Original Article

The association of body mass index and adverse clinicopathological characteristics in non-metastatic breast cancer

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Abstract

Background: Obesity is a global health problem. It is becoming increasingly prevalent in Saudi Arabia. High body mass index (BMI) is a risk factor for many diseases, including cancer. Noticeably, breast cancer (BC) cases in Saudi Arabia occur at a younger age than in western countries. Different lifestyle behaviors such as maintaining healthy body weight and physical activity may play a role in this. In this study, we investigated the association between BMI and BC adverse clinicopathological features. **Methods:** This retrospective study was conducted by reviewing the records of women with non-metastatic BC over 4 years. The association between BMI and patients' demographics, BC histological type, receptor status, differentiation grade, tumor size, involvement of axillary lymph nodes, and performed procedures were analyzed. **Result:** 315 patients with non-metastatic BC were studied. The mean age at the time of diagnosis was 52.43 years ± 11.63. The mean BMI was 30.21 ± 5.77. The mean tumor size was 3.19 cm ± 3.52. The mean age of diagnosis is significantly higher in obese women than in other BMI groups ($P = 0.025$). Obese female patients aged ≥40 were more likely to present with larger tumor ($P = 0.022$) and numerically higher pathological axillary lymph nodes, trending toward statistical significance ($P = 0.092$). **Conclusion:** The relationship between BMI and developing more aggressive BC is still not clear; in this study, we found that obese patients presented at an older age, with larger tumor and more pathologic lymph nodes. Further research to understand the impact of this finding on outcomes is warranted.

Keywords: Body mass index, breast cancer, clinicopathologic characteristics, obesity, postmenopausal

Introduction

Obesity is a prevalent global health problem, defined by a body mass index (BMI) ≥30.0 kilogram/meter squared. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016.[1] In the Arab region, including Saudi Arabia, obesity has reached 66–75% among adults, which increases the risk of developing several diseases such as coronary artery diseases, hypertension, diabetes, hyperlipidemia, osteoarthritis, and cancer.[2-4]

Breast cancer (BC) is the most common malignancy and the leading cause of cancer-related death among women worldwide.[5,6] In Saudi Arabia, there is a significant increase in the number of BC cases that occurs at an earlier age than in Western countries, and with advanced stage of the disease.[7] An unmatched case-control study from Saudi Arabia showed

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that the proportion of overweight/obese (BMI ≥25) females was significantly higher among breast cancer patients (75.8%) than among healthy controls (61.3%).[8] However, it did not investigate the impact of increasing BMI on the adverse clinical and pathological features of breast cancer.

Breast cancer is a diverse disease with different clinical presentations that are classified differently according to hormonal receptor status, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[9,10] Among the commonly described histology are ductal carcinoma *in situ* (DCIS), lobular carcinoma *in situ* (LCIS), invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC). Other miscellaneous histologies include but not limited to tubular, medullary, metaplastic and papillary.[11] In recent meta-analysis, BC-specific death among obese women is higher compared to normal weight women.[12] Another study among women aged 65–79 years old indicated that high BMI is associated with a higher risk of having IDC, although it was not statistically significant.[13] As for hormonal receptor status, a study concluded that overweight/obese postmenopausal women develop hormone receptor (HR)-positive tumors more frequently.[14] Altogether is supporting the need for better understanding of the means by which obesity causes poor outcomes in patients with BC.

Several reports from different populations showed a correlation between BMI and tumor grade,[15] tumor size, and axillary lymph node involvement.[14,16] We locally do not have evidence on the effect of increasing BMI on the adverse clinical and pathological presentation of breast cancers. This relationship is yet to be investigated in our population.

Our study aimed to investigate the potential association between BMI and adverse clinic pathological features (tumor size, lymph node involvement, hormonal receptors, grade and histological subtypes) in patients with non-metastatic breast cancer from Saudi Arabia, Jeddah.

Methodology

Study design and setting

We conducted a retrospective patients' record review at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia. Institutional Review Board (IRB) at KAUH approved the study after the satisfaction of the institutional requirements. All names and file numbers of patients were concealed, and only anonymous data were used to ensure privacy and confidentiality.

Sample size

From February 2014 to February 2018, all females aged 18-year-old and above with non-metastatic BCs that were operated on before receiving preoperative chemotherapy were enrolled. We reviewed 766 medical records, and some patients were excluded due to the presence of a benign lesion, distant organ metastasis, and missing data. The final sample size was 315.

Data collection

Data were collected from the electronic medical record system. The following variables were obtained, patients' demographics: (age at diagnosis and nationality), BMI, which is measured by the equation; weight in kilogram (kg) divided by height in meters (m), squared and defined as per World Health Organization (WHO): underweight BMI <19 kg/m2; normal BMI ≥19 and <25 kg/m2; overweight BMI ≥25 and <30 kg/m^2; obese BMI ≥30.0 kg/m2). Breast cancer histological types (DCIS, LCIS, IDC, ILC), receptor status (ER, PR, HER2), grade of differentiation (well (I), moderately (II) and poorly (III) differentiated), tumor size; was classified into three categories (tumor size ≤1 cm, 1–2 cm, and ≥2 cm), the involvement of axillary lymph node, and the surgical procedures performed; (modified radical mastectomy (MRM) or lumpectomy were recorded. Study cohort was sub-classified according to age.

Data analysis

Frequencies of categorical variables were computed and presented. Tumor characteristics were cross-tabulated among young patients <40 and older patients ≥40 years old. The relationship to BMI was assessed using univariate and multivariate analysis with a significance value ($P \leq 0.05$ considered significant). Data were analyzed by the statistical package for the social sciences version 21 (SPSS).

Result

We studied 315 patients with non-metastatic breast cancer who fulfilled the inclusion criteria spanning 4 years from 2014 to 2018. The mean age at the time of diagnosis is 52.43 years ± 11.63 (range 25–85 years). Saudi patients accounted for 40.6% of our sample. The mean BMI is 30.21 ± 5.77 (range, 17- 55). Nearly half of our sample (47.9%) has a BMI of ≥30. Distribution of BMI based on age; ≥40 years and <40 years is shown in Table 1. A significant association between age and BMI was demonstrated as follow: the mean age of obese patients is 54.24 ± 11.09, overweight patients is 50.63 ± 11.90, normal-weight patients is 51.58 ± 12.10 and underweight patient is 42.75 ± 6.1 ($P = 0.025$).

Histological types and receptor status

Invasive ductal carcinoma is the most frequently reported histological type, reported in 237 (84.6%) among women aged 40 years and above, and in 29 (82.9%) of women aged <40 years [Table 2 and 3]. ER-positive tumors are the most common in both age groups, with 185 (66.1%), 23 (65.7%) among ≥40 years and, <40 years, respectively. Interestingly, HER2/neu positive tumors accounted for more than one-third in both age groups [Table 2 and 3].

Tumor size

The mean tumor size was 3.19 cm ± 3.52. Sixty-one patients (19.4%) had a tumor of ≤1 cm, 31 (9.8%) had a tumor size ranged from 1 to 2 cm, and 223 (70.8%) patients with a tumor size

of ≥2 cm. Two-hundred and one patients (72%) aged 40 years and older has tumor size ≥2 cm with 50% (101 out of 201) were being obese patients $P = 0.022$ [Table 2 and 3].

Lymph node involvement and grade

Lymph node metastasis was found in 171 patients; 154 of them (55%) were 40 year-old and older. Tumor grade was reported as follows: 173 (55%) patients had a moderately differentiated tumors followed by poorly differentiated tumors in 85 (%27), and well differentiated in 57 (18.1%).

Type of procedure

The majority of the patients underwent MRM 216 (68.6%), followed by lumpectomy in 99 patients (31.4%). In women aged 40 and above, 192 (68.6%) had MRM, and 88 (31.4%) had a lumpectomy. In women aged <40, 24 (68.6%) patients had MRM and 11 (31.4%) had a lumpectomy.

Table 1: BMI distribution in the study sample categorized by age

BMI Classification	<40 years	≥40 years
Underweight	1 (2.9%)	3 (1.1%)
Normal weight	5 (14.3%)	48 (17.1%)
Overweight	15 (42.9%)	92 (32.9%)
Obesity	14 (40%)	137 (48.9%)
Total	35 (100%)	280 (100%)

Discussion

Although the impact of BMI on developing BC is consistently described, the association between increasing BMI and adverse pathological features of breast cancer has been speculative. In this present study, we have found that obese women, especially those who are 40 years and older, tend to have a larger tumor. Our findings are consistent with what was described in other populations.[17,18] Having an increased proportion of older women presenting with larger tumors can be explained by the increased activity of aromatase enzyme seen in women with BMI ≥30, which converts androstenedione to estrogens in peripheral adipose tissue, leading to an increase in the level of estrogen. Moreover, an elevated level of insulin-like growth factor (IGF) and other growth factors such as VEGF, TNF-a, Leptin, IL-6 that may enhance tumor growth, promote angiogenesis, accelerate metastasis, and inhibit apoptosis.[19] Insulin itself stimulates ovarian synthesis of androgens, stimulates expression of growth hormone (GH) receptors, reduces liver production of sex hormone-binding globulin (SHBG) and two IGF-binding proteins (IGFBP-1 and -2), resulting in raising the bioavailability of sex hormones and IGF-1.[14,20]

Half of the older patients (aged ≥40) with hormone receptor (HR)-positive tumors were having BMI ≥30. However, no statistically significant relationship between hormone and HER2 receptors status and BMI was observed in the current study. Although HR-positive tumors were numerically more frequent,

Table 2: Clinico-pathologic features in women aged less than 40 according to BMI distribution

Characteristics	BMI Classification					*P*
Tumor size	**Underweight**	**Normal weight**	**Overweight**	**Obese**	**Total**	
≤1 cm	0	3 (8.6%)	3 (8.6%)	4 (11.4%)	10 (28.6%)	0.374
>1 cm <2 cm	0	1 (2.8%)	1 (2.8%)	1 (2.8%)	3 (8.6%)	
≥2 cm	1 (2.8%)	1 (2.8%)	11 (31.4%)	9 (25.7%)	22 (62.7%)	
Grade						
I	0	1 (2.8%)	4 (11.4%)	3 (8.6%)	8 (22.9%)	0.353
II	0	4 (11.4%)	5 (14.3%)	8 (23%)	17 (48.7%)	
III	1 (2.8%)	0	6 (17%)	3 (8.6%)	10 (28.6%)	
Lymph node						
Yes	1 (2.8%)	2 (5.6%)	9 (25.7%)	5 (14.3%)	17 (49%)	0.338
No	0	3 (8.6%)	5 (14.3%)	9 (25.7%)	17 (49%)	
PR						
Yes	0	2 (5.6%)	9 (25.7%)	10 (28.6%)	21 (60%)	0.373
No	1 (2.8%)	3 (8.6%)	6 (17%)	4 (11.4%)	14 (40%)	
ER						
Yes	0	3 (8.6%)	11 (31.4%)	9 (25.7%)	23 (65.7%)	0.558
No	1 (2.8%)	2 (5.6%)	4 (11.4%)	5 (14.3%)	12 (34.3%)	
HER2						
Positive	1 (2.8%)	2 (5.6%)	5 (14.3%)	5 (14.3%)	13 (37.1%)	0.732
Negative	0	2 (5.6%)	9 (25.7%)	6 (17%)	17 (48.6%)	
Equivocal	0	1 (2.8%)	1 (2.8%)	3 (8.6%)	5 (14.3%)	
Histological type						
DCIS	0	0	2 (5.6%)	2 (5.6%)	4 (11.4%)	1.000
LCIS	0	0	2 (5.6%)	0	2 (5.6%)	0.647
IDC	1 (2.8%)	5 (14.3%)	11 (31.4%)	12 (34.3%)	29 (82.8%)	0.653
ILC	0	0	4 (11.4%)	0	4 (11.4%)	0.174

Table 3: Clinico-pathologic features in women aged 40 and older according to BMI distribution

Characteristics	BMI Classification					*P*
Tumor size	Underweight	Normal weight	Overweight	Obesity	Total	
≤1 cm	1 (0.4%)	2 (0.7%)	24 (8.5%)	24 (8.5%)	51 (18%)	0.022
>1 cm <2 cm	0	8 (3%)	8 (3%)	12 (4.3%)	28 (10%)	
≥2 cm	2 (0.7%)	38 (13.6%)	60 (21.4%)	101 (36%)	201 (72%)	
Grade						
I	0	11 (4%)	17 (6%)	21 (7.5%)	49 (17.5%)	0.172
II	2 (0.7%)	21 (7.5%)	46 (16.4%)	87 (31%)	156 (55.7%)	
III	1 (0.4%)	16 (5.7%)	29 (10.4%)	29 (10.4%)	75 (26.8%)	
Lymph node						
Yes	0	32 (11.4%)	50 (18%)	72 (25.7%)	154 (55%)	0.092
No	3 (1%)	16 (5.7%)	42 (15%)	63 (22.5%)	124 (44%)	
PR						
Yes	1 (0.4%)	25 (9%)	50 (18%)	78 (28%)	154 (55%)	0.811
No	2 (0.7%)	23 (8.2%)	42 (15%)	59 (21%)	126 (45%)	
ER						
Yes	2 (0.7%)	29 (10.4%)	61 (22%)	93 (33%)	185 (66%)	0.829
No	1 (0.4%)	19 (6.8%)	31 (11%)	44 (15.7%)	95 (33.9%)	
HER2						
Positive	2 (0.7%)	16 (5.7%)	34 (12%)	39 (14%)	91 (32.5%)	0.638
Negative	1 (0.4%)	26 (9.3%)	50 (18%)	79 (28%)	156 (55.7%)	
Equivocal	0	6 (2%)	8 (3%)	19 (6.8%)	33 (12%)	
Histological type						
DCIS	0	3 (1%)	14 (5%)	9 (3.2%)	26 (9.3%)	0.135
LCIS	0	0	1 (0.4%)	2 (0.7%)	3 (1%)	1.000
IDC	3 (1%)	41 (14.6%)	75 (27%)	118 (42%)	237 (84.6%)	0.776
ILC	0	7 (2.5%)	12 (4.3%)	19 (6.8%)	38 (13.6%)	0.982

the statistical significance could not be demonstrated. This may imply that a larger number of patients is needed to demonstrate significance. Different studies showed a variable relationship between HR-status and body weight. Some correlated positively[21,22] while others did not show such correlation.[14,23] All reported studies focused on having an increased number of positive HR among patients with increased BMI; however, the lack of HR expression is considered an adverse feature. Therefore, we ran an analysis in women who were ≥40 with HR- negative status and high BMI exploring the association. There was no statistical or numerical association between HR-negative tumor and high BMI in our sample.

Most of the patients with lymph node metastasis were obese. Lymph node involvement was more prominent in older patients and showed a trend toward statistical significance ($P = 0.092$). This finding is consistent with many studies.[14,18,24] However, results from other studies are contradictory, for instance, Eichholzer M *et al.*[25] found no association between BMI and tumor size or lymph node status in postmenopausal women. We observed that women with high BMI were older at diagnosis (mean age 54.24 ± 11.09) than the ones with average to low BMI (51.58 ± 12.10 and 42.75 ± 6.1, respectively). This finding might be explainable by the lack of health awareness in general among those patients, represented by an unhealthy lifestyle leading to obesity. Nonetheless, higher BMI is associated with more body fat, which makes the clinical palpation difficult; hence this results in women presenting with larger tumor size and more lymph node metastasis.

Modified radical mastectomy (MRM) accounted for the majority of the surgical option. Selection bias could have cofounded this finding as we selected patients who underwent upfront surgery in order to ascertain accurate pathologic staging based on the complete surgical specimen. Similar proportion in both age groups had MRM (68.6%) and lumpectomy (31.4%). The majority of both groups had a tumor ≥2 cm, considerably high percentage of lymph node involvement, and nearly one third with HER2 positive tumor and high grade, which possibly contributed to MRM being the most common procedure. Invasive ductal carcinoma was the most frequent type among our patients, and the majority were obese, but were not different from what observed in the average BMI group. Differentiation Grade of breast cancer was not significantly associated with increasing BMI in our study. Moderate differentiation was the predominant grade across all BMI groups.

The main limitation of this study was that body weight and height were the only anthropometric information found in the records at the time of diagnosis of breast cancer. This favored the use of BMI as a sign of general obesity. However, visceral obesity that is detected by waist-hip ratio and waist circumference could not be examined because these measures were not routinely reported. Although BMI is used as a marker of obesity, it does

not distinguish between slim/fat mass or central/peripheral fat distribution.

The majority in this cohort presented with histologically invasive carcinoma, larger tumor and more pathological lymph nodes. There is a recognized need to advocate awareness of obesity and its impact on health in general and as a potential contributing factor for the development of breast cancer with probably more advanced and aggressive features.

The knowledge of how obesity can affect the risk of developing several morbidities including breast cancer, specifically breast cancer with more aggressive features, will help primary care and family practice physician in identifying the population in need for better awareness and education. Emphasizing the pivotal role of primary care providers in promoting healthy life style, healthy diet, and exercising to help maintain healthy body weight and avoid obesity-related complications.

Conclusion

Higher BMI showed an association with larger tumor size and pathological lymph nodes in older patients with breast cancer. Histological types, receptor status, and grade did not show statistically significant association. Obese women had an older age at diagnosis with BC than those with average BMI. Data from this research will help in investigating the impact of obesity on breast cancer (outcomes, presentation, prognosis) in Saudi Arabia.

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Conflicts of interest

There are no conflicts of interest.

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