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ORIGINAL ARTICLE

# The prognostic impact of obesity on molecular subtypes of breast cancer in premenopausal women

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## Summary

***Purpose:*** *The increasing incidence of obesity throughout the world will result in expansion of the number of women at risk for developing breast cancer. Obesity is associated with adverse outcomes in postmenopausal women with breast cancer. İn premenopausal women, the association is less clear. We investigated the impact of obesity on tumor features, hormonal status, recurrence and mortality in premenopausal breast cancer patients, classified according to molecular subtypes.*

***Methods:*** *818 premenopausal women with nonmetastatic breast cancer were analysed. Patients were classified into 3 groups according to body mass index (BMI): i) normal body weight (BMI: 18.5-24.9 kg/m$^2$); ii) overweight (BMI: 25-29.9 kg/ m$^2$); and iii) obese (BMI:>30 kg/ m$^2$). Clinocopathologic characteristics and survival rates were analyzed for triple negative, HER-2 overexpressing and luminal subtypes.*

***Results:*** *Obese patients compared with normal-weight women were older at diagnosis (p<0.001) and more often had high grade tumor (57.1 vs 42.3%; p=0.04) with lymphovascular invasion (79.5 vs 63.9%; p=0.03). The median follow-up period after diagnosis was 29 months. According to the molecular subtypes, overall survival (OS) and disease free survival (DFS) were significantly shorter in obese patients with triple negative breast cancer (TNBC) (p=0.001 and p=0.006, respectively). Obesity (HR 1.4; 95% CI 1.0-2.1; p=0.04) and lymphovascular invasion (HR 2.1; 95% CI 1.3-3.3; p=0.02) were found to be independent prognostic factors for TNBC mortality.*

***Conclusion:*** *Obesity is associated with estrogen (ER) and progesterone receptor (PR) negative tumors and poor OS in premenopausal women with breast cancer.*

***Key words:*** *breast cancer, molecular subtypes, obesity, premenopausal, prognosis*

## Introduction

The prevalence of obesity and overweight is increasing in both developed and developing countries. Obesity is an established risk factor for postmenopausal breast cancer [1,2]. The relative risk of postmenopausal breast cancer was found to be 1.26 (95% CI:1.09-1.46) in women with BMI of 28 kg/m$^2$ or above on an analysis of pooled data from 7 prospective cohort studies [3]. It has been reported that overweight/obese women have higher estrogen levels due to the conversion of androgen to estrogen in excess adipose tissue and this estrogen milieu is important in the initiation and the progression of postmenopausal breast cancer [4-6].

Studies among premenopausal women have generally found modest inverse associations between BMI and breast cancer incidence [7,8]. The mechanism for the protective effect of obesity in premenopausal women is less well understood. In obese premenopausal women, the hormonal milieu is different and obesity has been associated with low serum hormone-binding globulin, hyperandrogenism, hyperinsulinemia, increased insulin-like growth factor-I and high serum leptin levels, suggesting a pathway not mediated by endogenous sex hormones [5,9-13]. Previous studies

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have noticed a negative association between obesity and survival of breast cancer, regardless of menopausal status [14-16].

There are no prior studies that evaluated the influence of premenopausal obesity on molecular subtypes of breast cancer individually. The focus of this cohort study was to investigate the impact of BMI on tumor features, hormonal status, recurrence and mortality in premenopausal breast cancer survivors, classified according to molecular subtypes.

## Methods

From 2001 through 2011, 818 premenopausal women with nonmetastatic breast cancer who have been followed up at the Department of Medical Oncology, Hacettepe University Institute of Oncology, were evaluated. Patients with missing data of height or weight (N=78) were excluded. Patients with unknown ER, PR and HER-2 status (N=12) were also excluded. After exclusion 733 cases were eligible for analysis.

Tumor characteristics, including size, grade, lymphovascular and perineural invasion, extracapsular extension, ER/ PR/ HER-2 status and number of involved axillary nodes were abstracted from the relevant diagnostic pathology reports. Expression of HER-2 was 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 performed on all 2+ tumors. ER and PR were also assessed by immunohistochemical assays. Nuclear staining in more than 5% of tumor cells was considered as positive for ER and PR.

Breast cancer is characterized by its molecular and clinical heterogeneity: luminal (ER positive and/or PR positive, HER-2 negative); HER-2 overexpressing (ER negative, PR negative, HER-2 positive); and TNBC (ER negative, PR negative, HER-2 negative).

Body weight and height of all patients at the time of admission to the clinic had been recorded accurately. BMI was calculated as BMI=weight (kg) / height$^2$ ($m^2$). BMI was classified according to World Health Organization criteria: underweight (<18.5 kg/$m^2$), normal weight (18.5-24.9 kg/$m^2$), grade 1 overweight (25.0-29.9 kg/$m^2$), grade 2 overweight (30.0-39.9 kg/$m^2$) and grade 3 overweight (≥40 kg/$m^2$). There were 14 patients in the underweight group and 3 patients in the grade 3 overweight group. We combined the underweight group with the normal weight group and the grade 2 overweight group with the grade 3 overweight group, resulting in 3 BMI categories: i) normal body weight (18.5-24.9 kg/$m^2$); ii) overweight (25-29.9 kg/$m^2$) and iii) obese (≥30.0 kg/$m^2$).

OS was measured from the date of diagnosis to the date of death from breast cancer. DFS was defined as the interval from the date of diagnosis to the date of locoregional or distant recurrence which was abstracted from medical records.

*Statistics*

Comparison of the characteristics of patients in 3 different categories of BMI were analyzed by using analysis of variance (ANOVA) for means and Pearson chi-square test for frequencies. We used the Kaplan-Meier method with log-rank test for assessing breast cancer-specific mortality distributions in relation to BMI among all women and stratified for breast cancer subtypes. Cox proportional hazards model for outcomes related to survival was also performed in the overall study population according to breast cancer subtypes and BMI. To select those factors with independent significant influence on outcomes, multivariate analyses were carried out in a stepwise Cox regression analysis. Prior to this application, univariate analyses were performed for a preliminary exploration of marked associations. All data was entered and analysed using the 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).

## Results

Normal weight had 43.7% of the patients, 33.0% were overweight and 23.3% were obese at diagnosis. The mean age was 38.4±6.7 years in the normal weight group, 40.6±6.4 in the overweight group and 42.7±6.2 in the obese group. Obese patients, compared with normal and overweight women were significantly older at diagnosis (p<0.001).

*Tumor features*

When compared with normal weight women, obese women more often had high tumor grade (57.1 vs 42.3%; p=0.04) with lymphovascular invasion (79.5 vs 63.9%; p=0.03). There was no difference between BMI groups regarding perineural invasion (13.2 vs 10.4%), extracapsular extension (41.7 vs 42.9%) and axillary lymph node involvement. Table 1 shows the tumor characteristics according to BMI.

ER and PR levels were significantly lower in obese breast cancer patients (p<0.001 and p=0.002, respectively). Overall, 76.5% (N=561) had luminal, 8.9% (N=65) had HER-2 overexpressing and 14.6% (N=107) of the patients had TNBC. Luminal breast cancer was the most common subtype in all BMI groups. However, the proportion of luminal breast cancer patients was lowest among those with

BMI ≥30 kg/m$^2$ (66.7%; p=0.002). The percentages of patients with TNBC (19.9 vs 11.9%; p=0.04) and HER-2 overexpressing breast cancer (13.5 vs 5.6%; p=0.012) were significantly higher among obese compared to normal weight women.

*Recurrence and mortality*

Chemotherapy was administered to 655 (89.6%) patients. Of these, 90.2% were treated in the adjuvant setting and 9.8% in the neoadjuvant setting. Standard doses of combined chemotherapy regimens (cyclophosphamide, anthracyclines, taxanes, methotrexate, fluorouracil and trastuzumab) were given to all BMI groups. There were no significant differences in receiving chemotherapy among groups (p=0.671).

The median follow-up period after diagnosis was 29 months (range 1-161). The median OS was 106 months (95% CI, 88.5-123.4) in normal weight, 80 months (95% CI, 56.2-103.7) in overweight and 58 months (95% CI, 34.9-81.1)

**Table 1.** Distribution of tumor characteristics by body mass index

| | *Body Mass Index (kg/m$^2$)* | | | | | | |
|---|---|---|---|---|---|---|---|
| *Characteristics* | *18.5 ≤ BMI < 25* | | *25 ≤ BMI < 30* | | *BMI ≥ 30* | | *p- value* |
| | *(N)* | *(%)* | *(N)* | *(%)* | *(N)* | *(%)* | |
| Tumor size | | | | | | | 0.165 |
| T1-2 | 259 | 80.9 | 181 | 74.8 | 129 | 75.4 | |
| T3-4 | 61 | 19.1 | 61 | 25.2 | 42 | 24.6 | |
| Lymph node involvement | | | | | | | 0. 787 |
| Negative | 137 | 42.9 | 97 | 40.1 | 70 | 41.2 | |
| Positive | 182 | 57.1 | 145 | 59.9 | 100 | 58.8 | |
| Grade | | | | | | | 0.042 |
| 1 | 33 | 11.6 | 22 | 9.5 | 16 | 9.4 | |
| 2 | 131 | 46.1 | 101 | 43.7 | 57 | 33.5 | |
| 3 | 120 | 42.3 | 108 | 46.8 | 97 | 57.1 | |
| Lymphovascular invasion | | | | | | | 0.025 |
| No | 52 | 36.1 | 35 | 28.9 | 23 | 20.5 | |
| Yes | 92 | 63.9 | 86 | 71.1 | 89 | 79.5 | |
| Perineural invasion | | | | | | | 0.758 |
| No | 129 | 89.6 | 105 | 89.7 | 79 | 86.8 | |
| Yes | 15 | 10.4 | 12 | 10.3 | 12 | 13.2 | |
| Extracapsular extension | | | | | | | 0.951 |
| No | 84 | 58.3 | 66 | 56.4 | 52 | 57.1 | |
| Yes | 60 | 41.7 | 51 | 43.6 | 39 | 42.9 | |
| Estrogen receptor | | | | | | | <0.001 |
| Negative | 69 | 21.6 | 75 | 31.0 | 69 | 40.4 | |
| Positive | 251 | 78.4 | 167 | 69.0 | 102 | 59.6 | |
| Progesterone receptor | | | | | | | 0.002 |
| Negative | 69 | 21.6 | 67 | 27.7 | 62 | 36.3 | |
| Positive | 251 | 78.4 | 175 | 72.3 | 109 | 63.7 | |
| HER-2 (IHC/FISH) | | | | | | | 0.068 |
| Negative | 258 | 80.6 | 175 | 72.6 | 127 | 74.7 | |
| Positive | 62 | 19.4 | 66 | 27.4 | 43 | 23.4 | |
| Subtypes of breast cancer | | | | | | | 0.002 |
| Luminal | 264 | 82.5 | 183 | 75.6 | 114 | 66.7 | |
| HER-2 overexpressing | 18 | 5.6 | 24 | 9.9 | 23 | 13.5 | |
| Triple negative | 38 | 11.9 | 35 | 14.5 | 34 | 19.9 | |

**Table 2.** Overall survival according to breast cancer subtypes

| | *Body Mass Index (kg/m²)* | | | |
|---|---|---|---|---|
| *Tumor subtypes* | *18.5 ≤ BMI < 25* *OS (95% CI)* | *25 ≤ BMI < 30* *OS (95% CI)* | *BMI ≥ 30* *OS (95% CI)* | *p- value* |
| Luminal | 120 (95.4-144.6) | 96 (62.9-129.1) | 84 (57.3-90.7) | 0.433 |
| HER-2 overexpressing | 100 (79.5-120.5). | 51 (30.1-71.9) | 77 (33.8-100.2) | 0.891 |
| Triple negative | 106 (84.6-127.4) | 53 (44.4-61.6) | 34 (23.9-44.1) | 0.015 |

**Table 3.** Disease free survival according to breast cancer subtypes

| | *Body Mass Index (kg/m²)* | | | |
|---|---|---|---|---|
| *Tumor subtypes* | *18.5 ≤ BMI < 25* *DFS (95% CI)* | *25 ≤ BMI < 30* *DFS (95% CI)* | *BMI ≥ 30* *DFS (95% CI)* | *p- value* |
| Luminal | 73 (54.4-91.6) | 62 (11.1-112.9) | 72 (47.0-96.9) | 0.723 |
| HER-2 overexpressing | 42 (26.4-57.6) | 25 (12.8-37.1) | 36 (24.4-47.6) | 0.390 |
| Triple negative | 60 (48.9-71.3) | 39 (29.1-48.9) | 23 (11.5-34.5) | 0.006 |

in obese patients ($P_{log\text{-}rank}$ =0.012) (Figure 1). According to the subtypes, median OS was significantly shorter in obese patients with TNBC (34 months, $P_{log\text{-}rank}$=0.001) (Table 2).

The median DFS was 61 months (95% CI, 47.5-74.5) in normal weight, 51 months (95% CI, 44.7-57.3) in overweight and 44 months (95% CI, 30.9-56.0) in obese patients. Regarding the overall study population, there was a trend towards poor DFS in obese patients, with a borderline p value ($P_{log\text{-}rank}$ =0.065) (Figure 2). DFS showed a significant inverse relation to BMI in TNBC patiens ($P_{log\text{-}rank}$ =0.006). Table 3 shows median DFS with 95% CI according to BMI and breast cancer subtypes.

Of the 733 patients 157 (21.4%) died and 236 (32.2%) had a breast cancer recurrence. Five-year OS and DFS rates were 55% and 26% for normal weight, 40% and 20% for overweight and 28% and 18% for obese women. Overall, obese compared with normal weight women had an increased risk of breast cancer mortality (HR 1.8, 95% CI 1.2-2.7; p=0.006) and recurrence (HR 1.5, 95% CI 1.1-2.1; p=0.02).

When the patients were stratified by the breast cancer subtypes, we found no association between BMI and survival among luminal (HR 1.5, 95% CI 1.0-2.2; p=0.27) and HER-2 overexpressing (HR 1.4, 95% CI 1.1-2.1; p=0.07) breast cancer patients; however, this association was clearly evident in TNBC patients (HR 1.7, 95% CI 1.1-2.5; p=0.02). After adjustment for the prognostic factors (age, tumor size, nodal involvement, grade, lymphovascular and perineural invasion, extracapsular extension and hormonal status), obesity (HR 1.4, 95% CI 1.0-2.1;p=0.04) and lymphovascular invasion (HR 2.1, 95% CI 1.3-3.3; p=0.02) remained independent prognostic factors for TNBC mortality, whereas no significant associations were found for HER-2 overexpressing and luminal breast cancer mortality (p=0.037 and p=0.40, respectively). Obesity was also associated with recurrence in TNBC (HR 1.4, 95% CI 1.0-2.0; p=0.04) and HER-2 overexpressing breast cancer (HR 1.5, 95% CI 1.0-2.1; p=0.03). However, after adjustment, we found no significant associations.

## Discussion

In our cohort, obese compared with normal weight women, were older at diagnosis and more often had high grade tumors with lymphovascular invasion. Studies have shown that, obese/overweight women tend to be diagnosed at older age with higher histological grade and larger tumor size than normal weight women, which may explain the poor survival [14,15,17-20]. Demirkan et al. found vascular invasion as an independent prognostic factor for survival in postmenopausal women with BMI ≥30 kg/m² [21]. Lymphovascular invasion was determined as an independent prognostic factor for TNBC mortality in the present study.

Obese/overweight patients are more likely to present with lymph node involvement and advanced clinical stage at diagnosis. This association has been observed in some studies [5,9-13], but not in others [14,15,17,22], and the conflicting reports may be a result of differences in the study populations. We found no significant differences in nodal status or tumor size between normal weight and obese women.

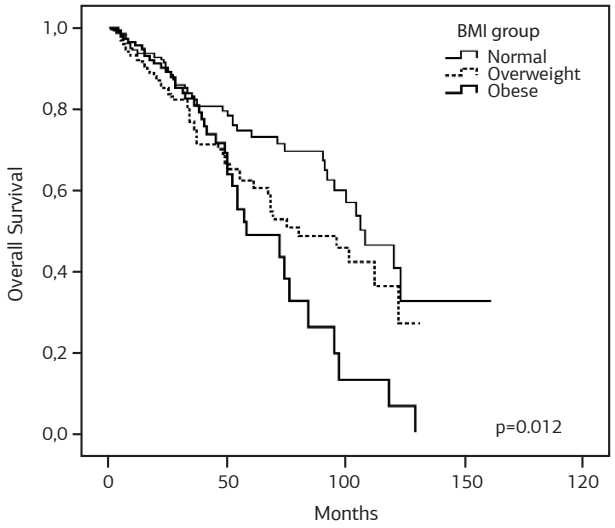


**Figure 1.** Overall survival of premenopausal patients according to body mass index.

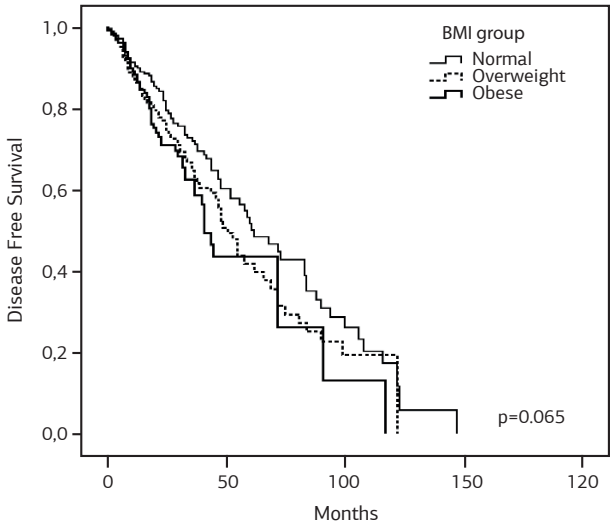


**Figure 2.** Disease free survival of premenopausal patients according to body mass index.

Several studies have shown an association between BMI and risk of ER positive breast cancer, regardless of menopausal status [23,24]. In contrast, Millikan et al. reported a slight inverse association between BMI and ER positive breast cancer in premenopausal women [25]. Daling et al. also found that obesity is in combination with ER negative tumors [14]. In our study there was a strong association between obesity and ER/PR negative tumors. Maehle at al. reported that premenopausal obese women are more likely to have hormone receptors' negative tumors [26]. Vona-Davis et al. denoted that the breast cancers of obese premenopasual women are most often ER and PR negative, and are dependent on growth factors such as insulin, insulin-like growth factor-I (IGF-I) and leptin [27]. Elevated serum concentrations of IGF-I have been linked to risk of premenopausal breast cancer development[5]. Leptin exerts stimulatory effects on ER negative breast cancer cell proliferation, invasion and angiogenesis, where estrogen action is not a factor, both directly and by way of induction of vascular endothelial growth factor (VEGF) and heparin-binding epidermal growth factor-like growth factor (HBEGF) and hepatocyte growth factor (HGF) expressions [28-31].

We observed significantly high percentage of obese women with TNBC. A study reported that central obesity is more strongly related to the risk of TNBC than to other subtypes [25]. The association between obesity and poor survival for breast cancer patients, regardless of the hormonal status, has been previously reported. We showed that obesity is an independent prognostic factor for TNBC mortality. Furthermore, in our view, this is the first study, showing obesity as an independent prognostic factor for TNBC mortality. However, we had only 118 patients with TNBC and further studies are needed to confirm our data. Vona-Davis et al. found that more of the patients with TNBC were obese and suggested that a relationship could exist between obesity and triple-negative receptor status with risk of recurrence and poor outcome [27]. We found a significant inverse association between BMI and DFS in TNBC patients. Liu et al. reported that a polymorphism in the leptin receptor gene at codon 109 was more frequent in overweight patients. Among patients with the LEPRO-109RR phenotype, higher serum leptin concentrations were present in those with TNBC [32]. These data suggest an interaction among obesity, adipokines, triple-negative tumors, and poor prognosis compared with other types of breast cancer [29,30,33].

We also observed high percentage with HER-2 overexpressing breast cancer among obese women. However, our present study is in discordance with two previous studies that showed no association between obesity and erbB-2 expression [34,35]. The insignificant effect of obesity in premenopausal patients with HER-2 overexpressing breast cancer could be related to the small size of this subgroup (N=65).

We found that a high BMI was associated with 1.8-fold increase in mortality among women who were premenopausal at the time of breast cancer diagnosis. A recent cohort study reported that breast cancer patients with BMI ≥30 kg/m$^2$ at diagnosis had a HR of total mortality of 1.55 (95% CI 1.10-2.17) compared with patients with normal BMI [18]. Several large-scale cohort stud-

ies indicated that overweight/obesity lead to poor survival for both premenopausal and postmenopausal women diagnosed with breast cancer even in early stage disease [11,14,15,36]. Ewertz et al. found that the risk of dying as a result of breast cancer after 30 years of follow-up was increased by 38% (HR 1.38, 95% CI 1.11-1.71; p=0.003) in obese women [36]. Regarding the study population, BMI was significantly and inversely associated with OS (p=0.01). This finding was consistent with earlier studies that have shown a poorer OS with increasing BMI [4,11,12,14,16]. In 7 randomized clinical trials of 6,792 eligible patients conducted by the International Breast Cancer Study Group, BMI had a significant and independent negative impact on OS [15]. We observed a trend towards poor DFS in obese patients with a borderline p value. Many studies have analyzed the influence of obesity on DFS specifically in premenopausal breast cancer patients. Some of these studies showed a significant association, with hazard ratio of >1 [14,15,37]. On the other hand, some studies did not show any significant association between BMI and recurrence in premenopausal women with breast cancer [22,38]. In our cohort, obese compared with normal weight women had 1.5-fold increased risk of breast cancer recurrence.

One limitation of our study is that there are no measurements for waist-to-hip ratio or waist circumference, which are specific measurements for central or abdominal adiposity. However, BMI is generally accepted to be well correlated with body fat in young women [39]. The other limitation was the small number of the patients wtih HER-2 overexpressing breast cancer. Also, treatment changes during 10 years of follow-up time could bias the results.

In conclusion, we found that obesity is associated with ER/PR negative tumors and poor OS in premenopausal women with breast cancer. However, as obesity has previously been shown as an independent prognostic factor for survival of breast cancer, our findings suggest that obesity is an independent prognostic factor for TNBC mortality. Obesity and weight gain are modifiable risk factors for breast cancer occurrence and survival and women, particularly those diagnosed with TNBC, should be advised to maintain their weight within normal limits after breast cancer diagnosis.

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