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# EVALUATING SERUM LEVEL OF VITAMIN D IN HEALTHY WOMAN AND PATIENTS WITH BREAST CANCER

**KARIM MOVLA[1], AHMAD AHMADZADEH[2], MEHDI NOORIJANGI[*3], MASUMEH NOORIJANGI[4] ALIREZA NOORIJANGI[5]**

1-Associate professor, Ahvaz Jundishapur University, Ahvaz, Iran

2-Assistant professor, Ahvaz Jundishapur University, Ahvaz, Iran

3-Department of Hematology, Internal assistant, Ahvaz Jundishapur University, Ahvaz, Iran (mehdinoorijangi@yahoo.com)

4-Department of Infectious Diseases, infectious assistant, University of Medical Sciences, Bu-Ali Hospital, Zahadan, Iran

5-Veterinary Medicine, Zabol University, Zabol, Iran

## ABSTRACT

Breast cancer is the most common cancer among women. It is involved with heavy expenses for both the patients and the society. The role of vitamin D in the prevention of a number of diseases is proven. However, its role as an effective preventive factor of breast cancer is pending .In this epidemiologic case control study; two groups of women were selected. One group included the 163 women with breast cancer and the other one included 163 healthy women. The serum levels of 25(OH) vitamin D were measured with the electro chemiluminescent immunoassay method in the two groups .The mean of the serum level of vitamin D in the patients was 21.30±8.68ng/ml and in the healthy group it was 33.86±27.53ng/ml. A significant correlation was found between serum level of vitamin D and disease ($p<0.001$). With older age, the prevalence of vitamin D deficiency in the patient group significantly increased. Our findings indicate that prevalence of vitamin D deficiency in the breast cancer patients is more than that of the healthy group, and it increased in patients with older age.

**Keywords: 25 (OH) vitamin D; breast cancer**

## INTRODUCTION

Breast cancer is the commonest diagnosed cancer and the worldwide cause of cancer-related mortality among women, amounting to 23% of the total new cancer cases in 2008 (Jemal et al, 2011). The vitamin D receptor, which is activated by 1, 25dihydroxyvitamin D [1, 25(OH) D], is found in nearly all tissues and organs in the human body and is responsible for the transcription of numerous genes related to cell-cycle control (Pike et al., 2007). Accumulating evidence from human observational studies suggests that both dietary and blood measures of vitamin D are inversely associated with incident breast cancer risk (Knight et al., 2007). The vitamin D receptor (VDR) is expressed in breast tissue, and patients with VDR-positive breast tumours have longer disease-free survival compared to those with receptor-negative tumours (Colston et al, 1989). The VDR ligand is the vitamin D metabolite, 1, 25 dihydroxyvitamin D3, which has potent effects on cell growth and differentiation (Bretherton et al., 2001). After synthesis in the skin or oral intake, vitamin D is converted into 25 hydroxyvitamin D [25(OH) D] in the liver. Then, 25(OH)D undergoes renal hydroxylation, tightly regulated by parathyroid hormone (PTH) and calcium concentrations, into the vitamin D hormone calcitriol [1,25-dihydroxyvitamin D; 1,25(OH)2D], the biologically active metabolite (Holick et al., 2011). High levels of 1,25(OH)2D in the breast might have antitumor effects through the induction of cell differentiation, inhibition of cell growth, and regulation of apoptosis in normal and malignant cells, including human breast cells (Eisman et al., 1980). In addition to direct influences on the cell cycle and apoptosis, vitamin D may also exert its protective effect by influencing sex hormones and other crucial peptides (Pirianov et al., 2001). Vitamin D analogues successfully inhibit the growth of mammary tumors (Pirianov et al., 2001) and an estrogen-independent mechanism exists whereby vitamin D may reduce the proliferative effects of insulin-like growth factor I, which is a potent mitogen (Pirianov et al., 2001). For the studies that found that individuals with low serum 1, 25(OH)2D had high risk of breast cancer (Janowsky et al., 1999). More studies found an inverse association between (25) OH) D and breast cancer risk at premenopause than at postmenopause (Abbas et al., 2008). Because a threshold of 30 ng/mL has been suggested as being necessary to minimize deleterious health consequences in terms of both bone health and other diseases ,(25)OH) D3 at <30 ng/mL was considered insufficient and 20 ng/mL deficient (Holick et al., 2007) in the present article. In our study and in this pooled analysis, this estimate is consistent with ours, which showed a 27% lower risk of breast cancer for women with 25(OH)D serum concentrations higher than 27 ng/mL compared with those with serum concentrations lower than 19.8 ng/mL (Engel et al.,2010). Serum 25(OH) D levels of at least 30 ng/mL to 45 ng/mL are the minimum necessary to maintain normal parathyroid hormone levels, and at least 400 IU of supplemental vitamin D3 per day is needed to maintain serum 25(OH) D at a range consistent with normal parathyroid hormone levels in young and middle-aged adults (Chapuy et al., 2007). Because of effects of vitamin D overdosage, such as bone demineralization, hypercalcemia despite these reassuring studies, the public health and medical communities have not adopted use of vitamin D for cancer prevention (Coleman et al., 2006). While vitamin D is relatively safe, a review of randomized or quasi-randomized trials found adverse effects of hypercalcemia, gastrointestinal symptoms and renal disease significantly increased by vitamin D adminis tration in conventional dosage (<1,000 IU/day) (Avenell et al., 2013). According to another hypothesis, higher 25(OH)D serum concentrations could reduce subsequent breast cancer risk in premenopausal women, as shown by the recent finding of reduced progesterone and estradiol serum concentrations with higher circulating 25(OH)D levels (Knight et al., 2010). Estrogen deficiency also seems to reduce vitamin D activation and Vitamin D Receptor (VDR) expression, suggesting that older and postmenopausal women might be at an increased risk (Peterlik et al., 2009), and that higher vitamin D concentrations would be necessary to achieve the same benefit in postmenopausal as in premenopausal women. Women regularly exposed to sunlight, and consumers of above-average amounts of vitamin D, had significantly lower incidence rates of breast cancer (John et al., 1999). Vitamin D status is assessed by the level of 25(OH) D in the serum (Garland). Regarding the nutritional status, the lack of processed food products with vitamin D supplements, circumstances climate lives of apartment type of coverage of cultural issues veil, as well as with regard to the review of the literature refer to the lower serum levels of vitamin D that increase the incidence of breast cancer we decided to investigate this relation in the woman of the Ahwaz (Iran) region.

## MATERIALS AND METHODS

### *Study population, sampling and study design*

The study was observational, epidemiological analysis as control- case groups to evaluate serum levels of vitamin D in healthy women and those with breast cancer patients aged 25 to 65 years in the Khuzestan region (Iran). Given the inclusion and exclusion criteria in the study and after completion of a questionnaire to collect data to see who had the cause of non-clinical issues related to vitamin D, including endocrinology, gastroenterology, hematology, rheumatology without the disease had been admitted, after screening and an ultrasound examination if necessary, in the same age range with a maximum 5-year age difference were selected and women with breast cancer that admitted for chemotherapy in the Shafa Hospital (Ahvaz) completed the baseline examination. The sample size in this study to detect a difference of 10 units of vitamin D levels between groups, considering the standard deviation 25 per group of 95 percent and with a significant level of $\alpha = 0.05$ was estimated 163 people in each group.

***Inclusion criteria to study:*** Healthy women aged 25 to 65 years and for women with breast cancer with the same age range with pathologically that proven patient those.

***Exclusion criteria to study:*** 1. Women who have a family history of breast cancer. 2. Women who have a history of using vitamin D supplements. 3. Women who have a history of vitamin D deficiency.
4. Women who have a history of using sunscreen.

**METHODOLOGY**

All samples from healthy women visited by Dr. Mowla at the clinic, and individuals visited by Dr. Ahmad zadeh after observing the conditions of inclusion and exclusion in study presented in Noor lab in Ahvaz. All the information of the patients was registered in the form. The study population was divided into two groups including a control group and patients with breast cancer.

The patients' age ranged from 25 to 65 years. Women with breast cancer whose disease had previously had been approved by the doctor and pathobiology tests completed the questionnaire in the center of Shafa containing person's demographic information and the inclusion and exclusion criteria, and then their blood sample was obtained (5 cc) by the laboratory. Serum concentration of vitamin D was measured by laboratory kits. Blood sampling and analysis for the serum concentration of vitamin D in control group were performed with the same volume and procedure by the laboratory.

***Means for data collection:*** Observation and laboratory examination and questionnaire to collect data that had been collected.

**Materials**

Measurement of serum vitamin D was performed by Electrochemist illumining immunoassay method (kubasdevice 601 i). Vitamin D levels were observed as a number after placing a small amount of serum with specifies kit.

**Data analysis:**

Collected the necessary data, has been entered in SPSS software, and Mean ± SD of vitamin D was reported in tables, and serum levels of vitamin D of the groups were compared and analyzed using statistical methods Mann Whitney, t-test. Also covariate test was used for adjusted the variables.

Observance of ethical issues: - The names and information of women remain confidential. - Managers in this study are responsible for any side effects in patients during the examination.

**RESULTS**

This study as cases- controls the women included 163 breast cancer patients (case group) and 163 following a negative screening (control group) investigated to determine the serum concentrations of the vitamin D. The mean age of the participants was 46.31 ± 10.97 and 45.50 ± 11.10 years in case and control group, respectively. Difference of age between the groups was not statistically significant (p = 0.5). Prevalence and percent of residential region (rural or citizen), was not different between the groups (p=0.22) (Table 1). Also about the diabetes incidence, no difference was observed between the groups (p=0.16) (Table 2). In the case group, tumor local in 101 individual (62%) was in the left breast and, tumor local in 62 individual (38%) was in the right breast. The patients had the distribution of tumor sizes (> 2cm in diameter) in patients (44.2%) and (2-5cm in diameter) in 91 patients (55.8%). Also lymph nodes were diagnosed in 123 (75.5%) patients. Eight patients (4.9%) had metastasis and in all of them metastasis local was in bone. The vitamin D serum concentration was significantly lower for the patient group compared with the control group (p= 0.001) with 21.30±8.68 and 33.86±27.53, respectively. According to the study conducted by Holick et al (2011), Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml, and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (Michael et al., 2011). Therefore, prevalence of vitamin D deficiency and insufficiency (52.8 versus 39.3% and 30.1 versus 18.4%, respectively) was higher in the patients with breast cancer compared with control group

($p<0.001$) (Table 3). As shown in table (4), prevalence of vitamin D deficiency increased with an increase in age in the patient group ($p<0.01$). But the relation has not beenobserved between vitamin D deficiency and age in the control group ($p>0.05$). The Mann-Whitney test was used to assess different between age groups. Results show significantly different between age groups about vitamin D condition ($p<0.05$). As shown in table (6), patients who have vitamin D deficiency had a 1.3 times more risk of breast cancer than those without vitamin D deficiency.

**DISCUSSION**

Breast cancer is the most common cancer among women, and the cause of cancer-related mortality amounting to 23% and 14% of the total cancer cases and deaths in 2008, respectively in world (Jemal et al, 2011). In recent years, there has been considerable interest that vitamin D inhibits breast cancer development (Giovannucci et al., 2005), therefore reduced risk has been associated with high dietary vitamin D intake and occupational sun exposure (John et al., 1999). Results of studies indicate that vitamin D promotes cell differentiation and retards or terminates proliferation of breast cancer cells (Welsh et al., 2003). Therefore, we aimed to evaluate and compare the serum concentrations of vitamin D in women with breast cancer and healthy ones. In this study as cases- controls the cohort women includes 163 breast cancer patients (case group) and 163 following a negative screening (control group) were investigated to determine the serum concentrations of the vitamin. The mean age of the participants was 46.31 ± 10.97 and 45.50 ± 11.10 years in case and control groups, respectively. The difference between the age of the groups was not significant ($p = 0.5$). The vitamin D serum concentration was significantly lower for the patient group compared with the control group ($p= 0.001$) and it was 21.30±8.68 and 33.86±27.53, respectively. Prevalence of vitamin D deficiency and insufficiency (52.8 versus 39.3% and 30.1 versus 18.4%, respectively) was higher in the patient with breast cancer compared with the control group ($p<0.001$). Vitamin D deficiency is defined as a 25(OH) D below 20 ng/ml, and vitamin D insufficiency as a 25(OH) D of 21–29 ng/ml (Michael et al., 2011). Also, with an increase in age in the patient group, prevalence of vitamin D deficiency increased ($p<0.01$). But no relation wasobserved between vitamin D deficiency and age in the control group ($p>0.05$). Neuhouser et al (2008) observed that 75.5% of the 790 women with breast cancer had low serum

25(OH)D. Although this study reported higher prevalence of vitamin D deficiency more than other studies, it should be taken into consideration that many factors as developed disease can cause different results in different studies. When vitamin D serum levels are high (>29.1 ng/ ml,mean) vs. low (<21 ng /ml, mean) the risk of death from breast cancer decreased by 42% (40). Goodwin et al (2009) reported that women patient with breast cancer with 25(OH) D serum concentrations of >30 ng/mL had a 50% lower risk of mortality than those with concentrations of <30 ng/mL in the five years after diagnosis (Goodwin et al., 2009). Mohr et al (2014) found that higher serum concentrations of 25(OH) D were associated with lower mortality rates after diagnosis of breast cancer. Results of the study as pooled analysis indicated that women with serum 25(OH)D of approximate 52 ng/ml had 50% lower risk of breast cancer than those with serum <13 ng/ml (3). Although information is insufficient on direct prognostic effects of vitamin D in breast cancer, but low vitamin D levels in healthy women have been associated with increased breast cancer mortality (Goodwin et al., 2009). Since vitamin D metabolism has been influenced by sun exposure; therefore, there are inverse relations between sun exposure and breast cancer risk as John et al (2007) reported that among women with the highest sun exposure index, risk reduced by 47 percent. John et al (2007) observed that women with breast cancer diagnosed in summer had better chance for prognosis than those with breast cancer diagnosed in winter. High residential and occupational sun exposure has been associated with lower breast cancer mortality (Freedman et al., 2002). It was reported that reduced breast cancer risk in non-Hispanic White women has been associated with high early-life residential solar radiation (John et al., 1999). From the existing results of studies, we identified factors that influence serum vitamin D concentrations, including region as a surrogate of UV-B radiation exposure, behaviors related to sun exposure, skin pigmentation, body mass index (BMI) and season (Yin et al., 2010). On the basis of literature and the results of this study, diagnosis of vitamin D deficiency and its treatment may be associated with prevention of breast cancer risk and prognosis. Finally, Chlebowski et al (2011) suggested the measurement of serum 25-hydroxy vitamin D level at the initial diagnostic test in patients at risk for breast cancer.

## CONCLUSIONS

In conclusion, findings of this study indicate that prevalence of vitamin D deficiency in

breast cancer patients is more than patients.
healthygroup and increased in older

**Table 1.Prevalence of the participants according to group and residential region**

| | residential region | | | | |
|---|---|---|---|---|---|
| | city | | rural | | |
| **group** | **prevalence** | **percent** | **prevalence** | **percent** | **p- value (Chi-square)** |
| case | 146 | 89.6 | 17 | 10.4 | 0.22 |
| control | 153 | 93.9 | 10 | 6.1 | |

**Table 2:Prevalence of the patient with diabetes according to investigated group**

| | diabetes | | | | |
|---|---|---|---|---|---|
| | positive | | negative | | |
| **group** | **prevalence** | **percent** | **prevalence** | **percent** | **p- value (Chi-square)** |
| case | 49 | 30.1 | 114 | 69.9 | |
| control | 37 | 27.7 | 126 | 77.3 | 0.16 |

**Table 3: Prevalence of the individual vitamin D condition according to investigated group.**

| | group | | | | |
|---|---|---|---|---|---|
| | case | | control | | |
| **vitamin D condition** | **prevalence** | **percent** | **prevalence** | **percent** | **p- value (Mann-Whitney test)** |
| deficiency | 86 | 52.8 | 64 | 39.3 | |
| insufficiency | 49 | 30.1 | 30 | 18.4 | <0.001 |
| sufficiency | 28 | 17.1 | 69 | 42.3 | |
| total | 163 | 100 | 163 | 100 | |

**Table 4: Prevalence of the vitamin D condition in group case individual according to age groups**

| | Age groups | | | | | | |
|---|---|---|---|---|---|---|---|
| | <35 year | | 35-50 year | | >50 year | | |
| **vitamin D condition** | **prevalence** | **percent** | **prevalence** | **percent** | **prevalence** | **percent** | **p- value Kruskal-Wallis) test)** |
| deficiency | 6 | 20 | 32 | 42.7 | 48 | 82.8 | |
| insufficiency | 11 | 36.7 | 31 | 41.3 | 7 | 12.1 | <0.001 |
| sufficiency | 13 | 43.3 | 12 | 16 | 3 | 5.1 | |
| total | 30 | 100 | 75 | 100 | 58 | 100 | |

**Table 5: Prevalence of the vitamin D condition in group control individual according to age groups**

| | Age groups | | | | | | |
|---|---|---|---|---|---|---|---|
| | <35 year | | 35-50 year | | >50 year | | |
| **vitamin D condition** | **prevalence** | **percent** | **prevalence** | **percent** | **prevalence** | **percent** | **p- value Kruskal-Wallis) test)** |
| deficiency | 15 | 48.4 | 33 | 40.2 | 16 | 32 | |
| insufficiency | 5 | 16.1 | 11 | 13.4 | 14 | 28 | <0.001 |
| sufficiency | 11 | 35.5 | 38 | 46.3 | 20 | 40 | |
| total | 31 | 100 | 82 | 100 | 50 | 100 | |

**Table 6: Relationship between 25(OH)D and breast cancer risk.**

| | Breast cancer | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | positive | | negative | | P-value (Chisquare) | CI 12% | Odds ratio | Relative risk |
| | prevalence | percent | prevalence | percent | | | | |
| vitamin D deficiency | | | | | 0.011 | 1.11 | 1.72 | 1.31 |
| positive | 15 | 48.4 | 33 | 40.2 | | | | |
| negative | 5 | 16.1 | 11 | 13.4 | | | | |
| total | 163 | 100 | 163 | 100 | | | | |

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