Overview of Obesity and Breast Cancer in Brazil: 24 Years of Follow-Up

Andrea Z Pereira[1]*, Bianca de Almeida-Pitito[2], Rogério Ruscitto do Prado[1], Andre Mattar[3], Roberto Hegg[3], Jorge Yoshinori Shida[3] and Luiz Henrique Gebrim[3]

[1]Department of Oncology and Hematology, Albert Einstein Hospital, Brazil

[2]Department of Preventive Medicine, UNIFESP, Brazil

[3]Department of Breast Cancer, São Paulo State Government Women's Health Reference Center (Pérola Byington Hospital), Brazil

Abstract

Background: There is a higher risk of Breast Cancer (BC) in postmenopausal obese women and with a worse outcome of all ages.

Objectives: To evaluate obesity prevalence in BC patients and its association with survival, age, Surgery Complications (SC), and molecular BC subtypes.

Methods: A retrospective cohort study was performed with 5925 between 1994 and 2018. Survival analysis was performed according to Body Mass Index (BMI) groups. The database contains information about molecular BC subtypes and SC.

Results: They had a mean (SD) age of 54 (12.0) years. There were 769 (13%) deaths, and the mean survival was 20 (2.0) years. 1,787 (30%) patients with obesity and 4,138 (70%) without obesity. Patients with obesity were older (56 (11.0) years) (p<0.001) and they had lower frequencies of luminal B (33 *vs.* 67%, p=0.02) and HER2- (31 *vs.* 69%, p=0.04) subtypes. There was a difference between obesity in BC patients and the Brazilian population (p<0.005). Patients with obesity had more infections as a SC (p=0.01). The Kaplan-Meier curve shows the estimates of survival for patients with obesity and patients without obesity with BC.

Conclusion: We found a high prevalence of obesity in BC patients, more than in the general Brazilian women population. Our patients with obesity were older and had lower frequencies of luminal B and HER2-subtypes than women without obesity. Besides that, patients with obesity had more infections after surgery, mainly in HER2+, Negative triple, and HER2+ Hybrid.

Keywords: Breast cancer; BMI; Obesity; Follow-up-infection

Introduction

Obesity is one of the significant public health problems of this century, being a significant global health epidemic in developed and developing countries [1-3]. The future of obesity prevalence in the USA in 2030 will rise to adult obesity and severe obesity, respectively, 49% and 24%, with considerable variation across states [4]. In Brazil, among women, there was an increase in obesity over the last 25 years, from 13% to 20% [5-7].

Besides the well-established effects on type 2 diabetes and cardiovascular disease, there is convincing evidence today that obesity also increases the risk of several types of cancer, including colorectal cancer, endometrial cancer, renal cell carcinoma, esophageal adenocarcinoma, pancreatic cancer, and liver cancer [8]. Existing literature suggests a relationship between increased BMI and an increased risk for developing breast cancer [9-13], especially postmenopausal breast cancer [8].

Obesity is a risk factor for several types of cancer, including breast cancer [14]. In the world and Brazil, Breast Cancer (BC) is the primary cancer and cause of cancer deaths among the female population [15,16]. Obesity is associated with an increased risk of postmenopausal breast cancer, and some reports suggest central obesity may be associated with an increased risk of premenopausal breast cancer [12,17,18].

Many mechanisms have associated BC with obesity, mainly in the postmenopausal period, such as increased levels of estrogens due to excessive aromatization by adipose tissue; central adiposity as

an independent predictor; hypercholesterolemia; excessive oxidative stress; overexpression of pro-inflammatory cytokines; insulin and/or Insulin-like growth factors as a potent mitogen for normal and transformed breast epithelial cells; to be fuel cancer cell growth by providing excess substrate for Adenosine Triphosphate (ATP) production and lipid membrane generation; hyperinsulinemia, insulin resistance and drive glucose uptake associated with activation of cell growth, cell proliferation, and angiogenesis and lower the barrier for oncogenic transformation; large visceral lipid stores may support tumor progression and uncontrolled cellular growth [3,14,19].

Overweight, obesity or underweight may increase the risk of BC relapse, death, some complications from BC treatment, and several co-morbidities. However, the effect of weight change on prognosis is not established [20,21].

In addition, multiple factors contribute to the unfavorable survival rates in patients with obesity with cancer, including a higher likelihood of comorbid conditions and adverse tumor characteristics and systematic underdosing of chemotherapy, which occurs in up to 40% of patients [22].

Our goal was to describe obesity prevalence in breast cancer patients during a 24 years follow-up and evaluate the association of survival rate with age, surgery complications, anti-human KI67 antibody (KI67), and molecular subtypes BC, including Human Epidermal Growth Factor Receptor 2 (HER2), luminal A and B and triple-negative.

Methods

Patients

A retrospective cohort study with 8,824 breast cancer patients was performed between 1994 and 2018 at the Breast Cancer Department, São Paulo State Government Women's Health Reference Center (Pérola Byington Hospital), São Paulo, Brazil. From those, 2,899 patients were excluded because they did not have the description of either their weight or Body Mass Index (BMI). Therefore, we analyzed 5,925 patients. The study was approved by the Hospital Ethics and Research Committee 2.213.876.

Data source

Pérola Byington is a hospital specialized in women's health and BC treatment in the Brazilian public setting. The registry was developed by the hospital to help in the support, management, and follow-up process of these patients and it includes data from all BC patients from the hospital. The database (1994-2018) contains information from patients' medical records, evidencing the actual clinical practice over anti-human KI67 antibody (KI67) and molecular subtypes BC, including Human Epidermal Growth Factor Receptor 2 (HER2), luminal A and B, and triple-negative. Surgery complications such as dehiscence, hematoma, and infection were cited in our database either.

Anthropometric measurement

Anthropometric measurements were performed in the first visit to the clinic. To determine the height (m), a stadiometer (with a total height of 2.0 m and precision of 1.0 mm) was used, duly posted on the wall, with the patient standing, barefoot, with their heels together, with the back straight and arms outstretched at the sides of the body. The weight measurement (kg) was performed by a properly calibrated scale, with the patient standing in the center of the scale base, barefoot, and wearing light clothing.

Body Mass Index (BMI) calculated as weight (kg) divided by the squared height (m) [23]. BMI was used to classify nutritional status of the adult patients as: <16 kg/m²: Malnutrition grade III; 16 kg/m² to 16.9 kg/m²: Malnutrition grade II; 17 kg/m² to 18.4 kg/m²: Malnutrition grade I; 18.5 kg/m² to 24.9 kg/m²: Normal; 25 kg/m² to 29.9 kg/m²: Overweight; 30 kg/m² to 34.9 kg/m²: Obesity grade I; 35 kg/m² to 39.9 kg/m²: Obesity grade II; ≥ 40 kg/m²: Obesity grade III [23].

Data analysis

Quantitative variables were described as mean, standard deviation, median, interquartile range, and extreme. In addition, the variables were evaluated for their distribution through histogram and the Shapiro-Wilk test was performed. Those in which the assumption of normality was not rejected had the mean and standard deviation measures were presented. Qualitative variables were described by absolute frequency and percentage [24].

The sample was stratified according to the exposure variable, the BMI, in obese (BMI ≥ 30 kg/m²) and non-obese (BMI<30 kg/m²). Socio-demographic variables, presence of anti-human KI67 antibody (KI67), molecular subtypes for the tumor, surgery complications and relapse cases were compared between the two groups.

The prevalence rates of obesity in the study sample and Brazilian women population were compared across the 24 years of follow-up [6,25-27].

Association between obesity in Brazil, age, survivorship, KI67, molecular subtypes and surgical complications variables and the difference between measurements studied at 24 years was assessed by multiple linear models with time to take as an outcome and measurements as an explanatory variable in conjunction with obesity (BMI ≥ 30).

Kaplan-Meier analysis was applied to calculate survival considering patients with and without obesity. Multivariate regression analysis was used related to obesity with age.

All analyses were carried out with SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.), and p-values less than 0.05 were considered statistically significant.

Results

From the total sample of 5,925, 1,787 (30%) participants were stratified as obese (BMI ≥ 30 Kg/m²) and 4,138 (70%) non-obese. The participants had a mean (SD) age of 54 (12.0) years and weight of 70 (15.0) kg, and a BMI of 28 (5.5) kg/m². From a total of 5,925 women with a breast cancer diagnosis (1994-2018), 3,259 (55%) had negative HER2 and 5,273 (89%) negative KI67. Regarding the subtype 850 (20%) patients were luminal A, 1,591 (37.2%) luminal B, 528 (12.3%), HER2+ Hybrid and 646 (15.1%) negative triple. We observed that 71 (1.2%) showed relapse in this follow-up. Besides non-patients with obesity were submitted more neoadjuvant chemotherapy (p=0.03) and radiotherapy (p=0.007) (Table 1).
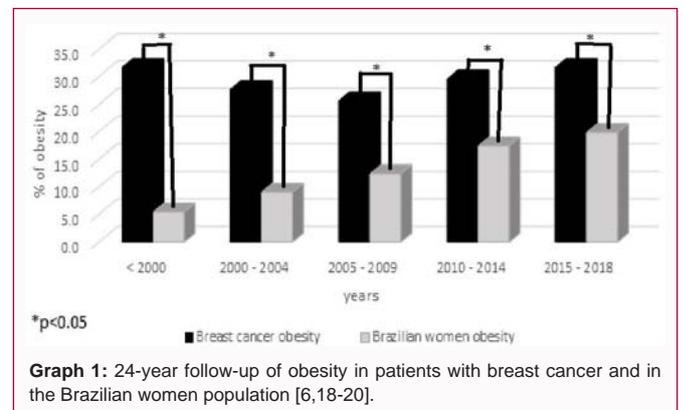
We observed that the prevalence of obesity did not change throughout the 24 years of follow-up. Comparing the prevalence of obesity in the study sample and the Brazilian women population [6,25-27], we observed that the frequencies of obesity in women with breast cancer were higher than those related to the Brazilian women

Table 1: Characteristic of obese and non-obese patients with breast cancer.

Variables	Non-obese		Obese		Total		p
	n	%	n	%	n	%	
Time							
<2000	26	0.6	12	0.7	38	0.6	0.285
2000-2004	63	1.5	24	1.3	87	1.5	
2005-2009	192	4.6	66	3.7	258	4.4	
2010-2014	2264	54.8	958	53.5	3222	54.4	
2015-2018	1590	38.5	730	40.8	2320	39.2	
HER2							
Negative	2228	53.9	1009	56.4	3237	54.6	0.077
Positive	1907	46.1	781	43.6	2688	45.4	
KI67*							
Negative	2452	89.3	1094	89.2	3546	89.3	0.979
Positive	295	10.7	132	10.8	427	10.7	
Luminal A**							
	592	69.6	258	30.4	850	19.8	
Luminal B**							
	1059	66.6	532	33.4	1591	37.2	
HER2 + Hybrid**							**0.024**
	391	74.1	137	25.9	528	12.3	
Negative triple**							
	646	69.7	281	30.3	646	15.1	
KI67*							
Negative	2452	89.3	1094	89.2	3546	89.3	0.979
Positive	295	10.7	132	10.8	427	10.7	
Relapse							
No	4088	98.9	1768	98.8	5856	98.8	0.761
Yes	47	1.1	22	1.2	69	1.2	
Surgery complications							
No	3985	70.1	1703	29.9	5688	96	**0.026**
Yes	150	63.3	87	36.7	237	4	
Breast side							
Right	2022	48.9	890	49.7	2912	49.1	0.562
Left	2113	51.1	900	50.3	3013	50.9	
Family story							
No	3387	81.9	1466	81.9	4853	81.9	0.992
Yes	748	18.1	324	18.1	1072	18.1	
Neoadjuvant Chemotherapy							
No	3087	74.7	1289	72	4376	73.9	**0.033**
Yes	1048	25.3	501	28	1549	26.1	
Adjuvant Chemotherapy							
No	2031	49.1	881	49.2	2912	49.1	0.943
Yes	2104	50.9	909	50.8	3013	50.9	
Palliative Chemotherapy							
No	3839	92.8	1668	93.2	5507	92.9	0.636
Yes	296	7.2	122	6.8	418	7.1	
Hormone Therapy							
No	1590	38.5	728	40.7	2318	39.1	0.108
Yes	2545	61.5	1062	59.3	3607	60.9	
Radiotherapy							
No	1584	38.3	620	34.6	2204	37.2	**0.007**
Yes	2551	61.7	1170	65.4	3721	62.8	
Neoadjuvant Radiotherapy							
No	4131	99.9	1786	99.8	5917	99.9	0.254*
Yes	4	0.1	4	0.2	8	0.1	
Adjuvant Radiotherapy							
No	1677	40.6	679	37.9	2356	39.8	0.058
Yes	2458	59.4	1111	62.1	3569	60.2	
Palliative Radiotherapy							
No	4054	98	1741	97.3	5795	97.8	0.06
Yes	81	2	49	2.7	130	2.2	
Total	**4135**	**100**	**1790**	**100**	**5925**	**100**	

Chi-square test; KI67: Anti-Human KI67 Antibody; * Fisher's exact test; ** Total of 4,274 patients

Graph 1: 24-year follow-up of obesity in patients with breast cancer and in the Brazilian women population [6,18-20].

population. There was a difference between obesity in cancer patients and the Brazilian women population (p<0.005) (Graph 1).

Obese were older (56 (11.0) years) than non-patients with obesity (53 (12.5) years) (p<0.001). They had lower frequencies of luminal B (33 *vs.* 67%, p=0.02) and HER2- (31 *vs.* 69%, p=0.04) subtypes than women without obesity. There was not a significant difference in frequencies of KI67, recovering and survival between groups. Non-patients with obesity had fewer surgical complications (p=0.026); however, after surgery, patients with obesity had more infections (p=0.01). The sample power was 49%, based on the result of the complication.

Cox multiple regression for age considering subtypes (luminal A, luminal B, HER2+, HER2+ Hybrid and negative triple), obesity and surgical complications were significant for HER2+ and negative triple (p<0.001) and HER2 + Hybrid (p=0.001) (Table 2).

In survival analysis, the Kaplan-Meier curve shows the estimates of survival for obese and non-patients with obesity with breast cancer from 1994 to 2018 (n=5925). There were 769 (13%) deaths and the mean survival was 20 (2.0) years for the whole sample of the study. There was no significant difference between mean survival in obese and non-patients with obesity, respectively 19 and 20 years (Graph 2).

Discussion

In 24 years of follow-up, we observed a higher prevalence of obesity among patients with breast cancer concerning the general Brazilian population in all these years. Our patients with obesity were older, had high prevalence lower frequencies of luminal B and HER2

Table 2: Cox multiple regression for age considering breast cancer subtypes, obesity and surgical complications.

Variable	HR	CI (95%)		p
		Inferior	Superior	
Age (years)	1.001	0.993	1.008	0.89
Luminal A (ref.)	1			
Luminal B	1.12	0.86	1.46	0.396
HER2+	1.92	1.39	2.66	**<0,001**
HER2+ Hybrid	1.68	1.24	2.28	**0.001**
Negative triple	2.21	1.72	2.84	**<0.001**
SC	1.08	0.72	1.62	0.7
Obesity	1.1	0.92	1.31	0.315

CI: Confidence Interval; HR: Hazard Ratio; SC: Surgical Complications
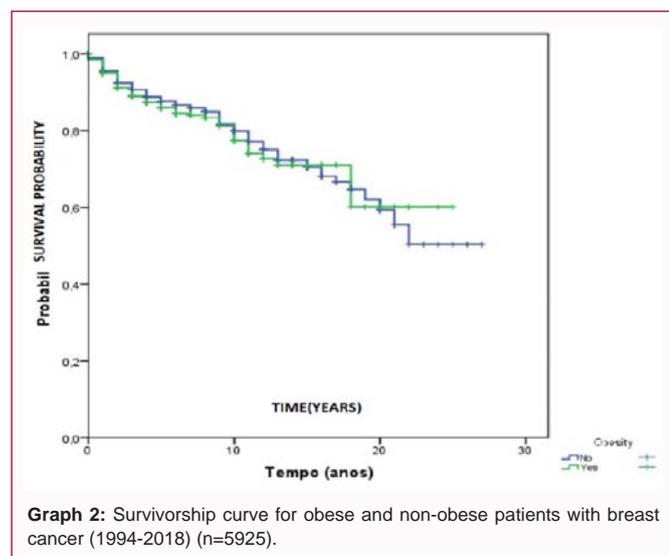
Graph 2: Survivorship curve for obese and non-obese patients with breast cancer (1994-2018) (n=5925).

subtypes than women without obesity. Their survivorship was not different from non-patients with obesity. Non-patients with obesity had fewer surgical complications; however, patients with obesity had more infections after surgery. Obesity and surgical complications were significant for HER2+, Negative triple and HER2+ Hybrid.

Obesity is a global problem, and in Brazil, it is no different. In 1974, there were 2.8% and 11.8%, respectively, of males and females with obesity in Brazil. In 2018, there was a 20% mean of obesity [5,6]. Our study has shown a mean of 30% of obesity for 24 years. Obesity was not different among years of follow-up, however, its prevalence was significantly higher in our sample related to the general Brazilian population in the same period [5,6]. Our finding suggested a significant bulk of obesity in breast cancer patients, higher than the general population, for 24 years. It shows the impact of BMI in this severe disease.

Many studies found an association between obesity, breast cancer, and its outcomes [28-34]. The association of obesity with breast cancer risk is complex. There is convincing evidence that after menopause, obesity increases the risk of breast cancer [35]. Weight gain in adulthood probably also increases postmenopausal breast cancer risk. Conversely, before menopause, obesity probably decreases breast cancer risk [35].

We found a positive association between obesity and age; therefore, our patients with obesity were older. Postmenopausal women have excess fat tissue, conversion of androgens to estrogens by the aromatase enzyme; all these factors increase breast cancer risk and body weight [28,29,36].

These opposing associations are most likely mediated *via* endogenous sex hormones, primarily estradiol, which is likely to have tumor-promoting activities. After menopause, adipose tissue is the major source of estrogens, and obesity is associated with higher estrogen concentrations, which may explain the higher breast cancer risk. Interestingly, the higher risk of postmenopausal breast cancer associated with obesity is primarily seen for estrogen and progesterone receptor-positive disease, and it is limited to women not using hormone replacement therapy, which gives indirect evidence to support the hypothesis that estrogens may be the crucial link [37].

The inverse association between obesity and premenopausal breast cancer is primarily thought to be due to reduced exposure to endogenous progesterone because of obesity-induced ovarian hyperandrogenism [37]. There is limited evidence showing that among breast cancer patients, obesity is related to poorer survival [35].

Several cohort studies have investigated whether the association of overweight/obesity with survival differs by molecular subtype of breast cancer. A 2012 meta-analysis with twenty-one studies found that all-cause mortality was higher in patients with the highest *vs.* lowest category of BMI for patients with both estrogen receptor-positive and estrogen receptor-negative tumors [38]. The same meta-analysis found a statistically significant association between heavier *vs.* lighter weight and risk of breast cancer-specific mortality in patients with estrogen receptor/progesterone receptor-positive tumors. For women with estrogen receptor/progesterone receptor-negative breast cancer, heavier *vs.* lighter weight was associated with a no statistically significant increase in breast cancer-specific mortality. A combined analysis of 15,538 breast cancer patients from the National Surgical Adjuvant Breast and Bowel Project trials found some variability in the association of BMI with survival, suggesting that the effect of obesity on survival was limited to women with estrogen receptor-positive disease [39].

A smaller number of studies have looked at the association of obesity with survival by other classifications of tumor type and patients, including tumor genetics, locally advanced or inflammatory breast cancer, and young patients [40-44]. In general, obesity increases the risk of poor survival, although some may be more affected than others.

A meta-analysis on weight status and breast cancer survival included 213,075 breast cancer patients from eighty-two prospective cohort studies, with 41,477 deaths (of which 23,182 were breast cancer-specific deaths) [45]. Thirty-five studies (114,012 women; 17,894 deaths) provided categorical results on BMI within 12 months after diagnosis, using WHO standard classifications. The meta-analysis did not identify any subgroups of patients that were statistically significantly different from other subgroups in terms of weight associations with mortality, including menopausal status, hormone receptor status, sample size (number of deaths), length of follow-up, geographic location, or method of ascertaining height and weight (measured *vs.* self-reported). Adjustment for potential confounders also did not substantially influence effect size, including tumor stage, cancer treatment, presence of diabetes or other co-morbidities, physical activity, or smoking [45].

According to another study, we found a significant association between HER2- and obesity [46]. Nonetheless, our sample did not show a high BMI related to K167 [46].

Many studies find obesity to be related to poor breast cancer outcomes [28,30,31,34]. However, survivorship depends on tumor subtype, and characteristics and obesity are more related to mortality in HER2+ breast cancer [32-34]. Besides, obesity could be favorable for the response to immune checkpoint inhibitors in different tumors by the role of leptin and other adipokines [29]. Most of our patients with obesity were HER2-, which could explain why we did not find an association between obesity and mortality in our sample.

Some studies have reported on body fat distribution concerning breast cancer prognosis, with suggestions of increased breast cancer mortality risk with android body fat distribution defined as the high waist: Hip ratio or as high supra iliac: Thigh ratio [47,48]. Unfortunately, we have not been able to access this parameter in our study.

Obese breast cancer patients are at increased risk for morbidities, including surgical wound complications, lymphoedema and possibly, congestive heart failure if treated with doxorubicin [49]. Obesity may also increase the risk of developing endometrial cancer among women with breast cancer treated with tamoxifen [50]. Obesity increases the risk of several cancers in addition to breast and endometrium, including kidney, esophageal adenocarcinoma, colon and others [50]. Finally, overweight or obese breast cancer survivors may suffer from obesity-related co-morbidities, including type II diabetes, hypertension, CVD, osteoarthritis, and pulmonary disease [51,52].

Several studies have investigated interactions between overweight/obesity and adjuvant therapy effectiveness. A National Surgical Adjuvant Breast and Bowel Project analysis of 3,385 clinical trial patients from a randomized, placebo-controlled trial evaluating tamoxifen for lymph node-negative, estrogen receptor-positive breast cancer found that obese women benefited from tamoxifen therapy as much as lighter weight women [53]. Compared with normal-weight women, however, obese women had more significant all-cause mortality and non-breast cancer mortality. Several studies have found evidence that obesity reduces the effectiveness of some, but not all, aromatase inhibitors [34]. In our data, the prognosis of patients with obesity did not differ from without obesity.

We have used the BMI at diagnosis in our study, as the weight can vary during the treatment; the best is to have both initial and at the end weight. But a meta-analysis showed that obesity is associated with poorer overall and breast cancer survival in pre-and postmenopausal breast cancer, regardless of when BMI is ascertained. Being overweight is also related to a higher risk of mortality [45].

Our results should be interpreted considering study limitations and strengths. Although our sample has a great number of patients in a significant period of follow-up, we did not have weight and height for all of them, waist: Hip ratio, neither leptin, glucose, nor adipokines serum levels. In 24 years of follow-up, some details were lost or were not considered essential to be stored in the past. Nevertheless, strength of this study is the fact that the analysis is based on an extended follow-up, the first one with this number of patients and years in Brazil in which we evaluated obesity in breast cancer patients, compared to the general population, and their outcomes.

Conclusion

Obesity is a worldwide pandemic associated with several types of cancer, such as breast cancer. We found a high prevalence of obesity, more than in the general Brazilian women population, in breast cancer patients.

Our patients with obesity were older, had high prevalence lower frequencies of luminal B and HER2 subtypes than non-obese women, and their survivorship was not different from non-patients with obesity. Besides, patients with obesity had more infections after surgery. Obesity and surgical complications were significant for HER2+, Negative triple, and HER2+ Hybrid.

Obesity is a significant risk factor in breast cancer and its surgical treatment, and these patients must be evaluated carefully by a multidisciplinary oncology team.

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