

ORIGINAL ARTICLE

Effect of body mass index on the efficacy of adjuvant tamoxifen in premenopausal patients with hormone receptor-positive breast cancer

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Summary

Purpose: Obesity has been confirmed to be an adverse prognostic factor in patients who were treated with aromatase inhibitors; however, such relationship has never been thoroughly investigated in patients treated with tamoxifen. The purpose of this study was to examine the effect of body mass index (BMI) on the efficacy of adjuvant tamoxifen in premenopausal patients with hormone receptor-positive breast cancer.

Methods: Newly diagnosed premenopausal and non-metastatic hormone receptor-positive breast cancer patients were enrolled in the study. Patients with BMI ranging between 18.5 and 24.9 kg/m² were considered as normal weight patients (Arm A, n = 408), and patients with a BMI $\geq$ 25 kg/m² were considered as overweight and obese patients (Arm B, n = 418).

Results: In both normal weight and overweight patients, the baseline clinicopathologic properties and the treatment history with radiotherapy and chemotherapy were

similar and no statistical significant difference could be detected. Tamoxifen in combination with luteinizing hormone-releasing hormone (LHRH) agonist was used in 33% (136/408) of the patients in Arm A and in 22% (91/418) of patients in Arm B ($p < 0.001$). Three-year disease free survival (DFS) rates were 89% and 87% in arm A and arm B, respectively ($p = 0.39$). Three-year overall survival (OS) rates were 99% in arm A and 94% in arm B which appeared to be of significance ($p = 0.028$). In univariate analysis no statistical significant effect of LHRH agonist usage on DFS ($p = 0.58$) and OS ($p = 0.96$) was found.

Conclusion: Although BMI had no negative effect on recurrence risk, poor OS was observed in overweight and obese premenopausal breast cancer patients with hormone-receptor positive tumors who were treated with tamoxifen.

Key words: aromatase inhibitors, body mass index, breast cancer, obesity, premenopausal, tamoxifen

Introduction

Breast cancer is the most commonly diagnosed cancer in women and it is estimated to account for 29% of all new cancers in women [1]. Aromatase inhibitors and tamoxifen are the main hormonal treatment options in hormone receptor-positive breast cancer [2-4]. Although, aromatase inhibitors are not appropriate for women with intact ovarian function, they have been wide-

ly used in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer, and shown to provide better progression free survival (PFS) rates compared to that of tamoxifen in early breast cancer cases [5]. In hormone receptor-positive breast tumors, adjuvant tamoxifen significantly decreases the risk of recurrence and mortality both in premenopausal and postmeno-

pausal patients [6,7]. Due to intact ovarian function, adjuvant tamoxifen is the main treatment option for premenopausal patients with hormone receptor-positive breast cancer.

Obesity is recognized as an independent risk factor for the development of breast cancer [8,9]. The risk of developing breast cancer has been reported to increased threefold in overweight or obese postmenopausal women compared to normal weight postmenopausal women [8,10]. This risk was attributed to the abnormally high expression of the aromatase enzyme in the breast, an enzyme which is responsible for the production of increased local estrogen, thus predisposing the breast tissue to hyperplasia and cancer which appeared to be more common in overweight postmenopausal patients [11]. Compared to postmenopausal patients, increased BMI is associated with a lower risk of developing breast cancer in premenopausal women in the pooled analysis of seven prospective cohort studies [12]. The exact pathophysiology of this finding is still unknown. Although, the risk of developing breast cancer significantly differs between pre- and postmenopausal women, obesity is shown to be associated with poor outcome in postmenopausal women, whereas conflicting results were reported in premenopausal women [13-18].

In recently published combined analyses of TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) trials, it was shown that adjuvant exemestane plus ovarian suppression significantly reduced recurrence compared to tamoxifen plus ovarian suppression in premenopausal hormone-receptor positive early breast cancer patients, but the outcome of treatment arms according to the BMI distribution was not given [19]. In the subgroup analyses of German-BRENDA project (Breast Cancer Care Under Evidence-based guidelines), recurrent free survival (RFS) decreased significantly in obese breast cancer patients who were hormone receptor-positive and treated with endocrine therapy compared to non-obese patients (hazard ratio/HR=1.45, $p=0.002$) whereas no influence was found between BMI and RFS in patients with hormone receptor-negative tumors [20]. Similarly in the ATAC trial (Arimidex, Tamoxifen Alone or in Combination), the risk of recurrence increased significantly in postmenopausal hormone receptor-positive breast cancer patients with BMI >35 kg/m² compared to patients with BMI <23 kg/m², whereas there was no significant difference in the recurrence risk according to the BMI in pa-

tients who were treated with tamoxifen [21]. Although anastrozole was significantly less effective in obese postmenopausal breast cancer patients, both letrozole and tamoxifen were equally effective across all BMI categories in postmenopausal breast cancer patients according to the subgroup analyses of BIG (Breast International Group) 1-98 trial with a median 8.7 years follow-up [22]. In the randomized phase III TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial, BMI was not associated with a risk of relapse in the exemestane alone and tamoxifen followed with exemestane arms in postmenopausal patients with hormone receptor-positive breast cancer with a median 5.1 year follow-up [23]. In addition, in our single-center study, we showed that aromatase inhibitors had similar efficacy according to the BMI and in the subgroup analyses both letrozole and anastrozole were equally effective in hormone-receptor positive postmenopausal breast cancer patients [24].

In the subgroup analyses of NSABP (National Surgical Adjuvant Breast and Bowel Project) B-14 trial, obesity (BMI ≥ 30 kg/m²) did not increase the risk of recurrence or breast cancer mortality, whereas the risks of contralateral breast cancer and other primary cancers increased significantly in patients with lymph node-negative, estrogen receptor-positive breast cancer [25]. In a randomized ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group) trial it was shown that anastrozole increased the risk of disease recurrence and death significantly in overweight patients compared to normal weight patients treated with anastrozole and patients treated with tamoxifen in hormone receptor-positive premenopausal breast cancer [26].

In the recently reported Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trial that investigated the role of obesity in 80,000 breast cancer patients, BMI was significantly associated with breast cancer mortality in hormone receptor-positive breast cancer patients, regardless of the menopausal status whereas no association was found between BMI and breast cancer mortality in hormone receptor-negative breast cancer patients [27]. After adjustment for risk factors, significant association between BMI and breast cancer mortality was found only in hormone receptor-positive premenopausal and perimenopausal breast cancer patients [27].

There are contradictory results leading to discussions about the efficacy of tamoxifen in relation to the BMI as an adjuvant treatment of

Table 1. CONSORT diagram of the study. BMI: body mass index

Total 3233 patients with breast cancer between 1998-2014	
2407 patients excluded	
Postmenopausal patients (N=1515)	
Metastatic premenopausal breast cancer patients (N=245)	
Triple negative (N=185)	
Receptor negative HER2 overexpression (N=160)	
Unavailable BMI value (N=81)	
Tamoxifen not used (N=126)	
Missing follow-up (N=95)	
Total 826 hormone receptor-positive premenopausal patients	
Arm A; 408 patients	Arm B; 418 patients
BMI: 18.5-24.9 kg/m ²	BMI: BMI $\geq$ 25 kg/m ²

hormone receptor-positive premenopausal breast cancer. Thus, in this study we aimed to examine retrospectively the effect of BMI on the efficacy of adjuvant tamoxifen in premenopausal patients with hormone receptor-positive breast cancer.

Methods

Breast cancer patients diagnosed between November 1998 and April 2014 in the Department of Medical Oncology of Ankara Numune Education and Research Hospital and in the Department of Medical Oncology of Hacettepe University Cancer Institute were retrospectively analyzed. There were 3233 patients with breast cancer who were identified for the study. Of them, hormone receptor-positive breast cancer patients using tamoxifen, who were premenopausal at the time of diagnosis, were enrolled in the study. Postmenopausal breast cancer patients, patients with triple-negative tumors or hormone receptor-negative but human epidermal growth factor receptor 2 (HER2) positive tumors were excluded. Also patients who had metastatic disease at the time of diagnosis, patients who did not use tamoxifen and patients with unavailable BMI values were excluded from analysis. Finally, a total 826 hormone receptor-positive premenopausal breast cancer patients were analyzed (Table 1).

In patients with BMI ranging between 18.5 and 24.9 kg/m² were considered as normal weight patients (Arm A, n=408), and patients with a BMI $\geq$ 25 kg/m² were considered as overweight and obese patients (Arm B, n=418). Demographic and medical data including age, menopausal status, weight, height, type of breast

surgery, breast cancer treatment history, radiotherapy history, hormonal treatment history and comorbid diseases were collected from the medical charts. BMI was calculated with baseline height and weight (BMI = weight in kilograms divided by the square of height in meters). Tumors were graded according to the modified Bloom-Richardson scoring system and staged according to the TNM criteria. The data on estrogen receptor (ER), progesterone receptor (PR), and HER2 were obtained through standard clinical testing, using immunohistochemistry (IHC) for ER and PR and the HerceptTest for HER2 status. For ER and PR, receptor positivity was based on >1% of cells testing positive. The patients were categorized as triple-negative if they were negative for ER, PR and HER2.

Statistics

Statistical analyses were performed by using SPSS for Windows version 18.0 (SPSS Inc., Chicago, ILL). Baseline characteristics of normal weight patients were compared with overweight and obese patients by χ^2 test (for categorical variables) or two-sample t-test (for continuous variables). Tumors with missing values were omitted from analyses. DFS was defined as the time interval from time of diagnosis to first disease recurrence or death from any cause if disease recurrence did not occur. OS was defined as the time interval from diagnosis to death from any cause. The data were retrospectively analyzed for DFS and OS according to the BMI. Kaplan-Meier survival analysis was carried out for DFS and OS and the log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided p values of <0.05 were considered statistically significant.

Results

The mean BMI was 22.1 $\pm$ 1.8 kg/m² and 29.2 $\pm$ 3.3kg/m² in Arm A and Arm B, respectively (p<0.001). The median follow-up time for this analysis was 37.5 months (range 6-320). All of the participants were female and their median age was 39.5 (range 22-57) and 43 (range 20-56) years in Arm A and Arm B, respectively (p=0.20). Baseline clinical characteristics of the participants are described in Table 2. In both arms, histology of the primary tumor and the type of surgery were similar and no statistical significant could be detected. Also in both arms the incidence of lymphovascular invasion, perineural invasion, extracapsular extension, HER2 positivity and histopathological grade were similar, without statistical differences. There were no apparent differences in baseline nodal status (p=0.61), tumor size (p=0.21) and tumor stage (p=0.36) between the two treatment arms.

Table 2. Baseline clinical characteristics by body mass index of hormone receptor-positive premenopausal breast cancer patients

	Arm A BMI < 25 kg/m ²		Arm B BMI ≥ 25 kg/m ²		p value
	N	%	N	%	
Total	408	100	418	100	
Histology of primary tumor					
IDC	305	74.8	308	73.7	0.85
ILC	18	4.4	18	4.3	
IDC+ILC	52	12.7	49	11.7	
Others	33	8.1	43	10.3	
Type of surgery					
BCS	150	36.8	155	37.1	0.36
MRM	258	63.2	263	62.9	
LVI					
Positive	121	29.7	137	32.8	0.36
Negative	287	70.3	281	67.2	
PNI					
Positive	45	11.0	50	12.0	0.74
Negative	363	89.0	368	88.0	
ECE					
Positive	51	12.5	52	12.4	1.00
Negative	357	87.5	366	87.6	
HER2					
Positive	63	16.2	84	21.4	0.07
Negative	325	83.8	308	78.6	
Histological grade					
I	51	14.2	42	11.0	0.28
II	171	47.8	178	46.6	
III	136	38.0	162	42.4	
Tumor size at diagnosis					
T1	164	40.2	147	35.2	0.21
T2	181	44.4	196	46.8	
T3	58	14.2	63	15.1	
T4	5	1.2	12	2.9	
Lymph node status					
N0	211	51.7	207	49.5	0.61
N1	112	27.5	107	25.6	
N2	51	12.5	58	13.9	
N3	34	8.3	46	11.0	
TNM stage					
I	93	22.8	106	25.4	0.36
II	183	44.9	191	45.7	
III	132	32.3	121	28.9	

BMI: body mass index, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, HER2: human epidermal growth factor receptor 2, BCS: breast conserving surgery, MRM: modified radical mastectomy, LVI: lymphovascular invasion, ECE: extracapsular extension, PNI: perineural invasion

Baseline treatment modalities of the participants in both groups are described in Table 3. In both groups the treatment history with radiotherapy ($p=0.22$) and chemotherapy ($p=0.59$) was similar and no statistical significant difference could be detected. LHRH agonists in combination with tamoxifen were significantly used more in Arm A compared to arm B (136/408 [33.3%] in Arm A and

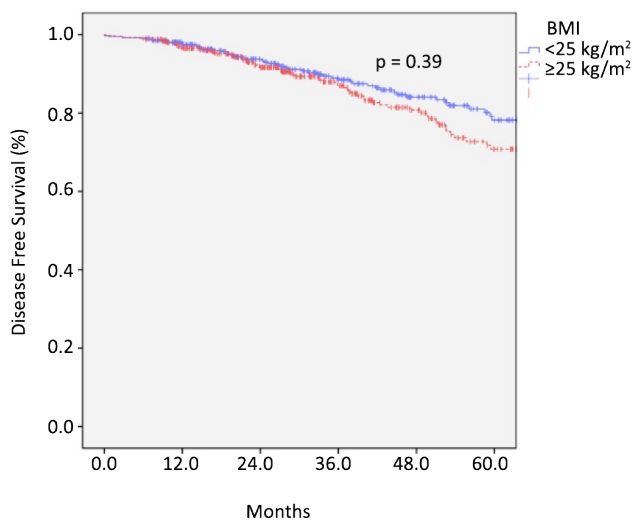
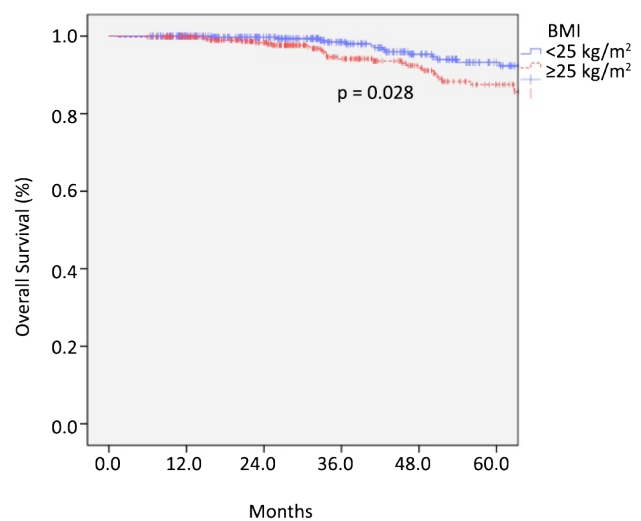
91/418 [21.8%] in Arm B; $p<0.001$).

Three-year DFS rates were 88.5% and 87.0% in arm A and in arm B, respectively (Figure 1 ; $p=0.39$). Three-year OS rates were 98.5% and 94.1% in arm A and B, respectively (Figure 2 ; $p=0.028$). In univariate analysis no significant effect of LHRH agonists usage on DFS ($p=0.58$) or OS ($p=0.96$) was noted.

Table 3. Patients' treatment modalities by body mass index

Treatment modalities	Arm A BMI < 25 kg/m ²		Arm B BMI ≥ 25 kg/m ²		p value
	N	%	N	%	
Total	102	100	399	100	
Chemotherapy					
No	91	22.3	101	24.2	0.59
Adjuvant	289	70.8	284	67.9	
Neoadjuvant	28	6.9	33	7.9	
Chemotherapeutic agents					
Anthracyclines	114	36.0	118	37.2	0.28
Taxanes	9	2.8	3	0.9	
Anthracyclines plus taxanes	164	51.7	175	55.2	
Others	30	9.5	21	6.6	
Trastuzumab					
No	352	86.3	345	82.5	0.15
Yes	56	13.7	73	17.5	
Radiotherapy					
No	104	25.5	91	21.8	0.22
Yes	304	74.5	327	78.2	
LHRH agonists					
No	272	66.7	327	78.2	<0.001
Yes	136	33.3	91	21.8	

BMI: body mass index, LHRH: luteinizing hormone-releasing hormone

**Figure 1.** Analysis of disease free survival according to the body mass index.**Figure 2.** Analysis of overall survival of according to the body mass index.

Discussion

Obesity is a well-known risk factor for the development of breast cancer, especially for postmenopausal women and the prevalence increases in adult population day by day [28,29]. Adipose tissue is the major source of estrogens, thus higher aromatase enzyme levels in obese patients can increase the estrogen levels. As the expres-

sion of aromatase enzyme increases with high BMI, this may subsequently influence the effect of aromatase inhibitors [30]. Four randomized (ATAC, BIG 1-98, TEAM and ABCSG-12) studies have investigated the role of BMI on the effectiveness of aromatase inhibitors versus tamoxifen in the adjuvant treatment of early breast cancer [21,22,26,31]. In three of these four trials (ATAC, BIG 1-98 and TEAM) which investigated the effec-

tiveness of aromatase inhibitors in the adjuvant treatment of postmenopausal setting, it was only the ATAC trial which described obesity as an increased risk factor of recurrence whereas obesity was not found as a prognostic factor in BIG 1-98 and TEAM trials [21,22,31]. On the other hand, in the premenopausal setting, in ABCSG-12 trial, obesity was associated with poor outcome only in the anastrozole arm [26]. Although the efficacy of aromatase inhibitors can change according to the BMI, obesity was not found as a predictor of response in patients treated with tamoxifen according to the above-mentioned four randomized trials that investigated the effectiveness of aromatase inhibitors versus tamoxifen [21,22,26,31].

In our study, in premenopausal hormone receptor-positive patients who were treated with tamoxifen, the 3-year DFS rates were similar according to the BMI, whereas the 3-year OS rates were significantly worse in the overweight and obese group. In the ABCSG-12 trial, however, the BMI appeared to have no prognostic impact neither on DFS (HR 0.94; $p=0.76$) nor on OS (HR 0.83; $p=0.65$) in patients treated with tamoxifen [26]. In contrast to the ABCSG-12 trial, although obesity did not increase the risk of recurrence or breast cancer mortality in patients with lymph node-negative, estrogen receptor-positive breast cancer who were treated with tamoxifen or placebo, the overall mortality was significantly increased in the NSABP B-14 trial which was similar to our study [25]. Ewertz and colleagues have investigated the effect of BMI in 18,967 premenopausal or postmenopausal women who were treated for early breast cancer in the Danish Breast Cancer Cooperative Database and they found that the risk of distant recurrences and the risk of death were increased significantly in obese patients whereas no effect on locoregional recurrences was found [13]. Moreover, they reported that both chemotherapy and endocrine therapy were less effective in obese patients. In the Breast Cancer Pooling Project study, Kwan et al. reported that pre-diagnosis underweight and obese patients had a statistically significant increased overall death rate compared to the normal weight patients [32]. Of note, after adjustment for risk factors in a recently reported EBCTCG trial, the association between BMI and breast cancer mortality was significant only in hormone receptor-positive premenopausal and perimenopausal breast cancer patients [27].

In our study, LHRH agonists in combination with tamoxifen were used in 33% and 22% of normal weight patients, and overweight and obese

patients, respectively. In univariate analysis there was no significant effect of LHRH agonists usage on DFS and OS. In the Eastern Cooperative Oncology Group (ECOG) E-3193 trial, no significant difference for DFS and OS was found when ovarian suppression was added to tamoxifen in premenopausal women with node-negative, hormone receptor-positive breast cancer who did not receive adjuvant chemotherapy with a median follow-up of 9.9 years [33]. In the recently published SOFT trial, which aimed to determine the value of adding ovarian suppression to tamoxifen, no significant benefit was found with adding ovarian suppression in hormone receptor-positive early breast cancer in premenopausal women [34]. On the contrary, a meta-analysis performed by the EBCTCG in 11,906 premenopausal patients with hormone receptor-positive breast cancer showed that addition of LHRH agonists to tamoxifen, chemotherapy or both improved significantly the recurrence risk and survival, whereas LHRH agonists used as the only systemic adjuvant treatment did not have any significant effect in reducing the recurrence risk or improving survival [35].

In our study we have analyzed the premenopausal hormone receptor-positive breast cancer patients who were treated with tamoxifen. To the best of our knowledge, our study is the first to compare the efficacy of adjuvant tamoxifen in premenopausal hormone receptor-positive breast cancer patients according to BMI.

Our study presents some limitations which are inherent to its retrospective nature. Some studies have indeed shown that obese patients may receive reduced doses of adjuvant chemotherapy which was shown to be associated with a poorer outcome [36,37]. We did not have data if optimal doses of chemotherapy were not given to obese patients compared to normal-weight patients. Another limitation of our study is that we had only data of baseline BMI values. Our baseline data does not reflect the possibility that some previously 'normal' BMI women might have become overweight or obese during the follow-up period or *vice versa*. Weight gain was a common problem in patients treated with tamoxifen but in the NSABP-B14 and the NSABP-P1 trials adjuvant tamoxifen therapy was not associated with weight gain [38-40]. Similarly, Francini et al. investigated the effects of adjuvant hormonal therapy on body composition and lipids profile and they found no statistically significant changes in lipids and body weight in patients treated with tamoxifen [41]. Also, the 3-year follow up in our study is too

short for hormone receptor-positive breast cancer patients. Perhaps another important limitation of the present study is that, although we registered the data regarding patient comorbidities, we did not analyze them as to whether obese patients had more significant comorbidities; this may have a negative influence on the survival outcome and, due to the retrospective nature of our study, it might be difficult to report on breast cancer specific survival instead of OS.

In conclusion, our retrospective analyses showed that BMI has no negative impact on recurrence risk, despite significantly poor survival outcome in premenopausal overweight and obese patients with hormone-receptor positive breast cancer.

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