

The relationship between body mass index and clinical properties/survival in patients with breast cancer

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ABSTRACT

Objectives: The aim of this study was to investigate relationship between body mass index (BMI) and recurrence/survival and to determine whether body mass index is a risk factor.

Methods: A retrospective study of 125 patients with breast cancer was performed. Age, sex, menopausal situation, body mass index, tumor size, axillary lymph node involvement and number, tumor degree, hormone receptor situation, cerbB-2 overexpression, tumor grade, chemotherapy dose and treatments, radiotherapy, metastasis, comorbidity, total survival and time of death were evaluated. Patients were compared as BMI < 30 kg/m² and BMI ≥ 30 kg/m². Kaplan-Meier method and Log Rank test was utilized for the overall survival of patients.

Results: In these 72 patients, 57.6% of patient's body mass index BMI < 30 kg/m² (non-obese) while 53 of the group (42.4%) BMI ≥ 30 kg/m² (obese) were found in the group. The median follow-up was 158.32 months (95% CI: 130.45 to 186.19). The mean follow-up was 146 ± 46 months (95% CI: 55.36-236.63) and 144 ± 28 months (95% CI: 88.19-199.81) for non-obese patients and obese patients respectively. Kaplan Meier plots were drawn for determination of the effect of body mass index in total survival. No significant difference was found statistically between two groups.

Conclusions: No significant difference was found statistically between BMI and recurrence/death. The future studies with long term follow up are needed to investigate the effect of body mass index on recurrence and survival in patients with breast cancer.

Keywords: Breast cancer, body mass index, survival, relapse, obesity

Breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases followed by lung, colorectal, prostate and stomach cancers IN 2020 according to GLOBOCAN for Research on Cancer Reports [1]. Since 1990, breast cancer incidence rates have been increasing approximately 1.5% yearly [2]. Although

advances in diagnosis and treatment, breast cancer rank first resulting in death among women worldwide.

According to reports of Ministry of Health in 2015, breast cancer is the most common cancer type among women in Turkey with a rate of 25% [3]. Surgical techniques, chemotherapy and radiotherapy have been used for the treatment of breast cancer as well as



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other cancer types. In addition, hormone therapy has been applied particularly in the treatment of breast cancer in recent years. However, between 5 and 20 years after primary diagnosis, the risk of distant recurrence ranged from 13% to 41% depending on the tumor and nodal status of the primary tumor [4].

Breast cancer is a multi-step disorder which factors like genetic, endocrine, nutrient play a crucial role in the development and spread. Several studies showed that obesity or increased body mass index as two significant side effects is associated with breast cancer. The first one is the connection between increased body mass index in pre- and the post-menopausal women and advanced breast cancer. The second one is that increased body mass index correlated with a poor prognosis and accordingly an increase of metastasis to distant sites and high mortality [5-7]. On the other hand, few studies have observed no association between body mass and breast cancer prognosis [8-12]. Up to now, it is uncertain if obesity is related to the risk of occurring particular breast cancer subtypes (luminal A, luminal B, basal-like and human epidermal growth factor receptor (HER-2)) in before and after menopause.

The purpose of this study are to evaluate relationship between BMI and recurrence/survival and to determine whether BMI is a risk factor in breast cancer patients.

METHODS

Patients

The Ankara University Ibn Sina Hospital Database was searched and 125 patients with breast cancer from 2005 to 2014 were identified. The institutional review board approved the retrospective evaluation of medical records for the aim of this study.

Age, sex, menopausal situation, body mass index, co-morbidity, total survival and time of death were recorded. Tumor properties, comprising size, grade, number of involved axillary nodes, and estrogen and progesterone receptor status, *HER-2* overexpression were summarized from related diagnostic pathology papers. Other knowledge taken from medical reports contain adjuvant therapy components (chemotherapy, hormonal therapy, radiotherapy) and details on first distant recurrence and death.

Obesity was determined according to body mass index (BMI), identified by weight in kilograms (kg) divided by the square of height in meters (m²). According to National Centre for Disease Control and Prevention guidelines [13], body mass index were categorized as underweight, < 18.5 kg/m²; normal weight, 18.5-24.9 kg/m²; overweight, 25.0-29.9 kg/m²; obese, ≥ 30 kg/m². Self-reported height and weight 1 year, as reported in diagnosis were used.

Inclusion and Exclusion Criteria

Breast cancer patients at least 18 years old were included in Ankara University Faculty of Medicine, Oncology Department. Studies were eligible for exclusion in retrospective analysis if they met the following criteria: (i) had a metastasis to distant organs, (ii) not applied in clinics for the last 2 years and (iii) had a synchronic or metachronous malignite.

Pathology

Breast pathologists examined all pathologic samples. The grade and immunohistochemical analysis of estrogen receptor (ER), progesterone receptor (PgR), and HER-2 status were decided. In brief, invasive breast cancer was diagnosed by needle biopsy of breast. Clinical stage was specified by the 6th edition of Cancer Staging Manual of the American Joint Committee on Cancer [14]. The histological special type of cancer was determined consistent with the classification system of WHO [15]. The grade was specified on the authority of modified Black's nuclear grading system. Immunohistochemical evaluation to find ER and PGR status was carried out using standard immunohistochemistry methods with monoclonal antibodies. Nuclear staining 10% was regarded a positive outcome. HER-2 status was determined using immunohistochemistry or by fluorescence in situ hybridization. Polymerase chain reaction (pCR) was specified as no basis of invasive breast carcinoma and axillary lymph nodes at surgery.

Treatment

Generally, all patients were given 3 to 6 courses of anthracycline or taxane-based chemotherapy regimens. All patients had axillary staging with axillary lymph node dissection or sentinel node biopsy. Radiation therapy was applied in case of breast conservation surgery, locally advanced disease, primary tumor

size before chemotherapy of 5 cm and ≥ 4 involved axillary nodes. Hormonal therapy was given on the authority of standard practice.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows version 15.0 (standard version) programme (SPSS Inc., Chicago, IL). Numeric data are given as mean \pm standard deviation (SD).

Chi-square test incorporating Yates correction and Fisher's exact test were used for 2×2 probability tables in nonnumeric data. Spearman rho correlation test was done for correlation analyses between quantitative parameters. To compare groups, one-way or multi-way analysis of variance (ANOVA) were used. Kruskal Wallis-H variance analyses was used for more than two groups in case of non-normal distribution. For survival analysis, Kaplan-Meier curves were plotted, and differences between the curves were analyzed with the log-rank test. Results of $p < 0.05$ were considered statistically significant at 95% confidence interval.

Disease-free survival (DFS) is defined as the time between diagnosis of disease and recurrence or distant metastasis. Overall survival is defined as the time from diagnosis of disease to death of patients of breast cancer.

RESULTS

Total of 125 operated breast cancer patients were studied retrospectively. Among these women, the mean age was 55 ± 12 years. 38.4% of patients were under the age of 50, while 61.6% were up to 50 years. Of the participants who reported menopausal status at diagnosis, 52% were pre-menopausal and 48% were post-menopausal. Blood group A is the most frequent blood group (65.6%) among patients with breast cancer. The mean height of the study participants was 158 ± 5.6 cm, and mean weight was calculated as 73 ± 18.7 kg. The mean BMI was of 28.6 ± 5.43 kg/m². BMI of 72 patients (57.6%) was non-obese group (BMI < 30 kg/m²), while BMI of 53 patients (42.4%) were found obese (BMI ≥ 30 kg/m²).

As can be seen in Table 1, the relationship between BMI and other prognostic factors of breast cancer were evaluated. Significant correlation was found be-

tween BMI and age, axillary dissection, stage, comorbidity. No relationship was found between BMI and histology, grade, ER, PGR, HER2 positivity, tumor diameter, positive lymph nodes, lymphovascular invasion, surgical procedure type, tamoxifen use, smoking, blood groups, hormone therapy, radiation therapy, chemotherapy, a number of localization in recurrence statistically. The most common diseases were diabetes (29.87%) and hypertension (28.57%) was observed.

No relationship was found between BMI and and CA-15-3/CEA values. No significant difference was found between obese and non-obese cases from the point of BMI and CA-15-3/CEA values ($p = 0.08$ and $p = 0.509$). The average of CA-15-3 and CEA values to BMI were given in Table 2.

To determine the relationship between BMI and death in univariate analysis, no significant difference was found between average BMI of death group and average BMI of survival group using Mann Whitney U test ($p = 0.6$). To group all patients according BMI, no significant difference was found BMI and death using Pearson chi square test (BMI > 30 kg/m² vs BMI 18.5-24.9 kg/m² $p = 0.81$). A total of 125 patients, 82 patients (65.6%) is still alive, 43 patients (34.4%) were dead.

Kaplan Meier plots were withdrawn to establish the impact of BMI in cerbB2 and disease-free survival (DFS) period. As can be seen in Fig. 1, there were no significant differences between 2 groups statistically ($p = 0.1566$). The mean DFS follow-up was 34 ± 5.4 months (95% CI: 23.34-44.66) and 25 ± 3.12 months (95% CI: 18.87-31.12) for non-obese patients and obese cases, respectively.

To establish BMI in CEA value, the mean DFS follow-up was 31 ± 3.80 months (95% CI: 23.54-38.46) and 28 ± 5.61 months (95% CI: 16.98-39.013) for non-obese patients and obese patients, respectively. The mean overall survival follow-up was 70 ± 7 months (95% CI 57-83) and 70 months ± 10 (95% CI 50-90) for non-obese patients and obese patients, respectively.

To establish BMI in CA-15-3 value, the median DFS follow-up was 28 ± 2.32 months (95% CI: 23.45-32.55) and 35 ± 9.31 months (95% CI: 16.74-53.25) for non-obese patients and obese patients, respectively. The mean overall survival follow-up was 70 ± 4 months (95% CI: 62-78) and 97 ± 26 months (95% CI: 45-149) for non-obese patients and obese patients, re-

Table 1. Relationship between BMI and patient properties in non-obese and obese patients

	Body Mass Index (BMI)				<i>p value</i>
	< 30		≥ 30		
	n	%	n	%	
Age					0.536
< 50	15	44.1	33	36.3	
≥ 50	19	55.9	58	63.7	
Menopausal Situation					0.689
Pre	19	55.9	46	50.5	
Post	15	44.1	45	49.5	
Grade					0.954
1	1	3.1	2	2.3	
2	15	46.9	43	48.9	
3	16	50	43	48.9	
Stage					0.02
1	4	12.5	5	5.7	
2	18	56.3	35	44.2	
3	10	31.3	48	48.3	
ER					0.528
Negative	13	38.2	29	31.9	
Positive	21	61.8	62	68.1	
PGR					1
Negative	9	26.5	24	26.7	
Positive	25	73.5	66	73.3	
HER-2					0.544
Negative	21	61.8	49	53.8	
Positive	13	38.2	42	46.2	
Positive Lenf Node					1
No	15	44.1	39	43.8	
Yes	19	55.9	50	56.2	
Axillary Dissection					0.024
No	12	35.3	14	15.4	
Yes	22	64.7	77	84.6	
Lenfovacular Invasion					1
Negative	11	33.3	31	35.2	
Positive	22	66.7	57	64.8	
Surgery Type					0.734
Mastectomy (MRM)	30	88.2	83	91.2	
Prophylactic (BCS)	4	11.8	8	8.8	
Tamoxifen Usage					0.193
No	14	41.2	25	27.5	
Yes	20	58.8	66	72.5	
Cigarette Usage					1
No	28	82.4	73	80.2	
Yes	6	17.6	18	19.8	
Hormone Therapy					1
No	13	38.2	35	39.3	
Yes	21	61.8	54	60.7	
Radiation Therapy					0.081
No	14	41.2	22	24.7	
Yes	20	58.8	67	75.3	
Comorbidity					0.026
No	25	73.5	46	50.5	
Yes	9	26.5	45	49.5	

ER = Estrogen receptor; HER-2 = Human epidermal growth factor receptor, PGR = Progesterone receptor, MRM = Modified Radical Mastectomy, BCS = Breast-conserving Surgery

Table 2. Relationship between BMI and c-erbB2, CA-15-3, CEA values

Body Mass Index (kg/m ²)	c-erbB-2 (%)	CA 15-3	CEA
< 18.5	50	494.7	25
18,5-24.9	357	47.31	5.86
25-29.9	47.5	55.43	9.45
≥ 30	45.5	43.,26	13.68

BMI = Body Mass Index, CA 15-3 = Carcinoid antigen, CEA = Carcinoembryonic antigen

spectively.

Kaplan Meier plots were withdrawn to establish the impact of BMI in DFS period. As can be seen in Fig. 2, there were no significant differences between 2 groups statistically ($p = 0.761$). The mean DFS follow-up was 28 ± 4.49 months (95% CI: 19.18-36.81) and 31 ± 3.35 months (95% CI: 24.44-37.56) for non-obese patients and obese patients, respectively.

Kaplan Meier plots were drawn to establish the effect of BMI in overall survival. As can be seen in Fig. 3, there were no significant differences between 2 groups statistically ($p = 0.659$). The mean overall survival follow-up was 75 ± 4.49 months (95% CI: 56-

94) and 73 ± 3.35 months (95% CI: 46-100) for non-obese patients and obese patients, respectively.

DISCUSSION

In this study, there was no significant difference between BMI and recurrence/death. Overall survival of non-obese patients ($< 30 \text{ kg/m}^2$) was found to be longer compared to obese patients ($> 30 \text{ kg/m}^2$) in survival analysis.

To date, relationship between obesity and risk of developing different breast cancer subtypes have not been clarified. In our study, a statistically significant association of obesity with HER2 status was not identified in terms of disease-free survival as can be seen in Fig. 1. Evaluation of HER2 status in the large groups would be of particular interest because that would allow investigation of obesity associations in women with HER2(+) as well as HER2(-). Biglia *et al.* [16] studied BMI effect in disease-free survival in 2150 women that experienced breast tumor surgery and follow up. In conclusion, a larger tumor size has been found to be associated high BMI both pre and postmenopausal women. Obese pre-menopausal women had large number of metastatic axillary node

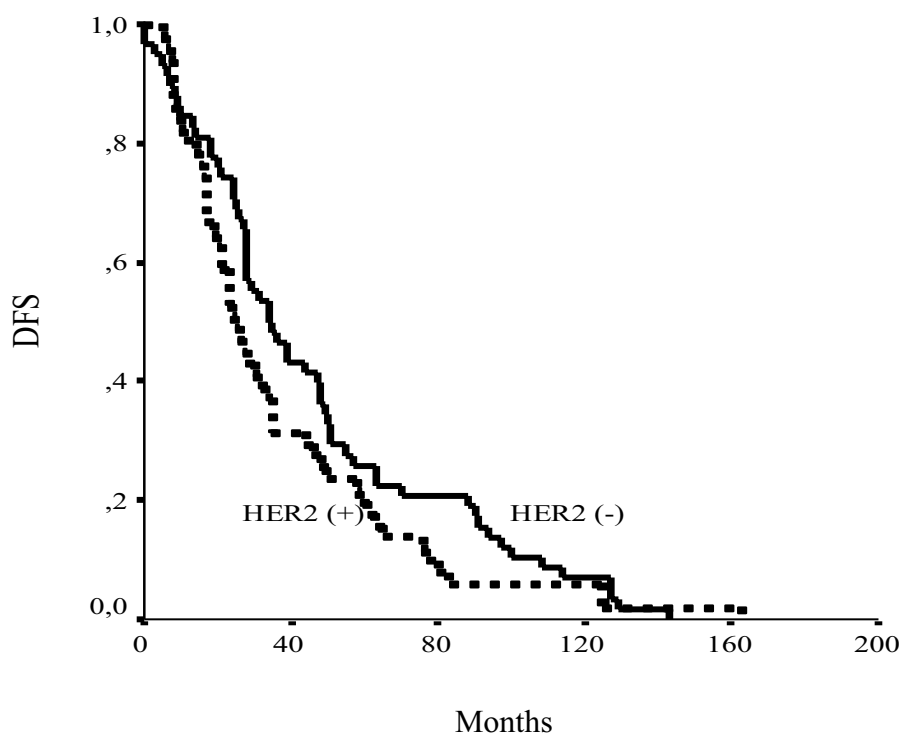


Fig. 1. Disease-free survival graphics between BMI and c-erbB2.

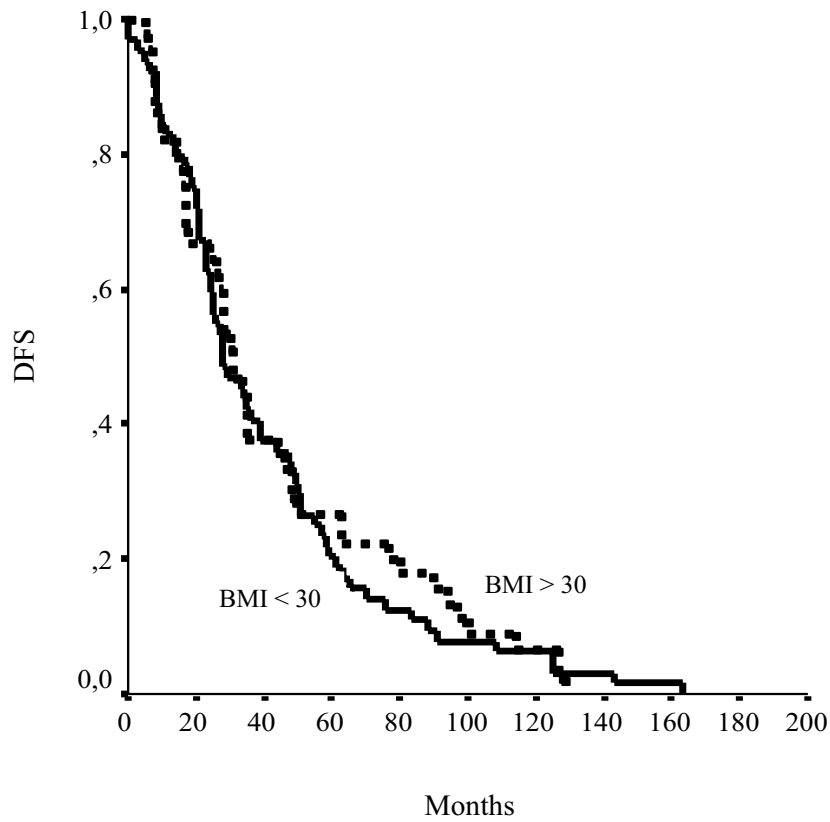


Fig. 2. Relationship between BMI and disease-free survival.

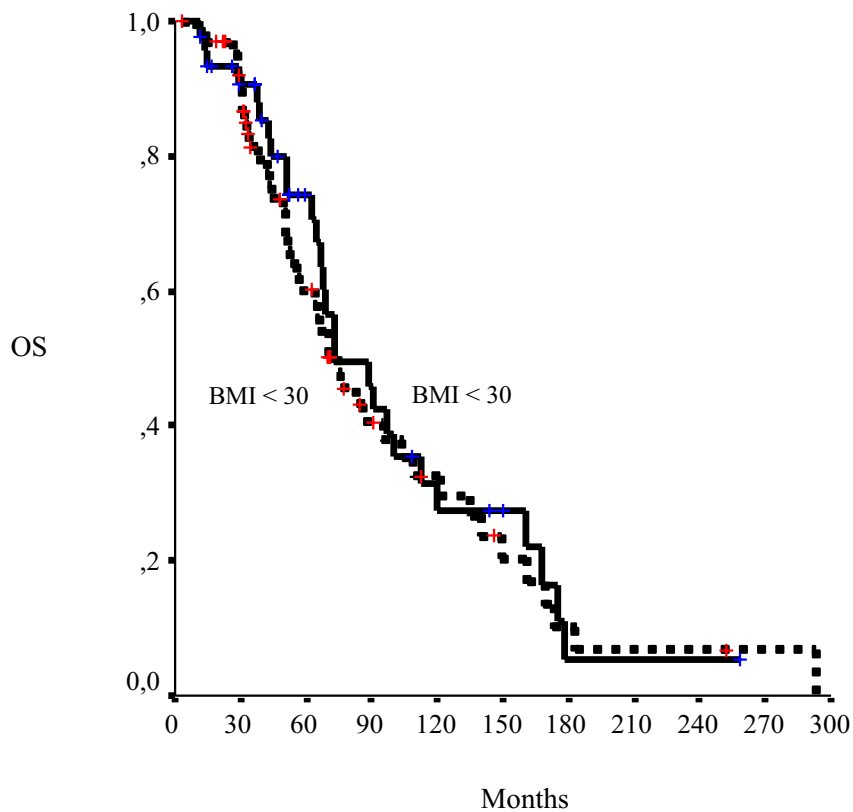


Fig. 2. Relationship between BMI and overall survival.

and a more commonly tumor vascular invasion than non-obese women [16]. Turan *et al.* [17] searched the relationship of breast cancer and breast cancer subtypes with menopausal status and body mass index. It was found that the number of overweight and obese patients was statistically significantly higher in the postmenopausal group. However, no statistically significant correlation was found in the analyses performed between BMI and breast cancer immunohistochemical subtypes in either group. The findings of this study support that obesity causes an increased risk of breast cancer in the postmenopausal period, independent of breast cancer immunohistochemical subtypes. The relationship between obesity and breast cancer should be evaluated together with risk factors [17].

Beypinar *et al.* [18] studied BMI effect to prognosis in young breast cancer patients. Computed tomography (CT) was applied to determine body composition precisely. Although the median overall survival cannot be reached at the end of the follow-up period for both groups (sarcopenic and non-sarcopenic), the difference between groups statistically insignificant. In this study, sarcopenia, may be seen in patients with breast cancer under 40 years old, was not found to be have a prognostic effect [18].

De Azambuja *et al.* [19] studied the impact of BMI on OS and DFS in node-positive breast cancer cases who doxorubicine and docetaxel-based adjuvant chemotherapy. Estimated five years overall survival was 87.5% and 82.9% for non-obese and obese cases, respectively ($p = 0.013$). Estimated five years DSF survival was 75.9% and 70.0% for non-obese and obese cases, respectively ($p = 0.041$). In a multivariate model, obesity continued an independent prognostic determinant for overall and disease-free survival [19].

Chan *et al.* [20] searched for 82 follow-up meta analysis of breast cancer patients with BMI before and after diagnosis, and total and cause-specific mortality until 2013. For BMI previous to diagnosis, comparison with non-obese women, the relative risks of total mortality were 1.41 for obese (BMI > 30.0), 1.07 for overweight (BMI 25.0- < 30.0) and 1.10 for underweight (BMI < 18.5) women, respectively. Obesity is related with poor overall survival and breast cancer survival in pre-menopausal and post-menopausal breast cancer. Being overweight is also associated with a higher risk of mortality [209].

Dawood *et al.* [21] examined the prognostic effect of obesity amongst women with early stage triple receptor-negative breast cancer (TN), a subtype of breast cancer known to be related poor prognosis. Five years DFS was 61%, 62%, and 62% amongst patients with BMI of < 25, 25 to 29.9, and ≥ 30 , respectively. There was no significant increase among all groups in risk of distant metastases. Patients with TN disease were shown a poor prognostic result without considering BMI category. The outcome of this study suggest that obesity did not have a function as a prognostic indicator amongst patients with TN disease [21]. In another study, no significant relation was found between obesity and recurrence-free survival (RFS) or overall survival emerged in patients with TN disease after controlling for clinically significant factors [22].

Ewertz *et al.* [23] searched BMI effect in recurrence and survival for 18,967 women treated for early-stage breast cancer. Both chemotherapy and hormone therapy appear less efficient after ≥ 10 years for cases with BMI greater than 30 kg/m². In addition, obesity is an independent predictive component for occurring distant metastases and for death as a consequence of breast cancer [23].

Absence of significant molecular biomarkers such as *cerbB2* in previous studies and breast cancer which is a heterogenous group in current studies can be interpreted as main reasons of differences between studies. Although no significant differences were observed between *cerbB2*, CEA, CA 15-3 and DFS, overall survival as a result of analysis between BMI and tumor markers in our study, significant difference is expected to be seen by increasing the patient data.

In this study, it was found to be significant difference between BMI and comorbidity. Diabetes (29.8%) and hypertension (28.6%) are the most common type of disease, body mass index 30 kg/m² is greater (obese) patients are seen by 59.3%. Several studies confirmed that hypertension and diabetes in women with breast cancer is related to decreased survival. However, there is no explanation about comorbidity cause whether increase of breast cancer recurrence and breast cancer-specific mortality risk. At the same time, which comorbidities that affect the mechanism of recurrence risk has not been announced yet. Comorbidities are associated with particularly poor quality of life, especially physical health [24]. Lower scores in physical health scale are related to low physical activ-

ity and obesity is also linked to high concentrations of circulating estradiol [25].

Tobias *et al.* [26] studied the relationship between BMI and mortality among patients with type 2 diabetes. No confirmation was obtained lower mortality amongst patients with diabetes who were overweight or obese at diagnosis, in comparison with non-obese patients, or of an obesity paradox. Patterson *et al.* [27] studied whether comorbid medical conditions predict additional breast cancer events and all-cause mortality in women with a history of early-stage breast cancer. Patients with diabetes has two times more risk in terms of incidence and mortality. The presence of multiple comorbidities was found to be significantly lost on additional breast cancer events.

In this study, it was found to be significant difference between BMI and stage. Obese patients have advanced cancer compared with non-obese patients. Although, obesity is known risk factor in postmenopausal breast cancer, relationship between obesity and stage can not be explained. Many hypothesis declared that increased breast size cause to delay diagnosis of breast cancer.

Cui *et al.* [28] examined whether there is an association between BMI and stage in breast cancer. At the end of this study, higher BMI was found to be related advanced breast cancer. Due to difficulties of palpation and access to mass which is the most common symptom, diagnosis delays so women with higher BMI are be diagnosed at a later stage of breast cancer [28]. In addition, several studies showed that women with higher BMI has larger tumors and advanced breast cancer compared to women with low BMI [29].

Limitations

Our work that is a retrospective cohort study is a limiting factor. Due to limitation of patient data, access to patients by phone, follow up in other medical centers, treatment schemes and death time, a number of patients leads to limited. The prognostic effect of obesity in breast cancer and new treatment approaches should be considered with long follow up studies. In the future, a large number of randomized, prospective studies will provide more appropriate treatment approaches. It can be described that obesity has any negative effects before and after diagnosis of breast cancer. Therefore, we think that ideal weight is be considered in follow up for breast cancer patients.

CONCLUSION

In conclusion, no significant difference was observed between BMI and recurrence/death. The coming studies with long-term follow up are required to search the effect of body mass index on recurrence and survival in breast cancer patients.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Ankara University School of Medicine.

Authors' Contribution

Study Conception: BE, GU; Study Design: BE, GU, AD; Supervision: GU; Funding: GU; Materials: GU; Data Collection and/or Processing: BE, GU; Statistical Analysis and/or Data Interpretation: GU; Literature Review: BE, GU; Manuscript Preparation: BE, GU and Critical Review: GU.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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