The Impact of Body Mass Index on Clinicopathological Features and Survival Outcomes in Breast Cancer Patients: A Retrospective Cohort Study.

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Abstract

Breast cancer remains the most common cancer among women, yet the precise relationship between obesity/overweight and its outcomes remains unclear. This retrospective cohort study, conducted at Suez Canal University Hospital from January 2013 to December 2018. A total of 273 breast cancer patients were included and categorized by Body Mass Index (BMI) into normal weight (9.89%), overweight (21.24%), and obese (68.86%) groups, and then compared across clinico-pathological characteristics, disease-free survival, and 10-year overall survival. Obese patients were generally older at diagnosis (average 50 years) and more often postmenopausal (61.7% obese). Both obese and overweight patients presented with larger tumor sizes and more advanced tumor stages compared to normal weight individuals. Specifically, T2 tumors were prevalent in 62.1% of overweight and 68.6% of obese patients, contrasting with 33.3% in normal weight patients. Stage III disease was also higher in overweight (44.8%) and obese (27.1%) groups than in normal weight patients (22.2%). Normal weight patients showed a higher incidence of local recurrence (14.8%) and positive family history. Obesity did not appear to affect overall or disease-free survival. While the impact of obesity on breast cancer prognosis remains a subject of debate, this study indicates that obese and overweight breast cancer patients tend to have more aggressive disease presentations, characterized by larger tumor sizes and advanced stages. The higher local recurrence in normal weight patients might be linked to their younger age and increased incidence of triple-negative breast cancer. Further research is necessary to fully understand how obesity influences breast cancer prognosis.

Key words: ***Breast cancer, obesity, prognosis, clinicopathologic.***

Introduction

Globally, breast cancer is the most common malignancy in women and ranks as the second leading cause of cancer death, surpassed only by lung cancer [(1)]. It represents 32.0% of cancer cases among Egyptian females [(2)]. Established risk factors include age at menarche and menopause, parity, age at first childbirth, genetic profiles, and a history of prior cancer. Additional risk factors encompass alcohol use, metabolic syndrome, obesity, overweight, and hypercholesterolemia, with regular exercise

identified as a potential preventive measure. However, the precise impact of these lifestyle factors on breast cancer requires further elucidation [3].

At diagnosis, obese women with breast cancer frequently present with more advanced disease, characterized by larger tumor size and greater lymph node involvement. Furthermore, higher body mass indices (BMIs) are associated with increased resistance to both chemotherapy and hormone therapies [4].

Obesity at the time of breast cancer diagnosis is associated with diminished overall and disease-free survival across all breast cancer subtypes. Increased adiposity is correlated with a higher risk of recurrence and mortality in patients with estrogen receptor-positive (ER+) breast cancer and has been implicated in postmenopausal breast cancer development [5]. These adverse outcomes may be attributable to the secretion of estrogen and other mitogens, as well as fibrosis, vascularity, and inflammation, all of which contribute to breast cancer progression [6].

However, in premenopausal women, some studies indicate that obesity may have a protective effect against the development of breast cancer, indicating that the relationship between obesity and breast cancer varies depending on menopausal status [7].

Overweight and obesity have been linked to aggressive clinicopathological features, according to prior study results. Compared to individuals of normal weight, those that had been overweight or obese were more likely to have aggressive carcinoma, which is characterized by larger tumor sizes, nuclear grade III, lymph vascular invasion (LVI), and triple-negative subtype (TNBC). There is hypothesis that obese females are less likely to undergo breast screening, and it is more difficult to detect small lumps due to fatty breasts, so obese patients tend to have more advanced disease at initial diagnosis [8].

Another study found that both obesity and overweight were not associated with poorer outcomes in women with metastatic disease and did not predict survival [9].

Martel et al. also did not find an association between body mass index and clinical outcomes in Human Epidermal Growth Factor Receptor-2 Neu (HER2neu) -positive metastatic breast cancer [10].

To date, the relationship between obesity/overweight and outcomes of breast cancer patients has not been well defined.

Therefore, this study aimed to investigate the impact of body mass index (BMI) on clinicopathological features, response to treatment, and prognosis in breast cancer patients in our society.

Methods

A. Aim of the work

To investigate the impact of body mass index on clinicopathological features and prognosis of breast cancer patients.

B. Objectives

1- Determine the influence of obesity on clinicopathological features of breast cancer patients.
2- Detect the impact of high BMI on response to treatment in breast cancer patients.
3- Study the impact of obesity on progression free survival and 10-year overall survival.

C. Study Design and Population

This retrospective cohort study was conducted at the Clinical Oncology and Nuclear Medicine Department, Suez Canal University Hospital (SCUH), Ismailia, Egypt. Data were collected from the medical records of breast cancer patients who attended SCUH between January 2013 and December 2018. The study sample was selected using convenience sampling and stratified into three groups based on their Body Mass Index (BMI).

a. Group A: normal weight patients: Patients with BMI = 18.5 – 24.9 kg/m2.
b. Group B: overweight patients: Patients with BMI = 25 – 29.9 kg/m2.
c. Group C: obese patients: Patients with BMI ≥ 30 kg/m2.

D. Description of the study sample in terms of:

i. Inclusion criteria:
    1. Patients diagnosed pathologically and radiologically with invasive breast cancer.
    2. 2-Adult (≥18 years) female patients.
    3. Available weight and height in patient's medical records.
    4. Body mass index ≥ 18.5.

ii. Exclusion criteria:
    1. Overweight secondary to medical condition (Cushing syndrome or hypothyroidism).
    2. Patients were metastatic from the start.
    3. Double pathology patients.
    4. Non-complaint patients on treatment.

E. Data management

a. Patient's data was coded then entered into a Microsoft Excel sheet and then analyzed using the Statistical Package for Social Sciences (SPSS) software program version 25.0.
b. Data was presented as tables and graphs, as suitable.
c. For descriptive analysis, numerical data was expressed as mean ± standard deviation, whereas categorical data was expressed as frequencies and percentages.
d. For assessment of differences in the distribution of study variables between overweight and obese group and normal weight group; Fisher's exact test and chi-square test were used for categorical variables as appropriate. An analysis of continuous variables was performed by independent t-test or nonparametric Mann-Whitney U-test according to the normality of the distributions. Survival functions were calculated using the Kaplan-Meier method, and the log-rank test was used to compare the survival curves. For all tests, a probability value of less than 0.05 was considered statistically significant.

F. Ethics approval

The protocol was reviewed and approved by the Ethics Committee of faculty of medicine, Suez Canal University. Number of ethical approval (4906, dated: 12/4/2022).

Results

This retrospective cohort study investigated the impact of Body Mass Index (BMI) on the clinicopathological features and prognosis of breast cancer patients. We included 273 breast cancer patients who met the inclusion criteria and attended the Oncology and Nuclear Medicine Department at Suez Canal University Hospital between January 2013 and December 2018. Patients were categorized into three groups based on their BMI: Group A: normal-weight breast cancer patients (9.89%), Group B: overweight breast cancer patients (21.24%) and Group C: obese breast cancer patients (68.86%).

A statistically significant difference was observed in age groups across normal weight, overweight, and obese patients, with respective mean ages of 41, 44, and 50 years ($P < 0.001$). Menopausal status also varied significantly among the three groups ($P = 0.011$), with 61.7% of obese patients being postmenopausal, compared to 44.4% of normal weight and 41.4% of overweight patients.

Regarding the family history of breast cancer, a statistically significant difference was noted ($P = 0.029$), as 14.8% of normal weight and 13.8% of overweight patients reported a family history, in contrast to only 4.8% of obese patients. Furthermore, while 60.3% of the total study population presented with various comorbidities, predominantly diabetes and hypertension, a significant difference was specifically identified for hypertension across the groups ($P = 0.027$). Here, 30.3% of obese patients had hypertension, compared to 11.1% of normal weight and 17.2% of overweight patients. (Table 1).

Analysis of disease staging at diagnosis revealed statistically significant differences across the three BMI groups ($P = 0.049$). Stage I disease was more prevalent in normal weight patients (40.7%) compared to overweight (20.7%) and obese (38.3%) groups. Conversely, Stage III disease was observed more frequently in the overweight group (44.8%), relative to normal weight (22.2%) and obese (27.1%) patients.

Furthermore, a statistically significant difference was found in tumor stage (T) ($P = 0.014$). T1 tumors were present in 40.7% of normal weight patients, whereas they were less common in overweight (22.4%) and obese (17.6%) patients. Conversely, T2 tumors were more prevalent among overweight (62.1%) and obese (68.6%) patients, compared to 33.3% of normal weight patients. While no other staging parameters showed statistically significant differences, it's notable that N3 disease was identified in 7.4% of normal weight patients, compared to 29.3% of overweight and 16.5% of obese patients. (Table 2).

The majority of obese patients presented with Infiltrating Ductal Carcinoma (82.4%), a left-sided lesion (54.8%), extranodal extension (35.1%), lymphovascular invasion (28.7%), and perineural invasion (4.3%). However, there was no statistically significant difference between groups and histopathological variables. Her2neu positive was reported in 10.3% of overweight patients compared to 3.7% and 5.3% of normal weight and obese patients. Also, Triple negative was reported more in normal weight patients 22.2% compared to 10.3% of overweight and 10.1% of obese.

No statistically significant difference was observed among the three BMI groups regarding their response to neoadjuvant treatment. Among the 21 patients who received neoadjuvant chemotherapy, only 1.8% achieved an R0.

The study population exhibited varied treatment strategies across the different BMI groups. Nearly all patients, with the exception of 1.1% in the obese group, received adjuvant chemotherapy. Neoadjuvant chemotherapy was administered to 7.4% of normal weight patients, 6.9% of overweight patients, and 8.0% of obese patients. Radiotherapy was used in all normal weight patients, 96.6% of overweight patients, and 97.3% of obese patients.

Specific treatment modalities within each group were as follows:

- Normal Weight Group: 77.8% received hormonal treatment, 22.2% received targeted therapy, and 96.3% underwent Modified Radical Mastectomy (MRM).
- Overweight Group: 82.8% received hormonal treatment, 24.1% received targeted therapy, and 86.2% underwent MRM.
- Obese Group: 86.7% received hormonal treatment, 15.4% received targeted therapy, and 87.8% underwent MRM.

Analysis of disease progression parameters, including local recurrence and metastasis, revealed distinct patterns within the study groups. A local recurrence developed in only 12 cases (4.4%) across the entire study population. A statistically significant difference in the local recurrence rate was observed between the groups (P = 0.01): 14.8% in normal weight patients, 6.9% in overweight patients, and 2.1% in obese patients. Metastasis was observed in 24.9% of the total study population, though no statistically significant difference was found between the BMI groups (P = 0.4). Bone was the most frequently reported site of metastasis, followed by the lung and liver. Most common site of metastasis in normal weight were Liver and bone, in overweight was lung and in obese was Bone. (Table 3).

Analysis of Disease-Free Survival (DFS) across the study groups revealed cumulative survival rates of 54.2% for normal weight patients, 64.2% for overweight patients, and 67.8% for obese patients. However, despite these differences in cumulative rates, there was no statistically significant difference in DFS among the groups. The mean survival time was 7.71 years for normal weight, 7.87 years for overweight, and 6.1 years for obese patients. (Table 4).

The 10-year cumulative Overall Survival (OS) rates were 46.6% for normal weight, 50.6% for overweight, and 52.4% for obese patients. However, there was no statistically significant difference in 10-year OS among the study groups. The mean survival time was 7.74 years for normal weight patients, 8.27 years for overweight patients, and 9.08 years for obese patients. (Table 5).

Discussion

The impact of BMI on the prognosis of breast cancer is still controversial. Obesity is linked to breast cancer pathogenesis through multiple mechanisms. This study aimed to investigate the impact of obesity on clinicopathological data and prognosis of breast cancer patients attending Oncology and Nuclear Medicine department, Suez Canal University hospital.

In our breast cancer patients, 9.89% (27 patients) had normal weight, 21.24% (58 patients) were overweight and 68.86% (188 patients) were obese. This pattern aligns with findings from a study conducted in Saudi Arabia by Alshamsan et al., who reported that at the time of diagnosis, 15.6% of

breast cancer patients were normal weight/underweight, 30.9% were overweight, and 53.4% were obese [12].

The median age among all patients at diagnosis was 48 years, which is in concordance with previous data from Saudi Arabia (45.7 years) and Asia (47.3 years), but lower than that in United States (60 years). It could be attributed to the younger age structure of the population in these regions compared to that in the United States, which might be due to environmental and genetic factors. Patients who had higher BMI tended to be older at diagnosis, and thus more likely to be postmenopausal. These results were consistent with earlier findings by other research groups who indicated a greater proportion of obese women among older breast cancer patients (mean age 50 years) [13,14].

In our study, a positive family history of breast cancer was reported by 7.7% of all patients, 14.8% of normal weight and 13.8% of overweight compared to 4.8% of obese patients. Supporting previous studies found lower family history index in obese and overweight women. Luís et al. also reported an association between obesity and sporadic breast cancer—lack of family history [15,16].

Meanwhile, about 60.3% of the total population had different comorbidities. Diabetes and hypertension were the most reported comorbidities. 30.3% of obese patients had hypertension compared to 11.1% and 17.2% of normal weight and overweight, respectively. Obesity and hypertension are closely interrelated as abdominal obesity interferes with the endocrine and immune systems and carries a greater risk for insulin resistance, diabetes, hypertension, and cardiovascular disease. Furthermore, obesity is recognized as a major risk factor for hypertension among both adults and children, regardless of race, ethnicity, and gender. That could lead to an increase in mortality of obese patients [17].

In our study, T1 was more common on normal weight patients (40.7%), meanwhile T2 was more common among overweight patients 62.1% and obese patients 68.6%. That is matched with several studies demonstrating that obese women develop a significantly larger tumor size compared to normal weight women [14].

We also found that stage I was reported in 40.7% of normal weight and stage III was reported more in overweight group (44.8%). This is similar to Alshamsan et al. who reported that obesity was positively associated with an advanced clinical stage in their patients [12].

These findings are probably related to the biological impact of obesity on breast cancer development. However, some researchers have suggested that obesity is a potential barrier for screening compliance and effectiveness [13].

Increased levels of free estrogens due to aromatization of adipose tissue, inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and prostaglandin E2, insulin resistance and hyperactivation of insulin-like growth factors pathways, and adipokines such as adiponectin have all been reported to contribute to carcinogenesis [18].

There was another hypothesis that obese women perform less breast screening, and they are more difficult to find small lumps due to excessive fatty tissue in the breast, so obesity patients tend to have more advanced disease at initial diagnosis [8].

Association studies between BMI and differentiation grade are controversial. Several studies found no significant relationship between histopathology grading and BMI, but numerous other studies found

obesity to be associated with poorly differentiation tumors [15]. Our results reveal that tumor grade did not differ by the BMI group.

There was no significant association between lympho-vascular invasion and obesity which is in agreement with previous studies [13,19]. Although these findings are in contrast to those of Haakinson et al., other studies reported higher rates of angiolymphatic invasion among obese patients with breast cancer at presentation [20].

Histopathological types did not differ by the BMI group in our population which is consistent with previous study [21]. Most common histopathological type was luminal type (70.7% of all study groups). However, Her2neu positive reported in 10.3% of overweight patients comparing to 3.7% and 5.3% of normal weight and obese patients. Also, Triple negative reported more in normal weight patients 22.2% compared to 10.3% of overweight and 10.1% of obese.

Our result is in contrast with a recently published observation by Pantelimon et al. demonstrating that patients diagnosed with aggressive tumors subtypes (HER2-positive and TNBC) had a significantly higher BMI than luminal-type breast cancer patients. However, the small number of patients with such conditions (seven were HER2-positive and five were TNBC, respectively, versus twenty-seven were luminal breast cancer patients) included in the cited study does not allow a proper comparison [22].

In contrast to the prevailing view, a higher BMI has no effect on local recurrence and normal weight associated with high risk of local recurrence.

In the present study, patients who were normal weight tended to have three major risk factors for local recurrence in common: young age, triple negative and positive family history. Therefore, these factors might confound the results of the present study.

In the present study, distant metastasis, contralateral breast affection and overall survival were not affected by obesity which is in agreement with previous study [12].

In contrast to Sun et al. who found that overweight and obesity were independent predictors for increased risks of 5-year breast cancer relapse and mortality [14].

However, Kawai et al. reported that obesity was an independent risk factor for breast cancer death but not for recurrence, and overweight had no association with breast cancer prognosis [23].

This study's limitations include its retrospective, single-institution design with a relatively small sample size. Incomplete patient data, particularly the absence of Ki67 status, and a lack of information on hormone replacement therapy and oral contraceptive pill use, may have influenced our findings. Other measures of obesity, such as waist circumference and waist-hip ratio, were not collected as these measures were not routinely reported and therefore could not be investigated in relation to the presentation of breast cancer.

Declarations

- **Ethics approval and consent to participate:** The protocol was reviewed and approved by the Ethics Committee of faculty of medicine, Suez Canal University. Number of ethical approval (4906, dated: 12/4/2022).
- **Consent for publication:** (Not applicable).

- **Availability of data and material:** All data and material will be available.
- **Conflict of interest:** No conflicting of interests is stated by the authors.
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Tables

Table 1. Clinical Characteristics and Social Data of Study Groups.

Variables	Total (n=273)	Study groups			p-value
		Normal weight (n=27)	Overweight (n=58)	Obese (n=188)	
Age at diagnosis, mean ± SD	48.1 ± 10.59	41.96 ± 10.09	44.28 ± 10.35	50.16 ± 10.1	**<0.001** [a]
Occupation, n (%)					
Unemployed	264 (96.7)	27 (100)	54 (93.1)	183 (97.3)	0.15 [b]
Employed	9 (3.3)	0 (0)	4 (6.9)	5 (2.7)	
Marital status, n (%)					
Married	244 (89.4)	22 (81.5)	53 (91.4)	169 (89.9)	
Single	10 (3.7)	4 (14.8)	3 (5.2)	3 (1.6)	0.1 [b]
Widow	19 (7)	1 (3.7)	2 (3.4)	16 (8.5)	
Menopausal status, n (%)					
Premenopausal	121 (44.3)	15 (55.6)	34 (58.6)	72 (38.3)	**0.011** [b]
Postmenopausal	152 (55.7)	12 (44.4)	24 (41.4)	116 (61.7)	
Family History, n (%)					
No	252 (92.3)	23 (85.2)	50 (86.2)	179 (95.2)	**0.029** [b]
Yes	21 (7.7)	4 (14.8)	8 (13.8)	9 (4.8)	
Co-morbidities, n (%)					
Hypertension	70 (26.5)	3 (11.1)	10 (17.2)	57 (30.3)	**0.027** [b]
Diabetes	47 (17.2)	2 (7.4)	6 (10.3)	39 (20.7)	0.07 [b]
Chronic liver disease	25 (9.2)	4 (14.8)	5 (8.6)	16 (8.5)	0.6 [b]
Chronic kidney disease	1 (0.4)	0	0	1 (0.5)	0.9 [b]
Cardiac disease	19 (7)	0 (0)	4 (6.9)	15 (8)	0.3 [b]

[a] p-values are based on ANOVA test. Statistical significance at $P < 0.05$

[b] p-values are based on Chi square test. Statistical significance at $P < 0.05$

Table 2. Staging Parameters at Time of Diagnosis among Study Groups.

Variables	Total n (%) (n=273)	Study groups, n (%) Normal weight (n=27)	Overweight (n=58)	Obese (n=188)	p-value
TNM staging*					
(T): Tumor size					
T1	57 (20.9)	11 (40.7)	13 (22.4)	33 (17.6)	
T2	174 (63.7)	9 (33.3)	36 (62.1)	129 (68.6)	**0.014** [a]
T3	28 (10.3)	5 (18.5)	8 (13.8)	15 (8)	
T4	14 (5.1)	2 (7.4)	1 (1.7)	11 (5.9)	
(N): Nodal					
N0	86 (31.5)	9 (33.3)	14 (24.1)	53 (33.5)	
N1	85 (31.1)	10 (37)	16 (27.6)	59 (31.4)	0.24 [a]
N2	52 (19)	6 (22.2)	11 (19)	35 (18.6)	
N3	50 (18.3)	2 (7.4)	17 (29.3)	31 (16.5)	
Grade					
1	16 (5.9)	3 (11.1)	2 (3.4)	11 (5.9)	
2	223 (81.7)	18 (66.7)	46 (79.3)	159 (84.6)	0.47 [a]
3	34 (12.5)	6 (22.2)	10 (17.2)	18 (9.6)	
Staging					
I	95(34.8)	11 (40.7)	12 (20.7)	72 (38.3)	
II	95(34.8)	10 (37)	20 (34.5)	65 (34.6)	**0.049** [a]
III	83(30.4)	6 (22.2)	26 (44.8)	51 (27.1)	

[a] p-values are based on Chi square test. Statistical significance at $P < 0.05$

Table 3. Comparison between Study Groups and Disease Progression

Variables	Total n (%) (n=273)	Study groups, n (%) Normal weight (n=27)	Overweight (n=58)	Obese (n=188)	p-value
Local recurrence					
Absent	261 (95.6)	23 (85.2)	54 (93.1)	184 (97.9)	0.01 [a]
Present	12 (4.4)	4 (14.8)	4 (6.9)	4 (2.1)	
Contra-lateral breast					
Free	270 (98.9)	26 (96.3)	58 (100)	186 (98.9)	0.4 [a]
Affected	3 (1.1)	1 (3.7)	0	2 (1.1)	
Metastasis					
Absent	205 (75.1)	18 (66.7)	42 (72.4)	145 (77.1)	0.4 [a]
Present	68 (24.9)	9 (33.3)	16 (27.6)	43 (22.9)	
Liver	26 (9.5)	6 (22.2)	9 (15.5)	11 (5.9)	
Bone	46 (16.8)	6 (22.2)	7 (12.1)	33 (17.6)	
Brain	13 (4.8)	1 (3.7)	7 (12.1)	5 (2.7)	
Lung	28 (10.3)	5 (18.5)	10 (17.2)	13 (6.9)	
Nodal metastasis	3 (1.1)	0	1 (1.7)	2 (1.1)	

[a] p-values are based on Chi square test. Statistical significance at $P < 0.05$

Table 4. Comparison between the Study Groups Regarding their Disease-Free Survival (DFS).

Survival duration	Total	Study groups			Log rank	p-value
		Normal weight (n=27)	Overweight (n=58)	Obese (n=188)		
DFS						
Cumulative survival rate	**65%**	**54.2 %**	**64.2%**	**67.8%**		
Total survival rate	**73.3%**	**63%**	**70.7%**	**75.5%**		
Mean survival time	9.38	7.71	7.875	6.10	1.64	0.4 [a]
Standard error (SE)	0.267	0.663	0.478	0.312		
95% Confidence interval	(8.85 – 9.9)	(6.41 – 9.01)	(6.94 – 8.81)	(8.99 – 10.2)		

[a] p-values are based on Log-Rank (Mantel-Cox) U test. Statistical significance at $P < 0.05$

Table 5. Comparison between the Study Groups Regarding their Overall Survival (OS).

Survival duration	Total	Study groups			Log rank	p-value
		Normal weight (n=27)	Overweight (n=58)	Obese (n=188)		
OS						
Cumulative survival rate	**52.3%**	**46.6%**	**50.6%**	**52.4%**		
Total survival rate	**69.2%**	**59.3%**	**72.4%**	**69.7%**		
Mean survival time	9.07	7.74	8.27	9.084	0.3	0.84 [a]
Standard error (SE)	0.241	0.542	0.397	0.29		
95% Confidence interval	(8.6 – 9.55)	(6.68 – 8.8)	(7.49 – 9.05)	(8.52 – 9.65)		

[a] p-values are based on Log-Rank (Mantel-Cox) U test. Statistical significance at $P < 0.05$