Independent and joint effects of serum 25-hydroxivitamin D and calcium on breast cancer ratio in an Iran population: A cross-sectional study

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Abstract

Background:

It has been suggested that Vitamin D and calcium have protective effects against breast cancer. The results about breast cancer and serum Vitamin D and calcium levels are still controversial, indefinite, and insufficient to determine the amount of nutritional needs. Thus, we investigated the association between serum 25-hydroxyvitamin D(25-OH-D) and calcium on the ratio of breast cancer at diagnosis time.

Materials and Methods:

We carried out a hospital-based cross-sectional study in a population of Iran. It comprised 57 breast cancer cases, who were newly diagnosed, and 85 controls in 2013. The serum 25-OH-D and calcium levels were measured.

Results:

There was not any significant association between 25-OH-D and breast cancer ratio. Odds ratio (OR) comparing the highest quartile to the lowest quartile was 1.03(95% confidence interval[CI] 0.33–3.22, P-trend 0.95). Having sufficient (>75 nmol/L) serum 25-OH-D levels compared to insufficient serum 25-OH-D levels was not associated with a significantly decreased ratio of breast cancer (OR 0.55, 95% CI 0.23–1.29, $P = 0.17$). Furthermore, an association between calcium and breast cancer did not get statistical significance (OR 0.51, 95% CI 0.17–1.49, P-trend 0.31). The joint effect was negative interaction.

Conclusion:

Vitamin D and calcium do not act on decreasing ratio of breast cancer. Decreasing ratio of breast cancer in relation to serum calcium and Vitamin D level at diagnosis time needs more assessments.

Keywords: 25-hydroxyvitamin D, breast cancer, calcium, serum

INTRODUCTION

Some research results show that the low intake of Vitamin D may increase breast cancer risk, although the

results are controversial.[1] The relationship between the specific metabolites of Vitamin D and development of breast cancer is unknown.[2] To the best of our knowledge, this is the first cross-sectional study that examines the serum 25-hydroxyvitamin D(25-OH-D) and calcium and odds ratio (OR) of breast cancer in Iran. The objective of this study was to examine possible independent and joint effect of Vitamin D and calcium on the OR of breast cancer.

MATERIALS AND METHODS

This cross-sectional hospital-based study was conducted at the private office of Yazd in 2013. Following an informed consent, the subjects were sent to laboratory for performing 25-OH-D and calcium test. 85.1% of subjects were resident of Yazd, Hormozgan, and Kerman provinces. 4.9% residual were from the other provinces of Iran. The data about age, residency region, menopausal status, and family history of breast, colon, and ovary cancer were collected through face-to-face interview. In this study, postmenopausal women are women who had spent at least 6 months since their last menstrual cycle, without surgical menopause. 57cases were with histological confirmation of which 45 (78.9%), 8 (14.0%), 2 (3.5%), and 2 (3.5%) were, respectively, with cancer of infiltrating ductal carcinoma, medullary, invasive lobular, and comedo. All the patients, in the case group, were newly diagnosed and only one case was with recurrent. Of the total 85 subjects, 51 (60.0%), 31 (36.0%), 2 (2.4%), and 1 (1.2%) had, respectively, fibrocystic breast condition, normal, fibroadenoma, and lipoma, and none of them have breast cancer risk.

Vitamin D and calcium were measured in some laboratories, and then the units were got identical by unit conversion. This study was approved by Ethic Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Statistical analysis

The descriptive statistics as median and % are calculated for calcium and 25-OH-D and mean (standard deviation) for all other data.

Cut-off points of quartiles for both 25-OH-D and calcium were determined by distribution among controls. Binary logistic regression was used for calculation of OR with 95% confidence interval (95% confidence interval[CI] with OR) for breast cancer in the different quartiles of 25-OH-D and calcium. The lowest quartile was as a reference category. For linear trend, the median of each quartile of plasma Vitamin D and calcium as a continuous variable were entered in the logistic regression model and tested by sig Wald test. This test should be performed as a part of process during logistic regression performance, not before doing it. The effect of adjustment for age and menopausal status is surveyed in multivariate models. Furthermore, the analyses for Vitamin D in two discrete groups, postmenopausal and nonpostmenopausal women, were performed. The mentioned results were not reported because of not being statistically significant. The secondary analysis for women with sufficient/insufficient Vitamin D (>75 nmol/L) was performed.

To determine the probable synergistic effect of 25-OH-D and calcium, we categorized the subjects into four groups on the basis of combined 25-OH-D and calcium status of each subject.(I) Low 25-OH-D/low calcium–women with both 25-OH-D and calcium in the first three quartiles that is 25-OH-D Q1, Q2, Q3 and calcium Q1, Q2, Q3. This was the reference category,(II) high 25-OH-D/low calcium–women whose 25-OH-D were within the forth quartile, but their calcium levels were within the first three quartiles (25-OH-D Q4 and calcium Q1, Q2, Q3), (III) low 25-OH-D/high calcium–women whose 25-OH-D were within the first three quartiles, but their calcium levels were within the forth quartile (25-OH-D Q1, Q2, Q3 and calcium Q4), and (IV) high 25-OH-D/high calcium–both 25-OH-D and calcium levels were within the forth quartile (25-OH-D Q4 and calcium Q4). All statistical analyses were performed by SPSS 18(Chicago, IL) for windows. Two-sided P <0.05 was considered statistically significant.

RESULTS

The mean age of cases was 49.14 (range: 17–80) years. About 25 (44.6%) women were postmenopausal and 1 (1.8%) women had total abdominal hysterectomy (TAH). Only 2 (3.5%) had familial history of breast or colon cancer. 47(82.5%), 5 (8.8%), and 5 (8.8%) women were, respectively, in stage (II), stage (III), and stage (I).

The mean age of controls was 46.25 (range: 28–80) years. About 8 (9.4%) women were postmenopausal, 3(3.5%) women had TAH, and 7 (8.2%) had familial history of breast cancer. Table 1 shows mean age, median 25-OH-D, and calcium concentration (10th and 90th percentile) for cases and controls.

Odd Ratio comparing the forth quartile of serum 25-OH-D concentration to the first quartile was 1.33 (95% CI 0.46–3.83, P-trend 0.95). Adjusting for age and menopausal status, the OR was OR 1.03(95% CI 0.33–3.22, P-trend 0.61) [Table 2]. Women with sufficient 25-OH-D concentrations (>75 nmol/L) compared to those with insufficient serum concentration did not have a significantly reduced ratio of breast cancer (OR 0.55, 95% CI 0.23–1.29, $P = 0.17$), though the numbers of women with sufficient serum 25-OH-D concentration were small (38 women, 13case, and 25 controls).

The inverse association between serum calcium concentration and breast cancer ratio was not statistically significant. Comparing the highest quartile of calcium to the lowest, crud and adjusted OR were, respectively, 0.56 (95% CI 0.20–1.59, P-trend 0.377) and 0.51 (95% CI 0.17–1.49, P-trend 0.308) [Table 3].

Compared to women with low 25-OH-D/low calcium concentrations, those with high 25-OH-D/high calcium had an OR of 0.23 (95% CI 0.05–1.21). Similarly, the OR among women with low 25-OH-D/high calcium and high 25-OH-D/low calcium were, respectively, 0.62 (95% CI 0.21–1.82) and 0.86 (95% CI 0.31–2.41) [Table 4]. The interaction is negative.

DISCUSSION

To the best our knowledge, this is the first cross-sectional study that examines the association of both serum 25-OH-D and calcium levels with the breast cancer OR in Iran. Our finding:(I) There is not any significant association between serum calcium and 25-OH-D, separately, with breast cancer OR (II) There is a negative interaction between 25-OH-D and calcium concentrations with respect to breast cancer OR.

In some, not all, studies an inverse relationship between diet calcium and breast cancer was reported.[3,4,5,6,7,8] For instance, some studies show that intake of calcium or Vitamin D is not statistically significantly associated with breast cancer risk in postmenopausal women.[3,5,7] It should be noted that one of the reasons for not being significant in the association of postmenopausal and nonpostmenopausal can be the different definition of menopausal status. In this study, lasting more than 6 months, not 1year, is considered as a postmenopause definition. Serum calcium does not reflect diet calcium intake because this relationship is affected by Vitamin D, PTH, and other dietary factors. For instance, a Norwegian study did not observe any significant effect of calcium and Vitamin D dietary intake on serum calcium concentration in women.[9] Biological process by which calcium may be effective on breast cancer contains participating in regulating apoptosis, cell proliferation, and differentiation. Calcium can prevent mammary carcinogenesis caused by 7,12-dimethylbenz (α) anthracene.[6]

Like calcium, some studies has found a significant reverse relationship between serum 25-OH-D and breast cancer risk and some others report a marginal or statistically nonsignificant association.[6] When Toriola *et al*., excluded the cases whose cancers were diagnosed within 1–3 years of serum sampling, the OR decreased slightly and trend test got to statistically significant.[9] Bertone-Johnson *et al*., found that the mean of 25-OH-D levels at the first diagnosis are not different on the basis of disease status.[2] The result of the later study is consistent with those of our study on the basis of not being significant.

On the other hand, the samples were taken at the time of diagnosis in our study. Hence, another reason for not being significant can be study design, i.e.,cross-section.

Two other prospective studies showed that there is not any relationship between breast cancer and the main source of 25-OH-D, i.e. sunlight.[10] Chlebowski *et al*., concluded that 25-OH-D levels are not associated with consequent breast cancer risk.[5]

We observe a negative interaction between serum Vitamin D and calcium on breast cancer ratio. Vitamin D and calcium are not independently associated with breast cancer ratio regardless of each other. The notion of probable synergistic effect of Vitamin D and calcium on health outcomes is suggested because of continuous observation in experimental and epidemiologic studies.[9] The mechanistic basis of calcium and

Vitamin D is not clear. Calcium supplement has this potential to decrease 25-OH-D levels, which can have detrimental effect on cancer prevention. Conversely, Vitamin D supplement may decrease luminal calcium in large bowel and interfere in antineoplastic effect of calcium.[11]

Most epidemiological studies about 25-OH-D and calcium levels on breast cancer risk are carried out in North America and Europe.[6] Hence, this is interesting to examine this relationship in other populations such as Iran, and it is one of the strong points of this study.

Our study has the following limitations: We did not have sufficient data about oral contraceptive pill, body mass index, and the season of donating blood sample. Hence, it may exist residual confounding. It is, however, very likely that serum 25-OH-D levels in various seasons are not different very much because of women's culturally specific covering in Iran. Therefore, it is suggested that, in future studies, serum 25-OH-D levels in both men and women will be examined with respect to season of year in Iran. The same weather of the subject's residency region is another positive point. Menopausal status had a big effect on the results.[3,4,5,7,12,13] Furthermore, postmenopausal women had spent more than 1year since their last menstrual cycle without surgical menopause;[14] but in this study, they had spent more than 6 months since that. Moreover, they do not remember when was it (recall bias or exposure misclassification). Because of the cross-sectional observational design, we cannot establish that there is not any cause and effect relationship. It should be noted that 25-OH-D and calcium levels were measured in some laboratories which the units were got identical by unit conversion.

CONCLUSION

Serum 25-OH-D and calcium levels did not decrease the breast cancer ratio. Moreover, the synergistic effect between serum 25-OH-D and calcium levels was not observed. The relationship among decreased ratio of breast cancer, serum 25-OH-D, and calcium levels needs more assessments.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

	Cases (*n*=57)	Controls (*n*=85)
Mean age (±SD) at serum sampling (cancer diagnosis), years	49.14 (±12.0)	46.25(±9.2)
25-(OH) D concentration nmol/L, median (10th, 90th percentile)	45.18 (14.0, 143.9)	41.18 (10.3, 146.4)
Calcium concentration nmol/L, median (10th, 90th percentile)	2.32 (2.2, 2.4)	2.32 (2.2, 2.5)

SD – Standard deviation; 25-(OH) D – 25-hydroxyvitamin D

Baseline characteristic of breast cancer cases and controls

Table 2

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	Q4 versus Q1-3
Quartile values, nmol/L	<21.3	21.3-41.2	41.3-82.2	≥82.3		
n (%), cases/control	9 (15.8)/21 (24.7)	18 (31.6)/22 (25.9)	18 (31.6)/21 (24.7)	12 (21.1)/21 (24.7)		
OR	1.0 (reference)	1.9 (0.70-5.18)	2.0 (0.73-5.45)	1.33 (0.46-3.83)	0.948	0.81 (0.36-1.82)
OR, adjusted[a]	1.0 (reference)	1.81 (0.66-4.97)	1.93 (0.69-5.36)	1.03 (0.33-3.22)	0.606	0.64 (0.26-1.55)

[a]Adjusted for age and menopause state. OR – Odds ratio; CI – Confidence interval; 25-(OH) D – 25-hydroxyvitamin D

OR, with 95% CI of breast cancer by quartile of serum 25-(OH) D among women newly diagnosed in the sample donation

Table 3

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
Quartile values, mmol/L	<2.2	2.2-2.3	2.3-2.4	≥2.4	
n (%), cases/control	15 (26.3)/22 (25.9)	21 (36.8)/25 (29.4)	13 (22.8)/17 (20.0)	8 (14)/21 (24.7)	
OR	1.0 (reference)	1.23 (0.51-2.96)	1.12 (0.42-2.98)	0.56 (.20-1.59)	0.377
OR, adjusted[a]	1.0 (reference)	1.20 (0.49-2.93)	1.10 (0.41-2.96)	0.51 (0.17-1.49)	0.308

[a]Adjusted for age and menopause state. OR – Odds ratio; CI – Confidence interval

OR, with 95% CI of breast cancer by quartile of serum calcium among women newly diagnosed in the sample donation

Table 4

	Group 1	Group 2	Group 3	Group 4
n (%), cases/control	39 (68.4)/52 (61.2)	10 (17.5)/12 (14.1)	6 (10.5)/12 (14.1)	2 (3.50)/9 (10.6)
OR, adjusted[a]	1.0 (reference)	0.86 (0.31-2.41)	0.62 (0.21-1.82)	0.23 (0.05-1.21)

[a]Adjusted for age and menopause state. Low Vitamin D/low calcium – Vitamin D (Q1, Q2, Q3) and calcium (Q1, Q2, Q3); High Vitamin D/low calcium – Vitamin D (Q4) and calcium (Q1, Q2, Q3); Low Vitamin D/high calcium – Vitamin D (Q1, Q2, Q3) and calcium (Q4); High Vitamin D/high calcium – Vitamin D (Q4) + calcium (Q4). 25-(OH) D – 25-hydroxyvitamin D; OR – Odds ratio; CI – Confidence interval

Joint effect of exposure of 25-(OH) D and calcium on OR, with 95% CI of breast cancer among women newly diagnosed in the sample donation