ORIGINAL ARTICLE

Association between serum Vitamin D levels and prognostic factors in nonmetastatic breast cancer patients

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Background: Breast cancer is among the most common malignancies in women around the world. There is evidence of high prevalence of serum/blood Vitamin D deficiency in Iranian women. Considering the multitude of factors that may be involved in the prognosis and lifespan of breast cancer patients, this study investigated the level of Vitamin D in Iranian patients with nonmetastatic breast cancer. **Materials and Methods:** This cross-sectional study was carried out on 214 women diagnosed with breast cancer, who were referred to the radio-oncology department. Serum Vitamin D level of the patients was measured. Prognostic factors were determined based on demographic and pathological characteristics. The results were analyzed using descriptive statistics tests, Chi-square, one-way analysis of variance, Kaplan–Meier, and Cox regression model in SPSS v22. For all cases, the significance level was considered to be $P < 0.05$. **Results:** The total mean of 25-hydroxyvitamin D serum level was 25.15 ± 17.68 ng/ml. There was no significant relationship between levels of Vitamin D with disease stage, tumor size, tumor grade, estrogen receptor, progesterone receptor, and Human epidermal growth factor receptor 2 ($P > 0.05$). The mean survival time was 5 years and 45 days. **Conclusion:** No relationship was found between serum Vitamin D levels and the factors affecting the prognosis of nonmetastatic breast cancer. The Cox analysis showed that the survival time was not influenced by Vitamin D as a prognosis factor.

Key words: Breast cancer, prognosis, Vitamin D

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INTRODUCTION

Breast cancer is one of the most common malignancies in women worldwide.[1-4] Although the reported incidence of this cancer is higher in developed countries, its mortality rate is higher in less developed countries.[5-9] This cancer is one of the important causes of death in women.[10] In recent years, there has been an increase in the incidence of breast cancer among Iranian women and it has become one of the main causes of death in this group.[11-13] This cancer imposes great burdens on patients and their families as well as the healthcare system and the economy.[14-16]

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The Vitamin D receptor with ligand 1α, 25 (OH) 2D3 is involved in the moderation of the genome of epithelial cells.[17,18] In recent studies on cancer, Vitamin D has been considered a factor of interest.[19] Various studies suggest that Vitamin D receptors play a role in cell replication and differentiation.[20] Hypervitaminosis D plays a role in the prognosis of some cancers.[21] There exist some evidence showing a relationship between the level of Vitamin D and the risk of breast cancer.[22-24] However, in another study, no relationship was found between Vitamin D and breast cancer.[25] In addition, a correlation has been reported between the serum level of 25 (OH) D and breast cancer prognosis.[26] Additional evidence suggests that Vitamin D deficiency is highly prevalent

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among Iranian women.[27,28] Considering the multitude of factors that may be involved in the prognosis and lifespan of breast cancer patients, as well as the high prevalence of breast cancer in Iranian women, the relationship between Vitamin D and prognosis factors in this population was addressed herein, investigating the level of Vitamin D in Iranian patients with nonmetastatic breast cancer.

METHODS

This cross-sectional study was conducted on 214 women diagnosed with breast cancer. Every eligible breast cancer patient who was referred to the radiology department between January 2013 and January 2017 entered the study. Vitamin D nonsupplemented patients were also included. Eligibility criteria included women with histologically confirmed primary, incident, breast cancer, with no prior cancer history except nonmelanoma skin cancer. A blood specimen taken with a mean of 30.1 days prior to surgery was used to determine the total 25-OH Vitamin D level (the sum of 25-OH Vitamin D2 and 25-OH Vitamin D3). Controls were selected between the ages of 40 and 70 who had their total 25-OH Vitamin D level. Inclusion criteria were: Consent, aged 18–75 years, diagnosis of nonmetastatic breast cancer, and no use of Vitamin D and complementary medications during the 6 months before breast surgery.

The data collection instruments were a demographic inventory, a breast cancer pathology information form, and laboratory investigation of Vitamin D levels. Patients at all serum Vitamin D levels received adjuvant therapy (chemotherapy, radiotherapy, and hormone therapy) as needed. A serum 25-hydroxyvitamin D concentration of <10 ng/ml was classified as deficiency, 10–30 ng/ml as insufficiency, 100–30 ng/ml as sufficiency, and >100 ng/ml was classified as toxic.[29]

The results were analyzed using descriptive statistics, Chi-square test, one-way analysis of variance (ANOVA), Kaplan–Meier analysis (for univariate analysis), and Cox regression (for multivariate analysis) with the SPSS v. 22 software (IBM SPSS Statistics, Developed by IBM, Armonk, New York, USA). In all cases, the significance level was set at <0.05. This study was approved by the vice president for research at Shahid Behshti University of Medical Sciences (Ethical code: IR.SBMU.MSP.REC.1397.812).

RESULTS

A total of 214 women with nonmetastatic breast cancer who were referred to the radiology department were studied. The mean age of participants was 52.02 ± 11.51 years, and 93.5% of them were married. The total mean of 25-hydroxyvitamin D serum level was 25.15 ± 17.68 ng/ml. The overall prevalence of deficiency is estimated at 24.8%. Among the rest of the patients, 87 cases (40.7%) had insufficiency and 74 (34.6%) had sufficiency. In 81.3% of cases (n = 174) invasive ductal pathology was confirmed. In 86% of patients (n = 184) the breasts were preserved. Demographic characteristics and prognosis factors are listed in Table 1. Of all cases with Vitamin D deficiency,

Table 1: Demographic data of the cancer patients enrolled in the study

Variable	*n* (%)	Variable
<49 years	26 (12.4)	Age
>49 years	184 (87.6)	
Invasive ductal	174 (81.3)	Pathology of breast cancer
Invasive lobular	21 (9.8)	
Medullary	1 (0.5)	
Invasive ductal and lobular	18 (8.4)	
Positive	87 (40.7)	Lymph Nodes
Negative	127 (59.3)	
Total	214 (100)	
1	70 (32.7)	Stage
2	112 (52.3)	
3	32 (14.9)	
Total	214 (100)	
Right	109 (50.9)	Location of tumor
Left	103 (48.1)	
Both	2 (9)	
Total	214 (100)	
T1 (2≥)	93 (43.5)	Tumor size
T2 (2<-5)	102 (47.7)	
T3 (5<)	19 (8.9)	
Total	214 (100)	
1	20 (9.3)	Grade tumor
2	114 (53.3)	
3	80 (37.4)	
Total	214 (100)	
Positive	174 (81.3)	Estrogen receptor
Negative	40 (18.7)	
Total	214 (100)	
Positive	158 (73.8)	Progesterone receptor
Negative	56 (26.2)	
Total	214 (100)	
Positive	50 (23.4)	HER2
Negative	164 (76.6)	
Total	214 (100)	
Positive	47 (22)	PNI
Negative	167 (78)	
Total	214 (100)	
Positive	74 (34.6)	LVI
Negative	140 (65.4)	
Total	214 (100)	
Yes	201 (93.8)	Radiotherapy
No	13 (6.2)	
Total	214 (100)	
Yes	188 (87.9)	Hormone therapy
No	26 (12.1)	
Total	214 (100)	

PNI=Perineural invasion; LVI=Lymphovascular invasion

45.3% were observed in tumor sizes of T1 (2≥), 41.5% in T2 (2<–5), and 13.2% in T3 (5<) (P = 0.204). Furthermore, 9.4% of all the Vitamin D deficiency cases were in Grade I tumors, 50.9 in Grade II tumors, and 39.6 in Grade III tumors (P = 0.957). Among the patients, 83% of Vitamin D deficiency cases were in estrogen receptor (ER)-positive patients, and 17% were in ER-negative patients (P = 0.930). In addition, serum Vitamin D deficiency was noted 77.4% in subjects with positive progesterone receptor and 22.6% in subjects with negative progesterone receptor (P = 0.650). Finally, of all cases with serum Vitamin D deficiency, 20.8% had positive human epidermal growth factor receptor 2 (HER2) and 79.2% had negative HER2 (P = 0.874). Chi-square test showed no statistically significant relationship between Vitamin D level and the tumor size, grade, ER, progesterone receptor, or HER2 (P > 0.05). Table 2 shows the breast-cancer-related information of patients based on their serum Vitamin D levels. The results of ANOVA showed no statistically significant relationship between the mean Vitamin D level and the stage of the disease (P > 0.05) [Table 3]. In the Kaplan–Meier analysis, the overall, 1-year, 2-year, 3-year, and 4-year survival rate of patients was found to be 100%, 99.5%, 98.8%, 97.5%, and 87.5%, respectively. Out of the 214 patients followed up for 4 years, 7 died. The mean survival time was 5 years and 45 days [Figure 1]. The 1-year, 2-year, and 3-year disease-free survival rate for these patients was 99%, 97.3%, and 94.2%, respectively. Of all the cases, only 9 underwent metastasis. The mean time of metastasis for these patients was 5 years and 22 days [Figure 2]. A multivariate analysis (tumor size, tumor grade, posterior nipple line, lymphovascular invasion, ER, progesterone receptors [PR], and HER2) and a Cox regression model were used to determine the factors influencing the survival time. But none of the variables were found to be significant in this model. In patients with positive lymph nodes, those

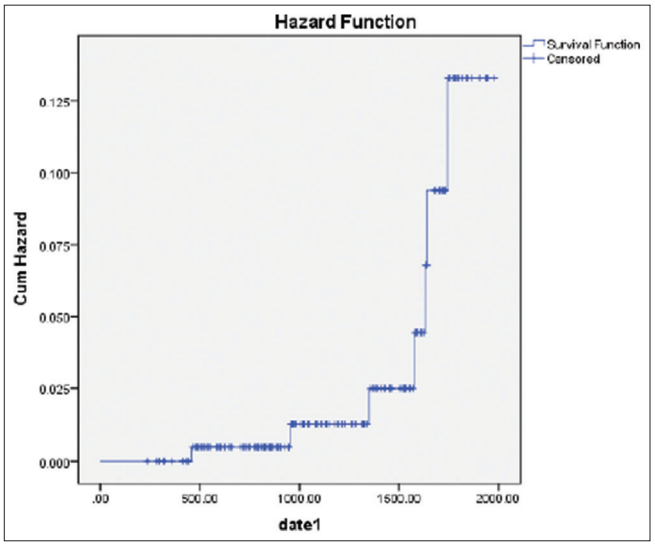

Figure 1: Diagram of survival

Table 2: Data on breast cancer based on the serum levels of Vitamin D

Variable	Deficiency, *n* (%)	Insufficiency, *n* (%)	Sufficiency, *n* (%)	*P*
Tumor size				
T1 (2≥)	33 (44.6)	24 (45.3)	36 (41.9)	0.204
T2 (2< -5)	39 (52.7)	22 (41.5)	41 (47.1)	
T3 (5<)	2 (2.7)	7 (13.2)	10 (11.5)	
Total	74 (100)	53 (100)	87 (100)	
Grade tumor				
1	6 (8.1)	5 (9.4)	9 (10.3)	0.957
2	42 (56.8)	27 (50.9)	45 (51.7)	
3	26 (35.1)	21 (39.6)	33 (79.9)	
Total	74 (100)	53 (100)	87 (100)	
Estrogen receptor				
Positive	60 (81.1)	44 (83.0)	70 (80.5)	0.930
Negative	14 (18.9)	9 (17.0)	17 (19.5)	
Total	74 (100)	53 (100)	87 (100)	
Progesterone receptor				
Positive	52 (70.3)	41 (77.4)	65 (74.7)	0.650
Negative	22 (29.7)	12 (22.6)	22 (25.3)	
Total	74 (100)	53 (100)	87 (100)	
Positive	18 (24.3)	11 (20.8)	21 (24.1)	0.874
Negative	56 (75.7)	42 (79.2)	66 (75.9)	
Total	74 (100)	53 (100)	87 (100)	
Lymph nodes				
<=3	39 (86.6)	65 (84.4)	68 (83.9)	0.917
>3	6 (13.3)	12 (15.5)	13 (16.0)	
Total	45 (100)	77 (100)	81 (100)	

with elevated serum Vitamin D level had 4.34 times higher mortality risk than those with lower Vitamin D levels. Among the patients with negative lymph nodes, those who had elevated serum Vitamin D levels had 0.971 times lower mortality risk than those with lower levels of Vitamin D, although this is not statistically significant. The Cox model was used to study the effect of serum Vitamin D in different levels of lymph node variables. No analysis was conducted for patients with less than three positive lymph nodes, as there was no mortality among them. In the patients who had more than three positive lymph nodes, the mortality risk of those with high serum Vitamin D levels was 1.581 times higher than those with low levels of serum Vitamin D, which is not statistically significant. Figure 3 shows the survival curve for patients in relation to their serum Vitamin D levels.

DISCUSSION

This study investigated the level of serum Vitamin D in Iranian women with nonmetastatic breast cancer. The results showed no relationship between Vitamin D level levels and the stage of the disease or the factors affecting the prognosis of nonmetastatic breast cancer patients.

Vitamin D suppresses the 17-beta-estradiol induced proliferation and regulation of ERs. It affects the estrogen function pathway at multiple stages as well as the ability of these receptors to act as transcriptional activators.[30] Kim *et al.* showed in 310 Korean breast cancer patients before surgery that serum 25-hydroxyvitamin D concentrations did not significantly correlate with Her2/neu prognosis ($P = 0.245$).[31] In another study in Korea, in breast cancer patients who received neoadjuvant chemotherapy, the serum levels of 25 (OH) D had no relationship with survival rates.[32] In another study, this relationship was observed only in white women and not those of other races.[33] These results are consistent with the findings of the present study. Herein, the mean serum 25-hydroxyvitamin D level was generally low, and even in the cases that were classified as normal, the serum levels were mostly in the lower half of the normal range. This may explain the insignificant relationship between serum Vitamin D level and the disease stage and the factors affecting the prognosis of nonmetastatic breast cancer patients.

Elsamany *et al.* showed that Vitamin D deficiency had a significant relationship with negative ER/PR phenotype and lymphatic system invasion.[34] Ismail *et al.* also reported that Vitamin D deficiency had a significant positive relationship with the increase of tumor size, cancer stage, grade, positive status of lymph node, and HER2/neu expressions.[35] In an analytical cross-sectional study conducted by De-Sousa-Almeida-Filho *et al.* in 192 Brazilian women, the relationship between Vitamin D deficiency before treatment and prognosis of breast cancer was assessed in postmenopausal women. The results showed a higher prevalence of deficient serum 25 hydroxyvitamin D levels in high-grade tumors, advanced diseases, and local metastasis (greater number of positive lymph nodes) compared to positive PR tumors and Ki-67 ($P < 0.05$).[36] Janbabai *et al.* found that low levels of Vitamin D have a statistically significant relationship with advanced stages

Table 3: Mean and standard deviation of serum Vitamin D in different stages of breast cancer

Variable	Mean±SD	*P*
Stage 1	25.57±19.61	0.940
Stage 2	25.15±16.86	
Stage 3	24.24±17.57	
Total	25.15±17.68	

SD=Standard deviation

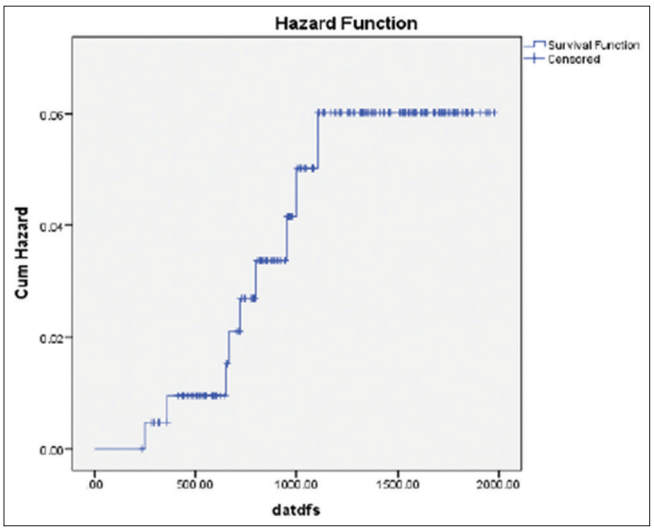

Figure 2: Kaplan–Meier graph

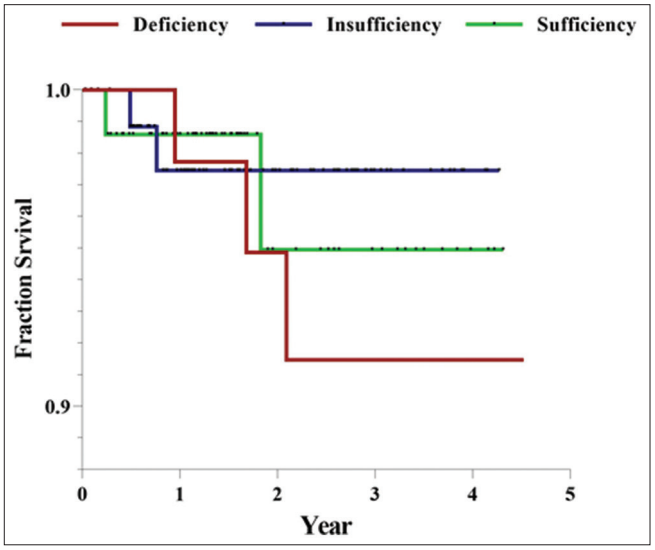

Figure 3: Survival curve of patients in relation to their serum Vitamin D levels

of breast cancer, especially in postmenopausal women.[37] Another study also reported that the prognosis of breast cancer patients is correlated with blood 25-OH Vitamin D level.[38] These results are not consistent with the findings of the present study. This inconsistency may be due to genetic differences or differences in sample size and study durations.

The results of several of these studies point to the potential role of Vitamin D in breast cancer, with altered Vitamin D signaling may lead to illness.[39] On the other hand, Vitamin D has an anticancer effect that is partly related to sex hormones.[40] The inconsistencies in the results of past studies with the causal relationship or the role of Vitamin D in the risk and prognosis of breast cancer highlight the need for further research in this area.[30]

The limitations of this study included a small sample size and the lack of control for all confounding factors that may affect survival. Therefore, further studies with larger sample size and longer follow-up period on the relation of blood/serum Vitamin D levels with factors affecting the survival and prognosis of breast cancer are warranted.

CONCLUSION

No relationship was found between serum Vitamin D levels and factors affecting the prognosis of nonmetastatic breast cancer. Cox analysis showed that the survival time was not influenced by serum Vitamin D as a prognosis factor. This relationship should be assessed more accurately in a randomized prospective study with a large sample size.

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Conflicts of interest

There are no conflicts of interest.

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