BJO
Brazilian Journal of Oncology

ORIGINAL ARTICLES CLINICAL ONCOLOGY

Clinicopathological correlation between trophic-adipose levels and poor prognosis outcomes in Brazilian women diagnosed with breast cancer

Correlação clínico-patológica entre níveis trófico-adiposos e desfechos de mau prognóstico em mulheres brasileiras diagnosticadas com câncer de mama

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ABSTRACT

Objective: To describe the clinicopathological profile of breast cancer patients and association with excess body weight. **Methods:** This was a descriptive observational study of 126 women with breast cancer lesions treated between 2015 and 2017 at a cancer referral hospital for 27 municipalities in southwestern Paraná. Patients were categorized according to age at diagnosis, body mass index, menopausal status, molecular subtyping of tumors, histological characteristics, and risk stratification. Data were coded for analysis using the Statistical Package for Social Sciences (SPSS) 22.0.0 software. **Results:** There were 126 patients diagnosed with breast cancer and more than half of these had an excessive body weight (mean BMI 27.5kg/m^2). There was a predominance of the triple negative molecular subtype in overweight women; they also had a higher frequency of tumors larger than 2cm and high histological grade tumors. There were significant associations in the overweight/obese subgroup such as tumors in the intermediate grade luminal B subtype, presence of angiolymphatic emboli, and a high-risk of disease recurrence. **Conclusion:** The data indicate that being overweight is a determinant of worse prognosis in women with breast cancer in southwestern Paraná.

Keywords: Breast neoplasms; Obesity; Prognosis.

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Financial support: Fundação Araucária, Programa de Pesquisa para o SUS.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.

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Received on: February 19, 2021 | **Accepted on:** August 19, 2021 | **Published on:** September 24, 2021
DOI: https://doi.org/10.5935/2526-8732.20210027

RESUMO

Objetivo: Descrever o perfil clínico-patológico de pacientes com câncer de mama e sua associação com o excesso de peso corporal. **Métodos:** Trata-se de um estudo observacional descritivo com 126 mulheres com lesões de câncer de mama atendidas entre 2015 e 2017 em um hospital referência em câncer de 27 municípios do sudoeste do Paraná. Os pacientes foram classificados de acordo com a idade ao diagnóstico, índice de massa corporal, estado da menopausa, subtipagem molecular de tumores, características histológicas e estratificação de risco. Os dados foram codificados para análise por meio do software Statistical Package for Social Sciences (SPSS) 22.0.0. **Resultados:** Foram 126 pacientes com diagnóstico de câncer de mama e mais da metade delas apresentava peso corporal excessivo (IMC médio de 27,5kg/m^2). Houve predomínio do subtipo molecular triplo negativo em mulheres com sobrepeso; também apresentaram maior frequência de tumores maiores que 2cm e tumores de alto grau histológico. Houve associações significativas no subgrupo com sobrepeso/obesidade, como tumores no subtipo luminal B de grau intermediário, presença de êmbolos angiolinfáticos e um alto risco de recorrência da doença. **Conclusão:** Os dados indicam que o excesso de peso é um determinante de pior prognóstico em mulheres com câncer de mama no sudoeste do Paraná.

Descritores: Neoplasias mamárias; Obesidade; Prognóstico.

INTRODUCTION

Breast cancer is the most common malignant neoplasm in women.[1] Determinant risk factors include reproductive history, family history, and lifestyle. These factors are responsible for clinical and pathological differences.[2] Although widely studied, the main risk factors associated with the occurrence of breast cancer in women from different regions of Brazil are poorly understood perhaps because of the large geographical area involved in Brazilian studies.

Previous Brazilian studies suggest classic risk factors for breast cancer development and aggressiveness such as aging and menopausal status.[3,4] Other studies show more complex associations such as more aggressive disease and worse prognostic tumors such as triple-negative tumors in overweight and/or obese women.[5] Factors such as social vulnerability[6] and history of psychological stress[7] are also possible risks particularly in southern Brazil. These factors do not explain the occurrence of disease alone and have been widely reported as associated with each other.

Thus, we seek more detailed information about the profile of breast cancer patients in Brazil where studies on regional risk factors are still scarce and inconclusive. There is no official documentation of such data from specific regions of the country including southwestern Paraná. Thus, this study characterized the epidemiological profile and possible regional risk factors identified in women diagnosed with breast cancer treated between 2015 and 2017 in a cancer referral hospital of 27 municipalities that make up the 8th Regional Health of Paraná.

METHODS

This is a retrospective descriptive observational study which proposal was submitted to the Institutional Ethics and Human Research Committee approved under the CAAE (certificate of presentation of ethical appreciation) number 35524814.4.0000.0107 and under opinion No. 810.501. All participants gave informed consent on the study objectives. Their anonymity was ensured, and they could withdraw at any time. The inclusion criteria were patients referred for surgery with lesions suggestive of unilateral infiltrative ductal carcinoma (ICD) at any clinical stage attended by the Francisco Beltrão Cancer Hospital from May 2015 to August 2017. These patients were from the 8th Regional Health of Paraná covering an estimated population of 350,000 inhabitants located at 27 municipalities (Figure 1).

Figure 1. Geographic limitation of the study population corresponding to the Eighth Health Region of Western Paraná and its municipalities.

Patients who do not meet this criterion were excluded. Thus, from this initial cohort of 200 women, there were 126 women with a histologically-confirmed diagnosis of breast cancer by biopsy. These women had complete clinicopathological data for subsequent frequency analysis. The medical records were consulted for data collection.

The data were compared for possible existing correlations with age at diagnosis; tumor size; histological grade; expression pattern of receptors and molecular subtypes; lymph node invasion; presence of angiolymphatic emboli; TNM (tumor, lymph nodes, and metastasis) clinicopathological staging; menopausal status; body mass index (BMI); and recurrence risk stratification. Data were categorized and analyzed using Statistical Package for Social Science (SPSS) statistical software (version 25.0.0, IBM) to obtain the frequencies and apply the chi-square test and logistic regression analysis. Only the significant correlations/associations were shown in the results, considering $p<0.05$ as significant.

RESULTS

This study compiled sequential data from 200 serially collected biopsy specimens from women presenting with lesions suggestive of breast cancer diagnosed by imaging exams such as mammography, ultrasound, or magnetic resonance imaging (MRI) as well as physical examination. Ten patients were excluded due to a lack of clinicopathological data. Of the 190 samples, 127 were confirmed as breast cancer (66.8%). One patient was excluded for a lack of sufficient data leaving 126 participants.

Since there was no statistically significant difference between the overweight and obese groups (the obese group was only 6% of the sample), we decided to combine these two BMI categories into one group and compare them with the eutrophic patients. Table 1 shows the main clinicopathological findings regarding such groups.

We found that 57.1% of the patients were overweight at diagnosis, and the mean BMI was 27.54kg/m^2 (18.22kg/m^2 to 44.15kg/m^2, Figure 2). Regarding the frequency of molecular subtypes of tumors, 68.3% of patients with triple-negative tumors fell into the overweight subgroup with an equal distribution of the other subtypes between the eutrophic and overweight groups. Further, overweighed/obese patients had larger tumors: 62.5% of tumors with diameters between 2 to 5cm and 94.1% of tumors with diameter greater than 5cm.

There was also a predominance of high histological grade tumors in overweight/obese patients (70.4% of the tumors diagnosed in the study within this category), with a high recurrence rate (65%). Statistical analyses (Table 2) showed significant associations only in the overweight/obese patients, including the presence of intermediate histological grade luminal B subtype tumors (β=0.630; 95%CI: 0.184-1.075 and p=0.006). There was a positive association between tumors of intermediate grade and tumors between 2 and 5cm in diameter (β=0.294; 95%CI=0.057-0.531 and p=0.016). There was positive association between the presence of angiolymphatic emboli and high stratification. There was a higher-risk of recurrence in this group (β=0.169; 95%CI: 0.039-0.298 and p=0.012). No significant association was found in the eutrophic group.

Table 1. Clinicopathological data of breast cancer patients distributed according to their trophic-adipose levels.

Subgroups	Eutrophic	Overweight/obese
Percentage of individuals	57.1%	42.9%
Molecular subtypes		
Luminal A	34.5%	65.5%
Luminal B	37.0%	63.0%
Luminal HER-2	60.0%	40.0%
HER-2	50.0%	50.0%
Triple negative	31.8%	68.2%
Histological grade		
Low	32.3%	67.7%
Intermediate	42.6%	57.4%
High	29.6%	70.4%
Tumor size		
Up to 1cm	66.7%	33,3%
1-2cm	45.2%	54.8%
2-5cm	37.5%	62.5%
Over 5cm	5.9%	94.1%
Recurrence		
Yes	35.0%	65.0%

Legends: LN - = Negative lymphnodal commitment; LN + = Presence of lymphnodal metastasis; HER-2 = Human epidermal growth factor receptor 2.

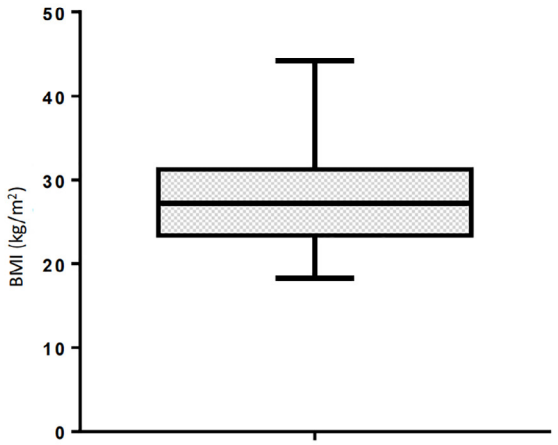

Figure 2. Distribution of women with breast cancer included on the study according their body mass index (BMI). The boxplot expresses the average (central-line) and the minimum and maximum gap.

DISCUSSION

In recent decades, obesity has emerged as an important risk factor associated with the development of several cancers including breast cancer. In postmenopausal women, excess body fat is directly implicated in the development of triple negative tumors with worse prognostic outcomes regardless of age.[8] A wide range of mediators are implicated in this context including molecules that perpetuate chronic inflammation that have a well-established role in breast cancer carcinogenesis and progression.[9,10]

Similar to other studies, we found that Brazilian women with a BMI over 30kg/m^2 have an elevated risk of developing breast cancer.[3] In addition, both obesity and overweight are risk factors for the development of triple negative tumors in a Brazilian population.[5] In fact, we found that the excessive body weight seems to be the main risk factor in this population. Adipose tissue is known to fuel a chronic inflammatory state that can influence breast tissue transformation via the production of carcinogenesis-promoting mediators resulting in worse outcomes.[11]

A predominance of triple negative tumors in obese/overweight women was identified in our study. The presence of triple negative tumors in women with excess body fat is already well established in the literature and is common in people of African descendants.[12] We note that the population studied here is predominantly Caucasian (over 90%), which rules out the association between a high prevalence of triple negative tumors and race or BRCA (breast cancer) gene mutations.[13] Our patients were screened for germinative pathological variants and we found a low prevalence of pathogenic variants in BRCA (2 cases).

Excessive body weight was also associated with tumors larger than 2cm. This finding suggests that deregulation of fat metabolism may occur locally in breast tissue and lead to carcinogenesis. Indeed, breast tissue is in a continuous proinflammatory state in high BMI subjects – especially in patients with excess visceral fat.[14] Furthermore, localized excess breast fat can induce adipocyte death and activate macrophage recruitment including activation of important pathways that maintain chronic inflammation such as NFκB (factor nuclear Kappa B).[15] Such metabolic and immunological changes would eventually generate a microenvironment that is conducive not only to carcinogenesis but also cellular phenotypic transformation, increased proliferation, and increased tumor mass.[16]

Malignant transformation also seems to be associated with excess fat, and this could explain the high prevalence of high histological grade tumors found in the overweight/obese cohort. Mediators such as leptin – whose production is increased proportionally to the increase in body fat – are positively associated with the development of high-grade breast tumors[17] as well as the occurrence of triple-negative tumors[18] seen here. In addition, increased waist circumference in women with breast cancer has also been described as a predictor of the development of high-grade tumors[19] suggesting that fat may affect the process of breast tissue differentiation. In this sense, experimental evidence suggests that suppression of endogenous lipogenesis may reverse the malignant breast cancer cell phenotype and reprogram breast cells to follow the normal process of cell differentiation.[20]

Our study showed some important associations between the parameters evaluated in overweight women. There was a positive association between tumors of intermediate histological grade and luminal molecular subtype B. There was also correlation of intermediate grade with 2-5cm tumors. Both associations suggest that tumors formed in the presence of excess body fat have greater proliferative capacity. This implies the formation of larger masses and accelerated cellular de-differentiation.

There was also an association between the presence of angiolymphatic emboli and the high-risk of recurrence in the overweight/obese cohort. Increased embolus formation is common in both cancer and obesity alone due to the endothelial activation triggered by chronic inflammation.[21] Such formation may be correlated to the development of hypoxia in the tumor tissue – this process that can be potentially aggravated in overweight or obese patients with breast cancer and hypercoagulability states.[22]

Despite the total number of individuals included in the study is good, the small sample size observed for each group is an important limitation for further conclusions. Also, the retrospective design limited data collection limited for some clinical parameters as survival information and chemotherapy response.

CONCLUSION

Immunological and endocrine changes in the tumor microenvironment due to excess body fat might trigger the development of more proliferative

Table 2. Significant associations regarding the clinicopathological variables from breast cancer patients.

Overweight/obese patients associations *	B-value	*p*-value	Confidence interval
Luminal B x intermediary grade	0,630	0,006	0,184 – 1,075
Tumor size between 2 and 5cm x intermediary grade	0,294	0,016	0,057 – 0,531
Angiolymphatic emboli x high recurrence probability	0,169	0,012	0,039 – 0,298

Legends: *Chi-square test and logistic regression analysis.

tumors, larger tumors, and tumor with accelerated cell de-differentiation. The endothelial injury caused by a continuous and systemic proinflammatory state due to obesity can lead to neoplastic cell dissemination leading in turn to metastatic disease and more advanced clinical staging.

CONFLICTS OF INTEREST

The authors have no conflicts to declare.

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