O Experimental ONCOLOGY

HIGH BODY-MASS INDEX IS NOT ASSOCIATED WITH WORSE CLINICOPATHOLOGICAL CHARACTERISTICS IN PREDOMINANTLY OBESE BREAST CANCER PATIENTS

Y. Kemal[1],*, G. Demirag[2], F. Teker[2], E. Kut[2], M. Kefeli[4], K. Ekiz[3], I. Yucel[2]
[1]Samsun Education and Research Hospital, Department of Medical Oncology, Samsun 55100, Turkey
[2]19 Mayis University, Faculty of Medicine, Department of Medical Oncology, Samsun 55270, Turkey
[3]19 Mayis University, Faculty of Medicine, Department of Internal Medicine, Samsun 55270, Turkey
[4]19 Mayis University, Faculty of Medicine, Department of Pathology, Samsun 55270, Turkey

Background: Breast cancer (BC) is the most common cancer among women. A high body-mass index (BMI) is related to increased incidence of BC with poorer prognosis. *Aim*: The aim of the study was to evaluate the association in patients with BC between BMI at the time of diagnosis and biological characteristics, according to the menopausal status. *Materials and Methods*: This retrospective study comprised a total of 318 women with BC. Clinicopathological differences between normal, overweight and obese patients according to menopausal status were evaluated. *Results*: Premenopausal women had a significantly lower BMI than postmenopausal patients (28.7 vs. 31.5, respectively; $p = 0.00001$). No statistically significant association was determined between BMI and clinicopathological characteristics in either the premenopausal or the postmenopausal group (all p values are > 0.05). *Conclusions*: There are many conflicting results in literature on this relationship. The results of this study showed that a high BMI is not associated with worse clinicopathological characteristics in a predominantly obese population. In current medical oncology practice, BC should be evaluated on an individual patient basis and the impact of obesity on BC prognosis seems to be difficult to estimate especially in an obese population.
Key Words: breast cancer, body-mass index, prognosis.

Breast cancer (BC) is the most frequent invasive neoplasm in women. It has been estimated that by 2015 the annual global incidence of BC will be 1.6 million women [1]. The impact of both genetic and environmental risk factors on BC etiology has been well established. Positive associations of reproductive risk factors such as early menarche, late menopause, nulliparity, hormone replacement therapy and postmenopausal obesity are reportedly stronger for estrogen receptor (ER)-positive (ER+) than for ER-negative (ER−) BC [2, 3]. However, the prevelance of obesity has increased dramatically and if current trends continue, over 50% of the world's population will be obese by the year 2030 [4].

Besides its established role as a risk factor, there is now widespread consensus on the importance of obesity as a negative prognostic factor for BC [5, 6]. BC is, however, a biologically heterogeneous disease and definitive evidence is still lacking on the impact of obesity on prognosis. Some authors [7] have found that obese women develop BC with a significantly higher proliferation index, nuclear grade and larger size compared to normal and underweight women. It has also been suggested that obesity at diagnosis is associated with a higher number of metastatic axillary nodes [8]. According to the data from an ATAC (anastrozole, tamoxifen, alone, or in combination) trial, postmenopausal women with high body-mass index (BMI) treated with anastrozole showed significantly more distant recurrences than those with a low BMI [9].

Furthermore, Berclaz et al. [10] demonstrated that elevated BMI is significantly associated with a worse prognosis, especially for pre- and perimenopausal patients. Consistent with these studies, Kawai et al. [11] found that higher BMI was associated with an increase in mortality for premenopausal patients. Their analysis of subgroups showed a positive association between higher BMI and a worse prognosis for patients with hormonal receptor-positive tumors. Thus, the effect of BMI on BC incidence and prognosis seems to be restricted to ER-positive BC. However, it is not yet clear why prognosis mostly correlates with the BMI of premenopausal patients. If the occurrence of BC in patients with high BMI is the result of an increase in estrogen status, these tumors must be highly estrogen dependent, thus resulting in a favorable prognosis. However, a poorer prognosis for patients with high BMI may indicate that BMI plays a significant part in BC etiology and prognosis by mediation through various mechanisms.

The exact reason remains unclear, but different hypotheses have been suggested to explain the poorer survival in obese women. For example, obese women undergo less screening [12] so tend to have more advanced disease at presentation, they have an increased risk of developing second primary cancer [13], obese women develop more complications and toxicity due to chemotherapy [14] and have more aggressive tumors [15]. To determine the crucial role of BMI, the relationship between tumor biological characteristics and the BMI of patients, therefore needs more attention, as to date there have been very few studies on this subject in literature.

The aim of this study was to analyze the association between BMI at the time of diagnosis and biological

characteristics in BC patients, focusing specifically on ER, PR, and stage according to menopausal status.

MATERIALS AND METHODS

The study comprised 318 cases of invasive BC treated with mastectomy or breast-conserving surgery at 19 Mayis University Hospital between 2008 and 2012. Approval for the study was granted by the Ethics Committee of 19 Mayis University; approval number: 2012/502. Detailed information was obtained from the electronic database of the patient archives.

Patient weight and height were recorded before surgery and the BMI is calculated based on the following formula:

$$BMI = bodyweight\,(kg)/height^2\,(m^2).$$

Women were categorized according to the WHO criteria: underweight — BMI < 19 kg/m^2; normal — BMI ⩾ 19 and < 25 kg/m^2; overweight — BMI ⩾ 25 and <30 kg/m^2; obese — BMI ⩾ 30 kg/m^2.

Menopausal status was defined by 1 year of amenorrhea, or previous bilateral oophorectomy. Pathologic tumor grade, estrogen and progesterone receptor (ER and PR) expression, tumor size, lymph node metastasis and HER-2/neu status were recorded from the electronic patient database for statistical evaluation.

Immunohistochemical staining. All the tumor tissues were fixed in formalin and then embedded in paraffin. Tissue sections were cut at 3–4 μm for immunohistochemical staining. Immunohistochemical staining and *in situ* hybridisation were performed using the Ventana BenchMark XT autostaining system (Ventana Medical Systems, Tucson, AZ, USA). ER (Clone 6F11, Novocastra) and PR (Clone 16, Novocastra) antibodies were used and a value of > 1% was accepted as positive. For HER-2 positivity, 3+ HER-2 (Clone CB-11, Biogenex) immunohistochemical staining or a positive HER-2 silver *in situ* hybridization (SISH) test was accepted as HER-2 positive.

Statistical analysis. Statistical analysis were performed using SPSS software for Windows, version 15. In all tests, p < 0.05 was considered statistically significant. The association between BMI and BC characteristics (nuclear grade, ER and PR expression, tumor size, lymph node metastasis and HER-2/neu status) was determined using the χ^2 test (we hypothesized the effect of BMI on prognostic and predicting clinicopathological tumor features).

RESULTS

A total of 318 women with BC were enrolled in this retrospective study. The mean age of the study participants was 50.0 ± 9.7 years (range 27–77 years). Of the total patients, 156 were premenopausal and 162 were postmenopausal. The premenopausal women had a significantly lower BMI than the postmenopausal women (28.7 vs. 31.5, respectively; *p* = 0.00001) (Table 1). A total of 78% of premenopausal women were classified as overweight/obese, while, in the postmenopausal group, nearly all the patients (92%) were overweight/obese (Table 2).

Table 1. Relationship between BMI and menopausal status of BC patients

Characteristics	Premenopausal, n (%) N = 156	Postmenopausal, n (%) N = 162	p value
Age[1] (years)	43.1 (6.2)	56.5 (7.8)	0.00001
BMI (kg/m^2)	28.7 (4.9)	31.5 (5.3)	

Note: [1]Mean (Standard deviation).

Table 2. BMI distribution

BMI distribution	Premenopausal women, n (%) N = 156	Postmenopausal women, n (%) N = 162	p value (χ^2 test)
Normal weight (19 < BMI < 24.9)	36 (22.1)	13 (8.0)	
Overweight (25 < BMI < 29.9)	54 (35.0)	51 (31.5)	0.001
Obese (BMI > 30)	66 (42.9)	98 (60.5)	

Correlation between BMI and clinicopathological characteristics of BC. The patients were divided into three groups based on BMI; the normal weight group (BMI smaller than 24.9 kg/m^2) comprised 49 patients, the overweight group (BMI between 25 and 30 kg/m^2) 105 patients and the obese group (BMI > 30 kg/m^2) 164 patients.

In both the premenopausal and the postmenopausal group no statistically significant association was determined between BMI and clinicopathological characteristics (all *p* > 0.05) (Table 3, 4).

Table 3. Relationship between BMI and clinicopathological characteristics in premenopausal patients

Characteristics	Normal weight, n (%) N = 34*	Overweight, n (%) N = 54	Obese, n (%) N = 66	p value
Nuclear grade				
1	1 (2.9)	5 (9.3)	8 (12.1)	0.221
2	27 (79.4)	32 (59.3)	45 (68.2)	
3	6 (17.6)	17 (31.5)	13 (19.7)	
Tumor size				
1	8 (23.5)	20 (37.0)	26 (39.4)	
2	20 (58.8)	25 (46.3)	29 (43.9)	0.767
3	4 (11.8)	7 (13.0)	9 (13.6)	
4	2 (5.9)	2 (3.7)	2 (3.0)	
Lymph node metastasis				
Negative	13 (38.2)	20 (37.0)	30 (45.5)	0.627
Positive	21 (61.8)	34 (63.0)	36 (54.5)	
ER				
ER$^+$	28 (82.4)	36 (66.7)	49 (74.2)	0.263
ER$^-$	6 (17.6)	18 (33.3)	17 (25.8)	
PR				
PR$^+$	21 (61.8)	31 (57.4)	42 (63.6)	0.781
PR$^-$	13 (38.2)	23 (42.6)	24 (36.4)	
HER2				
Positive	8 (23.5)	21 (38.9)	14 (21.2)	0.081
Negative	26 (76.5)	33 (61.1)	52 (78.8)	

Note: *grade and other characteristics are reached 34 of 36 patients.

DISCUSSION

Consistent with many previous studies, the results of this study have shown that the BMI of postmenopausal patients was significantly higher than that of premenopausal patients. The strength of this study is the homogeneity in patient management as all the patients were treated and detected in a single institution. However, no significant association was determined between BC characteristics and the BMI of the patients in the study group.

Table 4. Relationship between BMI and clinicopathological characteristics in postmenopausal patients

Characteristics	Normal weight, n (%) N = 13	Overweight, n (%) N = 51	Obese, n (%) N = 98	p value
Nuclear grade				
1	1 (7.7)	9 (17.6)	17 (17.3)	0.375
2	6 (46.2)	31 (60.8)	60 (61.2)	
3	6 (46.2)	11 (21.6)	21 (21.4)	
Tumor size				
1	3 (23.1)	19 (37.3)	42 (42.9)	
2	8 (61.5)	28 (54.9)	45 (45.9)	0.745
3	1 (7.7)	3 (5.9)	8 (8.2)	
4	1 (7.7)	1 (2.0)	3 (3.1)	
Lymph node metastasis				
Negative	7 (53.8)	27 (52.9)	39 (39.8)	0.249
Positive	6 (46.2)	24 (47.1)	59 (60.2)	
ER				
ER$^+$	9 (69.2)	40 (78.4)	70 (71.4)	0.615
ER$^-$	4 (30.8)	11 (21.6)	28 (28.6)	
PR				
PR$^+$	4 (30.8)	25 (49.0)	53 (54.1)	0.276
PR$^-$	9 (69.2)	26 (51.0)	45 (45.9)	
HER2				
Positive	5 (38.5)	11 (21.6)	28 (28.6)	0.418
Negative	8 (61.5)	40 (78.4)	70 (71.4)	

Many studies in literature have investigated the association between BMI and DC. It is well-known that a high BMI is positively associated with increased ER($^+$) BC risk in postmenopausal women due to enhanced production of circulating estrogens [16, 17]. Recently, new studies have focused on the importance of obesity as a negative prognostic factor. Some authors [18, 19] have found that obese women develop aggressive BC with a significantly higher number of metastatic axillary nodes, higher proliferation index, nuclear grade and larger size compared to normal and underweight women. If obesity results in more BC because of high estrogen levels, these tumors must be estrogen dependent with a favorable prognosis. However, various mechanisms play a role in aggressive prognosis. Overweight women have high levels of insulin-like growth factor and other growth factors such as leptin, TNF-α, IL-6 and VEGF, which promote angiogenesis, tumor growth, metastasis and inhibit apoptosis [20].

Although BC is a biologically heterogeneous disease, definitive evidence is still lacking on the impact of obesity on BC prognosis. In different studies, different associations have been found between clinicopathological characteristics and BMI with no standard result reached as yet. Recently, Yanai et al. [21] reported that a high BMI showed significantly higher lymph node metastasis, and Mazzarella et al. [22] found that obesity significantly correlates with overall survival and increases distant metastasis in ER(−)/Her/neu-positive BC. In contrast, Biglia et al. [23] could not find any statistically significant correlation between BC subtypes and BMI in both pre- and postmenopausal patients. When planning current treatments according to molecular classification and genomic characteristics, an easy to apply factor such as BMI can be of benefit and positive research studies in support of this are undoubtedly important as obesity is a modifiable risk factor.

The results of this study did not support some previous studies which have stated that a higher BMI is associated with worse clinicopathological characteristics in BC patients. The current study population consisted of predominantly obese patients with mean BMI of 28.7 in the premenopausal group and 31.5 in the postmenopausal group. These values are considerably higher than those of previously reported studies. In a recent similar study by Lino-Silva et al. [24] of endometrial carcinoma in obese patients, it was reported that a high BMI is not a prognostic factor of a worse condition. However, that study did not include a high number of patients which may have been sufficient to show small but significant differences.

In conclusion, obesity, which is increasing dramatically and becoming a major global healthcare problem, is a variable risk factor for BC. It is difficult to treat and follow obese BC patients because of complications and comorbidities. Cancer is different in each patient and personalized treatment should be a priority. In current clinical practice, there should be intervention against obesity although a direct relationship between BMI and simple clinical and pathological characteristics was not determined. BC is a heterogeneous disease and the impact of obesity on BC prognosis seems to be difficult to estimate. Future studies are needed to evaluate the relationship between molecular characteristics of BC and BMI.

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