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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Impact of Obesity on Breast Cancer: A Retrospective Review

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ABSTRACT

Background. Obesity has been linked to many adverse health consequences, including breast cancer; however, the impact on clinical presentation, tumor characteristics, and survival outcomes has yet to be clearly defined.

Methods. Retrospective review of a prospectively collected database of patients treated at a single institution for invasive breast cancer from 2000–2008 comparing two groups: nonobese (body mass index of <30) and obese (body mass index of ≥30) patients. Continuous variables, categorical variables, and survival data were analyzed.

Results. Of 1352 total patients, 76% were classified as nonobese and 24% were obese. When comparing age, obese patients presented less frequently than nonobese patients <50 years old (10% vs. 90%), and when comparing patients >50 years old (18% vs. 82%, $P = 0.0019$). Obese patients were more likely to present with disease detected by imaging when compared to nonobese patients (67% vs. 56%, $P = 0.0006$). Obese patients had larger tumors (1.7 cm vs. 1.4 cm, $P < 0.001$) and higher rates of lymph node (LN) metastases (31% vs. 25%, $P = 0.026$). On multivariate analysis, obesity was associated with nonpalpable tumors, larger tumors, a higher incidence of LN metastasis, lower incidence of Her2 positivity, lower incidence of multifocality, and less likely to undergo reconstruction after mastectomy.

Conclusions. Obese patients clinically present at older ages with mammographically detected breast cancer at more advanced stages than nonobese patients. Strategies to encourage screening among the obese patient population are important.

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Breast cancer remains a nationwide epidemic as being the most frequently diagnosed cancer and the second most lethal cancer in women in the United States.[1] Similarly, according to the 2000 census, obesity is a growing plague within this country, with nearly 20% of the United States population classified as obese with a body mass index (BMI) of ≥30 kg/m^2.[2] Obesity caused by poor diet and a sedentary lifestyle has been implicated as the second leading cause of death in the United States, second to cancer.[3,4] Coincidentally, obesity has not only been linked with comorbid health conditions such as diabetes and hypertension, but also with various cancers, including breast cancer.[5,6]

The link between obesity and breast cancer is complex and has been abundantly documented in the literature. Obesity has not only been shown to be an independent risk factor for the development of postmenopausal breast cancer, but also a poor prognostic factor in patients already diagnosed with breast cancer.[7,8] Numerous studies have demonstrated obesity to be associated with a poorer prognosis overall and disease-free survival among breast cancer patients.[9,10] These unfortunate outcomes are likely related to a multitude of factors including advanced stage at diagnosis, suboptimal treatment from inadequate chemotherapy dosing, and accompanying comorbid conditions.[11–16]

Although the correlation of obesity and breast cancer is broadly accepted, there is a lack of consensus in the literature on the associated tumor characteristics seen in obese patients. Previously, it had been postulated that obese patients were more likely to have estrogen receptor (ER)-positive disease with elevated estrogen levels from aromatase activity in the excess adipose tissue, therefore stimulating the growth of these tumors.[17,18] However, some studies have shown higher

rates of ER-negative disease, including triple-negative disease (i.e., ER negative, progesterone receptor negative, and lack of Her2 overexpression).[19–21]

Additional controversial tumor characteristics postulated to be connected with obese breast cancer patients include high histologic grade and the presence of angiolymphatic invasion.[22,23] However, others show a weak association with these factors or directly contradict these results.[24–26]

Given the lack of consensus in the literature, the complexity of patient comorbidities, and the presence of diverse contributing biologic factors, the connection of breast cancer and obesity remains an active area of investigation and debate. As the U.S. obesity population rises, it is essential that the relationship between this nationwide condition and breast cancer be defined in order to decrease morbidity and mortality, and to increase awareness, screening, and effective treatment. Therefore, the focus of our study was to review the characteristics of two cohorts of patients with breast cancer consisting of obese and nonobese patients to illustrate the impact of obesity on initial clinical presentation, tumor characteristics, and survival outcomes of patients with breast cancer.

METHODS

Patient Selection

Included in this study were all women treated for invasive breast cancer at Mayo Clinic Arizona from 2000 to 2008. BMI was calculated by the Quetelet Index and categorized according to World Health Organization criteria.[27] Patients were divided into two groups according to BMI: those with a BMI of <30 kg/m^2 were classified as nonobese, and those with a BMI of ≥30 kg/m^2 were considered obese.

Data Collection

A prospectively collected database was queried and a detailed medical record review was performed to supplement the database as needed. Clinical presentation information and patient demographics such as age, race, menopausal status, personal/family history of breast cancer, and prior breast cancer screening practices were obtained. Strong family history was defined as having more than one family member with breast cancer, including at least one first-degree relative. Tumor characteristics were captured from the final pathology report. Treatment characteristics were also recorded including surgical treatments, hormone therapy, chemotherapy, and radiotherapy.

Analyses

Several variables including patient demographics, presentation of disease, tumor characteristics, and treatment characteristics were analyzed. Descriptive statistics were generated for the variables. Continuous variables were analyzed by ANOVA F tests, and categorical variables were obtained by Chi-square tests. Results were considered statistically significant when p values were less than or equal to 0.05. Multivariate logistic regression analyses were performed for those variables shown to be significant on univariate analyses. A Cox proportional hazard model was analyzed. Survival data were analyzed by the Kaplan–Meier method.[28]

This study was reviewed and approved by the institutional review board at Mayo Clinic. All patient data were protected and HIPPA guidelines strictly followed.

RESULTS

A total of 1352 women were identified, of whom 1026 (76%) were classified as nonobese with a BMI of <30 kg/m^2 and 327 (24%) as obese with a BMI of ≥30 kg/m^2. Median follow-up for these patients was 2.5 years, with a range of 0–9.3 years. Demographic data are shown in Table 1. Obese patients had a higher mean age at diagnosis ($P = 0.002$). No significant differences were found with regard to strong family history of breast cancer. Obese patients were more likely to present with disease by imaging rather than by clinical or self breast examination

TABLE 1 Patient characteristics

Characteristic	Total ($N = 1352$)	BMI <30 kg/m^2 ($n = 1025$)	BMI ≥30 kg/m^2 ($n = 327$)	P
Age, y, mean (range)	66 (20–95)	64 (20–95)	67 (32–91)	0.068
Age group				0.002
<40 y	46 (3%)	39 (4%)	7 (2%)	
40–50 y	171 (13%)	146 (14%)	25 (8%)	
>50 y	1135 (84%)	840 (82%)	295 (90%)	
Significant family history	138 (10%)	100 (10%)	38 (12%)	0.332
Genetic testing for *BRCA1/2*	113 (8%)	89 (9%)	24 (7%)	0.447

BMI body mass index

TABLE 2 Clinical presentation

Presentation	Total ($N = 1352$)	BMI <30 kg/m^2 ($n = 1025$)	BMI ≥30 kg/m^2 ($n = 327$)	*P*
Palpable	557 (41%)	449 (44%)	108 (33%)	0.001
Imaging only	796 (59%)	577 (56%)	219 (67%)	
SBE	477 (35%)	385 (38%)	92 (28%)	
CBE	80 (6%)	64 (6%)	16 (5%)	0.007
Mammography	773 (57%)	559 (55%)	214 (65%)	
Other	23 (2%)	18 (2%)	5 (2%)	

BMI body mass index, *SBE* self breast examination, *CBE* clinical breast examination, *Other* imaging other than mammogram

($P = 0.007$) (Table 2). Despite having nonpalpable tumors, obese patients presented with a greater percentage of larger tumors ($P < 0.001$) as well as lymph node metastases ($P = 0.026$) (Table 3). Multifocal breast cancer was less prevalent in obese patients ($P = 0.025$). No statistically significant differences were seen in histologic grade or subtypes, tumor biomarkers (ER, progesterone receptor, and Her2) or angiolymphatic invasion.

There were few differences between the obese and nonobese patient groups with regard to their cancer treatment (Table 4). Equivalent rates of breast conserving therapy were seen; however, fewer obese women underwent immediate reconstruction after mastectomy. Prevalence of adjuvant hormone therapy, chemotherapy, and radiotherapy were similar in the two groups despite the more advanced stage at presentation in the obese patients.

Multivariate regression analyses revealed several concomitant variables to be significant (Table 5). Obesity was found to be independently associated with mammographically detected tumors, larger tumor size, lymph node positivity, lower incidence of Her2 overexpression, and lower incidence of multifocality; in addition, obese patients were less likely to undergo reconstruction after mastectomy.

The rates of locoregional recurrence were 2% for both obese and nonobese patients ($P = 0.82$). By Kaplan–Meier analysis, we found that obese patients trended toward a worse overall survival with regard to BMI (Fig. 1). This result approached, but did not achieve, statistical significance with a hazard ratio of 1.53 [95% confidence interval (CI) 0.97–2.53]. Overall survival with regard to BMI was then stratified by stage of disease. Only stage II disease reached statistical significance for obesity to impact overall survival with a hazard ratio of 2.282 (95% CI 1.000–5.209) compared to a hazard ratio of 1.252 (95% CI 0.668–2.345) for stage I disease and a hazard ration of 1.343 (95% CI 0.259–6.950) for stage III disease. Cox proportional hazard model was used to determine the association with impact of

TABLE 3 Tumor characteristics

Characteristic	Total ($N = 1352$)	BMI <30 kg/m^2 ($n = 1025$)	BMI ≥30 kg/m^2 ($n = 327$)	*P*
Mean tumor size, cm	1.7 (1.4)	1.6 (1.4)	2.0 (1.7)	<0.001
T stage				0.005
T1 (<2 cm)	1042 (77%)	812 (79%)	230 (71%)	
T2 (2.1–5 cm)	266 (20%)	185 (18%)	81 (25%)	
T3/T4 (>5 cm)	40 (3%)	26 (3%)	14 (4%)	
Multifocal	242 (18%)	197 (19%)	45 (14%)	0.025
LN positive	354 (26%)	253 (25%)	101 (31%)	0.026
Histology				0.534
IDC	905 (67%)	688 (67%)	217 (66%)	
ILC	170 (13%)	134 (13%)	36 (11%)	
Mixed	130 (10%)	97 (10%)	32 (10%)	
Other	149 (11%)	107 (10%)	42 (13%)	
Grade				0.893
1	424 (32%)	324 (32%)	100 (31%)	
2	624 (47%)	469 (46%)	155 (48%)	
3	287 (22%)	218 (22%)	69 (21%)	
Tumor markers				0.096
Triple negative	117 (11%)	82 (11%)	35 (14%)	
Her2 positive	206 (20%)	165 (22%)	41 (16%)	
ER positive/Her2 negative	703 (69%)	520 (68%)	183 (71%)	
Angiolymphatic invasion	184 (14%)	136 (14%)	48 (15%)	0.558

LN lymph node, *IDC* infiltrating ductal carcinoma, *ILC* infiltrating lobular carcinoma, *Mixed* both IDC and ILC, *Other* other type or unknown, *Triple negative* estrogen and progesterone receptor negative and Her2 normal, *ER* estrogen receptor

TABLE 4 Breast cancer treatment characteristics

Characteristic	Total ($N = 1352$)	BMI <30 kg/m^2 ($n = 1025$)	BMI ≥30 kg/m^2 ($n = 327$)	*P*
Surgical treatment				
BCT	948 (70%)	722 (70%)	26 (69%)	0.006
Mastectomy	234 (17%)	162 (16%)	72 (22%)	
Mastectomy with reconstruction	170 (13%)	141 (14%)	29 (9%)	
Medical treatment				0.685
Neoadjuvant	36 (3%)	27 (3%)	9 (3%)	
Adjuvant chemotherapy	370 (30%)	279 (30%)	91 (31%)	
Adjuvant hormone therapy	543 (45%)	406 (44%)	137 (46%)	
None	275 (23%)	216 (23%)	59 (20%)	
Radiotherapy	67	68	66	0.695
Bilateral procedure	134 (10%)	105 (10%)	29 (9%)	0.469
Locoregional recurrence	27 (2%)	‘20 (2%)	7 (2%)	0.818

BCT breast-conserving therapy

TABLE 5 Multivariate analysis of univariately significant variables

Variable	Odds ratio	95% Wald confidence limit	
		Upper	Lower
Tumor size	1.202	1.082	1.336
LN status (positive vs. negative)	1.480	1.058	2.072
Her2 status (overexpression vs. normal expression)	0.644	0.437	0.951
Multifocal (present vs. not present)	0.529	0.346	0.809
Presentation (palpable vs. nonpalpable tumor)	2.291	1.648	3.185
Surgery			
Mastectomy with reconstruction	0.679	0.405	1.137
Mastectomy	1.309	0.877	1.952

LN lymph node

obesity on overall survival with regard to node status and to tumor size and stage. There was no statistically significant difference.

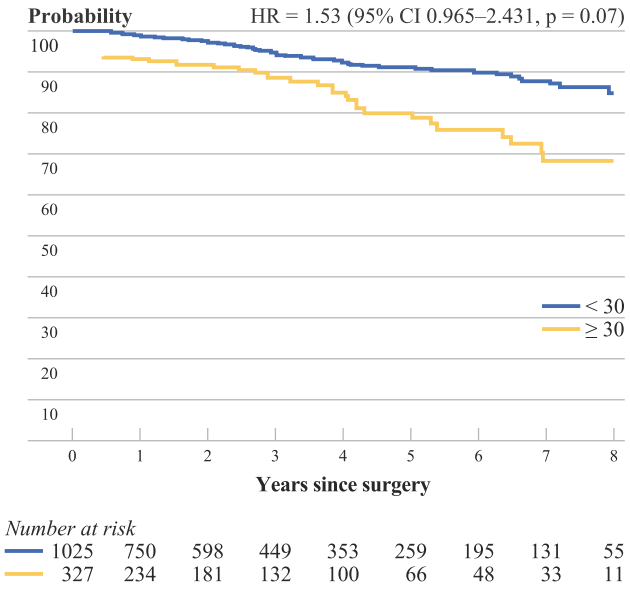

FIG. 1 Overall survival of obese vs. nonobese patients by BMI

DISCUSSION

In the current study, obesity (BMI of ≥30 kg/m^2) was associated with a difference in tumor detection and stage of cancer at initial presentation. Additionally, there was a reduced likelihood of Her2 overexpression and multifocal tumors. Treatment modalities were similar between patient populations except for the type of surgical management among mastectomy patients. There was suggestion of poorer survival for obese breast cancer patients; however, this did not achieve statistical significance except for those who presented with stage II disease. The reason for this is still debated in the literature; likely it is multifaceted, including lifestyle and other comorbidities associated with obesity. Further investigation needs to be done to assess the possibility of the influence of tumor biology. A larger patient population may show a more convincing statistical significance for all stages.

In our study, we found that this obese patient cohort was found among our older breast cancer patients. This is especially true for patients aged >50 years. Obese patients comprised 26% of this age group, compared to 15% of patients <50 years old ($P = 0.002$). In the past,

premenopausal obesity had shown to be somewhat protective in the absence of a strong family history.[29,30] If premenopausal obesity is protective, then this may explain the shift in incidence of breast cancer among obese women into an older age group. A more logical explanation would relate to the increased prevalence of obesity as one ages.[31]

The present study also demonstrated a higher likelihood of detection of breast cancer in obese patients by radiologic imaging. This was unexpected in light of the fact that obese patients presented with larger tumors. The reasons for this phenomenon are unclear, although we speculate that obese patients have more breast tissue, which may make lesions more difficult to palpate.[32] We could not ascertain from our data whether obese patients had a different prevalence of screening mammography or self breast examination, but these are two other factors that could influence the method of detection. Previous studies have shown that obese patients actually have a decreased rate of mammographic screening, including a systematic and meta-analysis review of 17 articles including over 275,000 patients showing that morbidly obese women were less likely to report recent mammographic screening.[33,34] This was especially true for white women. On the basis of our data, we can hypothesize that even though the obese patients are undergoing screening, the screening interval may be longer than what is recommended. The other point that is of importance is even though our obese patients presented with larger tumors, they were not detected by self or clinical breast examination. This suggests that the ability to palpate tumors is more difficult in an obese patient, despite the larger tumor size. This highlights the need for obese patients to follow screening mammogram guidelines in order to possibly detect breast cancer earlier.

Furthermore, obese patients presented with greater incidence of lymph node metastasis. This later stage at diagnosis is not surprising, given their presentation with larger tumors. The later stage at presentation in obese patients has been described in the literature.[12,24,35] In a population-based study, Deglise et al. observed a greater incidence at presentation of cancers >1 cm in size, N2 or N3 disease, and stage III and IV disease.[24] Past research has proposed various reasons for delayed diagnosis of breast cancer. A German population-based study showed that obese women who did palpate an abnormality in their breasts or have breast symptoms were twice as likely to delay presentation to their physician for 3 months after first having symptoms.[36] Other factors that may play a role for late presentation include a patient-related factors such as poor self-esteem or self-image, which delays the pursuit of medical care, or physician-related factors where the treatment of comorbidities may encumber the referral for preventative services such as mammograms.[37,38]

Other explanations for this were evaluated at the molecular level and tumor biology with the production of certain chemokines such as leptin, which is usually found in high levels in obese patients. Fiorio et al. showed a possible correlation between Her2 expression and leptin.[39] However, our data do not support this finding; we found a lower incidence of Her2 positivity among obese patients. Another connection between cancer and diabetes is insulin and insulin-like growth factor (IGF) because cancer cells have more IGF receptors on their cell surface and are sensitive to the growth effects by insulin and IGF.[40] High levels of IGF and increased breast cancer incidence have been observed.[41,42] As a result of the correlation between IGF and cancer, a number of therapeutic interventions, including metformin and targeted agents to IGF, are currently being investigated.[42,43]

Given that our study did not show clear evidence for the cause of more advanced presentation with regard to tumor biology, the source still warrants further investigation. The data available regarding tumor markers, obesity, and breast cancer are inconclusive. Daling et al. found that obese women over the age of 45 were more likely to have higher histologic grade and ER-negative tumors.[19] Triple-negative tumors were shown to occur at higher rates in obese women in two recent studies as well.[20,21] In another report, severe obesity was found to be independently associated with the presence of angiolymphatic invasion [odds ratio (OR) 1.8, 95% CI 1.08–2.99], and that premenopausal obese women with diabetes had a higher incidence of ER-negative (OR 5.22, 1.12–24.29) and triple-negative (OR 14.8, 1.92–113.91) disease.[23] Our data show that Her2-positive tumors occurred less frequently in obese patients, which is inconsistent with some of the literature, as discussed above. Our data show that triple-negative and ER-positive tumors are relatively equal within our patient population, with a lower incidence of Her2-positive tumors in the obese group, although this did not reach statistical significance. Again, this is inconsistent with current conclusions in the literature. Several other groups have demonstrated higher rates of angiolymphatic invasion in obese patients with breast cancer, but our data did not demonstrate a significant difference.[23,44,45] Currently, a larger population-based study is needed to determine whether different phenotypes are more strongly related to obesity.

Despite having larger tumors, obese patients underwent breast-conserving therapy at a comparable rate to nonobese patients, although fewer obese women underwent reconstruction after mastectomy. We were not able to assess the reasons behind these decisions; however, in our institution, it is routine to offer reconstruction to all patients, even those with obesity comorbidities, because this has been proven safe in the past.[46] Conversely, others have reported

a higher risk of wound complications in obese women, which may affect the decision for complicated reconstruction options.[6,47,48] Both reconstruction with implants and deep inferior epigastric perforator or transverse rectus abdominis myocutaneous flap reconstruction have challenges in the obese population, which are often compounded by the presence of diabetes or hypertension.[49–51]

The obese patients in our study did have similar rates of adjuvant therapies as their nonobese counterparts. Despite this, they had worse overall survival, which approached statistical significance and which is in accord with numerous other studies.[9,10] One reason postulated for this difference in survival is poor pharmacokinetics results in insufficient dosing of chemotherapy in the obese patient.[15] Another group has shown a relationship between BMI and a worse pathologic response after neoadjuvant chemotherapy.[52] Comorbidities, or the perception thereof, may influence the decision to undertake more aggressive systemic therapy and may contribute to a worse overall survival even if disease-specific survival is equivalent.

In conclusion, with the obesity epidemic, increased awareness of unique challenges in the obese breast cancer patient in important. Obese patients diagnosed with breast cancer are more likely to have their disease initially detected by imaging, have a larger tumor size, and have lymph node metastases. Although the treatment provided was similar to that provided to nonobese patients, obese patients trended toward worse overall survival. Given these findings, obese women should be encouraged and educated on the importance of obtaining routine mammographic screening, and the clinician should anticipate the complications and increased morbidity of breast cancer in this patient population.

CONFLICT OF INTEREST There are no disclosures for any of the authors.

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