.

In this study, a review of the literature on BC was carried out, with emphasis on carcinogenesis and lifestyle, including diet, alcohol intake, smoking, obesity, physical activity, occupational exposure, hormonal factors (hormone therapy, contraceptives), reproductive factors (menarche, menopause, nulliparity, pregnancy, breastfeeding). Our objective was to expand our knowledge of the subject and raise awareness about preventive care.

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METHODS

A bibliographic search was conducted in the indexed databases MEDLINE, Embase, JAMA and NEJM, with articles published between 2003 and 2022. The keywords used were "breast cancer", "lifestyle" and "carcinogenesis", and 31 articles in English and Portuguese were analyzed.

RESULTS

Mammary carcinogenesis

BC begins with a genetic mutation in a single cell in the ductal-tubular unit of the breast. This embryonic or somatic stem cell develops an altered cell clone that grows and proliferates according to the phenotypic characteristics it acquires from exposure to new damage to DNA: genome instability and loss of integrity of the repair mechanisms of these modifications[2-4].

There is expansion of mutant clones, during tumorigenesis, along with secretion of growth factors from cell contact. In a healthy state, cells have the ability to trigger the apoptotic chain when there is DNA damage that cannot be repaired, in such a way that in neoplastic genesis, an important step is the breakdown of this homeostatic mechanism, in which tumor cells obtain the capacity of apoptotic inhibition in situations where, physiologically, the ideal would be to initiate the process of programmed cell death[5].

Chronic inflammation is a process resulting from unwholesome habits — stress, medication use, sedentary lifestyle, poor diet. This process leads to an increase in oxidative stress, without adequate repair of cellular changes, and also to cell damage, in addition to changes in the intestinal microbiome. All of this together makes a perfect scenario for the onset of chronic diseases such as cardiovascular disease, diabetes, obesity and also cancer. In all these cases, there is an increase in the formation of mutated cells and a decrease in the body's repair capacity[6].

The presence of an inflammatory process, which would originally be beneficial for the tissue to repair it, may also facilitate tumor progression, as inflammation may result in the appearance of new blood vessels, which can nourish the neoplastic cells, and the release of growth factors, which can promote proliferative cell growth. Finally, there are "immortal" mutant cells, with the capacity to proliferate, being able to invade the lamina propria, lymphatic tissues and bloodstream.

Epigenetics

Epigenetics is an emerging area of research that studies the alteration of gene expression, either by silencing or activating genes, without changing the structure of DNA.

The set of genes that make up DNA is called the genome. The modifications that regulate the activity (expression) of these genes constitute the epigenome. The activation or silencing of some genes determines, in turn, the final product of that cell. These gene modifications can be passed on to "daughter cells" in the process of cell division, and they can also be passed from generation to generation (the child inherits these maternal and paternal DNA modifications).

Lifestyle plays an important role in epigenetics, since it is directly related to this gene activation/silence process. Diet, physical activity, sleep and stress can modify gene expression and thus protect neoplasms or stimulate their appearance[7,8].

Lifestyle

Diet

Studies show that different food components can impact cellular health through different processes that relate to the onset of BC.

A diet high in refined carbohydrates and trans fats has been linked to inflammatory diseases, while healthy eating patterns are associated with lower levels of inflammation[9].

Oxidative stress is a state of imbalance between antioxidants and oxidative factors, leading to the formation of free radicals. Under oxidative conditions, pro-oxidants are dominant over antioxidants, potentially leading to direct damage to lipids, proteins or DNA. Both inflammation and oxidative stress play an important role in increasing the risk of cancer[9-12].

Regarding the use of artificial sweeteners (used in many foods and beverages), a recent cohort study of 102,865 participants in France investigated the associations between consumption of artificial sweeteners and cancer risk. Among them, the most consumed are aspartame, acesulfame-K and sucralose. This study showed that the first two (aspartame and acesulfame-K) have a high association with BC (n=979 cases, HR=1.22 [95%CI 1.01 to 1.48], p=0.036, for aspartame). Great care must be taken when consuming industrialized and ultra-processed products. The consumption of these types of sweeteners should be discouraged for all people[13].

Physical activity

IA patient's level of physical activity appears to be another significant factor in the pathogenesis of BC, as it affects several regulatory systems in the body, including inflammatory mediators, sex hormones, metabolic hormones, adipokines and gut microbiota. Physical activity is responsible for regulating other mechanisms that also appear to be important in carcinogenesis such as telomere elongation, DNA hypomethylation, immune function and reduction of oxidative stress[14,15].

Women with high estrogen and androgen levels are at greater risk of developing BC. A meta-analysis investigated the impact of physical activity on sex steroids, showing that this practice decreases the risk of developing BC, since it decreases the level of sex hormones and reduces obesity, reducing the peripheral conversion of androgens into estrogens by aromatase, an enzyme

present in the subcutaneous tissue. As to the effects of physical activity on BC, it is observed that the beneficial effect is more evident in the postmenopausal period[16].

Pizot et al. conducted a meta-analysis of 38 prospective studies with 116,304 cases of BC, comparing the light or high level of physical activity, and they found that the risk reductions were not influenced by the type of physical activity, fat or menopausal status[17]. Risk reductions increased with increasing amount of exercise. Results indicate that a physically inactive woman (less than 150 minutes per week of vigorous physical activity) would increase her lifetime risk for BC by 9%[18].

An article published in JAMA in 2022 analyzed a population of adults and tried to establish the relationship between the level of physical activity practiced by them and the risk of death, with about 100 thousand participants. A reduction in mortality was observed for all participants who engaged in physical activities compared to sedentary individuals, mainly activities practiced with rackets and running were the ones that had the greatest impact. Even low-intensity physical activities were associated with reduced mortality in older patients studied (71 years old) in this study, showing that physical activity can be an ally in reducing the risk of cancer mortality[19].

Studies on physical activity and BC are also important because they address an important and sometimes neglected risk factor, sarcopenia. Sarcopenia is muscle wasting, associated with loss of function, which occurs progressively with aging. Some authors associate the loss of muscle mass with a worsening of the clinical outcome during and after cancer treatment, in BC as well. Care with nutritional support and encouragement of resistive exercise are essential in all stages of treatment to prevent or minimize this muscle loss[20].

Body mass index

Obesity is an isolated risk factor for several cancers; it is related to altered hormone levels, insulin and elevated adipokines, factors related to breast carcinogenesis.

There are several criteria for defining obesity, but body mass index (BMI) is a practical and accessible measurement. An individual is considered obese if BMI is above 30. Between 28–30 is classified as overweight, and below 25 is considered normal. Waist circumference measurement is also a useful and easy measurement. Values are normal up to 88 cm for women. Measurements above this value are associated with obesity and higher cardiovascular, cancer and mortality risk.

Both in cases of obesity and overweight, there is an increase in adipose tissue and, consequently, an increase in aromatase activity. Ultimately, the peripheral conversion of androgens to estrogens increases circulating levels of this hormone as well. Elevated estrogen levels are associated with BC by increasing bioavailable estrogen and, consequently, stimulating angiogenesis and cell proliferation. Obesity is related to a higher prevalence of insulin resistance, in which there is an increase in serum insulin and also in insulin-related growth factor (IGF-1). These two factors, as well as estrogen, stimulate cell proliferation and also angiogenesis. Finally, obesity alters the production of adipokines and inflammatory cytokines (adiponectins, IL-6, TNFα, leptin). This alteration, in addition to inducing cell proliferation, also acts on cell survival mechanisms, which stimulates the growth of tumor clones[21]. BC risk is related to BMI but depends on menopausal status.

Postmenopausal woman

In a meta-analysis by Keum et al., a total of 50 studies were included. For every 5-kg increase in adult weight gain, the relative risk was 1.11 (95%CI 1.08 to 1.13) for postmenopausal BC among users of hormone replacement therapy (HRT)[22].

Associations between adult BMI and postmenopausal BC have been observed in several studies, particularly for estrogen receptor-positive tumors. Waist circumference and body weight gain in adulthood were also associated with postmenopausal BC risk.

Premenopausal woman

The 2018 Continuous Update Project Expert Report (CUP) identified 37 dose-response meta-analyses of premenopausal BC (n=13,371 cases) and showed a statistically significant 7% decrease in risk per 5 kg/m^2 in all incidence and mortality studies.

In the Iowa Women's Health Study, which evaluated 34,000 women, weight loss of at least 5% before or after menopause reduced the risk of cancer by 25% to 40% compared with women who continued to gain weight. On the other hand, Eliassen et al. reported a 50% risk reduction in women with a 10% weight loss compared to women with stable weight in the Nurse's Health Study of 37,000 women[23].

Alcohol and smoking

Epidemiological studies have shown an association of alcohol and smoking with cancer. Specifically for BC, research has shown that alcohol use is a risk factor for developing this disease[24].

Several studies suggest that there is an increased risk for BC with the use of alcohol, and there is no safe amount for consumption. A meta-analysis of observational studies reported that postmenopausal women who drank alcohol had a 22% greater relative risk of BC (95%CI 9% to 37%) than those who did not consume alcohol. The analysis estimated that every additional 10 g of ethanol consumed per day (approximately one drink) was associated with a 10% (95%CI 5% to 15%) increased relative risk of BC[25-27].

In a multicenter, case-control study, with n=1578, it was concluded that the greater the cumulative consumption of alcohol throughout life, the greater the risk of BC, especially in postmenopausal women. Exposure to these modifiable risk factors should be reduced if necessary.

Sleep

Sleep is an important moment of anyone's day, in which several cellular mechanisms are activated or inhibited, regulating gene expression and DNA itself. These mechanisms, in turn, are stimulated, or not, by hormones secreted from triggers aligned with the circadian cycle.

The circadian cycle is, as the name implies, the cycle of a day (from the Latin "*circa diem*") and is regulated by light intensity. Our body perceives light and its absence through photoreceptors in the retina. From this perception, several hormones are secreted in sequence.

An article published in 2016 reviews the mechanisms related to breast biology and the consequences caused by changing the circadian cycle. The authors describe alterations in the circadian cycle resulting from aging, genetic alterations and also work issues (night workers or workers who work rotating shifts). In addition to these issues, the modern world has several situations that contribute to changes in the circadian cycle — greater exposure to screens and home office work, in addition to the so-called social jet lag (when people distort the circadian cycle every weekend for social commitments). Regardless of the cause of the alteration of this sleep rhythm, its consequences are perceived by alteration of the cell cycle and inhibition of apoptosis, as well as metabolic alterations and melatonin secretion.

Occupational exposure

According to a study published in 1981, *The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today*, occupational exposures account for 4% of cancers.

In Brazil, the publication by INCA on guidelines for the surveillance of work-related cancer presents a list of specific agents for each type of cancer. The agents found with regard to BC were pesticides, benzene, low frequency electromagnetic fields, magnetic fields, volatile organic compounds, hormones and dioxins. And the related occupations were: hairdresser, radio and telephone operator, nurse and nursing assistant, flight attendant and night worker[28].

Literature reviews confirm the risk of night work, especially for health professionals, on the basis of the work process of nurses[29] and flight attendants[30]. The explanation mechanism has been called *light-at-night* (LAN), which associates exposure to artificial light with reduced melatonin secretion, which regulates the secretion of ovarian hormones, including estradiol.

The mechanisms associated with the increase in BC in night workers are related to a decrease in cell apoptosis, changes in cell cycle regulation mechanisms, changes in metabolism inducing proliferation, changes in melatonin levels, favoring tumor growth and also altering epithelial-mesenchymal transition and favoring metastasis processes.

Metals such as iron, nickel, chromium, zinc, cadmium, mercury and lead have been found in higher concentrations in BC biopsies than in breast biopsies in women without cancer. These metals function as endocrine disruptors[31].

These data alert us to prioritize prevention measures, such as removing the carcinogenic substance, avoiding exposure to these agents and eliminating their use.

Hormonal factors

Menarche

Early menarche alone is related to a higher incidence of BC, and the earlier this event, the greater the risk. This is likely due to having menses longer, with a longer period of estrogen exposure. In addition, early menopause is associated with other risk factors for BC, such as parity, earlier age at first birth, height and BMI, as well as increased adiposity throughout life. The opposite findings hold for women who had a later menarche. When confounding factors are accounted for, high BMI lowers the risk difference between patients diagnosed with postmenopausal BC. Early menopause seems to play a more important role as a risk factor for patients with lobular BC compared to patients with ductal BC[32]. Later menarche is associated with reduced risk of triple-negative BC and likely reduces the risk of luminal A BC[33]. Early menarche has a greater impact on the risk of developing postmenopausal BC than does late menopause[32]. This relationship is also found in patients carrying the BRCA1 mutation but not in patients with the BRCA2 mutation (Pan, 2013).

Menopause

Later menopause is also a known risk factor for BC due to longer exposure to estrogen. It is known that the risk of BC shows great variability in the climacteric period, given the hormonal influence: there is a greater risk in premenopausal women than in postmenopausal women, with an intermediate risk in perimenopausal women. Adiposity attenuates the difference between groups: premenopausal women with BMI <25 have a higher risk of BC than patients with BMI ≥25, with the opposite observed in postmenopausal women. This happens because postmenopausal women with greater adiposity have higher levels of circulating estrogens due to the peripheral conversion of androgens into estrone. Estrogen receptor-positive tumors increase in incidence with age in pre- and postmenopausal women, but there is a reduction in estrogen receptor-positive tumors after menopause, with the same occurring for lobular tumors. When analyzing postmenopausal women, the later the age at which menopause occurred, the greater the risk was for developing BC, with no difference between induced menopause (oophorectomy or hormonal blockade) and natural menopause, this relationship being more important in estrogen receptor-positive tumors and lobular tumors. The differences found were attenuated by the BMI of the patients, in which a high BMI provided a greater risk of neoplasia in the postmenopausal period, and the opposite occurring in the premenopausal period[32].

Use of hormonal therapy

HRT consists in estrogen supplementation, with or without progestogens, in postmenopausal patients with symptoms of hypoestrogenism. It is known that endogenous or exogenous estrogen exposure confers an increased risk of developing BC. However, when it comes to HRT, estrogen replacement combined with medroxyprogesterone acetate has an increased risk of BC. The WHI study showed that, in patients with a previous hysterectomy, estrogen alone implied a reduction in the risk of developing BC. Recent observational studies point to an increased risk with therapy alone, as opposed to the WHI trial[34]. The risk seems to be related to the duration of therapy, with women who received estrogen + progesterone for less than three years did not seem to have a significantly increased risk[34]. The most closely related subtypes are estrogen receptor-positive and lobular BC[32]. After stopping HRT, the risk of developing BC drops every year. The tumors most related to the use of HRT are luminal A, and some studies point to a relationship with luminal B tumor[33].

Contraceptives

Women exposed to combined oral contraceptives (OCs) for up to 10 years have a small increase in the risk of developing BC after discontinuing the OCs. Furthermore, BC related to OC use has a lower risk of metastasis than BC in patients who have never used OCs. Duration of use appears to increase the risk of developing BC. Patients who discontinued use more than 10 years ago do not appear to be at increased risk[35,36].

The effect of OCs on the development of BC is related to duration, dose, pattern of use, type of OCs and age at first use. Two main theories are proposed to explain the increased risk of developing BC in this population: the first would be due to the use of estrogen in OCs, which is related to the development of BC; and the second is related to the fact that contraception reduces the number of pregnancies per woman, and, as a consequence, these women spend long periods of their life exposed to estrogen, since, during pregnancy, the levels of this hormone are reduced. However, patients who engage in physical activity while using OCs have reduced estrogen levels and, as a consequence, lower risk of developing BC[37]. Exposure to OCs is related to the development of triple-negative tumors, and some studies have shown a reduction in the risk of luminal A BC[33].

Breastfeeding

Breastfeeding acts as a protective factor in BC both by local breast factors (breastfeeding supports the differentiation of breast cells after pregnancy, and differentiated cells are less likely to become cancerous; the processes involved during its interruption such as apoptosis may decrease the risk of cancer by removing cells with early DNA damage from breast tissue)[38] and by reducing estrogen levels and other associated factors. During breastfeeding, prolactin exerts an inhibitory effect on the hypothalamic-pituitary-ovarian axis, which decreases circulating levels of progesterone and estrogen, thereby reducing the risk of developing hormone-dependent BC. Therefore, patients who do not breastfeed are at increased risk of developing BC because of the absence of this mechanism[37]. Women who exclusively breastfeed have a relative risk of developing BC that is 28% lower than in women who have had children and have not breastfed. In addition, without considering the breastfeeding regimen, duration longer than one year increases this protective factor[39]. The duration of breastfeeding appears to reduce the risk of luminal A, luminal B and triple-negative cancers[33]. Exclusive breastfeeding has a more important hormonal effect, since it demands more energy for milk production, greater mobilization of fat and glucose stores by the breast, decreasing insulin levels. Furthermore, exclusive breastfeeding leads to longer periods of postpartum amenorrhea by reducing estrogen exposure. Finally, women who exclusively breastfeed generally do so for longer periods, further reducing their risk of developing BC[39].

Reproductive characteristics

Nulliparity is an important risk factor in the development of BC and may carry up to a 30% risk of developing BC. This relationship is directly linked to the fact that these women do not breastfeed and, therefore, have a long exposure to estrogen. Multiparity seems to reduce the risk of luminal A BC, but a few studies relate multiparity to triple-negative BC[33].

Parity does not influence the risk of developing BC in patients with a BRCA1 or BRCA2 mutation. Later age at first birth is associated with a lower risk of BC in BRCA1 mutation carriers, but does not influence BRCA2 carriers[40].

Age at first delivery is related to the risk of developing luminal AC A; the younger the age, the lower the risk[33]. However, it does not seem to interfere with the risk of developing BC in patients with BRCA1 and BRCA2 mutations[40].

The differences found between patients with BRCA1 and BRCA2 mutations suggest different hormonal responses in BC subtypes. This can be reinforced by the fact that only 10%–24% of BRCA1 mutation-related BCs are estrogen receptor negative, in contrast to 65%–79% of BRCA2[40].

It is plausible to presume that hormone exposure is related to the risk of developing estrogen receptor-positive BC[40].

DISCUSSION

The relationship between the incidence of BC and lifestyle has been increasingly discussed by professionals who treat this disease. The modifiable risk factors that increase the incidence of BC should be known by every physician who deals with women's health, and guidance about these factors should be given at every consultation. Women at high risk for developing BC should

be especially advised about lifestyle changes that can modulate genetic expression inherited from their ancestors.

This article brings information about lifestyle points that should be discussed with women, offering the doctor data that may be useful at the time of this conversation. It is up to the doctor to know each of these factors and know how to provide guidance in relation to carcinogenesis, diet, alcohol and tobacco use, physical activity, sleep and also the use of hormonal therapies in various stages of life. Combating obesity is a key point in this scenario of reducing modifiable risk factors, since this is an important risk factor not only for the outcome of BC but for other chronic diseases that impact women's morbidity and mortality.

CONCLUSIONS

Understanding the carcinogenesis of BC and knowledge of its modifiable and non-modifiable risk factors are of utmost importance for the monitoring and counseling of patients in the prevention of BC.

Today, the main modifiable risk factors for BC are alcohol consumption (10 g/day), both premenopausal and postmenopausal, and obesity, especially in postmenopausal women. The use of contraceptives (period of 10 years) shows a small increase in risk, as does the use of hormone replacement therapy with estrogen and progesterone. There is a need to weigh risks and benefits for the use of these therapies individually.

Reproductive factors such as breastfeeding, adoption of healthy habits with the consumption of a varied diet with fruits and vegetables, practice of physical activity and maintenance of a low BMI minimize the risk of BC in premenopause and postmenopause. Furthermore, these changes may lower risk in populations at increased risk, such as patients with early menarche and late menopause.

AUTHORS' CONTRIBUTION

KPCL: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. VFWM: Data curation, Investigation, Methodology, Project administration, resources, Software, Writing – original draft. TPM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. RCSF: Formal analysis, Validation, Visualization, Writing – original draft. FMOC: Conceptualization, Data curation, Methodology, Software. MFSVG: Conceptualization, Data curation, Methodology, Software. JTA: Conceptualization, Formal analysis, Project administration, Supervision, Validation.

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ORIGINAL ARTICLE
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Can TILs be associated with prognostic factors and survival rates in breast cancer? A retrospective analysis

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ABSTRACT

Introduction: The relationship between the tumor inflammatory infiltrate, also known as tumor-infiltrating lymphocytes (TILs), and invasive breast carcinomas has been extensively studied in recent years to verify its association with prognosis and response to treatment. The goal of this study was to associate the presence of TILs with patient's survival time. **Methods:** We studied prognostic clinicopathological characteristics already established in the literature and their impact on overall five-year survival time of patients with invasive breast cancer treated at *Hospital Santa Casa* in Belo Horizonte, Minas Gerais, Brazil, in 2011 (n=290). This was an observational and retrospective study. **Results:** The presence of TILs was associated with tumors of no special type (p=0.018) and with younger age of the patients (p=0.042). Smaller tumor size (HR: 19.24; 95%CI 4.30–86.15; p<0.001), absence of metastasis to the axillary lymph nodes (HR: 2.80; 95%CI 1.02–7.70; p=0.002), positivity for progesterone receptor (HR: 0.39; 95%CI 0.17–0.87; p=0.022), and presence of TILs (HR: 0.23; 95%CI 0.08–0.65; p=0.005) were associated with longer survival times. **Conclusions:** This study suggests that the presence of TILs, along with other clinicopathological characteristics, is a prognostic factor in breast cancer.

KEYWORDS: survival analysis; breast cancer; immunohistochemistry; tumor-infiltrating lymphocytes; tumor biomarkers; prognostic factors.

INTRODUCTION

Breast cancer comprises a diverse group of lesions that differ in their microscopic presentation and biological behavior. Malignant breast tumors respond differently to cancer therapy[1,2].

Breast cancer is the most common malignancy among women and the leading cause of cancer-related deaths worldwide. In 2018, more than two million new cases were diagnosed, with more than six hundred thousand deaths[3]. Breast cancer surpasses lung cancer as the leading cause of cancer throughout the world in 2020, with an estimate of 2.3 million new cases, representing 11.7% of all cancer cases[3,4]. For the year 2023, 704,000 new cases of cancer were estimated in Brazil, with female breast cancer being the one that most affects women, corresponding to 30.1%, with an estimate of 73,610 new cases for 2023[5].

Ample evidence suggests that host antitumor immunity plays an important role in combating tumor cells, with recognition of tumor antigens and their immunogenicity leading to a subsequent adequate response in three phases: elimination, equilibrium, and escape[6,7]. Thus, much emphasis in clinical research has been placed on targeted therapies, such as the use of antibodies and other factors that stimulate the immune system[8]. Tumor inflammatory infiltrating is a potential mechanism for identifying patients who will benefit from immunotherapy or checkpoint inhibition[9].

The clinicopathological characteristics of tumors, such as intrinsic tumor biology, microenvironment, and stage of the disease at the time of diagnosis, contribute to the evaluation of the risk of disease relapse, and can be used to identify patients

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for whom adjuvant therapy is unnecessary[10]. Immunotherapy and specific targeted therapies have been employed with good results for certain tumor types[8]. The presence of pre-existing intra-and peritumoral lymphocytic infiltrates seems to have a positive impact on the patient's response to treatments and the prognosis of these diseases. The association between the presence of tumor-infiltrating lymphocytes (TILs) and survival rates has been widely studied in addition to that between TILs and treatment response[11]. The number of present TILs varies according to the breast cancer tumor subtype. The levels of lymphocyte subpopulations can be identified as additional strategies in patients with a low to moderate presence of TILs[12,13]. Patients with triple-negative tumors (e.g., negative for estrogen (ER) and progesterone receptors (PR) and without overexpress HER2 membrane protein), and who presented elevated levels of CD8+ and CD4+ T lymphocytes, had a greater response to systemic treatment and longer survival times. Recent studies have revealed that TILs are independent prognostic factors for triple-negative invasive breast cancer[10], and that intratumor heterogeneity is associated with less immune cell infiltration, less activation of the immune response, and worse survival rates in breast cancer[14].

The aim of this study was to evaluate the association between clinicopathological characteristics and the level of tumor-infiltrating lymphocytes (TILs) with the overall survival rate over five years of follow-up in patients diagnosed with invasive breast cancer and treated at *Hospital Santa Casa* in Belo Horizonte, a public referral hospital for the treatment of this disease in the State of Minas Gerais, Brazil, in 2011.

METHODS

Ethical procedures

The study was approved by the Ethics Committee of the Teaching and Research Institute of Santa Casa in Belo Horizonte on October 2, 2017 under number 1.958.532, and was conducted according to the Resolution of the Ministry of Health No. 466/12. Data were obtained from the records of *Hospital Santa Casa* in Belo Horizonte, and the patients were treated according to the institution's protocols. The privacy and confidentiality of the information were protected. There are no conflicts of interest to the researchers in charge of the study.

Study design and location

This retrospective and observational study was conducted at *Hospital Santa Casa* in Belo Horizonte, a public hospital of the Brazilian Unified Health System (SUS).

Population and eligibility criteria

The study population comprised patients diagnosed with invasive breast cancer in 2011, whose anatomopathological analysis was carried out in the Laboratory of Anatomical Pathology at *Hospital Santa Casa* in Belo Horizonte, and who were treated at this hospital as well.

Exclusion criteria

Patients with incomplete or missing information or absence of pathological results, and patients who underwent biopsy at Santa Casa and were treated at another hospital or who abandoned treatment were excluded (n=46, 15.9%). For the survival analysis, patients with zero follow-up time recorded or those with missing data were also excluded (n=68, 23.4%).

Variables

A breast pathologist (CBN) reviewed the anatomopathological diagnosis and immunohistochemical profile and evaluated the presence of TILs. The variables included were patient age, histological type, histological grade, estrogen (ER), progesterone (PR) receptor and HER2 protein status, T (tumor size), N (lymph nodes involved), M (distant metastases), sex (female or male), tumor inflammatory infiltrate (absent or present), and survival at the five-year follow-up visit. Estrogen and progesterone receptor status and HER2 protein expression were evaluated according to ASCO/CAP international recommendations[15,16]. Clinical staging of these patients followed the recommendations of the American Joint Committee on Cancer categories[17]. Tumors were classified and graded according to the WHO classification for breast tumors, 5th edition, published in 2019[18]. The protocols established by the breast surgery and clinical oncology services of *Hospital Santa Casa* in Belo Horizonte were followed. The standard operating procedure used to perform the immunohistochemical reaction (polymer method) followed the recommendations of the ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists)[15,16]. TILs were evaluated through the microscopic analysis of the slides stained with hematoxylin and eosin, based on the recommendations of the College of American Pathologists and International Immuno-Oncology Biomarker Working Group guidelines for TILs assessment in invasive breast carcinoma[19]. We searched for mononuclear cells (mainly lymphocytes) within the stroma between the carcinoma cells (stromal TILs), and classified them as absent or present. Immune infiltrates outside the tumor borders, for example, in adjacent normal tissue or areas of DCIS, were not included. In addition, TILs in areas with crush artifacts, necrosis, and/or extensive central regressive hyalinization were not evaluated. The same evaluation method was used for all histological tumor types. Patient data were collected to generate the survival curves. Table 1 illustrates the methods used to assess HER2, ER, and PR statuses.

Data analysis

The student's t-test was used to compare differences in means for age, and categorical variables were compared using Fisher's

Table 1. Clinicopathological characteristics of patients with invasive breast cancer diagnosed and treated at *Hospital Santa Casa* in Belo Horizonte (MG), Brazil, in 2011 (n=244).

Variable		n	(%)
Gender			
Female		241	98.7
Male		3	1.3
Age in years – mean (SD)	58.4 (14.0)	244	100
Histological types – invasive tumors			
Invasive carcinoma of no special type (ductal NOS)		218	89.3
Invasive lobular carcinoma		14	5.7
Other special types		12	4.9
Histological grade			
I		16	6.5
II		139	57.0
III		89	36.5
Tumor size (according to pathological staging)			
T1 (up to 2 cm)		103	42.2
T2 (>2 cm and up to 5 cm)		118	48.4
T3 (>5 cm)		15	6.1
T4 (any size, extension to chest wall or skin)		5	2.1
No information		3	1.2
Lymph nodes (according to pathological staging)			
0 (no positive lymph nodes)		120	49.2
1 (up to 3 positive lymph nodes)		85	34.8
2 (4–9 positive lymph nodes)		28	11.5
3 (10 or more positive lymph nodes)		7	2.9
No information		4	1.6
Estrogen receptor (ER)			
Negative		53	21.7
Positive		191	78.2
Progesterone receptor (PR)			
Negative		91	37.2
Positive		153	62.7
HER2 status			
0/1+ (negative)		213	87.3
2+ (equivocal)		7	2.9
3+ (positive)		22	9
No information		2	0.8
Pathological stage			
I		103	42.2
II		118	48.4
III		15	6.1
IV		5	2
No information		3	1.2
Presence of TILs			
Absent		34	13.9
Present		207	86.9

SD: standard deviation; TILs: tumor-infiltrating lymphocytes.

exact test. Statistical significance was set at $p<0.05$. A statistical analysis was performed to associate the presence of inflammatory cells with clinicopathological factors already established in the literature. Additionally, patient survival was evaluated in the follow-up years. Kaplan-Meier curves were constructed and compared using the log-rank test. The Cox model was used for univariate and multivariate analyses with SPSS software version 21 (Statistical Package for Social Sciences) for Mac. Variables with a p-value <0.25 in the univariate analysis were included in the multivariate model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the univariate and multivariate analyses. For survival analysis, only overall survival was considered, and calculated as the time between the date of diagnosis and the date of death due to breast cancer (this was the event of interest) or the date of the last available medical record information for the patients who survived.

RESULTS

The results are presented in the following two sections. First, the clinicopathological characteristics of patients diagnosed with invasive breast cancer treated at *Hospital Santa Casa* in Belo Horizonte in 2011 (n=244) and the association between these characteristics and tumor inflammatory infiltrate (Tables 1 and 2) are shown.

Secondly, the survival data are shown, illustrating the association between the tumor inflammatory infiltrate and the clinicopathological characteristics of patients diagnosed with invasive breast cancer treated at *Hospital Santa Casa* in Belo Horizonte in 2011 (n=222) (Tables 3 and 4; Figure 1).

Characteristics of patients and tumors

Of 290 patients, 46 (15.9%) were excluded due to lack of complete data. Two hundred forty-one patients (98.7%) were female, and three (1.3%) were male, with a mean age of 58.2 (standard deviation±13.8 years). The predominant histological type was invasive carcinoma with no special type (ductal NOS), which corresponded to 218/244 (89.3%) patients, and the predominant histological grade was II, which represented 139/244 (57.0%) patients. The tumors were positive for estrogen and progesterone receptors in 191/244 (78.2%) and 153/244 (62.7%) patients, respectively. There were 213/244 (87.3%) HER2-negative cases, of 22/244 (9.0%) HER2-positive cases, and of 7/244 (2.9%) cases with equivocal HER2 status. Most patients were classified as stage II (118/244 patients, 48.4%).

TILs were present in 86% of the primary tumors studied, and were absent in 14% (Tables 1 and 2). The histological type was associated with the presence of TILs (p=0.018); 192/218 (88.1%) cases of invasive breast cancer with no special type (ductal NOS) had TILs, whereas TILs were present in only 9/14 cases (64.3%) of invasive lobular carcinomas. The presence of TILs was associated

Table 2. Association between the clinicopathological characteristics of patients with invasive breast cancer diagnosed at *Hospital Santa Casa* in Belo Horizonte (MG), Brazil, in 2011 and the tumor inflammatory infiltrate (n=244).

Variable	n	TILs absent (n = 34)	(%)	TILs present (n = 210)	(%)	p
Gender						
Female	241	34	14.1	207	85.9	1.000
Male	3	0	0	3	100	
Age in years – mean (SD)		62.9 (13.8)		57.7 (13.9)		**0.041**
Histological types						
Invasive carcinoma with no special type (ductal NOS)	218	26	11.9	192	88.1	
Invasive lobular carcinoma	14	5	37.5	9	64.3	**0.018**
Other special types	12	3	25	9	75	
Histological grade						
I	16	3	18.8	13	81.3	
II	139	24	17.3	115	82.7	**0.058**
III	89	7	7.9	82	92.1	
Tumor size pathological						
1	103	17	16.5	86	83.5	
2	118	15	12.7	103	87.3	
3	15	1	6.7	14	93.3	0.825
4	5	1	20.0	4	80.0	
No information		0		3		
Lymph nodes (according to pathological staging)						
0	120	19	15.8	101	84.2	
1	85	10	11.8	75	88.2	
2	28	3	10.7	25	89.3	0.589
3	7	1	14.3	6	85.7	
No information		1		3		
Estrogen receptor (ER)						
Negative	53	29	15.2	162	84.8	0.372
Positive	191	5	9.4	48	90.6	
Progesterone receptor (PR)						
Negative	91	25	16.3	128	83.7	0.184
Positive	153	9	9.9	82	90.1	
HER2						
0/1+	213	33	15.5	180	84.5	
2+	7	0	0	7	100	0.073
3+	22	0	0	22	100	
No information	2	2	0.87			
Clinical stage						
I	103	17	16.5	86	83.5	
II	118	15	12.7	103	87.3	
III	15	1	6.7	14	93.3	0.500
IV	5	1	20	4	80	
No information	3	3				

SD: standard deviation; TILs: tumor-infiltrating lymphocytes; p<0,05 are in bold.

Table 3. Univariate analysis (Cox model) – Survival of patients with invasive breast cancer treated at *Hospital Santa Casa* in Belo Horizonte (MG), Brazil, in 2011 (n=222).

Variable	Hazard ratio	p
Tumor size		
T1*	1	<0.001
T2	4.68 (1.36–16.18)	0.015
T3	20.52 (5.11–82.40)	<0.001
T4	12.74 (2.12–76.56)	0.005
Presence of TILs	0.57 (0.23–1.41)	0.222
Histological type		
Invasive carcinoma with no special type (ductal NOS)	1	0.270
Invasive lobular carcinoma	2.45 (0.83–7.30)	0.106
Other special types	1.24 (0.168–9.17)	0.835
Histological grade		
Grade I*	1	0.020
Grade II	1.41 (0.18–11.13)	0.744
Grade III	3.97 (0.52–30.36)	0.184
Axillary status		
N0	1	0.008
N1	3.26 (1.22–8.69)	0.018
N2	4.93 (1.59–15.29)	0.006
N3	10.25 (2.04–51.46)	0.005
Stage		
Stage I*	1	<0.001
Stage II	2.74 (0.6–12.49)	0.194
Stage III	10.80 (2.41–48.30)	0.002
Stage IV	20.46 (2.86–146.30)	0.003
Hormone receptors		
Positivity for estrogen receptor	0.64 (0.27–1.52)	0.316
Positivity for progesterone receptor	0.35 (0.16–0.73)	0.005
HER2		
0 or 1+*	1	0.283
2+	3.21 (0.76–13.62)	0.114
3+	0.98 (0.23–4.14)	0.973

*Reference category (i.e., used for comparison with other categories). TILs: tumor-infiltrating lymphocytes.

with a younger age (mean age of patients with TILs present, 57.7 years, and 62.9 years for patients without TILs, p=0.041). All tumors with HER2 overexpression (3+) and equivocal cases (2+) showed the presence of TILs, corresponding to 100% of these patients (29/29) (p=0.073).

Patients with tumors of a higher histological grade had more TILs, although the diference was not statistically significant (p=0.058), corresponding to 82/89 cases (92.1%) of grade III tumors (Table 2). Tumor size, lymph node positivity, and hormone receptor status were not associated with the presence of TILs.

Table 4. Multivariate analysis (Cox model) - Survival of patients with invasive breast cancer treated at *Hospital Santa Casa* in Belo Horizonte (MG), Brazil, in 2011 (n=222).

Variable	Category	Hazard ratio	p
Tumoral size			
T1*		1	0.001
T2		4.63 (1.27–16.87)	0.020
T3		19.24 (4.30–86.15)	< 0.001
T4		6.97 (1.00–48.68)	0.050
Histological grade			
Grade I*		1	0.920
Grade II		0.81 (0.10–6.96)	0.846
Grade III		0.95 (0.11–8.56)	0.967
Progesterone receptor (PR)			
PR negative*		1	0.004
RP positive		0.39 (0,17–0.87)	0.022
TILs			
Absent*		1	0.200
Present		0.23 (0.08–0.65)	0.005
Axillary status			
No positive nodes*		1	0.002
At least one positive node		2.80 (1.02–7.70)	0.046

*Reference category. TILs: tumor-infiltrating lymphocytes.

Survival analysis

The median follow-up time was 63.5 (1-84.2) months. In univariate analysis, tumor size, stage, progesterone receptor positivity, and negative axilla were associated with a longer survival time (Table 3). The overall survival rate of the entire cohort in the follow-up years was 85.2%. The presence of TILs was not associated with survival time (p=0.222; HR: 0.57; 95%CI 0.23–1.41).

In the multivariate analysis, when tumor and patient characteristics were added to the model, smaller tumor size (HR, for T3 versus T1, 19.24; 95%CI 4.30–86.15); p<0.001), absence of metastasis to the axillary lymph nodes (having a positive axilla versus no positive axillary nodes), (HR 2.80; 95%CI 1.02–7.70; p=0.002), positivity for progesterone receptor (HR: 0.39; 95%CI 0.17–0.87; p=0.022), and presence of TILs (HR: 0.23; 95%CI 0.08–0.65; p=0.002) were associated with longer survival times (Table 4, Figure 1).

DISCUSSION

In this study, we showed the relationship between TILs and the clinicopathological characteristics of patients with invasive breast cancers diagnosed and treated at *Hospital Santa Casa* in Belo Horizonte in 2011, and the five-year survival rate. A high frequency of tumors with TILs was identified, corresponding to

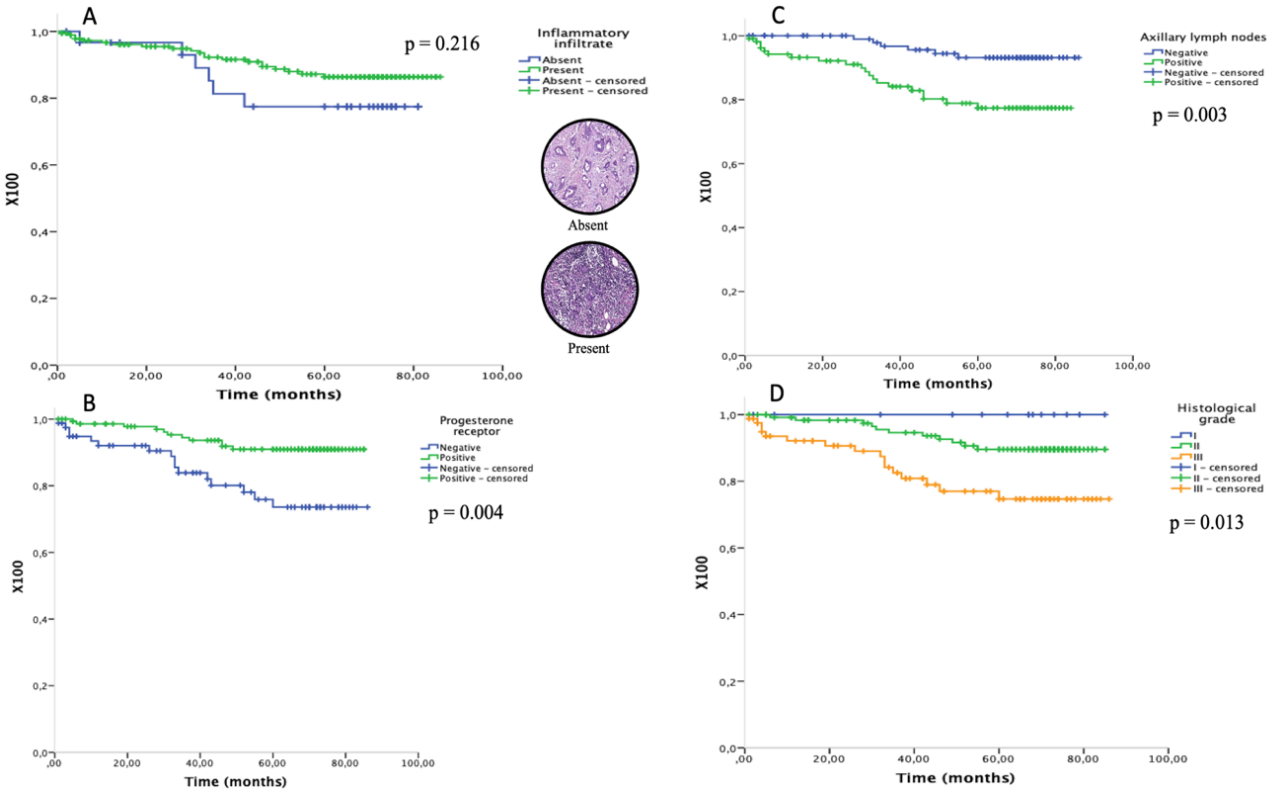

Figure 1. Overall survival curve of patients diagnosed with invasive breast tumors treated at *Hospital Santa Casa* in Belo Horizonte (MG), Brazil – 2011: (**A**) associated tumor inflammatory, infiltrate absent or present, magnification 400x, invasive carcinomas NST, (**B**) associated progesterone receptor, negative or positive, (**C**) associated with axillary lymph nodes, negative or positive, and (**D**) associated with histological grade I, II or III. p-values refer to the log-rank test.

207/244 (85.9%) patients. Additionally, the presence of TILs was associated with the tumor type, especially invasive carcinoma of no special type (ductal NOS), tumors of a higher histological grade, and younger age, corroborating the results described in the medical literature[20,21]. All tumors with HER2 overexpression (3+) and equivocal cases (2+) showed the presence of TILs, corresponding to 100% of these patients (29/29). Most hormone receptor positive tumors also show the presence of TILs. The characteristics of the patients and their tumors were like those reported in the literature[22], with a predominance of invasive carcinoma of no special type (ductal NOS), followed by invasive lobular carcinoma and histological grade II. Furthermore, survival time is associated with classic prognostic factors, such as tumor size and grade, positivity of regional lymph nodes, and PR positivity[17].

The association between inflammatory infiltrates and survival time is mediated by factors related to both patients and tumors[23]. TILs have a potential role in predicting the improved survival benefits achieved with several therapies, and the quantification of TILs is feasible on H&E-stained tissue sections during diagnostic procedures[9,17]. In our study, patients with TILs had longer survival times in multivariate analysis, which suggests that the presence of TILs is an independent prognostic factor in breast cancer. Unfortunately, detailed information on treatment strategies was only available for approximately 20% of our cohort, making the evaluation of different therapies unreliable.

Previous studies have revealed that the presence of TILs is associated with longer overall survival times in triple negative and HER2-positive cancers but shorter time in luminal HER2-negative breast cancer[24,25]. HER2-overexpressing and triple-negative tumors are more immunogenic, suggesting that an immunosuppressive mechanism could explain the shorter overall survival time observed in some of these patients, as described by some authors.[25,26] In some previous studies, on ER-positive and HER2-negative tumors, no significant association was found between TILs and survival rates. We believe that this could be explained by the substantial heterogeneity of the disease and the fact that patients with these subtypes usually already have long survival times[24,27]. In contrast, patients with HER2-negative tumors and a higher concentration of TILs usually have a worse prognosis and shorter disease-free and overall survival times, suggesting diverse biological behaviors for TILs and the microenvironment in different tumor types[8,23,28].

The complexity of the immune response to tumors is likely oversimplified in current measurement models[29]. In our study,

TILs were not stratified into subpopulations; only the presence or absence of TILs was evaluated through the microscopic analysis of the slides stained by H&E used for the anatomopathological diagnosis of the patients, which is a limitation. No immunohistochemical study has been performed to verify the type of inflammatory cells, as was the case in other studies[8,11,20]. International collaborative efforts are standardizing the histopathologic reporting of immune infiltrates to allow the application of these parameters in clinical and research settings[24]. The recognition of the prognostic value of the immune infiltrate has been the basis for establishing a breast cancer immunological grade[17,24,29].

Immunotherapy associated with chemotherapy and/or hormone therapy shows promising results for patients with metastasis or residual disease after treatment, especially for patients with triple-negative tumors. TILs can be used as predictors of response to chemotherapy and immunotherapy. Understanding tumor immunobiology and TILs is a huge challenge for science, and through gaining this knowledge, new diagnostic and therapeutic approaches for cancer patients can be validated[13,30,31].

Several studies have shown that the response to conventional antitumor agents (chemotherapy, radiotherapy, and target-specific therapy) appears to be mediated in part by their effects on the immune system, both in stimulating tumor immunogenicity and modulating the immune system and its microenvironment within the tumor[12,30,31]. The interaction between the signaling pathways of the estrogen and progesterone receptors and the immunological tumor microenvironment is largely unknown and needs to be studied in more detail[9].

One of the strengths of this study is the analysis of all patients admitted over the course of one year for diagnosis and treatment of their disease at a reference service for breast cancer in a public hospital of the Brazilian Unified Health System (SUS). All patients underwent their diagnosis, tumor excision, and therapy protocol performed by the same surgeons, pathologists, and oncologists, leading to a more homogeneous group for comparative studies. Unfortunately, in 2011, equivocal HER2 cases (2+) were not retested for HER2 gene amplification (FISH), because this test was not available in our public health system. Furthermore, anti-HER2 therapy (trastuzumab) was not available at our hospital at that time; thus, patients with HER2-overexpressing tumors did not receive anti-HER2 therapy.

Another possible limitation was the follow-up period. The patients' follow-up time for the survival analysis was limited to five years, which is a short period for the evaluation of the overall survival rate of patients diagnosed with invasive breast cancer; however, significant differences were demonstrated. Perhaps, a greater difference in survival times could be found with a 10- or 15-year follow-up period. The low socioeconomic status of most participants, the social stigma associated with cancer, and the delay in obtaining complementary examinations by the public health system, even though patients were admitted to a referral hospital, could be possible factors responsible for the considerable number of patients who were lost to follow-up. Additionally, there was some difficulty in accessing data because, in our country, most hospitals that treat patients within the public health system do not have computerized charts with integrated data on the evolution and treatment of these patients.

TILs can be easily identified by pathologists through H&E slides, and they can be used as prognostic markers as well as predictive markers of response to treatment in conjunction with other markers already established in the literature and by other molecular analyses. The presence of TILs could contribute to the classification and staging of tumors, as well as to determining the immunological profile of the disease at different times over the course of treatment. In our study, not only were TILs associated with some tumor characteristics, but they were also independent prognostic factors for breast cancer survival time.

CONCLUSIONS

In our study, an analysis of patients diagnosed with invasive breast cancer treated at *Hospital Santa Casa* in Belo Horizonte, Minas Gerais, Brazil, in 2011, revealed a significant association between the presence of TILs with invasive carcinomas of no special type and a younger age of patients. TILs were not significantly associated with high histological grade, estrogen receptor and progesterone receptor status, HER2 expression status, disease stage, tumor size, or axillary lymph node status. Some factors had a greater impact than others on survival in the multivariate analysis, such as tumor size, which had a greater impact than the axillary status, and T3 tumors had a worse outcome when compared to other tumor sizes. The presence of TILs was associated with longer survival time in the multivariate analysis, which confirms that TILs are a prognostic factor in breast cancer.

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AUTHORS' CONTRIBUTIONS

FMAF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resoucers,

Validation, Visualization, Writing – original draft, Writing – review & editing. CBN: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. FCLS: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing. MAB: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. DB: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing.

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SPECIAL ARTICLE
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Recommendations of the Brazilian College of Radiology, the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics Associations for breast cancer screening in Brazil

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ABSTRACT

Objective: To present the updated recommendations of the Brazilian College of Radiology and Imaging Diagnosis, the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics Associations for breast cancer screening in Brazil. **Methods:** Between January 2012 and July 2022, searches for scientific evidence published in MEDLINE, Embase, Cochrane Library, EBSCO, CINAHL and LILACS were carried out. The recommendations were based on this evidence, with the consensus of a committee of experts from the three institutions. **Recommendations:** The annual mammography screening is recommended for normal-risk patients aged between 40 and 74 years. For women aged more than 75 years, it is reserved for those whose life expectancy is longer than seven years. Women whose risk is higher than normal, such as those with dense breasts, personal history of atypical lobular hyperplasia, classic in situ lobular carcinoma, atypical ductal hyperplasia, women undergoing breast cancer treatment or thoracic irradiation before the age of 30, or those with genetic mutation or strong family history, benefit from complementary screening, being considered in an individual manner. Tomosynthesis is an evolution of mammography and should be considered in screening whenever accessible and available.

KEYWORDS: breast cancer screening; mammography; ultrasound; magnetic resonance.

INTRODUCTION

In 2021, breast cancer became the most frequently diagnosed cancer in the world, and the main cause of death among women[1]. In Brazil, in 2023 73,610 new cases of breast cancer were estimated, which represents an adjusted incidence rate of 41.89 cases per 100 thousand women[1]. Screening is an efficient method to detect the disease in an early stage, thus reducing its mortality. Besides, the early diagnosis allows a greater range of therapeutic options and reduces treatment morbidity[2-4].

In 2012 and 2017, the Brazilian College of Radiology (CBR) and Imaging Diagnosis, the Brazilian Society of Mastology (SBM), and the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo), through the National Mammography Commission (CNM), published the recommendations of breast cancer screening[5,6]. The objective of this update is to publish the available evidence about screening and to provide information for the decision-making of women with different risks for developing the disease.

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METHODS

The following databases were searched: MEDLINE (via PubMed), Embase, Cochrane Library, EBSCO, CINAHL and LILACS (via Bireme), using as many keywords, descriptors and MeSH terms as possible, in order to find scientific evidence about breast cancer screening with mammography (MG), ultrasound (US), magnetic resonance imaging (MRI) and tomosynthesis (TMS), in women at normal, intermediate and high risk for breast cancer, published between January 2012 and July 2022, in Portuguese, English, French and Spanish. Complementary searches were conducted in websites, on-line tools and in the references of the analyzed studies. The most recent and qualified processed evidence were selected for analysis (systematic reviews and meta-analyses), as well as those that better responded the structured questions. At their absence, primary studies (clinical trials or cohorts) were included. The risk of bias of the studies was assessed using the following tools: ROBIS (Risk of Bias in Systematic Reviews), RoB 2.0 (Cochrane Risk of Bias Tools for Randomized Controlled Trials version 2.0), QUADAS-C (Quality Assessment of Diagnostic Accuracy Studies – Comparative) and ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions). The global quality of the set of evidence for each outcome was assessed by GRADE *(Grading of Recommendations Assessment, Development and Evaluation*).

The recommendations were based on this evidence, with the consensus of the commission of experts from the three institutions (CBR, SBM and Febrasgo), defined after at least 75% of agreement among the members with the recommendation. In the absence of an initial agreement, a second round of discussion and voting took place, and the simple majority was required to define a consensus. The recommendations were classified in five categories:

- Category A – Strong recommendation in favor, based on high quality evidence.
- Category B – Strong recommendation in favor, based on moderate quality evidence.
- Category C – Weak recommendation in favor, based on low quality evidence.
- Category D – Recommendation in favor, based only on the consensus of experts.
- Category E – Recommendation against, because the evidence is insufficient to support its use.

Recommendations for screening

Screening for women at normal risk

Mammography

The annual screening with MG is recommended for women aged between 40 and 74 years, preferably with digital technology (category A).

After the age of 75, screening is recommended if there are no comorbidities that reduce life expectancy, which should be of at least seven years (category D).

Ultrasound

The US is not recommended as a supplementary or isolated screening method for women at normal risk (category E).

Note: The US is considered for specific situations of higher risk (see session about dense breasts, intermediate risk and high risk).

Magnetic resonance

MRI is not recommended as a supplementary or isolated screening method for women at normal risk (category E).

Note: The use of MRI is considered for specific situations of higher risk (see session about dense breasts, intermediate risk and high risk).

Tomosynthesis

TMS, when combined with synthesized 2D MG or with standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening among women with dense breasts

Mammography

The annual screening with MG is recommended for women aged between 40 and 74 years, preferably with digital technology (category A).

After the age of 75, screening is recommended if there are no comorbidities that reduce life expectancy, which should be of at least seven years (category D).

Ultrasound

The annual US can be considered as an adjunct to MG in women with dense breasts, except when MR is performed (category B).

Magnetic Resonance

The recommendation is that a biennial MRI can be considered as adjunct to MG in extremely dense breasts (category C).

Tomosynthesis

The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening of women with personal history of biopsy with atypical lobular hyperplasia, classic in situ lobular carcinoma, and atypical ductal hyperplasia

Initial note: It is recommended that women with atypical lobular hyperplasia (ALH), classic in situ lobular carcinoma (ISLC) or atypical ductal hyperplasia (ADH) be assessed by risk calculation

models that include these variables together with other clinical data, including family history and breast density, to estimate the risk of breast cancer.

Mammography

For women with risk estimation <20% throughout life, an annual MG is recommended after the age of 40 (category A).

For women with risk estimation ≥20% throughout life, an annual MG is recommended after the diagnosis (not before the age of 30) (category B).

Ultrasound

For women with risk estimation of 15 to 20% throughout life, the US can be considered as adjunct to MG (category D).

For women with risk estimation ≥20% throughout life, the US is recommended as an alternative method for those who cannot undergo MR, for any reason (category B).

Magnetic Resonance Imaging

For women with risk estimation ≥20% throughout life, an annual MRI should be considered as adjunct to MG after diagnosis (not before the age of 25) (category B).

Tomosynthesis

The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening of women with personal history of invasive breast cancer or in situ ductal carcinoma

Mammography

Women treated with conservative surgery should undergo an annual MG (category A), starting at least six months after the conclusion of radiotherapy.

Women treated with mastectomy should undergo an annual MG only of the contralateral breast, starting one year after the end of the treatment (category A).

Women who underwent nipple-sparing mastectomy can consider MG after up to one year to assess the residual fibroglandular tissue, to determine the need for maintaining mammography screening (category D).

Ultrasound

The US can be used as complementary screening to MG when MR is indicated, however, for whatever reason, cannot be performed (category C).

Magnetic Resonance Imaging

Women treated with conservative surgery or mastectomy (for the evaluation of the contralateral breast), who were diagnosed with breast cancer before the age of 50, or with dense breasts, should have an annual MRI (category C), starting one year after the end of treatment.

Tomosynthesis

The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening of women with personal history of thoracic radiotherapy

Mammography

Women with history of thoracic irradiation before the age of 30 should undergo an annual MG eight years after radiotherapy (not before the age of 30) (category A).

Ultrasound

The US should be used for screening only when MG, for whatever reason, cannot be performed (category B).

Magnetic Resonance Imaging

Women with history of thoracic irradiation before the age of 30 should undergo an annual MR eight years after radiotherapy (not before the age of 25) (category A).

Tomosynthesis

The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening of women with genetic mutation or strong family history of breast cancer (risk ≥20% throughout life)

Mammography

Women with pathogenic mutation of the BRCA1 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MG after the mutation is diagnosed (not before the age of 35) (category A).

Women with pathogenic mutation of the TP53 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MG after the mutation is diagnosed (not before the age of 30) (category A).

Women with BRCA2 pathogenic variant or others, with moderate or high risk for breast cancer, besides those who are not tested, but have first-degree relatives who carry them, should undergo an annual MG after the mutation is diagnosed (not before the age of 30) (category A).

Women with risk ≥20% throughout life, calculated by one of the mathematical models based on family history, should have

an annual MG starting 10 years before the age of the youngest relative at diagnosis (not before the age of 30) (category A).

Ultrasound

The US should be used for screening only when MRI, for whatever reason, cannot be performed (category B).

Magnetic Resonance Imaging

Women with pathogenic mutation of the BRCA1 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MRI after the mutation is diagnosed (not before the age of 25) (category A).

Women with pathogenic mutation of the TP53 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MG after the mutation is diagnosed (not before the age of 20) (category A).

Women with BRCA2 pathogenic variant or others, with moderate or high risk for breast cancer, besides those who were not tested, but with first-degree relatives who carry them, should perform an annual MR after the mutation is diagnosed (not before the age of 30) (category A).

Women with risk ≥20% throughout life, calculated by one of the mathematical models based on family history, should undergo an annual MRI starting 10 years before the age of the youngest relative at diagnosis (not before the age of 30) (category A).

Tomosynthesis

The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Justification

The benefits of mammography screening were assessed through cohort studies, systematic reviews and randomized clinical trials, demonstrating a reduction of mortality specifically caused by breast cancer from 22% to 30%, in women aged between 40 and 74 years[2-4,7]. When other major outcomes were analyzed, it was possible to observe better quality of life measured by QALY (qualy-adjusted life-years), resulting from less aggressive treatments[2], besides higher rates of initial tumors, with better prognostic characteristics and negative axilla[3], and 28% less advanced tumors[4].

Age of beginning and periodicity of screening

The beginning of screening at the age of 40 reduces mortality in 10 years by breast cancer in 25%; however, it increases the false-positive (FP) rate from 4.8 to 7%[7]. In Brazil, it is observed that 41.1% of the women diagnosed with breast cancer are younger than 50, according to data from the AMAZONA study[8]. As to screening interval, the biennial one is related to larger risk of advanced tumors (RR=1.28), larger than 15 mm and with worse prognostic factors[7]. Therefore, CNM recommends the annual screening with MG after the age of 40.

Considerations about women aged less than 40 years

Screening is not recommended in this age group, due to the lower incidence of breast cancer (about 7% of the cases). However, the AMAZONA III study showed that, in Brazil, this rate is 17%, with larger tumors and worse prognosis at diagnosis, in comparison to women aged more than 40 years[9]. Therefore, in agreement with other international societies[10,11], CNM recommends that the assistant doctor perform an evaluation of the estimated risk for breast cancer for all women who are older than 30, through mathematical models, to better stratify those with increased risk that might benefit from special screening.

When to interrupt screening

Prospective, controlled and randomized studies did not include women aged more than 74 years, so there are no direct data about screening at this age group. However, women's life expectancy has increased, and the incidence of breast cancer in the age group above 75 years is increasing as well. Currently, 26% of deaths caused by breast cancer occur in women diagnosed after the age of 74 years[12,13]. Considering those factors, many medical organizations recommend the decision be individualized and discussed with the woman.

Adverse effects of screening

Some adverse effects have been reported, however, the quality of evidence for their analysis is low. Overdiagnosis is a discussed effect, but its estimation is variable due to the difficulty to determine which tumor would or would not lead the patient to death[14]. The risk of carcinoma induced by the radiation used in mammography screening is low, however, it is higher in women with large breasts, for whom the dose of radiation is higher, as well as in those who undergo complementary incidences[15]. It has also been associated with a 2.9% increase in the risk of biopsies with benign outcome (BO), which can create anxiety[14]. However, the reduction in mortality of the cancer that is detected early through screening overcomes the risks of the damage caused by the exposure to radiation.

Considerations about breast TMS

TMS is an evolution of digital MG. Several studies confirm the efficacy of this technology in breast cancer screening, which increases the detection rate in up to 50%[16-20] and reduces the rate of recall for additional images from 9 to 29%[19,20]. The detected tumors have similar histological and immunohistochemical characteristics to those detected by the MG[21-23], and the results remain in the subsequent rounds[24]. Therefore, TMS is recommended as a screening

method, when accessible and available, by the CNM, as well as by different medical societies, such as the American College of Radiology (ACR)[10], American Cancer Society (ACS)[25], European Society of Breast Imaging (EUSOBI)[26], Société d'Imagerie de la Femme (SIFEM)[27], National Comprehensive Cancer Network (NCCN)[11] and European guidelines on breast cancer screening and diagnosis[28].

TMS should be used in combination with standard 2D MG (Combo) or synthetized 2D MG, the latter with the advantage of reducing the dose of radiation[15,17,18]. Since the Brazilian Health Regulatory Agency (Anvisa) has not established the levels of reference and tolerance of the glandular dose for TMS in Brazil, the recommendation is that each service perform a survey of the average glandular doses, using a sample of patients with different breast thickness, thus establishing local reference and tolerance levels[29,30].

Considerations about screening of women with dense breasts

The dense breast is a risk factor for breast cancer and is associated to reduced mammography sensitivity. Therefore, supplementary methods have been proposed. All supplementary modalities improved sensitivity regarding isolated MG, thus allowing the detection of early-stage cancers hidden in MG[31-38].

MRI is the supplementary technique with higher additional detection rate when it comes to cancer[31]. This increases the chances of less invasive and more curative treatments. Data on critical outcomes, such as mortality, are not available. However, randomized trials showed that the supplementary use of US in the dense breast or the MR in extremely dense breasts reduced the rate of interval cancer, an important substitute outcome centered on the patient[24,34,39]. Regarding damage, the use of supplementary modalities is associated with increasing False Positive (FP) rates and biopsies[31,33,35-38]. Therefore, for women with dense breasts and no other risk factors, the CNM recommends annual screening with MG after the age of 40, and as an option the use of supplementary methods such as US or MRI. For extremely dense breasts, there is scientific evidence suggesting the superiority of MRI.

Considerations about screening in women with personal history of diagnosis of atypical lobular hyperplasia, classic lobular carcinoma in situ and atypical ductal hyperplasia

Atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and classic in situ lobular carcinoma in situ (LCIS) are considered as non-obligatory precursor lesions for in situ ductal carcinoma and invasive carcinoma[40]; they represent increased relative risk for their subsequent development throughout life, being from 2.6 to 5.0 times for ADH; 3.2 to 4.8 times for ALH; and 6 to 10 times for LCIS[41-49].

There are few studies to evaluate screening in this group, based on retrospective series that estimated the risk for in situ and invasive subsequent carcinomas. The current strategy to define screening in this subgroup is based on the calculation of risk for breast cancer throughout life[11]. Factors such as age of diagnosis and breast density have a direct impact on the risk of cancer, which can be estimated by risk calculation tools based on mathematical models[47]. Currently, a few models contemplate this group in the calculation of risk, such as: *Breast Cancer Risk Assessment Tool* (the Gail model) and *IBIS Breast Cancer Risk Evaluation Tool* (Tyrer-Cuzick model), and these should be preferably used[11,47].

Considerations about screening of women with personal history of treatment for invasive breast cancer and ductal carcinoma in situ

Women with personal history of breast cancer present seven times more chances of developing a second ipsilateral or contralateral malignant breast neoplasm[48]. In patients treated with conservative surgery, MG presents less sensitivity due to surgical changes and higher incidence of interval carcinoma[49], thus justifying the need for supplementary screening.

Complementary screening with MRI can detect from 8.2 to 18.1 additional cancers in relation to MG in one thousand women[50-55]. The performance of MRI in this scenario has been similar to that of patients with high genetic risk, considering the sensitivity, detection rate, FP and positive predictive value (PPV) of biopsies[56-58]. However, scientific evidence for MRI in this population is weak, based mostly on retrospective studies[49,50,55-59]. In this heterogeneous group, the benefit of MRI is more well established in young patients (age of diagnosis <50 years), and with dense breasts[49-52].

A few studies assessed the accuracy of the US, with detection rate of additional cancers to MG of 2.4 to 4.1/1,000 women; however, with increasing FP and lower PPV for biopsies. When performed in addition to MRI, the US does not result in improved sensitivity[53,54], but it can be used as supplementary screening when the MRI is not available.

In patients with personal history of breast cancer treated with mastectomy, the image screening of the treated breast, with or without reconstruction, is not indicated due to the low detection of asymptomatic cancers through MG, US or MRI[59].

Considerations about screening in women with history of thoracic radiotherapy

Women treated with thoracic radiotherapy before the age of 30 have average risk of developing breast cancer 13.4 higher than the general population, similarly to patients with BRCA1 gene mutation[60]. The increase in incidence occurs about 10 years after treatment, persisting 30 years later. The highest incidence occurs when the treatment took place between the ages of 10 and 14

(RR=22.0) and 15 and 19 years (RR=14.3)[61]. For this group, there is evidence about the importance of screening with MG and MRI starting at the age of 25 or eight years after radiotherapy, in accordance with the recommendations of other medical institutions, such as the *Children's Oncology Group* and the *International Guideline Group*[60].

Screening of women with genetic mutation or strong family history of breast cancer (risk ≥20% throughout life)

Gene mutations that lead to predisposition to breast cancer are classified as high risk when they cause an increase of five times or more in comparison to women who do not carry them (BRCA1, BRCA2, TP53, PTEN, among others), or intermediate risk when they increase the chances in 1.5-5 times (ATM, CHEK 2, BARD1, among others)[62-64]. In Brazil, a study has shown that the most mutated genes were BRCA1 (27.4%), BRCA2 (20.3%), TP53 (10.5%), ATM (8.8%), CHEK2 (6.2%) and PALB2 (5.1%)[64]. The Brazilian variant TP53 R337H was strongly associated with the risk of breast cancer (OR = 17.4)[64]. In the case of women with strong family history of breast cancer, however, with no known mutation, high risk was defined for those with estimation ≥20% of risk throughout life, calculated using mathematical models[62]. These women present cancer at an early age, with peaks of incidence between 20-35 years old for the PT53 mutation, as well as between 40-59 years old for high family risk[62-65].

For this risk group, there is strong scientific evidence about the importance of MRI screening, due to the reduction of interval cancer and higher rates of detecting tumors at early stages, which can reduce the need for chemotherapy and mortality, despite the higher number of FPs[54,55,65-67]. As to MG, its role in patients with BRCA1 mutation has been questioned. A metanalysis[68] demonstrated that the addition of MG to MRI in patients with the BRCA1 mutation modestly increased sensitivity (3.99%), with reduction in specificity (4%). As to the BRCA2 mutation, the increase in sensitivity was higher (12.6%), with small reduction in specificity (5%). Thus, the CNM recommends screening with MRI associated with MG, however, not starting MG before the age of 35 for BRCA1, and the age of 30 for the other groups. Additional US examinations do not produce additional cancer detection, if the MRI is performed, so it should be reserved for a posterior evaluation or as a guide for the biopsy of findings identified in the MRI.

As to the impact on mortality, a relevant study was published by Bae et al.[54], which, despite being retrospective, demonstrated that high risk women who underwent screening with MG and MRI presented better global survival rates and tumors diagnosed at stages with better prognosis than patients in the group who only underwent MG.

CONCLUSION

This guideline shows the consensus of the recommendations based on current data for breast cancer screening in Brazil, subdivided in sessions according to the risk for developing breast cancer, since the approach by women of normal risk, who represent approximately 80% of the patients diagnosed with breast cancer, until women with increased risk.

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AUTHORS' CONTRIBUTIONS

LABDU: Project administration, Formal analysis, Conceptualization, Data curatorship, Writing – first draft, Writing – Revision and editing, Investigation, Methodology, Obtaining funding, Resources, Software, Supervision, Validation, Visualization. LFC: Conceptualization, Data curatorship, Writing – first draft, Writing – Revision and editing, Investigation, Methodology, Obtaining funding, Software, Supervision, Validation, Visualization. IBP: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. SPB: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. MBS: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. ALKO: Writing – first draft, Writing – revision and editing, Investigating, Software, Validation, Visualization. CS: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. TMGO: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. PCM: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. BMMM: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. FEA: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. SJFR: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. EOC: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization.

HLC: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. GMB: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. JLEF: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. TPM: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. RRJ: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. JEP: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization.

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ARTIGO ESPECIAL
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Recomendações do Colégio Brasileiro de Radiologia, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para o rastreamento do câncer de mama no Brasil

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RESUMO

Objetivo: Apresentar a atualização das recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para o rastreamento do câncer de mama no Brasil. **Métodos:** Foram feitas buscas das evidências científicas publicadas nas bases MEDLINE, Embase, Cochrane Library, EBSCO, CINAHL e LILACS, entre janeiro de 2012 e julho de 2022. As recomendações foram baseadas nessas evidências, mediante consenso da comissão de especialistas das três entidades. **Recomendações:** O rastreamento mamográfico anual é recomendado para as mulheres de risco habitual entre 40 e 74 anos. Acima de 75 anos deve ser reservado para as que tenham expectativa de vida maior que sete anos. Mulheres com risco maior que o habitual, entre elas as com mamas densas, com história pessoal de hiperplasia lobular atípica, carcinoma lobular *in situ* clássico, hiperplasia ductal atípica, tratamento de câncer de mama ou de irradiação no tórax antes dos 30 anos, ou ainda portadoras de mutação genética ou com forte história familiar, se beneficiam do rastreamento complementar, sendo consideradas de forma individualizada. A tomossíntese é uma evolução da mamografia e deve ser considerada no rastreamento, sempre que acessível e disponível.

PALAVRAS-CHAVE: rastreamento do câncer de mama; mamografia; ultrassonografia; ressonância magnética.

INTRODUÇÃO

Em 2021, o câncer de mama se tornou o câncer mais frequentemente diagnosticado no mundo, sendo a principal causa de morte entre as mulheres[1]. No Brasil, para o ano de 2023, foram estimados 73.610 novos casos de câncer de mama, o que representa uma taxa ajustada de incidência de 41,89 casos a cada 100 mil mulheres[1]. O rastreamento é uma medida eficaz para detectar a doença no estágio inicial e reduzir sua mortalidade. Além disso, o diagnóstico precoce permite maior gama de opções terapêuticas e redução da morbidade do tratamento[2-4].

Em 2012 e 2017, o Colégio Brasileiro de Radiologia e Diagnóstico por Imagem (CBR), a Sociedade Brasileira de Mastologia (SBM) e a Federação Brasileira das Associações de Ginecologia e Obstetrícia (Febrasgo), por meio da Comissão Nacional de Mamografia (CNM), publicaram as recomendações para o rastreamento do câncer de mama[5,6]. O objetivo da presente atualização é publicar as evidências disponíveis sobre o rastreamento e fornecer informações para a tomada de decisões em mulheres com diferentes riscos para o desenvolvimento da doença.

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MÉTODOS

Foram feitas buscas nas bases de dados MEDLINE (via PubMed), Embase, Cochrane Library, EBSCO, CINAHL e LILACS (via Bireme), utilizando o máximo de palavras-chaves, descritores e termos MeSH, a fim de encontrar evidências científicas sobre o rastreamento do câncer de mama com mamografia (MG), ultrassonografia (US), ressonância magnética (RM) e tomossíntese (TMS), em mulheres de risco habitual, intermediário e alto para o câncer de mama, publicadas entre janeiro de 2012 e julho de 2022, nos idiomas português, inglês, francês e espanhol. Buscas complementares foram feitas em *websites*, ferramentas *on-line* e nas referências dos estudos analisados. Foram selecionadas para análise as evidências processadas mais recentes e de maior qualidade (revisões sistemáticas e metanálises) e que melhor respondiam às perguntas estruturadas. Na ausência delas, estudos primários (ensaios clínicos ou coortes) foram incluídos. O risco de viés dos estudos foi avaliado com as ferramentas ROBIS (*Risk of Bias in Systematic Reviews*), RoB 2.0 (*Cochrane Risk of Bias Tools for Randomized Controlled Trials* versão 2.0), QUADAS-C (*Quality Assessment of Diagnostic Accuracy Studies – Comparative*) e ROBINS-I (*Risk of Bias in Non-randomised Studies of Interventions*). A qualidade global do conjunto da evidência para cada desfecho foi avaliada pelo GRADE (*Grading of Recommendations Assessment, Development and Evaluation*).

As recomendações foram baseadas nessas evidências, mediante consenso da comissão de especialistas das três entidades (CBR, SBM e Febrasgo), definido como concordância de, pelo menos, 75% dos membros com a recomendação. Na ausência de concordância inicial, em uma segunda rodada de discussão e votação, maioria simples era necessária para definir consenso. As recomendações foram classificadas em cinco categorias:

- Categoria A – Recomendação forte a favor, baseada em evidência de alta qualidade.
- Categoria B – Recomendação forte a favor, baseada em evidência de moderada qualidade.
- Categoria C – Recomendação fraca a favor, baseada em evidência de baixa qualidade.
- Categoria D – Recomendação a favor, baseada somente em consenso de especialistas.
- Categoria E – Recomendação contra, pois a evidência é insuficiente para apoiar seu uso.

Recomendações para o rastreamento

Rastreamento das mulheres com risco populacional usual

Mamografia

Recomenda-se o rastreamento anual com MG para as mulheres entre 40 e 74 anos, preferencialmente com tecnologia digital (categoria A).

A partir dos 75 anos, recomenda-se continuar o rastreamento se não houver comorbidades que reduzam a expectativa de vida e que esta seja de, pelo menos, sete anos (categoria D).

Ultrassonografia

Não se recomenda a US como rastreamento suplementar ou como método isolado para mulheres com risco habitual (categoria E).

Nota: O uso da US é considerado em situações específicas de maior risco (vide sessão sobre mamas densas, risco intermediário e alto risco).

Ressonância magnética

Não se recomenda a RM como rastreamento suplementar ou como método isolado para mulheres com risco habitual (categoria E).

Nota: O uso da RM é considerado em situações específicas de maior risco (vide sessão sobre mamas densas, risco intermediário e alto risco).

Tomossíntese

Recomenda-se que a TMS em combinação com a MG 2D sintetizada (MGs) ou com a MG 2D padrão (Combo) deve ser considerada no rastreamento, quando disponível (categoria B).

Rastreamento das mulheres com mamas densas

Mamografia

Recomenda-se o rastreamento anual com MG para as mulheres entre 40 e 74 anos, preferencialmente com tecnologia digital (categoria A).

A partir dos 75 anos, recomenda-se continuar o rastreamento se não houver comorbidades que reduzam a expectativa de vida e que esta seja de, pelo menos, sete anos (categoria D).

Ultrassonografia

Recomenda-se que a US anual pode ser considerada como adjunta à MG nas mulheres com mamas densas, exceto quanto a RM for realizada (categoria B).

Ressonância magnética

Recomenda-se que a RM bienal pode ser considerada como adjunta à MG nas mamas extremamente densas (categoria C).

Tomossíntese

Recomenda-se que a TMS em combinação com a MG 2D sintetizada (MGs) ou com a MG 2D padrão (Combo) deve ser considerada no rastreamento, quando disponível (categoria B).

Rastreamento das mulheres com história pessoal de biópsia com hiperplasia lobular atípica, carcinoma lobular in situ clássico e hiperplasia ductal atípica

Nota inicial: É recomendado que as mulheres com hiperplasia lobular atípica (HLA), carcinoma lobular in situ clássico

(CLIS) ou hiperplasia ductal atípica (HDA) sejam avaliadas por modelos de cálculos de risco que incluam essas variáveis em conjunto com outros dados clínicos, incluindo antecedentes familiares e densidade mamária para se estimar o risco de câncer de mama.

Mamografia

Para mulheres com estimativa de risco <20% ao longo da vida, recomenda-se MG anual a partir dos 40 anos (categoria A).

Para mulheres com estimativa de risco ≥20% ao longo da vida, recomenda-se MG anual a partir do diagnóstico (não antes de 30 anos) (categoria B).

Ultrassonografia

Para mulheres com estimativa de risco de 15% a 20% ao longo da vida, a US pode ser considerada como adjunta à MG (categoria D).

Para mulheres com estimativa de risco ≥20% ao longo da vida, a US é recomendada como método alternativo para aquelas que não possam realizar a RM, por quaisquer motivos (categoria B).

Ressonância magnética

Para mulheres com estimativa de risco ≥20% ao longo da vida, a RM anual deve ser considerada como adjunta à MG a partir do diagnóstico (não antes dos 25 anos) (categoria B).

Tomossíntese

Recomenda-se que a TMS em combinação com a MG 2D sintetizada (MGs) ou com a MG 2D padrão (Combo) deve ser considerada no rastreamento, quando disponível (categoria B).

Rastreamento das mulheres com história pessoal de tratamento de câncer de mama invasor ou carcinoma ductal in situ

Mamografia

Mulheres tratadas com cirurgia conservadora devem realizar MG anual (categoria A), com início, no mínimo, seis meses após o término da radioterapia.

Mulheres tratadas com mastectomia devem realizar MG anual apenas da mama contralateral, com início um ano após o término do tratamento (categoria A).

Mulheres submetidas a adenomastectomia podem considerar realizar MG em até um ano para avaliação do tecido fibroglandular residual, a fim de determinar a necessidade da manutenção do rastreamento mamográfico (categoria D).

Ultrassonografia

A US pode ser utilizada no rastreamento complementar à MG quando a RM for indicada, porém, por quaisquer motivos, não puder ser realizada (categoria C).

Ressonância magnética

Mulheres tratadas com cirurgia conservadora ou mastectomia (para avaliação da mama contralateral) que tiveram diagnóstico do câncer de mama antes dos 50 anos ou com mamas densas devem realizar RM anual (categoria C), com início um ano após o término do tratamento.

Tomossíntese

Recomenda-se que a TMS em combinação com a MG 2D sintetizada (MGs) ou com a MG 2D padrão (Combo) deve ser considerada no rastreamento, quando disponível (categoria B).

Rastreamento das mulheres com história pessoal de radioterapia torácica

Mamografia

Mulheres com história de irradiação no tórax antes dos 30 anos de idade devem realizar MG anual a partir do 8º ano após o tratamento radioterápico (não antes dos 30 anos) (categoria A).

Ultrassonografia

A US deve ser utilizada no rastreamento apenas quando a RM, por quaisquer motivos, não puder ser realizada (categoria B).

Ressonância magnética

Mulheres com história de irradiação no tórax antes dos 30 anos de idade devem realizar RM anual a partir do 8º ano após o tratamento radioterápico (não antes dos 25 anos) (categoria A).

Tomossíntese

Recomenda-se que a TMS em combinação com a MG 2D sintetizada (MGs) ou com a MG 2D padrão (Combo) deve ser considerada no rastreamento, quando disponível (categoria B).

Rastreamento das mulheres portadoras de mutação genética ou com forte história familiar de câncer de mama (risco ≥20% ao longo da vida)

Mamografia

Mulheres com mutação patogênica do gene BRCA1 ou não testadas, mas com parentes de primeiro grau portadoras, devem realizar MG anual a partir do diagnóstico da mutação (não antes dos 35 anos) (categoria A).

Mulheres com mutação patogênica do gene TP53 ou não testadas, mas com parentes de primeiro grau portadoras, devem realizar MG anual a partir do diagnóstico da mutação (não antes dos 30 anos) (categoria A).

Mulheres com mutação patogênica BRCA2 ou outros genes de moderado ou alto risco para câncer de mama, além daquelas não testadas, mas com parentes de primeiro grau portadoras,

devem realizar MG anual a partir do diagnóstico da mutação (não antes dos 30 anos) (categoria A).

Mulheres com risco ≥20% ao longo da vida, calculado por um dos modelos matemáticos baseados na história familiar, devem realizar MG anual iniciando 10 anos antes da idade do diagnóstico do parente mais jovem (não antes dos 30 anos) (categoria A).

Ultrassonografia

A US deve ser utilizada no rastreamento apenas quando a RM, por quaisquer motivos, não puder ser realizada (categoria B).

Ressonância magnética

Mulheres com mutação patogênica do gene BRCA1 ou não testadas, mas com parentes de primeiro grau portadoras, devem realizar RM anual a partir do diagnóstico da mutação (não antes dos 25 anos) (categoria A).

Mulheres com mutação patogênica do gene TP53 ou não testadas, mas com parentes de primeiro grau portadoras, devem realizar RM anual a partir do diagnóstico da mutação (não antes dos 20 anos) (categoria A).

Mulheres com mutação patogênica BRCA2 ou outros genes de moderado ou alto risco para câncer de mama, além daquelas não testadas, mas com parentes de primeiro grau portadoras, devem realizar RM anual a partir do diagnóstico da mutação (não antes dos 30 anos) (categoria A).

Mulheres com risco ≥20% ao longo da vida, calculado por um dos modelos matemáticos baseados na história familiar, devem realizar RM anual iniciando 10 anos antes da idade do diagnóstico do parente mais jovem (não antes dos 30 anos) (categoria A).

Tomossíntese

Recomenda-se que a TMS em combinação com a MG 2D sintetizada (MGs) ou com a MG 2D padrão (Combo) deve ser considerada no rastreamento, quando disponível (categoria B).

Justificativa

Os benefícios do rastreamento mamográfico foram avaliados por meio de estudos de coorte, revisões sistemáticas e ensaios clínicos randomizados, demonstrando redução da mortalidade específica por câncer de mama de 22% a 30%, nas mulheres de 40 a 74 anos[2-4,7]. Quando analisados outros desfechos importantes, observou-se também melhor qualidade de vida mensurada pelo QALY (*quality-adjusted life-years*), decorrente de tratamentos menos agressivos[2], além de maior taxa de tumores iniciais, com características prognósticas melhores e axila negativa[3] e 28% menos tumores avançados[4].

Idade de início e periodicidade do rastreamento

O início do rastreamento aos 40 anos reduz em 25% a mortalidade em 10 anos por câncer de mama, porém aumenta o falso-positivo (FP) de 4,8% para 7%[7]. No Brasil também se observa que 41,1% das mulheres com diagnóstico de câncer da mama possuem menos de 50 anos, de acordo com dados do estudo AMAZONA[8]. Quanto ao intervalo de rastreamento, nota-se que o bienal está relacionado a maior risco de tumores avançados (RR=1,28), maiores que 15 mm e com piores fatores prognósticos[7]. Dessa forma, a CNM recomenda o rastreamento anual com MG a partir dos 40 anos.

Considerações sobre as mulheres abaixo de 40 anos

Não é recomendado o rastreamento nesse grupo etário, em razão da menor incidência do câncer de mama (cerca de 7% dos casos). Entretanto o estudo AMAZONA III demonstrou que, no Brasil, esse número é de 17%, com tumores de maiores dimensões e pior prognóstico ao diagnóstico, comparativamente às mulheres acima de 40 anos[9]. Portanto, em concordância com outras sociedades internacionais[10,11], a CNM recomenda que o médico assistente realize uma avaliação da estimativa do risco de câncer de mama para todas as mulheres acima de 30 anos, por meio dos modelos matemáticos, para melhor estratificação das com risco aumentado que poderiam se beneficiar de rastreamento diferenciado.

Quando interromper o rastreamento

Os estudos prospectivos, controlados e randômicos não incluíram mulheres acima de 74 anos, não havendo dados diretos sobre o rastreamento nessa faixa etária. No entanto a expectativa de vida das mulheres tem aumentado, com incidência crescente do câncer de mama na faixa etária acima dos 75 anos. Atualmente, 26% das mortes por câncer de mama ocorrem em mulheres com diagnóstico após os 74 anos[12,13]. Considerando esses fatores, muitas organizações médicas recomendam a individualização da decisão, que deve ser discutida com a mulher.

Efeitos adversos do rastreamento

Alguns efeitos adversos são relatados, porém a qualidade da evidência para análise deles é baixa. O sobrediagnóstico é um efeito discutido, mas sua estimativa é variável, em razão da dificuldade de determinar qual tumor levaria ou não a paciente a óbito[14]. O risco de carcinoma induzido pela radiação empregada no rastreamento mamográfico é baixo, porém é maior em mulheres com mamas volumosas, nas quais a dose de radiação é maior, assim como nas submetidas a incidências complementares[15]. Também foi associado a aumento de 2,9% no risco de biópsias com desfecho benigno (FP), que podem gerar ansiedade[14]. Entretanto a redução da mortalidade do câncer detectado precocemente pelo rastreamento supera os riscos dos danos causados pela exposição à radiação.

Considerações sobre a TMS mamária

A TMS é uma evolução da MG digital. Numerosos estudos confirmam a eficácia dessa tecnologia no rastreamento do câncer de mama, que aumenta a taxa de detecção em até 50%[16-20], bem como

reduz a taxa de reconvocação para imagens adicionais de 9% a 29%[19,20]. Os tumores detectados têm características histológicas e imuno-histoquímicas semelhantes aos detectados pela MG[21-23], com os resultados se mantendo nas rodadas subsequentes[24]. Dessa forma, a TMS é recomendada como método de rastreamento, quando acessível e disponível, pela CNM, assim como por várias sociedades médicas, entre elas o *American College of Radiology* (ACR)[10], *American Cancer Society* (ACS)[25], *European Society of Breast Imaging* (EUSOBI)[26], *Société d'Imagerie de la Femme* (SIFEM)[27], *National Comprehensive Cancer Network* (NCCN)[11] e *European guidelines on breast cancer screening and diagnosis*[28].

A TMS deve ser usada em combinação com a MG 2D padrão (Combo) ou com a MG 2D sintetizada (MGs), esta última com a vantagem de reduzir a dose de radiação[15,17,18]. Como no Brasil a Agência Nacional de Vigilância Sanitária (Anvisa) ainda não estabeleceu os níveis de referência e de tolerância da dose glandular para TMS, a recomendação é que cada serviço deve realizar um levantamento das doses glandulares médias, utilizando uma amostra de pacientes com mamas de diversas espessuras, estabelecendo níveis locais de referência e de tolerância[29,30].

Considerações sobre o rastreamento das mulheres com mamas densas

A mama densa é um fator de risco para câncer de mama e se associa a redução da sensibilidade mamográfica. Por essas razões, métodos suplementares têm sido propostos. Todas as modalidades suplementares melhoraram a sensibilidade em relação à MG isolada, permitindo a detecção de cânceres em estádios iniciais ocultos na MG[31-38].

A RM é a técnica suplementar com maior taxa de detecção adicional de câncer[31]. Isso aumenta a probabilidade de tratamentos menos invasivos e curativos. Dados sobre desfechos críticos, como a mortalidade, não estão disponíveis. Entretanto ensaios randomizados mostraram que o uso suplementar da US na mama densa ou da RM na extremamente densa reduziram a taxa de câncer de intervalo, um importante desfecho substituto centrado na paciente[24,34,39]. Em relação aos danos, o uso de modalidades suplementares se associa a aumento de FPs e biópsias[31,33,35-38]. Dessa forma, a CNM recomenda, para mulheres com mamas densas sem outros fatores de risco, o rastreamento com MG anual a partir dos 40 anos, com a opção do uso de métodos suplementares como a US ou a RM. Para mamas extremamente densas, há evidências científicas sugerindo a superioridade da RM.

Considerações sobre o rastreamento das mulheres com história pessoal de diagnóstico de hiperplasia lobular atípica, carcinoma lobular *in situ* clássico e hiperplasia ductal atípica

A hiperplasia ductal atípica (HDA), a hiperplasia lobular atípica (HLA) e o carcinoma lobular in situ clássico (CLIS) são considerados lesões precursoras não obrigatórias para o carcinoma ductal *in situ* e carcinomas invasivos[40] e conferem aumento de risco relativo para desenvolvimento subsequente destes ao longo da vida, sendo de 2,6 a 5,0 vezes para HDA, de 3,2 a 4,8 vezes para HLA e de 6 a 10 vezes para CLIS[41-49].

Os trabalhos para avaliação do rastreamento neste grupo são poucos e baseados em séries retrospectivas que estimaram o risco para carcinomas *in situ* e invasivos subsequentes. A estratégia atual para se definir o rastreamento neste subgrupo se baseia no cálculo de risco para câncer de mama ao longo da vida[11]. Fatores como a idade ao diagnóstico e a densidade mamária impactam diretamente o risco de câncer, o qual pode ser estimado por ferramentas de cálculo de risco baseado em modelos matemáticos[47]. Atualmente, poucos modelos contemplam esse grupo no cálculo de risco, entre eles o *Breast Cancer Risk Assessment Tool* (modelo de Gail) e o *IBIS Breast Cancer Risk Evaluation Tool* (modelo de Tyrer-Cuzizk), devendo ser estes preferencialmente utilizados[11,47].

Considerações sobre o rastreamento das mulheres com história pessoal de tratamento por câncer de mama invasor e carcinoma ductal *in situ*

Mulheres com história pessoal de câncer de mama apresentam risco sete vezes maior de desenvolver uma segunda neoplasia maligna da mama ipsilateral ou contralateral[48]. Nas pacientes tratadas com cirurgia conservadora, a MG apresenta menor sensibilidade por causa das alterações cirúrgicas e maior incidência de carcinoma intervalar[49], justificando a necessidade de rastreamento suplementar.

O rastreamento complementar com RM pode detectar de 8,2–18,1 cânceres adicionais à MG a cada mil mulheres[50-55]. O desempenho da RM nesse cenário tem-se mostrado similar ao de pacientes com alto risco genético, considerando sensibilidade, taxa de detecção, FP e valor preditivo positivo (VPP) das biópsias[56-58]. Entretanto as evidências científicas para a RM nessa população são fracas, baseadas em estudos predominantemente retrospectivos[49,50,55-59]. Entre esse grupo heterogêneo, o benefício da RM é mais bem estabelecido em pacientes jovens (idade de diagnóstico <50 anos) e com mamas densas[49-52].

Poucos estudos avaliaram a acurácia da US, com taxa de detecção de cânceres adicionais à MG de 2,4 a 4,3/1.000 mulheres, porém com aumento de FP e menor VPP para biópsias. Quando realizada adicionalmente à RM, a US não resulta em melhora da sensibilidade[53,54], mas pode ser utilizada como rastreamento suplementar quando a RM não estiver disponível.

Em pacientes com história pessoal de câncer de mama tratadas com mastectomia, o rastreamento por imagem da mama tratada, com ou sem reconstrução, não está indicada em razão da baixa taxa de detecção de cânceres assintomáticos pela MG, US ou RM[59].

Considerações sobre o rastreamento das mulheres com história de radioterapia torácica

As mulheres tratadas com radioterapia torácica antes dos 30 anos têm um risco médio de desenvolver câncer de mama de 13,4 vezes maior do que a população em geral, semelhante às portadoras da mutação do gene BRCA1[60]. O aumento da incidência ocorre cerca de 10 anos após o tratamento, persistindo 30 anos depois. A maior incidência ocorre quando o tratamento foi realizado entre 10 e 14 anos (RR=22.0) e entre 15 e 19 anos (RR=14.3)[61]. Para esse grupo existem evidências da importância do rastreamento com MG e RM, iniciando a partir dos 25 anos ou oito anos após a radioterapia, em conformidade com as recomendações de outras entidades médicas, como o *Children's Oncology Group* e o *International Guideline Group*[60].

Rastreamento das mulheres portadoras de mutação genética ou com forte história familiar de câncer de mama (risco ≥20% ao longo da vida)

As mutações em genes que causam predisposição ao câncer de mama são classificadas como de alto risco quando causam um aumento de cinco vezes ou mais em relação às mulheres não portadoras (BRCA1, BRCA2, TP53, PTEN, entre outros) ou de risco intermediário quando aumentam entre 1,5–5 vezes (ATM, CHEK 2, BARD1, entre outros)[62-64]. No Brasil, um estudo demonstrou que os genes mais comumente mutados foram BRCA1 (27,4%), BRCA2 (20,3%), TP53 (10,5%), ATM (8,8%), CHEK2 (6,2%) e PALB2 (5,1%)[64]. A variante brasileira TP53 R337H foi fortemente associada ao risco de câncer da mama (OR = 17,4)[64]. No caso das mulheres com forte história familiar de câncer de mama, porém sem mutação conhecida, definiu-se como de alto risco aquelas com estimativa ≥20% de risco ao longo da vida calculado pelos modelos matemáticos[62]. Essas mulheres apresentam o câncer em idade precoce, com picos de incidência entre 20–35 anos para a mutação PT53, 30–39 anos para a mutação BRCA1, 30–49 anos para as mutações BRCA2, assim como entre 40–59 anos para o alto risco familiar[62-65].

Para esse grupo de risco, existem fortes evidências científicas da importância do rastreamento com RM, em virtude da redução de câncer de intervalo e da maior taxa de detecção de tumores em estágios precoces, o que pode reduzir a necessidade de quimioterapia e a mortalidade, apesar do maior número de FPs[54,55,65-67]. Quanto à MG, recentemente tem-se questionado seu papel nas pacientes com mutação BRCA1. Uma metanálise[68] demonstrou que a adição da MG à RM em pacientes com mutação BRCA1 aumentou a sensibilidade de forma modesta (3,99%), com redução na especificidade (4%). Já na mutação BRCA 2, o aumento na sensibilidade foi maior (12,6%), com pequena redução da especificidade (5%). Dessa forma, a CNM recomenda o rastreamento com RM, associado a MG, porém não iniciando a MG antes dos 35 anos para BRCA1 e 30 anos para os demais grupos. Exames adicionais de US não produzem detecção adicional de câncer, se a RM for realizada, devendo ser reservada para avaliação posterior ou servir de guia para a biópsia de achados identificados na RM.

Quanto ao impacto na mortalidade, um estudo importante foi publicado por Bae et al.[54], que, apesar de retrospectivo, demonstrou que as mulheres de alto risco que fizeram o rastreamento com MG e RM tiveram melhor sobrevida global e tumores diagnosticados em estágios de melhor prognóstico do que as pacientes do grupo apenas com MG.

CONCLUSÃO

Esta diretriz traz o consenso das recomendações embasadas em dados atuais para o rastreamento de câncer de mama no Brasil, subdivididas em sessões de acordo com o risco para o desenvolvimento do câncer de mama, desde a abordagem por mulheres de risco habitual, que representam aproximadamente 80% das pacientes diagnosticadas com câncer de mama, até as mulheres de risco aumentado.

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CONTRIBUIÇÃO DOS AUTORES

LABDU: Administração do projeto, Análise formal, Conceitualização, Curadoria de dados, Escrita – primeira redação, Escrita – revisão e edição, Investigação, Metodologia, Obtenção de financiamento, Recursos, Software, Supervisão, Validação, Visualização. LFC: Conceitualização, Curadoria de dados, Escrita – primeira redação, Escrita – revisão e edição, Investigação, Metodologia, Obtenção de financiamento, Software, Supervisão, Validação, Visualização. IBP: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. SPB: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. MBS: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. ALKO: Escrita – primeira

redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. CS: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. TMGO: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. PCM: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. BMMM: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. FEA: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. SJFR: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. EOC: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. HLC: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. GMB: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. JLEF: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. TPM: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. RRJ: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização. JEP: Escrita – primeira redação, Escrita – revisão e edição, Investigação, Software, Validação, Visualização.

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ERRATUM
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In the manuscript "Axillary surgical approach in T1-T2N0M0 clinical breast cancer staging: Survival in a women's hospital cohort in Rio de Janeiro", DOI: 10.29289/2594539420220036, published in the Mastology 2022;32:e20220036, on pages 4-5:

Where it reads:

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.

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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)	
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)	

Continue...

Table 1. Continuation.

	Total*	Axillary surgery N(%)		x^2
	n (%)	SLNB	SLNB+AL[a]	p-value
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 statu				
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; x^2: Pearson's x^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.

ERRATUM
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AUTHORS' CONTRIBUTION

MACS: Writing – original draft.