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ORIGINAL ARTICLE

Impact of the obesity on lymph node status in operable breast cancer patients

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Summary

Purpose: *Although many studies have shown association of obesity and tumor size, the association with the lymph node status is not clear. We examined the relationship of the lymph node status and obesity and other possible factors in early breast cancer patients.*

Methods: *In this retrospective cohort study, 1295 breast cancer patients who had axillary dissection were included. Patients were grouped according to their body mass index (BMI) values at the time of diagnosis. We analyzed the relationship between BMI and patient and tumor characteristics, especially lymph node status.*

Results: *The median patient age was 48 years (range 20-84). Of the patients 69.6% had modified radical mastectomy and the remaining 30.4% had breast-conserving surgery and axillary disection. Median BMI of the patients was 27.2 kg/m² and 33.1% (N=429) of them had normal BMI, 36% (N=471) were overweight and 30.5% (N=395) were obese at the time of the diagnosis. Of the patients, 44.2% had N0 disease, and 55.8% had lymph node metastasis. N1 disease had 28.3% (N=367), 13.8% (N=179) had N2 and 13.7% (N=177) had N3 disease. When patients were classified as normal (≤24.9 kg/m²) and obese (>24.9 kg/m²) group, the total number of lymph nodes removed was higher in the obese group and this difference was statistically significant (18.12±10.48 and 20.36±11.37, respectively, p= 0.001).*

There was strong correlation between the number of the dissected lymph nodes and BMI (r=0.11; p<0.001). However, there was no statistically significant correlation between the number of metastatic lymph nodes and BMI. The mean number of the dissected and involved lymph nodes was higher in the HER2 positive group compared to the negative ones (21 vs 19, p=0.008; 6 vs 3, p<0.001; respectively)

Conclusion: *The number of the dissected lymph nodes was slightly higher in obese patients but there was no correlation between metastatic lymph node number and BMI. The number of the dissected and involved lymph nodes was higher in the HER2 positive group.*

Key words: *breast cancer, body mass index, lymph node, survival*

Introduction

Factors that increase the risk of breast cancer among obese women are not completely understood, whereas the most important one is long-term estrogen exposure. Increased levels of estrogen is important for the tumor initiation and progression process [1,2]. The level of free estrogen is inversely proportional to the level of sex hormone binding globulin (SHBG). SHBG levels were found to be lower in cases of breast cancer [2]. The main source of estrogen in postmenopausal women is peripheral adipose tissue where the conversion of androstenedione to estrogen occurs [1]. In most of the epidemiologic studies including postmenopausal women, increased risk of breast cancer has been observed in overweight or obese group (relative risk [RR]: 1.26, 95% confidence interval [CI]: 1.09-1.46) [3-7]. Ovaries are the main source of estrogen in premenopausal women. More anovulatory menstruel cycles, leading to less exposure to estrogen, have been observed in premenopausal groups. In several case-control and prospective cohort studies

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of premenopausal women, an inverse relationship between weight and breast cancer risk has been observed. In metaanalyses, the relative risk for breast cancer in premenopausal women has found to be decreased with increasing body mass index (BMI) (RR 0.6, 95% CI 0.4-0.8) [1,3-6].

Other factors that adversely affect the prognosis of breast cancer associated with obesity are large tumor diameter and lymph node involvement [7]. More frequent lymph node involvement, larger tumor size and worse prognosis were observed in obese breast cancer patients than in leaner ones [4,8]. In a study of 176 node-positive breast cancer patients, a significant correlation between obesity and early axillary nodal metastasis was found (p=0.0002) [9]. In another study supporting this theory, more axillary lymph node involvement was detected in obese postmenopausal patients than in leaner patients (p=0.001) [10]. In a study examining the effect of obesity in a mammography screening program, there was a statistically significant relationship between overweight and axillary lymph node involvement in the pre-screening group and screening controls ($p<0.05$) [11]. Berclaz et al. found a strong correlation between obesity and lymph node involvement in operable breast cancer patients [12].

Obesity also affects diagnostic assesment of obese patients negatively. Obese patients present with more advanced stage at diagnosis, and detection of primary tumor and enlarged axillary lymph node is more difficult [13]. In a study evaluating the mapping of axillary lymph nodes, BMI had affected the procedure inversely and mean BMI was greater in failed procedures [14].

Although there have been many studies evaluating the association between obesity and tumor size, a few studies examined the association between BMI and lymph node status.

Methods

In this retrospective cohort study, 1295 invasive breast cancer patients, who were followed up in the Department of Medical Oncology of Hacettepe University Cancer Institute 2001-2011, were included. The patient data related to BMI and lymph node status were analyzed. At first admission, demographic data, menopausal status, height and weight values were recorded. Postmenopausal status was defined as amenorrhea for 6 months. In patients with amenorrhea less than 6 months, menopausal status was defined by FSH and LH estimation levels. Perimenopausal patients were included in the premenopausal group in the statistical analysis.

Table 1. Body Mass Index groups

BMI (kg/m²)	*Weight groups*
20-24.9	Normal weight
25-29.9	Overweight
30-39.9	Obese
≥40	Morbidly obese

BMI: body mass index

To define obesity, BMI (weight in kg/height^2 in m^2) value was used. Patients were grouped according to their BMI values (Table 1). Classification was based on the NIH Clinical Guidelines on Obesity [15]. Obese and morbidly obese groups were analyzed together.

Histologic type, tumor size, grade, lymph node involvement, lymphovascular invasion, hormone receptor and HER-2 status were recorded from the hospital pathology database. Staging was done according to the National Compherensive Cancer Network (NCCN) Guidelines using tumor- lymph node- metastases (pTNM) classification system. Estrogen receptor (ER) and progesterone receptor (PR) status were assessed by immunohistochemistry. Nuclear staining in more than 5% of tumor cells was considered as positive. Expression of HER-2 was also determined immunohistochemically. HER-2 positivity (a score of 3+) was defined as strong complete membrane staining in more than 10% of tumor cells; scores of 0 and 1 were considered negative, and fluorescence *in situ* hybridization (FISH) was done for all 2+ tumors.

Type of surgery, chemotherapy, hormone therapy, radiotherapy and detailed information about their starting/ending dates were obtained from the medical records. All patients received adjuvant therapy. Overall survival (OS) was considered from the date of diagnosis to the date of last information or breast cancer death. The interval from the date of diagnosis to the date of locoregional or distant recurrence was defined as disease free survival (DFS).

Statistics

Comparison of the patient characteristics in 3 different categories of BMI were analyzed by using analysis of variance (ANOVA) for means and Pearson's chi-square test for frequencies. Kaplan-Meier method with log-rank test was used for assessing breast cancer-specific mortality distributions in relation to lymph node involvement among BMI groups. Univariate and multivariate analyses were carried out and Cox proportional hazards models for outcomes were also performed in the overall study population according to BMI and lymph node involvement. All data was entered and analysed using Statistical Package for Social Sciences version 15.0 (SPSS, Inc., Chicago, IL, USA). Appropriate statistical analysis was carried out with a two-sided level of 0.05 and/or 95% confidence interval (CI).

Table 2. General patient and tumor characteristics

Characteristics	*N (%)*
BMI	
Normal weight	429 (33.1)
Overweight	471 (36.4)
Obese	395 (30.5)
Menopausal status	
Pre	717 (55.4)
Post	578 (44.6)
Histologic type	
IDC	1018 (78.6)
ILC	68 (5.3)
IDC+ILC	126 (9.7)
Pathological tumor size	
T1	420 (32.8)
T2	660 (51.6)
T3	172 (13.4)
T4	27 (2.1)
Lymph node involvement	
N0	572 (44.2)
N1	367 (28.3)
N2	179 (13.8)
N3	177 (13.7)
Grade	
1	141 (11.9)
2	542 (45.7)
3	503 (42.4)
LVI	
Absent	91 (18.1)
Present	411 (81.9)
ER	
Negative	355 (27.5)
Positive	934 (72.5)
PR	
Negative	359 (28.0)
Positive	924 (72.0)
HER-2	
Negative	978 (77.9)
Positive	277 (22.1)

BMI: body mass index, IDC: infiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma, ER: estrogen receptor; PR: progesterone receptor, LVI: lymphovascular invasion

Results

Patient and tumor characteristics

The mean age of 1295 breast cancer patients was 48.9±10.7 years. Of the patients 33.1% were in the normal weight (N=429), 36% were in the overweight (N=471) and 30.5% were in the obese (N=395) group (Table 2). The mean age at diagnosis in normal weight, overweight and obese groups were 44.5±11.1 , 49.6±11.1 and 52.7±10.0 years, respectively (p=0.001). Of the patients 55.4% (N=717) were premenopausal and 44.6% (N=578) postmenopausal. The percentages of postmenopausal women according to their BMI were 28.4%, 46.7% and 59.7% in normal weight, overweight and obese group, respectively. Obesity was associated with older age (p= 0.001) and with postmenopausal status at diagnosis (p< 0.0001).

Infiltrating ductal carcinoma was the most common tumor histology (78.6%) in all groups, followed by mixed infiltrative carcinoma (9.7%) and infiltrative lobular carcinoma (5.3%). The mean tumor diameter among all groups ranged between 0.2 cm to 16 cm. The mean tumor diameter was 3.1±2.2 cm in the normal weight group, 3.1±2.2 cm in the overweight group and 3.3±2.1 cm in the obese group (p=0.31). Tumor characteristics according to BMI groups are shown in Table 3.

In 44.2% (N=572) of the patients there was no axillary lymph node involvement. The distribution of patients with lymph node involvement was as follows: 28.3% (N=367) had N1, 13.8% (N=179) had N2 and 13.7% (N=177) had N3 disease. The mean number of lymph nodes removed was 19.6±11.1. When patients were classified simply in 2 groups (as normal [≤24.9 kg/m^2] and obese [>24.9 kg/m^2]), the mean number of lymph nodes removed was 18.1±10.5 and 20.4±11.4, respectively (p=0.001). The percentages of patients with and without lymph node involvement were 53.8 vs 46.2% in the normal weight group, 56.5 vs 43.5% in the overweight group and 57.2 vs 42.8% in the obese group (p=0.58). When we looked at the association between lymph node involvement and molecular subtype, the ratio of patients with nodal involvement in luminal A, HER-2 positive, triple negative and luminal B were 53, 74, 50.6 and 64.2%,respectively, while the ratio of patients without nodal involvement in the same molecular groups was 47, 26, 49.4 and 35.8%, respectively. Lymph node involvement was more frequent in HER-2 positive breast cancer patients whereas least frequent in the triple negative group. The difference between molecular subtypes in terms of nodal involvement was statistically significant (p<0.001).

Most of the patients (86.2%) had grade 2-3 tumors. There was no association between tumor grade and BMI (p=0.24). A similar negative association was also observed in lymphovascu-

Table 3. Distribution of patient and tumor characteristics by BMI

Characteristics	*Normal weight N (%)*	*Overweight N (%)*	*Obese N (%)*	*p-value*
Menopausal status				<0.0001
Pre	307 (71.6)	251 (53.3)	159 (40.3)	
Post	122 (28.4)	220 (46.7)	236 (59.7)	
Pathological tumor size (pT)				0.107
pT1	156 (36.8)	152 (32.7)	112 (28.7)	
pT2	209 (49.3)	245 (52.7)	206 (52.8)	
pT3	53 (12.5)	55 (11.8)	64 (16.4)	
pT4	6 (1.4)	13 (2.8)	8 (2.1)	
Tumor grade				0.243
1	54 (13.8)	50 (11.5)	37 (10.2)	
2	184 (47.2)	201 (46.4)	157 (43.3)	
3	152 (39.0)	182 (42.0)	169 (46.6)	
Total dissected lymph node number (mean±SD)	18.1±10.5	20.4±11.4		0.001
Positive lymph node number (mean±SD)	3.15±6.1	3.7±6.4		0.104
Pathological nodal status (pN)				0.011
pN0	198 (46.2)	205 (43.5)	169 (42.8)	
pN1	121 (28.2)	138 (29.3)	108 (27.3)	
pN2	68 (15.9)	67 (14.2)	44 (11.1)	
pN3	42 (9.8)	61 (13.0)	74 (18.7)	
LVI				0.296
Absent	35 (22.0)	30 (16.9)	26 (15.8)	
Present	124 (78)	148 (8.1)	139 (84.2)	
ER				0.013
Negative	100 (23.4)	127 (27.1)	128 (32.6)	
Positive	327 (76.6)	342 (72.9)	265 (67.4)	
PR				0.264
Negative	111 (26.2)	127 (27.1)	121 (31.0)	
Positive	313 (73.8)	342 (72.9)	269 (69.0)	
HER-2				0.124
Negative	335 (81.3)	349 (75.9)	294 (76.8)	
Positive	77 (18.7)	111 (24.1)	89 (23.2)	

E: estrogen receptor, PR: progesterone receptor, LVI: lymphovascular invasion, SD: standard deviation

Table 4. General treatment modalities of the patients

Treatment	*All patients N (%)*	*Normal weight N (%)*	*Overweight N (%)*	*Obese N (%)*	*p-value*
Hormone therapy					0.008
No	268 (20.8)	74 (17.3)	92 (19.7)	102 (25.8)	
Yes	1023 (79.2)	354 (82.7)	376 (80.3)	293 (74.2)	
Chemotherapy					0.893
No	247 (19.1)	82 (19.1)	87 (18.5)	78 (19.7)	
Yes	1048 (80.9)	347 (80.9)	384 (81.5)	317 (80.3)	
Surgery					0.657
MRM	897 (69.6)	303 (70.8)	320 (68.1)	274 (70.1)	
BCS	392 (30.4)	125 (29.2)	150 (31.9)	117 (29.9)	

MRM: modified radical mastectomy, BCS: breast conserving surgery

lar invasion (LVI). The incidence of LVI in normal weight, overweight and obese group was 78, 83.1 and 84.2%, respectively. The incidence of LVI increased with the increasing BMI levels, but it didn't reach statisticall significance (p=0.29).

Overall, 78.7% of the patients had luminal A and B (N=1015), 8.1% had HER-2 overexpressing (N=104) and 13.2% (N=170) had triple negative breast cancer. The percentage of patients with HER-2 overexpressing breast cancer was significantly higher among obese compared to normal weight women (11.2 vs 5.2%; p=0.006). In patients with ER negative tumors, 37.5% had N0, 30.1% had N1, 13.8% had N2 and 18.6% had N3 disease. The frequency of N3 disease was 13% in normal weight, 17.3% in overweight and 24.2% in obese women (p=0.011).

All patients underwent surgery. Of these, 69.6% had modified radical mastectomy and 30.4% had breast conservation surgery and axillary disection. The number of patients treated with chemotherapy was 1048 (80.9%). Standard doses of combined chemotherapy regimens were given to all BMI groups and 1023 patients (79.2%) received endocrine therapy. The number of patients receiving endocrine therapy was less in the obese group depending on the hormone receptor status (74.2 vs 82.7%; p=0.008). Treatment modalities among BMI groups are shown in Table 4.

Survival

The median follow-up period was 30.4 months (range 1-161). During follow-up, 224 patients (17.3%) died and 375 (29.0%) developed recurrent disease. The median OS was 106 months (95%CI 96.6-113.4) in the normal weight group, 88 months (95% CI 62.2-115.6) in the overweight group and 74 months (95% CI 49.2-98.8) in the obese group (p=0.04) (Figure 1). The median DFS was 65 (95% CI 48.5-81.5), 58 (95% CI 51.3-64.7) and 55 (95% CI 45.7-64.1) months in the normal, overweight and obese group, respectively (p= 0.73) (Figure 2).

The risk of breast cancer-specific mortality was significantly higher in overweight (HR 1.41, 95% CI 1.01-1.95; p=0.04) and obese patients (HR 1.47, 95% CI 1.04-2.09; p=0.02), compared to normal weight women. When the mortality risk in patients with node-positive breast cancer was analyzed according to BMI groups, statistically significant increased risk was found in the overweight (HR 1.38; 95% CI 1.00-1.91; p=0.04) and the obese group (HR 1.50; 95% CI 1.06-2.10; p=0.02), compared to the normal weight group.

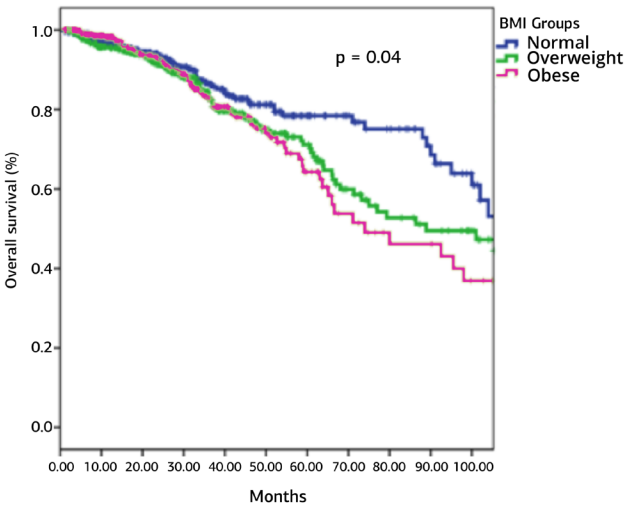

Figure 1. Kaplan-Meier overall survival according to body mass index groups.

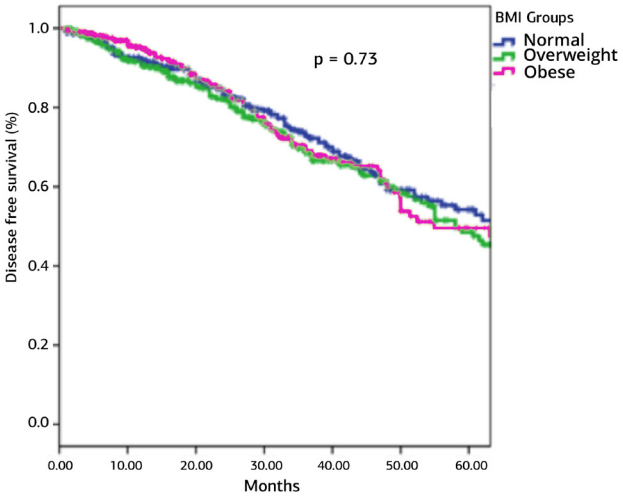

Figure 2. Kaplan-Meier disease free survival according to body mass index groups .

Discussion

In this study, the survival rates were negatively affected by increased BMI and lymph node status in node-positive breast cancer. Most of the studies have suggested that the survival rates are worse in obese than leaner patients even with early stage disease [1-3,5,8,10,12,16-22].

The increased risk of breast cancer with weight gain in postmenopausal women was supported in many studies [1,2,19]. Obesity was associated with older age and with being postmenopausal at diagnosis. BMI value was found to be higher in postmenopausal women than in premenopausal ones in many previous studies as well as in our study. The peripheral conversion of androgens to estrogens occurs in

fat tissue. In addition, the level of SHBG is inversely proportional to weight. Leptin is an angiogenic factor and leptin level correlates positively with total body fat and BMI [19]. Depending on these data, increased risk of breast cancer in postmenopausal women related to obesity and poor prognosis in these patients are now known facts.

In the present study we found a statistically significant association between the number of the excised lymph nodes and obesity (p=0.001), but no relation with BMI and the metastatic lymph node number was found. In studies investigating the relationship between the number of metastatic lymph nodes and BMI, controversial results have been obtained. In the Porter and colleagues study, an elevated risk of lymph node metastasis in association with increasing BMI was found [4]. Similarly, in a study of 176 node-positive breast cancer patients, a significantly increased risk of early axillary metastases was found in the obese group [9]. Schapira and colleagues also showed more common axillary lymph node involvement in obese postmenopausal patients than in leaner cases with unfavorable prognosis [10]. In the Greenberg and colleagues study, a statistically significant increase in the number of involved lymph nodes was determined in association with increasing weight, however this correlation had not any impact on survival [23].

In contrast to the literature [13,14], more axillary lymph nodes were removed in obese patients (>24.9 kg/m^2) in our study. This may be the reason for the greater number of metastatic lymph nodes in the obese group. Another reason for the greater number of the removed lymph nodes in obese patients maybe the metastatic lymph nodes detected during the frozen sections examination of the axillary dissection.

In some studies, similar increased risk of nodal involvement had been associated with tumor ER and PR status [5,7,24]. However, other studies had found no relation between BMI and lymph node involvement and hormone receptor status [3,4,10]. We found a significant association (p<0.001) between BMI groups and lymph node involvement in HER-2 positive breast cancer patients. According to the results of some studies, lymph node involvement was seen at least in triple negative patients [25,27]. Association between hormone receptor and HER-2 status of tumor tissue and axillary lymph node involvement was controversial [27,28]. In some studies, a positive association was found between nodal involvement and HER-2 positivity (35.8% in HER-2 vs 45.7% in HER-2+ ; OR=1.508). This relationship was more evident in triple positive breast cancer patients (35.7% non-triple positive vs 56.2% triple positive; OR=2.309) [25,26,28]. In the study by Van Calster et al., axillary nodal involvement was least likely in ER positive, PR negative, HER-2 positive patients. Due to molecular biology, the authors suggested an interaction between PR and HER-2 for tumor cell migration and nodal involvement [25]. In other studies, axillary nodal involvement was seen at least in the triple negative group [26,27]. Wiechmann et al. found a correlation between HER-2 positivity and 4 or more positive lymph nodes [26]. On the contrary, there was no relationship between HER-2 status, molecular subtypes and nodal invasion in some studies [27,28].

Maehle and colleagues had examined the effect of lymph node involvement on survival in obese patients and found that this effect depends on the tumor hormonal status. They showed that increased tumor size associated with obesity was observed especially in PR negative disease and the risk of tumor recurrence was also found to be higher in these patients [29].

In our study, obese women had more often large (18.5 vs 13.9%) and high grade tumors (46.6 vs 39.0%) than normal weight women; however, the difference did not reach statistical significance. A similar association was also observed in LVI. Schapira et al. demonstrated that obesity did not affect tumor size [10]. On the other hand, in the Porter and colleagues study, aggresive features of tumor (large tumor size and high grade) have been reported to increase with increasing weight (p=0.01 and p=0.03 respectively). They showed that T1 tumors were common in the normal and overweight groups, whereas T2-4 tumors were seen more frequently in the obese group [4]. Similar results were also supported by other studies [4,5,10-12,16].

In conclusion, we found a statistically significant association between lymph node involvement and obesity, especially in HER-2 positive breast cancer patients. This maybe due to the greater number of lymph nodes removed in the obese group, in contrast to most of the studies [13,14]. Moreover, we determined an increased risk of breast cancer-specific mortality in the overweight and obese patients compared to normal weight women. The mortality risk in node-positive breast cancer patients was higher in the overweight and obese groups. In the literature, this association is most probably attributable to hormonal (menopausal status, estrogen burden, insulin, insulin-like growth factors, leptin) and non-hormonal (dietary factors, later diagnosis in obese patients, cytokines) factors. Further studies showing the relationship between BMI and lymph node involvement and its impact on survival are needed.

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