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Association between Plasma 25-Hydroxyvitamin D and Breast Cancer Risk: A Matched Case-Control Study

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Abstract

Background: The protective role of vitamin D in the occurrence of breast cancer is nowadays a controversial matter. Based on conflicting results of the studies in this field and also considering the prevalence of vitamin D deficiency in Iranian women, this work was conducted to evaluate the association between vitamin D and breast cancer.

Method: This matched case-control study was conducted on 70 newly diagnosed breast cancer patients and 70 controls with the same age, menopause status, and time of blood sampling in Zanjan. Information regarding demographic, reproductive, history of diseases, medication, use of dairy products, and sunlight exposure was collected using a questionnaire. The serum level of vitamin D was measured with ELISA method. The data were analyzed utilizing chi-square test, independent t-test, and odds ratios using conditional logistic regression model.

Results: The mean level of vitamin D was 39.04 and 63.34 ng/ml in the cases and controls, respectively (P=0.046). The proportion of the cases in the highest quartile of vitamin D was significantly smaller than that in the controls compared with the lowest quartile (Ptrend=0.028). Using conditional logistic regression model, an inverse and independent association was observed between vitamin D and breast cancer after controlling main confounders. The risk of breast cancer was independently associated with body mass index and low income.

Conclusion: In this study, an inverse association was confirmed between vitamin D and breast cancer. Prospective intervention studies should be performed to explore its role in the prevention of breast cancer.

Keywords: Vitamin D, Breast neoplasms, Case-control

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Introduction

The association between vitamin D and breast cancer has been assessed in a number of studies, most of which have been case-control or cohort studies regarding dietary intake of vitamin D or its supplements. In two case-control studies, no correlations were reported between the total intake of vitamin D (diet or supplements) and breast cancer risk.[1,2] In other case-control studies, there was a significant relationship between dietary intake of vitamin D and a reduction in the risk of breast cancer.[3,4] Two cohort studies reported significant associations between vitamin D or calcium intake and breast cancer risk;[5,6] however, the results of a cohort study indicated that vitamin D intake (dietary or supplements) was not associated with the risk of breast cancer, but in people living in areas with the highest UV exposure, vitamin D intake was associated with a reduced risk of breast cancer.[7]

Studies on the relationship between serum 25 (OH), D concentrations, and breast cancer have also yielded different results. There were no significant correlations between serum 25 (OH) D and breast cancer in two case-control studies.[8,9] Engel et al. showed that the risk of breast cancer decreases with increased plasma concentrations of 25 (OH) D in a nested case-control study.[10] Moreover, in other case-control studies, the protective effect of vitamin D serum concentration in breast cancer was observed.[11-14] Contradictory results concerning the relationship between vitamin D and breast cancer risk and few evidence in developing countries, including Iran, necessitate further studies on this issue. Meanwhile, according to ecological studies, the incidence of breast cancer in populations with a low exposure to sunlight is greater than those with higher sunlight exposure.[15] Not enough sunlight exposure of women in Iran has led to low levels of vitamin D. The current study aimed to examine the association between breast cancer and vitamin D in this population considering the effects of a wide range of important risk factors.

Methods

Study population and data collection

In this matched case-control study, 144 women were enrolled, 71 of which were suffering from breast cancer; the remaining 73 were controls with no history of cancer. Among them, 70 breast cancer cases were matched with 70 controls on age (±2 years), menopausal status at diagnosis, and time (month) of blood collection. Cases were newly and histologically diagnosed with breast cancer at Zanjan Valiasr Hospital and the controls were selected from the individuals referred to the laboratory of the same hospital.

Information on breast cancer risk factors was obtained using a questionnaire completed at the time of blood collection. Age, age at menarche, age at first birth, parity, history of benign breast disease, family history of breast cancer, history of oral contraceptives use, history of breastfeeding, the mean daily sunlight exposure, and the mean daily dairy products intake were asked at baseline. Weight and height were measured at the time of blood collection. The study was approved by the Ethical Committee of the Zanjan University of Medical Sciences (IR.ZUMS.REC.1388.03) and informed consent was obtained from all the subjects.

25 (OH) D concentrations were measured via ELISA (Immunodiagnostic Services, UK). The coefficient of variation was 5.6% for intra-assay and 6.3% for inter-assay determination.

Statistical analysis

The Kolmogorov-Smirnov test was utilized to evaluate the distribution of quantitative variables. Values were expressed as number (percentage) and mean ± standard deviation (SD), as appropriate. The comparisons were performed with chi-square test for categorical variables, independent t-test for normally distributed, and Mann–Whitney test for non-normally distributed.

A conditional logistic regression was constructed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for this matched case-control study. All the statistical analyses were performed using the SPSS PC version 16.0 computer software program for Windows (SPSS, Chicago, IL, USA) and STATA 9 (Stata Corp,

Table 1. Characteristics and socio-demographic variables in breast cancer cases and matched controls

Variables	Cases (n=71)	Controls (n=73)	*P*
Age (years), mean ± SD	46.8 ± 11.3	47.4 ± 11.0	0.91
BMI (kg/m^2), mean ± SD	26.0 ± 4.2	27.7 ± 3.3	0.04
Residence area, n(%)			
Urban	54(76.1)	70(95.9)	0.001
Rural	17(23.9)	3(4.1)	
Marital status, n(%)			
Single	4(5.6)	1(1.4)	0.16
Married/Divorced	64(90.1)	72(98.6)	
Occupational status, n(%)			
Employed	10(14.1)	19(26)	0.07
Housewife	61(85.9)	54(74)	
Education, n (%)			
Illiterate	26(36.6)	16(21.9)	0.009
Primary school	18(25.4)	20(27.4)	
Secondary school	8(11.3)	7(9.6)	
Diploma	14(19.7)	9(12.3)	
Higher	5(7.0)	21(28.8)	
Income (Tomans),n(%)			
≤ 500000	24(35.8)	2(2.7)	<0.0001
500000 – 1000000	18(26.9)	7(9.6)	
1000000 – 1500000	18(26.9)	25(34.2)	
> 1500000	7(10.4)	39(53.4)	
Family history of breast cancer, n(%)			
Yes	10(14.1)	2(2.7)	0.014
No	61(85.9)	71(97.3)	
History of benign breast disease			
Yes	8(11.3)	1(1.4)	0.017
No	63(88.7)	72(98.6)	
Ever used calcium, n(%)			
Yes	7(10)	16(22.2)	0.05
No	63(0.9)	56(77.8)	
Duration of calcium use (months),mean ± SD	21.57 ± 27.71	38.92 ± 39.65	0.32
Ever used vitamin D, n(%)			
Yes	3(4.2)	64(87.7)	0.08
No	68(95.8)	9(12.3)	
Mean daily sunlight exposure (hours), n(%)			
Nothing or one hour	47(66.2)	49(67.1)	0.21
2-3 hours	11(15.5)	17(23.3)	
More than 3 hours	13(18.3)	7(9.6)	
Mean daily milk intake (glasses), n(%)			
Nothing	42(59.2)	39(53.4)	0.76
One glass	23(32.4)	26(35.6)	
Two glasses or more	6(8.5)	8(11)	
Mean daily yoghurt intake (bowls), n(%)			
Nothing	19(26.8)	6(8.2)	0.002
One bowl	46(64.8)	50(68.5)	
Two bowls or more	6(8.4)	17(23.2)	
Mean daily cheese intake (spoons), n(%)			
Nothing	8(11.3)	5(6.8)	<0.0001
One spoon	30(42.3)	57(78.1)	
Two spoons or more	33(46.5)	11(15.1)	

BMI= Body mass index, SD= Standard deviation

Table 2. Reproductive variables in breast cancer cases and matched controls

Variables	Cases (n=71)	Controls (n=73)	*P*
Age at menarche(years), mean ± SD	13.2 ± 1.8	13.7 ± 1.7	0.06
Age at first birth(years), mean±SD	21.1 ± 5.1	20.8 ± 5.3	0.80
Age at menopause(years), mean±SD	48.1 ± 4.6	51.5 ± 3.5	0.05
Parity, n(%)			
Yes	64(90.1)	67(91.8)	0.73
No	7(9.9)	6(8.2)	
Number of births, mean ± SD	4.1 ± 2.4	4.2 ± 2.9	0.57
Pregnancy, n(%)			
Yes	64(90.1)	68(93.2)	0.51
No	7(9.9)	5(6.8)	
Number of pregnancies, mean ± SD	4.4 ± 2.5	4.5 ± 3.0	0.54
Ever breast fed, n(%)			
Yes	63(94.0)	66(91.7)	0.75
No	4(6.0)	6(8.3)	
Duration of breastfeeding (months), mean ± SD	66.00 ± 59.78	70.86 ± 66.09	0.83
Ever used oral contraceptives, n(%)			
Yes	39(55.7)	42(57.5)	0.83
No	31(44.3)	31(42.5)	
Duration of oral contraceptives use (months), mean ± SD	44.06 ± 31.83	55.12 ± 56.83	0.39
Hormone therapy, n(%)			
Yes	0 (0.0)	2(2.9)	0.25
No	71(100.0)	68(97.1)	
Postmenopausal at study entry, n(%)			
Yes	40(56.3)	42(58.3)	0.81
No	31(43.7)	30(41.7)	

SD= Standard deviation

College Station, TX). $P < 0.05$ was considered to be statistically significant.

Results

Table 1 represents characteristics and socio-demographic variables for 71 breast cancer cases and 73 controls. The mean age of the patients and controls were 46.8 and 47.4, respectively ($P = 0.91$). The subjects with breast cancer were more from rural areas, had lower income, were less educated, and had a lower body mass index (BMI) compared with the controls. The proportion of those who had family history of breast cancer or history of benign breast disease was higher in the cases than the controls. Daily yoghurt and cheese intake on average were statistically different between the cases and controls. In table 2, reproductive variables are compared between the cases and controls. No significant differences were observed between the two groups.

The mean serum level of vitamin D was 39.4 in the breast cancer cases and 63.3 in the controls ($P = 0.046$, Table 3). When the levels of vitamin D were categorized based on quartile, the proportion of those with lower levels of vitamin D were more observed in the cases than controls (Ptrend = 0.028).

The association between 25(OH) D and risk of breast cancer was assessed employing conditional logistic regression. The variables that showed a significant association with breast cancer in univariate analysis were entered as covariates in the logistic regression model and OR estimates and 95% CIs were calculated to evaluate 25(OH) D levels as a continuous variable. The risk of breast cancer was inversely and independently associated with vitamin D levels, BMI, and income (Table 4).

Discussion

In this case-control study, the association between serum vitamin D levels and breast cancer

Table 3. The association between breast cancer and serum 25(OH)D concentration

Serum vitamin D levels(ng/ml)	Cases (n)(%)	Controls (n)(%)	*P*
Mean ± standard deviation	39.40 ± 37.78	63.34 ± 87.23	0.046
Quartiles			
1(13.10 – 21.85)	18(32.1)	11(17.5)	0.028**
2(21.86 – 26.60)	14(25.0)	17(27.0)	
3(26.61 – 49.90)	14(25.0)	12(19.0)	
4(> 49.90)	10(17.9)	23(36.5)	

***P* for trend

was examined. The results of this study showed a significant reverse association between serum 25 (OH) D levels and breast cancer risk, after controlling for confounding factors. In addition, the risk of the disease was correlated with BMI and income.

The relationship between serum vitamin D levels and breast cancer has also been shown in other studies. One nested case-control study in postmenopausal women had similar results; increased 25(OH)D and 25(OH)D3 had a reverse relationship with the risk of breast cancer in white women.[13] In a study conducted by Bertone-Johnson et al., the mean serum level of 25 (OH) D in breast cancer patients was significantly lower than the control group (31.5 versus 33.1 ng/ml, $P = 0.01$), which is consistent with the results of our study, although a stronger association was found in the age group of above 60.[14] Another case-control study by Lowe et al. in England, found that breast cancer risk in women with a serum vitamin D level of less than 50 nm (first quartile) compared with that of those with serum vitamin D levels above 150 nm (fourth quartile) were 5.83 fold (95% CI: 2.31-14.7).[16] In our study, the classification of serum vitamin D levels based on quartiles in univariate analysis showed that with the increase in the quartile, the proportion of patients in the case group reduced ($P = 0.028$). Additionally, in the study performed by Lowe et al., the mean serum level of 25(OH)D in patients with breast cancer was significantly lower than that in the control group (80.1 vs. 97.8 nm, $P < 0.001$), which is consistent with the results of our study.

In a nested case-control study conducted by Engel et al., the risk of breast cancer in women with a serum vitamin D level above 27 ng/mL (highest tertile) compared those whose serum vitamin D was less than 19.8 ng/mL (lowest tertile) was 0.73, (95% CI: 0.55 to 0.96).[10] This association was more pronounced in women less than 53 years of age; meanwhile, in our study, due to an insufficient number of cases, the evaluation of risk in young women was not feasible. In another case-control study, Crew et al. found that the risk of breast cancer in women with serum vitamin D levels above 40 ng/mL was lower than those with vitamin D deficiency, <20 ng/mL (OR = 0.56, 95% CI: 0.41-0.78).[12] Moreover, the mean serum levels of 25 (OH) D in breast cancer patients were significantly lower than that in the control group (27.1 vs 29.7 ng/mL, $P < 0.0001$), which is similar to our results.

In a study in Iran by Alipour et al., serum levels of vitamin D were categorized as higher than 35, 25 to 35, 12.5 to 25, and less than 12.5 ng/ml. These groups were respectively defined as normal levels of vitamin D, mild, moderate, and severe vitamin D deficiency. The mean serum vitamin D level in cancer patients was significantly lower than that in the control group (7.7 versus 8.7 ng/ml), which is in agreement with our findings.[17] However, in another Iranian case-control study, the mean serum level of 25(OH)D was 15.2 ± 8.2 ng/ml in breast cancer patients, while it was 15.5 ± 7.5 ng/ml in the control group with no significant differences.[18] The difference in the outcome of this study with ours may be due to the fact that a higher proportion of their cases and controls (about 40%) had vitamin D deficiency.

Different cut-off points were selected for serum vitamin D levels in various studies, based on which risk was calculated, making it difficult to compare the results of these studies to each other.

Table 4. Multivariate ORs and 95% CIs for breast cancer by study variables

Variables	OR (95% CI)	*P*
Serum vitamin D levels (ng/ml)	0.98 (0.97- 0.99)	0.02
BMI (Kg/m^2)	0.90 (0.82- 0.99)	0.03
Income (Tomans)		
< 1000000	1.00	0.002
≥ 1000000	0.016 (0.001- 0.22)	

OR= Odds ratio, CI= Confidence interval; BMI: Body mass index

For this reason, in this study, the relationship between vitamin D and breast cancer was examined from different cutting points mentioned in previous studies, as well as the quartile. Classification of serum vitamin D level in quartiles in univariate analysis and a comparison of mean serum levels of vitamin D between case and control groups in both univariate and multivariable analysis showed significant relationships.

Animal studies have proven the anticancer (anticarcinogenic) effects of vitamin D. As the active form of vitamin D increases cellular differentiation, it inhibits proliferation and growth in the epithelial cells of the breast. The presence of the receptor of vitamin D (VDR) and CYP27B1 (an enzyme that converts 25(OH)D into an active form of 1,25 (OH) 2 D) and vitamin D binding protein in breast cells confirm these anticancer effects.[11,19]

It is not possible to establish causality between serum vitamin D levels and breast cancer in case-control studies since the patients' serum vitamin D levels may change due to dietary changes, intake of vitamin D, or exposure to sunlight or cancer treatment. Meanwhile, our study was conducted on newly-diagnosed breast cancer patients whose cancer treatment had not yet begun. However, the half-life of 25 (OH) D is long and about three weeks[20] and according to available reports, remains fairly constant over time.[21] However, it is preferable to perform cohort studies so that the serum level of vitamin D be measured before cancer is diagnosed even though the best time of measurement to determine the risk of breast cancer is unclear and serum vitamin D level measurements might need to be repeated multiple times prior to diagnosis.

The results of a meta-analysis study investigating the relationship between plasma concentrations of 25 (OH)D and breast cancer risk showed a significant reverse relationship in the case-control studies that measured plasma concentrations of 25 (OH)D after the diagnosis of the disease. However, in the cohort studies that measured the concentration of 25 (OH) D years before diagnosis, this relationship was not significant.[22] Failure to observe a meaningful relationship in prospective studies may be due to the fact that the follow-up period for observing the effects of plasma vitamin D on breast cancer was not sufficient or that the protective role of vitamin D against cancer in the time, when its concentration was measured, was more effective.[23]

On the other hand, in our study, in univariate analysis, the risk of breast cancer was higher in women with a familial history of breast cancer or history of breast diseases. The association of these variables with breast cancer has also been reported in other studies. In a population-based case-control case study conducted in Germany, 16.6% of the control group and 13.3% of the case group had a history of breast cancer in first-degree family members ($P = 0.01$). In this study, the proportion of people with benign breast disease was 39% in the case group and 27.2% in the control group ($P < 0.01$).[11] In a large matched case-control study of women aged 50-74, the proportion of a positive history for breast cancer in first-degree family members was 13.1% in the case group and 3.9% in the control group ($P < 0.01$).[24]

In our study, in the multivariate analysis, in addition to vitamin D, BMI showed a significant and reverse association with the risk of breast cancer; this means increasing BMI has a protective effect on the risk. This is in contrast with the

results of other studies[3,9] that have reported a significantly higher BMI in the case group compared with the control group. This inconsistency may be due to late diagnosis of breast cancer in Iran, which leads to weight loss in cases at the time of diagnosis.

Another variable associated with breast cancer in our final model was income, in which the risk of breast cancer in people with lower income was higher. Few studies have investigated the relationship between socioeconomic status and breast cancer and variables; for instance, resident area and education have been used as indicators of social and economic status. In the present work, in univariate analysis, breast cancer was associated with all of the following variables: resident area, education, and income. In the study of Dr. Hajian et al., no relationships were observed between breast cancer and place of residence (city/village) or education level.[25] Another study by Lee et al. found that the risk of breast cancer in women with a less significant number of academic years was higher,[2] which is consistent with our findings on education, but no studies was found on the association between income and breast cancer. The association between low socioeconomic status and the increased risk of breast cancer in our study could be due to the possibility that patients with a high socioeconomic status were diagnosed and treated in centers outside of Zanjan.

One of the limitations of our study was the limited number of patients and controls compared with other studies due to the low incidence of breast cancer in this province and recruitment of new cases as the inclusion criteria for this study. On the other hand, obtaining information about a number of risk factors and performing individual matching on variables, such as age, menopausal status, and blood sampling time during the study, thereby controlling the effects of confounding factors, could be named as strengths of our study.

Conclusion

In this study, there was a significant, independent, and reverse association between serum vitamin D levels and breast cancer. The risk of obtaining breast cancer was also significantly and independently associated with BMI and income. However, prospective and intervention studies should be conducted in a way that serum levels of vitamin D be measured prior to cancer detection. They also provide more reliable data on concerning the role of vitamin D in prevention of breast cancer.

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Conflict of Interest

None declared.

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