



The Relationship between Bone Mineral Density and Estrogen Receptor Positivity in Patients with Breast Cancer

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ABSTRACT

Objective: The effect of estrogen on bone mineral density (BMD) and breast cancer has been known for a long time. The aim of this study was to compare of the BMD of patients with breast cancer and healthy individuals, and to investigate the degree of correlation of estrogen receptor (ER) with BMD.

Materials and Methods: Seventy-one patients with postmenopausal breast cancer and 79 healthy individuals were included in the study. The patient demographics (age, menopause age, body mass index, number of children, BMD, Z scores, and estrogen status for breast cancer patients) were taken from hospital records.

Results: No significant difference was detected between the case and control groups in lumbar region Z scores ($p=0.074$). At the femur neck, the control group Z scores was higher than patient group ($p=0.002$). BMI was higher in the patients with breast cancer ($p=0.001$). There was no statistically significant correlation between ER positivity, BMD, and BMI in ER-positive patients ($p=0.495$, $p=0.8$, $p=0.846$, respectively). There was no difference between the Z scores when the patients were divided into two groups as ER positive and negative ($p=0.156$, $p=0.335$, respectively).

Conclusion: This study revealed that there is no difference in lumbar region Z scores between patients with breast cancer and healthy controls; however, the Z scores were higher in the femur neck in the control group, and the BMI was lower in the patient group. Tumor ER positivity does not positively affect BMD.

Keywords: Breast cancer, bone mineral density, estrogen receptor, body mass index

Introduction

Breast cancer is the most prevalent cancer type and the second leading cause of death in women (1). Advanced age, early menarche, first-term pregnancy at a late age, late menopause, and long-term hormone replacement treatment are among the risk factors for breast cancer (2-4). The relationship between these risk factors and breast cancer are reported to be due to the estrogen-induced increase in mitotic activity in breast tissue, which results in mutations (5).

Estrogen hormone is an important risk factor for breast cancer; however, serum levels often vary, which obstructs correlating serum estrogen levels with the risk of breast cancer (6). Serum samples are not sufficient alone to diagnose breast cancer or identify the long-term estrogen level of tissues. Bone mineral density (BMD) should be considered a good indicator of tissue levels of estrogen because BMD elevates in parallel with the increase in estrogen level (7). Estrogen lessens bone destruction while amplifying bone volume and bone mineral density. When we consider this information, we may think that there is a correlation between BMD and breast cancer. Nevertheless, studies that investigated the relationship between bone mineral density and development of breast cancer revealed contradictory results (8-11).

In patients with breast cancer, the ratio of tumor estrogen receptor (ER) positivity enhances with age. In a study carried out on Turkish women, ER was found positive in 66% of pre-menopausal women, and this rate increased to 73% in menopausal women (12). Only a few studies in the literature have shown a link of the change in ER positivity with bone density, but none were conducted in Turkey.

The objective of this study was to compare the BMD of postmenopausal women with breast cancer with that of control subjects and thus to investigate the association between tumor estrogen receptor level and bone mineral density.

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Materials and Methods

We analyzed the data of 261 patients who presented to our clinic between January 2011 and December 2014 with breast cancer. Data including age, number of deliveries, breastfeeding duration, body mass index (BMI), pathologic stage, additional diseases, ER levels, and bone densitometry measurements prior to systemic chemotherapy were recorded. The control subjects were selected among individuals who applied to the Radiology Department of the Hospital during the same period for BMD measurement ensuring that their age was in line with that of the patients with breast cancer. Individuals with hypothyroidism and hyperthyroidism, steroid use, hormone replacement therapy, any disease that might cause of osteoporosis such as immobility, and those that took medication that may cause osteoporosis or for the treatment of osteoporosis were excluded from the study. Premenopausal patients were also not included in the study. The study was approved by the Hospital's Ethics Committee and started after the obtaining consent from the patients.

The 2nd to the 4th lumbar vertebrae and femoral neck BMD was measured using dual X-ray absorptiometry (DXA) (Hologic, Bedford, MA, USA), whose calibration is performed regularly at our clinic. The BMD of the study and control subjects were identified using the Z scores; a score ≤ 2 was regarded as osteoporosis (13).

Immunohistochemical estrogen receptor analysis was performed using a Benchmark LT (Ventana Medical Systems Inc.; California, USA) on formalin-fixed paraffin-embedded tissue sections with ab-Neomarkers-antibodies (Clone SP1) at concentration 1/100. Only nuclear staining was considered positive. The area where a number of stained cells was the highest was determined regarding the College of American Pathologists (CAP) criteria; 100 cells were counted, and the ratio of the staining was identified (14). Patients with an ER level $<10\%$ were classified as negative whereas those with an ER level $\geq 10\%$ were classified as positive.

Statistical analysis

The statistical analyses were performed using SPSS version 20.0 (IBM Corp. New York, USA). The mean, standard deviation, median, minimum, maximum, frequency and ratio values were used for the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test and independent sample t-test were used for the analysis of quantitative data in both groups, and Spearman's correlation analysis was used to identify correlations. The results of the study were evaluated in a 95% confidence interval considering $p < 0.05$ as significant.

Results

After the exclusion criteria were assessed, 71 postmenopausal patients were included in the study group, and 79 menopausal women without breast cancer were included in the control group. Among the patients in the study group, 31% (n=22) had stage 1 breast cancer; 53.6 (n=38) had stage 2 breast cancer; 8.4% (n=6) had stage 3 breast cancer, and 7% had stage 4 breast cancer. Table 1 shows other demographic data of the patients.

The study group and control group did not differ significantly regarding the mean age of the patients, whereas BMI was found higher in the study group (Table 1). Although the mean age of menarche was different between the groups ($p=0.001$), no significant difference was observed when the length of the period between menarche and menopause was compared ($p=0.33$). There was statistically significant differ-

ence between the groups regarding the L2-4 and femoral neck Z scores ($p=0.026$ and $p=0.002$, Table 2). When the patients were classified as <25 and ≥ 25 kg/m² according to BMI, the group with a BMI ≥ 25 kg/m² had significantly lower Z-scores of the femoral neck and lumbar spine compared with the control group (Table 3.1 and 3.2).

The receptor positivity level of the patients who had positive estrogen receptor was analyzed considering the BMI and the lumbar and femoral Z-scores; no significant correlation was found between these measurements ($p=0.495$, $p=0.8$, $p=0.846$ respectively) (Table 4). When the patients in the study group were divided into two sub-groups as ER-positive and ER-negative; there was no statistically significant difference between these two groups regarding Z scores. Furthermore, when the ER-positive and ER-negative patients were classified as with and without osteoporosis depending on their Z scores, no statistically significant difference was identified. However, the prevalence of osteoporosis in the lumbar spine and femoral neck was lower in the ER-positive patients compared with the ER-negative patients (23% vs. 8.6%; 7.7% vs. 1.7%) (Table 5).

Table 1. Demographics of the Control and Breast Cancer Group

Patient demographics	Study Group (n=71) Mean \pm SS (min-max)	Control Group (n=79) mean \pm SS (min-max)	P*
Age	59.28 \pm 7.38 (45.0-81.0)	59.63 \pm 10.8	0.94
BMI	29.98 \pm 5.49 (19.10-48.20)	26.9 \pm 4.9	0.001*
Number of birth	1.90 \pm 1.00 (0-5)0-5)	1.83 \pm 1.05	0.63
Age at Menarche	13.11 \pm 1.08 (11-16)	12.54 \pm 0.97	0.001*
Breast feeding(year)	1.05 \pm 0.23 (1-2)	1.08 \pm 0.28	0.45
Age of menopause	49.6 \pm 3.9 (37-63)	49.45 \pm 4.3	0.77
Fertility time (year)	36.57 \pm 3.57	36.91 \pm 4.40	0.330

BMI: Body mass index; Min: minimum; max: maximum
* $p < 0.05$

Table 2. Z Scores of the Control and study group in the lumbar and femur neck regions

Z score	Study Group (n=71) Mean \pm SS (min-max)		Control Group (n=79) mean \pm SS (min-max)		p
L2-L4 DEXA	-0.37 \pm 1.12	-0.40 (-2.60-2.78)	0.06 \pm 1.29	-0.30 (-2.60-2.90)	0.029*
Femur DEXA	-0.27 \pm 0.87	-0.40 (-2.00-1.70)	0.18 \pm 0.93	0.10 (-2.70-2.30)	0.002*

* $p < 0.05$ was considered significant.

Table 3. 1. Classification of the control and study group according to BMI 25

	BMI	≤25	>25
Study group	8 (11.2%)	63 (88.8%)	71 (100%)
Control group	31 (39.2%)	48 (60.8%)	79 (100%)

BMI: body mass index

Table 3. 2. Analysis of Z Scores of patients with BMI ≤25

BMD measurement region	Study Group (n=63)	Control group (n=48)	P
Femur	-0.24±0.89	0.34±0.85	0.001*
L2-4	-0.37±1.08	0.45±1.3	0.003*

*p<0.05 was considered significant.
BMD: bone mineral density

Table 4. The Level of Positive Correlation of BMI and Bone Density

Hormone receptor		BMI	L2-4 DEXA	Femoral DEXA
The rate of estrogen receptor positivity	r	-0.091	-0.034	-0.026
	p	0.495	0.800	0.846

r: rho coefficient
*p<0.05 was considered significant.
BMI: body mass index

Table 5. The comparison of the ER-negative and ER-positive patients regarding BMD

BMD		ER-negative (digit, %)	ER-positive (digit, %)	p
L2-4-DEXA	Normal	10 (76.9%)	53 (91.4%)	0.156
	Osteoporosis	3 (23.1%)	5 (8.6%)	
Femur-DEXA	Normal	12 (92.3%)	57 (98.3%)	0.335
	Osteoporosis	1 (7.7%)	1 (1.7%)	

*p<0.05 was considered significant.
BMD: bone mineral density

Discussion and Conclusion

Besides being a crucial hormone for bone metabolism, estrogen also plays a role in the etiology of breast cancer. In this regard, high BMD is considered to be associated with breast cancer (6, 16). Klift et al. (10) indicated a correlation between increased lumbar spine BMD and breast cancer; the same correlation was not observed between femoral

BMD and breast cancer. In the study of Kim et al. (8) on Korean women, a similar relationship was demonstrated between breast cancer and lumbar and femoral BMD. Contrary to the studies mentioned above, Kerliowske et al. (9) claimed that lumbar and femoral BMD did not correlate with breast cancer risk. In the present study, the Z-scores of the lumbar spine and femoral neck were lower in patients with breast cancer. The conflicting results of the study may be related to the fact that various factors affect bone metabolism and play a role in the development of breast cancer. Moreover, due to polymorphisms in genes involved in the biosynthesis and metabolism of estrogen, tissues in the body may have different estrogen sensitivity (17).

On the other hand, no correlation was demonstrated in studies that analyzed the BMD-breast cancer relationship in premenopausal women (7, 18). Therefore, we did not enroll premenopausal patients in the study.

Douchi et al. (19) conducted a study on ER-positive postmenopausal women with breast cancer and showed BMD to be higher in the patients with cancer as compared with the control group. Bayraktar et al. (20) examined BMD and tumor characteristics in postmenopausal patients, no correlation was found between the ER-positive and ER-negative patients regarding BMD. Even though we also found no significant difference between ER-positive and ER-negative patients considering the Z scores, when the patients were classified as with and without osteoporosis the rate of osteoporosis was found lower in patients with positive ER. However, these results can be explained by the small number of ER-negative patients.

Obesity has been indicated to elevate the risk of breast cancer in postmenopausal women (21-23). Obesity has such an effect that ovaries no longer produce hormones in the postmenopausal period whereas fat tissue stands out as the most important source of estrogen (24). Obesity is also linked with increased bone density due to the same mechanism. Similarly, we found significantly higher BMI levels in patients with breast cancer compared with the control group. Additionally, according to the evaluation of the Z-scores in the obese postmenopausal patients who were expected to have higher serum estrogen levels, the Z scores were observed to be greater in the control group compared with patients with a BMI ≥25 kg/m². This result may be due to the small number of patients and control subjects or due to different impacts of the regional polymorphism in the estrogen genes on bone and breast tissue.

High bone mineral density is known to be an indicator of serum estrogen level; however, we found no significant association between estrogen receptor level of tumor tissue and bone mineral density. Also, the estrogen receptor positivity was correlated with BMD. There is a need for further larger studies to be performed with more patients to evaluate the link between bone density and ER receptor.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

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