Original Study

Breast Cancer: Metastasis, Molecular Subtypes, and Overweight and Obesity in Veracruz, Mexico

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Abstract

The high prevalence of both obesity and breast cancer has had a major impact in Mexico. We performed a cross-sectional study with a considerably larger sample size. The results showed that obese and morbidly obese women are affected by more aggressive subtypes and concomitant pathologic features. These findings reinforce the hypothesis of a greater incidence of the triple-negative type with premenopause.

Introduction: We assessed the association between overweight, obesity, and morbid obesity with the incidence of the most aggressive breast cancer subtypes in women. **Methods and Materials:** A cross-sectional study was performed. We conducted a record review to identify the following aspects: body mass index, sociodemographic features, tumor characteristics, and reproductive and molecular aspects. Descriptive statistics and univariate analysis were performed to identify the association between the molecular subtypes and the study variables. In addition, we used multivariate analysis to identify the association between obesity and the presence of metastatic lymph nodes. **Results:** We included 1446 women with an average age of 52.5 ± 12.1 years. Of the 1446 patients, 47% were premenopausal and 75% were overweight. Univariate analysis indicated a statistically significant association between obesity and advanced disease stage, as well as nulliparity and multiparity. Similar results were found for women with morbid obesity. Model 1 of the multivariate analysis showed an association between the presence of metastatic lymph nodes and obesity (odds ratio [OR], 1.6; $P = .008$) and histologic grade 2 or 3 (OR, 2.4; $P = .003$). Using model 2, an association was identified between an advanced disease stage and 2 factors: morbid obesity (OR, 1.9; $P = .02$) and positive human epidermal growth factor receptor 2 (OR, 1.8; $P = .045$). **Conclusion:** We found that obesity is associated with the more advanced stages of breast cancer. Further studies are needed to evaluate the role of obesity in breast cancer progression in women.

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Keywords: Body mass index, Luminal, Metastatic lymph nodes, Reproductive factors, Triple negative

Introduction

The high prevalence of both obesity and breast cancer (BC) has had an alarming effect in Mexico.[1,2] The excess of adipose tissue might promote the advent of more aggressive tumors, recurrence, and a greater adverse survival ratio associated with greater mortality.[3-7]

The reproductive factors (eg, menarche, parity, nulliparity, and menopause) have had a greater effect in obese women owing to the hormonal pathways.[4,5,8-11] The distinct molecular subtypes result in marked differences depending on the ethnic group.[12-14] Hispanic women have more favorable estrogen profiles, and several therapeutic options are available for them.[12,13] Within the population of premenopausal women with the worst prognosis, several cases of triple-negative breast cancer with overexpression of human epidermal growth factor receptor 2 (HER2) have been observed.[12,14-17]

We sought to determine the association among the molecular BC subtypes within a population of overweight women, who were either pre- or postmenopausal.

Materials and Methods

We performed a cross-sectional study of women with a diagnosis of BC enrolled from 2012 to 2016 (1473 cases). Those patients with height or weight data missing and without immunohistochemical tests were excluded. Thus, 1446 cases were included in the

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Table 1 Clinical and Histologic Characteristics Stratified by Menopausal Status

Characteristic	Premenopausal (n = 676; 46.7%)	Postmenopausal (n = 770; 53.3%)	*P* Value[a]
BMI[b]			.338
Normal weight	181 (26.8)	176 (22.9)	
Overweight	257 (38.0)	317 (41.2)	
Obesity	164 (24.3)	189 (24.5)	
Morbid obesity	74 (10.9)	88 (11.4)	
Associated comorbidities			.001
Yes	111 (16.44)	319 (41.48)	
No	564 (83.56)	450 (58.52)	
Metastatic lymph nodes			.007
Yes	313 (46.79)	302 (39.68)	
No	356 (53.21)	459 (60.32)	
Metastasis			.412
Yes	85 (12.71)	108 (14.19)	
No	584 (87.29)	653 (85.81)	
Histologic grade			.205
1	93 (14.88)	128 (17.85)	
2-3	532 (85.12)	589 (82.15)	
Clinical stage			.001
Early	238 (36.39)	352 (46.75)	
Advanced	416 (63.61)	401 (53.25)	
Luminal			.001
Luminal A	236 (40.48)	312 (47.42)	
Luminal B	110 (18.87)	153 (23.25)	
HER2-like	71 (12.18)	67 (10.18)	
Triple negative	166 (28.47)	126 (19.15)	

Abbreviations: BMI = body mass index; HER2 = human epidermal growth factor receptor 2.
[a]Using χ^2 test for difference of proportions.
[b]Overweight, > 25 kg/m^2; obesity, > 30 kg/m^2; and morbid obesity, > 35 kg/m^2.

present study. The clinical and pathologic data were obtained after reviewing the medical records. The information obtained at baseline included tumor demographic data and reproductive and family history, including smoking and alcohol consumption. The State Cancer Center (*Centro Estatal de Cancerología*) research ethics committee approved the present study.

Defining Variables

Overweight and obesity were defined using the body mass index (BMI) classification proposed by the World Health Organization.[18] A patient was considered to be postmenopausal by the absence of menstruation for ≥ 12 months. Those patients aged < 45 years who had experienced their last menstrual period ≤ 3 months earlier were considered premenopausal.

Tumor Features

The predominant tumor morphology was infiltrating ductal carcinoma. The histologic grade was assessed using the standard institutional protocols (with consideration of the differentiation status: well, moderately, and poorly differentiated and unknown). Regarding the molecular BC subtypes, positive estrogen receptor and progesterone receptor cases were defined as ≥ 1% positively stained cells for estrogen receptors using immunohistochemistry. HER2$^+$ cells were defined by a 3+ score, intensity > 10 positive cells, 2+ weakness. These criteria were in accordance with the 2015 Colima Declaration of Consensus.[19]

Statistical Analysis

Patients were categorized by their menstrual status, as summarized using descriptive statistics. To perform a comparison of the nominal variables, we used either the χ^2 test or the Fisher exact test. A multivariate binary logistic regression analysis was conducted to identify those factors associated with the presence of metastatic lymph nodes (dependent variable). The main independent variable for model 1 was obesity (BMI > 30 kg/m^2), and the main independent variable for model 2 was morbid obesity (BMI > 35 kg/m^2). Both models included the following covariables: age, type of population (urban vs. rural), history of diabetes mellitus and hypertension (yes vs. no), estrogen or progesterone receptor status (positive vs. negative), HER2 status (positive vs. negative),

Table 2 Demographic, Reproductive, and Clinical Factors Related to Molecular Subtypes of Breast Cancer

	Molecular Subtype						
		Luminal B		HER2$^+$		Triple Negative	
Variable	Luminal A, n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Age group, y							
≤ 40	75 (13.7)	26 (9.9)	1.44 (0.90-2.31)	25 (18.1)	1.30 (0.90-1.90)	63 (21.5)	1.40 (1.13-1.73)
> 40	474 (86.3)	237 (90.1)	1 (Ref)	113 (81.9)	1 (Ref)	230 (78.5)	1 (Ref)
Menopausal status							
Before	236 (43.1)	110 (41.8)	1.05 (0.78-1.41)	71 (51.4)	1.31 (0.97-1.76)	166 (56.8)	1.43 (1.19-1.73)
After	312 (56.9)	153 (58.2)	1 (Ref)	67 (48.6)	1 (Ref)	126 (43.2)	1 (Ref)
Overweight							
Yes	225 (63.7)	100 (62.1)	1.05 (0.81-1.37)	52 (59.8)	1.14 (0.78-1.68)	111 (60.9)	1.08 (0.85-1.37)
No	128 (36.3)	61 (37.9)	1 (Ref)	35 (40.2)	1 (Ref)	71 (39.1)	1 (Ref)
Obese							
Yes	128 (50.0)	70 (53.4)	1.05 (0.91-1.21)	37 (51.4)	1.01 (0.90-1.14)	73 (50.7)	1.03 (0.68-1.55)
No	128 (50.0)	61 (46.6)	1 (Ref)	35 (48.6)	1 (Ref)	71 (49.3)	1 (Ref)
Morbidly obese							
Yes	62 (32.6)	28 (31.5)	1.04 (0.72-1.50)	11 (23.9)	1.42 (0.77-2.65)	31 (30.4)	1.07 (0.76-1.51)
No	128 (67.4)	61 (68.5)	1 (Ref)	35 (76.1)	1 (Ref)	71 (69.6)	1 (Ref)
Metastatic lymph nodes							
Yes	243 (44.6)	115 (43.7)	0.97 (0.72-1.30)	63 (45.7)	1.01 (0.94-1.09)	124 (42.9)	0.94 (0.70-1.25)
No	303 (55.4)	148 (56.3)	1 (Ref)	75 (54.3)	1 (Ref)	165 (57.1)	1 (Ref)
Metastasis							
Yes	57 (10.4)	47 (17.9)	1.87 (1.23-2.84)	22 (15.9)	1.63 (0.96-2.78)	38 (13.1)	1.10 (0.93-1.31)
No	491 (89.6)	216 (82.1)	1 (Ref)	116 (84.1)	1 (Ref)	252 (86.9)	1 (Ref)
Clinical stage							
Early	276 (51.5)	94 (36.7)	1 (Ref)	46 (33.8)	1 (Ref)	93 (32.6)	1 (Ref)
Advanced	260 (48.5)	162 (63.3)	1.21 (1.10-1.33)	90 (66.2)	1.15 (1.07-1.25)	192 (67.4)	1.30 (1.18-1.44)

Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; OR = odds ratio; Ref = reference.

histologic grade (2 or 3 vs. 1), and educational level (less than vs. more than elementary). An adjustment was made in each model using the conditional forward method. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to identify any associations between the variables. A P value $\leq .05$ was considered to indicate statistical significance. The analysis was performed using the SPSS statistics software, version 23.0 (IBM Corp., Armonk, NY).

Results

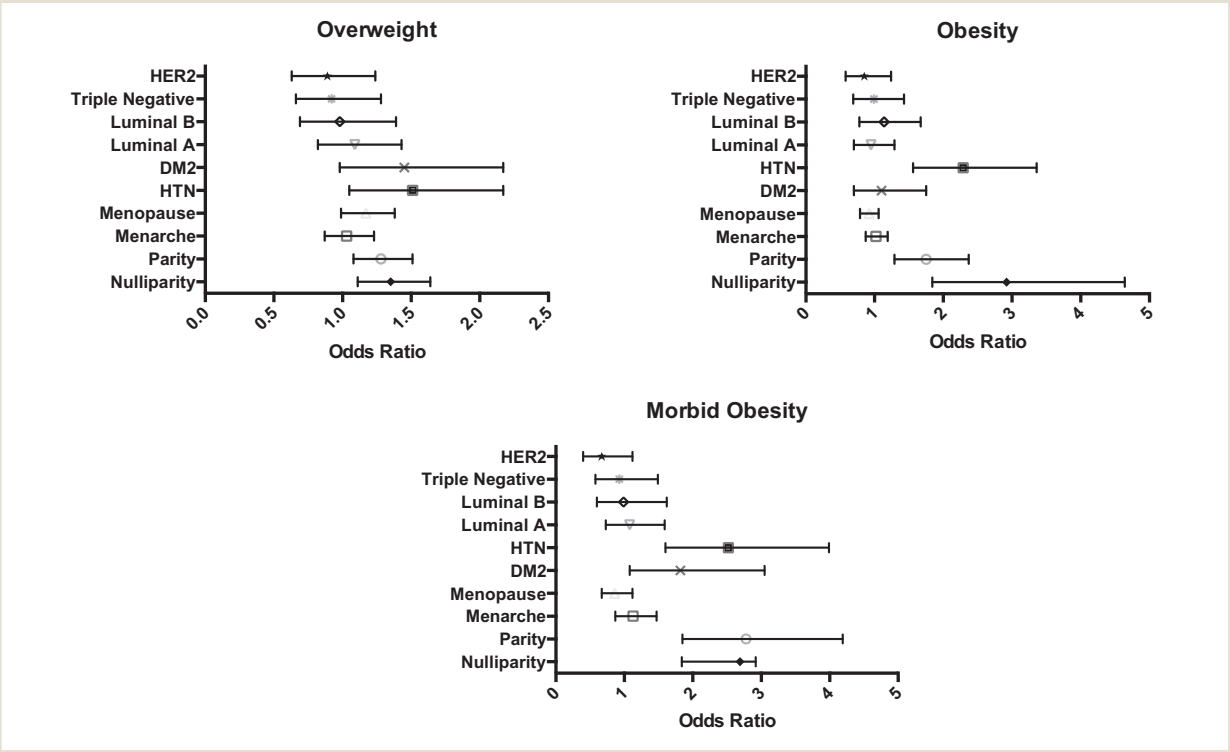
The mean age at diagnosis was 52.5 ± 12.1 years. Of the 1446 patients, 53.3% were postmenopausal, 75% were overweight, obese, or morbidly obese, and 58% had advanced-stage BC. The reproductive features (pre- and postmenopausal, early menarche, nulliparous, multiparous) were compared, and ≥3 full-term birth and abortions yielded statistically significant differences ($P = .001$). These differences were also observed for premenopausal women and the presence of metastatic lymph nodes ($P = .007$), high histologic grade, and more advanced clinical stages ($P = .001$; Table 1).

The following BC variables were significantly associated with aggressive molecular subtypes (TNBC): age < 40 years (premenopausal) and ≥ 3 full-term births. Tobacco consumption increased the probability of the molecular TNBC phenotype two- to threefold. Similarly, the presence of other comorbidities such as hypertension was identified. Statistical significance was observed for all molecular subtypes in advanced stages characterized by histologic grade 2 or 3 (Table 2).

The relationship among the different variables (clinical, histopathologic, and reproductive) and the independent variable (BMI) showed a positive association with the presence of metastatic lymph nodes, obesity (OR, 1.55; 95% CI, 1.14-2.10), and morbid obesity (OR, 1.51; 95% CI, 1.03-2.22). Of the reproductive variables included in the present study, nulliparity was associated with both obesity (OR, 2.2; 95% CI, 1.84-4.64) and morbid obesity (OR, 2.69; 95% CI, 1.46-4.94). Similarly, ≥ 3 full-term births was significantly related in obese and morbidly obese subjects compared with nulliparous obese (OR, 1.75; 95% CI, 1.29-2.37) and morbidly obese (OR, 2.78; 95% CI, 1.85-4.19) subjects, respectively. Likewise, hypertension was significantly associated with both morbid obesity (OR, 2.52; 95% CI, 1.60-3.99) and diabetes (OR, 1.82; 95% CI, 1.08-3.05) compared with women with a BMI < 25 kg/m^2 (Figure 1).

The adjusted logistic regression analysis for the presence of metastatic lymph nodes in model 1 showed a statistically significant

Figure 1 Reproductive Factors, Comorbidities and Molecular Subtypes Related to Breast Cancer According to the Body Mass Index (Overweight > 25 kg/m^2; Obesity > 30 kg/m^2; Morbid Obesity > 35kg/m2)



Abbreviations: DM2 = diabetes mellitus type 2; HTN = hypertension.

association between obesity (OR, 1.6; 95% CI, 1.1-2.4) and the presence of histologic grade 2 or 3 (OR, 2.4; 95% CI, 1.3-4.3). Additionally, the multivariate analysis model 2 showed significant differences between morbidly obese women and the HER2 subtype (Table 3).

Discussion

Overweight and obesity are common health issues in Mexico, and their prevalence has been increasing worldwide.[1-3] An association between advanced BC and obesity (OR, 1.6; 95% CI, 1.1-2.4) and morbid obesity (OR, 1.9; 95% CI, 1.1-3.1) was observed in the present study. This finding is in contrast to the results from other studies in which either a positive association was found or opposite findings were observed.[20,21] Our study cohort was characterized by a high percentage of obese women and by an ineffective access to health care, which as correlated with a low socioeconomic and educational level. When the association between obese and morbidly obese women with BC was assessed after stratification by menopausal status. Both groups showed unfavorable molecular subtypes.

The present data suggest a twofold increased probability of the presence of histologic grade 2 or 3 tumors. This is in agreement with the results reported by other investigators, who reported a significant histologic grade more frequently with stage III-IV disease associated with visceral metastases in obese women.[22,23]

If a correlation is to be established between tumor features and the more aggressive subtypes, it is important to emphasize that the findings observed in our study reinforce the hypothesis that proposed a greater incidence of the TNBC subtype among premenopausal patients ($P = .001$).[12] Similarly, menopause and, in particular, premenopause, were found to be a statistically significant factor contributing to TNBC development (OR, 1.43; 95% CI, 1.19-1.73). The latter finding is contradictory to the greater incidence of the TNBC subtype among postmenopausal patients.[14] Some reports have suggested that the BMI is an independent factor in patients with BC,[24] and other studies have reported an increased risk associated with a high BMI. This relationship appears to be even more significant among younger postmenopausal women.[25]

The results obtained from the multivariate analysis also showed a significant association with HER2$^+$ disease. This is consistent with the international data reporting enhanced aggressiveness in tumors harboring the HER2 genotype.[12,13,15,16] Although other results have been positively associated with all luminal subtypes,[26] our data are in agreement with the findings from other investigators who reported similar results in Hispanic populations.[12,15,27]

Recent studies on the reproductive factors associated with BC risk have suggested a possible relationship with hormonal status changes.[15,27,28] Our results are in agreement with the increasing evidence between parity (≥ 3 full-term births) and a greater risk of the HER2$^+$ and TNBC subtypes. Paradoxically, in our study, the

Table 3 Multivariate Analysis of Factors Associated With Presence of Metastatic Lymph Nodes

Covariable	Model Without Adjustment		Model Adjustment[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1				
Obesity (BMI $\geq$ 30 kg/m^2)	1.6 (1.1-2.4)	.02	1.6 (1.1-2.4)	.008
Age (years)	0.98 (0.97-1.0)	.04	NA	.054
Urban population	0.8 (0.6-1.2)	.34	NA	.14
Type 2 diabetes mellitus	1.3 (0.8-2.3)	.30	NA	.41
Arterial hypertension	1.1 (0.7-1.8)	.76	NA	.87
ER$^+$	0.9 (0.5-1.6)	.73	NA	.92
PR$^+$	1.4 (0.8-2.6)	.22	NA	.36
HER2$^+$	1.6 (1.0-2.5)	.05	NA	.053
Histologic grade 2-3	2.4 (1.3-4.4)	.004	2.4 (1.3-4.3)	.003
Primary school education or less	0.7 (0.5-1.2)	.25	NA	.37
Model 2				
Obesity (BMI $\geq$ 30 kg/m^2)	1.7 (1.0-2.9)	.06	1.9 (1.1-3.1)	.02
Age (years)	0.98 (0.96-1.0)	.12	NA	.11
Urban population	0.8 (0.5-1.4)	.49	NA	.23
Type 2 diabetes mellitus	1.7 (0.8-3.7)	.14	NA	.37
Arterial hypertension	0.9 (0.4-2.0)	.83	NA	.52
ER$^+$	0.5 (0.2-1.3)	.15	NA	.76
PR$^+$	2.5 (1.1-6.1)	.04	NA	.27
HER2$^+$	1.8 (1.0-3.3)	.06	1.8 (1.01-3.2)	.045
Histologic grade 2-3	1.9 (0.9-4.2)	.10	NA	.10
Primary school education or less	0.8 (0.4-1.6)	.55	NA	.82

Dependent variable: presence of metastatic lymph nodes.
Abbreviations: BMI = body mass index; CI = confidence interval; ER$^+$ = estrogen receptor positive; HER2$^+$ = human epidermal growth factor receptor 2 positive; NA = not applicable (ORs and CIs not calculated for variables removed from the model); OR = odds ratio (binary logistic regression); PR$^+$ = progesterone receptor positive.
[a]Model was adjusted using the "forward conditional" method; age was introduced as a continuous variable.

patients with greater parity were obese (OR, 2.08; 95% CI, 1.35-3.19). Similarly, previous studies have reported the predominance of these phenotypes as a function of ethnicity, with the greatest values observed among Hispanic populations.[10,27] Reproductive events might be relevant and their effect might be heterogeneous and dependent on the BC subtype.[10,29]

The scenario that includes an obese population and BC jeopardizes the sustainability of the health care system, because the risk of death and the development of other conditions concomitant with obesity, such as diabetes mellitus and cardiovascular disease, are increased. Because diabetes is more frequent in women with BC, consideration of its effects as risk factors for BC is more controversial; thus, it is critical to assess its long-term impact.[30] Insulin resistance results in mammary epithelium overstimulation mediated by estrogens. These effects mimic cancer cell proliferation and progression and increases the risk of BC and the development of an aggressive phenotype.[31,32]

The strong aspects of the present study were the inclusion of a large sample size, standardized data collection, specific parameters required by the protocol (weight, height, immunohistochemical data), and limited loss during the follow-up period. The information bias was reduced by corroborating all clinical files with the records from the hospital's functional unit for breast cancer. An approved criterion was established when multidisciplinary decisions were required.

In addition to the retrospective study design, our study had another limitation. We only considered the BMI, even if data on the obesity index were available. Also, no information was available on the proportions of body muscle tissue and fat.

Conclusion

The results of the present study have shown that obese and morbidly obese women are affected by advanced BC with histologic grade 2 or 3 and HER2$^+$ compared with women with a normal weight. In addition, these data support the results relating the TNBC subtype to premenopausal status. Similarly, a significant association was found for women who had had several pregnancies and the presence of concomitant morbidities, such as hypertension.

These findings highlight the current context of BC in specific areas where special public health strategies are required to prevent an increasing prevalence of obesity. Furthermore, obesity has been identified as an important risk factor related to the most aggressive BC subtypes. However, our findings require confirmation by a longitudinal study.

Clinical Practice Points

- In routine clinical practice, the subtype of breast cancer is usually approximated using immunohistochemical markers.
- More recently, genomic trials have become a useful tool to define the prognostic characteristics and therapeutic strategy.
- However, in usual clinical practice, stratification of the cancer subtype has shown that an increased BMI is a risk factor for breast cancer in postmenopausal women and has been associated with more aggressive tumor biology and a poor prognosis.
- The effects of obesity on cancer are only beginning to change clinical practice.
- In particular, tumors in obese patients have tend to result in more distant metastases, although the biology behind this observation remains poorly understood.
- Although for several decades, obesity has been known to be associated with increased cancer mortality, studies that can establish a causal link are still ongoing, and efforts to effectively intervene with weight reduction strategies in the cancer population have not yet been established in routine clinical practice.
- The risk of specific subtypes of breast cancer might be associated with the BMI in both pre- and postmenopausal breast cancer.
- However, obesity might be related to an increased risk of premenopausal breast cancer with negative hormone receptors.
- Further studies are necessary to clarify the likely mechanisms involved in the pathogenesis of premenopausal breast cancer.
- Recently, the stratification of risk has aroused interest as an innovative approach for the detection and prevention of some neoplasms.
- The approach effectively personalizes individual risk, allowing for detection and prevention interventions adapted to subpopulations exposed to harmful environmental factors.

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Disclosure

The authors declare that they have no competing interests.

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