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EDITORIAL
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ARTIFICIAL INTELLIGENCE AND BREAST RADIOLOGY

A inteligência artificial e a radiologia mamária

Linei Urban[1]*

Artificial intelligence (AI) is a branch of computer science that researches the development of intelligent machines. Its current success results from a history of ups and downs. Since its development in the 1950s, it had moments of complete neglect, mainly in the decades of 1970 and 1980, with cuts in research funding due to discouraging initial results (called AI winter). However, its prestige started to improve at the end of the 1990s, especially after the Deep Blue computer, from IBM, defeated the world chess champion, Garry Kasparov, for the first time. In 2016, AI had another extraordinary victory. A neural network model called AlphaGo beat the world's greatest player of the board game Go, Lee Sedol. Currently, the progress of AI had an impact so large that its true history may be just beginning. The development of machine learning (ML) and deep learning (DL), the latter inspired in biology and mimicking the human cortex, made it possible to process a large volume of data and make complex inferences, often impossible for humans[1,2].

This technology is now reaching the medical field. Specifically in radiology, it can change the way exams are analyzed. Nonetheless, assuming that the role of AI would be restricted to this stage would be too naive. It has the potential to change the whole structure of a radiology clinic, from patient arrival to the delivery of results, reducing costs, and increasing agility[3]. Clinical practice has been implementing four fundamental systems in its procedures:

- Lesion detection system: can identify and classify lesions with better performance than the traditional computer-aided detection (CAD);
- Lesion quantification system: can quantify the lesion regarding its diameter, volume, and distance from anatomical structures (papillae, skin, and others), in addition to comparing the new exam with previous ones automatically;
- Decision support system: helps to decide the best approach for the case, that is, it suggests an algorithm for research;
- Differential diagnosis system: indicates the most likely diagnosis for the lesion, as well as the main differential diagnoses.

However, some points still constitute obstacles for the wide implementation of AI in daily practice: the need for large databases, appropriately cataloged and with a broad representation of populations; a large number of different clinical scenarios for each pathology; and a high number of image findings for each condition. Another known issue is the usual difficulty of introducing to clinical practice a new technology that has been approved in clinical research[3,4].

Moreover, another essential aspect has not been defined yet: AI *regulations and legal liability*. Among the few existing publications, one from the European Union determines that no AI program can finalize a diagnosis, that is, the doctor is legally responsible for it. In the United States, in 2018, the Medical Law included the principle that "physicians must be responsible for diagnosis and therapeutic decisions," given the risk of error that still exists with AI[5]. Nonetheless, in April 2018, the Food and Drug Administration (FDA) approved the first AI device capable of diagnosing retinal lesions without the supervision of a physician. Since then, a series of tools were approved, but all of them are considered closed devices, i.e., their performance does not improve with use. The main issue is regulating devices that can enhance their performance alone. The FDA has recently published a notice declaring that it "is seeking a regulatory balance that will allow promising products to enter the market as soon as possible. However, the approval requires data demonstrating the safety of these tools in a real clinical environment"[5]. Brazil still has no legislation on the subject.

If the current questioning concerns whether AI will replace radiologists or mastologists, the answer is no. At least not in the short run, as we should take two facts into account: first, AI will probably substitute doctors who only describe their findings in an exam. Second, we will need a smaller number of radiologists to perform the same tasks. Nevertheless, the fear and resistance in the face

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of what we do not know are common and expected[6,7]. Thus, it is crucial to clarify some AI-related points:

- AI can work like the human brain: in the most different areas, AI performs only specific tasks in a given context. Each system created is limited to a set of activities. A system as complex and comprehensive as the human brain is still a distant reality;
- AI will eliminate all jobs: AI can store and analyze billions of data, in addition to carrying out tasks based on these analyses, but it cannot create strategies nor solve problems from scratch. Besides, everything that involves humanization will still depend on the interaction between a person and the machine. Jobs, as we know it today, will change, many will cease to exist, but several new ones will be created;
- AI will change the world in a few years: despite the large percentage of positions that have automated part of their processes, currently, this technology can entirely replace less than 10% of activities.

Therefore, the integration between physicians and AI has the potential to improve the workload, enhance individual performance, and reduce the risk of human error. Numerous studies have demonstrated that, currently, for a physician to have access to all information published in their specialty, they would have to study 167 hours per week, that is, more than 20 hours per day. This situation goes beyond our capacity for individual processing. If we can take advantage of the transformative potential of new technologies, we have a great chance of humanizing medicine, elevating the profession, and giving more satisfactory answers to patients regarding their need to be heard and participate in health management and promotion.

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ORIGINAL ARTICLE
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THE COSMETIC OUTCOME OF BREAST RECONSTRUCTION: REPRODUCIBILITY OF DIFFERENT METHODS ASSESSED BY DIFFERENT PROFESSIONALS

Resultado estético após reconstrução mamária: reprodutibilidade de diferentes métodos avaliados por diferentes profissionais

Hugo Andrade Bayeh[1], Regis Resende Paulinelli[1], Leonardo Ribeiro Soares[1], Ana-Carolina Lagos Prates[1], Pauline Camargo Morais[1], Izabela Cristina Souza de Albuquerque[1], Aloisio Garcia Souza[2], Tuanny Roberta Beloti[2], Ruffo Freitas-Junior[1]*

ABSTRACT

Objective: To compare the reproducibility of different methods for assessing the cosmetic outcome of breast reconstruction, which was assessed by different health professionals. **Methods:** Photographs of 270 breast cancer patients who had been submitted to breast reconstruction of some type were included. A plastic surgeon, a resident in plastic surgery, two mastologists, two residents in mastology, and two psychologists performed the evaluation. The modified Garbay and Harvard scales and the objective BCCT.core software program were used. Cohen's Kappa and Spearman correlation coefficients were calculated. **Results:** The mean age of the patients was 55.7 (±11.1) years. Overall, 145 women (53.7%) underwent partial breast reconstruction and 125 (46.3%), total breast reconstruction. The mean follow-up time was 63.7±45.6 months. By applying the Harvard scale, the interobserver reproducibility among the different professionals was minimal; whereas the Garbay scale had no agreement. The correlations between the BCCT.core software program and the Harvard and modified Garbay scales were moderate. **Conclusion:** Correlations between both the modified Garbay scale and the Harvard scale and the objective (BCCT.core) test were moderate. There was less interobserver variability with the Harvard scale compared to the modified Garbay scale.

KEYWORDS: breast neoplasms; reconstructive surgical procedures; surgery, plastic.

RESUMO

Objetivo: Comparar a reprodutibilidade de métodos diferentes de avaliação dos resultados estéticos de cirurgias reconstrutivas da mama, por avaliadores distintos. **Métodos:** Foram incluídas fotografias de 270 pacientes portadoras de neoplasia da mama que passaram por cirurgias reconstrutivas da mama. As notas da avaliação foram dadas por um cirurgião plástico, um residente em cirurgia plástica, dois mastologistas, dois residentes em mastologia e dois psicólogos. Foram utilizadas as escalas de Harvard e Garbay modificada e a nota objetiva do programa BCCT.core. Foram calculados os índice Kappa de concordância interobservador e de correlação de Spearman. **Resultados:** A média de idade das pacientes foi de 55,7 anos (±11,1). No geral, 145 (53,7%) mulheres foram submetidas a tratamento conservador com cirurgia oncoplástica e 125 (46,3%) passaram por mastectomia e reconstrução total. A média de tempo de seguimento foi de 63,7±45,6 meses. Para a escala de Harvard, houve uma reprodutibilidade interobservador razoável para os diferentes profissionais, enquanto na escala de Garbay, a reprodutibilidade foi pobre entre os profissionais. De forma geral, a nota dada pelo programa BCCT.core correlacionou-se moderadamente com a escala de Harvard e a de Garbay modificada. **Conclusão:** As escalas de Harvard e de Garbay modificada correlacionam-se igualmente de forma moderada com o teste objetivo (BCCT.core). A escala de Harvard tem menor variabilidade interobservador, se comparada com a escala de Garbay.

PALAVRAS-CHAVE: neoplasias da mama; procedimentos cirúrgicos reconstrutivos; cirurgia plástica.

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INTRODUCTION

Breast-conserving surgery is widely used today in the treatment of locoregional breast cancer[1]. When radical surgery is required, immediate or delayed, breast reconstruction can be performed in a large proportion of cases. The breast reconstruction cosmetic outcome may vary. Its assessment in a standardized manner is difficult[2]. Some methods have been developed to standardize cosmetic evaluation, including the BCCT.core software program[3], the Garbay[4] and Harvard scales[5-7].

Difficulties involved in aesthetic evaluation following breast cancer surgery include the lack of a gold-standard method. Likewise, considerable interobserver variability has been found[6], and there is a lack of agreement when the results of evaluation are compared between healthcare professionals and the patients themselves.

BCCT.core is an objective method that was initially developed to standardize and quantify the cosmetic outcome of breast-conserving surgery[7]. It was later validated for the breast reconstruction evaluation following mastectomy[8]. This software program performs a photographic evaluation of the breasts by analyzing different parameters related to symmetry, scarring, and skin coloring[3,7]. BCCT.core is currently the most commonly used method for the aesthetic evaluation of breast cancer patients. Its results are classified as excellent, good, fair, or poor[9].

The method developed and modified by Garbay et al.[4] takes the volume, shape, and placement of the breast into consideration, as well as the location of the inframammary fold and the final scar appearance. One advantage of this scale is the number of analyzed parameters, which may result in a more complete evaluation of the outcome[10]. The Harvard scale, on the other hand, evaluates only postoperative symmetry and classifies it in four categories according to the degree of distortion of the operated breast in relation to the normal breast[11].

Few studies have been published on the reproducibility of different methods of evaluating cosmetic outcome in the same population, from the patient's point of view and in the opinion of a multidisciplinary healthcare team[10,12]. The present study aimed to compare the reproducibility of three methods used to evaluate the breast reconstruction cosmetic outcome according to the type of evaluator.

METHODS

This was a retrospective cohort study conducted in a private clinic and in a tertiary referral hospital for the treatment of breast pathologies. Frontal photographs of 270 patients who had completed six months since radiotherapy (or since having surgery if radiotherapy was not required) were included in the study. All the patients had been diagnosed with breast cancer and submitted to breast-conserving surgery or radical mastectomy, with partial or total breast reconstruction. Data were collected between January 2015 and September 2016, when the patients returned for a scheduled follow-up visit. Patients with local recurrences that could negatively affect the cosmetic outcome were excluded from the study, as were those undergoing reconstruction with the use of a temporary tissue expander who had not exchanged it yet for a permanent breast implant.

Evaluation methods

Evaluation was conducted by members of a multidisciplinary team, consisting of a plastic surgeon and a plastic surgery resident, two breast specialists trained in breast reconstruction, two medical residents specializing in breast disease, and two psychologists. The analyses were performed blindly and randomly, without any type of patient or assistant team's identification. The Harvard scale[5-7], the modified Garbay scale[4] and the score given by the BCCT.core objective software tool were compared (Chart 1 and Figure 1).

Statistical analysis

The SPSS statistical software program and the <www.statstodo.com> internet page were used for the statistical analysis. Measures of central tendency and percentages were calculated, as well as Cohen's Kappa coefficient to measure interobserver agreement and Spearman's rank-order correlation (rho). The Kappa coefficient ranges from 0.0 to 1.0, and agreement was classified as:

- between 0.01 and 0.20: slight;
- between 0.21 and 0.40: fair;
- between 0.41 and 0.60: moderate;
- between 0.61 and 0.80: substantial;
- between 0.81 and 1.0: almost perfect[13,14].

Spearman's correlation coefficient ρ ranges from -1 to 1, and the closer it lies to one of these extremes, the greater the association between the variables.

Ethics approval and consent to participate

The internal review board of the Teaching Hospital from Universidade Federal de Goiás approved the study protocol (018/2015), and the procedures were conducted in accordance with the principles defined in the Helsinki convention. The participants were volunteers and signed an informed consent form prior to their admission to the study.

RESULTS

A total of 270 women were included in the study, in which 176 patients (65.2%) were from a private clinic and 94 (34.8%) were from a public hospital. Mean time of follow-up was 63.7±45.6 months. The mean age of the patients was 55.7±11.1 years. Breast cancer was classified as invasive ductal carcinoma in 200 cases (74.3%). In 208 cases (80.9%), the disease was at an early stage (0, 1 or 2). Breast-conserving surgery with partial breast reconstruction was

the treatment of choice in 145 cases (53.7%). In 144 women (53.3%), contralateral symmetrization was performed. Reconstruction was immediate in 254 cases (94.1%) and was performed by a breast specialist in 208 cases (77.9%). Breast reconstruction consisted of a one-stage surgical procedure in 185 cases (68.5%). The nipple-areola complex was reconstructed in 55 patients (45.8%) in whom it had been removed. Some type of early or late complication was found in 48% of the patients. Characteristics of the patients, disease, and treatment are provided in greater details in Table 1.

Interobserver reproducibility with the Harvard scale was fair among different professionals (Kappa=0.27) and poor between plastic surgeons and psychologists (Kappa=0.17); however, the difference was not statistically significant (Table 2). Reproducibility with the Garbay scale was equally poor among the different professionals (Kappa=0.12).

In general, correlation between the score provided by the BCCT.core software program and Harvard (Rho BCCT 0.39 to 0.61) and modified Garbay (Rho BCCT 0.37 to 0.58) scores was moderate, with no statistically significant difference between them. The plastic surgery resident (42.2%) and the plastic surgeon (15.6%) were more likely to rate the outcome as poor compared to the other professionals (range 3.0–14.1%) and to the BCCT.core program (6.7%). The BCCT.core program was more likely to rate the results as good and more likely to avoid the extremes (poor and excellent), as seen in Tables 3 and 4.

DISCUSSION

Evaluation of the breast reconstruction cosmetic outcome is controversial, not only with respect to the selection of optimal methods, but also regarding the interpretation of the obtained results. Nevertheless, these results need to be validated in different population subgroups. This is the largest study to focus specifically on the methodology of evaluation. In addition, it aimed at comparing the Harvard scale, the modified Garbay scale, and the BCCT.core software program.

The greater the number of involved parameters and the more complex the model of evaluation, the poorer a method

Chart 1. Chart showing the modified Garbay[10] and Harvard scales[5-7] for the breast reconstruction cosmetic outcome.

Garbay scale			
Parameter / Score	**0 points**	**1 point**	**2 points**
Breast volume	Marked discrepancy relative to contralateral side	Mild discrepancy relative to contralateral side	Symmetrical volume
Breast shape	Marked contour deformity or shape asymmetry	Mild contour deformity or shape asymmetry	Natural or symmetrical contour
Breast placement	Marked displacement	Mild displacement	Symmetrical and aesthetic placement
Inframammary fold	Poorly defined / unidentified	Defined, but asymmetrical	Defined and symmetrical
Breast scars	Poor (hypertrophy, contracture)	Fair (wide scars, poor color match, but no hypertrophy or contracture)	Good (thin scars, good color match)
Harvard scale			
Category	**Results**		
Excellent	Treated breast nearly identical to untreated breast		
Good	Treated breast slightly different from untreated breast		
Fair	Treated breast clearly different from untreated breast, but not seriously distorted		
Poor	Treated breast seriously distorted		

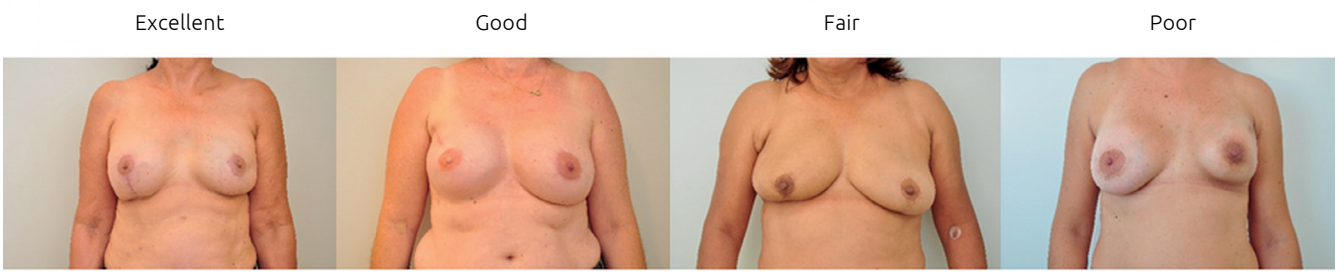

Figure 1. Examples of photograph classification according to evaluations performed with the BCCT.core computer software program regarding the breast reconstruction cosmetic outcome.

reproducibility tends to be[15]. This statement is also valid for the present study, in which the Harvard scale, which is the simplest, also proved to be the most reproducible among healthcare professionals. Thus, in view of the inherent limitations of the evaluation methods and absence of a gold-standard method to evaluate the breast reconstruction cosmetic outcome, it may be advisable to perform the evaluation using more than one method and with more than one professional.

Correlations between the objective test (BCCT.core) and both the modified Garbay scale and the Harvard scale were equally moderate. The lowest interobserver variability was found with the Harvard score, because it is simpler, with fewer categories. Despite the poor reproducibility between the used scales, the correlation between both scales and the objective (BCCT.core) evaluation was similar and either can be used according to the observer's preference.

Patients tend to be more satisfied with the outcome of breast reconstruction compared to observers from the healthcare professions, with this rater role being generally played by surgeons[16,17]. This is expected, since both the BCCT.core program and the Harvard and modified Garbay scales concentrate on symmetry. Thus, symmetry does not always coincide with the beauty concept. Therefore, patients could have symmetrical breasts but be dissatisfied with their appearance and, inversely, despite a certain degree of asymmetry, they may consider their breasts more attractive than they were before the cancer treatment, for

Table 1. Descriptive data on characteristics of the patients, the tumors, and the treatment provided.

	Mean	SD	n	%
Patients' characteristics				
Age (years)	55.7	11.2		
Body mass index	26.3	4.15		
Smoker			13	4.9
Former smoker			31	11.7
Diabetic			25	9.3
Hypertensive			97	36.5
Previous breast surgery			65	27.4
Disease characteristics				
Clinical size of the tumor (mm)	34.5	23.5		
Clinical staging				
0			7	2.7
I			81	31.5
II			120	46.7
III			46	17.9
IV			3	1.2
Histological type				
Invasive ductal carcinoma			200	74.3
Invasive lobular carcinoma			16	5.9
In situ ductal carcinoma			34	12.6
Grade 2			148	59
Subtype*				
Luminal A			103	45.0
Luminal B			46	20.1
Luminal B/HER			36	15.7
HER			18	7.9
Triple negative			26	11.3
Follow-up (months) 63.7 45.6				
Local recurrence			9	3.3
Metastases			6	2.2
Treatment characteristics				
Reconstruction				
Partial			145	53.7
Total			125	46.3
Immediate			254	94.1
Delayed			16	5.9
Contralateral symmetrization			132	48.9
Reconstruction of the nipple-areola complex (when removed)			55	45.8
Number of surgeries				
1			185	68.5
2			51	18.9
≥3			34	12.6
Type of reconstruction				
Oncoplasty			134	51.1
Prosthesis/tissue expander			58	22.1
Pedicle TRAM flap			66	25.2
Latissimus dorsi flap			4	1.5
Surgeon performing breast reconstruction				
Breast specialist			208	77.9
Plastic surgeon			59	22.1
Chemotherapy			176	65.2
Hormone therapy			216	81.2
Trastuzumab			32	12.1
Radiotherapy			197	74.4
Early complication			98	36.3
Late complication (>2 months)			83	30.9
Any complication**			131	48.7

*Luminal A (ER+ and/or PR+, HER2- and Ki67<14%), Luminal B (ER+ and/or PR+, HER2- and Ki-67≥14%), Luminal B/HER (ER+ and/or PR+, HER2+), HER (ER-, PR- and HER2+), and Triple negative (ER-, PR- and HER2-); **early and/or late complication; TRAM: transverse rectus abdominis myocutaneous; HER2: human epidermal growth-factor receptor 2; ER: estrogen receptor; PR: progesterone receptor; SD: standard deviation.

Table 2. Interobserver variability according to the Harvard and Garbay scales.

Harvard scale	Kappa	95%CI
Among breast specialists	0.35	0.32–0.38
Among plastic surgeons	0.27	0.19–0.34
Among psychologists	0.23	0.14–0.32
Between breast specialists and plastic surgeons	0.28	0.26–0.29
Between breast specialists and psychologists	0.33	0.31–0.35
Between plastic surgeons and psychologists	0.17	0.14–0.20
Among all professionals	0.27	0.26–0.29
Garbay scale	**Kappa**	**95%CI**
Among breast specialists	0.13	0.11–0.15
Among plastic surgeons	0.16	0.10–0.22
Among psychologists	0.16	0.09–0.22
Between breast specialists and plastic surgeons	0.12	0.11–0.13
Between breast specialists and psychologists	0.14	0.12–0.15
Between plastic surgeons and psychologists	0.1	0.08–0.12
Among all professionals	0.12	0.11–0.13

CI: confidence interval of 95%.

instance. Hence, new evaluation methods should be developed and investigated to include a broader measure of cosmetic appearance that would better correspond to the patients' expectations and possibly to their degree of satisfaction[18].

In the majority of previous evaluations made by patients, professionals or the BCCT.core program, outcome was reported as good or excellent, with rates similar to those cited in the literature, depending on the criteria taken into consideration[3,6,17]. In the present study, curiously, the scores awarded by plastic surgeons for the cosmetic outcome were the lowest. Nevertheless, the correlations between their scores and the objective evaluation made by the computer software program were similar to those of other professionals, rendering them equally valid. Conversely, Leonardi et al. found that plastic surgeons and male professionals tended to provide better scores for the outcome[6]. The explanation given by those investigators for this phenomenon was that, in such study, the plastic surgeons were rating their own results and thus tended to be more tolerant and more aware of the difficulties involved in each case. A similar explanation could be given here, since the breast specialists performed over three-quarters of breast reconstructions.

In the present study, more than half of the patients underwent partial breast reconstruction, a procedure usually associated with

Table 3. Correlation between the scores awarded by professionals according to the Harvard Scale and the scores given by the BCCT.core software program.

Frequency (%)	Poor		Fair		Good		Excellent		Rho BCCT	95%CI
	n	%	n	%	n	%	n	%		
Senior breast specialist	13	4.8	82	30.4	115	42.6	60	22.2	0.61	0.51–0.70
Junior breast specialist	38	14.1	59	21.9	91	33.7	82	30.4	0.49	0.39–0.60
Second-year resident/ breast disease program	24	8.9	97	35.9	86	31.9	63	23.3	0.5	0.38–0.59
First-year resident/ breast disease program	25	9.3	88	32.6	63	23.3	94	34.8	0.42	0.32–0.53
Senior plastic surgeon	42	15.6	98	36.3	80	29.6	50	18.5	0.48	0.38–0.59
Plastic surgery resident	114	42.2	65	24.1	68	25.2	23	8.5	0.48	0.38–0.59
Senior psychologist	22	8.1	74	27.4	120	44.4	54	20.0	0.54	0.42–0.63
Junior psychologist	8	3.0	37	13.7	116	43.0	109	40.4	0.39	0.29–0.51
BCCT.core	18	6.7	77	28.5	144	53.3	31	11.5	1	–

CI: confidence interval of 95%.

Table 4. Modified Garbay Scale: mean scores and correlation with scores given by the BCCT.core software program.

	Mean (±SD) 95%CI		Rho BCCT (95%CI)	
Senior breast specialist	7.16 (±1.93)	6.92–7.39	0.58	0.47–0.67
Junior breast specialist	7.37 (±2.68)	7.05–7.69	0.51	0.39–0.60
Second-year resident/ breast disease program	7.04 (±1.74)	6.83–7.25	0.46	0.36–0.57
First-year resident/ breast disease program	7.07 (±2.27)	6.8–7.35	0.42	0.31–0.53
Senior plastic surgeon	5.68 (±2.49)	5.38–5.98	0.41	0.31–0.53
Plastic surgery resident	6.36 (±2.08)	6.11–6.61	0.49	0.40–0.61
Senior psychologist	6.66 (±2.34)	6.38–6.94	0.48	0.37–0.59
Junior psychologist	7.47 (±1.71)	7.27–7.67	0.37	0.29–0.51

CI: confidence interval; SD: standard deviation.

lower morbidity, better aesthetic results, greater degree of satisfaction and the same oncologic benefit[17,19,20]. The complication rates can be considered normal, since the criteria established for recording the complications were extremely rigorous and even minimal changes were considered to represent events, including a slightly wider than normal scar, a small seroma, a small depression, or an oil cyst seen at mammography, for example. The complication rates cited in literature vary widely as a result of the different adopted criteria. Most of the studies fail to clearly describe their complication definition and fail to report on the severity of events. Hence, while some authors already consider the presence of subclinical fat necrosis following a transverse rectus abdominis myocutaneous (TRAM) flap procedure to be a complication, others only register a complication when there is flap necrosis with losses exceeding 20%[21-23].

Some potential limitations of our study were the retrospective design and the evaluation of results by the same team that operated the patients. However, the analyses were performed blindly and randomly, which reduces the possibility of measurement bias. Also, patients with different postoperative periods were included, which may have influenced the distribution of results considered to be poor, fair, good or excellent. Finally, the limitations inherent in the photographic registration[24] may also justify small differences in cosmetic results between different methods and populations.

CONCLUSION

Correlations between the modified Garbay and the Harvard scales and the objective test (BCCT.core) were equally moderate. Interobserver variability was lower with the Harvard scale. Although scores may vary depending on the observer, all correlations were valid in accordance with the objective test.

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BREAST CANCER SURVIVORS HAVE LESS LEAN MASS AND LOWER PHASE ANGLE AFTER CANCER TREATMENT

Sobreviventes do câncer de mama tem menos massa magra e menor ângulo de fase após o tratamento oncológico

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ABSTRACT

Objective: To evaluate the weight status and body composition of women who survived breast cancer after cancer treatment. **Methods:** This is a before and after clinical study, in which 27 breast cancer survivors were evaluated before (T0) and after (T1) cancer treatment (surgical and clinical). Current weight and height were measured to determine the body mass index (BMI). Body composition was assessed by tetrapolar bioelectrical impedance. The percentage of fat and lean mass and the phase angle were calculated. We used Student's *t*-test to assess the difference among means of anthropometric variables and body composition between T0 and T1, and the McNemar's test to evaluate differences in the prevalence of overweight, adopting a 5% significance. **Results:** Patients have a mean increase of 2.6 kg in weight after treatment (p=0.00) and 1.15 km/m^2 in BMI (p=0.00). The percentage of fat mass increased by 0.6% (p=0.003) in T1, while the lean mass decreased (p=0.03). Concerning the phase angle, the mean decrease is 0.6 (p=0.026) after treatment. **Conclusion:** Breast cancer survivors have increased adiposity, decreased lean mass, and compromised cell integrity after cancer treatment, suggesting elevated risk factors for disease recurrence.

KEYWORDS: breast cancer; survivors; drug therapy; body composition.

RESUMO

Objetivo: Avaliar o estado do peso e a composição corporal de mulheres sobreviventes do câncer de mama após tratamento oncológico. **Metodologia:** Trata-se de estudo clínico do tipo antes e depois, em que 27 pacientes sobreviventes do câncer de mama foram avaliadas antes (T0) e depois (T1) do tratamento oncológico (cirúrgico e clínico). Aferiram-se peso atual e estatura para definição do índice de massa corporal (IMC). A avaliação da composição corporal deu-se por impedância bioelétrica tetrapolar, sendo aferidos percentual de massa gorda e de massa magra e ângulo de fase. Aplicou-se o teste *t* de Student para avaliar a diferença de médias das variáveis antropométricas e de composição corporal entre T0 e T1, bem como o teste de McNemar para avaliar diferenças na prevalência de sobrepeso, adotando significância de 5%. **Resultados:** As pacientes têm aumento médio de 2,6 kg após o tratamento (p=0,00) e 1,15 kg/m^2 no IMC (p=0,00). O percentual de massa gorda aumenta 0,6% (p=0,003) e há redução na massa magra (p=0,03) no T1. Em relação ao ângulo de fase, há diminuição média de 0,6 (p=0,026) após o tratamento. **Conclusão:** Mulheres sobreviventes do câncer de mama têm aumento de adiposidade, redução da massa magra e piora da integridade celular após o tratamento oncológico, o que sugere acréscimo de fatores de risco para recidiva da doença.

PALAVRAS-CHAVE: câncer de mama; sobreviventes; tratamento farmacológico; composição corporal.

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INTRODUCTION

Breast cancer is the most prevalent kind of neoplasm among women. It is considered a serious public health problem[1]. In 2012, the number of women diagnosed with breast cancer worldwide was 1.67 million, corresponding to 25% of all cancers[2]. According to an estimate from the International Agency for Research on Cancer (IARC)[3], there will be more than three million new cases and about 900,000 deaths from breast cancer in 2040. In Brazil, the epidemiological pattern is similar to that of the world, with the emergence of 57,900 cases of breast cancer among women being expected for the biennium 2018/2019. Among them, 11,800 will occur in the Northeast Region, representing 20.3% of all cases[1].

In parallel with the high incidence, breast cancer treatments have resulted in more effective outcomes, with a consequent increase in disease-free survival time[4]; however, important side effects are associated with antineoplastic therapies. Weight variation is a common condition during and after breast cancer treatment, and 50 to 96% of women in the early stage of the disease experience significant weight gain in this period. In addition to weight gain, breast cancer patients present unfavorable changes in body composition, with a significant increase in the percentage of adipose tissue and decreased lean body mass[5].

In this sense, body composition emerged as an important prognostic factor in cancer patients[6], because most of the adipose tissue is associated with the presence of chronic low-grade inflammation, with the consequent increase in cell proliferation and decrease in apoptosis[7]. Also, the smaller amount of muscle mass raises the risk of surgical complications and reduces quality of life and survival[8]. Despite the evidence, studies that assess the body composition of Brazilian women who survived breast cancer before and after cancer treatment are still scarce[9].

In this study, we hypothesize that breast cancer survivors gain weight and undergo changes in their body composition after cancer treatment, with increased fat mass and reduced lean mass. Thus, we aimed at evaluating the weight status and body composition of breast cancer survivors after cancer treatment.

METHODS

This is a before and after clinical study, conducted at Centro Regional Integrado de Oncologia (CRIO), in Fortaleza (CE), Brazil, with 27 patients diagnosed with breast cancer. Data were collected in two moments:

- T0: before the start of clinical treatment;
- T1: at the end of clinical treatment (chemotherapy or radiotherapy), between January 2010 and March 2011.

The study used a consecutive non-probabilistic convenience sample, and patients aged over 19 years and under 60 years, without previous clinical cancer treatment, were considered eligible.

Information about age, years of schooling, family income in minimum wages (MW), tumor location, clinical staging (CS), and type of clinical treatment performed (chemotherapy or chemotherapy + radiotherapy) was gathered by means of direct interview and search of medical records.

Current weight (CW), height, and body composition were considered and measured in moments T0 and T1 to establish the nutritional diagnosis. A Welmy® mechanical scale, with a capacity of 150.0 kg and precision of 100.0 g, was used to measure the CW. The stadiometer of the scale was used to measure the height. Body mass index (BMI) was calculated using the equation weight (kg)/height^2 (m) and evaluated according to the classification of the World Health Organization (WHO)[10]. Percentages of fat mass (%FM) and muscle mass (%MM) and the phase angle (PA) were obtained by bioelectrical impedance analysis (BIA) using the BIA 450e bioimpedance analyzer from Biodynamics®. The evaluation of the patients' %FM followed the Lohman classification[11], and the PA reference values followed the parameters described by Barbosa-Silva et al.[12].

Qualitative variables are presented as simple frequency and absolute numbers. Quantitative data are expressed as mean and standard deviation. The normality of the variables was verified using the Kolmogorov-Smirnov test to continue the evaluation of the difference in weight, BMI, %FM, %LM, and PA averages between moments T0 and T1. The normal distribution of the variables allowed the use of Student's *t*-test to compare the means. McNemar's test verified the difference in overweight prevalence between the two moments. All analyses used the Statistical Package for Social Sciences (SPSS), version 20.0, considering a 5% significance.

The Research Ethics Committee of the Universidade de Fortaleza (No. 359/2009) and CRIO approved this study. All participants were informed about the study and signed the informed consent form.

RESULTS

Patients had a mean age of 47 years (±6.6). Most had five or fewer years (62.9%) of schooling and a family income lower than three MW (77.8%). Regarding the clinical profile, all women had ductal carcinoma, and 25.9% were in CS III (Table 1). Out of the 27 patients evaluated at T0, 18 were assessed at T1. We lost three patients throughout the follow-up, as they refused to participate in T1, one who died, and five because we were not able to contact them again. The overweight prevalence (including obesity) was similar before (77.7%) and after treatment (83.3%) (p=0.50).

A significant weight increase (p=0.00) was present among women after cancer treatment, ranging from 0.4 to 4.8 kg, with a mean of 2.6 kg. BMI also showed a significant increase of 1.15 kg/m^2 (p=0.00) (Table 2).

Table 1. Description of socioeconomic and clinical characteristics and body mass index (BMI) status of patients.

Variable	n	%
Schooling		
<5 years	17	62.9
>5 years	10	36.1
Family income		
0–3 MW	21	77.8
>3 MW	6	22.2
Tumor location		
Ductal	27	100
Lobular	0	0
Clinical staging		
I	4	14.8
II	5	18.5
III	7	25.9
Not described*	11	40.8
BMI status†		
Moment T0		
Normal weight	6	22.3
Overweight**	21	77.7
Moment T1§		
Normal weight	3	16.7
Overweight**	15	83.3

MW: Minimum wage (MW in 2010: R$ 510/MW in 2011: R$ 545); BMI: body mass index; T0: before the first cycle of chemotherapy; T1: end of the last cycle of chemotherapy and/or radiotherapy; *information not described in the medical records; **overweight and obesity; §only 18 women were reevaluated at T1; †McNemar's Test: difference between the prevalence of overweight at T0 and T1 (p=0.50).

Table 2. Weight, body mass index (BMI), and body composition status at moments T0 and T1.

Variable	Moment of evaluation	Values	p
Current weight	T0	66.6	0.00*
	T1	69.2	
BMI	T0	28.4	0.00*
	T1	29.5	
%LM	T0	65.3	0.03*
	T1	64.5	
%FM	T0	34.7	0.04*
	T1	35.3	
PA	T0	6.6	0.026*
	T1	6.0	

T0: before the first cycle of chemotherapy; T1: end of the last cycle of chemotherapy and/or radiotherapy; %LM: lean mass percentage; %FM: fat mass percentage; PA: phase angle; *Student's *t*-test (p<0.05).

Evaluating body composition, we found a significant reduction in %LM (p=0.03) and PA (p=0.026) and a significant increase in %FM (p=0.04) after cancer treatment (Table 2).

DISCUSSION

This study aimed to evaluate the body composition of breast cancer survivors after cancer treatment and show that patients have an increase in %FM and a reduction in %LM and PA. Also, an important weight and BMI increase stood out after clinical antineoplastic treatment. These findings reveal a worrying scenario among breast cancer survivors living in Northeastern Brazil, given the presence of adiposity, clearly described as a risk factor for disease recurrence[13] because of the numerous metabolic changes triggered by the state of chronic low-grade inflammation[14].

Weight gain during chemotherapy treatment can range from 2.5 to 6.2 kg, and gains of more than 10 kg[15] are not uncommon. This condition has been reported in the literature since 1985, when Heasman et al.[16] revealed this change in women with breast cancer for the first time. Our group has previously described this condition in patients living in the Southeast Region of Brazil, who, after three months of chemotherapy treatment, presented an average weight gain of 3 kg and an increase of 1 kg/m^2 in BMI[9]. However, in the Northeast Region, socioeconomic conditions are very different, especially in relation to income and schooling, aspects that greatly interfere in the nutritional status of individuals. The region has the highest prevalence of inadequate macro and micronutrient intake[17] in Brazil according to results from the survey *Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (Vigitel),[18] which indicate that the increase in overweight and obesity among Brazilian women is greater in those with lower levels of education. Thus, the findings of the present study fill this gap in the national literature concerning weight status and body composition of Northeastern women who survived cancer. In addition, they answer a call from the third report of the World Cancer Research Fund (WCRF)[19] entitled *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective,* which indicates the lack of studies that assess diet, nutrition, and physical activity in cancer patients from low-income countries.

The causes for weight gain after breast cancer diagnosis are unclear; however, they might involve changes in the woman's energy metabolism, including reduced basal metabolic rate, decreased physical activity and thermogenesis, and increased food intake[20]. In our study, weight gain ranged from 0.8 to 4.8 kg, and more than 80% of patients showed overweight after treatment. This result is similar to that found by Yeo et al.[21], who evaluated women with breast cancer and found that 52.1% of patients reached a BMI corresponding to overweight/obesity. This condition of weight gain and change in nutritional status has been widely discussed[6], especially when it comes to weight gain in adulthood[22], notably

recognized as a risk factor for breast cancer. However, weight gain in surviving women, which begins during cancer treatment, needs to be seen as a risk factor for recurrence, lower survival, and worse quality of life for these patients. Some authors have recognized[23] the value of providing guidance on lifestyle modification for these patients in order to minimize weight gain and ensure a better prognosis, given the importance of understanding that self-care affects patient survival.

Several mechanisms seek to explain the relationship between obesity and the worse prognosis for breast cancer patients, and all of them converge on endocrine and metabolic changes promoted by excess adipose tissue[24]. This fact has been attributed, in part, to the high levels of circulating estrogen caused by the increased expression of aromatase, stimulated by the high percentages of adipose tissue, and also due to the presence of inflammatory mediators chronically released by this tissue. Among these mediators, tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) act by stimulating the cell cycle and inhibiting apoptosis, which contributes to tumor progression[24].

In addition, insulin, insulin-like growth factor (IGF-1), and leptin increase in the presence of obesity and favor breast carcinogenesis[14]. Insulin indirectly influences cancer growth and metastatic potential, because the rise in its levels promotes synthesis and intensifies IGF-1 activity. In turn, IGF-1 is involved in regulating the growth, survival, and differentiation of neoplastic cells and, together with other growth factors, can act synergistically to increase the mitogenic potential of these cells[13]. Similarly to insulin and IGF-1, leptin plays pro-carcinogenic roles, such as stimulation of normal and tumor cell growth, cell migration and invasion, and enhancement of angiogenesis, which suggest its direct relationship with an aggressive type of breast cancer or its participation in increasing tumor aggressiveness with a higher chance of metastasis[14].

Thus, the importance of knowing, besides weight and BMI, the body composition of these patients becomes clear, given the evidence of a change in body composition after the diagnosis and treatment of breast cancer, with increased adipose tissue and reduced lean tissue, leading to the development of sarcopenic obesity[25]. Women evaluated in this study presented reduced lean mass and increased fat mass after cancer treatment, corroborating the results by Cisneros et al.[26], in which women with the same cancer diagnosis had increased fat mass and reduced lean mass after chemotherapy.

In addition to excess fat, the reduction in lean mass identified in the patients evaluated also needs attention. Literature has shown an association between lower muscle mass and the diagnosis for a variety of cancer types, including breast cancer. Also, this decrease in muscle mass raises the risk of surgical complications and reduces quality of life and survival[9]. Mazzuca et al. [27] identified %LM below the desired in women with breast cancer soon after diagnosis, and that this percentage continued to drop after cancer treatment, corroborating our results. Individuals with less lean mass should receive higher doses of chemotherapy per unit of body weight, which may lead to greater treatment toxicity. Besides, recent studies attest to deleterious effects caused by the loss of lean mass in breast cancer patients, resulting in longer hospital stay, toxicity, and mortality[6].

In addition to fat and lean mass, PA has been described as an important predictor of clinical prognosis among body composition parameters. It is understood as a marker of cell integrity and cell membranes that attributes a functional status to these structures. Low PA suggests cell death or decreased cell integrity, while higher PA indicates healthy cell membrane[28]. Thus, low PA values point to changes in cell integrity, which, in cancer patients, may be associated with worse prognosis, lower survival, and quality of life impairment[28].

In this study, patients had lower PA after chemotherapy, which may indicate a worse prognosis. According to Gupta et al.[29], who investigated PA as an indicator of the prognosis for breast cancer, the mean PA score in these patients was 5.6 (1.5–8.9). Those with PA≤5.6 had a median survival of 23.1 months, while patients with a value >5.6 had survival of 49.9 months. The difference is statistically significant (p=0.031), associating PA with survival. In our study, the mean PA value was 6.6 at T0 and 6.0 at T1, both higher than those presented in the literature; however, we underline the significant reduction after cancer treatment and that this measure can be a potential marker of clinical prognosis.

We emphasize an important limitation of the present study, which concerns the number of patients evaluated, considering the high prevalence of breast cancer. However, we highlight that this study presents significant results regarding cancer survivors, a population still little studied in our country, especially in the Northeast Region. In addition, these patients were selected in a reference cancer center in the state that treats people with low socioeconomic status. Therefore, they experience social vulnerability factors that favor the late diagnosis of the disease, lack of follow-up after treatment, and exposure to a higher risk of recurrence and lower survival rate.

Thus, the assessment of these patients, knowing the possible changes in weight, nutritional status, and, mainly, body composition, allows targeting health actions to this public to minimize risk factors related to lifestyle and help to prevent recurrence. Besides, this study has a significant follow-up time of patients, which strengthens the findings presented. We also filled a gap in the national and international literature concerning the evaluation of cancer patients in different regions of Brazil, contributing to expand the knowledge about patients from low- and middle-income countries.

CONCLUSION

The breast cancer survivors evaluated had their body composition changed after cancer treatment, with reduced lean mass and

increased fat mass. They also presented a significant weight gain and a rise in BMI, factors suggestive of higher risk of recurrence among women already diagnosed with more advanced tumors. In addition, PA decreases during treatment, which indicates a change in cell integrity, culminating in another factor suggestive of a worse prognosis. Thus, we recommend evaluating nutritional status and body composition at the time of diagnosis of breast cancer and including direct and individualized nutritional guidance after diagnosis. These strategies can minimize weight gain and changes in body composition in clinical practice, besides contributing to a better prognosis, survival, and quality of life among breast cancer survivors.

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THE IMPLEMENTATION OF PATIENT NAVIGATION TO IMPROVE MAMMOGRAPHY COVERAGE AND ACCESS TO BREAST CANCER CARE IN RIO DE JANEIRO

Trazendo a navegação de pacientes para melhorar a cobertura mamográfica e o acesso aos cuidados de câncer de mama no Rio de Janeiro

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ABSTRACT

This study evaluates the Patient Navigation Program (*Programa de Navegação do Paciente* - PNP), which was introduced to a community in the municipality of Rio de Janeiro. The objectives were: to establish the viability of the PNP in this context; identify barriers to mammogram screening; and ensure mammogram coverage for 70% of women recruited between 50 and 69 years old. From March to September 2018, 678 women with an average age of 58 years old were recruited from the Andaraí community. Follow-up was performed through the patient browser (PB), by telephone, email and text messages. Twelve percent of women refused to participate in the PNP for cultural reasons. The main barriers reported by women were: systematic problems with health care programming (100%), financial problems (64%), concerns about communicating with medical staff (58%), fear (44%), and social support (14%). The PNP obtained 100% satisfaction, and the mammogram coverage rate goal was exceeded, reaching 88%. The PN promoted an increase in the rate for mammogram coverage, aided in the transmission of quality information, reduced individuals' fear of mammography, and facilitated access to breast health care.

KEYWORDS: breast neoplasms; mammography; patient navigation; primary health care.

RESUMO

Este estudo avalia a introdução do Programa de Navegação do Paciente (PNP) em uma comunidade do município do Rio de Janeiro. Os objetivos são: estabelecer a viabilidade do PNP nesse contexto; identificar as barreiras ao rastreamento mamográfico; e assegurar cobertura mamográfica de 70% das mulheres recrutadas entre 50 e 69 anos. De março a setembro de 2018, foram recrutadas 678 mulheres com idade média de 58 anos da comunidade do Andaraí. O acompanhamento foi realizado pelo navegador de pacientes (NP) por telefone, *e-mail* e mensagens de texto. Doze por cento das mulheres recusaram-se a participar do PNP por razões culturais. As principais barreiras relatadas pelas mulheres foram: problemas do sistema com programação de cuidados de saúde (100%), problemas financeiros (64%), preocupações relacionadas à comunicação com a equipe médica (58%), medo (44%) e apoio social (14%). Foram obtidos 100% de satisfação com o PNP, e a meta de taxa de cobertura mamográfica foi superada, atingindo o percentual de 88%. O NP promoveu aumento na taxa de cobertura mamográfica, auxiliou na transmissão de informações de qualidade, reduziu o medo da mamografia e facilitou o acesso aos cuidados de saúde da mama.

PALAVRAS-CHAVE: neoplasias da mama; mamografia; navegação de pacientes; atenção primária à saúde.

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INTRODUCTION

In Brazil, breast cancer is the most common cancer and the leading cause of cancer death among women, with 14,206 deaths in 2013 and 59,700 new cases estimated for 2019. Barriers to cancer care access in Brazil lead to delays in diagnosis and treatment with the consequent result of the cancer reaching advanced stages and then producing a high mortality rate among patients[1].

Delayed diagnosis and treatment of breast cancer leads to the presentation of more advanced stages and poor survival outcomes[2]. The delay can be attributed to two reasons: a patient delay and a healthcare system delay. The health care delay - the time between a first consultation and when treatment is begun - is significantly longer in middle- and low-income countries compared to high-income countries[3]. In Brazil, a patient with breast cancer takes an average of 6–7 months to receive a definitive diagnosis after the first consultation with a doctor[4]. A study from Rio de Janeiro found that the average time from first consultation to a diagnosis is 6.5 months[5].

In low- and middle-income countries, long delays in diagnosis and treatment often lead to a clinical progression of the disease: in the United States, 60% of breast cancers are diagnosed at an early stage of the disease, while in Brazil these are only 20% of the diagnoses[4]. In a study of 87,969 Brazilian women with breast cancer, 53.5% were considered to be at an advanced stage (≥IIB stage)[6], and in another study cohort, 78.8% of women were at stage II-IV[7]. The latest report from the Global Breast Health Initiative highlights the importance of guidelines developed for early detection, diagnosis and treatment of breast cancer, ultimately with the goal of reducing mortality[8].

Even in Brazil, staging and survival statistics vary according to sociodemographic characteristics, such as type of health insurance. There are two types of insurance in the Brazilian health system: insurance obtained through the public system - *Sistema Único de Saúde* (SUS) - or through private providers[9]. About 75% of Brazilians receive coverage exclusively through SUS, and despite progress in universal healthcare coverage across the country, large disparities affecting cancer care remain. Women treated in the public system have a more advanced disease than women in the private sector, and women in the public sector have worse disease-free and overall survival rates (which can be partly attributed to a longer delay and advanced stages at the time of diagnosis)[9].

The main method of breast cancer screening is mammography. Recognizably, a public health measure with proven effectiveness in screening for breast cancer requires mammography to be accessible to the population[10]. Screening for breast cancer may be opportunistic when the test is offered to women seeking healthcare facilities, or population-based when the test is directed toward women in the target population who are recruited for periodic screening. In developed countries, coverage of at least 70% of the target population can reduce mortality by 20-30% in women over 50. The model adopted by Brazil is opportunistic screening[11].

Breast cancer control requires access to mammography and strategies for diagnosis and treatment of suspected cases, ensuring the quality of these services[12]. In the document of technical parameters for the screening of breast cancer from the National Cancer Institute José Alencar Gomes da Silva (INCA), an ideal parameter of one mammograph per 240 thousand inhabitants has been proposed. This is considering that the equipment is working properly. But the existence of a mammogram machine does not in itself provide that the exam will take place, since the procedure requires adequate conditions for operation, continuous maintenance of the equipment, availability of supplies, trained staff and quality assurance. Increasing the supply of exams for greater coverage of the target population depends on sufficient numbers of mammograms, geographic distribution of equipment, and productivity[12].

With this in mind, it is important to identify the availability of mammograph machines, as well as the regional distribution of equipment and examinations performed[13]. This is even more important for the state of Rio de Janeiro, which has been identified with the highest gross incidence rate of female breast cancer in the country, estimated at 92.90 new cases per 100,000 women for the year 2019[1].

According to one study, the distribution of mammograms in Rio de Janeiro, especially the mammograms from SUS, even though they were not equal, followed the percentage distribution of the population according to state regions[13]. However, even if mammograms were not lacking in comparison with the national parameter, they were not necessarily utilized regularly. In the state of Rio de Janeiro, the estimated population for 2016 was 16,635,996, which would require 68 machines to be in accordance with the national parameter[13]. Both the total number of mammographs in use (546) and the total number available for SUS (142) for the state of Rio de Janeiro, in 2012, surpassed oversupply, according to the national parameter. Therefore, according to all of the points analyzed in all of the regions, the state of Rio de Janeiro did not have an equipment deficit[13]. However, a study conducted to estimate mammogram coverage in opportunistic screening performed by SUS in Brazil, its regions and its Federal Units, found that in Rio de Janeiro, the coverage rate was 14.6% - with 150,994 tests performed when 1,034,567 were expected[14].

Despite the high frequency of this kind of tumor, in Rio de Janeiro there is no structure that allows women assisted by SUS, a system that covers the vast majority of Brazilian women, to be guaranteed decent care that is focused not only on treatment, but also on prevention and early diagnosis. International experience has shown that organized screening has better results and lower costs. In countries that have implemented effective screening programs that reach the target population, and have high quality tests and appropriate treatment, breast cancer

mortality has been decreasing. Evidence of the impact of screening on mortality from this type of cancer justifies the adoption of cancer screening as a public health policy, as recommended by the World Health Organization (WHO)[15].

In this context, the Patient Navigation Program (PNP), "a coordinated process of individualized care offered to patients in order to overcome barriers in access to timely and quality care in complex health systems," can potentially enable organized screening of breast cancer[16]. The Patient Navigation Program (PNP) is designed to address health disparities and reduce obstacles for timely cancer treatment. Patient Navigators (PNs) are trained healthcare professionals who facilitate the handling of patients in the healthcare system, helping them to overcome institutional, socioeconomic and personal barriers to access. It also provides services such as scheduling diagnostic and follow-up appointments, facilitating referrals from the health system, and coordinating communication between patients and health professionals. PNs help patients receive timely medical care and reduce care delays and the rate of missed follow-up appointments[16].

Despite the great success of the PNP among underserved populations in the United States, this program has not been widely studied in middle- and low-income countries[17]. Patients in these countries face structural barriers that are similar to those faced by underprivileged US patients. Due to lack of awareness, fragmentation and complexity of health systems, low socioeconomic statuses, cultural barriers, and limited funding and human resources in public health institutions, these patients often do not receive timely cancer care[18]. The PNP has already proven to be a valuable tool for addressing these barriers in the United States and could potentially be adapted and deployed to do the same in middle- and low-income countries such as Brazil[17].

OBJECTIVES

The overall objective of the study was to promote adherence to breast cancer screening with mammograms as recommended by the Ministry of Health, with the help of PNs. As secondary objectives, the study proposed to:

- establish the viability of the PNP in this context;
- identify barriers to mammogram screening;
- ensure mammogram coverage for 70% of women recruited between 50 and 69 years old, as considered acceptable by the WHO.

METHODOLOGY

Study Location

The study was conducted at the Family Health Strategy of the Odalea Firmo Dutra Family Clinic, which opened in February 2018 and is located in the Program Area (PA) 2.2 of Grande Tijuca, Rio de Janeiro. This clinic has health professionals who coordinate, support, analyze, promote and execute health actions in the area that includes the Andaraí and Grajaú neighborhoods, and encompasses a population in need that has not been assisted for many years.

There are eight Family Health Teams with eight doctors, eight nurses and 32 community agents working in the Andaraí region. The PNs accompanied the work of registering the target population for mammograms.

Patient Navigator

Patient Navigator Eligibility Criteria

- Social worker with knowledge of the National Regulation System (*Sistema Nacional de Regulação* - SISREG) of the municipality and the state (SER) of Rio de Janeiro.
- Experience with breast cancer patients.
- Availability to work with the PNP designed for Rio de Janeiro.

Patient Navigator Responsibilities

- Guide the patient through the health system.
- Help the patient fill out insurance documentation.
- Guide the patient to perform clinical and radiological examinations and timely treatment.
- Identify local resources and support available to the patient, including transportation allowances, childcare resources, etc.
- Help the patient schedule consultations at Family Health and referral centers.
- Remind the patient about upcoming appointments.
- Facilitate communication between the patient and health professionals.
- Make sure the information provided to the patient has been clearly understood by the patient and help answer any of their follow-up questions.

Patient Population

Inclusion Criteria

- Women with no complaints of palpable breast lesions (asymptomatic) aged 50 to 69 years old.
- Assistance in the public sector for consultation in the Family Health Strategy.

Exclusion Criteria

- Women with no personal documents.
- Women with private health insurance.
- Women in need of supportive care (prognosis of survival of less than 6 months).
- In the terminal phase of some other disease (prognosis of survival of less than six months).

- Women experiencing homelessness.
- Women with a history of drug abuse or alcoholism.
- Women suffering from major psychotic disorders or uncontrolled psychiatric disorders.
- Women with cognitive disabilities.
- Imprisoned women.

Study Metrics

The study metrics were divided into two parts - principal questionnaires and a psychosocial interview:

- Main questionnaires for collecting general information on patient characteristics and barriers to health care. These questionnaires were designed for this study and include:
  (i) patient population data, as measured by the enrollment questionnaire, in order to collect information on the barriers reported by the patients;
  (ii) clinical reference information, measured through an information form, to record relevant clinical information;
  (iii) patient satisfaction, as measured by a patient satisfaction survey, to ensure that the patients and their families consider the navigation to be useful.
- Psychosocial interview to collect more detailed information about patients' illnesses and their struggles.

The success threshold for this study was that at least 70% of the recruited patients had up-to-date mammograms.

RESULTS

An initial listing of 678 asymptomatic women aged 50 to 69 years old was provided by the community clinic's community health workers (CHA), and came with the telephone number and name of the Family Health Team to which they each belonged.

Of the 678 women listed, 181 were excluded from the interview recruitment process for the following reasons:

- 79 women reported not having to have a mammogram or their partner forbade a mammogram or clinical examination of the breasts (cultural reasons). This group represented 12% of the population found;
- 102 women were symptomatic, under 50 or over 69 years old and had a family history of breast cancer. This group represented 15% of the population involved that underwent a mammography and a clinical examination of the breasts. The youngest woman was 31 years old and the oldest was 76. In this group, six women (0.9%) were identified with a palpable breast lump and a mammography radiographic category of 4 or 5 from the Breast Imaging-Reporting and Data System (BI-RADS®). These cases were referred for diagnostic confirmation, in which the breast biopsy revealed to be a malignant neoplasm.

497 women were recruited to participate in the PNP. Table 1 shows the radiological classification of the mammograms of these women. All women with a category 0 or 3 mammography BI-RADS® underwent a breast ultrasound that came back normal. In the end, the 88% mammogram coverage rate was achieved.

Of the women recruited, 100 were randomly invited to participate in interviews to compose the study metrics (Table 2). The PNP obtained 100% satisfaction among the patients. The main impressions reported by patients about the PNP were: ease of access to breast care (41%), reduced fear of mammography (25%), promotion of quality health information (19%) and need for continuation to benefit other women in the community and other communities (15%). All patients indicated one to six barriers to obtaining breast health care, with an average of three barriers. The main barriers found are presented in Chart 1.

Table 1. Radiological category of mammograms of the women recruited for the study (n=497).

Radiological Category (RC)	N (%)
RC 0	32 (6%)
RC 1	123 (25%)
RC 2	330 (67%)
RC 3	12 (2%)

Table 2. Characteristics of the patients who answered the main questionnaires (n = 100).

Variables	Value
Family risk for breast cancer	23%
Have you ever had a mammogram?	90%
Radiological Category (RC)	
RC 0	7%
RC 1 and RC 2	84%
RC 3	9%
Smoking	23%
Regular Physical Activity*	30%
BMI	
Normal weight	29%
Overweight	37%
Obesity Grade I	27%
Obesity Grade II	6%
Obesity Grade III	1%
Comorbidities**	66%
Death***	2 cases

*Main activities: walking, water aerobics and dancing at least twice a week;
** main comorbidities: systemic arterial hypertension and diabetes *mellitus*;
*** cause of death: acute myocardial infarction; BMI: body mass index.

DISCUSSION

The Patient Navigation Program (PNP) is designed to address health disparities and reduce obstacles for timely cancer treatment. PNs are trained healthcare professionals who facilitate the handling of patients in the healthcare system, helping them overcome institutional, socioeconomic and personal barriers to access. It also provides services such as scheduling diagnostic and follow-up appointments, facilitating referrals from the health system, and coordinating communication between patients and health professionals. PNs help patients receive timely medical care and reduce care delays and the rate of missed follow-up appointments[19].

The pioneering PNP was in the Harlem district of New York in the 1990s, and it was designed to improve timely access to cancer care among low-income, low-educated patients. The program achieved impressive results, improving the five-year survival rate for breast cancer from 39 to 70% in the target population[19]. Further studies have proven that PNP can improve time to diagnosis and treatment resolution, reduce missed follow-up rates, minimize health disparities, and increase patient awareness[20]. The PNP has increased attendance at screening appointments by providing patient-oriented education, making them more likely to attend all regular medical appointments compared to those not in the program[21]. Another important benefit is that it significantly shortens the time between lesion detection and diagnosis[22]. In addition, navigator results include lower rates of missed appointments, increased screening rates, and better equity for vulnerable patients[23].

The Global Cancer Institute has already proposed an action agenda aimed at successfully implementing the PNP in middle- and low-income countries[17] and this same agenda could be applied to the Brazilian context to guide the implementation of this program in the country[17], possibly helping to guarantee adherence to mammogram screening and integrate services in the country's health system. One of the objectives of the implementation of the PNP is to influence health authorities and hospital administrators to integrate PNs into existing health system infrastructure[17]. Thus, policy makers are involved in PNPs, from the planning to implementation stages. This is important so that the PNP is not seen as an additional expense to health systems, but rather as an opportunity for a reallocation of funds, focusing on the use of scarce resources in prevention and early treatment rather than in the final stage of the disease[17].

For the early detection program and the treatment of breast cancer to be efficient and effective in the near future, political will, cooperation of the medical entities and civil society involved in the discussion, and consistent and regular allocation of financial resources are fundamental. However, there will only be progress with modern management, with well-defined goals and indicators, which are constantly audited and evaluated, otherwise it is possible to be lost in good intentions[24].

Limitations of guideline implementation strategies in low- and middle-income countries may be related to issues such as scarcity or poor distribution of health professionals and inadequate availability of medical products and supplies, which are clearly not restricted to the provision of services related to breast health[18]. Similarly, the issues of access to services and the ability (or inability) to receive funding go beyond the reach of this project because they are truly systemic[18].

Each location needs to plan and customize its PNP. The main barriers were identified and effectively minimized. The PNP achieved 100% satisfaction and an 88% mammogram coverage rate, exceeding initial expectations of the 70% coverage rate. The PN's work in the Andaraí community was based on three

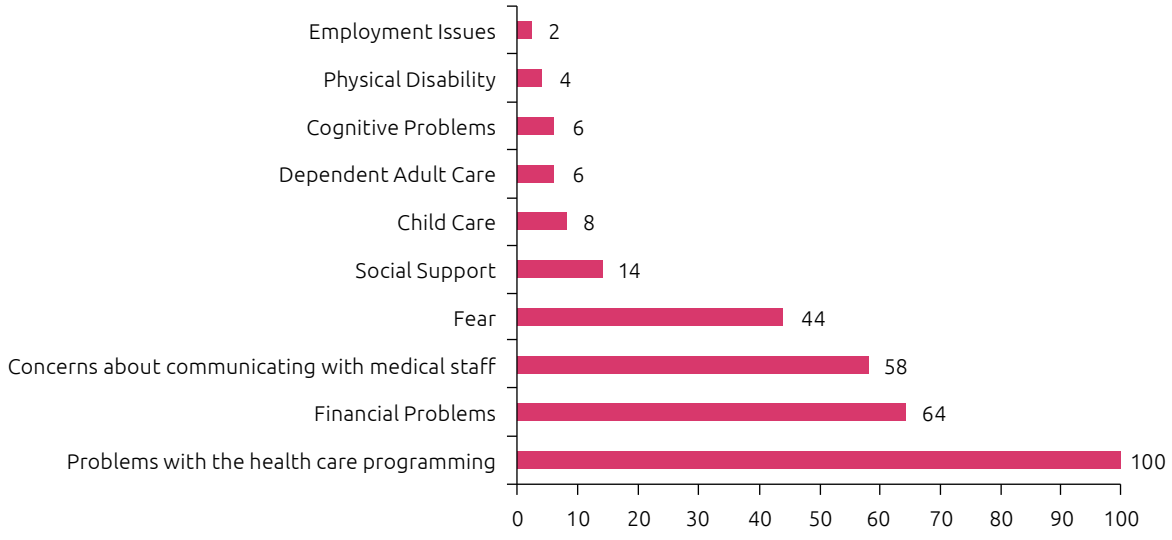

Chart 1. Barriers reported by patients for breast health care in primary care in the Andaraí community (n = 100%).

pillars: informed woman; trained primary care health professional; and commitment to breast health care. PNs are the link between patients and the health services, promoting individualized care and assistance in overcoming potential barriers (economic, social, cultural, religious, logistical, and those related to the health system) to breast health[16].

The health teams were observed to have low autonomy with regard to addressing the barriers that women face[24]. The need for local leadership, who specialize in breast diseases and believe in the importance of PNs for improving care for women becomes critical for the continuity of a PNP in primary care[24]. Six women with early stage breast cancer were identified in this group, and they were properly referred for treatment.

The family clinic needs to address the lifestyle change of the target population due to the high incidence of comorbidities, physical inactivity and obesity, known risk factors for breast cancer. Because of the high incidence of family risk for breast cancer in this population, genetic counseling and specific management for the high-risk population need to be further explored[25]. It was observed that patients and health professionals from the Andaraí family clinic have difficulty in identifying risk factors and specific actions related to breast health. In practice, the engagement of breast cancer specialists in primary health care is necessary to optimize the training of health professionals and patients[25].

CONCLUSIONS

The PNP for breast cancer in the Andaraí community proved viable in the SUS context. The main barriers to mammography in this community were identified and minimized. The PN promoted an increase in the rate for mammogram coverage, aided in the transmission of quality information, reduced individuals' fear of mammography, and facilitated access to breast health care. The PNP obtained 100% satisfaction among the patients and was successful, with a mammogram coverage rate of 88%.

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ORIGINAL ARTICLE
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SURGICAL ANALYSIS OF LYMPH NODE POSITIVITY AFTER NEOADJUVANT THERAPY

Análise cirúrgica da positividade linfonodal após neoadjuvância quimioterápica

Análisis quirúrgico de la positividad de los ganglios linfáticos después de la quimioterapia neoadyuvante

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ABSTRACT

Introduction: Breast cancer is the most prevalent tumor in women around the world, affecting 1 in 10 women in Brazil. Therefore, providing surgeries that can increase cure rates and provide less comorbidities than those that occur today is a challenge. Until the last decade, performing lymphadenectomy, after neoadjuvant therapy was mandatory. However, new studies could prove that, for some cases, the sentinel lymph node biopsy can be an option. **Objective:** To analyze the positivity rates of lymphadenectomy, after neoadjuvant therapy. **Methods:** A total of 152 patients who underwent lymphadenectomy were assessed, from 2012 to 2014; they were separated into two groups of arms: those that had clinically positive armpit results before chemotherapy in one arm, and those that had negative armpit results before chemotherapy. **Results:** Out of 152 patients, 57 had negative armpit results before chemotherapy, 71% continued to have negative results following lymphadenectomy. In the group containing 95 patients with positive armpit results (following neoadjuvant therapy), 43.6% of them were free from neoplasms after undergoing lymphadenectomy. **Discussion:** The results of this study were similar to those found in worldwide literature for lymph node rates in all groups. It means that both the staging before chemotherapy and neoadjuvant therapy are performed with the same efficacy rates as in other studied hospitals. Moreover, there is evidence on the authorization to perform sentinel lymph node biopsy after chemotherapy in those patients who had clinically negative armpit results prior to neoadjuvant therapy. **Conclusion:** Sentinel lymph node biopsy is a safe and efficient technique to be used in patients who underwent chemotherapy and had negative armpit results. Whenever needed, such technique should always be encouraged.

KEYWORDS: breast cancer; sentinel lymph nodes; diagnosis.

RESUMO

Introdução: O câncer de mama é a neoplasia que mais acomete mulheres no mundo, sendo uma a cada 10 mulheres que irão ser acometidas, no Brasil. Portanto, proporcionar cirurgias que tenham menor morbidade com as mesmas ou maiores taxas de cura é um desafio. De acordo com o exposto, até a década passada realizar linfadenectomia após quimioterapia neoadjuvante era mandatório, porém novos estudos estão conseguindo provar que para alguns casos a biópsia de linfonodo sentinela pode ser uma opção. **Objetivo:** Este estudo analisou o índice de positividade de linfadenectomias pós-quimioterapia neoadjuvante. **Métodos:** Foram avaliadas 152 pacientes, entre 2012 e 2014, que realizaram cirurgia de linfadenectomia, separado-as em dois braços, aquelas que eram axilas positivas clinicamente antes da quimioterapia em um braço, e no outro, axilas negativas antes do tratamento quimioterápico. **Resultados:** Desmembrando os 152 pacientes, 57 desses com axilas negativas anteriores à quimioterapia, obtivemos que 71% permaneceram negativas após linfadenectomia. No grupo de 95 pacientes com axilas positivas, após neoadjuvância quimioterápica, 43,6% resultaram estarem livres de comprometimento neoplásico após linfadenectomia . **Discussão:** Os resultados denotados no índice de positividade de linfonodos em todos os grupos foram muito semelhantes à literatura mundial, demonstrando que nosso estadiamento antes da quimioterapia e nosso tratamento neoadjuvante são realizados com a mesma eficácia do que de outros hospitais já estudados. Também pudemos denotar que estamos autorizados a realizar biópsia de linfonodo sentinela pós-quimioterapia naquelas pacientes as quais eram negativas as axilas clinicamente, antes do tratamento neoadjuvante. **Conclusão:** A biópsia de linfonodo sentinela é uma técnica segura e eficaz em pacientes pós-quimioterapia com axilas negativas e devemos sempre incentivar essa técnica, quando for indicado.

PALAVRAS-CHAVE: câncer de mama; linfonodo sentinela; diagnóstico.

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INTRODUCTION

Apart from non-melanoma skin cancer, breast cancer is the most prevalent in the female population all over the world. It responded for 25% of all types of cancer in 2012, that is, roughly 1.7 million cases[1].

In Brazil, when not considering non-melanoma skin cancers, breast cancer is also the most prevalent among women from all regions, except from the North region, where cervical cancer ranks first. In 2016, 57,960 new cases were estimated, which represents an incidence rate of 56.2 cases per 100 thousand women[2].

Between 1894 and 1907, Halsted described his radical mastectomy technique, which included removing the breasts and chest muscles through axillary lymph node dissection/lymphanedectomy, with a 31% rate of patients free from the disease within five years[3].

In the early 1970s, Kett et al. reported that the first regional lymph node could be identified in breast cancer. Thereafter, primary tumor was found to be drained by afferent lymph vessels, that travel to the first sentinel lymph node, and in case metastasis occurs, it will affect primarily that lymph node[4].

Until 1990, axillary lymphadenectomy was mandatory, but Giuliano et al. demonstrated, with selective lymphadenectomy, which is the sentinel lymph node with vital isosulfan blue staining, a technique with less morbidity rates and more safety to define axillary staging[5].

In 2003, Veronesi et al. established that sentinel lymph node biopsy (SNB) was a safe and accurate technique for identifying axillary metastasis in women with small breast tumors[6].

Since 1970, neoadjuvant chemotherapy has been employed to treat locally advanced tumors. It has high response rates and allows surgery for initially unresectable tumors and breast-conserving surgery[5].

Tumor resection with total axillary lymphadenectomy is a practice in most hospitals worldwide, after neoadjuvant chemotherapy. In 2009, however, Van Deurzen et al. conducted a systematic review, including 27 studies, with a total of 2,148 patients undergoing neoadjuvant chemotherapy, and showed that the detection rate of the sentinel lymph node was 90.9% and that of false negative, 10.5%. Despite that, data were still insufficient to indicate sentinel lymph node as a standard procedure after neoadjuvant chemotherapy[7].

After several studies, such as Sentina and the National Surgical Adjuvant Breast and Bowel Project Protocol B-27 (NSABP-27), the practice of sentinel lymph node became a possibility[7]. In 2015, Mautner et al. performed a review and analyzed that sentinel lymph node after neoadjuvant chemotherapy is acceptable, provided that two tracers are used to identify sentinel lymph nodes and at least three lymph nodes are found[8,9].

The treatment protocol of the Gynecology and Breast Service of Hospital Erasto Gaertner recommends neoadjuvant chemotherapy for patients with:

- Clinically positive axillary lymph node at diagnosis;
- Tumors greater than 25% of breast size, even with negative lymph node.

After the end of neoadjuvant therapy (around six months), these patients are taken to surgery for local tumor treatment (radical mastectomy or conservative surgery followed by radiotherapy), and regionally, undergoing axillary lymphadenectomy, including if they present total clinical response, axillary lymph nodes or even those that were previously clinically negative armpits.

However, imaging studies are proving that the clinical and pathological correlation of axillary lymph node positivity and the postoperative histological results have been confirmed. In this context, with the concept of sentinel lymph nodes, it has been possible to better stratify patients who are candidates for axillary lymphadenectomy.

The concept of sentinel lymph node advocates the injection of contrast with periareolar radiolabel on the eve of surgery, followed by the investigation of the first lymph node of the intraoperative drainage pathway, with detection aided by a Gamma Probe. After the sentinel lymph node is identified and resected, it is sent for a histopathological examination through intraoperative frozen section procedure. If positive, complete axillary lymphadenectomy is indicated. In case it results negative, the surgery is terminated. Studies support the safety of not performing axillary lymphadenectomy in case of negative sentinel nodes, due to the low incidence of metastases.

Axillary lymphadenectomy is a procedure of relative morbidity and low impact on the patients' quality of life. Of all cases, 20% evolve with operated limb lymphedema, movement restriction and the possibility of serious complications such as thrombosis, or even amputation. In this sense, it must be indicated for carefully selected cases, without any harm to cancer treatment.

OBJECTIVE

To analyze the positivity rates of post-lymphadenectomy and post-neoadjuvant axillary lymph nodes and the possibility of sentinel lymph node biopsy.

METHODS

An analytical, descriptive and retrospective hospital-based study was performed. The eligible population consisted of women with breast cancer (ICD 10 C50 — malignant breast cancer), whose data were obtained from the Hospital Cancer Records of Hospital Erasto Gaertner, through the system based on medical record review (physical and electronic — Tasy System), which covers all patients operated between 2012 and 2014, eligible for the survey.

The inclusion criterion for research was to be a patient who underwent neoadjuvant chemotherapy, after a medical examination and designation for this therapy. Patients who failed to complete at least half of the initially proposed chemotherapy cycle were excluded.

All patients, after treatment, underwent lymphadenectomy associated with breast resection, either total or partial. A total of 162 cases were selected, and 152 patients were eligible for the study at the end of the evaluation. These 152 women were grouped into two large categories: a group with those who, in the clinical examination performed by the mastology team (resident and preceptor) and by the clinical oncology team (resident and preceptor) at initial care, had clinically negative armpit results; and the other group with those with clinically positive armpit results. In both groups, all patients underwent neoadjuvant chemotherapy and breast resection surgery with axillary lymphadenectomy. The outcome of the pathological anatomy of the axillary lymph node specimen was evaluated according to:

- unaffected lymph nodes: pN0;
- from 1 to 3 affected lymph nodes: pN1;
- from 4 to 9 affected lymph nodes: pN2;
- 10 or more affected lymph nodes: pN3;

The tumor, node, metastasis (TNM) system was another factor used to designate arms in the groups; T represents the tumor size (T1, T2, T3, and T4).

For data collection, a questionnaire containing the most important information was the medical record number, clinically assessed primary tumor, clinically regional lymph node, clinically distant metastasis, pathological primary tumor, pathological regional lymph node, pathological distant metastasis, histological type, immunohistochemical profile, surgery performed, and drugs used in chemotherapy. The collected data were tabulated and evaluated using the OpenEpi program, which allows data analysis based on descriptive statistics.

RESULTS

The study population consisted of 152 patients with breast cancer. Of these, 57 (37.5%) were grouped into a first category of patients with clinically negative armpit results.

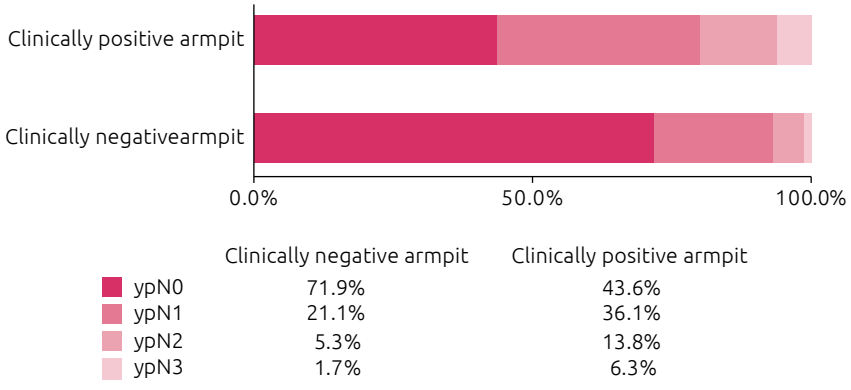
A distinction considering arms was made as to TNM, as follows: T2N0 25 (43.8%) women, T3N0 28 (49.1%), and T4N0 4 (7.01%).

Of the 25 T2N0 patients, after lymphadenectomy, the rates were as follows: 17 (68%) ypN0; 6 (24%) ypN1; and 2 (8%) ypN2. Of the 28 T3N0 cases (women who underwent lymphadenectomy), 20 (71.4%) were ypN0; 6 (21.4%) ypN1; 1 (3.5%) ypN2; and 1 (3.5%) ypN3. In the last arm, there were 4 (7.01%) T4N0 women, all ypN0 (see Table 1). When all these 57 patients were allocated only according to the lymph nodes studied in the pathological anatomy, 41 (71.9%) were ypN0; 12 (21.05%) ypN1; 3 (5.26%) ypN2; and 1 (1.75%) ypN3, according to Graphic 1.

Regarding the 95 (62.5%) patients from the other group (those with clinically positive armpit results), 2 (2.1%) T1N1 were evaluated after lymphadenectomy, of which 1 (50%) ypN0, and 1 (50%) ypN1. Of the 36 (37.89%) T2N1 cases, that underwent lymphadenectomy, 13 (36.11%) were ypN0; 18 (50%) ypN1; 4 (11.11%) ypN2; and 1 (2.77%) ypN3. Only 1 (10.52%) patient was clinically diagnosed

Table 1. Groups and their percentages as to the number of negative armpit results, according to the physical examination.

Negative armpit	T2N0: 43% (25)	ypN0: 68% (17)
		ypN1: 24% (6)
		ypN2: 8% (2)
	T3N0: 49.1% (28)	ypN0: 71.4% (20)
		ypN1: 21.4% (6)
		ypN2: 3.5% (1)
		ypN3: 3.5% (1)
	T4N0: 7.01% (4)	ypN0:100% (4)



Graph 1. Proportion of negative and positive armpits.

T2N2, and the pathological lymph node status observed was ypN1. As to T3N1, 25 cases (26.31%) were reported. Of these, 15 (60%) ypN0; 5 (20%) ypN1; 3 (12%) ypN2; and 2 (8%) ypN3. Of the 7 T3N2 (7.36%) women, 2 (28.57%) were ypN0; 4 (57.14%) ypN1; and 1 (14.28%) ypN2. Besides that, 18 T4N1 (18.94%) case were observed, of which 10 (55.55%) were ypN0; 4 (22.22%) ypN1; 2 (11.11%) ypN2; and 2 (11.11%) ypN3. Finally, 6 (5.26%) cases were T4N2, with 1 (16.6%) pN1; 4 (66%) pN2; and 1 (16.6%) pN3, according to Table 2. When the total of 95 patients was allocated only according to the lymph nodes studied in the pathological anatomy, 41 cases (43.6%) were ypN0; 34 (36.1%) ypN1; 14 (14.1%) ypN2; and 6 (6.3%) ypN3.

DISCUSSION

Over the last two decades, scientific publications have been more concerned with the morbidity caused by breast cancer treatment, without reducing the effectiveness of the treatment[8]. Studies have also investigated the percentage of positive armpits results following neoadjuvant chemotherapy and the possibility of SNB in these cases.

In the 1990s, the NSABP B-18 study had already shown that lymph node positivity was of 40% post-chemotherapy and lower compared to patients who underwent surgery first, i.e., 58%.

Table 2. Groups and their percentages as to the number of positive armpit results, according to the physical examination.

Positive armpit	T1N1: 2.1% (2)	ypN0: 50% (1)
		ypN1: 50% (1)
	T2N1: 37.8% (36)	ypN0: 36.1% (13)
		ypN1: 50% (18)
		ypN2: 11.1% (4)
		ypN3: 2.7% (1)
	T2N2: 1.05% (1)	ypN1:100%
	T3N1: 26.3% (25)	ypN0: 60% (15)
		ypN1: 20% (5)
		ypN2:12% (3)
		ypN3: 8% (2)
	T3N2: 7.3% (7)	ypN0: 28.5% (2)
		ypN1: 57.1% (4)
		ypN2:14.2% (1)
	T4N1: 18.9% (18)	ypN0: 55.5% (10)
		ypN1:22.2% (4)
		ypN2: 11.1% (2)
		ypN3: 11.1% (2)
	T4N2: 6.3% (6)	ypN1: 16.6% (1)
		ypN2: 66% (4)
		ypN3: 16.6% (1)

The largest single-hospital experience occurred at MD Anderson Cancer Center by Hunt et al., between 1997 and 2007, in which 575 patients with negative sentinel lymph node by aspiration biopsy first underwent chemotherapy, and then underwent axillary lymphadenectomy. In 97.4% of these patients, sentinel lymph node was identified, with a false negative rate of 5.9%. The authors demonstrated that a false negative event was more likely when fewer than two lymph nodes were removed. In these patients, in case of T2, lymph node positivity was 20.5%, and for T3, 30.4%[10].

After that, most studies focused on observing the post-chemotherapy lymph node identification rate, as in the article by Classe et al., from 2009. In this study, sentinel lymph node biopsy was identified for patient N1 at 81.5%. and, for N0, 94%, with a false negative rate of 15% as opposed to 9.4% for each case, respectively[11].

In two meta-analyses by Xing et al. and Kelly et al., who evaluated SNB after chemotherapy in 3,072 patients, sentinel lymph node biopsy was found reliable after neoadjuvant chemotherapy[12,13].

In 2010, when clinically assessing the reliability of lymph node evaluation, Chung et al. reported that the positive predictive value (PPV) of axillary ultrasound (US) compared to physical examination was 93 vs. 83%, respectively. The negative predictive value (NPV) of US was 58%, compared to 52% of the physical examination. These findings agree with those from parallel studies. An algorithm was recommended: if the patient has clinically negative armpit results, she will perform the axillary US, by needle aspiration, if any suspicious nodules are detected. If axillary US does not identify any suspected axillary lymph nodes, the SNB should be performed before chemotherapy is initiated, or after the neoadjuvant treatment[14].

Of the 152 patients, 57 with clinically negative armpit results were examined. In T3N0 patients, the positivity in lymphadenectomy was 28.6%, slightly lower than in other studies; T2N0 had 32% of positivity, higher than that found in other articles. Interestingly, all T4N0 patients presented negative armpit results. When only lymph nodes were evaluated, there is a 28.1% of positivity of armpit results, which is consistent with other statistics, such as that by Hunt et al.[10]. Such data confirms that the neoadjuvant treatment at Hospital Erasto Gaertner brings similar results to those presented in other articles, regarding axillary lymph nodes.

In the 95 patients who had positive armpit results in the clinical examination prior to chemotherapy, a still high lymph node positivity rate of 54 (56.4%) patients after axillary lymphadenectomy was detected. However, in 41 cases (43.6%), lymphadenectomy was negative for lymph nodes, suggesting that chemotherapy could have spared these patients from unnecessary lymphadenectomies. On the other hand, as stated by Van Deurzen et al., in patients with positive armpit results, chemotherapy acts on metastatic lymph nodes causing fibrosis, which may alter the local lymphatic drainage pattern[7].

Another aspect to be considered are the low detection rates of the sentinel lymph node, which are 80.1% after chemotherapy, reported by Classe et al., in 2009, and Kuehn et al. in the 2013 Sentina study, values described by these authors as unacceptable[8,11].

In short, in the book *Diseases of the breast* by Harris et al., sufficient data are said to be already available to demonstrate that sentinel lymph node surgery following neoadjuvant systemic treatment is an appropriate treatment for patients with clinically negative lymph node results. As for patients with positive lymph nodes, there are not enough studies for systematic performances. Surgery can be performed individually in each case[15].

CONCLUSION

In several articles and a base textbook of Mastology and Oncology, the SNB, following neoadjuvant chemotherapy in clinically negative armpit results can and should be performed. As to patients with positive lymph nodes, literature does not have enough data for not practicing lymphadenectomy. We observed that clinical analysis before chemotherapy and neoadjuvant treatment at Hospital Erasto Gaertner provide similar rates compared to those from literature worldwide on lymph node positivity. The algorithm proposed by Chung et al.[14], previously described in the study, could be used at Erasto Gaertner Hospital, without causing major additional costs and significantly improving morbidity rates, thanks to the axillary lymphadenectomy surgery.

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CASE REPORT
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HIDRADENITIS SUPPURATIVA: SURGICAL TREATMENT WITH LATISSIMUS DORSI MUSCLE FLAP

Hidradenite supurativa: tratamento cirúrgico com retalho do músculo grande dorsal

Jessica Ponte Portella[1], Igor Araújo da Silva[1], Laurinda Castellani[1], Gustavo Zucca Matthes[1]

ABSTRACT

The authors present a case report of a 53-year-old female patient who was admitted to the mastology and breast reconstruction sector, at Barretos Cancer Hospital, in 2018, to treat an invasive ductal carcinoma in the right breast. At admission, the patient complained of hidradenitis in the armpits and groin area, with no previous success with clinical or surgical treatment. Hidradenitis is a disease in which there is chronic inflammation of the apocrine glands. With this in mind, an extensive resection of the armpit lesion was performed, and the same right armpit incision was utilized for the sectionectomy and radiopharmaceutical-guided sentinel lymph node biopsy. As for the armpit reconstruction, a bilateral latissimus dorsi flap was used, resulting in an improvement of the patient's quality of life. With this case report, the authors demonstrate that a breast reconstruction technique could be used to treat a disease that so far had no surgical solution that would not result in confining anatomic consequences for the patient.

KEYWORDS: breast reconstruction; breast cancer; armpit; hidradenitis.

RESUMO

Os autores apresentam relato de caso de um paciente do sexo feminino e com 53 anos que foi admitido no serviço de mastologia e reconstrução mamária do Hospital de Amor, de Barretos, em 2018, para tratamento de carcinoma ductal invasivo de mama direita. Durante sua admissão, o paciente queixou-se de hidradenite de axilas e virilha, sem sucesso prévio com tratamento clínico ou cirúrgico. A hidradenite é uma patologia em que ocorre inflamação crônica nas glândulas apócrinas. Diante desse quadro, foi feita a ressecção extensa das lesões axilares, e utilizou-se a mesma incisão axilar direita para a realização da setorectomia e da biópsia de linfonodo sentinela guiados por radiofármaco. Para a reconstrução axilar, optou-se pelo retalho do músculo grande dorsal bilateralmente, que resultou em ganho de qualidade de vida para a paciente. Por meio do relato do caso, os autores demonstram que, com a utilização da técnica de reconstrução mamária, tratou-se uma doença que, até o momento, não apresentava nenhuma proposta cirúrgica que não resultasse em consequências anatômicas limitantes.

PALAVRAS-CHAVE: reconstrução da mama; câncer de mama; axila; hidradenite.

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INTRODUCTION

Hidradenitis suppurativa is a disease characterized by chronic inflammatory conditions in the apocrine glands, such as in the axillary and anogenital region. The prevalence ranges from 1 to 4%. Infundibular hyperkeratosis, hyperplasia of the follicular epithelium and periphericululitis are the main histological features of hidradenitis suppurativa. Known risk factors are smoking and obesity, which are present in more severe cases[1]. It usually begins after age 40 and is more common in females (3.6/1 ratio)[2].

Treatment focuses on reducing the progression and extension of lesions and preventing new lesions, while minimizing scarring[2]. The type of therapy used depends on the stage of the disease based on the Hurley classification (Table 1)[2].

In more advanced cases, the treatment of this disease is a challenge and has a substantial impact on patients' quality of life. We report a case of bilateral axillary hidradenitis suppurativa in which surgical treatment was with the latissimus dorsi muscle flap.

CASE REPORT

A female patient, 53 years old, was admitted to the Department of Mastology and Breast Reconstruction at Hospital de Amor in Barretos, Brazil in 2018, due to a diagnosis of invasive stage IIA ductal breast carcinoma on the right side. During evaluation, the patient reported an earlier diagnosis of underarm and groin hidradenitis and was already undergoing clinical and surgical treatment in another service, without success. She reported that due to severe hidradenitis suppurativa, no new surgical treatment was chosen because of the risk of loss of mobility in the region and lack of skin for closure. On physical examination, it was found the presence of extensive hidradenitis in the armpits with purulent discharge (Figure 1).

In the surgical treatment, extensive resection of the axillary lesions was chosen using the same right axillary incision for the radiopharmaceutical-guided sentinel lymph node and occult lesion localization and sectionectomy and biopsy (SNOLL). On the basis of the experience of the service and the quality of the flap, reconstruction was planned using a bilateral latissimus dorsi flap (Figure 2). The patient evolved well postoperatively, without flap distress, and was discharged with clindamycin 300 mg every 6 h for 14 days (due to infectious hidradenitis). For adjuvant treatment, the patient underwent chemotherapy, radiotherapy and hormone therapy. At outpatient visits, the surgical wound appeared to be in good shape, with dehiscence at small points (Figure 3). A small fistula was formed in the left armpit fold, with improvement after dressing. At 12-month follow-up, the patient showed excellent results, with substantial improvement in her quality of life (Figure 4).

Table 1. Hurley classification of hidradenitis.

Hurley classification	
Stage I	Abscess, without fistulization or scars
Stage II	Recurrent abscess with bridging and scars
Stage III	Diffuse abscesses or interconnected bridges and multiple abscesses

DISCUSSION

Hidradenitis suppurativa, being a chronic inflammatory disease, is difficult to treatment, where there are local recurrences.

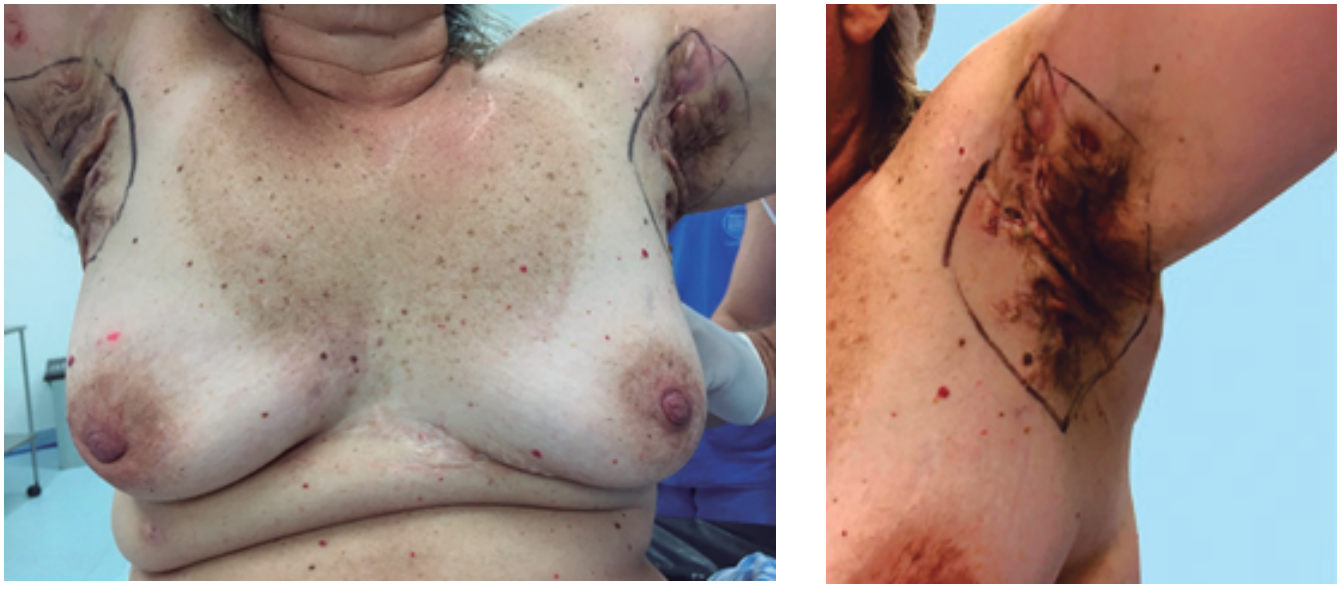

Figure 1. Bilateral axillary hidradenitis: preoperative.

Treatment can be done with antibiotics, immunomodulators, antiandrogens and immunosuppressants and laser and surgery therapies[3]. Antibiotics are used as initial treatment for severe hidradenitis, and the main treatment regimen is clindamycin + rifampicin. Isotretinoin, derived from vitamin A, is also widely used for inhibiting sebaceous secretion, but there are controversies regarding its efficacy[2]. Tumor necrosis factor alpha (TNF-alpha) inhibitors provide evidence of their benefit in inflammatory response, but because of the high cost, they should be used in selected cases[4]. Another drug option is finasteride, an antiandrogen that inhibits the inflammatory response in the hair follicles and should be used with caution in men and women of childbearing age (with feminization even in male fetuses)[2]. Even with a series of medications, there can be treatment failure, and surgery is needed to control the disease.

The major issue of surgical treatment is the large resections of the lesions, making it difficult to close the surgical wounds. Thus, it is necessary to use a flap to close them. In axillary hidradenitis, the thoracodorsal fasciocutaneous flap is one of the most commonly performed procedures in this type of disease, but has some complications, such as seroma, dehiscence and infection[5]. New flaps should be evaluated to improve the effectiveness of hidradenitis treatment.

The latissimus dorsi myocutaneous flap was initially described in 1906 by Tansini, where it was modified over the years, making it a safe and widely used flap[6]. Its technique is based on the preservation of the thoracodorsal pedicle, with rotation of the donor skin island towards the anterior trunk wall[7]. In the clinical case, due to the proximity of the axillary region, the flap was easily taken to close the resection.

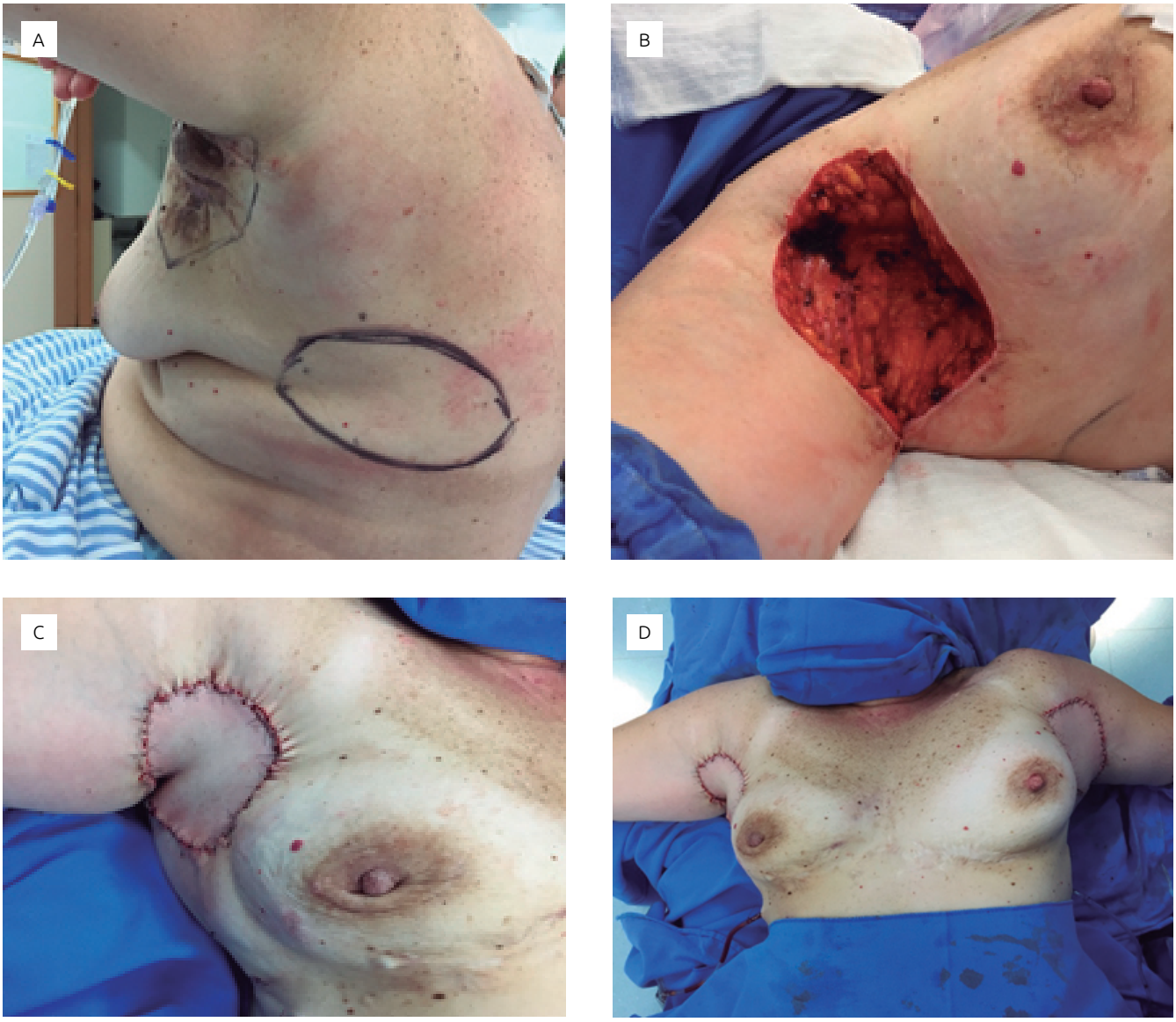

Figure 2. Rotation of latissimus dorsi flap for bilateral axillary resection closure. (A) Surgical marking of the skin island; (B) broad resection of axillary hidradenitis; (C) immediate result of right flap; (D) immediate bilateral result.

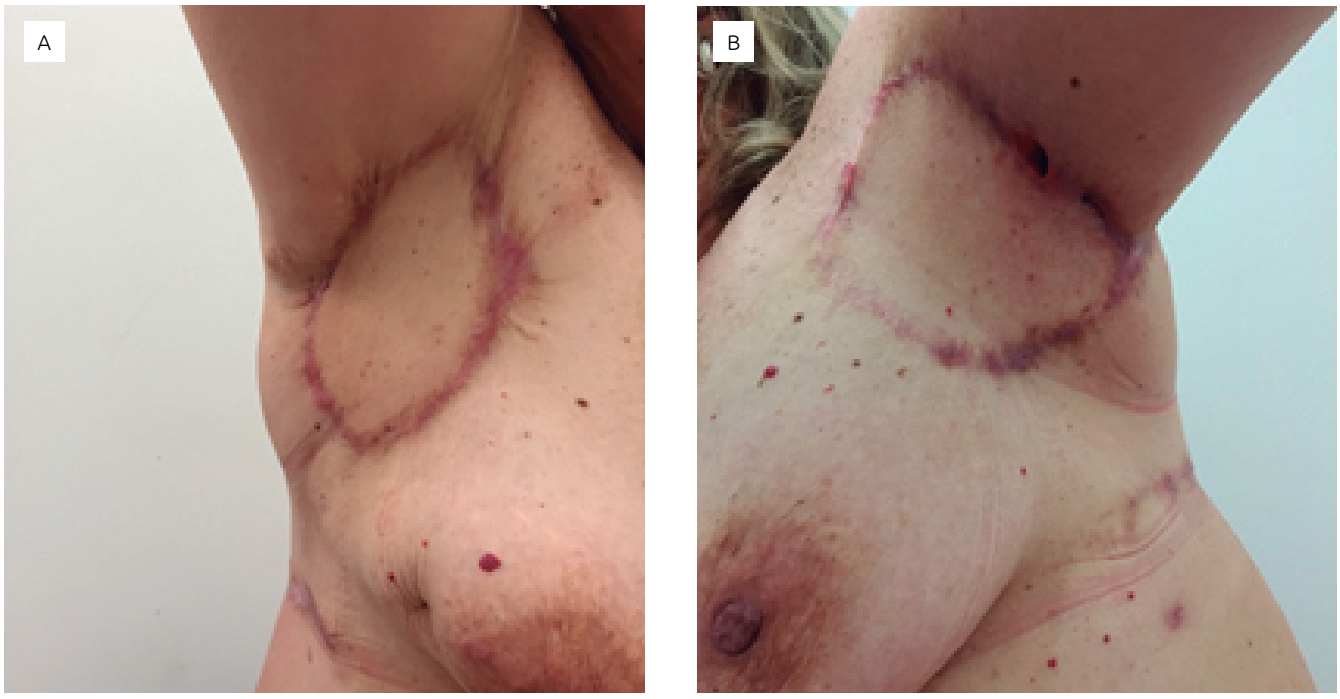

Figure 3. Early postoperative: (A) result of right axilla; (B) result of left axilla, with presence of fístula.

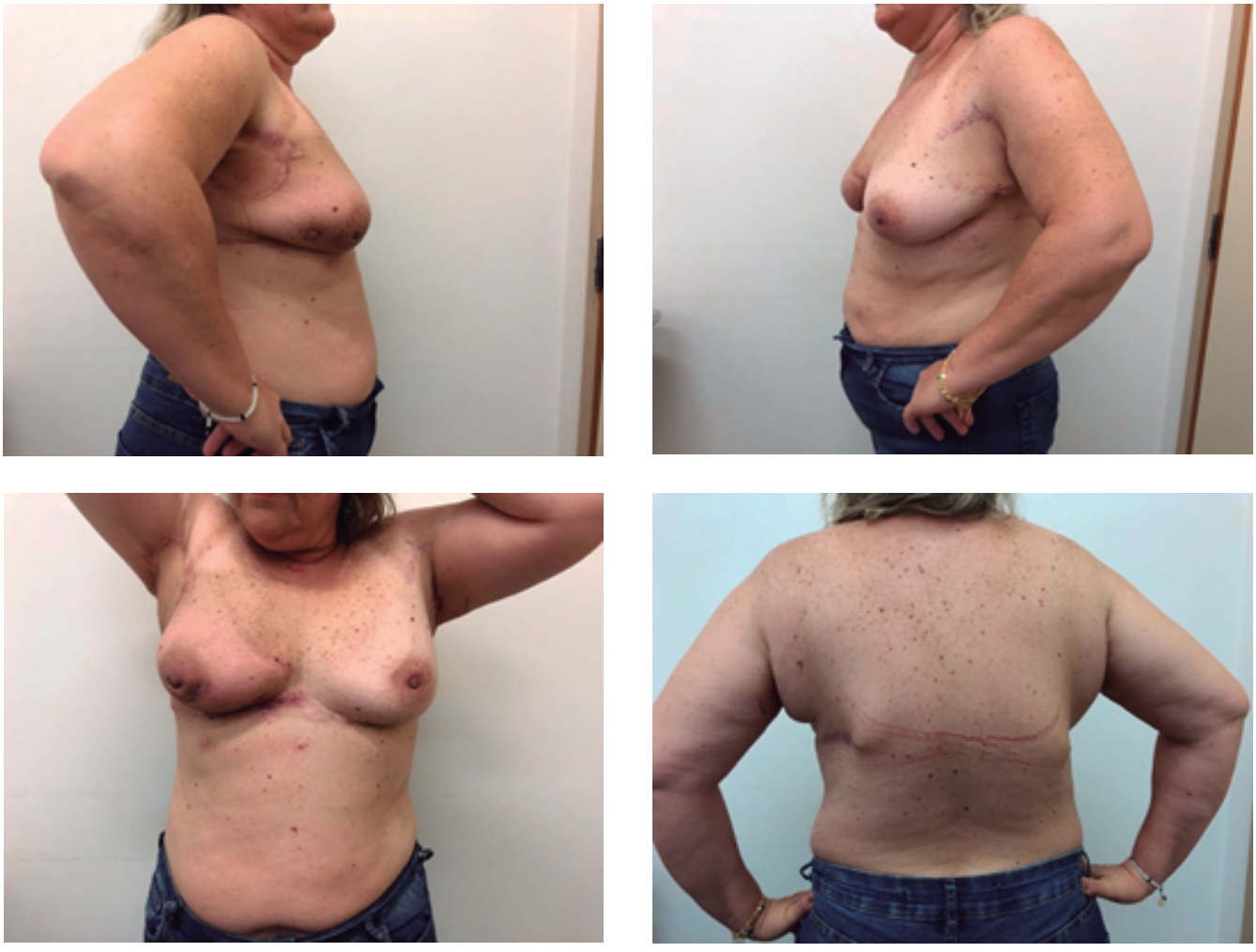

Figure 4. Late postoperative.

Complications are expected with myocutaneous flaps. In the case of the latissimus dorsi, the main complication is donor area seroma[7]. In this report, there was no occurrence of this type of complication, but the presence of a fistula in the left axilla required dressings to accelerate its closure. This complication can be expected because of the large resection and previous infectious state of the surgical site, an issue that is not considered serious, and in the end, there was a satisfactory aesthetic result.

Hidradenitis, especially when severe, has a major impact on the patient's quality of life, affecting well-being. The pain and lesions make it difficult to live with other people, even in a marital relationship[3,8], which can trigger depressive symptoms[9]. Thus, in planning the treatment of such a condition, we must always think of the broad concept of health: physical, mental and social well-being, as proposed by the World Health Organization.

In the reported case, the initial treatment was for right breast cancer, but another pathology, i.e., hidradenitis suppurativa, was observed, which had a major impact on the patient's life. Thus, the use of a surgical technique in breast reconstruction to treat a disease that had not previously been proposed for surgery led to a significant improvement in the patient's quality of life.

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CASE REPORT
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BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA IN LI-FRAUMENI SYNDROME: CASE-BASED LITERATURE REVIEW

Linfoma anaplásico de grandes células associado a implante na síndrome de Li-Fraumeni: relato de caso baseado em revisão de literatura

Marina Sonagli[1]*, Camila Souza Guatelli[1], Maria Nirvana da Cruz Formiga[1], Joel Abdala Junior[1], Almir Galvão Vieria Bittencourt[1], Fabiana Baroni Makdissi[1]

ABSTRACT

Breast implant-associated anaplastic large cell lymphoma is a rare disease related to chronic seroma around breast implants. Breast implant-associated anaplastic large cell lymphoma has been recently recognized by the World Health Organization as a type of T-cell non-Hodgkin lymphoma of the breast. The main features comprise chronic seroma which develops a year posterior to breast surgery, with symptoms such as breast pain, swelling, skin hyperemia and a nodule or mass of the breast. Li-Fraumeni Syndrome is associated with germline *TP53* mutation and enhances the risks of developing many types of cancers, including breast and hematologic malignancies. We report a case of a 56-year-old female with Li-Fraumeni Syndrome and a history of breast cancer who underwent a mastectomy to treat breast cancer and prophylactic contralateral nipple-sparing mastectomy followed by bilateral breast implant reconstruction with textured silicone implants. This patient developed Breast implant-associated anaplastic large cell lymphoma seven years later. A literature review on multidisciplinary approach to this condition was performed.

KEYWORDS: lymphoma; Li-Fraumeni syndrome; breast implants; breast cancer; anaplastic large cell lymphoma.

RESUMO

O linfoma anaplásico de células grandes associado ao implante mamário é uma doença rara relacionada ao seroma crônico em torno dos implantes mamários. O linfoma anaplásico de células grandes associado ao implante foi recentemente reconhecido pela Organização Mundial de Saúde como um tipo de linfoma não-Hodgkin de células T da mama. As principais características incluem o seroma crônico que se desenvolve um ano depois da cirurgia da mama, com sintomas como dor na mama, inchaço, hiperemia da pele e um nódulo ou massa da mama. A síndrome de Li-Fraumeni está associada à mutação da linha germinativa no TP53 e aumenta o risco de desenvolvimento de muitos tipos de câncer, incluindo neoplasias mamárias e hematológicas. Relatamos um caso de uma mulher de 56 anos de idade com Síndrome de Li-Fraumeni e um histórico de câncer de mama submetido a uma mastectomia para tratar câncer de mama e mastectomia profilática contralateral poupadora de mamilo seguida de reconstrução bilateral de implantes mamários com implantes de silicone texturizados. Esta paciente desenvolveu linfoma anaplásico de células grandes associado ao implante mamário sete anos depois. Foi realizada uma revisão da literatura sobre uma abordagem multidisciplinar para essa condição.

PALAVRAS-CHAVE: linfoma; síndrome de Li-Fraumeni; implantes de mama; neoplasias da mama; linfoma anaplásico de células grandes.

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INTRODUCTION

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare form of T-cell non-Hodgkin lymphoma of the breast. The first case was reported by Keech and Creech[1] in 1997 and only in 2016 the World Health Organization (WHO) classified it as a new type of lymphoid neoplasm[2]. This recent recognition was important to allow specific recommendations for treatment of this disease.

Doren et al.[3] reported that lifetime prevalence of BIA-ALCL was approximately 1 in 30,000 for women with textured implants. Other series estimate lifetime risk range from 1:1000 to 1:10,000 in women with textured implants[4]. Up to date, more than 500 cases of BIA-ALCL have been confirmed worldwide[5]; nevertheless, the exact incidence is difficult to define due to unfamiliarity with this new entity.

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome caused by germline mutations in *TP53* gene, associated with a high lifetime risk of multiple types of cancer[6-8]. In adults, LFS tumor spectrum is dominated by pre-menopausal breast carcinomas and soft-tissue sarcomas[6-8]. In LFS patients, there are no data available on increased risk of BIA-ALCL compared to non-carriers of *TP53* gene mutation.

The aim of this study is to report a case of BIA-ALCL in a patient with LFS that presented breast swelling associated with chronic seroma around the implant with adjacent mass, seven years after breast surgery, and to perform a literature review on the multidisciplinary approach to this condition.

CASE REPORT

A 56-year-old white female carrier of LFS underwent left radical modified mastectomy in 2009 due to Paget's Disease associated with ductal microinvasive carcinoma, and right risk reduction nipple-sparing mastectomy followed by bilateral breast implant reconstruction with textured silicone implants. Seven years later, she reported right-sided recurrent breast swelling that had started 18 months before. A magnetic resonance image (MRI) of the breast showed moderate fluid collection surrounding the right implant, with focal capsular nodules, peripheral enhancement and right axillary lymph node with cortical thickening. Fine needle aspiration cytology (FNAC) was negative for carcinoma.

The following year, patient manifested skin hyperemia around the right nipple-areolar complex (NAC). Breast ultrasound revealed a circumscribed hypoechogenic mass adjacent to the breast implant, without fluid collection, localized in the low-inner quadrant (LIQ), associated with a right axillary lymph node with cortical thickening. An MRI showed a 6 cm heterogenous mass with peripheral peri-prosthesis contrast enhancement, NAC enhancement and enlarged ipsilateral axillary lymph nodes (Figure 1).

A core-biopsy of the mass revealed eosinophilic infiltration of the fibrous tissue of the capsule, interspersed with atypical lymphoid cells (hematoxylin and eosin), which showed strong and diffuse expression of CD 30 and P53 protein, and no expression of ALK (immunohistochemistry). The right axillary lymph node FNAC presented atypical lymphoid cells. These findings confirmed BIA-ALCL diagnosis.

Staging positron emission tomography (PET-CT) detected enhanced metabolic activity only in the right breast (Figure 2). The patient underwent surgical treatment with excision of the right mass, ipsilateral lymph node axillary dissection and bilateral implant removal (Figure 3). Adjuvant treatment was not necessary.

DISCUSSION

Primary breast lymphomas are rare, accounting for 0.04–0.5% of all breast cancers and less than 10% of them are of T-cell origin[5]. BIA-ALCL is a subset of T-cell lymphoma of the breast with a typical indolent progression[9]. On average, diagnosis is made over 7 to 10 years after breast implantation[4,10].

Theories explaining the etiology of BIA-ALCL encompass a correlation between chronic T-cell stimulation due to Gram-negative bacteria, chronic seroma around textured implants and host genetics in genetically susceptible patients[2,5]. These data are supported by the evidence that a higher number of T-cells have been found around textured breast implants with a high bacterial load in patients with BIA-ALCL, associating the bacterial antigen stimulation with the chronic inflammation produced by the textured implants[11].

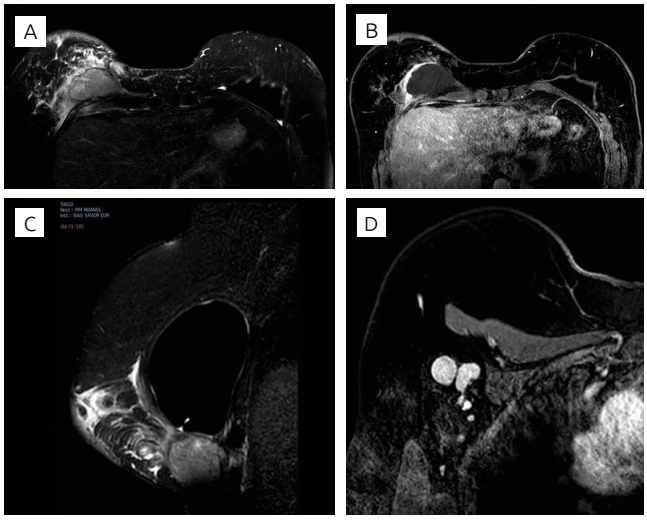

Figure 1. Magnetic Resonance Image (MRI) revealed a (A, B, C) 6 cm heterogenous mass in the junction of the inferior quadrants, with peripheral contrast enhancement, NAC enhancement and (D) enlarged ipsilateral axillary lymph nodes.

In a series of 55 patients from Australia and New Zealand, all cases of BIA-ALCL had exclusively occurred in textured implants[10]. The hypothesis for this relationship is that textured implants have a greater surface area and rough interface, which enhances bacterial adhesion and biofilm burden, triggering a T-cell clonal expansion[10,11].

BIA-ACLC is a CD30+, ALK negative lymphoma[9]. Pathological findings report atypical cells, interspersed in an eosinophil background, and immunophenotype reveals a diffuse expression of CD30 and negative ALK in malignant cells[12,13]. In addition, a somatic mutation of TP53 protein was described in BIA-ALCL[4], consistent with the case reported.

Li-Fraumeni syndrome (LFS) is an autosomal-dominant genetic disorder inherited by means of *TP53* mutations. From LFS patients listed in the International Agency for Research on Cancer (IARC) germline TP53 database, 2,550 different tumors are documented and only 4.7% of these tumors are hematological neoplasias[7], including lymphoid and myeloid leukemia, myelodysplastic syndrome and, to a lesser extent, lymphoma[8]. Also, the risk of breast cancer in LFS patients exceeds the risk of lymphoma. Analysis of LFS carriers by the National Cancer Institute (NCI) revealed a cumulative incidence rate of 54% by age 70 for breast cancer among female carriers[14].

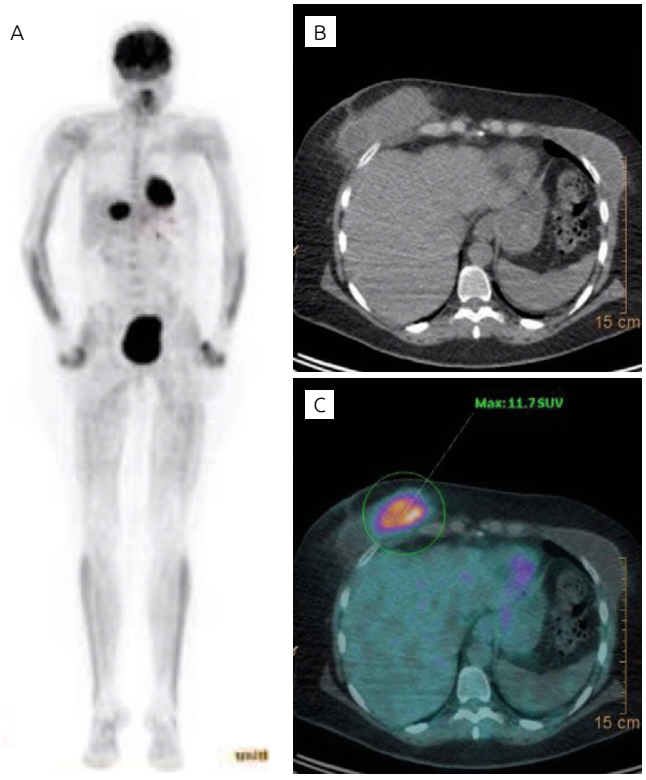

Figure 2. Staging positron emission tomography (PET-CT) detected enhanced metabolic activity only in the right breast with a standard uptake value=11,6. (A) Coronal maximum intensity projection image; (B) axial nonenhanced CT image; (C) axial PET-CT fused image.

Despite unavailable data of increased risk of BIA-ALCL in LFS patients, the literature reports a case relating BIA-ALCL in a LFS patient[15]. In Brazil, the incidence of *TP53* mutation in southern and southeastern Brazil is higher than worldwide[16]. We report a second case linking BIA-ALCL and LFS.

BIA-ALCL most often presents seroma around the breast implant (60-80%) with a variable volume of 20–1,000 mL and may manifest with breast pain, swelling, skin hyperemia or asymmetric capsular contracture[2-4,12,13]. Less frequent clinical manifestations include breast mass (10–20%) or nodules and lymph node involvement (15%) that are related to a more aggressive disease[4,9,10]. The median age of presentation is 52 years[12] and time between surgery and onset of the symptoms has been estimated to be of 7 to 10 years[3,4]. A seroma that appears a year after breast surgery not associated to trauma or implant infection, should be investigated due to the risk of BIA-ALCL, which is estimated at approximately 10%[2,4]. In our case report, the patient manifested the first symptoms 7 years after breast surgery.

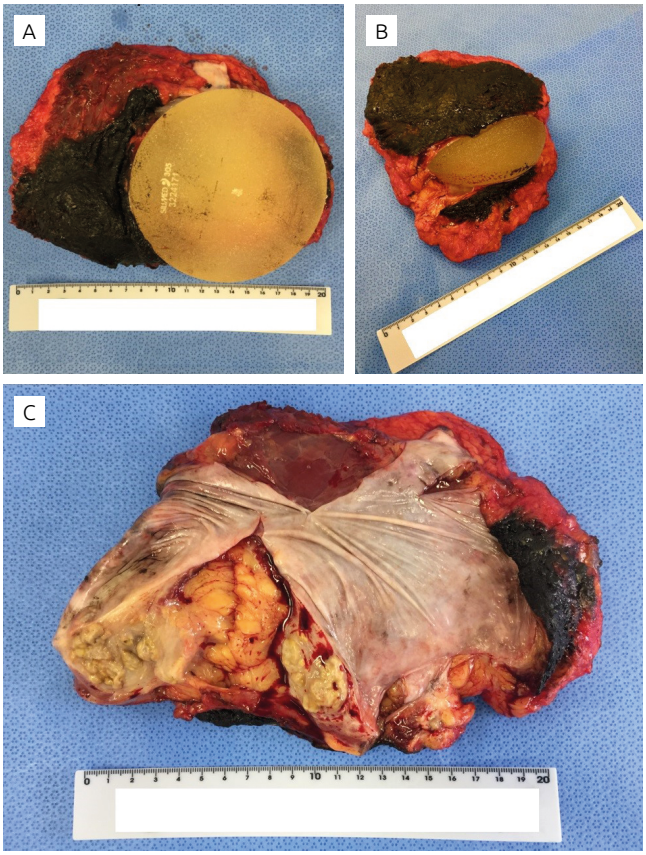

Figure 3. Relationship between breast tissue, capsule implant, deep margins and neoplastic mass. (A, B) Right breast tissue, weighing 725 g and breast implant sizing of 11.5 cm surrounded by a fibrous capsule and deep margin marked with ink. (C) Right breast tissue with heterogenous neoplastic mass in lower inner quadrant, measuring 4.0 × 3.8 × 3.5cm, underlying the implant capsule and adjacent to the deep margin (black ink).

BIA-ALCL is subdivided in two histological groups:

- *in situ* disease characterized by cell proliferation confined to the implant fibrous capsule, clinically presented as a seroma;
- invasive disease characterized by cell proliferation infiltrating the capsule and/or adjacent tissues, often manifested as a breast mass[13].

In addition, *in situ* and invasive BIA-ALCL can coexist; besides, *in situ* disease can advance to invasive form[13].

Diagnosis of BIA-ALCL requires a multidisciplinary approach. Breast ultrasound (US) is the first exam performed to define the extent of the seroma, the presence of capsular masses or regional lymphadenopathy. US is also useful to guide seroma aspiration and for tissue biopsy[5]. Sensitivity and specificity of US for detecting a seroma (84 and 75%) and a mass (46 and 100%) in BIA-ALCL patients is similar or better than computed tomography (CT) or magnetic resonance imaging (MRI)[2]. Breast MRI or PET/CT is indicated for cases with doubtful findings, and to evaluate invasion of chest wall prior to surgical treatment[2]. Pet-scan is also recommended for staging and to investigate the presence of disease out of the breast[2,4]. Pathological analysis of the seroma cytology or core-biopsy of the nodule or mass are necessary for BIA-ALCL diagnosis[2,4].

Literature reveals two staging systems for BIA-ALCL: the Lugano revision of the Ann Arbor Staging System, which stages it as a "liquid tumor"[2,5], and the American Joint Comitte on Cancer (AJCC), which stages it as a "solid tumor", based on tumor, lymph node and metastasis (TNM)[2]. According to the Lugano staging system, stage IE corresponds to disease limited to one breast only and stage IIE to ipsilateral lymph node involvement[17]. As per TNM classification, stage IA corresponds to disease confined to the effusion, stage IB to an early capsular invasion, stage IC to a mass confined to the capsule, stage IIA to a spread external to the capsule, stages II and III to lymph node involvement and stage IV to metastasis(es) to distant sites[2]. BIA-ALCL is often present as an early-stage disease, with 83% of the patients presenting stage IE (Lugano) and 35.6% stage IA, 11.5% stage IB, 13.8% stage IC and 25.3% stage IIA (TNM)[2].

Recommended treatment is capsulectomy, implant removal, excision of the breast mass with free pathological margins and of suspicious lymph nodes[2,4]. Removal of the contralateral implant may be considered since 4.6% of the cases also revealed BIA-ALCL on the contralateral breast[2,9]. It is essential to provide a perspective of future breast reconstruction for patients. We recommend this orientation to be performed prior to the surgical procedure in order to minimize resulting trauma. When performed, further reconstruction should be done with smooth implants[4]. Psychological follow-up is always recommended.

The role of adjuvant therapy remains unknown[4]. There is no standard approach to treatment of patients in cases of incomplete margins, locoregional spread or disseminated disease[4]. Adjuvant chemotherapy was based on treatment of systemic T-cell lymphoma[5] and NCCN guidelines support using anthracycline-based chemotherapy or alternatively, Brentuximab vedotin[2]. Radiotherapy should be considered in the cases of residual, localized or unresectable disease and after local recurrence[4].

BIA-ALCL appears to be an indolent disease with an excellent prognosis when confined to the capsule and treated with complete surgical resection[18]. The overall survival rate estimated by Clemens et al., after analyzing eighty-seven BIA-ALCL patients, was 94 and 91% at 3 and 5 years, respectively, and the 3-year and 5-year event free survival rates were both 49%[9]. Local recurrence rate is related to incomplete surgical excision, which reaffirms surgical importance in the treatment of the disease[4,9].

In Brazil, this is the second case of BIA-ALCL to be reported, and the second LFS-related BIA-ALCL worldwide. Due to the remarkable risk of breast cancer in LFS women, it is still important to discuss indication of risk-reducing mastectomy in female carriers, even if it involves breast implant placement. Because of the possible risk of BIA-ALCL, it is relevant to consider the use of smooth implants or autologous flap in these patients.

CONCLUSION

BIA-ALCL is a rare and newly recognized disease whose pathogenesis is still under research. It should be suspected in patients that manifest chronic seroma associated with the presence of breast implants, even more so if the patient is a carrier of a genetic mutation that enhances the risk of developing malignancies. Diagnosis requires an approach with imaging exams and a biopsy, and all the findings should be discussed by a surgeon, a radiologist and a pathologist together. In cases that any genetic syndromes are involved, when reconstructive surgery will be performed, the use of smooth implants or of an autologous flap is recommended.

Moreover, in clinical practice, it is necessary to focus on patient education, to clarify the rarity of the disease, but that its existence is real and can occur. In addition, knowledge of the disease characteristics allows patients to remain alert to the initial symptoms. Another relevant aspect is the patient's conscious choice to use or not silicone implants, which should always be considered at the time of a surgical indication.

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CASE REPORT
DOI: 10.29289/2594539420192019003

IDIOPATHIC GRANULOMATOUS MASTITIS: CASE SERIES

Mastite granulomatosa idiopática: série de casos

Laís Neiva Rego Siqueira[1], Danilo Rafael da Silva Fontinele[2]*, Sabas Carlos Vieira[3], Lina Gomes dos Santos[4]

ABSTRACT

Idiopathic granulomatous mastitis is a rare disease that mimics other pathological conditions, including breast adenocarcinoma, breast tuberculosis, and abscess. Three patients diagnosed with idiopathic granulomatous mastitis were analyzed, receiving corticosteroid treatment, antibiotic therapy in cases of abscesses, and, in one case, resection of the affected breast segment. All patients exhibited regression of symptoms.

KEYWORDS: mastitis; granulomatous mastitis; breast; anti-bacterial agents; corticosteroids.

RESUMO

A mastite granulomatosa idiopática é uma doença rara que mimetiza outras condições patológicas, incluindo adenocarcinoma de mama, tuberculose de mama e abscesso. Foram analisados três pacientes com diagnóstico de mastite granulomatosa idiopática, que receberam como tratamento corticosteroide, antibioticoterapia em casos de abscessos e, em um caso, ressecção do segmento mamário afetado. Todas as pacientes evoluíram com regressão dos sintomas.

PALAVRAS-CHAVE: mastite; mastite granulomatosa; mama; antibacterianos; corticosteroides.

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM), also known as granulomatous lobular mastitis, is a rare disease of chronic inflammatory nature, well-defined, and of slow progression[1]. IGM can be mistakenly diagnosed as breast carcinoma, breast abscess, plasma cell mastitis, fat necrosis, or breast tuberculosis[2].

Although the cause of the disease is unknown, the general consensus is that reproductive age, recent pregnancy, breastfeeding, and history of contraceptive pill use are the main conditions associated with the illness, which is prevalent in emerging countries[3].

In this scenario, we evaluated three IGM cases diagnosed in a private clinic in Teresina, from March 12, 2013 to December 11, 2018. All participants signed the informed consent form.

CASE REPORT

First case

A 41-year-old patient had a painless 5-cm nodule in the left upper outer quadrant (UOQ). She underwent mammography and ultrasound, which revealed a cystic lesion measuring 4 × 4 cm, with solid areas in between, thick capsule, and without flow on Doppler examination. The acid-fast bacilli (AFB) culture was negative, and the surgical biopsy revealed the presence of IGM. After one month, the patient returned with infection, which was surgically drained, starting a corticosteroid therapy with dose escalation (20 mg for one month; 10 mg for 20 days; and 5 mg for 10 days) associated with a proton pump inhibitor. The patient came back after treatment presenting a decrease in the lesion, and, ten months after treatment, she had no complaints.

Second case

A 30-year-old patient presented a typical sign of abscess (Figure 1) and a nodule in the right UOQ one month before her appointment.

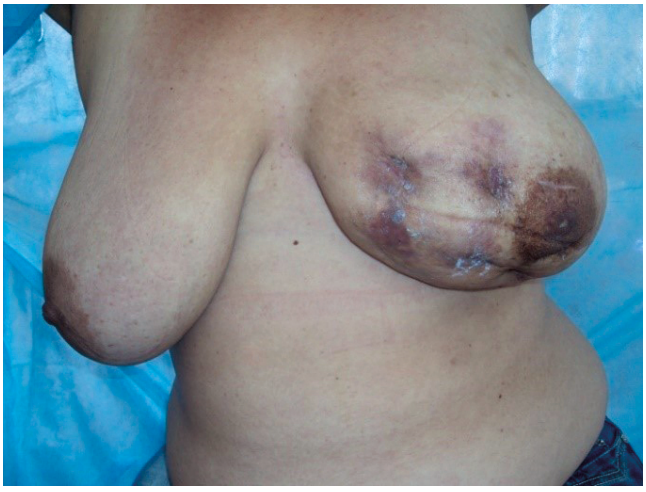

Figure 1. Patient, 30 years old, presenting lesion compatible with an abscess in the left breast, with four erythematosus foci.

Mammography revealed an area of hyperdensity in the right UOQ, without other findings. Ultrasound showed an irregular nodule of 6 × 4 cm in the right UOQ, without flow on Doppler and without posterior acoustic shadowing. Surgical biopsy identified IGM with foci of suppuration. Partial resection of the lesion (8 cm) and abscess drainage were performed, with negative AFB culture. Antibiotic therapy consisted of cefadroxil administered for 15 days associated with corticosteroid with dose escalation for two months. After five months, the patient returned without complaints, and the physical examination showed an area compatible with scar fibrosis at the surgical site.

Third case

A 41-year-old patient had a retroareolar nodule in the left breast two months before her appointment. In the physical examination, the left breast presented a hardened retroareolar area associated with hyperemia with drainage of serosanguineous fluid through a fistulous orifice. The patient denied fever. She underwent mammography, which revealed a retroareolar nodule with ill-defined contours, extending to the UOQ and measuring 5 × 4 cm. Ultrasound showed an irregular hypoechoic lesion, no flow on Doppler, and no posterior acoustic shadowing. The biopsy confirmed IGM and abscess. The therapeutic approach adopted was antibiotic therapy with cefadroxil and corticosteroid with dose escalation for two months. After this period, the patient returned presenting considerable recovery of the left breast.

DISCUSSION

The main signs and symptoms of IGM are the presence of unilateral breast nodule, pain, skin lesions, and fistulas[4]. Patients predominantly presented abscess (Figure 1) and unilateral breast nodules.

The IGM diagnosis is by exclusion, along with biopsy, because only a histopathological examination can establish a definitive diagnosis[4]. Specific histological findings are characterized by non-caseating and non-vascular granulomatous inflammatory changes, which can be observed in the center of the lobes[5]. Mammography radiological findings are not precise, and ultrasound is characterized by the presence of multiple irregular hypoechoic lesions and collections with finger-like tubular connections[4].

All patients in this series underwent biopsy, tuberculosis test, and ultrasound. In all cases, the biopsy revealed fibrosis and chronic granulomatous inflammatory process (Figures 2 and 3), the tuberculosis test was negative, and the ultrasound showed hypoechoic nodules associated with cystic areas with thick content.

New studies demonstrate the importance of imaging records. Images, such as those from magnetic resonance, are useful in monitoring IGM behavior and clinical improvement, particularly in patients conservatively managed[6]. Also, elastography as adjuvant for conventional B-scan ultrasound, together with the calculated

stress rate, helps to differentiate IGM from malignant breast lesions[7]. These tests were not performed in the cases described.

There is no consensus on the best treatment approach yet. Surgical excision and steroid therapy are the most adopted[8]. However, in case of complications such as abscess, fistulas, and persistent wound infections, surgical resection can be considered the main treatment modality with curative intention, as well as in cases of localized diseases[9,10].

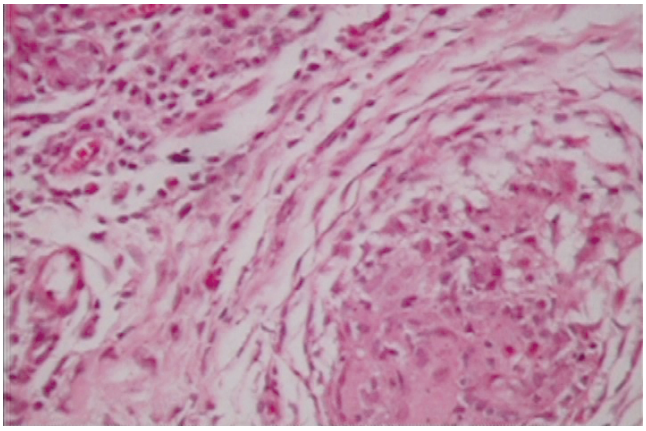

Figure 2. Microscopy of a sample stained with hematoxylin-eosin, showing the presence of an edge of fibroblasts and connective tissue with T cells infiltrate, characterizing a granulomatous inflammatory process.

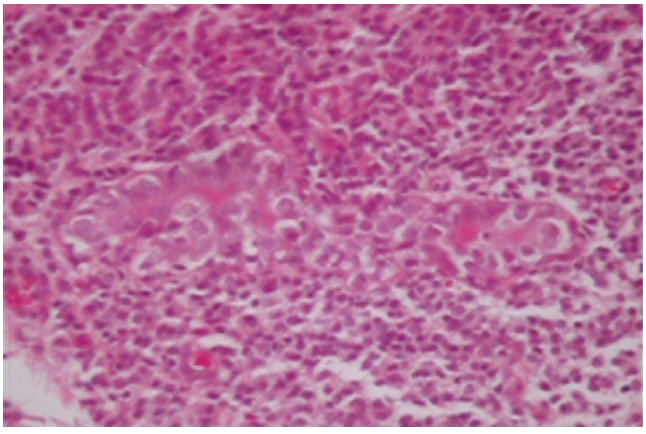

Figure 3. Microscopy of a sample stained with hematoxylin-eosin, showing a large macrophage and T lymphocyte infiltration, characterizing a chronic inflammatory process.

Thus, complete resection of the affected tissue, with or without using corticosteroids, is often recommended as an ideal treatment, although it has long follow-up, recurrence in up to 38% of patients, and slow wound healing[10]. Nonetheless, surgical excision may be useful in providing accurate diagnosis[10]. After excision, if there is no infection, recurrence, or wound healing impairment, the treatment can be completed[10,11].

DeHertogh et al.[12] were the first to recommend the use of corticosteroids to treat IGM. Steroid treatment can be administered after excision in complicated and resistant cases, or in patients who had only an incisional biopsy and in initially unresectable lesions before surgery[11,13]. Early diagnosis and administration of corticosteroids may prevent repetitive and deforming breast biopsies, as well as long-term recurrence[13]. However, the weighting of possible risks and benefits of the therapy is still difficult due to the lack of broader studies and the small number of reported cases[10-13].

The use of immunosuppressants (methotrexate and azathioprine) is indicated in cases of resistance to corticosteroid therapy. The administration of immunosuppressants is more effective in controlling the inflammatory process and preventing future complications. The combination of methotrexate and azathioprine has been useful in the treatment of primary and recurrent diseases[14].

A meta-analysis demonstrated that the IGM remission/resolution (RR) rate, with the use of oral corticosteroids was 71.8% with a recurrence rate of 20.9%, while remission with the use of topical corticosteroid was 98.8% with a recurrence rate of 14.3%. The association of oral corticosteroids with surgical resection presents resolution in 94.5% of the cases and a recurrence rate of 4%. This meta-analysis assessed 15 scientific publications, including 602 cases[15].

CONCLUSION

In the present study, all patients with IGM showed remission of the disease using corticosteroid therapy after an average follow-up of three months.

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CASE REPORT
DOI:10.29289/2594539420192019002

BREAST METASTASIS OF GASTRIC SIGNET RING CELL CARCINOMA MIMICKING BREAST LYMPHANGITIC CARCINOMATOSIS

Metástase mamária de carcinoma gástrico em anel de sinete simulando linfangite carcinomatosa da mama

Raffaela Levy de Andrade[1]*, Mauricio Nunes Buzzellin[1], Adriana Viana Cançado[1], Douglas de Miranda Pires[1]

ABSTRACT

Introduction: The incidence of breast metastasis from gastric adenocarcinoma is extremely low. Since 1908, 44 cases have been reported in the literature, of which 30 are signet ring cell type. **Case report:** A 49-year-old patient being investigated for digestive bleeding was found to have left axillary lymphadenopathy, associated with breast asymmetry, associated with breast asymmetry, edema and thickening of the skin. Breast ultrasonography showed a heterogeneous lesion in the left breast. Core biopsy histology was compatible with Lauren diffuse gastric adenocarcinoma with signet ring cells. There was positive immunohistochemical staining for CK7, CK20 and CDX2 and negative for RE, RP and ERB2. Our findings were compatible with gastric adenocarcinoma (lymphatic embolism), favoring the possibility of a secondary neoplasm. At the time of diagnosis, the patient already had radiological signs of multiple metastases. **Discussion:** Breast metastases of gastric carcinoma differ from primary breast cancer in histopathological features. The clinical manifestations of gastric cancer metastasis vary, but it is known that there is a greater tendency for inflammatory disorders compared to primary tumors. In the metastatic process, breast involvement may be the first event or occur in a context of multiple metastases. Most patients have a one-year survival after diagnosis. There is no gain in survival with breast surgery, but it can alleviate the symptoms in some cases. **Conclusion:** Gastric cancer with breast metastasis is a rare condition associated with poor prognosis. The diagnosis is based on clinical history, histological findings and immunohistochemical markers, differing from primary tumors of the breast, to provide patients with adequate treatment.

KEYWORDS: breast neoplasm; metastasis; stomach neoplasms; carcinoma, signet ring cell; immunohistochemistry.

RESUMO

Introdução: A incidência de metástase mamária de adenocarcinoma gástrico é extremamente baixa. De 1908 até o momento, 44 casos foram relatados na literatura, dos quais 30 são do tipo em anel de sinete. **Relato do caso:** Paciente de 49 anos em propedêutica de sangramento digestivo alto. Apresentava linfadenomegalia axilar esquerda, associada a assimetria mamária, edema e espessamento de pele. Ultrassonografia mamária evidenciou lesão heterogênea em mama esquerda. Histologia de *core biopsy* da área compatível com adenocarcinoma gástrico tipo difuso de Lauren, com células em anel de sinete. Imuno-histoquímica positiva para pancitoqueratinas CK7, CK20, CDX2 e negativa para RE, RP e ERB2. Achados compatíveis com adenocarcinoma gástrico (embolia linfática), favorecendo a possibilidade de neoplasia secundária. Ao momento do diagnóstico, a paciente já apresentava sinais radiológicos de múltiplas metástases. **Discussão:** As metástases mamárias do carcinoma gástrico diferem do câncer de mama primário nas características histopatológicas. As manifestações clínicas das metástases de câncer gástrico são variadas, mas é sabido que há tendência maior de alterações inflamatórias que nos tumores primários. No processo metastático, o envolvimento mamário pode ser o primeiro evento ou ocorrer em um contexto polimetastático. A maioria dos pacientes tem sobrevida inferior a

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um ano. Não há ganho de sobrevida com a cirurgia de mama, mas ela pode aliviar os sintomas em alguns casos. **Conclusão:** O câncer gástrico com metástase na mama é uma condição rara associada a mau prognóstico. O diagnóstico é baseado em história clínica, achados histológicos e marcadores imuno-histoquímicos, o que diferencia a metástase de um tumor primário da mama, a fim de oferecer aos pacientes o tratamento adequado.

PALAVRAS-CHAVE: neoplasias da mama; metástase neoplásica; neoplasias gástricas; carcinoma de células em anel de sinete; imuno-histoquímica.

INTRODUCTION

Breast metastases of gastric carcinoma are extremely rare events. Forty-four cases of this condition are described in the literature. Clinically and radiologically, metastatic tumors resemble primary breast tumors. The correct diagnosis of breast metastasis is of fundamental importance for the proper treatment of the disease. Lymphatic dissemination is the likely mechanism of metastasis.

CASE REPORT

A female patient, 49 years old, was hospitalized for the diagnosis of digestive hemorrhage, where gastric malignancy was suspected, and she was still awaiting anatomopathological confirmation. She had axillary lymphadenomegaly, so a lymph node biopsy was requested. On examination, there was breast asymmetry (left breast larger than right) and edema in the lateral third to the left breast nipple-areola complex, without hyperemia or palpable nodules (Figure 1). Left axillary lymphadenomegaly with hardened and fixed lymph nodes was observed. There were free supra- and infraclavicular fossa and absence of nipple discharge. Imaging examinations were requested.

Chest, abdomen and pelvic tomography yielded multiple findings: cervical lymphadenomegaly, bilateral and axillary inferior paratracheal; paramediastinal septal thickening in right upper pulmonary lobe suspected of carcinomatous lymphangitis; massive bilateral pleural effusion; nonocclusive thrombosis of the left subclavian vein; stenosing concentric parietal thickening, ulcerated in antrum and gastric pylorus; atypical lymphadenomegaly in portal hepatic, infrapyloric and mesenteric chain; sclerotic nodules in the bone marrow of the T6 and T11 vertebrae and in the right iliac bone, and the possibility of secondary neoplasia needed to be considered.

A mammogram showed skin thickening and predominance of dense fibroglandular tissue, without other relevant findings — CAT 2 Breast Imaging Reporting and Data System (BI-RADS®) (Figure 2).

Breast ultrasound revealed a heterogeneous area with poorly defined margins in the upper left breast quadrant junction, measuring 13 × 19 × 0.9 mm, with posterior acoustic shadow, and pathological left axillary lymph nodes — CAT 4 BI-RADS® (Figure 3).

A core biopsy from a suspected area was performed and histology was consistent with diffuse gastric adenocarcinoma

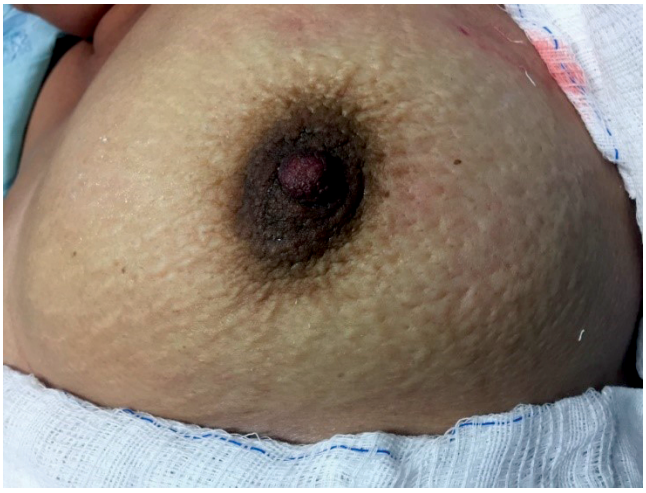


Figure 1. Clinical presentation: breast edema and skin thickening.

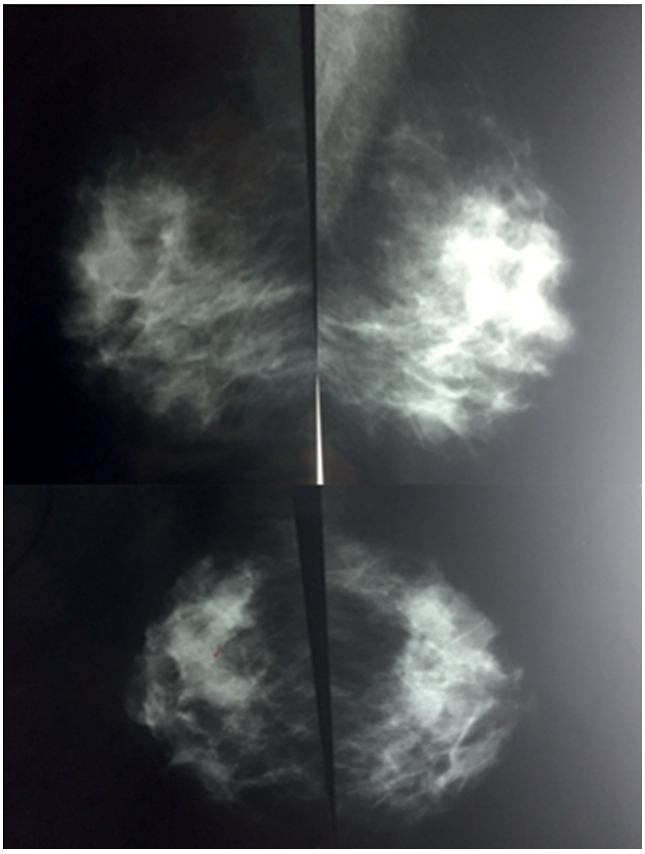


Figure 2. Mammogram.

according to Lauren, with signet ring cells (Figures 4A and 4B). An immunohistochemical study revealed immunopositivity for pancytokeratins CK7, CK20 CDX2 (Table 1, Figures 5A and 5B). Findings were compatible with gastric adenocarcinoma (lymphatic embolism). Negativity for RE and PR favored the possibility of secondary neoplasia, with the stomach being a possible primary site.

The anatomopathological examination of the gastric biopsy confirmed diffuse gastric adenocarcinoma Lauren of the signet ring cell type. The patient had poor performance status and was referred to oncology for consideration of palliative chemotherapy.

DISCUSSION

Breast metastases from non-breast sites are rare events, accounting for 0.3–2.7% of all malignant breast tumors[1-3]. Melanomas and lymphomas are the main sources of breast metastases, followed by lung, ovarian, kidney, stomach, oropharynx and carcinoid tumors[4]. Regarding breast metastasis from gastric cancer, including the present report, there are only 44 cases reported in the literature, as described in Table 2. Of these, 66.6% (30) are signet ring cell type, which corresponds to only 10% of all gastric cancers. The median age of presentation of this rare condition is 46 years, younger than the average diagnosis of primary breast cancer (which is 56 years[21]).

Gastric cancer metastases in the breast are mostly of the signet ring cell type and should be distinguished from primary breast signet ring cell carcinomas, which were first described as a subtype of lobular tumors by Steinbrecher and Silverberg in 1976[5]. Primary breast signet ring cell carcinomas have aggressive biological behavior and a higher tendency for metastasis to the abdomen. Still, cases of metastasis to the stomach have been described[6-8].

Breast metastases from gastric carcinoma differ from primary breast cancer in histopathological features. Immunohistochemical findings are generally negative for estrogen and progesterone receptors, and for c-erbB-2 as well. There are no signs of *in situ* component or loss of desmoplastic response. In contrast, lymphatic emboli and epithelial markers such as CK7, CK20 and CEA are usually present[9,10].

The clinical manifestations of gastric cancer metastases reported in the literature are varied. Of the 44 cases described, 22 were clinically palpable nodules and 11 had inflammatory changes. Chang et al.[11] reported that the incidence of inflammatory changes (local redness, swelling, bumps or warmth)

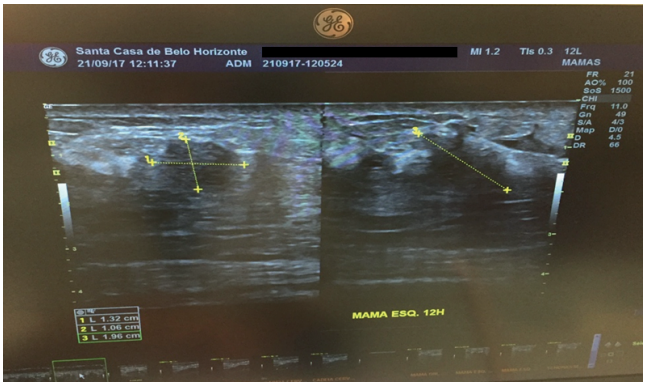
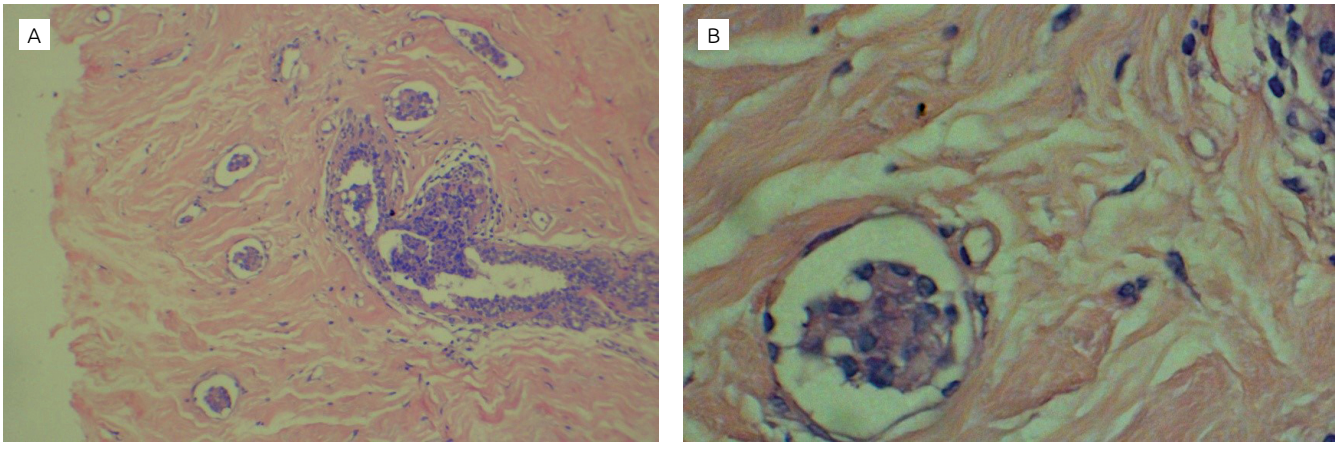


Figure 3. Breast ultrasound.

Table 1. Immunohistochemical study of core biopsy fragment.

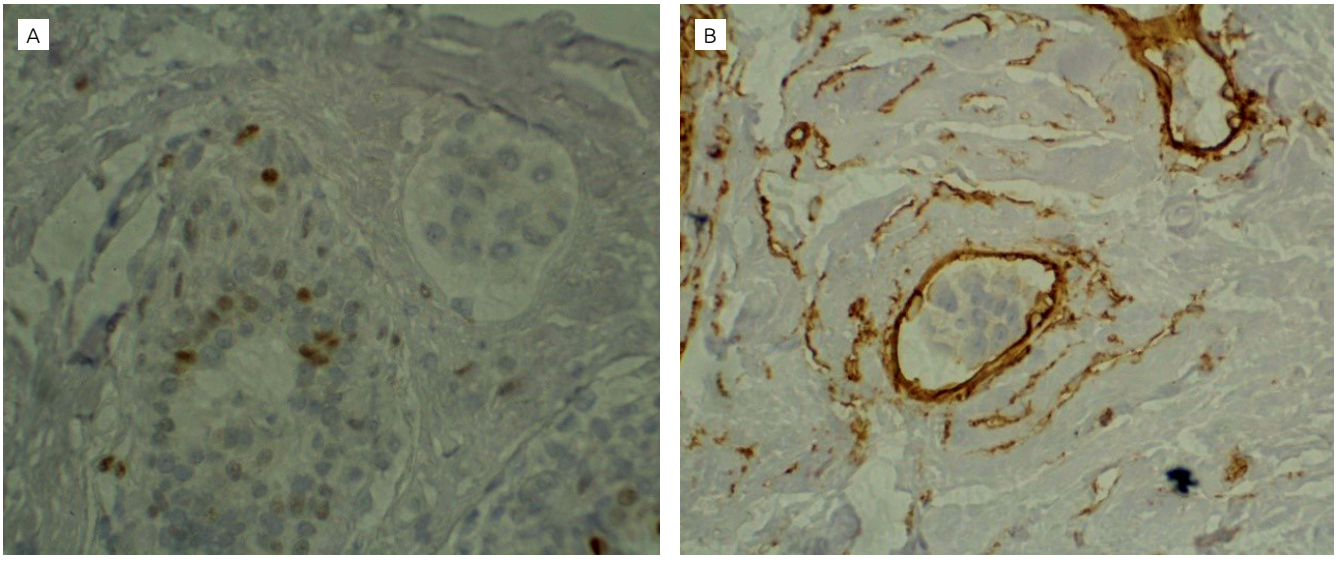
Antibody	Result	Antibody	Result
Pancytokeratins	+	CDX2	+
KI67	+ (30%)	RE	-
CK7	+	RP	-
CK20	+	HER-2/neu	-
CD34	+		

Source: Dr. Maurício Buzzellin of the Pathological Anatomy Laboratory, Santa-Casa de Belo Horizonte.



Source: Dr. Maurício Buzzellin of the Pathological Anatomy Laboratory, Santa-Casa de Belo Horizonte.

Figure 4. (A) Anatomopathological examination of core biopsy fragment; (B) Anatomopathological examination of core biopsy fragment at higher magnification. Note lymphatic embolism with signet ring cell.



Source: Dr. Maurício Buzzellin of the Pathological Anatomy Laboratory, Santa-Casa de Belo Horizonte.

Figure 5. (A) Immunohistochemical staining. Note the immunonegativity for RE; (B) Immunohistochemical staining. Note the immunopositivity for CD34.

Table 2. Forty-four cases of breast metastasis from gastric cancer reported in the literature*.

Authors	Sex	Age	Histological type	Clinical presentation of breast lesion
Reitmann[a]	F	33	Scirrhous carcinoma	–
Kreibich[a]	F	65	Scirrhous carcinoma	–
Mourier et al.[a]	F	31	Mucinous carcinoma	–
Stahr[a]	M	46	Anaplastic carcinoma	–
Dawson[a]	F	25	Mucinous carcinoma	–
Abrams et al.[a]	F	–	–	–
Sandison[a]	F	56	Signet ring cell carcinoma	–
Nance et al.[a]	F	59	–	Inflammatory
Hajdu et al.[a]	F	–	Adenocarcinoma	–
Schmutzer et al.[a]	F	22	Poorly differentiated adenocarcinoma	Nodules
Silverman et al.[a]	F	–	Mucin-producing carcinoma	–
Toombs et al.[a]	F	–	–	–
Satake et al.[a]	F	39	Signet ring cell carcinoma	Nodule
Togo et al.[a]	F	70	Signet ring cell carcinoma	Nodule
Nielsen et al.[a]	F	59	Mucinous carcinoma	Nodules
Champault et al.[a]	F	65	Adenocarcinoma	Nodule
Kasuga et al.[a]	F	48	Signet ring cell carcinoma	Nodules
Tachibana et al.[a]	F	46	Signet ring cell carcinoma	–
Alexander et al.[a]	F	28	Mucinous carcinoma	Nodules
Hamby et al.[a]	F	31	Signet ring cell carcinoma	Nodule
Mishina et al.[a]	F	36	Signet ring cell carcinoma	–
Cavazzini et al.[a]	F	50	Signet ring cell carcinoma	Inflammatory
Domanski[a]	F	48	Signet ring cell carcinoma	Nodule
de la Cruz Mera[a]	F	61	Signet ring cell carcinoma	Nodule

Continue...

Table 2. Continuation.

Authors	Sex	Age	Histological type	Clinical presentation of breast lesion
Briest et al.[a]	F	46	Signet ring cell carcinoma	Inflammatory
Kudo et al.[a]	F	46	Signet ring cell carcinoma	Nodule
Kwak et al.[4]	F	41	Signet ring cell carcinoma	Inflammatory
Kwak et al.[4]	F	23	Signet ring cell carcinoma	Inflammatory
Madan et al.[a]	F	39	Signet ring cell carcinoma	Nodule
Di Cosimo et al.[a]	F	39	Signet ring cell carcinoma	Nodule
Boutis et al.[13]	F	37	Signet ring cell carcinoma	Inflammatory
Qureshi et al.[a]	F	34	Signet ring cell carcinoma	Nodule
Isobe et al.[a]	F	48	Signet ring cell carcinoma	Nodule
Hasegawa et al.[a]	F	61	Signet ring cell carcinoma	Nodule
Makni et al.[12]	F	40	Signet ring cell carcinoma	Nodule
Gugić et al.[a]	F	43	Signet ring cell carcinoma	Nodule
Sato et al.[19]	F	67	Signet ring cell carcinoma	Inflammatory
Cil et al.[a]	F	63	Signet ring cell carcinoma	Inflammatory
Cil et al.[a]	F	65	Signet ring cell carcinoma	Inflammatory
Iesato et al.[10]	F	41	Signet ring cell carcinoma	Inflammatory
Iesato et al.[10]	F	34	Signet ring cell carcinoma	Nodule
He et al.[20]	F	48	Signet ring cell carcinoma	Nodule
Wei et al.[17]	F	49	Signet ring cell carcinoma	Nodule
Tian et al.[5]	F	39	Signet ring cell carcinoma	Nodule

*Clinical information is given in in the table only if available from the authors. Inflammatory: indicating redness, swelling, tightness or warmth in the chest; - not described; [a]references included in [10]; F: females; M: male.

in gastric carcinoma breast metastasis was at least four times higher than in primary breast cancer.

Imaging diagnosis of breast metastasis from gastric carcinoma can be flawed. Mammograms can show circumscribed nodules and skin thickening, and ultrasound can identify irregular hypoechoic nodules, diffuse irregular areas, and skin thickening, but none of the examinations can show significant changes.

In this case, the patient had left breast edema associated with skin edema (*peau d'orange*) without hyperemia or palpable nodules. Tomography revealed left subclavian vein thrombosis, which could be one of the differential diagnoses of clinically noted breast asymmetry.

Usually about 40% of breast metastases are found during or up to one year after the diagnosis of the primary site[10]. In the metastatic process, breast involvement could be the first event or occur in a polymetastatic manner[12]. In a literature review covering 41 cases of gastric cancer metastasis to the breast, 28 patients had other metastasis sites, including axillary, supraclavicular, ovarian, peritoneal, pleural, hilar lymph nodes and liver, among others[10].

Selective invasion of hormone-dependent organs (ovaries, breast) especially in premenopausal women is intriguing[9]. Some authors propose that breast blood supply is the mechanism for the increased incidence of breast metastasis in premenopausal women[13,14]. However, another explanation may be the fact that gastric cancer has a more aggressive biological behavior in younger groups[15]. The appearance of breast metastases in men with gynecomastia supports the latter hypothesis[16].

The prognosis of patients with breast metastases from gastric carcinoma is quite poor. Most patients survive less than one year after the diagnosis of breast metastasis[1]. Systemic treatments include neoadjuvant chemotherapy appropriate for the primary tumor and curative or palliative surgery for the primary cancer or breast metastasis[17]. There is no survival gain with breast surgery, but it can alleviate symptoms in some cases[18,19].

CONCLUSION

The present case represented an extremely rare condition, with few cases reported in the literature, usually associated with poor prognosis. In cases of breast tumors showing the presence of signet ring cells without associated *in situ* lesions, the possibility of gastric cancer should be considered. Clinical history and anatomopathological and immunohistochemical examinations are important to distinguish metastatic cancer from primary breast cancer, allowing patients to receive appropriate treatment.

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RISK FACTORS RELATED TO BREAST CANCER DEVELOPMENT

Fatores de risco relacionados ao desenvolvimento do câncer de mama

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ABSTRACT

Breast cancer is a disease that affects women worldwide, and therefore is a health problem of global concern. Despite scientific and technological advances in basic researches and in clinical studies, breast cancer still presents numerous obstacles that need to be overcome in order to ensure better survival for patients affected by this disease. Science's work is not only to predict the best methods of treatment, but also to prevent the onset of symptoms and, consequently, of the tumor. Recent articles discuss numerous factors which may contribute to tumor initiation and progression. They take into consideration social habits, such as smoking, alcohol drinking, diets that contribute to hyperlipidemia or increased availability of antagonist molecules that act on the cell in order to create a favorable microenvironment to tumorigenesis. In addition to that, factors related to family history and hereditary predisposition are important, even though they explain a minimal portion of cases. Thus, the purpose of this article is to address modifiable and non-modifiable risk factors, related to breast cancer progression.

KEYWORDS: breast cancer; risk factors; neoplasms.

RESUMO

O câncer de mama é uma doença que acomete mulheres em todo o mundo, sendo por isso um problema de saúde de preocupação global. Apesar dos avanços científicos e tecnológicos nas pesquisas básicas e nos estudos clínicos, o câncer de mama ainda apresenta inúmeras barreiras que necessitam ser transpostas, a fim de garantir melhor sobrevida às pacientes acometidas por essa doença. A atuação da ciência consiste não apenas em prever as melhores formas de tratamento, mas também de como evitar o aparecimento dos sintomas e, por consequência, do tumor. Artigos recentes discutem inúmeros fatores que podem contribuir para a iniciação e progressão tumoral. São considerados os hábitos sociais, como o ato de fumar, ingestão de bebidas alcoólicas, dietas que contribuam para a hiperlipidemia ou aumento da disponibilidade de moléculas antagonistas que agem sobre a célula de modo a construir um microambiente favorável à tumorigênese. Além disso, fatores ligados ao histórico familiar e predisposição hereditária são importantes, apesar de explicar uma parcela mínima dos casos. Com isso, o presente artigo tem por objetivo abordar sobre fatores de risco modificáveis e não modificáveis, relacionados com a progressão do câncer de mama.

PALAVRAS-CHAVE: câncer de mama; fatores de risco; câncer.

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INTRODUCTION

Breast cancer is a disease of worldwide interest that affects women on a global scale and a small part of the male population[1-3]. Statistics of the project Globocan/IARC (International Agency for Research on Cancer) of 2018 highlight that breast cancer ranked the second most common type of cancer worldwide (2,089 million), only behind lung cancer (2,094 million), and it is eligible as the fifth leading cause of death, considering both genders, rising to first place of most incident type and at the top of mortality when only women are counted[4,5].

According to Atlas of Cancer Mortality (2018), 15,593 breast cancer deaths were registered in Brazil during 2015, being 187 men and 15,403 women[6]. In Brazil, breast cancer is responsible for 29.5% of all new cases each year. Its incidence in 2018 is estimated at 59,700, with an approximate risk of 56.33 per 100,000 women. In the state of São Paulo, statistics estimated 16.340 new cases of breast cancer in 2018. In the metropolis of São Paulo, the prediction was 5,900 new cases of breast cancer per 100,000 inhabitants, and the risk was approximately 90,41[6].

It is known by the scientific community that certain aspects directly or indirectly affect the progression of breast cancer, the so-called risk factors[7,8].

This article aims to address, briefly, the main risk factors which have been discussed in world literature.

RISK FACTORS

Risk factors for breast cancer incidence include the ones classified as modifiable and non modifiable[7,8]. Modifiable factors are those in which a direct or indirect action becomes possible to minimize the risk of development of the disease, such as obesity, sedentarism, alcohol and 0tobacco consumption, in addition to the use of hormone replacement therapy and, more recently, the administration of hormones with the objective of gender transitioning has been discussed[9]. On the other hand, non-modifiable factors — like family history and hereditary aspects — are the ones on which no action can be taken in order to have a significant impact over the individual[7].

Modifiable factors

Hyperlipidemia and physical activity

The practice of physical activity has been suggested as an important factor to improve life quality in patients with breast cancer, including the protector effect this activity has on reducing the risk of tumor development in the mammary region[8,10]. Lahart et al. conducted a meta-analysis, in which twenty-two prospective cohort studies were chosen to be part of the analysis, with a total of 123,574 participants. The researchers concluded that physical activity is of great importance in reducing mortality among patients affected by the disease, even if the onset of activities occurred after cancer diagnosis[11].

In a recent review, Buss and Dachs gathered works by other authors and presented a proposal regarding the action of hyperlipidemia over breast cancer progression[12]. In fewer words, cholesterol metabolism leads to the production of a metabolite called 27-hydroxicholesterol (27HC) that is able of activating Estrogen Receptors (ER) in mammary cells, inducing their proliferation, or even their acting on the epithelial-mesenchymal transition (EMT), with the activation of Liver X Receptor (LXR). The pathways through which LXR leads to EMT are not clear yet. In addition, cholesterol appears as the protagonist in macrophage recruitment, which in turn, is involved in chronic inflammation and, therefore, in tumorigenesis. The signaling of PI3K/AKT pathway, frequently dysregulated in human cancers, is one of the molecular targets of cholesterol that is directly involved in increasing cellular proliferation. Finally, androgen signaling pathways still lacking study are raised in this review[12].

The physical activity role is suggested as an important factor to decrease the overall levels of cholesterol, fact that implies minimization of the factors discussed above. Furthermore, physical activity is able to improve the immune system, so that defense cells are more effective in recognizing and eliminating the tumoral cell, also contributing to the decrease of insulin 1 growth factor (IGF-1) and to the improvement of IGF 3 binding protein (IGFBP-3). Even though physical exercises act by decreasing the level of body lipids, the high-cholesterol diet is also responsible for the increase and maintenance of lipids bioavailability and, therefore, it is capable of contributing to the risk of development of the disease[12,13].

Diet

The prevention related to eating habits, considering not only mammary tumors, is something that still meets resistance, either from the patient, or from researches that need to go further in the complexity of the subject. Strategies have been adopted to contribute to the reduction of incidence of breast cancer and other comorbidities, emphasizing vegetable sources and fiber intake[8,14].

Adequate intake of fiber and green vegetables, fruits, vegetables, lean proteins and whole grains has been associated with reduced serum levels of estradiol and estrogen and increased sex hormone binding globulin (SHBG)[15]. Estrogen levels are related to susceptibility to breast cancer development[8,16]. On the other hand, meat consumption in general, both red and processed, was related to a higher risk of breast cancer[17].

One of the points discussed about the increase in the incidence of breast cancer cases includes obesity, caused by unbalanced dieting. In the Eastern Mediterranean region, a clear body weight gain in the population was directly related to the number of new cases of cancer in the mammary tissue[18].

Aryl hydrocarbon receptor (AhR) has been identified with strong relation to BRCA1 methylation in triple-negative tumor samples. AhR agonists are found in foods and have been shown

as contributors, increasing the risk of development of the mammary disease, as well as the dietary AhR antagonists provided a preventive effect against breast cancer[19].

Obesity

Obesity is defined as an excessive fat accumulation in tissues, and can be diagnosed when the body mass index (BMI) is ≥30 kg/m^2 [20]. It is a public health problem that affects more than 600 million people worldwide. Developed countries show the highest rates of adults affected by obesity. While the impact of BMI on diabetes and on heart disease is well known, the relation to breast cancer and other human cancers remain a current topic[21,22]. Obesity is an important risk factor to breast cancer development and there is a substantial association with postmenopausal women, as well as worse prognosis for women at all ages[21]. About 9% of cases of women with postmenopausal breast tumors are believed to be affected due to overweight of the patients[8].

Breasts are composed of three special structures: adipose tissue, mammary glands and fibrous tissue. The adipose tissue is subdivided into yellow and brown, being the former able to produce a wide range of metabolites, hormones and cytokines, called adipocytokines[20]. The adipose tissue may also undergo aromatization, leading to the increase of estrogen levels, upregulation of pro-inflammatory cytokines, insulin resistance, hyperactivation of IGF, adipocytes-adipokines derivatives, hypercholesterolemia, and excessive oxidative stress, thus contributing to the development of breast pathology[23,24].

Positive correlations between triple-negative breast cancer and high BMI have been reported, reflecting the importance of obesity control to improve the prognosis of these patients[23].

Alcohol Consumption

Alcohol consumption is associated with the development of a wide range of diseases, including cancer of the colon, rectum, female breast, oral cavity, larynx, pharynx, liver, and esophagus[8,25].

There are multiple cellular mechanisms, promoted by alcohol consumption whose consequence is enhancement in tumoral aggressiveness:

- alcohol metabolism, which produces acetaldehyde, a toxic and carcinogenic substance with affinity to DNA and proteins;
- production of reactive oxygen species, which may favor tumorigenesis based on the oxidation process (oxidative stress);
- reduced absorption performance of important nutrients and vitamins;
- increased serum estrogen levels;
- reduced immune system performance[8,26,27].

Additionally, there may be alterations on the menstrual cycle promoted by the versatile role of alcohol[28].

Exposure to alcohol can help in the promotion of carcinogenesis; even with the existing malignancy, consuming alcohol can contribute to enhance the progression and aggressiveness of existing tumors by promoting cell mobility, EMT and angiogenesis[25,27]. Furthermore, cancer stem-like cells (CSC) are directly influenced by alcohol consumption and may increase their population, which may result in different behaviors of the tumor mass, leading to different therapeutic responses[25,27].

Zakhari and Hoek discuss high and moderate consumption of alcohol, highlighting the importance of the analysis of molecular signatures that can better assess the causal relationships with breast cancer and suggesting different roles based on the levels of consumption[29].

Tobacco Consumption

The use of tobacco is related to the development of numerous pathologies, including lung cancer that represents the leading cause of cancer death worldwide, including both the male and the female population[30]. Regarding breast cancer, studies have demonstrated that not only active smoking, but also passive smoking, can predispose the individual to the risk of developing the disease[8,31].

Among the thousands of chemical products found in tobacco, 69 different compounds are classified as carcinogenic, specifically, the 4-(methylnitrosamino) -1- (3-pyridyl) -1-butanone (NNK) (Nicotine-derived nitrosamine ketone), considered the most aggressive nitrosamine among the ones present in tobacco[31]. NNK is found in cigars, cigarettes, electronic cigarettes, tobacco and in the smoke from these products, causing nitrosamines to affect not only the consumer, but also non-smokers or passive smokers exposed to environmental tobacco pollution[31]. On the other hand, environmental exposure to tobacco was criticized, and a meta-analysis published by Lee and Hamling assessed 47 studies. A weak association between non-smoking women and breast cancer development and stratified results were observed, having higher association in Asian than in European countries[32].

Gaudet et al., aiming at defusing the controversy between tobacco smoking and breast cancer risk, performed a meta-analysis in which the data of 73,388 women were analyzed. The work showed that active smoking is significantly associated to the risk of breast cancer development in women that began tobacco consumption before their first childbirth. Moreover, the authors discuss the role that tobacco may play on tumor initiation[33].

Hormone replacement therapy (HRT)

Hormone replacement therapy (HRT) is a procedure to relieve the climacteric symptoms of menopause and its applicability has decreased after studies linking it to the increased risk of developing breast cancer[34]. The use of HRT was associated to lobular breast cancer, positive ER and low level, concerning its immunohistochemical characteristics[34,35].

Wang et al. analyzed prospective cohort studies and case control studies evaluating HRT users. Among the observed variables and

in order to identify the dose relationship, the time of use and the abandonment of HRT use were considered. The authors concluded that HRT application was associated with he risk of breast cancer[35].

Non-Modifiable Factor

Family history

Brewer et al. conducted a study aiming at analyzing the relation between family history and the risk of developing breast cancer. A score was assigned to this relation and a significant connection was found to those who reported a family history of female breast cancer[36]. Haber et al. observed a significant association not only in relation to first-degree relatives with breast cancer and women with breast cancer, but they could also verify the significant risk that first-degree relatives with any other kind of cancer could exert on women with breast cancer[37].

Early menarche and late menopause

Menarche is the first menstrual bleeding of a woman, while menopause is the period in which ovaries stop producing reproductive hormones. This period between menarche and the menopause is a hypothesis of risk of breast cancer, consequence of mitotic activity of mammary cells, driven by estrogen and progesterone exposure, during the luteal phase of the menstrual cycle[38].

Hereditary predisposition

In addition to the factors described above, numerous germ-line mutations are related to hereditary predisposition to breast cancer, among them are noteworthy the mutations in genes p53, BRCA1 and BRCA2 (breast cancer susceptibility 1 and 2), responsible for conferring high risk. Other genes that can undergo mutations are CHEK2 (Checkpoint Kinase 2), PTEN (Phosphatase and tensin homolog), PALB2 (Partner and localizer of BRCA2), RAD51C (S. cerevisiae, homolog of C), CDH1 (cadherin 1) PPM1D (Protein phosphatase, Mg2+/Mn2+ dependent 1D) and genes that determine Lynch syndrome that pose moderate to high risk[39–41]. Furthermore, more than 90 other common low penetrance variants are mentioned[42].

Breast cancers of hereditary origin are different from the ones of somatic origin not only concerning the mutations involved but also regarding the pathological characteristics, being more aggressive and with a worse prognosis, besides affecting younger women[41].

Mutations on genes BRCA1 and BRCA2 constitute major susceptibility genes for the development of ovarian and breast cancer[43]. However, only 10% of the predisposed families present some mutation in the coding regions of these genes[43]. Thereby, efforts have been performed trying to identify mutations in non-coding regions, and in relation to the action of associated epigenetic factors — as well as the activity of non-coding RNAs, like the microRNAs (miRNAs) — involved in the process of gene silencing and in the role of long non-coding RNA (lncRNAs), both in BRCA1 and BRCA2, as well as in a variety of other related genes[43-46].

CONCLUSION

Breast cancer is a multifactorial disease. Scientific advances in understanding tumor appearance and behavior have provided effective tools for prevention, treatment, and aftercare.

Nevertheless, epidemiological and ***in vivo*** studies are still necessary to better understand the mechanism of intra- and extracellular action modulated by exposure to the risk factors described in this study and, consequently, to resolve the contradictions found in the meta-analyses and reviews referred to herein.

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IMPLEMENTATION STRATEGIES FOR THE GUIDELINES FOR THE EARLY DETECTION OF BREAST CANCER IN BRAZIL

Estratégias de implementação das diretrizes para a detecção precoce do câncer de mama no Brasil

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ABSTRACT

This research project aimed to identify strategies for implementing guidelines for early detection of breast cancer in Brazil. Regarding the specific objectives, it aimed to identify studies in the specialized literature on the difficulties and strategies for implementing the guidelines for early detection of breast cancer in the health systems of different countries; to evaluate the applicability of the results found in the Brazilian context; and to recommend priority actions in accordance with the implementation strategies of the guidelines to the organizations responsible for these processes in the public health context. A review of systematic reviews was carried out using the supporting policy relevant reviews and trial (SUPPORT) tools to assist in structuring searches and analyzing data. The databases used were PubMed/MEDLINE, Cochrane Library, Virtual Health Library (VHL)/Latin American and Caribbean Health Sciences Literature (Lilacs) and Embase from January 1, 2008 to May 1, 2018. The study of nine selected systematic reviews identified successful actions in developed and developing countries. The strategies identified were: promotion of leadership fronts committed to the implementation of the guidelines, better governance of health services close to the target audience, national mass dissemination campaign and patient navigation program.

KEYWORDS: early detection of cancer; breast neoplasms; public health policy.

RESUMO

Este projeto de pesquisa teve como objetivo geral identificar estratégias de implementação das diretrizes para a detecção precoce do câncer de mama no Brasil. Em relação aos objetivos específicos, propôs-se a identificar, na literatura especializada, estudos sobre as dificuldades e as estratégias de implementação das diretrizes para a detecção precoce do câncer de mama nos sistemas de saúde de diferentes países; a avaliar a aplicabilidade dos resultados encontrados no contexto brasileiro; e a recomendar ações prioritárias conforme as estratégias de implementação das diretrizes às organizações responsáveis por esses processos no âmbito da saúde pública. Foi realizada uma revisão de revisões sistemáticas utilizando as ferramentas *supporting policy relevant reviews and trial* (SUPPORT), para auxiliar na estruturação das buscas e na análise de dados. As bases de dados utilizadas foram PubMed/MEDLINE, Cochrane Library, Biblioteca Virtual em Saúde (BVS)/Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) e Embase de 1º de janeiro de 2008 a 1º de maio de 2018. O estudo de nove revisões sistemáticas selecionadas identificou ações exitosas em países desenvolvidos e em desenvolvimento. As estratégias identificadas foram: fomento de lideranças comprometidas com a implementação das diretrizes, melhor governança dos serviços de saúde próximos ao público-alvo, campanha nacional de divulgação em massa e programa de navegação de pacientes.

PALAVRAS-CHAVE: detecção precoce de câncer; neoplasias da mama; políticas públicas de saúde.

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INTRODUCTION

Breast cancer is generally considered to have a good prognosis when diagnosed and treated early. However, mortality rates for this type of cancer remain high in Brazil, most likely because is still diagnosed in advanced stages. In Brazil, only 20% of breast cancer cases are diagnosed at an early stage[1]. Women treated in the public health system have unfavorable outcomes compared to women treated in the private system, with worse disease-free and overall survival rates[2-5].

The main strategies for breast cancer control are: primary prevention (identification and correction of preventable risk factors), secondary prevention (early detection and treatment) and tertiary prevention (rehabilitation and palliative care). Secondary prevention strategies promote a reduction in mortality rates and therefore receive attention from national health systems in general[6]. Mammography is the method of choice for screening standard-risk populations, with no clinical examination or technology being superior to it so far[7].

Breast cancer screening programs require well-structured health systems, with assessment of the best cost-effectiveness and the availability of a wide range of management tools. About two decades ago, some developed countries implemented breast cancer screening programs, and nowadays show significant reductions in mortality from breast cancer[8].

There has been a trajectory of breast cancer prevention and control actions in Brazil since the 1970s. It was during this period that the first initiatives to understand cancer as a major health problem emerged, to be contained by a planned government action[9]. This trajectory included the implementation of breast cancer control actions, activities, programs and policies and the elaboration of the Guidelines for the Early Detection of Breast Cancer in Brazil in 2015[10].

Identifying possible barriers and the best strategies for the implementation of the guidelines for early detection of breast cancer in Brazil is relevant, as it pushes for improvements in the policy, potentially reducing the magnitude of this issue in the country. Challenges in implementing the guidelines may require changes at several levels, including: changes in the behavior of users and health professionals, organizational changes and changes in the health system. Strategies for achieving these changes are most likely to succeed if they address the barriers to their implementation. However, little is known about the effectiveness or about the different methods of identifying barriers and how to propose interventions to address them[11].

A structured investigation to identify those barriers can help ensure that none of them are underestimated. This requires a theoretical framework for systematically considering potential barriers and identifying and assessing evidence for the presence of potentially important barriers[11].

The present study aimed to identify strategies to assist policy makers and those who assist them in implementing the guidelines for early detection of breast cancer in Brazil, focusing on what health systems in other countries that are being more successful in this policy — with better indicators — are adopting. To assist in the structuring of the data search and analysis, the SUPPORT tools were used, which were designed for evidence-informed policy-making (EIPM) based on the best available scientific evidence[12].

METHODOLOGY

This study carried out a review of systematic reviews, a type of study designed to provide a synthesis and integrate information from various studies in order to reduce uncertainty in decision-making and ensure that this process is supported by the best scientific evidence available[13]. For the development of this study, the SUPPORT toolset was adopted, which provides the basis for the elaboration of policies informed by scientific evidence[11].

In the first stage, the issue to be addressed was characterized and structured to motivate the detailing of its confrontation. In the second stage, effective strategies were identified to deal with the issue through structured search in the following indexed bases:

- PubMed/MEDLINE;
- Cochrane Library;
- Virtual Health Library (BVS)/Latin American & Caribbean Health Sciences Literature (Lilacs);
- Embase.

Regarding the search, the period was restricted from January 1, 2008 to May 1, 2018, because an extended period did not add to the number of publications of interest. Inclusion criteria were: year and period of publication; availability of the full systematic review article in English, Portuguese, French or Spanish; and use of descriptors. The search filter for systematic reviews used — with adaptations depending on the source — is detailed in Chart 1.

All articles found were randomly organized for analysis based on their abstracts. The information was arranged in a data extraction table. The main study question was: what are the barriers to overcome strategies for implementing early breast cancer detection guidelines in developed and developing countries? The articles were selected according to the PICO format, with P (problem) being the barriers to the implementation of early detection guidelines, I (intervention) being the strategies to overcome barriers, C (comparison) being the different strategies used in developing countries and O (outcome) being greater adherence to the guidelines.

After reading the selected texts, duplicate studies and those that did not meet the interest criteria were excluded, that is, those that did not explore the strategies to overcome barriers (Figure 1). Selection criteria were applied to the full text of potentially eligible

reviews, and the reliability of reviews that met all other selection criteria was assessed, as shown in Chart 2.

Fields used for data extraction in the studies were: lead author, year of publication, place of study, study reliability, objective(s), results, barriers, and implementation strategies. Details of the included articles can be found in Chart 3.

Examples of how the different implementation strategies worked in the locations studied, considering the different determinants of organizational change in the system, practitioners' practice, and users' use of health services[11], are shown in Chart 4. These actions, ultimately, aimed at increasing mammographic coverage rate and quality of services, optimizing time for diagnosis and treatment, and reducing morbidity and mortality.

DISCUSSION

These nine reviews summarize the evidence base that supports strategies for implementing guidelines aimed at early detection of breast cancer globally. Each location selected strategies considering the existing barriers, resources and health structure[15].

The studies presented strategies for implementing early detection guidelines in the most vulnerable populations, such as low-income, low-educated individuals in developed countries, Latinos, Asians, Native Americans, Alaskan natives, African Americans. Patients in low- and middle-income countries face structural barriers that are similar to those faced by deprived patients in developed countries[14-22].

Chart 1. Filtro de buscas para revisões sistemáticas usadas.

PubMed/MEDLINE
((Health Plan Implementation[mh] OR "Health Plan Implementation"[tiab] OR "barriers to implementation"[tiab] OR "implementation strategies"[tiab] OR health policy[mh] OR health polic*[tiab] OR guidelines as topic[mh] OR guideline*[tiab] OR barriers[tiab])) AND ((Early Detection of Cancer[mh] OR "early detection"[tiab] OR early diagnosi*[tiab]) AND ((Breast Neoplasms[mh] OR breast[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR tumour*[tiab] OR tumour*[tiab] OR onco*[tiab] OR carcinoma*[tiab])))) AND (Review[ptyp] AND "2008/05/07"[PDat]: "2018/05/04"[PDat] AND "humans"[MeSH Terms] AND (English[lang] OR French[lang] OR Portuguese[lang] OR Spanish[lang]))
Cochrane Library
(([mh "Health Plan Implementation"] or "Health Plan Implementation":ti,ab or "barriers to implementation":ti,ab or "implementation strategies":ti,ab or [mh "health policy"] or health polic*:ti,ab or [mh "guidelines as topic"] or guideline*:ti,ab or barriers:ti,ab) and (([mh "Early Detection of Cancer"] or "early detection":ti,ab or early diagnosi*:ti,ab) and (([mh "Breast Neoplasms"] or breast:ti,ab) and (neoplasm*:ti,ab OR cancer*:ti,ab OR tumour*:ti,ab or tumour*:ti,ab or onco*:ti,ab or carcinoma*:ti,ab))))
BVS/LILACS
(tw:("Health PlanImplementation" OR "implementação de planos de saúde" OR "implementación de planes de salud" OR "barrierstoimplementation" OR "barreiras para implementação" OR "barreras para laimplementación" OR "implementationstrategies" OR "estratégias de implementação" OR "estrategias de implementación" OR "healthpolicy" OR "políticas de saúde" OR "políticas de salud" OR guidelines OR guias OR barriers OR barreiras OR barreras)) AND (tw:("earlydetection" OR "earlydiagnosis" OR "detecção precoce" OR "deteccionprecoz" OR "diagnóstico precoce" OR "diagnostico precoz")) AND (tw:("BreastNeoplasms" OR breast* OR "neoplasias da mama" OR "cancer de mama" OR mama)) AND (tw:(neoplas* OR cancer* OR tumour* OR tumour* OR onco* OR carcinoma*)) AND (instance:"regional") AND (db:("LILACS") AND year_cluster:("2011" OR "2009" OR "2013" OR "2012" OR "2016" OR "2010" OR "2015" OR "2014" OR "2008")
Embase
('health care planning'/exp OR 'community health planning':ti,ab OR 'health and welfare planning':ti,ab OR 'health care planning':ti,ab OR 'health plan implementation':ti,ab OR 'health planning':ti,ab OR 'health planning councils':ti,ab OR 'health planning database':ti,ab OR 'health planning guidelines':ti,ab OR 'health planning organisations':ti,ab OR 'health planning organizations':ti,ab OR 'health planning support':ti,ab OR 'health planning technical assistance':ti,ab OR 'health priorities':ti,ab OR 'health resources':ti,ab OR 'health systems plans':ti,ab OR 'healthcare planning':ti,ab OR 'medically underserved area':ti,ab OR 'national health planning information center':ti,ab OR 'national health planning information center (u.s.)':ti,ab OR 'regional health planning':ti,ab OR 'regional medical programmes':ti,ab OR 'regional medical programs':ti,ab OR 'state health planning and development agencies':ti,ab OR 'state health plans':ti,ab OR 'strategic stockpile':ti,ab OR 'underserved neighborhood':ti,ab OR 'barriers to implementation':ti,ab OR 'implementation strategies':ti,ab OR 'health care policy'/exp OR 'health care policy':ti,ab OR 'health care reform':ti,ab OR 'health policy':ti,ab OR 'healthcare policy':ti,ab OR 'healthcare reform':ti,ab OR 'patient protection and affordable care act':ti,ab OR 'policy, health care':ti,ab OR 'practice guideline'/exp OR 'clinical practice guidelines':ti,ab OR 'guidelines':ti,ab OR 'guidelines as topic':ti,ab OR 'practice guideline':ti,ab OR 'practice guidelines':ti,ab OR 'practice guidelines as topic':ti,ab) AND ('early cancer diagnosis'/exp OR 'early cancer diagnosis':ti,ab OR 'early detection of cancer':ti,ab OR 'early diagnosis'/exp OR 'diagnosis, early':ti,ab OR 'early diagnosis':ti,ab) AND ('breast tumor'/exp OR 'breast gland tumor':ti,ab OR 'breast gland tumour':ti,ab OR 'breast mass':ti,ab OR 'breast neoplasms':ti,ab OR 'breast neoplasms, male':ti,ab OR 'breast tumor':ti,ab OR 'breast tumour':ti,ab OR 'female breast neoplasm':ti,ab OR 'female breast tumor':ti,ab OR 'female breast tumour':ti,ab OR 'mamma tumor':ti,ab OR 'mamma tumour':ti,ab OR 'mammary gland tumor':ti,ab OR 'mammary gland tumour':ti,ab OR 'mammary neoplasms':ti,ab OR 'mammary tumor':ti,ab OR 'mammary tumor cell':ti,ab OR 'mammary tumour':ti,ab OR 'mammary tumour cell':ti,ab OR 'unilateral breast neoplasms':ti,ab) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py)

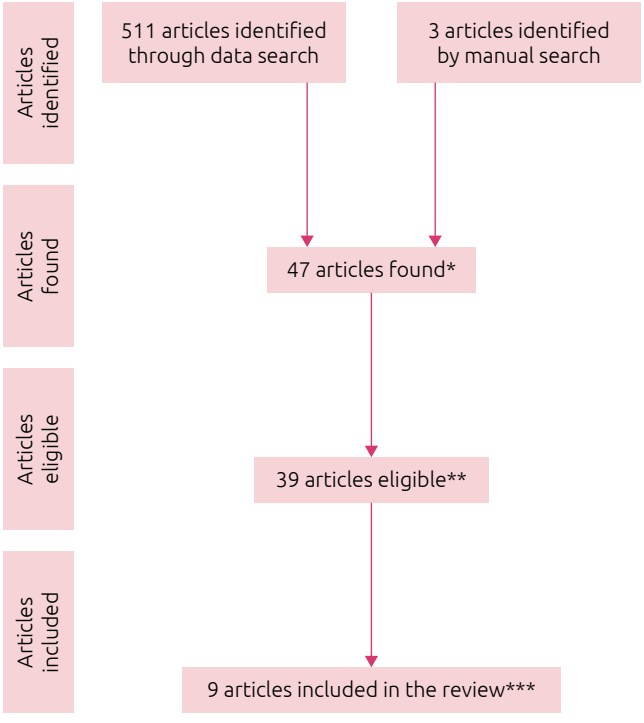
VHL: Virtual Health Library; Lilacs: Latin American and Caribbean Health Sciences Literature.

In peripheral countries, deprived urban populations, remote populations or indigenous people often cannot receive cancer care in a timely manner due to lack of awareness, fragmented and complex health systems, low socioeconomic status, cultural barriers and limited financial and human resources in public health institutions[8]. This helps in the applicability of the strategies identified in the study in the Brazilian scenario, prone to low adherence to early detection recommendations due to socioeconomic and cultural factors[23].

Limitations in applying the guideline implementation strategies in low- and middle-income countries may be related to issues such as scarcity or poor distribution of health professionals and insufficient availability of medical products and supplies, which are clearly not limited to the provision of breast health related services. Similarly, the issues associated with access to services and the ability (or inability) to finance them transcend the issues of this review due to being truly systemic[24].

Health organizations

Strategies for implementing guidelines at the health organization level have the following determinants: inadequate internal communication, inadequate processes and inadequate leadership. Examples of actions to reduce structural barriers and direct costs to patients and to involve leaders and experts in breast cancer in primary care educational activities were explored[15-17,20-22].



*By inclusion criteria, no duplicate articles; **only systematic reviews; ***by criteria of interest, strategies to overcome barriers.

Figure 1. Flowchart of the article selection process.

The studies[15-17,20-22] evaluated interventions to facilitate the delivery of care services to the population. Interventions to reduce structural barriers and costs to the patient were addressed. Structural barriers are non-economic barriers that prevent access to guideline recommendations. Interventions to lower these barriers were explored, providing: services close to the target population; alternative service hours; mobile mammographs; convenient service locations such as schools, clubs, and churches; home visit; female health professionals; text messages to remember appointments, diagnostic and follow-up exams, and patient navigator.

Using a patient navigator facilitates the proper and efficient use of services. It is considered an indicator of quality in many health services in the United States, Canada and Europe and is still poorly studied in peripheral countries. The navigator is a health worker trained to be a case manager and serves as a link between patients and the system, health professionals and providers, bringing equity to vulnerable populations[24,25].

Bowser et al.[16] reported greater adherence to the guidelines when female health professionals were involved in clinical care and imaging. This gender-related barrier for health professionals was very relevant for assessing the applicability of interventions in the Middle East and North Africa region.

Lu et al.[17] identified studies proving the effectiveness of home visits by health professionals in countries such as Thailand, New Zealand, India, Pakistan, Bangladesh and Singapore. Women receive health education and letters or reminders to undergo screening. This approach increases adherence to other health care procedures, such as colpocytology and control of systemic arterial hypertension, diabetes mellitus and dyslipidemia.

The use of mobile mammographs aims to supply places with repressed demand and with a long wait for mammography, as well as to stimulate the screening and early diagnosis of breast cancer. There are several factors that can lead women to not get screened, including lack of time, fear of pain and embarrassment during the exam and, in some cases, the distance to go to a mammography service. Hence the importance of a continuous screening program combined with mobile mammographs[14,17,18,20].

Baron et al.[15] evaluated studies that addressed reducing costs to patients as an effective action to promote adherence to guidelines in the United States, such as performing regular screening mammograms by the target population or mammograms for diagnosis. The use of vouchers, reduced co-participation, reimbursements and state insurance coverage were exemplified.

Sabatino et al.[19] conducted an update of systematic reviews that recommend the engagement of active leadership and breast cancer specialists working in educational groups with patients and primary care health professionals. Interactive education programs addressing the advantages of adhering to the guidelines promote continuous improvement in the quality of breast health processes.

Chart 2. SUPporting POlicy relevant Reviews and Trials (SUPPORT) Summary Checklist for judgment about how much confidence to place in a systematic review.

Study:	
Date:	
Section A: Methods used to identify, include and critically evaluate studies	
A.1 Were the criteria used to decide studies included in the reported review?	
The authors specified: - Types of Studies - Participants/contexts/population - Intervention(s) - Result(s) Coding guide - check the answers above: YES: All four should be yes. Comments (please note important limitations or uncertainties)	Yes Partially No
A.2 Was the search for evidence reasonably comprehensive?	
The following was ensured: - Language bias avoided (no language-based inclusion restriction) - No inclusion restriction based on publish status Relevant databases searched (including PubMed/MEDLINE + Cochrane Library) - Reference lists verified in the articles included - Contacted Authors/Experts Coding guide — check the answers above: YES: All five should be yes. PARTIALLY: The relevant databases and reference lists are both checked. Comments (please note important limitations or uncertainties)	Yes Partially No
A.3 Is the review reasonably up to date?	
Have the researches been conducted recently enough that it is unlikely to find newer researches or to alter the results of the review? Coding guide: Consider how many years have passed since the last research (for example, if it was more than 10 years ago, the review is unlikely to be up to date) and if there are any ongoing researches Comments (please note important limitations or uncertainties)	Yes Partially No
A.4 Was there bias in the selection of articles avoided?	
The authors specified: - Explicit selection criteria - Independent full-text screening by at least two reviewers - List of included studies provided - List of excluded studies provided Coding guide — check the above: YES: All four should be yes. Comments (please note important limitations or uncertainties)	Yes Partially No
A.5 Did the authors use appropriate criteria to assess the risk of bias in the analysis of the included studies?	
- The criteria used to assess the risk of bias have been reported - A table or summary of the evaluation of each study included for each criterion was reported - Sensitive criteria focusing on risk of bias (not other study qualities such as accuracy or applicability) were used Coding guide — check the above: YES: All three should be yes. Comments (please note important limitations or uncertainties)	Yes Partially No
A.6 General - How should you use the methods used to identify, include and critically evaluate studies?	
The summarized assessment score A relates to the five questions above. If "No" or "Partially" is used for any of the above questions, the review is likely to have important limitations. Examples of important limitations may include not reporting explicit selection criteria and not providing a criterion for including studies or assessing the risk of bias in the included studies. Comments (please note important limitations or uncertainties)	**- Major limitations** (limitations that are important enough that the review results are unreliable and should not be used in the policy summary) **- Important limitations** (limitations important enough to search for another systematic review and to interpret the results of that review with caution if another review cannot be found) **- Reliable** (minor limitations only)

Continue...

Chart 2. Continuation.

Section B: Methods used to analyze findings	
B.1 What are the characteristics and results of included studies reported as reliable?	
- Been there: Independent data extraction by at least two reviewers - A table or summary of participant characteristics, interventions and outcomes for included studies - A table or summary of the results of the included studies. Coding guide — check the above: YES: All three should be yes. Comments (please note important limitations or uncertainties)	Yes Partially No Not applicable (e.g., no studies included)
B.2 Regarding the methods used by reviewers to analyze the results of the included studies, were they reported?	
Comments (please note important limitations or uncertainties)	Yes Partially No Not applicable (e.g., no studies included)
B.3 Did the review describe the extent of heterogeneity?	
- Did the review ensure that the included studies were similar enough to make sense to combine them, to split the included studies sensibly into homogeneous groups, or to reasonably conclude that it did not make sense to combine or group the included studies? - Did the review discuss to what extent there were significant differences in the results of the included studies? - If a meta-analysis was performed, were the I^2, the x^2 test for heterogeneity, or other appropriate statistics reported? Comments (please note important limitations or uncertainties)	Yes Partially No Not applicable (e.g., no studies included)
B.4 Have the results of relevant studies been combined (or not combined) appropriately in relation to the primary issue that the review addresses and the available data?	
How was data analysis carried out? - Descriptive, only - Vote count based on effect direction - Vote count based on statistical significance - Description of effect size range - Meta-analysis - Meta-regression - Other: Specify - Not applicable (e.g.: no studies or no data) How were the studies weighted in the analysis? - Equal weights (this is done when vote count is used) - By quality design or study (this is rarely done) - Inverse variance (this is done in the anamnesis analysis) - Number of participants - Other: Specify - Not clear - Not applicable (e.g.: no studies or no data) Did the review address the errors in the analysis unit? - Yes, it took into account the grouping (for example, intracluster correlation coefficient used) - No, but the issue of errors in the analysis unit has been recognized - No mention of the problem - Not applicable — no clustered studies or studies included - Coding guide — check the above: If narrative OR vote counting (where quantitative analysis would have been possible) OR inadequate table, graph or meta-analysis OR analysis unit error not addressed (and should have been), the likely answer is NO. If considered appropriate and the graphic analysis, the appropriate weights and the extent of heterogeneity were taken into account, the likely answer is YES. If there are no studies/no data: NOT APPLICABLE If you are unsure: CAN'T SAY/PARTIALLY Comments (please note important limitations or uncertainties)	Yes Partially No Not applicable (e.g., no studies included)

Continue...

Chart 2. Continuation.

B.5 Does the analysis examine the extent to which specific agents can explain the differences between included studies?	
- The factors pointed out by the authors should be considered as explanatory factors described clearly? - Was a sensible method used to explore the extent to which key factors explained heterogeneity? - Descriptive/textual - Meta-regression - Graphic - Others Comments (please note important limitations or uncertainties)	Yes Can't say/Partially No Not applicable (e.g.: few studies with no major differences in the results of the included studies or the included studies were so different that it would make sense to explore the heterogeneity of the results)
B.6 Overall, how would you rate the methods used to analyze findings related to the primary issue addressed in the review?	
A pontuação da avaliação resumida B relaciona-se com as cinco perguntas desta seção, referentes à análise. Se a opção "Não" ou "Parcialmente" for usada para qualquer uma das cinco perguntas anteriores, a revisão provavelmente terá limitações importantes. Exemplos de grandes limitações podem incluir não relatar características críticas dos estudos incluídos ou não relatar os resultados dos estudos incluídos. Use comentários para especificar se é relevante, para marcar a incerteza ou necessidade de discussão	**- Major limitations** (limitations that are important enough that the review results are unreliable and should not be used in the policy summary) **- Important limitations** (limitations important enough to search for another systematic review and to interpret the results of that review with caution if another review cannot be found) **- Reliable** (minor limitations only)
Section C: Review reliability overall assessment	
C.1 Are there any other aspects of the review not mentioned before that leads you to question the results?	
	- Additional Methodological Issues - Interpretation - Robustness - Conflicts of interest (from review authors or included studies) - Other - No other quality issues identified
C.2 Based on the assessments of the above methods, how would you rate the reliability of the review?	
- Major limitations (exclude); briefly (and politely) state the reasons for excluding the review by completing the following sentence: This review has not been included in this policy summary for the following reasons: Comments (briefly summarize any key messages or useful information that may be extracted from the review for analysis by policy makers or managers): - Important limitations; briefly (and politely) state the most important limitations by editing the following sentence, if necessary, and specifying the important limitations: This review has important limitations. - Reliable; carefully note any comments that should be noted regarding the reliability of this review by editing the following sentence if necessary: This is a systematic review of good quality, with only minor limitations.	

Health professionals

Actions to increase adherence by health professionals to early detection guidelines revolve around the following pillars: knowledge, competence, attitudes and motivation to change. Professionals performing the first care procedures on women are not always able to detect and manage cases of breast disease and/or to be aware of guidelines[23].

The following are recommended for the training of health professionals: dissemination of educational materials; educational activities or visits to reference units for breast cancer diagnosis and treatment; dissemination of information about the severity of the problem, including relevant comparisons; presence of expert leaders; dissemination of information aimed to motivate health professionals to change their practices; financial or other incentives; reducing the burden of the changes in practices[16,17,19,21].

Peterson et al.[18] studied systematic reviews that assessed the impact of communication between health professionals and patients on adherence to early detection of breast cancer. In general, the results suggested that professional recommendation was necessary but not sufficient for optimal adherence to early detection guidelines. Studies that examined the quality of communication indicated that information and shared decision-making were more closely related to behavior favoring recommendations. Training professionals on communication is an effective tool for improving adherence to recommendations.

The training of primary care health professionals, as a tool to improve patient flow to the breast health care line, should be supported by managers and involve breast cancer specialists[26]. The study conducted by researchers at Imperial College London, in collaboration with the Ministry of Health's Oswaldo Cruz Foundation's Center for Health Knowledge and Data Integration

Chart 3. Details of the studies included in the review.

Main author	Country of publication	Year	Countries involved	Population involved	Study reliability	Sample (N) of articles included in the study	Objective(s)	Results
Baron RC[14]	United States	2008	United States, Canada, England, Italy, Australia, China, Singapore, Israel	American Indians, Alaskan natives, Asian population, Hispanic Latino population and African American population; low-income, low-educated population in developed countries	Reliable	124	Customer-driven demand-focused interventions to increase early detection	Benefits: customer reminders (written or spoken messages, phone calls, etc.); small media (posters, booklets, pamphlets, newsletter); individualized education (individual information over the phone or in person to remove barriers)
Baron RC[15]	United States	2008	United States, Canada, England, Italy, Australia, China, Singapore, Israel	American Indians, Alaskan natives, Asian population, Hispanic Latino population and African American population; low-income, low-educated population in developed countries	Reliable	25	Customer-driven access-focused interventions to increase early detection	Benefits: improve service structure (flexible hours, easily accessible places); alternative services (mobile mammographs, transportation, dependent care, limiting the number of return appointments); allowances to remove examination barriers (co-participation, refunds, vouchers, etc.)
Bowser D[16]	United States	2017	United States, Canada, Mexico, Puerto Rico, Israel, Iran, Jordan, Saudi Arabia, Qatar, Egypt, Spain, Switzerland, Turkey, Korea, Thailand, Malaysia, Samoa	Latinos, Asians and African Americans; Jews, Arabs; low-income and low-educated population in developed countries.	Reliable	55	To identify barriers and enablers that impact access to early detection both globally and more specifically in the Middle East and North Africa (MENA) region, with a specific focus on Egypt, Jordan, Oman, Saudi Arabia, United Arab Emirates (UAE) and Kuwait, with a specific focus on the health system	Providing a female health professional; Quality healthcare services (confirmation of appointments, patient follow-up, improved doctor-patient relationship, appropriate language and encouragement); Health services in places and at times that are most convenient to the population; Demystification of fear of the disease, diagnostic tests and treatment.
Lu M[17]	Canada	2012	United States, Canada, England, Australia, Thailand, Korea, Vietnam, China, Japan, Philippines, India, Pakistan, Bangladesh, Cambodia	Asians	Reliable	18	Knowledge on the effectiveness of existing intervention strategies to improve early detection in Asian women	Employing a combination of multiple strategies is more likely to succeed than single interventions; Effectiveness of community-based or workplace-based group education programs increases when additional support is provided, such as exam and consultation scheduling assistance and mobile screening services; Combining training of health professionals can help overcome language and cultural barriers; Culturally sensitive media campaigns and mailed print materials may be ineffective.

Continue...

Chart 3. Continuation.

Main author	Country of publication	Year	Countries involved	Population involved	Study reliability	Sample (N) of articles included in the study	Objective(s)	Results
Peterson EB[18]	United States/ Qatar	2016	United States, France, Israel	North American, Latin American, French, Israeli	Reliable	35	To analyze studies that focused on the role of provider-patient communication in early detection behavior	There is overwhelming evidence that provider recommendation significantly improves early detection rates; Studies that examined the quality of communication are heterogeneous in method, operation, and results, but suggested that information and shared decision making had a significant relationship with tracking behavior; Intervention studies were equally heterogeneous and showed positive results from communication interventions on screening behavior.
Sabatino SA[19]	United States	2012	United States, Canada, England, Italy, Australia, China, Singapore, Israel	American Indians, Alaskan natives, Asian population, Hispanic Latino population and African American population; low-income, low-educated population in developed countries	Reliable	45	Effectiveness of interventions to increase early detection: nine systematic updates to the Community Preventive Services Guide	Recommendations for individual and group education, customer reminder, reduction of direct costs, provider assessment and feedback, and reduction of structural barriers.
Spadea T[20]	Italy/ Netherlands	2010	United States, Switzerland, Italy, England, Spain	Americans, Europeans; low-income, low-educated population in developed countries	Reliable	29	Effectiveness of interventions to promote breast and cervical cancer care among lower socioeconomic groups	Tailor-made organized programs with cost-reducing interventions (eg, offering free trials and eliminating geographic barriers), greater involvement of primary care physicians, and individually tailored proactive communication, addressing the barriers
Task Force[21]	United States	2016	United States, Canada, England, Italy, Australia, China, Singapore, Israel	American Indians, Alaskan natives, Asian, Hispanic Latino, and African American populations; low-income, low-educated population in developed countries	Reliable	88	Recommend multicomponent interventions based on strong scientific evidence of effectiveness in increasing early detection	Multicomponent interventions combine two or more intervention approaches: Interventions to increase community demand: customer reminders, customer incentives, small media, mass media, group education, individualized education; Interventions to increase community access: reducing structural barriers, reducing direct costs to the customer; Interventions to increase the offer of service providers: provider evaluation and feedback, provider incentives, reminders to service providers; Multicomponent interventions can be coordinated through health care systems delivered in community settings or both.
Uy C[22]	United States	2017	United States, England, Spain, Malaysia, Israel	North American, European, Asian	Reliable	9	To evaluate the effect of text message interventions on early detection	Benefit from text messaging interventions, with a moderate increase in early detection rates.

(Fiocruz), found that the highest level of governance and increased health coverage in primary care in Brazilian municipalities are associated with reduced mortality[26]. The family health strategy can be a good context for initiating organized breast cancer screening in Brazil, contributing to the strengthening of the guidelines.

Healthcare Users

There are multiple barriers for users to get breast cancer care. The nine studies addressed these barriers and strategies for implementing early detection guidelines[14-22]. Prioritized actions are based on the following determinants: knowledge, competence, attitudes, access to care and motivation to change. Users may not recognize the effectiveness of the guidelines or agree with the recommendations for fear of the disease or lack of awareness of breast cancer issues. Economic, social, cultural or religious barriers make it difficult to change user behavior and seek effective care for early detection[14-22].

Reliable and accessible information on the problem should be sought, for example, using mass media, small media (leaflets, posters, newsletters) and community health professionals; reduce financial or physical barriers to care by using appointment and exam reminders, flexible appointment and exam times, mobile

Chart 4. Strategies for implementing early breast cancer detection guidelines.

Level	Determinants		Actions
Health organizations	Inadequate internal communication	The necessary communication between different levels of the health system may be lacking.	Structured reference sheets; involvement of breast cancer specialists in primary care education activities; patient navigator use.
	Inadequate processes	Patient referral and counter-referral processes may not be appropriate for the implementation of the guidelines.	Process redesign to facilitate appropriate and efficient use of services (continuous quality improvement); patient navigator use.
	Inadequate leadership	There may be insufficient leadership to implement the guidelines.	Identification of effective leaders; expert engagement; establishment of leadership systems.
Health professionals	Knowledge	Healthcare professionals may not be aware of the likely impacts of early detection guidelines.	Dissemination of educational materials.
	Competence	Healthcare professionals may not feel competent or may not have competence.	Educational activities or visits to reference units for the diagnosis and treatment of breast cancer.
	Attitudes	Health professionals may not agree that the implementation of the guidelines is effective.	Disclosure of information about the severity of the problem, including relevant comparisons; presence of opinion leaders and breast cancer experts.
	Motivation to change	Health workers cannot be motivated to change their practices.	Dissemination of information designed to motivate healthcare professionals to change their practices; financial or other types of incentives; reducing the burden of changing practices.
Health users	Knowledge	People may not be aware of the likely impacts of the early detection guidelines.	Dissemination of reliable and accessible information, for example using mass media, small media (flyers, posters, newsletters), community health workers, patient navigator.
	Competence	People may not recognize the effectiveness of the guidelines.	Provision of training and support; patient navigator use.
	Attitudes	People may not agree that implementing the guidelines is important due to fear of the disease or lack of awareness of the issue of breast cancer.	Disclosure of information about the severity of the problem, including relevant comparisons; patient navigator use.
	Access to care	People may not have access to the types of operations that are effective for early detection due to financial, social, cultural or religious constraints.	Reduction of financial or physical barriers to care; appointment and exam reminders; mobile mammographs; female health professionals; patient follow-up; better doctor-patient relationship, with proper language and encouragement; demystification of fear of the disease, the diagnostic tests and the treatment; flexible consultation and examination times; conscious employer; patient navigator use.
	Motivation to change	People may not be motivated to change their behaviors, for example by seeking effective care for early detection.	Dissemination of information designed to motivate people to, for example, seek care or undergo the recommended tests; use of financial or material incentives; patient navigator use.

mammographs; improve the doctor-patient relationship with appropriate language and encouragement; demystifying the fear of the illness, of the diagnostic tests and of the treatment; make the employer aware; provide financial or material incentive; make use of the patient navigator[14-22].

The patient navigator, a trained healthcare professional, facilitates the handling of patients in the healthcare system, helping them to overcome institutional, socioeconomic and personal barriers to healthcare access. Provides services such as scheduling diagnostic and follow-up appointments, facilitating referrals from the health system, and coordinates communication between patients and health professionals. This professional helps patients receive timely medical care and reduce care delays and missed follow-up rates[25].

A program for early detection of breast cancer should be accepted by the public to assist with expected outcomes, such as 70% mammographic coverage rate, timely diagnosis and treatment, and reduced mortality rate. Adherence to the programs is associated with public motivation and awareness. The low awareness rate in most developing countries is alarming and interventions to raise public awareness are needed[27].

CONCLUSIONS

The three contexts and the respective strategies identified in the most relevant literature which are applicable in Brazil are:

- organizational changes in the system: fostering leadership committed to the implementation of the guidelines, better governance of health services close to the target audience, flexible hours, patient navigation program and use of mobile mammographs, where appropriate;
- in the practice of health professionals: engagement of breast cancer specialists in primary care to optimize the training of health professionals and users;
- in the use of health services by users: national campaign for mass dissemination of guidelines involving multiple actors from the Ministry of Health, state and municipal health departments, civil and medical organizations.

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INSTRUCTIONS TO AUTHORS

Introduction

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If the paper involves the use of human subjects, the Authors should ensure that it has been carried out in accordance with The Code of Ethics of the World Medical Association(Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The Journal will not accept editorial material for commercial purposes.

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Original Articles: Describes experimental research or clinical research – prospective or retrospective, randomized or double blind. They must have 3,000 to 5,000 words, excluding illustrations (tables, figures [maximum of 5]) and references [maximum of 30]. Manuscripts containing original clinical or experimental research results will be prioritized for publication. All manuscripts must present: Title in English, Structured Abstract, Keywords, Abstract, Keywords, Introduction, Methods, Results, Discussion, Conclusions and References.

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The selection of themes is based on planning established by the Editor-in-Chief and Co-Editors. Articles in this category are usually ordered by publishers from authors with proven experience in the field. Spontaneous contributions may be accepted. It must present: Title, Abstract (without need of structuring), Keywords, Text (with or without subtitles), and References. The general instructions for figures, tables and references are the same as for the original articles.

Images in Mastology: Unusual images in clinical practice or associated with topics which are considerated as rare. The text will be continuos, expressing the rarity or singularity of the case, at maximum of 400 words, and no more than 10 references and 3 figures. They must present: Title, Abstract (non-structurated up to 150 words), Keywords, and References.

Case reports: They are manuscripts reporting unpublished, highly interesting and well-documented clinical cases from a clinical and laboratorial point of view. The text should express the rarity or singularity of the case, at maximum of 2,000 words, and no more than 20 references and 3 figures. They should observe the structure: Introduction, Case report (with patient description, results of clinical exams, follow-up, diagnosis), Discussion (with similarity data in the literature), and Conclusion. They must present: Abstract (unstructured), Keywords, and up to 20 References.

Letters to the Editor: They aim to comment or discuss papers published in the journal or report original research in progress. They will be published at the discretion of the Editors, with the corresponding reply where applicable. They must not exceed 600 words and 5 references.

Editorials: Editorials are comissioned by the Editors, commenting on relevant works of the Journal itself, relevant researches or communications from Editors. Authors who wish to contribute an Editorial to the Journal should contact the Editorial Office (biblioteca@sbmastologia.com.br) prior to writing and submitting the Editorial.

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A) Cover sheet

- Title of the article, in Portuguese and English, containing between 10 and 12 words, without articles and prepositions. The Title should be motivating and should give an idea of the objectives and content of work;
- full name of each author, without abbreviations;
- indication of the academic degree and institutional affiliation of each author, separately. If there is more than one institutional affiliation, indicate only the most relevant;
- indication of the Institution where the work was done;
- name, address, fax and e-mail of the corresponding author;
- sources of research assistance, if any;
- declaration of non-existence of conflicts of interest.

B) Second sheet

Abstract and Descriptors: Abstract, in Portuguese and English, with a maximum of 250 words. For The original articles, should be structured (Objective, Methods, Results, Conclusions), highlighting the most significant data of the work. For case reports, revisions or updates and a previous note, the summary should not be structured. Below the abstract, specify at least five and at most ten descriptors (Keywords) that define the subject of the work. The descriptors should be based on the DECS – Descriptors in Health Sciences – available at http://www.decs.bvs.br

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You should strictly obey the structure for each category of manuscript.

In all manuscript categories, the citation of the authors in the text should be numeric and sequential. Using Arabic numerals in parentheses and envelopes.

The standards to be followed were based on the format proposed by the International Committee of Medical Journal Editors and published in the article Uniform requirements for manuscripts submitted to biomedical journals also available for consultation at http://www.icmje.org/.

Presentation of the text

Preferably use the Microsoft Word® word processor.

Do not emphasize excerpts from the text: do not underline and do not use bold. Do not use capital letters in proper nouns (other than the first letter) in the text or Bibliographical References. When using acronyms or abbreviations, describe them in full the first time they are mentioned in the text.

Summary

The Summary should contain the relevant information, allowing the reader to get a general idea of the work. All articles submitted must have a summary in Portuguese or Spanish and in English (abstract), between 150 and 250 words. For Original Articles, abstracts should be structured including objectives, methods, results and conclusions. For the other categories, the format of the abstracts may be the narrative, but preferably with the same information. They should not contain quotations and abbreviations. Highlighting at least three and at most six indexing terms, extracted from the vocabulary "Descriptors in Health Sciences" (DeCS – www.bireme.br), when accompanying the abstracts in Portuguese or Spanish, and Medical Subject Heading – MeSH (Http://www.nlm.nih.gov/mesh/), when they follow the "Abstract". If no descriptors are available to cover the subject of the manuscript, terms or expressions of known use may be indicated.

Introduction

In this section, show the current state of knowledge about the topic under study, divergences and gaps that may possibly justify the development of the work, but without extensive review of the literature. For Case Reports, present a summary of the cases already published, epidemiology of the reported condition and a justification for the presentation as an isolated case. Clearly state the objectives of the work.

Methods

Start this section indicating the work planning: whether prospective or retrospective; Clinical or experimental trial; Whether the distribution of cases was random or not, and

so on. Describe the criteria for selection of patients or experimental group, including controls. Identify the equipment and reagents used. If the applied methodology has already been used, give the references in addition to the brief description of the method. Also describe the statistical methods employed and the comparisons for which each test was used. In the Case Reports, the sections Material and Methods and Results are replaced by the description of the case, remaining the remaining cases.

Results

It should be limited to describing the results found without including interpretations and comparisons. Present the results in logical sequence, with text, tables and figures.

Discussion

It should properly and objectively explore the results, discussed in light of other observations already recorded in the literature, highlighting the new and original information obtained in the research. Emphasize the appropriateness of the research methods used. Compare and relate the observations with those of other authors, commenting and explaining the differences that occur. Explain the implications of the findings, their limitations, and make recommendations. The discussion should culminate with the conclusions, indicating ways for new research or implications for professional practice. For Case Reports, base the Discussion on a broad and updated literature review.

Thanks

Collaborations of individuals, institutions or acknowledgments for financial support, technical aids, deserving recognition, but not justifying inclusion as the author, should be included.

References

References should be listed at the end of the article, numbered consecutively, following the order in which they were first mentioned in the text, based on the Vancouver style (see: "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Medical Publication "[http://www.nlm.nih.gov/bsd/uni-form_requirements.html]). All authors and works cited in the text should be included in this section and vice versa. Articles accepted for publication may be cited accompanied by the expression: accepted and awaiting publication, or "in press" indicating the periodical, volume and year.

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Articles of Journals or Magazines

Del Giglio A, Pinhal MA. Genetic profile in breast cancer: a brief review for the mastologist. Rev Bras Mastologia. 2005; 15 (1): 45-50.

My Account

Montoro AF. Mastology. São Paulo: Sarvier, 1984.

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Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Williams Obstetrics. 22nd ed. New York: McGraw-Hill; 2005. Chapter 39, Multifetal gestation. P. 911-43.

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Von Hoff DD, Hanauske AR. Preclinical and early clinical development of new anticancer agents. In: Kufe DW, Bast RC Jr, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, et al. Editors. Holland-Frei cancer medicine. 7th ed. Hamilton (ON): BC Decker Inc .; 2006. p. 600-16.

Theses and Dissertations

Steinmacher DI. Evaluation of percutaneous needle biopsy with automatic propellant in the propaedeutics of palpable and nonpalpable lesions of the breast [dissertation]. São Paulo: Federal University of São Paulo. Paulista School of Medicine; 2005.

Electronic publications

Henrique MA, Cosiski MHR. Mammographic density as a risk factor for breast cancer. Rev Bras Ginecol Obstet [Internet]. 2007 [cited 2008 Feb 27]; 29 (10): 493-6.

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