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IS LOW SERUM VITAMIN D LEVEL ASSOCIATED WITH CANCER?

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Abstract – *Objective:* *The aim of this study is to determine the importance of serum Vitamin D (VD) levels in cancer pathogenesis and to investigate its relationship with cancer subtypes.*

Patients and Methods: *This study included 4914 individuals, 1027 cancer patients and 3887 healthy subjects. The cancer patients were divided into five groups by cancer subtypes. The cancer patients and those in the control group were compared in terms of serum VD levels.*

Results: *In the patients with cancer, the mean serum VD level was found to be significantly lower than that in the control group (16.1 ± 10.6 ng/mL* vs. *19.6 ± 10.4 ng/mL,* p = *0.000). The VD levels were higher in breast cancer (BC) group than those in other cancer groups. The mean serum VD level was significantly lower in the BC group compared to the control group (18.1 ± 11.3 ng/mL* vs. *19.6 ± 10.4 ng/mL,* p = *0.004). In the ROC analysis, the cut-off VD value was determined as 15.2 ng/mL between those with and without cancer (area 0.634, OR: 95% CI 0.612-0.656,* p = *0.000). VD <15.2 ng/mL was independently associated with cancer (OR, 2.096; 95% CI: 1.595 – 2.756,* p = *0.000). Moreover, the decreased VD level was found to be independently associated with the increased cancer risk (OR, 1.048; 95% CI: 1.032- 1.065,* p = *0.000).*

Conclusions: *Although there was no difference in VD levels among the cancer patients and there was less difference in the BC patients compared to the healthy individuals, the VD level was significantly lower in all cancer patients compared to healthy people. In addition, there was an independent positive association between VD levels and cancer, with the VD values below 15.2 ng/mL increasing the cancer risk.*

KEYWORDS: *Serum Vitamin D level, Cancer, Cancer subtype.*

INTRODUCTION

Vitamin D (VD) is a steroid hormone that plays a role in calcium and phosphorus metabolism. In recent studies, VD deficiency has been associated with an increased risk of multiple sclerosis, rheumatoid arthritis, diabetes mellitus, and inflammatory bowel disease, developing cancer and cardiovascular disease[1,2].

VD level is evaluated by serum 25 (OH) D levels. 25 (OH) D indicates the VD intake and its endogenous production. The serum VD levels < 20 ng/mL, between 21 to 29 ng/mL, > 30 ng/mL, >150 ng/mL are classified as deficient, insufficient, normal and toxic, respectively[3] (Table 1).

Neoplastic cells are known to contain a Vitamin D receptor (VDR). When the 25 (OH) D level exceeds 30 ng/mL, cancer cells produce 1,25 (OH) D with 1 alpha hydroxylase enzyme. While 1,25 (OH) D decreases proliferation, invasion, angiogenesis, and metastasis, it increases differentiation and apop-

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TABLE 1. Distribution of individuals according to their VD level ranges.

VD levels	Description	Control group, n (%)	Cancer patients, n (%)
0-20 ng/mL	VD deficiency	2587 (66.55)	755 (73.54)
21-29 ng/mL	VD insufficiency	863 (22.21)	154 (14.98)
30-150 ng/mL	VD normal levels	437 (11.24)	118 (11.48)
>150 ng/mL	VD intoxication	0 (0)	0 (0)

tosis. VD is destroyed once it completes its function in the cancer cell and cannot enter the circulation, so it cannot affect the calcium metabolism[4]. Previous observational studies have found that the individuals with higher 25 (OH) D concentrations live longer than those with lower concentrations when diagnosed with cancer. This may be due to the effects of VD on cellular differentiation, proliferation, apoptosis, angiogenesis, and metastasis[5]. According to previous studies, when 25 (OH) D is lower than 20 ng/mL, the mortality due to colon, prostate, and lung cancer increases by 30-50%[6].

In this study, we aimed at comparing the VD levels of cancer patients with those of the control group and at evaluating the VD level in cancer subgroups.

PATIENTS AND METHODS

4914 individuals were included in the study. Of these, 1027 were cancer patients and 3887 were in the control group. Demographic data such as age, gender, cancer subtypes, and serum VD levels were screened retrospectively from the hospital automation system. The VD level first measured for each patient was accepted for the analysis. 30 ng/mL was considered as the lower limit for normal level. VD values were compared between cancer patients and the control group in terms of sex and age subgroups. In addition, it was evaluated whether there was a statistical difference between the cancer subgroups in term of VD level. The cancer patients were divided into the following groups: respiratory system cancers (lung cancer, larynx cancer, etc.), breast cancer (BC), gastrointestinal system cancers (gastric cancer, small bowel cancer, colon cancer, rectum cancer, pancreatic cancer, liver cancer, etc.), genitourinary system cancers (prostate cancer, ovarian cancer, uterine cancers, etc.), and other cancers [(central nervous system cancers, skin cancers (melanoma and non-melanoma), lymphoma, sarcoma, etc.)].

The required approval was obtained from Local Ethics Committee (decision number and date: 2020/153, 27.02.2020) for this study.

STATISTICAL ANALYSIS

IBM SPSS package program (v.22.0, IBM Corp., Armonk, NY, USA) was used in the statistical analysis of the data. By looking at the distribution of data in the comparison between groups, the categorical data were analyzed with chi-square test; one sample *t*-test and independent sample *t*-test were used for parametric data; and Mann-Whitney U test was used for non-parametric data. The statistical significance was set at < 0.05.

RESULTS

Of the 4914 individuals included in the study, 2826 (57%) were women and 2088 (43%) were men; 1027 were cancer patients and 3887 were healthy controls. About 47% ($n = 486$) of the cancer patients and nearly 60% ($n = 2340$) of the control group were female. The mean age of the cancer patients was 64.0 ± 14.1 years and that of the control group was 57.2 ± 13.1 (19-97) years. In our study, the mean serum VD levels in both groups were below the normal limits (< 30 ng/mL) (min: 3 ng/mL, max: 105.2 ng/mL). In the cancer patients, the mean serum VD level was found to be significantly lower than that in the control group (16.1 ± 10.6 *vs.* 19.6 ± 10.4, $p = 0.000$.) and there was no significant difference between genders in terms of VD level ($p = 0.341$). When the age was stratified in three groups as 20-50, 51-70 and ≥71 the VD levels of the cancer patients were found to be similar in all age groups ($p = 0.328$) and those of the control group were observed to increase with advanced age ($p = 0.009$). In the evaluation of VD level among the cancer patients and the control group according to age groups, the VD level was found to be significantly lower in the cancer patients compared to the control group ($p = 0.027$) (Table 2).

In our study, the mean VD level was found to be lower than the normal VD level in all cancer patients (16.1 ± 10.6 ng/mL) ($p < 0.001$). When the cancer patients were grouped by cancer types; the VD level was found to be statistically lower in all groups compared to the control group. (VD level in respiratory system cancer, 15.4 ± 10.1; BC, 18.1 ± 11.3; gastrointestinal cancers, 15.9 ± 10.4; genitourinary cancer, 15.6 ± 9.7; other cancers, 15.4 ± 11.3) ($p < 0.001$, all) (Table 3).

TABLE 2. The comparisons of VD levels by gender and age between groups.

Variables	*Cancer patients*	*Control group*	*p**
Gender n (%)			0.341*
Female	486 (47)	2340 (60)	
Male	541 (53)	1547 (40)	
Age (years) mean ± SD	64.0 ± 14.1	57.2 ± 13.1	0.045**
Age (years) groups			0.000**
20-50	156 (15)	2038 (52)	
51-70	482 (47)	1336 (34)	
≥ 71	389 (38)	513 (14)	
VD (ng/mL). mean ± SD	16.1 ± 10.6	19.6 ± 10.4	0.000**
VD by age (years). n (%)			0.027*
20-50	16.7 ± 11.2	18.6 ± 9.1	
51-70	16.4 ± 10.2	20.3 ± 11.0	
71-100	15.6 ± 10.8	21.9 ± 12.9	
p	0.321	0.009	
VD by gender			0.040**
Female	16.8 ± 11.4	19.9 ± 11.2	
Male	15.6 ± 9.9	19.3 ± 9.0	
p	0.062	0.093	
Total	1027 (100)	3887 (100)	

When the VD levels were evaluated among different cancer groups, a significant difference was found between the mean VD levels (p = 0.045). In the post-hoc analysis, it was observed that this difference was due to the significantly higher VD level in the BC patients compared to those in other cancer groups ($p < 0.05$, all). However, there was no difference between other cancer subgroups in terms of VD levels ($p > 0.05$, all) (Table 4). When the BC patients were compared with the control group, it was observed that the VD level was lower in the BC group (18.1 ± 11.3 *vs.* 19.6 ± 10.4 ng/mL, $p = 0.004$).

The VD levels of the female patients in the control group were statistically higher than those of the BC patients (19.9 ± 11.2, 18.1 ± 11.3 ng/mL) ($p < 0.001$). VD <15.2 ng/mL, female gender, and age >65 years were independently associated with cancer diagnosis (Table 5). In the ROC analysis, the cut-off value was determined as 15.2 ng/mL between those with and without cancer (area 0.634, 95% CI 0.612-0.656, $p = 0.000$). When the VD cut-off value was accepted as 15.2 ng/mL, it was observed that BC was a negative independent predictor in those with low VD value (OR: 0.654, 95% CI: 0.483 - 0.885; $p = 0.006$) (Table 6). Although the VD deficiency rate was significantly higher in cancer patients compared to control group, there was no difference among the cancer groups in terms of VD deficiency (Table 7).

DISCUSSION

VD was shown to reduce and prevent cancer development in the previous studies[1]. VD decreases the potential of metastasis by reducing the tumor invasion and slowing the tumor progression. VD

TABLE 3. Gender groups and VD values of cancer patients (N=486).

Variables	*Respiratory system cancer (n=168)*	*Breast cancer (n=213)*	*Gastro-intestinal cancers (n=289)*	*Genito-urinary cancer (n=182)*	*Other cancers (n=175)*	*Total (N=486)*	*p***
Female. n (%)	21 (12.5)	205 (96)	112 (38.7)	59 (32.5)	89 (51)	486 (47.3)	0.000
VD. mean ± SD	16.9± 10.0	18.2 ± 11.7	16.49 ± 10.2	13.89 ± 9.2	16.43 ± 11.7	16.9 ± 10.3	0.000
Male. n (%)	147 (87.5)	8 (4)	177 (61.3)	123 (67.5)	86 (49)	541 (52.7)	0.000
VD. mean ± SD	15.2 ± 10.3	15.4 ± 11.1	16.07 ± 10.7	17.11 ± 9.9	14.53 ± 11.1	15.8 ± 10.8	0.000
Total. n (%)	168 (16.3)	213 (20.7)	289 (28.1)	182 (17.8)	175 (17)	1027 (100)	0.045
VD. mean ± SD	15.4 ± 10.1	18.1 ± 11.3	15.9 ± 10.4	15.6 ± 9.7	15.4 ± 11.3	16.1 ± 10.6	0.000
p*	0.000	0.000	0.000	0.000	0.000	0.000	

*p**. One sample test; *p***. ANOVA test; VD. mean ± Standard Deviation (ng/mL).

TABLE 4. Post-hoc analysis of the relationship between VD levels by cancer types.

Groups		p*
Respiratory system cancers	Breast cancer	0.011
	Cancers of the gastrointestinal system	0.596
	Cancers of the genitourinary system	0.844
	Other system cancers	0.944
	Control group	0.000
Breast cancer	Respiratory system cancers	0.011
	Cancers of the gastrointestinal system	0.019
	Cancers of the genitourinary system	0.016
	Other system cancers	0.012
	Control group	0.042
Cancers of the gastrointestinal system	Respiratory system cancers	0.596
	Breast cancer	0.019
	Cancers of the genitourinary system	0.749
	Other system cancers	0.648
	Control group	0.000
Cancers of the genitourinary system	Respiratory system cancers	0.844
	Breast cancer	0.016
	Cancers of the gastrointestinal system	0.749
	Other system cancers	0.899
	Control group	0.000
Other system cancers	Respiratory system cancers	0.944
	Breast cancer	0.012
	Cancers of the gastrointestinal system	0.648
	Cancers of the genitourinary system	0.899
	Control group	0.000
Control group	Respiratory system cancers	0.000
	Breast cancer	0.042
	Cancers of the gastrointestinal system	0.000
	Cancers of the genitourinary system	0.000
	Other system cancers	0.000

also shows anti-inflammatory, anti-oxidative, and immunomodulatory effects[7]. It has been shown in many studies that VD has a protective role against colorectal, lung, ovarian, prostate cancers and other cancers[8,9]. According to the previous studies, when 25 (OH) D is lower than 20 ng/mL, the mortality due to colon, prostate, and lung cancer increases by 30-50%[6].

In our study, the VD levels in all groups were below the normal level, that is 30 ng/mL. The mean VD level was also lower than 20 ng/mL, showing a VD deficiency. It may be thought that there is a relationship between the VD levels and the cancer development, suggesting that VD deficiency may play a role in cancer development. Increasing the VD serum level to a minimum of 40 to 60 ng/mL throughout the year is expected to prevent approximately 58,000 new BC and 49,000 new colorectal cancer cases each year[9]. Daily intake of 1000 IU of VD is predicted to

TABLE 5. Post-hoc analysis of the relationship between VD levels by cancer types.

Variables	OR	95% Confidence Interval	p
Age		5.167 – 7.461	0.000
<65	1		
>65	6.209		
Gender		1.228 – 1.649	0.000
Male	1		
Female	1.423		
VD		1.595 – 2.756	0.000
>15.2	1		
<15.2	2.096		
VD decrease	1.048	1.032 – 1.065	0.000

Age (categorical), gender, VD (categorical) and VD serum level were included in this regression analysis.

TABLE 6. Factors associated with low VD (below cut-off value as: <15.2 ng/mL) in all groups.

Variables	*OR*	*95% Confidence Interval*	*p*
Age		1.207 – 1.546	0.000
<65	1		
>65	1.36		
Gender		0.944 – 1.200	0.311
Male	1		
Female	1.021		
Healthy population	1	1.595 – 2.756	
Respiratory Cancers	2.096		0.000
Breast Cancers			
Gastrointestinal Cancers			
Genitourinary Cancers			
Other Cancers			

Age (categorical), gender, VD (categorical) and VD serum level were included in this regression analysis.

reduce the colon cancer incidence by 50%[10]. In the literature, it was reported that the risk of developing colon, pancreas, prostate, and lung cancers, and Hodgkin lymphoma increased in those living in the North Pole compared to those living in the south pole[6]. Our study was conducted at 36° - 42° north latitude and 26°- 45° east longitude. In the literature, it has been suggested that sunlight is not sufficient for the production of VD in the skin between November and February at 42°- 20° north latitude[11].

The limitation of our study was that the VD levels were not measured for each month of the year. Future studies should cover the seasonal differences to achieve more accurate results. Sunlight exposure plays a critical role in vitamin synthesis; therefore, cancer patients living in the geographical regions can take VD supplement.

In the comparison between the gender groups in our study, the women's level of VD was found to be higher in both the cancer patients and the control group. It may be thought that female patients are more conscious to reduce the risk of osteoporosis than men, they often eat the diets rich in VD, and they are also exposed to more sunlight than men.

In our study, a statistically significant difference was found between the age groups in terms of VD level. Compared to the control group, the VD level decreased with age in the cancer patients. It can be thought that nutrition, VD absorption, and its bioavailability in cancer patients may decrease with age.

In our study, a significant difference was found among cancer groups in terms of VD level. This difference was due to the fact that the BC patients had significantly higher VD levels compared to other cancer patient groups. There was no difference between other cancer groups in terms of VD levels. In the studies on patients with lung cancer, a positive correlation was reported between serum VD level and overall survival[12,13]. People with serum VD levels below 20 ng/mL and calcium levels below 10.5 mg/dL were reported to have an increased risk of BC[14]. In a study conducted on premenopausal women, the risk of BC was observed to decrease with high doses of VD. However, such an effect has not been reported in postmenopausal women[7]. In the literature, colorectal cancer is the most common neoplasia developing due to VD deficiency in epidemiological studies[15]. Low VD levels may increase the risk

TABLE 7. VD deficiency (<20 ng/mL) according to groups.

Variables	*Cancer type*							*p***
	Respiratory system cancer	*Breast cancer*	*Gastro-intestinal cancers*	*Genito-urinary cancers*	*Other cancers*	*p**	*Healthy individuals*	
VD deficiency								
No. n (%)	45 (26.8)	69 (32.4)	85 (29.4)	50 (27.5)	50 (28.6)	0.768	1443 (37.1)	0.000
Yes. n (%)	123 (73.2)	144(67.6)	204 (70.6)	132 (72.5)	125 (71.4)		2444 (62.9)	

**p* for cancer groups.
***p* for all cancer groups and healthy individuals.

of colorectal cancer through the following potential mechanism; the 1-α-hydroxylase enzyme, which converts 25(OH)D into the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)2D). 1,25(OH)2D is believed to be important in the regulation of cell differentiation, the inhibition of cell proliferation, angiogenesis, metastasis, and the enhancement of apoptosis, thereby providing a strong biologic basis for a protective role of VD in colon cancer[16]. Many cell types, including colorectal epithelial cells, contain VDR, furthermore, VDR expression is increased in adenoma, and in well- or moderately-differentiated colorectal cancer tissues[17,18]. The risk of prostate cancer increases as the level of VD decreases[19]. There are some studies showing the role of VD and its receptor in the development of gynecological cancers. It has been revealed that VD affects the etiopathogenesis of cancer types such as BC, colorectal cancers, and lung cancer. Ecological studies have shown an inverse relationship between the exposure to Ultraviolet B and the gynecological cancer risk[20].

In our study, it was seen that the VD level was lower in the BC patients compared to the control group. In a meta-analysis involving the findings reached in 22 studies, it was found that there was direct relationship between VD deficiency and BC[21].

In our study, the VD level of the female patients in the control group was higher than that of the BC patients. This is another finding that supports the low VD levels observed in cancer patients. A case-control study showed that higher VD levels had a protective effect on women in terms of colorectal cancer risk[22].

Although the relationship between VD deficiency and its related cancer risk is controversial for some cancers, there may be a risk for many cancer types. For this reason, in order to prevent cancer, we recommend to maintain normal blood VD levels. Adequate VD levels can be achieved by sun rays, nutrients and, when necessary, drug therapy.

CONCLUSIONS

The serum VD levels were found to be lower in the cancer patients than in the healthy adults, this difference was limited to BC patients. However, there was no difference among cancer subgroups in terms of VD deficiency. In the cancer patients, VD deficiency was not independently associated with age, gender, and cancer types. VD level < 15.2 ng/mL was an independent prognostic factor for cancer. Future studies are needed to clarify the biological mechanisms underlying the relationship between VD and cancer development.

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