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Overall and disease-free survival in overweight/obesity women at diagnosis of breast cancer: A single-center observational study

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Abstract

Introduction: The objective of the present study was to evaluate the clinical, pathological, and histological characteristics of tumors and their associations with recurrence, metastasis, and prognosis in terms of overall and disease-free survival in overweight or obese patients at the time of diagnosis.

Materials and methods: A descriptive, longitudinal, retrospective study was conducted at a reference cancer center in Medellin. Information was collected from patients older than 18 years of age with early or advanced infiltrating breast cancer between 2012 and 2017 who had a BMI ≥ 25 kg/m2 at the time of diagnosis. Median survival rates were calculated using Kaplan–Meier curves, and differences were determined using the log-rank test.

Results: Information from 1,349 patients was analyzed. All-cause mortality was 13.6% and increased proportionally with BMI (HR = 1.03, CI 1.0-1.05). A total of 12.6% of the recurrences were identified, and the risk with increasing BMI was not significantly different (HR =1.02, CI 0.99 - 1.05). Patient characteristics such as poor tumor differentiation, lymphovascular invasion, and tumor stage were univariately associated with increased mortality.

Conclusion: Positive and independent associations were demonstrated between high BMI and mortality and between high BMI and the risk of recurrence in patients with breast cancer. In addition, there was an association between aggressive tumor phenotypes and worse prognostic characteristics. Lifestyle modifications and multidisciplinary management should be considered strategies for impacting these outcomes.

Keywords:

MeSH: Breast Neoplasms, Obesity, Overweight, Body Mass Index, Survival, Recurrence

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Introduction

The prevalence of breast cancer has increased significantly recently, positioning itself, according to the World Health Organization (WHO), as the most common neoplasm worldwide, with approximately 2.2 million cases by 2020 [1]. The prevalence of certain associated risk factors, such as obesity and overweight, has also increased considerably; in 2016, the global

prevalence of these conditions in the adult population was estimated to be 39% and 13%, respectively [2]. The literature suggests that a high BMI is a prevalent finding among patients diagnosed with breast cancer [3, 4] and is associated with an increased risk of developing neoplasia [5, 6]. Similarly, in addition to other populations and clinical factors, BMI could influence intrinsic tumor characteristics or even impact outcomes such as death and recurrence.

A linear association between BMI and the risk of lymph node metastasis has been described for tumor characteristics [7]. It has also been associated with developing aggressive tumor phenotypes, increased tumor size, cell proliferation, and vascular infiltration [8 - 10]; however, other studies have not shown such a relationship [11, 12]. Genetic and epigenetic mutations within each molecular subtype of breast cancer confer variability and could explain the heterogeneity observed even within the same group [13]. On the other hand, one of the clinical factors with the most diverse results associated with obesity or overweight is the menopausal state. Although postmenopausal status has been linked to a greater likelihood of developing breast cancer [14], other studies have also shown an association with premenopausal status [14, 17].

An increase in total mortality [9, 18], as well as in specific mortality among this group of patients [19 – 22], is a link between high BMI and breast cancer incidence. A decrease in recurrence time has even been described [9]. A tendency to develop increased metastasis has been observed, as was the case for a cohort that included 12,999 patients, in which an increase in the presentation of patients with breast cancer and breast metastasis was found the novo, as well as more aggressive clinical characteristics [23]. In contrast, the predictive value of factors such as menopausal status, hormone receptor levels, and other factors influencing BMI is still controversial.

Therefore, the main objective of the present study was to evaluate the overall and disease-free survival (DFS) rates of female patients who were obese or overweight at the time of breast cancer diagnosis. Additionally, we wish to characterize the study population clinically and sociodemographically, as well as to determine whether they presented higher-risk tumor characteristics and how these aspects are related to the time to death and relapse.

Materials and methods

Study design

This research was observational, descriptive, and longitudinal and included follow-up of a cohort. The source was retrospective.

Scenery

The study was carried out at the mastology service of the Las Américas-Auna Cancer Institute, Medellín, Antioquia, Colombia. The study period was from January 1, 2012, to December 31, 2017.

Participants

All medical records of women with infiltrating breast cancer; with stage I, II, or III disease (American Joint Committee on Cancer Staging Manual [AJCC]; and with reports of estrogen (ER) and progestin hormone receptor (PR) expression were included, considering the positive values > 1% by immunohistochemistry or according to the Allred scale and Her 2 result (positive ≥ 2.0 by fluorescence in situ hybridization, immunohistochemistry (IHC) (3+) or FISH). Patients who were overweight or obese were selected. The patients were divided into four groups according to the following criteria: overweight and grade I, II, and III obesity. Patients were excluded if they had a breast cancer registry in situ, exclusively palliative treatment, a personal history of another cancer (except skin cancer), a clinical registry with less than 25% of the data available, or a follow-up of less than six months, since the diagnosis of his illness.

Universe and sample

The sample was nonprobabilistic since all incidental cases from the study period were included.

Variables

Demographic variables such as age were recorded. Clinical characteristics: menopause. Histological type, Ki67 marker presence, and molecular subtype. Clinical stage, type of treatment, and overall survival.

Method

Medical records were observed, and data were collected from the electronic records. The clinical variables, age at diagnosis, menopausal status, and body mass index (BMI) were obtained from the clinical history. The BMI was calculated as the ratio of weight in kilograms to height in meters squared and was classified according to the WHO as overweight 25 kg/m²-29.9 kg/m2 and Grade I obesity 30 kg/m²-34.9 kg/m2. m², grade II obesity 35 kg/m²-39.9 kg/m² and grade III obesity 40 kg/m² and above.

Tumor histological characteristics such as histological pattern, histological grade, Ki67 index, estrogen (ER) and progestin receptor (PR) status, HER2 expression, and molecular subtype classification were obtained from the pathology report. The following classifications were used to define the molecular subtypes: "Luminal A" (ER and RP positive, Ki67 ≤10, Her2 negative), "Luminal B" (ER and RP positive, Ki67 >10, Her2 negative), "Luminal B Her two positive" (RE and RP positive, Ki67 >10, Her 2 positive), "Her 2 positive" (RE and RP negative, Her2 positive) and "Triple negative" (RE, RP and Her 2 negative). The histological grade was determined with the Nottingham classification. Estrogen hormone receptor (ER) and progestogen receptor (PR) expression was considered positive if the value was > 1%, as determined by immunohistochemistry or according to the Allred scale. A Her 2 result was considered positive if it was ≥ 2.0 according to fluorescence in situ hybridization, immunohistochemistry (IHC) (3+), or FISH. The variables lymphovascular invasion, positive nodes, and tumor stage was obtained from the medical history records. Disease staging was performed following the "AJCC Cancer Staging Manual, 8th Ed."

Disease-free survival was defined as the time from the time of treatment termination to the time of local or systemic relapse. Overall survival was measured as the time from the moment of diagnosis to the date of death, as complete data, or the date of last consultation, as censored data, for which the dates of death were reviewed in the Adres registry [24], both of which were obtained from the clinical history.

Statistical analysis

For the quantitative variables, averages and dispersion measures were obtained; for the qualitative variables, percentages were calculated. The averages were compared with the Student's t-test and the Mann–Whitney U test, as applicable. Group comparisons between categorical variables were performed with chi-square and Fisher tests; ANOVA and the Kruskal–Wallis test were used for continuous variables. Median survival was calculated using Kaplan–Meier curves, and the log-rank test was used to calculate differences according to covariates. The associations between time and covariates were calculated using Cox regression. A P value less than 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Study participants

The information of 1,349 patients who met the inclusion criteria was analyzed over five years of follow-up.

Patient general characteristics

The average age at diagnosis was 56.5 ± 12.3 years. Postmenopausal status was predominant in all categories, with a higher prevalence among patients with Grade II obesity (83.9%).

Tumor characteristics

Regarding tumor characteristics, the predominant histological type in all groups was invasive ductal carcinoma, which was more common in patients with Grade III obesity (97.1%) than in overweight patients (88%). In all categories, a high histological grade was predominant; in the group of patients with Grade III obesity, the histological grade was dominant (65.7%). Among all the categories, estrogen and progestin receptor levels were greater than 70%, with no significant differences between the groups.

Table 1. Clinical and histopathological characteristics regarding high BMI.

	Overweight n=797	Grade I obesity n= 380	Grade II obesity n=137	Grade III obesity n=35	*P*-Value
Age	55.6±12.8	57.6±11.3	58.8±11.3	57.3 ±11.6	0.006
Menopause	510 (64%)	293 (77%)	115 (83.9%)	26 (74.3%)	<0.0001
Histological Pattern					
Ductal	701 (88)	349 (91.8)	117 (85.4)	34 (97.1)	0.146
Lobular	62 (7.8)	20 (5.3)	11 (8.0)	0 (0)	
Other*	34 (4.3)	11 (2.9)	9 (6.6)	1 (2.9)	
Histological grade					
Low	115 (19.4)	68 (17.9)	26 (19)	2 (5.7)	0.096
Moderate	324 (40.7)	147 (38.7)	56 (40.9)	10 (28.6)	
High	318 (49.9)	165 (43.4)	55 (40.1)	23 (65.7)	
Ki Index 67 (%)					
< 10	99 (59.6)	42 (25.3)	22 (13.3)	3 (1.8)	0.450
≥10	506 (60.2)	236 (28.1)	79 (9.4)	20 (2.4)	
Rec- estrogens	643 (80.7)	317 (83.4)	110 (80.3)	29 (88.29)	0.913
Rec-progesterone	578 (72.7)	292 (76.8)	109 (79.6)	27 (77.1)	0.22
Molecular subtype					
Luminal A	214 (26.9)	108 (28.4)	37 (27)	7 (20)	0.724
Luminal B Her2+	99 (12.5)	36 (9.5)	12 (8.8)	7 (20)	
Luminal B Her2-	346 (43.5)	178 (46.8)	64 (46.7)	16 (45.7)	
Her2+	42 (5.3)	17 (4.5)	5 (3.6)	2 (5.7)	
Triple-negative	94 (11.8)	41 (10.8)	19 (13.9)	3 (8.6)	
Lympho-vasc invasion	125 (15.7)	54 (14.2)	28 (20.4)	5 (14.3)	0.39
Positive lymph nodes	3.4 ±5.1	3.5 ±5.6	4.8 ±6.5	6.8 ±11.34	0.049
Stadium					
Early	467 (59.1)	215 (27.2)	86 (10.9)	22 (2.8)	0.597
Locally Advanced	330 (59)	165 (29.5)	51 (9.1)	13 (2.3)	
Chemotherapy					
Neoadjuvant	327 (62.2)	144 (27.4)	40 (7.6)	15 (2.9)	0.150
Adjuvant	245 (57.6)	122 (28.7)	49 (11.5)	9 (2.2)	
Hormonotherapy					

Yes	622 (59.2)	299 (28.4)	104 (9.9)	26 (2.5)	0.867
No	175 (58.7)	81 (27.2)	33 (11.1)	9 (3.0)	

Rec: Receptors.

No statistically significant differences were observed between the molecular subtypes when comparing patients in each category with those in the high-BMI group (*P* >0.05). Lymphovascular invasion was similar in all groups; in the overweight subgroup, it occurred in 15.7%. Lymph node involvement was directly proportional to high BMI, while the overweight group had an average of 3.4 ± 5.1 positive nodes; the grade III obesity group had 6.8 ± 11.34 nodes. The early and locally advanced stages were predominant in the group of overweight patients, with a prevalence of 59.1% and 59%, respectively.

Overall survival

By the end of the follow-up period (81.65 ± 27.17 months), 184 patients had died from all causes, corresponding to 13.6% of the total participants. A trend toward decreasing survival was observed as BMI increased (Figure 1).

According to the univariate analysis, a statistically significant tendency toward greater mortality proportional to an increase in BMI was evident (HR=1.03, CI 1.0-1.05). All tumor characteristics, such as high histological grade (HR=4.32 CI 2.75-6.08), lymphovascular invasion (HR=1.85 CI 1.63-2.10), and tumor stage (HR=3.67, CI 2.83-4.75), were associated with increased mortality in a univariate analysis. However, menopausal status was an exception (HR=0.83 CI=0.63-1.90). According to the multivariate model, the relationship between BMI and mortality was the same (HR=1.025, CI=1.01-1.05). Except for estrogen receptor positivity, all clinical characteristics retained statistical significance, and menopausal status became associated with the risk of death according to the multivariate model (Table 2).

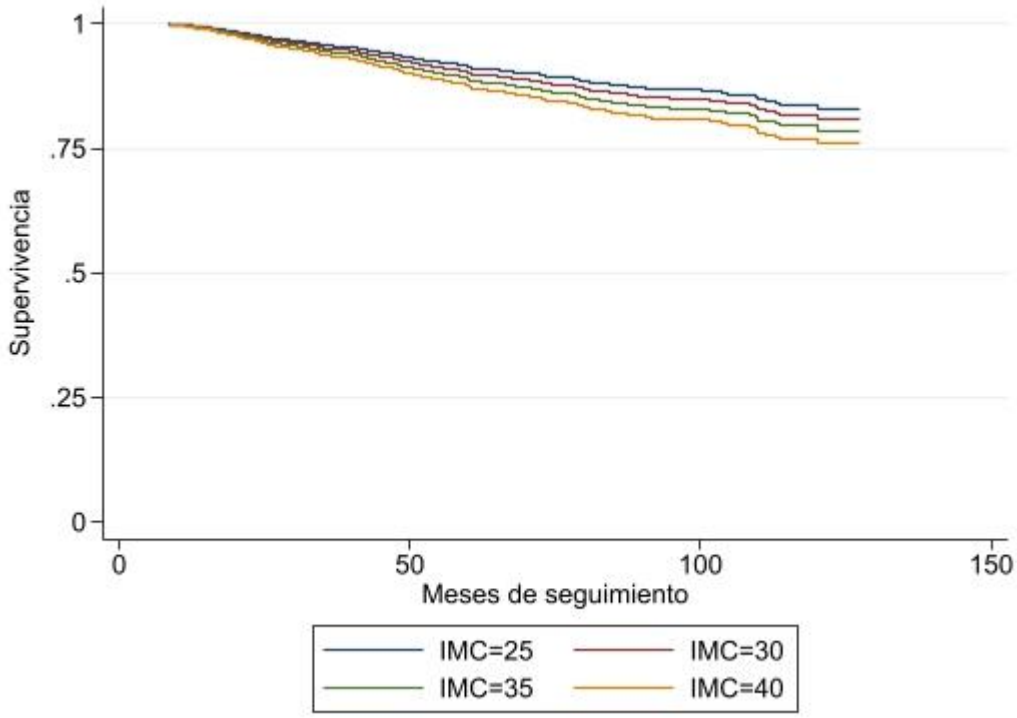

Figure 1. Overall survival adjusted by BMI categories

Disease-free survival

During the study, 171 (12.6%) disease recurrences were identified—12.9% in overweight patients, 11.1% in participants with grade I obesity, 12.4% in those with grade II obesity, and 25.7% in those with grade III obesity—showing a linear trend in the risk of recurrence related to BMI only among the group of obese patients. However, the risk of recurrence was not significantly different (HR=1.02, CI=0.99-1.05).

Table 2. Factors related to time to death.

Characteristic	Univariate		Multivariate	
	RH 95% (CI)	*P*	RH 95% (CI)	*P*
Body mass index (per one point increment)	1.03 (1.0-1.05)	0.008	1.025 (1.01-1.05)	0.013
Menopausal status (yes/no)	0.831 (0.634-1.09)	0.181	0.715 (0.54-0.94)	0.014
Histological grade				
Good	ref		ref	
Moderate	1.78 (1.09-2.88)	0.001	1.68 (0.82-3.43)	<0.0001
Evil	4.32 (2.75-6.08)		3.13 (1.58-6.19)	
Rec-estrogens (+/negative)	0.425 (0.32-0.55)	0.001		
Rec-progesterone (+/negative)	0.685 (0.605-0.775)	0.001	0.781 (0.64-0.94)	0.011
Molecular subtype				
Luminal A	ref		ref	
Luminal B her2+	2.50 (1.54-4.06)		2.47 (1.52-4.04)	
Luminal B her2-	2.69 (1.84-3.92)	0.001	2.47 (1.69-3.61)	<0.0001
Her2+	3.02 (1.64-5.56)		2.05 (1.03-4.08)	
Triple-negative	5.52 (3.60-8.47)		3.86 (2.23-6.67)	
Lymphovascular invasion	1.85 (1.63-2.10)	0.001	1.58 (1.38-1.81)	<0.0001
Positive lymph nodes	1.08 (1.06-1.09)	0.001	1.07 (1.05-1.08)	<0.0001
Stage (locally advanced/early)	3.67 (2.83-4.75)	0.001	2.53 (1.92-3.34)	0.043

Table 3. Factors related to time to recurrence.

Variable	Univariate		Multivariate	
	RH 95% (CI)	*P*	RH 95% (CI)	*P*
BMI (per one point increase)	1.02 (0.99-1.05)	0.114		
Menopausal status (yes/no)	0.66 (0.48-0.90)	0.01		
Histological grade				
Good	ref		ref	
Moderate	1.54 (0.81-2.95)	<0.0001	1.56 (0.60-4.06)	0.018
Evil	5.13 (2.83-9.29)		3.04 (1.21-7.63)	
Rec-estrogens (+/negative)	0.56 (0.48-0.66)	<0.0001		
Rec-progesterone (+/negative)	0.60 (0.51-0.70)	<0.0001		
Molecular subtype				
Luminal A	ref			
Luminal B her2+	5.04 (2.50-10.13)	<0.0001		
Luminal B her2-	4.34 (2.36-7.97)			
Her2+	5.20 (2.25-12.06)			

Triple-negative	11.87 (6.28-22.44)			
Lymphovascular invasion	1.84 (1.57-2.15)	<0.0001	1.25 (1.01-1.53)	0.04
Positive lymph nodes	1.08 (1.06-1.10)	<0.0001	1.06 (1.04-1.08)	<0.0001
Stage (locally advanced/early)	4.85 (3.43-6.86)	<0.0001		

In a multivariate manner, only high histological grade (HR=3.01, CI 1.21-7.63), lymphovascular invasion (HR=1.25, CI 1.01-1.53), and having positive nodes (HR=1.06, CI 1.04-1.08) were associated with a decrease in recurrence time in these patients. In univariate and multivariate analyses, estrogen and progestin hormone receptor levels had inverse relationships with recurrence time (HR=0.56, CI=0.48-0.66 and HR=0.60, CI=0.51-0.70, respectively).

Discussion

In the present study, a statistically significant relationship was found between mortality and high BMI at the time of diagnosis of invasive breast cancer. This association was preserved both independently and in the multivariate analysis. The relationship described was found to be linear and directly proportional, with an increase in the risk of mortality (HR=1.03 CI 1.0-1.05) per point, independently. Some studies support the above [24, 25]; for example, a meta-analysis and systematic review published in 2018 that included 1017 patients with breast cancer who were divided into subgroups according to their BMI at the time of diagnosis concluded that a BMI in the range of obesity or overweight was associated with a reduction in overall and disease-free survival. Several mechanisms attempt to explain the described association; one proposes a greater tumor sensitivity to estrogens that could be increased in the context of overweight/obesity since circulating levels are increased due to increased aromatase [26]. It is also proposed that, in a state of inflammation due to obesity, tissue remodeling increases the apoptosis of adipocytes and promotes the presence of macrophages and other inflammatory cells in the tissue, which leads to the secretion of proinflammatory cytokines that contribute to resistance to insulin and ultimately leads to a low-grade but persistent inflammatory state [9].

According to the sociodemographic characteristics of the population, approximately 70% of the patients were menopausal, which is expected in patients with breast neoplasia [27, 28]. Ductal carcinoma was the predominant histological type; in the Grade III obesity group, it reached a prevalence of 97.1%. Other studies have described a general prevalence close to 75% [29], which could suggest an association with high BMI. It is striking that in all categories, a poorly differentiated histological grade is prevalent, which could intrinsically depend on the tumor. However, in the context of obesity, the possibility has also been raised that physical examination of the breast is less sensitive than usual examination and becomes more difficult with the volume of the breast, ultimately delaying the diagnosis and finding more dedifferentiated tumors. Similarly, the increase in the incidence of positive nodes in a directly proportional manner with high BMI is interesting. The above findings suggest a close relationship between the number of nodes and overweight/obesity; therefore, these nodes theoretically confer greater tumor dissemination capacity; other studies have suggested the same association [7, 8].

Among the participants, an increase in mortality was found in women who were overweight or obese independently when lymphovascular invasion, positive nodes, poorly differentiated histological grade, and advanced stage were present. The above could support the hypothesis that a predisposition to develop aggressive tumor phenotypes in the presence of factors and pathophysiological pathways is favored by an increase in BMI. According to this, it has been proposed that chronic inflammation leads to cancer development, progression, resistance to treatment, and metastatic dissemination [30]. Insulin-like growth factor (IGF-1), TNF-α, IL6, leptin, and MCP-1 are some factors that promote inflammation and angiogenesis [31]. Likewise, it has been proposed that deregulating the PI3K/AKT/mTOR and RAS/RAF/MAPK pathways is responsible for increased proliferation [31]. For example, one

study found a linear relationship in which for every 1 kg/m^2 increase in BMI, the risk of lymph node metastasis increased by 0.89% [32]. Regarding disease-free survival, the phenotypic characteristics associated with a shorter recurrence time were a locally advanced stage, lymphovascular invasion, lymph node involvement, and high histological grade. These could be favored in a state of overweight/obesity and were independently associated.

According to the follow-up data of the cohort, the postmenopausal state was prevalent in all groups, a finding that, although it has been previously described [15, 33], is controversial since other studies have shown opposite results [18]; however, this could be explained by an increase in the expression of aromatase and, consequently, the availability of estrogen, increasing the risk of neoplasia [34].

Regarding the menopausal state outcomes, it was found that the postmenopausal state is a protective factor against mortality when there is a high BMI, compared to the premenopausal state, with a postmenopause/premenopause relationship (HR=0.831, CI 0.634-1.09), which was preserved in both the univariate and multivariate analysis. The relationship was held in the univariate analysis (HR=0.66, CI=0.48-0.90) but not in the multivariate analysis for recurrence time. A systematic review and meta-analysis of 173 studies revealed similar results between the two groups, with higher RRs in the premenopausal group; these findings are identical to the results of the present study; however, they did not find a statistically significant association [35]. In contrast, other studies have linked increased mortality in premenopausal patients or have found no association [6].

Although a prevalence of tumors with positive estrogen and progestogen receptor results of 81.4% and 74.6%, respectively, was observed among the participants, these findings were not associated with shorter overall or disease-free survival times [HR=0.425, CI=0.32-0.55] and [HR=0.685, CI=0.605-0.775], respectively; these findings have been described by other studies [8] and could be due to therapies directed against hormone receptors, which are vital options due to their favorable response for the treatment of patients with breast cancer. Regarding tumors with positive HER2 receptor expression, a prevalence similar to that of the general population (16.2%) was found (approximately 15%) [29], increasing mortality independently with a statistically significant relationship (HR=3.02, CI 1.64-5.56) and likewise increasing the risk of recurrence. On the other hand, the triple negative molecular subtype among the study participants had a prevalence of 2.1%, and it was also observed that it is associated with a high risk of mortality that is more than double that of any of the other clinical and tumor characteristics (HR=5.52). , IC 3.60-8.47).

The main strength of the present study is the analysis of multiple variables related to BMI over a long period (5 years). The above findings imply that the data were collected at various times and that interindividual or intergroup differences could be analyzed to determine the proposed hypothesis sequentially and temporally. However, there may also be multiple disadvantages when collecting data during the proposed period, such as a loss to follow-up.

On the other hand, the study cohort is unique. Since the same population is not available for comparison, statistics on how much the sample size increases compared to that of participants with average weight are limited. For reasons of access and ethical considerations, mortality from any cause was included; however, breast cancer-specific mortality was unknown. Additionally, although there are factors intrinsically associated with obesity and overweight that could have biological plausibility to support the hypothesis of increased mortality associated with high BMI, it should be considered that the same physical build could reduce the sensitivity of medical and physical examination and breast self-examination, thus delaying diagnosis and being associated with a longer duration of illness and, therefore, more advanced tumor characteristics.

Finally, the limitations of the present research must be taken into account. The information collected comes from secondary sources, making it impossible to recover information on some variables. Likewise, the information was collected only from a reference cancer center, limiting the extrapolation of the data to the general population due to marked differences in the sample. The sample used for this study is specific to this center and cannot be taken up by a larger population.

Conclusions

The study demonstrated a positive, directly proportional, and independent association between high BMI and mortality and risk of recurrence in patients with breast cancer. Furthermore, it was associated with aggressive tumor phenotypes and worse prognostic features, such as lymphovascular invasion, positive nodes, and advanced tumor stages. Lifestyle modifications, as well as multidisciplinary management of patients at risk of developing breast cancer during treatment, are interventions that can improve outcomes.

Abbreviations

HR: Hazard ratio.
BMI: body mass index.

Administrative information

Additional Files

None declared by the authors.

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Author contributions

Natalia Arturo Restrepo: conceptualization, validation, visualization, methodology, project administration, writing: review and editing.
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Paulina Rada González: conceptualization, data curation, formal analysis, acquisition of funds, research, resources, software.
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Elsa María Vásquez-Trespalacios: conceptualization, data curation, formal analysis, acquisition of funds, research, resources, and software.

All the authors read and approved the final version of the manuscript.

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Availability of data and materials
The data are available upon request to the corresponding author. No other materials were reported.

Statements

Ethics committee approval
The study protocol was approved by the institutional human research ethics committee of the CES University and the Colombian Institute of Cancerology-Clínica las Américas, with code 45-2021-C. This was a retrospective study without intervention in patient care, so informed consent was unnecessary. The anonymity and confidentiality of the data were guaranteed.

Consent for publication
Patient-specific images, MRIs, or CT studies were not available when they were not published.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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