Original Article

Breast cancer stage, molecular subtype and survival in patients with obesity: a real-world study

André Mattar[1*^], Marcelo Antonini[2*^], Francisco Pimentel Cavalcante[3*^], Felipe Zerwes[4,5*^], Eduardo Camargo Millen[6*^], Fabricio Palermo Brenelli[7*^], Antônio Luiz Frasson[8*^], Leonardo Ribeiro Soares[9^], Marcelo Madeira[10^], Marina Diógenes Teixeira[1], Andressa Gonçalves Amorim[2], Larissa Chrispim de Oliveira[1], Marcellus do Nascimento Moreira Ramos[2], Gil Facina[11], Ruffo Freitas-Junior[12], Henrique Lima Couto[13], Sabrina Monteiro Rondelo[1], Renata Montarroyos Leite[14], Renata Arakelian[1,15], Rogerio Fenile[16], Luiz Henrique Gebrim[17]

[1]Mastology Department, Women's Health Hospital, São Paulo, Brazil; [2]Mastology Department, State Public Servant Hospital-Francisco Morato de Oliveira, São Paulo, Brazil; [3]Mastology Department, Fortaleza General Hospital, Fortaleza, Brazil; [4]Mastology Department, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil; [5]Mastology Department, Oncolinics Group, Porto Alegre, Brazil; [6]Mastology Department, Americas Oncology, Rio de Janeiro, Brazil; [7]Mastology Department, State University of Campinas, Campinas, Brazil; [8]Mastology Department, Israelita Albert Einstein Hospital, São Paulo, Brazil; [9]Mastology Department, Federal University of Goias, Goiania, Brazil; [10]Mastology Department, Albert Einstein Hospital School of Medicine, São Paulo, Brazil; [11]Mastology Department, Federal University of São Paulo, São Paulo, Brazil; [12]Mastology Department, CORA Advanced Center for Breast Cancer Diagnosis-Federal University of Goias, Goiania, Brazil; [13]Mastology Department, Redimama-Redimasto, Belo Horizonte, Brazil; [14]Mastology Department, Oncolinics Group, Sergipe, Brazil; [15]Oncology Department, DASA Oncology, São Paulo, Brazil; [16]Mastology Department, Ipiranga Hospital, São Paulo, Brazil; [17]Mastology Department, Beneficiencia Portuguesa de São Paulo Hospital, São Paulo, Brazil

Contributions: (I) Conception and design: A Mattar, LH Gebrim; (II) Administrative support: A Mattar, LH Gebrim; (III) Provision of study materials or patients: A Mattar; (IV) Collection and assembly of data: A Mattar, M Antonini, LH Gebrim; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: André Mattar, MD, PhD. Mastology Department, Women's Health Hospital, Av. Rio Branco 1080, 683, São Paulo, SP 01206-001, Brazil. Email: mattar.andre@gmail.com.

Background: Breast cancer (BC) is a leading cause of cancer-related deaths worldwide. Obesity, an established risk factor for BC in postmenopausal women, may also affect prognosis. This study evaluated the impact of obesity on the survival of BC patients treated at a public reference center in Brazil.

Methods: A retrospective cohort study was conducted with 7,424 BC patients treated at Hospital da Mulher (São Paulo, Brazil) from January 2011 to June 2021. Patients were categorized into four groups based on body mass index (BMI): underweight, healthy weight, overweight, and obese. Clinical, pathological, staging, and immunohistochemistry data were analyzed. Survival outcomes (overall and progression-free) were assessed using Kaplan-Meier estimates, with comparisons via logistic and Cox regression.

Results: Among the patients, 67.81% were overweight or obese, and 64.82% were postmenopausal (assumed ≥50 years old). A total of 6,992 patients were included in the survival analysis, with 3.79% succumbing to BC. No statistically significant differences in overall or progression-free survival were observed across BMI categories.

Conclusions: While obesity is highly prevalent among Brazilian women with BC, it did not significantly impact survival outcomes in this study. These findings underscore the need for prospective studies to explore

^ ORCID: André Mattar, 0000-0001-5973-623X; Marcelo Antonini, 0000-0002-1996-7428; Francisco Pimentel Cavalcante, 0000-0002-7156-2890; Felipe Zerwes, 0000-0002-1643-727X; Eduardo Camargo Millen, 0000-0002-2113-6324; Fabricio Palermo Brenelli, 0000-0003-0589-1423; Antônio Luiz Frasson, 0000-0003-1860-6898; Leonardo Ribeiro Soares, 0000-0002-9448-6114; Marcelo Madeira, 0000-0001-9429-3067.

* These authors are members of BBREAST Group: Brazilian Breast Cancer Association Team.

potential confounding factors and long-term effects, as well as to inform tailored interventions in similar healthcare settings.

Keywords: Obesity; breast cancer (BC); overall survival (OS); prognosis; body mass index (BMI)

Submitted Dec 22, 2024. Accepted for publication May 13, 2025. Published online Oct 24, 2025.
doi: 10.21037/cco-24-139
View this article at: https://dx.doi.org/10.21037/cco-24-139

Introduction

Significant advances in breast cancer (BC) diagnosis and treatment have been achieved in the last decades, however, BC continues to be highly prevalent and lethal among women worldwide, accounting for over 2 million new cases and 665,684 deaths in 2020 (1). In Brazil, BC is the leading cause of cancer-related death among women, responsible for 14.23 deaths/100,000 women (2). Obesity is also a global public health problem as its incidence has tripled since 1975, especially in low- and middle-income countries. Currently, 13% of the adult population in the world is obese (3). Obesity is an established risk factor for several types of cancer, including BC, particularly in postmenopausal women (4). In Brazil, 3.8% of cancers are related to high body mass index (BMI), mostly in women (5). Case-control and cohort studies found that overweight and obesity increase the risk of BC by 1.5–2.24-fold in the Asian population, especially in postmenopausal women (6-9). Gaining weight along adult life also increases the risk of BC, as a Swedish study showed an odds ratio (OR) of 2.04 [95% confidence interval (CI): 1.20–3.48] for postmenopausal women who gain ≥30 kg in adult life (10).

Several mechanisms are involved in the tumorigenic effect of obesity. Metabolic syndrome causes hyperinsulinemia that leads to insulin resistance, stimulates insulin-like growth factor 1 receptor, and activates cell proliferation pathways, resulting in tumor growth (11). Patients with obesity have increased leptin levels, that is related to tumor growth, as leptin receptor stimulates proliferative pathways (JAK2/Stat2, PI3K, ERK1/2) and increases the risk of metastasis (11-13). The adipose tissue stimulates transcription factors and mitogenesis through the recruitment of macrophages and release of pro-inflammatory cytokines (14). Postmenopausal women with obesity may present high estrogen levels due to increased aromatase expression in adipose tissue (15) and low sex hormone-binding proteins, increasing estrogen's bioavailability (16).

Obesity may also be a prognostic factor for BC in all ages, as it increases the risk of surgery complication, decreases the response to chemotherapy, and increases mortality (17-19). Besides the altered hormonal and physiological environment contributing to tumor progression in obesity, we can expect a delay in the clinical diagnosis (non-screened) of BC in patients with obesity due to a greater volume of breasts, encumbering the early detection of a nodule (20). Patients with obesity or overweight tend to receive sub-

Highlight box

Key findings
- This large real-world cohort study of 7,424 breast cancer (BC) patients in Brazil revealed that over two-thirds were overweight or obese at diagnosis.
- Despite the high prevalence of obesity, no statistically significant differences in overall survival or progression-free survival were observed across body mass index (BMI) categories.
- Obesity did not affect pathological complete response rates in patients undergoing neoadjuvant therapy.

What is known and what is new?
- Obesity is a recognized risk factor for BC incidence and poorer prognosis, particularly in postmenopausal women. However, previous studies have yielded conflicting results regarding the impact of obesity on survival.
- This study is the largest real-world analysis in Brazil examining the prognostic role of obesity in BC and found no significant association between BMI and survival, even after stratification by stage and molecular subtype.

What is the implication, and what should change now?
- These findings suggest that in settings with opportunistic screening and constrained resources, BMI alone may not be a sufficient prognostic indicator.
- Public health efforts should still emphasize obesity prevention and management, but tailored approaches considering tumor biology, stage at diagnosis, and access to treatment may better guide interventions.
- Future prospective studies using more refined measures of body composition and treatment adherence are needed to clarify the relationship between obesity and BC outcomes.

optimal treatment affecting prognosis as standard doses of adjuvant chemotherapy are used instead of weight-based doses (21).

Further investigation of the factors involved in patients with obesity and BC is needed, because it contributes to create strategies to improve survival. This study aimed to evaluate if obesity was related to poor prognosis of patients with BC in Brazil. We present this article in accordance with the STROBE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-24-139/rc).

Methods

Study design and population

In this retrospective, single center, cohort study, an electronic database from Pérola Byington Hospital (in São Paulo, SP, Brazil) containing over 14,000 medical records of women with gynecologic cancer were used to select patients with BC followed between January 2011 and June 2021. All included women had a confirmed diagnosis of invasive BC, classified by histological type and immunohistochemistry according to the presence of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. Patients were divided into triple negative, luminal A (Ki-67 <15% and ER+ and PR+), luminal B (Ki-67 ≥15% and ER+ and PR+), and HER2+ [HER2 3+ or fluorescence in situ hybridization (FISH) test-positive or chromogenic in situ hybridization (CISH)-positive]. Patients were not included if data about BMI was missing, if they had T0N0 in diagnosis, or TXN0 at diagnosis and at surgery, or TXN0 at diagnosis and no information at surgery. Patients were excluded in the absence of date of death or date of last consultation, or the time period between diagnosis and death/or last medical appointment. Menopausal status was inferred using age ≥50 years as a proxy, as direct data was unavailable. Patients were divided in four groups according to BMI categories and it was calculated using height and weight measurements obtained at the time of BC diagnosis, defined by weight (kg)/height^2 (m^2): <18.5 kg/m^2, underweight; 18.5 to <25 kg/m^2, healthy weight; 25 to <30 kg/m^2, overweight; ≥30 kg/m^2, obese.

During the follow-up patients were treated according to institutional guidelines. Surgical treatment was conservative for tumors up to 3 cm in diameter with free surgical margins, followed by breast radiotherapy. Mastectomy was indicated in patients with tumors >3.0 cm or multifocal. Patients with positive receptor tumors (ER+ and/or PR+) were treated for at least 5 years with tamoxifen and/or aromatase inhibitors depending on their menopausal status and side effects. Patients with high-risk disease were treated for 10 years with tamoxifen, 7 years with aromatase inhibitors or a switch (5 years of tamoxifen followed by 5 years of aromatase inhibitors). Radiotherapy of the chest wall and breast was indicated in breast conservative surgery, or more than four lymph nodes involved. Axillary radiotherapy was indicated in cases of stage III BC or with more than four lymph nodes involved. The chemotherapy regimens used were based on anthracyclines and taxanes if patients had a high risk or needed chemotherapy up front. Most of intermediate risk luminal BC received anthracycline-based chemotherapy or docetaxel and cyclophosphamide (TC). Trastuzumab was approved for early HER2+ patients' treatment in the Brazilian public healthcare setting in July 2012; however, its provision was effective only in January 2013. Thus, we observed a proportion of patients who did not receive trastuzumab because of this gap between approval and provision. In addition, between 2012 and 2018, a molecular confirmation of HER2 amplification was mandatory for patients to be considered eligible to receive treatment with trastuzumab. Unfortunately, in some cases, a negative or inconclusive result excluded them to be treated with trastuzumab. Since 2018, however, all immunohistochemically HER2+ patients who have a tumor larger than 0.5 cm are considered eligible for adjuvant treatment with trastuzumab and CISH/FISH exam is no longer required. Only stage 3 or lymph node positive are eligible for trastuzumab in neoadjuvant setting. Among early HER2+ patients who received trastuzumab in (neo)adjuvant setting, we observed that most patient were treated with concomitant chemotherapy. According to the clinical protocol and therapeutic guidelines for BC published by the Brazilian federal government (22), an anthracycline-based regimen (doxorubicin plus cyclophosphamide followed by docetaxel or paclitaxel) is recommended for early HER2+ patients. Indeed, almost 90% of the patients received anthracycline in association to the trastuzumab. None of our patients received pertuzumab (neo, adjuvant or in the metastatic setting), approved for metastatic setting in 2021 or cyclin inhibitor (such as abemaciclibe, ribociclibe or palbociclibe) because these drugs were approved in 2022 and are not available yet in the Brazilian public health system.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of Women's Health Reference Center at Pérola Byington Hospital (reference No. 2.213.876). Informed consent was waived in this retrospective study.

Outcomes

The overall survival (OS) was the primary outcome, evaluated by the comparison of the incidence of death from BC among groups. Only deaths due to BC as a primary disease or metastasis of some organs as a primary disease and then BC were considered. For censored patients (without death), the date of the last consultation was considered. The start date was the date when BC was first diagnosed.

Progression-free survival (PFS) was measured using the period between the end of the latest adjuvant therapy session and the first local and systemic recurrence, or the date of surgery for those receiving neoadjuvant therapy and the date of recurrence. The date of the last consultation was considered for censored patients. Patients whose time between outcome/censored and beginning of adjuvant/neoadjuvant therapy was negative were excluded. The number of patients achieving pathological complete response (pCR) after neoadjuvant treatment were also evaluated. There are two ways to assess pCR, one considering the complete response and the *in situ* response (pT0N0 and pTisN0) and the other considering only the complete response (pT0N0) (23). In this study, we considered pCR as T0N0 or TisN0.

Statistical analysis

The descriptive analysis was expressed as continuous variables in summary measures (mean, median, standard deviation, and quartiles), while categorical variables were expressed in frequencies and percentages. The Kaplan-Meier method was used for survival graphs, the Log-rank method to evaluate the difference between the survival curves, and Cox regression to calculate the hazard ratio (HR) and OR for death. Multivariate Cox regression models were adjusted for age, tumor stage, histological type, and molecular subtype, while logistic regression was used to assess predictors of pathological complete response in patients undergoing neoadjuvant therapy. In our survival analysis, deaths from non-BC causes were treated as censored events. To explore potential stage-specific effects, we performed a stratified survival analysis by cancer stage (I, II, and III). The significance level adopted in the tests was 0.05, two-tailed hypotheses considered, and the CIs constructed are 95%. R version 4.1.1 software was used to carry out all analyses.

Results

A total of 10,117 patients were screened, 7,424 were included, and 6,992 were considered for the survival analysis (see flow-chart of patients' selection in *Figure 1*). Information about age were missing for nine patients; therefore 7,415 patients were considered for baseline characteristics according to BMI. The mean age was 55.12±12.47 years at diagnosis and the mean BMI was 27.97±5.55 kg/m^2.

Table 1 shows age, staging, and molecular subtype of the study population according to BMI groups. Patients with obesity corresponded to 30.81% of the study population, and 64.83% of them were ≥50 years old (postmenopausal) (P<0.001). For each BMI group, most patients were postmenopausal (P<0.001), without significant difference among groups (P=0.21). Considering staging by breast (n=6,872), 42.97% of the underweight group were stage III, 41.90% of the healthy weight, 42.79% of overweight, and 39.38% of obese groups were stage II (P<0.001 within-group; P=0.094 among groups). Molecular subtype did not differ neither within the group (P=0.068) nor among groups (P=0.12).

Survival outcomes

A total of 6,992 patients were included in the survival analyses, corresponding to 7,090 breasts. Characteristics of the population included in the survival analysis are presented in Table S1.

During the 10-year follow-up, 265 patients (3.79%) died from BC. *Figure 2* shows the Kaplan-Meier estimates of OS according to BMI (P=0.12). There was no statistical difference when comparing the degree of obesity (overweigh, grade I to III) with OS (Figure S1). There was no statistically significant difference in OS according to menopausal status (*Figure 3*).

According to the multivariate Cox-regression analysis results, none of the variables evaluated significantly

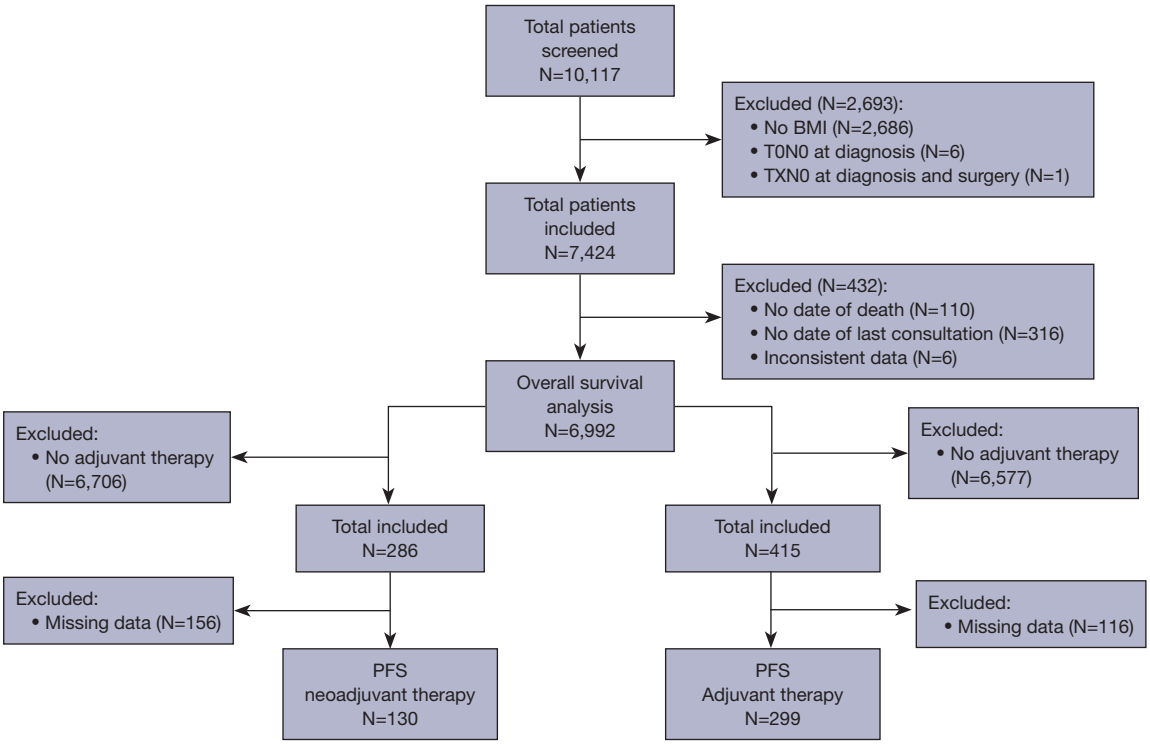

Figure 1 Flow-chart of patients' selection. BMI, body mass index; PFS, progression-free survival.

Table 1 Baseline characteristics of 7,415 Brazilian women with diagnosis of breast cancer by body mass index

Characteristics	Underweight	Healthy weight	Overweight	Obese	Overall	P value
Menopausal status						0.21
Number by patient	124 (1.67)	2,263 (30.52)	2,743 (37.00)	2,285 (30.81)	7,415 (100.0)	
Premenopausal (<50 years old)	40 (0.54)	917 (12.37)	963 (12.99)	688 (9.28)	2,608 (35.17)	
Postmenopausal (≥50 years old)	84 (1.13)	1,346 (18.15)	1,780 (24.00)	1,597 (21.54)	4,807 (64.83)	
Staging						0.09
Number by breast	121 (1.76)	2,095 (30.49)	2,538 (36.93)	2,118 (30.82)	6,872 (92.68)	
I	18 (0.26)	439 (6.39)	560 (8.15)	443 (6.45)	1,460 (21.25)	
II	40 (0.58)	878 (12.78)	1,086 (15.80)	834 (12.14)	2,838 (41.30)	
III	52 (0.76)	694 (10.10)	786 (11.44)	772 (11.23)	2,304 (33.53)	
IV	11 (0.16)	84 (1.22)	106 (1.54)	69 (1.00)	270 (3.92)	
Molecular subtype						0.12
Number by breast	114 (1.68)	2,058 (30.36)	2,506 (36.96)	2,102 (31.00)	6,780 (91.44)	
Luminal A	18 (0.27)	381 (5.62)	456 (6.73)	391 (5.77)	1,246 (18.39)	
Luminal B	43 (0.64)	764 (11.27)	961 (14.17)	872 (12.86)	2,640 (38.94)	
HER2+	24 (0.35)	449 (6.62)	505 (7.45)	373 (5.50)	1,351 (19.92)	
Triple negative	29 (0.43)	464 (6.84)	584 (8.61)	466 (6.87)	1,543 (22.75)	

Data are presented as n (%). HER2+, human epidermal growth factor receptor 2-positive.

impacted the OS of patients with BC (see *Table 2*).

To investigate whether the impact of BMI on prognosis varied by disease stage, we conducted a stratified survival analysis across cancer stages I, II, and III, but found no statistically significant differences in OS across BMI categories within each stage (Table S2).

To address the possible differences between the obesity grades, a subgroup analysis stratifying obesity into grades I, II, and III were made. The results showed no statistically significant differences in survival among these categories (Table S3).

No significant differences in OS across BMI categories were observed within each subtype. These results have been summarized in the "Results" section and are presented in detail in Table S4.

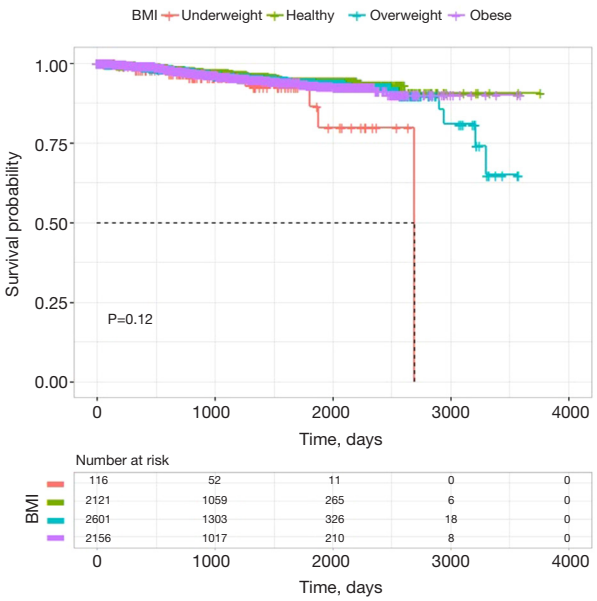

Figure 2 Breast cancer-specific survival by BMI categories. BMI, body mass index.

PFS

Of the 299 patients (stages I and II) receiving adjuvant therapy with complete data, 35 (11.7%) had a systemic recurrence. *Figure 4* shows the curves of PFS according to patients' BMI (P=0.44).

A total of 130 patients (stage III) receiving neoadjuvant therapy had complete information on recurrence. Forty-two presented systemic recurrence, without significant difference according to patients' BMI (P=0.39) (see *Figure 5*). Two patients presented local recurrence after neoadjuvant therapy, without any statistical difference among groups (P=0.62) (*Figure 6*).

For the logistic regression, patients who did not have a BMI value, T0N0 at diagnosis, or response value at surgery were excluded, leaving 6,527 patients or 6,617 breasts. The regression was constructed considering the breasts achieving pCR. BMI did not significantly impact the results (*Table 3*). The variables that significantly impacted the

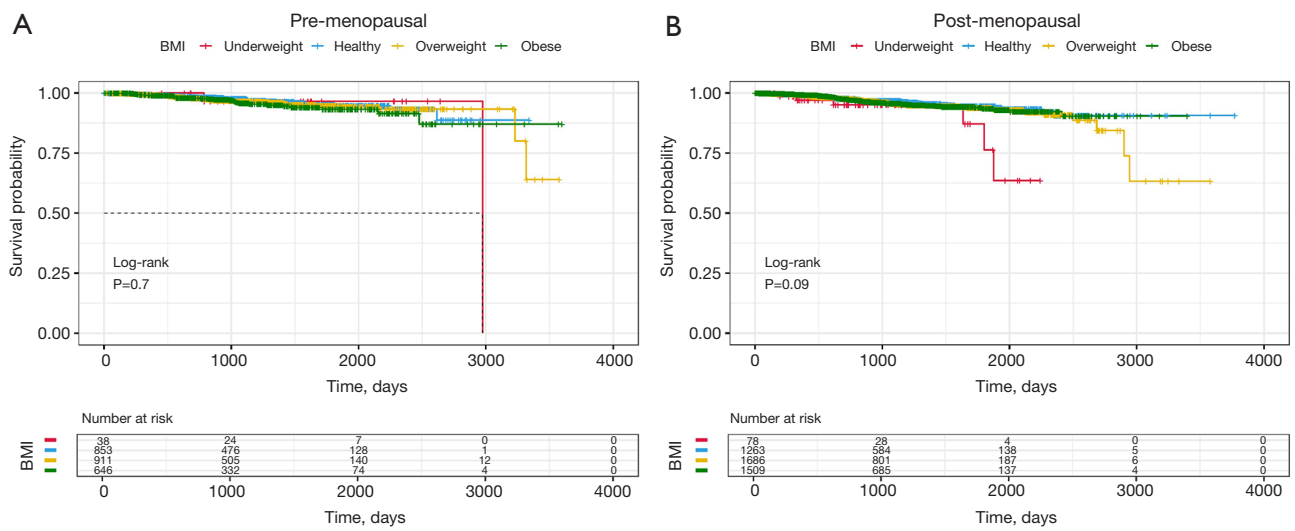

Figure 3 Breast cancer-specific survival according to menopausal status and BMI categories. (A) Pre-menopausal. (B) Postmenopausal. BMI, body mass index.

Table 2 Multivariate Cox-regression analysis in the overall survival of patients with breast cancer

Variable	Reference	Hazard ratio (95% CI)	P
BMI			
Healthy weight	Underweight	0.91 (0.08–9.86)	0.94
Overweight	Underweight	1.86 (0.17–20.08)	0.61
Obese	Underweight	0.93 (0.09–9.45)	0.95
Histological type			
Tubular carcinoma	Ductal in situ	0.00 (0.00–Inf)	>0.99
Mucinous carcinoma	Ductal in situ	0.69 (0.02–23.74)	0.84
Papillary carcinoma	Ductal in situ	0.00 (0.00–Inf)	>0.99
Lobular carcinoma	Ductal in situ	1.03 (0.04–25.76)	0.99
IDC-NST	Ductal in situ	0.47 (0.03–7.95)	0.60
Molecular subtype			
Luminal B	Luminal A	3.10 (0.38–25.12)	0.29
HER2+	Luminal A	3.80 (0.44–33.02)	0.23
Triple negative	Luminal A	5.96 (0.72–49.57)	0.10
Staging			
II	I	1.20 (0.27–5.20)	0.81
III	I	2.07 (0.47–9.13)	0.34
IV	I	0.00 (0.00–Inf)	>0.99
Zero	I	0.45 (0.02–9.38)	0.60
Bilaterality	Unilaterality	0.00 (0.00–Inf)	>0.99
Recurrence	No recurrence	0.00 (0.00–Inf)	>0.99
Systemic recurrence	No systemic recurrence	Inf (0.00–Inf)	>0.99
Radical surgery	Conservative surgery	1.77 (0.56–5.60)	0.33
Adjuvant therapy	No adjuvant therapy	0.86 (0.18–4.03)	0.85
Age at diagnosis	–	1.02 (0.99–1.06)	0.17
Time between diagnosis and surgery	–	1.00 (0.99–1.00)	0.61

BMI, body mass index; CI, confidence interval; HER2+, human epidermal growth factor receptor 2-positive; IDC-NST, invasive ductal carcinoma no specific type; Inf, infinite.

chances of pCR were HER2+ and triple-negative compared with luminal A, staging zero compared with I, recurrence, adjuvant therapy, age, and time between diagnosis and surgery (see *Table 3*).

Discussion

In our study, the prevalence of BC was higher in older women (postmenopausal), independently of the BMI. More than half of the patients were overweight or obese, which is not surprising knowing that 62.6% of women in Brazil are overweight and 29.5% are obese (24). Patients with high BMI, overweight or obese, have a higher risk for BC. A pooled analysis from seven prospective cohort studies including 337,819 women from Europe and North America showed a relative risk of 1.26 (95% CI: 1.09–1.46) for BC in postmenopausal women with BMI ≥28 kg/m^2 (25).

Our analysis showed no difference in staging or molecular subtype of BC according to BMI. Obesity was not related to more aggressive histological type, in contrast

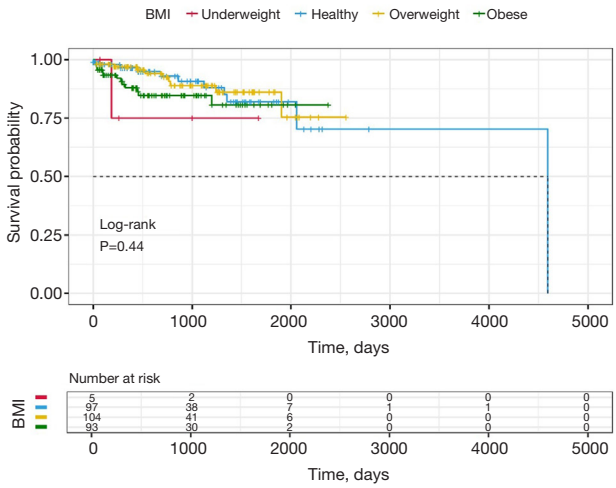

Figure 4 Progression-free survival and systemic recurrence in patients receiving adjuvant therapy. BMI, body mass index.

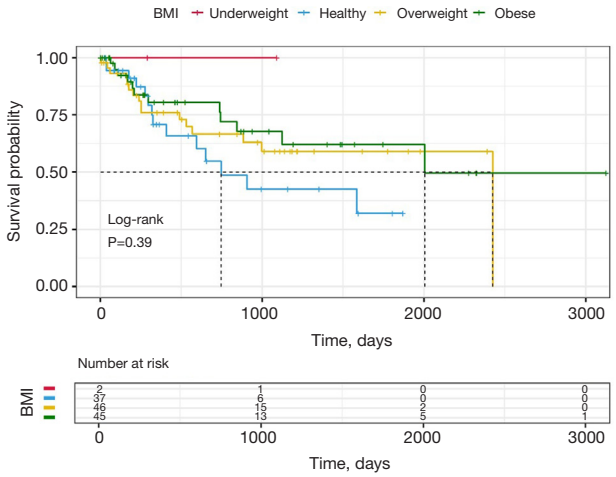

Figure 5 Progression-free survival and systemic recurrence in patients receiving neoadjuvant therapy. BMI, body mass index.

to the results from the CASH study, where authors found a direct relationship between BMI and incidence of triple-negative BC (26). Results from a meta-analysis including 11 studies also showed a higher incidence of triple-negative in patients with obesity (OR: 1.24, 95% CI: 1.06–1.46) (27).

According to our results, obesity did not impact the OS or PFS. To explore potential stage-specific effects, we performed a stratified survival analysis by cancer stage (I, II, and III), but found no statistically significant differences in OS across BMI categories within each stage. This approach was motivated by prior evidence suggesting that the

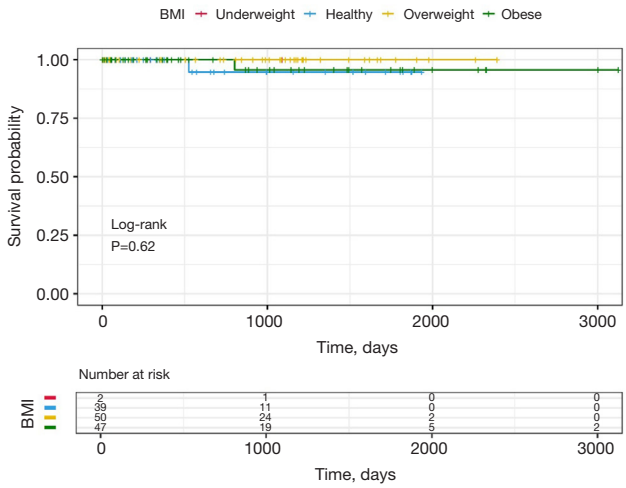

Figure 6 Progression-free survival and local recurrence in patients receiving neoadjuvant therapy. BMI, body mass index.

association between obesity and worse prognosis is more prominent in early-stage BC (28).

These findings differed from what we expected, considering that a previous study show higher mortality, especially in obese women with luminal BC subtypes (29). Our study showed worse prognosis of HER2+ or triple negative compared to luminal A, independent of BMI. Results from a meta-analysis (82 studies, n=213,075), considering all BC subtypes and ≥5-year follow-up, showed that patients with obesity had 1.41 (95% CI: 1.29–1.53) relative risk for death from all causes and higher BC-specific mortality (HR 1.35, 95% CI: 1.24–1.47) compared with healthy weight patients (30). In a meta-analysis including 21 studies (n=80,326), considering all BC subtypes and 5 to 20 years follow-up, the OS was worse in obese and overweight women, with a HR of 1.23 (95% CI: 1.07–1.42) for premenopausal and 1.15 (95% CI: 1.06–1.26) for postmenopausal patients (31). In our study, we chose to evaluate overweight and obesity separately and the menopausal status did not impact the OS of our population.

Other studies showing a significant impact of obesity in mortality have considered the BMI over 40 kg/m^2, while we considered ≥30 kg/m^2. The American Cancer Society's Cancer Prevention Study II (CPS-II), a prospective cohort study with 14-year follow-up including 424,168 postmenopausal women, found a relative risk of mortality from BC of 3.08 (95% CI: 2.09–4.51) for patients with BMI >40 kg/m^2 compared with BMI between 18.5 to 24.9 kg/m^2 (32). In a cohort with more than 400,000 women, patients with BMI ≥40 kg/m^2

Table 3 Multiple logistic regression: variable and pCR (T0N0 or TisN0)

Variable	Reference	Odds ratio (95% CI)	P
BMI			
Underweight	Healthy weight	0.47 (0.05–4.82)	0.52
Overweight	Healthy weight	1.19 (0.68–2.08)	0.55
Obese	Healthy weight	0.92 (0.50–1.68)	0.78
Histological type			
Tubular carcinoma	Ductal in situ	0.00 (0.00–Inf)	>0.99
Mucinous carcinoma	Ductal in situ	0.00 (0.00–Inf)	0.98
Papillary carcinoma	Ductal in situ	0.55 (0.04–7.39)	0.64
Lobular carcinoma	Ductal in situ	1.33 (0.27–6.56)	0.72
IDC-NST	Ductal in situ	0.39 (0.13–1.16)	0.09
Metaplastic carcinoma	Ductal in situ	0.00 (0.00–Inf)	>0.99
Molecular subtype			
Luminal B	Luminal A	2.03 (0.73–5.62)	0.17
HER2+	Luminal A	4.85 (1.69–13.94)	0.003*
Triple negative	Luminal A	6.90 (2.52–18.94)	<0.001*
Staging			
II	I	0.92 (0.41–2.07)	0.83
III	I	2.25 (0.97–5.21)	0.058
IV	I	0.00 (0.00–Inf)	0.98
Zero	I	10.31 (2.91–36.57)	<0.001*
Lymphocytic infiltration	No	1.03 (0.37–2.84)	0.95
Angiolymphatic invasion	No	0.31 (0.07–1.38)	0.12
Perineural invasion	No	0.45 (0.09–2.38)	0.34
Family history grandmother	No	1.70 (0.87–3.31)	0.11
Recurrence	No recurrence	0.31 (0.15–0.62)	0.001*
Radical surgery	Conservative surgery	1.01 (0.57–1.78)	0.97
Adjuvant therapy	No adjuvant therapy	0.14 (0.03–0.70)	0.01*
Neoadjuvant therapy	No neoadjuvant therapy	1.09 (0.48–2.47)	0.84
Age at diagnosis	–	0.98 (0.96–1.00)	0.02*
Time between diagnosis and surgery	–	1.00 (1.00–1.01)	<0.001*

*, significant P value. BMI, body mass index; CI, confidence interval; HER2+, human epidermal growth factor receptor 2-positive; IDC-NST, invasive ductal carcinoma no specific type; Inf, infinite; pCR, pathologic complete response.

had higher mortality, the relative risk of death was 2.12 compared with women with BMI between 18 and 24.9 kg/m^2, independent of the menopausal status (33). Our findings also differ from other multiple large-scale observational studies that have consistently reported an association between obesity and poorer BC outcomes. Several meta-analyses and cohort studies have demonstrated that higher BMI is linked to an increased risk of recurrence, BC-specific mortality, and overall mortality. For example, Chan *et al.* [2014] (30) found that obesity was associated with a

35% increased risk of BC-specific death. Similarly, Protani *et al.* [2010] (34), in a meta-analysis of 43 studies, concluded that obese women had a significantly worse OS and disease-free survival compared to women with normal BMI. These associations have been particularly evident among postmenopausal women and in hormone receptor-positive tumors, where excess adipose tissue contributes to estrogen production and chronic low-grade inflammation, both of which may promote tumor progression (35,36).

Our database did not have the information on hormone therapy, which could affect the outcomes. Rosenberg *et al.* found a direct relationship between obesity and mortality associated with hormone therapy replacement use (37). Evaluating only never-users, the difference in the risk of death between patients with obesity and healthy weight was not statistically significant (38).

In our study, PFS was similar among patients with different BMI. These results are consistent with the findings of Litton *et al.* who evaluated 1,169 women with invasive BC and had a 75% rate of PFS with a 5-year follow-up without significant difference among patients with obesity, overweight, or healthy weight (38). The difference may be in the molecular subtype, a pooled analysis of results from clinical trials including 3,496 advanced BC patients found a better PFS in patients HER2+ with obesity (P=0.034) (39).

It should be noted that the São Paulo Public Health System only performs opportunistic mammographic screening, resulting in a higher proportion of cases in stages II and III. In Brazil we do not have a BC screening organized for the public service, there is a recommendation from the Brazilian Ministry of Health and National Institute of Cancer consisting in the screening mammography every 2 years for women between 50 and 69 years old (40). However, most medical societies, including Brazilian Society of Mastology, suggest mammographic screening starting at age 40 years and ending at age 74 years or when life expectancy is greater than 8 years (41,42).

Previous Brazilian study had smaller number of included patients (n=236), and showed that women with obesity were more likely to have triple-negative BC (HR 4.489, 95% CI: 1.32–15.28) (43). A case-control study, with 500 Brazilian women (100 cases and 400 controls), found a higher risk of BC in postmenopausal women with obesity (OR 1.56, 95% CI: 1.11–2.21), but did not evaluate survival (44).

Even though our study did not show a significant impact of obesity in the prognosis of our patients during the study period, we believe that prevention and treatment of obesity must be incorporated in the strategies against BC. Lose weight reduces the risk of BC in women (45); however, larger studies are needed to evaluate the impact of weight loss in patients with obesity and BC (46).

This study provides robust epidemiological data on Brazilian patients with BC, representing a population rarely explored in the international literature. However, several limitations must be acknowledged. As a retrospective and observational study, it is inherently subject to certain biases. As with any retrospective study, our analysis is subject to potential biases, particularly selection bias—due to the exclusion of patients with incomplete data, information bias—related to the quality and completeness of medical records, and confounding bias, as not all relevant prognostic variables could be controlled for in the analysis.

One key limitation is the potential for reverse causation, given that BMI was measured only at the time of diagnosis. This single time-point assessment may not accurately reflect patients' usual or pre-illness body weight, particularly in those presenting with advanced-stage disease who may have already experienced cancer-related weight loss. Such bias may obscure the true relationship between body composition and prognosis, potentially underestimating the impact of adiposity on survival outcomes. As noted by Kroenke *et al.*, unintentional weight loss prior to diagnosis may lead to misclassification of patients with advanced disease into lower BMI categories, thereby confounding survival analyses (47). Similarly, Bradshaw *et al.* highlighted that BMI at diagnosis may not capture long-term weight patterns, which are more predictive of clinical outcomes (48).

In addition, BMI alone may not be an adequate surrogate for body composition. It does not differentiate between fat and lean mass, nor does it consider fat distribution (visceral *vs.* subcutaneous), which may have distinct biological effects on tumor progression. Caan *et al.* demonstrated that patients with normal BMI but reduced muscle mass (sarcopenia) had poorer outcomes, reinforcing the need for more precise tools such as imaging-based body composition analysis (49). In light of these factors, our findings should be interpreted with caution. We strongly recommend future prospective studies that incorporate longitudinal weight data and more nuanced measures of body composition to better define the role of obesity in BC prognosis.

Finally, the use of data derived from medical records introduces additional limitations common to retrospective studies. The exclusion of patients due to missing data or eligibility criteria may have introduced selection bias and limited the generalizability of our findings. The quality of the data depended heavily on the completeness and

accuracy of medical records. For instance, BMI values were only available at diagnosis, serial measurements throughout follow-up could have provided valuable insights into the impact of weight changes over time. Chemotherapy is known to influence body composition, and many patients with BC experience weight gain after diagnosis (50,51). Importantly, post-diagnosis weight gain has been associated with worse outcomes (52). Nevertheless, as a reference center, the hospital is expected to maintain high standards in clinical documentation. Although our overall sample size was large, small numbers in some subgroups may have reduced the statistical power to detect differences.

Deaths from non-BC causes were treated as censored observations in the survival analysis, although the number of such events was small, we acknowledge this as a limitation and note that competing risks models could provide a more accurate estimation in future studies. Lastly, the potential for publication bias must be considered, as studies with nonsignificant primary outcomes are less likely to be published. It is important to mention that Pérola Byington hospital is a public setting hospital, and the results should not be considered when evaluating the scenario in a private healthcare perspective.

Taken together, our findings suggest that the prognostic role of obesity in BC may vary by context and population. Future studies in diverse real-world settings, particularly those using longitudinal body composition data and accounting for treatment adherence and metabolic health, are needed to better understand the underlying mechanisms.

Conclusions

In conclusion, obesity did not impact the survival or progression of BC in this retrospective analyses. This study, despite not demonstrating significance in its primary objective, brings important epidemiological data from the Brazilian population with BC not previously published, with high prevalence of overweight and obesity among Brazilian women with BC and highlights the importance of further studies, especially prospective, addressing obesity and BC.

Acknowledgments

The authors would like to thank Dr. Mariana Matos, MD, for providing writing assistance on behalf of Springer Healthcare. This manuscript was prepared according to the International Society for Medical Publication Professionals-Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP3 Guidelines. They also would like to thank MAPES for statistical analysis. Prior presentation: partial results of this study was presented as a poster in San Antonio Breast Cancer Symposium in 2022 (abstract No. P3-03-20).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-24-139/rc

Data Sharing Statement: Available at https://cco.amegroups.com/article/view/10.21037/cco-24-139/dss

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-24-139/prf

Funding: This study was supported by Novo Nordisk Pharmaceuticals of Brazil LTDA, but had no participation on the design of the study, collection, analysis, and interpretation of data. They also provided financial support for writing assistance but played no role in the content of this publication.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-24-139/coif). A.M. works as principal investigator in clinical trials for Roche, Novartis, Pfizer, GSK, Merck and Exact Sciences and Consulting fees from Roche, Novartis, Merck and Exact Sciences. F.Z. works for Oncoclinics Group. E.C.M. works for Americas Oncology. H.L.C. works for Redimama Redimasto. R.M.L. works for Oncoclinics Group. R.A. works for Dasa Oncology. Novo Nordisk Pharmaceuticals of Brazil LTDA supported the study but none of the authors received any payment. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by Institutional Review Board of Women's Health Reference Center at Pérola Byington Hospital (reference

No. 2.213.876). Informed consent was waived in this retrospective study.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024,74:229-63.
2. Santos MdO, Lima FCdSd, Martins LFL, et al. Estimativa de Incidência de Câncer no Brasil, 2023-2025. Revista Brasileira de Cancerologia 2023. doi: 10.32635/2176-9745.rbc.2023v69n1.3700.
3. World Health Organization. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 6 Apr 2025 [Internet]. 2024 [cited Accessed 6 Apr 2025]. Available online: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
4. Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet 2014,384:755-65.
5. Rezende LFM, Arnold M, Rabacow FM, et al. The increasing burden of cancer attributable to high body mass index in Brazil. Cancer Epidemiol 2018,54:63-70.
6. Noh HM, Song YM, Park JH, et al. Metabolic factors and breast cancer risk in Korean women. Cancer Causes Control 2013,24:1061-8.
7. Sangrajrang S, Chaiwerawattana A, Ploysawang P, et al. Obesity, diet and physical inactivity and risk of breast cancer in Thai women. Asian Pac J Cancer Prev 2013,14:7023-7.
8. Suzuki S, Kojima M, Tokudome S, et al. Obesity/weight gain and breast cancer risk: findings from the Japan collaborative cohort study for the evaluation of cancer risk. J Epidemiol 2013,23:139-45.
9. Wang XL, Jia CX, Liu LY, et al. Obesity, diabetes mellitus, and the risk of female breast cancer in Eastern China. World J Surg Oncol 2013,11:71.
10. Magnusson C, Baron J, Persson I, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. Int J Cancer 1998,76:29-34.
11. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 2011,11:886-95.
12. Haque I, Ghosh A, Acup S, et al. Leptin-induced ER-α-positive breast cancer cell viability and migration is mediated by suppressing CCN5-signaling via activating JAK/AKT/STAT-pathway. BMC Cancer 2018,18:99.
13. Linares RL, Benítez JGS, Reynoso MO, et al. Modulation of the leptin receptors expression in breast cancer cell lines exposed to leptin and tamoxifen. Sci Rep 2019,9:19189.
14. Pallegar NK, Christian SL. Adipocytes in the Tumour Microenvironment. Adv Exp Med Biol 2020,1234:1-13.
15. McTiernan A, Rajan KB, Tworoger SS, et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. J Clin Oncol 2003,21:1961-6.
16. Kaye SA, Folsom AR, Soler JT, et al. Associations of body mass and fat distribution with sex hormone concentrations in postmenopausal women. Int J Epidemiol 1991,20:151-6.
17. Karatas F, Erdem GU, Sahin S, et al. Obesity is an independent prognostic factor of decreased pathological complete response to neoadjuvant chemotherapy in breast cancer patients. Breast 2017,32:237-44.
18. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. N Engl J Med 2016,375:794-8.
19. Panayi AC, Agha RA, Sieber BA, et al. Impact of Obesity on Outcomes in Breast Reconstruction: A Systematic Review and Meta-Analysis. J Reconstr Microsurg 2018,34:363-75.
20. Cui Y, Whiteman MK, Flaws JA, et al. Body mass and stage of breast cancer at diagnosis. Int J Cancer 2002,98:279-83.
21. Griggs JJ, Sorbero ME, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. Arch Intern Med 2005,165:1267-73.
22. Ministério da Saúde. Diretrizes Diagnósticas Terapêuticas, 2022. Available online: https://www.gov.br/conitec/pt-br/midias/consultas/relatorios/2024/RRPCDTCncerdeMama_CP.pdf
23. Pennisi A, Kieber-Emmons T, Makhoul I, et al. Relevance of Pathological Complete Response after Neoadjuvant Therapy for Breast Cancer. Breast Cancer (Auckl) 2016,10:103-6.

24. IBGE. Pesquisa Nacional de Saúde 2019. Atenção primária à saúde e informações antropométricas. Available online: https://biblioteca.ibge.gov.br/visualizacao/livros/liv101758.pdf [Accessed 21 Feb 2022. 2009].
25. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000,152:514-27.
26. Gaudet MM, Press MF, Haile RW, et al. Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. Breast Cancer Res Treat 2011,130:587-97.
27. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2013,137:307-14.
28. Ewertz M, Jensen MB, Gunnarsdóttir KÁ, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 2011,29:25-31.
29. Blair CK, Wiggins CL, Nibbe AM, et al. Obesity and survival among a cohort of breast cancer patients is partially mediated by tumor characteristics. NPJ Breast Cancer 2019,5:33.
30. Chan DSM, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol 2014,25:1901-14.
31. Niraula S, Ocana A, Ennis M, et al. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. Breast Cancer Res Treat 2012,134:769-81.
32. Petrelli JM, Calle EE, Rodriguez C, et al. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 2002,13:325-32.
33. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003,348:1625-38.
34. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010,123:627-35.
35. Cecchini RS, Costantino JP, Cauley JA, et al. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. Cancer Prev Res (Phila) 2012,5:583-92.
36. Sparano JA, Wang M, Zhao F, et al. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer 2012,118:5937-46.
37. Rosenberg L, Czene K, Hall P. Obesity and poor breast cancer prognosis: an illusion because of hormone replacement therapy? Br J Cancer 2009,100:1486-91.
38. Litton JK, Gonzalez-Angulo AM, Warneke CL, et al. Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. J Clin Oncol 2008,26:4072-7.
39. Modi ND, Tan JQE, Rowland A, et al. The obesity paradox in early and advanced HER2 positive breast cancer: pooled analysis of clinical trial data. NPJ Breast Cancer 2021,7:30.
40. INCA. Instituto Nacional de Câncer. Detecção precoce. Available online: https://www.inca.gov.br/controle-do-cancer-de-mama/acoes-de-controle/deteccao-precoce [Accessed 09 May 2022].
41. ACS. American Cancer Society. Recommendations for the early detection of breast cancer. Available online: https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html [Accessed 09 May 2024].
42. Sardanelli F, Aase HS, Álvarez M, et al. Position paper on screening for breast cancer by the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies from Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Israel, Lithuania, Moldova, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland and Turkey. Eur Radiol 2017,27:2737-43.
43. Jerônimo AFA, Weller M. Differential Association of the Lifestyle-Related Risk Factors Smoking and Obesity with Triple Negative Breast Cancer in a Brazilian Population. Asian Pac J Cancer Prev 2017,18:1585-93.
44. Gravena AAF, Romeiro Lopes TC, Demitto MO, et al. The Obesity and the Risk of Breast Cancer among Pre and Postmenopausal Women. Asian Pac J Cancer Prev 2018,19:2429-36.
45. Sjöström L, Gummesson A, Sjöström CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol 2009,10:653-62.
46. Ligibel JA, Alfano CM, Hershman D, et al. Recommendations for Obesity Clinical Trials in Cancer Survivors: American Society of Clinical Oncology

Statement. J Clin Oncol 2015,33:3961-7.
47. Kroenke CH, Chen WY, Rosner B, et al. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 2005,23:1370-8.
48. Bradshaw PT, Ibrahim JG, Stevens J, et al. Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. Epidemiology 2012,23:320-7.
49. Caan BJ, Emond JA, Natarajan L, et al. Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. Breast Cancer Res Treat 2006,99:47-57.
50. Goodwin PJ, Ennis M, Pritchard KI, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol 1999,17:120-9.
51. Ricci MD, Formigoni MC, Zuliani LM, et al. Variations in the body mass index in Brazilian women undergoing adjuvant chemotherapy for breast cancer. Rev Bras Ginecol Obstet 2014,36:503-8.
52. Daling JR, Malone KE, Doody DR, et al. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001,92:720-9.

Cite this article as: Mattar A, Antonini M, Cavalcante FP, Zerwes F, Millen EC, Brenelli FP, Frasson AL, Soares LR, Madeira M, Teixeira MD, Amorim AG, de Oliveira LC, Ramos MDNM, Facina G, Freitas-Junior R, Couto HL, Rondelo SM, Leite RM, Arakelian R, Fenile R, Gebrim LH. Breast cancer stage, molecular subtype and survival in patients with obesity: a real-world study. Chin Clin Oncol 2025;14(5):52. doi: 10.21037/cco-24-139