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The Relationship Between Vitamin D Level and Prognostic Factors in Patients Diagnosed with Breast Cancer

Meme Kanseri Tanılı Hastalarda D Vitamini Düzeyi ile Prognostik Faktörler Arasındaki İlişki

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ABSTRACT

Background: To examine the relationship between vitamin D level at the time of diagnosis and disease prognostic factors in patients diagnosed with breast cancer.

Materials and Methods: We studied 150 patients with breast cancer whose vitamin D levels were measured before treatment. The patients' vitamin D levels were compared with their estrogen receptor (ER) levels, progesterone receptor (PR) levels, human epidermal growth factor receptor 2 (Her-2/neu) status, ki-67 levels, and histopathological features.

Results: Vitamin D was found to be significantly positively correlated with ER (p<0.001) and PR (p=0.032) staining intensities and significantly negatively correlated with ki-67 level (p=0.001). Both the ER (p=0.003) and ki-67 index (p=0.024) were found to be significantly correlated with vitamin D level, 20 ng/mL below and above, and its relation with prognostic factors.

Conclusion: There may be a relationship between serum 25 hydroxy vitamin D [25(OH)D] level and breast cancer prognosis. Our study can be used as a guide for examining the contribution of supportive treatments that provide normal vitamin D levels (>30 ng/mL) to decrease breast cancer aggressiveness. More studies are needed to elucidate the relationship between breast cancer and vitamin D.

Keywords: Vitamin D, breast cancer, prognosis

ÖZ

Amaç: Meme kanseri tanılı hastalarda tanı anındaki D vitamini düzeyi ile hastalığın prognostik faktörleri arasındaki ilişkiyi incelemektir.

Gereç ve Yöntemler: Tedavi öncesi D vitamini düzeyi ölçülen 150 meme kanserli hastayı inceledik. Hastaların D vitamini düzeyleri östrojen reseptör (ER) düzeyleri, progesteron reseptör (PR) düzeyleri, insan epidermal büyüme faktörü reseptörü 2 (Her-2/neu) durumu, ki-67 düzeyleri ve histopatolojik özellikleri ile karşılaştırıldı.

Bulgular: D vitamininin ER (p<0,001) ve PR (p=0,032) boyama yoğunlukları ile anlamlı derecede pozitif, ki-67 düzeyi (p=0,001) ile anlamlı derecede negatif korelasyon gösterdiği bulundu. Hem ER (p=0,003) hem de ki-67 indeksi (p=0,024), 20 ng/mL altı ve üstü D vitamini düzeyleri ile anlamlı olarak ilişkili bulundu.

Sonuç: Serum 25 hidroksi vitamin D [25(OH)D] düzeyi ile meme kanseri prognozu arasında bir ilişki olabilir. Çalışmamız, normal D vitamini düzeylerini (>30 ng/mL) sağlayan destekleyici tedavilerin meme kanseri agresifliğini azaltmaya katkısını incelemek için bir rehber olarak kullanılabilir. Meme kanseri ve D vitamini arasındaki ilişkiyi aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: D vitamini, meme kanseri, prognoz

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Introduction

Globally, breast cancer is the most frequently diagnosed malignancy. It is also the leading cause of cancer death in women worldwide (1). Accumulated evidence indicates that various genetic and environmental factors may be associated with the initiation and progression of breast cancer. Ecological studies have found an inverse relationship between sunlight exposure and breast cancer risk (2).

Some factors have been shown to affect the course of the disease in breast cancer patients. These include histopathological features (type, grade, tumor stage, lymph node status), ki-67 level, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (Her-2) status. These factors can be affected by both genetics and socioeconomic status (3,4). Tumors positive for ER and PR have a better prognosis (5). Her-2 overexpression indicates a poor prognosis, especially if patients are not treated with chemotherapy and HER-2-directed agents (6). Diagnosis under 35 years of age, presenting with locally advanced disease, tumor size ⩾2 cm, axillary lymph node involvement, and high histological grade are poor prognostic criteria (7,8,9,10).

Vitamin D is a sterol derivative, and 25 hydroxy vitamin D [25(OH)D] is its main circulating form (11). Measurement of serum 25(OH)D concentration is the best laboratory test for vitamin D level. The lower limit of normal for 25(OH)D levels varies according to geographic location and the average amount of time the population is exposed to sunlight. According to the United States Medical Association, a serum 25(OH)D concentration of 20 ng/mL (50 nmol/L) and above is generally considered sufficient, while in other guidelines, the minimum amount required to minimize the risk of falls and fractures is 30 ng/mL (75 nmol/L) (12).

Numerous epidemiological studies have investigated the relationship between serum 25(OH)D level and breast cancer risk. In a review including nine prospective studies with 11,656 women in the postmenopausal period, it was shown that every 5 ng/mL increase in serum 25(OH)D level reduced the risk of breast cancer by 12% (13). In contrast, a randomized study conducted with 36,282 postmenopausal women found no relationship between serum 25(OH)D level and breast cancer risk when the group receiving 1.000 mg of elemental calcium and 400 units of vitamin D3 daily was compared with the placebo group (14). In a meta-analysis, vitamin D was shown to positively affect breast cancer survival (15). In another meta-analysis, newly diagnosed breast cancer patients had significantly lower serum 25(OH)D levels than healthy controls. A lower level of serum 25(OH)D has been correlated with aggressive breast cancer phenotypes (16).

Material and Methods

Study Population

Our study was carried out with patients who applied to University of Health Sciences Türkiye (Okmeydanı Training and Research Hospital and İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital Oncology Outpatient Clinic. Our study protocol complied with the principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşçıoğlu Hospital Clinical Research Ethics Committee (05/11/2019, number: 1471). The files of 624 patients with newly diagnosed premenopausal and postmenopausal breast cancer between January 2018 and August 2021 were scanned. We excluded 286 patients due to a lack of vitamin D value, 64 patients who were perimenopausal, and 124 patients due to distant organ metastasis. Thus, 150 female cases were included in the study. The case information was examined, and 25(OH)D levels at the time of diagnosis were recorded. The relationship between ER, PR, Her-2/neu, histological diagnosis, grade, tumor diameter, ki-67 status, lymph node metastasis status, and 25(OH)D levels were evaluated statistically. The values measured for 25(OH)D before and after the diagnosis during the 20-day period without antitumoral treatment were noted.

Statistical Analysis

Statistical analyses were performed using SPSS v. 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as a number and as a percentage for categorical variables, average, standard deviation, and minimum and maximum for numeric variables. The numerical variables did not meet the normal distribution condition, and comparisons of more than two independent groups were made using the Kruskal-Wallis test and comparisons of two independent groups were made using the Mann-Whitney U test. Comparisons of the ratios in the groups were made using the chi-square test. Spearman's correlation test was used to determine the level of correlation between vitamin D and prognostic factors. Statistical significance level of alpha was accepted as $p<0.05$.

Results

A total of 150 newly diagnosed female patients with breast cancer were included in the study. The mean age of the patients was 47.9±11.2 (range: 22-81) years. Of these, 85 patients (56.7%) were premenopausal, and 65 (43.3%) were postmenopausal. There were 48 (32.0%) ER-negative and 102 (68.0%) ER-positive patients. ER +, ++, and +++

patient numbers were 33 (22.0%), 65 (43.3%), and 4 (2.7%), respectively. The number of PR negative patients was 74 (49.3%), while the number of PR positive patients was 76 (50.7%). The number of PR +, ++, and +++ patients was 35 (23.3%), 32 (21.3%), and 9 (6.0%), respectively. The numbers of Her-2-negative and -positive patients were 113 (75.3%) and 37 (24.7%), respectively. All patients had invasive ductal cancer histology. When histological grades were examined, 8 patients (5.3%) were grade 1, 100 (66.7%) were grade 2, and 42 (28.0%) were grade 3. The mean tumor diameter of the patients was calculated as 23.2±16.3 mm (range: 1-85 mm). The mean ki-67 levels were 35.7%±25.4% (range: 2-90). The mean 25(OH)D levels were 17.8±10.2 ng/mL (range: 3.8-79.5 ng/mL) (Table 1).

In the correlation analysis between 25(OH)D levels and clinicopathological data, no correlation was found with age, Her-2 status, tumor diameter, or tumor grade. A statistically significant positive correlation was found for vitamin D with ER (p=0.306, p<0.001) and PR (p=0.175, p=0.032) staining intensities. A statistically significant negative correlation was observed between 25(OH)D levels and ki-67 (p=0.300, p=0.001) (Table 2).

When the relationship of patients' 25(OH)D levels was compared with ER, PR, Her-2, and menopause status, the mean vitamin D levels of ER-negative and -positive patients were 15.0±11.2 ng/mL and 19.1±9.5 ng/mL, respectively. For ER-positive patients, 25(OH)D levels were significantly higher than ER-negative patients (p=0.002). The mean vitamin D levels of PR-negative and -positive patients were 17.3±11.9 ng/mL and 18.2±8.2 ng/mL, respectively. Although 25(OH)D levels were lower for PR-negative patients than PR-positive patients, this difference was not significant. When analyzed according to menopause status and Her-2 status, no statistically significant differences were found between the groups (Table 3).

The patients' ER, PR, ki-67 status, Her2-neu status, menopausal status, lymph node metastasis, tumor grade, and tumor diameter were examined according to vitamin D levels. A statistically significant correlation was found between vitamin D level and ER (p=0.003). The ki-67 level was divided into two groups: Below and above 14%. There was a statistically significant relationship between vitamin D and ki-67 status (p=0.024) (Table 4).

Discussion

Breast cancer is the most common malignancy among women worldwide (17). Breast cancer subtypes were classified according to the expression of ER, PR, and HER2. The prognosis of each subtype was also closely associated with the expression of those receptors (18). Breast cancer cases with ER+ subtypes are associated with the best prognosis. By contrast, women with ER- subtypes, especially those with

Table 1. The patient's clinicopathological features

Age			**47.9±11.2 (22-81)**
ER	Negative (n=48)	Negative	48 (32.0%)
		+	33 (22.0%)
	Positive (n=102)	++	65 (43.3%)
		+++	4 (2.7%)
PR	Negative (n=74)	Negative	74 (49.3%)
		+	35 (23.3%)
	Positive (n=76)	++	32 (21.3%)
		+++	9 (6.0%)
Her-2		Negative	113 (75.3%)
		Positive	37 (24.7%)
Menopause		Postmenopause	65 (43.3%)
		Premenopause	85 (56.7%)
Tumor diameter (mm)			23.2±16.3 (1-85)
Grade		1	8 (5.3%)
		2	100 (66.7%)
		3	42 (28.0%)
Ki-67%			35.7±25.4 (2-90)
Vitamin D level (ng/mL)			17.8±10.2 (3.8-79.5)

ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor-2

triple-negative disease, suffer the worst prognosis (19). Multiple studies have shown associations between adequate circulating 25(OH)D levels, and decreased prognosis of breast cancer (20,21). In recent meta-analysis of 12 cohort studies involving 8.574 breast cancer patients suggested that low 25-hydroxyvitamin D level was associated with a worse survival (22). In breast cancer tissues, vitamin D has anticancer effects that are mediated through vitamin D reseptor acting as a transcription factor and regulating several genes with an antiproliferative, proapoptotic, and differentiation action (23). Vitamin D induces ER expression in ER-negative breast cancers, thereby restoring their response to anti-estrogens (24).

We investigated the relationship between serum 25(OH) D levels at the time of diagnosis and disease prognostic factors in 150 premenopausal and postmenopausal women with breast cancer. In a study conducted in 192 postmenopausal breast cancer patients, the relationship between 25(OH)D levels at the time of diagnosis and prognostic data was examined. Individuals with low 25(OH) D levels were found to be more likely to have positive lymph nodes, lower ER and PR ratios, and higher ki-67 levels (25).

Table 2. The correlation between vitamin D and prognostic factors

	Vitamin D level	
	rho	**p**
Age	0.024	0.773
ER	0.306	**<0.001**
PR	0.175	**0.032**
Her-2	-0.071	0.387
Ki-67	-0.300	**0.001**
Tumor diameter	-0.017	0.851
Grade	-0.159	0.070

ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor-2

In our study, we found that patients with low serum 25(OH) D levels had significantly lower ER and PR rates and higher ki-67 levels compared to those with high serum 25(OH)D levels. However, we did not find such a relationship with lymph node status.

In a study, serum 25(OH)D levels at the time of diagnosis were investigated from 50 female patients without primary invasive metastatic disease, and as a result, a significantly larger tumor size was observed in patients with low serum vitamin D levels (26). In a similar study, the 25-hydroxyvitamin D level had a significant inverse association with metastatic breast cancer. Low vitamin D levels were associated with advanced stages of the disease, tumor size, and grade in postmenopausal patients (27). However, in our study, we divided the serum 25(OH)D level into two groups (< and >20 ng/mL) and found no significant correlation between tumor size and serum 25(OH)D level.

Abdel-Rezaq (28) showed that patients with low vitamin D levels had larger tumor sizes (2.9% vs. 46.7%), more advanced disease (2.9% vs. 53.3%), higher grade tumors (33.3% vs. 2.9%), negative hormone receptors (73.3% vs. 51.4%), and higher Her-2 positive values (40.0% vs. 86.7%). Similarly, in our study, a positive correlation was found for vitamin D level with ER and PR staining intensities. However, no significant correlation was found with tumor diameter, grade, or Her-2 positivity. The 150 patients included in our study were both post-menopausal and pre-menopausal patients.

Peppone et al. (29) compared the 25(OH)D levels of 194 women who had undergone breast cancer surgery and 194 cancer-free controls. Vitamin D levels of breast cancer cases were found to be significantly lower than the control group. Women with serum 25(OH)D levels below 32 ng/mL had a significantly higher rate of ER negativity and triple negative cancer. In our study, 25(OH)D levels of ER-positive patients were found to be statistically significantly higher than in negative patients.

Table 3. Vitamin D levels in prognostic groups

		Vitamin D level (ng/mL)		
		Mean ± SD	**Min-max (median)**	**p**
ER	Negative	15.0±11.2	3.8-79.5 (13.7)	**0.002**
	Positive	19.1±9.5	3.9-52.9 (18.3)	
PR	Negative	17.3±11.9	3.8-79.5 (15.9)	0.073
	Positive	18.2±8.2	3.9-43.8 (18.6)	
Her-2	Negative	18.3±10.8	3.8-79.5 (17.0)	0.445
	Positive	16.8±9.1	3.9-52.9 (14.1)	
Menopause	Postmenopause	17.2±11.2	3.9-79.5 (16.3)	0.841
	Premenopause	18.2±9.4	3.8-52.9 (17.3)	

SD: Standard deviation, ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor-2

Table 4. The relationship of vitamin D levels with prognostic factors

Variable		D vit<20 ng/mL	D vit>20 ng/mL	*p
ER n=150	Negative	41	7	**p=0.003**
	Positive	63	39	
PR n=150	Negative	50	18	p=0.096
	Positive	48	28	
Ki-67 n=121	<14%	10	12	**p=0.024**
	>14%	70	29	
Menopause n=150	Premenopause	48	17	p=0.295
	Postmenopause	56	29	
Her-2 n=150	Negative	63	31	p=0.426
	Positive	41	15	
Lymph node metastasis n=75	None	22	8	p=0.169
	Detected	26	19	
Grade n=131	Low	62	34	p=0.173
	High	27	8	
Tumor diameter n=121	<20 mm	41	17	p=0.634
	>20 mm	42	21	

*Chi-square test, ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor-2

Study Limitations

The relationship between cancer and vitamin D has been investigated in many studies. We examined the relationship between vitamin D and disease prognostic factors. The limitation of this study is that it was retrospective.

Conclusion

Low vitamin D levels at the time of diagnosis in breast cancer are associated with low ER and PR levels and a high ki-67 index, which have been proven to be prognostic factors for breast cancer. These findings show that adequate vitamin D level can affect breast cancer prognosis in a good way.

Ethics

Ethics Committee Approval: Our study was carried out with patients who applied to University of Health Sciences Türkiye, (Prof. Dr. Cemil Taşçıoğlu Hospital and İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital Oncology Outpatient Clinic. Our study protocol complied with the principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşçıoğlu Hospital Clinical Research Ethics Committee (date: 05/11/2019, number: 1471).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: L.E., S.A., Design: L.E., S.A., Data Collection or Processing: L.E., S.A., Analysis or Interpretation: L.E., S.A., Literature Search: S.A., Writing: L.E.

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