RESEARCH ARTICLE

Role of Vitamin D Deficiency and Lack of Sun Exposure in the Incidence of Premenopausal Breast Cancer: a Case Control Study in Sabzevar, Iran

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Abstract

Background: Vitamin D has been suggested as one of the critical factors for female reproductive health with protective activities against different cancers but there are conflicting facts regarding its role on breast cancer without any clear data on premenopausal cases. This study aimed to evaluate the role of vitamin D from dietary sources and sunlight exposure on the incidence of premenopausal breast cancer. Materials and Methods: We conducted a case control study on 60 newly diagnosed premenopausal breast cancer patients and 116 normal women who lived in Sabzevar and surrounding villages in Razavi, Khorasan, a rural and conservative area of Iran. Results: The mean concentrations of 25-OH vitamin D in cases and controls were 15.2±8.15 *vs* 15.5±7/45 ng/ml, both well below normal values elsewhere. In fact 50% of analyzed individuals showed very severe or severe vitamin D deficiency and the rest (25%) were detected in suboptimal levels. Although the lack of vitamin D and calcium supplementation increased slightly the risk of premenopausal breast cancer (p=0.009, OR=1.115, CI 95%=1.049-1.187), higher prevalence of weekly egg consumption (86.66% *vs* 96.55%, p=0.023, OR=0.232, CI 95% 0.065-0.806) showed a slight protective role. The last but the most important risk factor was lack of sunlight exposure because the breast cancer patients had total body coverage from sun (p=0.007, OR=10.131, CI 98% 0.314-78.102). Conclusion: This study pointed out the role of vitamin D and other possible risk factors on the development and growth of breast tumors in this special geographical region. Although this study has revealed the interactions between hormonal and environmental factors in this province of Iran, understanding the deficiency pattern and its contribution to other lifestyle factors elsewhere is also necessary.

Keywords: Premenopausal breast cancer - vitamin D - risk factors - sun exposure - rural Iran

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Introduction

Vitamin D is one of the critical factors for female reproductive health which may have protective activities against many cancer types, including breast cancer. This vitamin is a secosteroid hormone which regulates the expression of a large number of genes in reproductive tissues which could emphasize the important role of this vitamin in female reproduction and health (Shao, et al., 2013). Vitamin D could be obtained mainly through sunlight exposure and in the absence of sufficient sunlight exposure; vitamin D deficiency may occur rapidly (Looker et al., 2008). Although individual factors like skin pigmentation and seasons may affect cutaneous synthesis of vitamin D , its deficiency could be correlated by obesity, low levels of dietary intake, lack of sun exposure, and older age (Wortsman et al., 2000).

Breast cancer (BC) is the most frequent female cancer (23% of all cancers) and the most fatal form of malignancy among women worldwide. It accounts for more than 16% of cancer deaths and this malignancy has been remained as a major health problem worldwide (Anderson and Jakesz, 2008). One recent study in Iran showed that severe vitamin D deficiency causes a three-fold increase in the risk of breast cancer while it is not the case for moderate and mild deficiency (Alipour et al., 2014). In Iran, BC is ranked as the most prevalent malignancy among women and its probability increases with the age in general (Harirchi et al., 2011) but we showed recently that premenopausal breast cancer may have different feature and etiology in Iran by occurring one decade earlier than their counterparts in other countries and as a result of hormonal and environmental interactions especially by higher exposure to endocrine disrupting chemicals (EDCs) and AhR expression (Bidgoli et al., 2010; 2011). Other than the role of EDCs and AhR, a reverse association has been found between breast cancer risk and serum vitamin D in premenopausal breast cancer women with poor prognostic indicators (Yao et al., 2011).

On the basis of this facts and some controversial

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information on the role of vitamin D in the incidence of malignant breast tumors in Iran (Alipour, 2014),this study aimed to compare the serological levels of Vitamin D between premenopausal BC patients and normal women as well as to examine the roles of a wide range of variables on the serological levels of vitamin D. Some important possible risk factors of Vitamin D deficiency including age, obesity, daily exposure to sunlight and all details regarding body coverage and physical activities, daily intake of vitamin D supplements, all dietary resources of Vitamin D, body measurements, occupation, and family history of breast cancer were concerned in this study.

Materials and Methods

Population study

A case-control study was conducted on 60 newly diagnosed premenopausal breast cancer patients and 116 normal women as control group. Both evaluated groups lived in Sabzevar and surrounding villages in Razavi Khorasan Province in northeastern Iran since last 10 years. We selected cases from patients who underwent surgery from 2010 to 2012 in Emdad Shahid Beheshti University hospital. Cases were identified from both self-reports registration and confirmed by pathological reports. The pathological feature of cases was collected from pathological reports in the pathology archive of the mentioned hospital.

Exclusion criteria

Cases who lived in cities other than Sabzevar and villages around, were excluded from this study. Exclusion criteria for cases and controls were menopausal evidence, any evidence of pregnancy, recent lactation and history of malignancy. Menopausal status at the time of recruitment was defined according to information on ovariectomy, hysterectomy, menstruation status (still menstruating, number of menses over the past 12 months). Women were considered postmenopausal if they had undergone a bilateral ovariectomy or if their menses had stopped 12 months or more (unless due to hysterectomy) ago. Women who were still menstruating by using exogenous hormones and women with no information on the number of menses over the past 12 months were excluded from this study. The control group was matched with cases for age±5 years. Cases and controls were selected from people who didn't expose to PAHs producing manufactures as well as X-ray resources according to their living and working addresses.

Questionnaires

All information was collected by expert nurses who were blinded to the serological levels of calcium and Vitamin D. All variables were recorded and utilized according to standardized questionnaires/protocols that have been previously developed and successfully used by us (Bidgoli et al., 2012). Other than daily exposure to sunlight and all details regarding body coverage ,daily intake of calcium and vitamin D and all dietary resources of mentioned factors were collected. Demographic data ,body measurements including weight, height, and calculated body mass index, occupation, physical activity (time spent in mild, moderate, and vigorous activities), and family history of breast cancer were recorded.

Serological levels of 25-OH Vitamin D

Serums of all patients who underwent surgery from 2010 to 2012 were collected and frozen for analyzing 25-OH vitamin D by EUROIMMUN 25-OH Vitamin D ELISA kit which is a reliable detection method for 25-OH vitamin D3 and 25-OH vitamin D2 with100% reliability due to an innovative monoclonal antibody. Free antibody binding sites are occupied by labelled 25-OH vitamin D. The intensity of the color formed after addition of the chromogenic/substrate solution is measured using a photometer. The color intensity is inversely proportional to the 25-OH vitamin D concentration in the serum or plasma. This test system is optimized for the *in vitro* determination of vitamin D level in human serum or plasma in suspected vitamin D deficiency, reduced intestinal vitamin D uptake, increased vitamin D metabolism, hypocalcaemia, hypophosphataemia, hypocalciuria, elevated alkaline phosphatase, reduced bone mineral content and in suspected vitamin D overdosing.

Background factors

Exact weight and height of cases and controls as well as their weight changes from menstruation to maturation, from pregnancy to breast feeding until present were recorded by pretested questionnaires. Body mass index (BMI) was calculated and compared between cases and controls.

Reproductive variables

Demographical variables were obtained from specific questionnaire items: i) Delivery related factors including mother's and grandmother's age, father and grandfather's age, mother's weight and birth weight at delivery; ii) Menstruation related factors including age, weight and height at menstruation, irregular menstruation, amenorrhea and dysmenorrhea), marriage related factors including marital status, age at marriage, age at first intercourse and frequency of intercourses per week.

Sunlight exposure questionnaire

The sunlight exposure assessment was added to our general questionnaire on the basis of existing literature review on sunlight exposure assessment as well as on a sunlight exposure questionnaire that had previously been used in several epidemiological studies of cancer (Wu et al., 2013). The questionnaire covered the possible skin reaction to sunlight exposure, time and frequency spent outdoors in the sun and personal protection against with special emphasis to dressing style. Questions relating to sunlight exposure included the following: residence (city, village); outdoor activities in the sun and the aver-age hours per day spent in the sun during the summer and the other 3 seasons, usual (usual was defined as >50% of the time) sun protection during the summer and the other 3 sea-sons, trips to summer climate locations during the winter and the frequency.

Supplements and nutritional factors:

Nutritional habits were recorded to assess the daily

consumption of vitamin D, calcium ,dairy products, meat and egg by validated questionnaires (Zhang et al., 2003). Daily use of cod liver oil, various types of fish, Fortified Cereals: Oysters, Caviar, Fortified Soy Products (Tofu and Soy Milk), Salami, Ham, and Sausages, Fortified Dairy Products eggs and mushrooms were considered as the major nutritional resources of vitamin D in present study.

Statistical analyses

Values were expressed as percent per population or as the mean±standard deviation (SD).To assess the association between clinicopathological data, student t-test or nonparametric chi-square test were used. Relative risks and Odds ratios were calculated by Cochran's and Mantel Haenszel statistics using SPSS 21.Probability values of <0.05 and Odds ratios >1 were considered significant.

Results

Demographic and pathological features

The pathological feature of cases was recorded before starting the interviews with patients and described in Table 1. Out of 60 patients, 65% of tumors were located at left side and 5% in both sides. The mean tumor sizes were 3.6±2.4cm and the tumors were mostly invasive, 35% showed lymphatic invasion, 5% showed vascular and 10% showed neural invasions in young premenopausal cases.

The mean age of patients whose serums were analyzed was 36.45±7.02 years whereas the mean age of controls was 34.2±5.7 years. Although the general demographical feature was not significantly different between cases and controls, higher rate of menstrual disorders (80% *vs* 62%) was considered as a preliminary risk factor of breast cancer (p=0.017, OR=2.44, CI 95% 1.72-5.1) in premenopausal women of this province of Iran. No association was found between menstrual disorder and serum levels of Vitamin D.

Serum levels of 25-OH Vitamin D: The serum levels of 25-OH vitamin D were compared between cases and controls in Table 3. The mean concentrations of 25-OH vitamin D (15.17±8.15 *vs* 15.47±7/45 ng/ml) didn't show any significant difference between cases and controls but more than 95% of women in each group were vitamin D deficient.No association was found between serological levels of 25-OH Vitamin D and any clinical and pathological feature of cases (data was not showed).

Supplements and nutritional factors

As we showed in Table 4, daily consumption of vitamin D and calcium supplements as well as the consumption pattern of dairy products were compared. In fact the major nutritional vitamin D resources especially different meat types, egg, liver oil, fish, fortified cereals, oysters, caviar, fortified soy products, Salami, Ham, and Sausages and mushrooms were compared (data didn't show). From religious, traditional or economical reasons nobody used Oysters, Caviar, Salami, Ham, and Sausages. Other nutritional habits including pattern of using dairy products (fortified dairies, milk, yoghurt and cheese) consumption,

Table 1. Pathological Feature of Breast Cancer Patients (N=60)

Pathological features		No. (%)
Tumor size (cm)		Mean: 3.6±2.4
Tumor location	Right beast	18 (30)
	Left breast	39 (65)
	Both sides	3 (5)
	Positive invasion	39 (65)
	Negative invasion	18 (30)
	Lymphatic Invasion	21 (35)
	Vascular invasion	3 (5)
	Lymphatic and Vascular invasion	9 (15)
	Neural and\Vascular invasion	6 (10)
	Neural, Lymphatic and Vascular invasion	3 (5)
Tumor stage	I	9 (15)
	II	18 (30)
	III	30 (50)
	IV	3 (5)
Tumor grade	Well differentiated	9 (15)
	Moderately differentiated	28 (47)
	Poorly differentiated	13 (21.50)
	Undifferentiated	10 (16.50)

Table 2. Comparison of Demographical Features between Cases and Controls

Characteristics	Breast cancer (60) No (%)	Control (116) No (%)	p value
Age	36.45±7.02	34.2±5.7	0.138
Marital Status			
Married	58 (97%)	110 (95%)	0.718
Single	2 (3%)	6 (5%)	
Age at marriage	20.27±2.62	18.89±3.83	0.015*
Body Measurements			
Weight	68.3±12.86	67.76±11. 57	0.889
Height	158.8±6.27	157.4±6.55	0.177
BMI	26.88±5.04	27.36±4.55	0.521
Weight at 18yrs	54.04±6.92	50.43±5	0.004*
Highest weight at lifetime	70.16±11.39	71.78±14.39	0.451
Age at highest weight	35.36±7.23	31.93±8.86	0.011*
Trends of weight gain after 18			
Increased	57 (95%)	101 (87.07%)	
Decreased	3 (5%)	15 (22.93%)	0.12
Reproductive features			
History of pregnanc			
Yes	56 (93.33%)	101 (87.06%)	0.305
No	4 (6.67%)	15 (12.94%)	
Age at first pregnancy	22.14±3	20.95±4.13	0.06*
Age at first menstruation	12.95±1.39	13.03±1.54	0.723
Menstrual Disorders**			
Yes	48 (80)	72 (62)	0.017*
No	12 (20)	44 (38)	

*Menstrual disorders were adjusted for logistic regression model; **2.444, 1.172-5.100

Table 3. Pathological Feature of Breast Cancer Patients (N=60)

25-OH vitamin D concentration	Cases (n=60)	Controls (n=116)
Mean level(ng/ml)	15.17±8.15	15.47±7.45
<5ng/ml: Very severe vitamin D deficiency	15%	13.88%
5-10 ng/ml: Severe vitamin D deficiency	15%	13.88%
10-20 ng/ml: vitamin D deficiency	40%	36.11%
20-30 ng/ml:Suboptimal vitamin D provision	25%	33.33%
Vitamin D deficient	95%	97.3%
30-50 ng/ml:optimal vitamin D leve	5%	2.80%
50-70 ng/ml: Upper norm	-	-
70-150 ng/ml:Overdose but not toxic	-	-
>150 ng/ml: Vitamin D intoxicatio	-	-

*All variables in table 4 were adjusted for logistic regression model

Table 4. Comparison of Some Vitamin D Related Factors between Cases and Controls

	Breast cancer No (%)	Control No (%)	p value	OR	CI 95%
Sunlight exposure					
Daily sunlight exposure (h)					
<0-0.5	12 (20)	36 (31)			
>0.5	48 (80)	80 (69)	0.153	0.556	0.264-1.170
Covering body against sunlight					
Total	59 (98.33)	99 (85.3)			
Half	1 (1.67)	17 (14.7)	0.007**	10.131*	1.314-78.102*
Supplements					
Calcium tab.					
Yes	1 (1.67)	21 (18.10)	0.001*	0.077	0.010-0.585
No	59 (98.33)	95 (81.90)			
Vit D					
Yes	0	12 (18.46)	0.009*	1.115*	1.049-1.187
No	60 (100)	104 (81.54)			
Dietary resources of Vit D					
Fish					
Yes	26 (43.33)	43 (37)	0.422	1.298	0.688-2.499
No	34 (46.67)	73 (63)			
Egg					
Yes	52 (86.66)	112 (96.55)	0. 023*	0.232	0.067-0.806
No	8 (13.34)	4 (3.45)			
Weekly profile of egg consumption (eggs/week)					
>3	29 (55.76)	88 (77.19)	0.006*	0.373	0.185-0.751
<3	23 (44.24)	26 (22.81)			

*Breast cancer=60; Control=116

didn't show any significant difference between two groups.

Data in Table 4 showed clearly the protective role of Vitamin D supplementation in premenopausal breast cancer patients. Nobody from the patients had previously received any type of Vitamin D supplement whereas in controls, 18.46% of women had previously received vitamin D supplements (p=0.009, OR=1.115, CI 95%=1.049-1.187). This finding may emphasis this fact that lack of Vitamin D supplementation may increase slightly the risk of premenopausal breast cancer.Similar results were seen for Calcium supplements (Table 4). Although few patients (1.67%) had previously received calcium supplement but this feature was observed in 18.1% of controls, (p=0.001, OR=0.077, CI 95%=0.01-0.585). Other than calcium and vitamin D supplementation, the next important dietary factor was egg. In our study using more than 3 eggs weekly showed slight protective role against early incidence of breast cancer (86.66% *vs* 96.55%, p=0.023, OR=0.232, CI 95% 0.065-0.806). In fact the general feature of egg consumption was significantly different between cases and control group (p=0.006).

Comparison of sunlight exposure between cases and controls

As we showed in table 4, the total sunlight exposure was not significantly different between cases and controls because the both groups were vitamin D deficient. The major difference between two groups was personal protection against sun with special emphasis to dressing style. Nearly all cases (98.33%) didn't have any sun exposure because of dressing style and total body coverage. This situation was considered in 85.3% of controls (p=0.007, OR=10.131, CI 98% 0.314-78.102).

Discussion

Premenopausal breast cancer is attributed to poorer clinical outcomes and higher rate of mortality but healthy eating practices and physical activity can prevent it and later may improve the quality of life in breast cancer survivors (Mohammadi et al., 2013). Breast cancer occurs one decade earlier in Iranian women than other countries (Harirchi et al., 2011) therefore special concerns should be done on the etiology of early breast tumor in Iran for cancer prevention goals. To undertand the specific etiology of premenopausal breast cancer in Iran we focused at first step on the role of environmental pollution and PAHs in the Tehran province and their role on the expression levels of AhR as their biomarker of exposure (Bidgoli et al., 2010; 2011). According to that initial studies we showed how the early breast cancer in Tehran could be affected by exposure to PAHs in this polluted area where the concentration of pollutants is higher than the standard levels worldwide (Naddafi et al., 2012). This time in present case control study in Sabzevar as a relatively unpolluted city in Khorasan Razavi Province ,we tried to focus on different ethiological factors in premenopausal breast cancer in a different region. This study has revealed the role of vitamin D deficiency, egg ,sunlight exposure and vitamin D and calcium supplementation in the incidence of premenopausal breast cancer in this province of Iran.

Vitamin D is obtained from both dietary sources and exposure to sunlight (Shao et al., 2012) and both ways were assessed in this study. Although the dietary sources of vitamin D in both cases and controls were relatively similar, egg consumption was significantly higher in normal women than cases (p=0.006, Table 4). The two naturally occurring forms of vitamin D are cholecalciferol (vitamin D3) from animal sources and ergocalciferol (vitamin D2) from plant sources and we tried here to record both ways of oral vitamin D administration in all women. However, most vitamin D in circulation is produced naturally when 7-dehydrocholesterol in the skin is exposed to ultraviolet B (UVB) radiation to produce vitamin D3 (Looker et al., 2008), the mean concentrations of 25-OH vitamin D in cases and controls (15.17±8.15 vs. 15.47±7/45 ng/ml) were below than normal average. This findings means 50% of our cases were categorized as very severe or severe Vitamin D deficient and the rest (25%) were detected in suboptimal levels.

There are conflicting facts regarding the protective role of vitamin D supplementation and cancer outcomes in postmenopausal women without any clear data in premenopausal women. Although in post-menopausal women according to the Women's Health Initiative studies, there was no risk reduction in women who randomly assigned to take calcium (1,000mg) and vitamin D3 (400 IU) daily, versus a placebo (Prentice and anderson, 2008) we showed different results in this study. In current work both case and control premenopausal groups were extremely Vitamin D deficient and lack of Vitamin D and calcium supplementation increased slightly the risk of premenopausal breast cancer.

An inverse association between total annual sunlight

exposure and age-adjusted breast cancer mortality in the U.S was reported for the first time in 1990 (Garland et al., 1990) but later more data suggested increasing evidences regarding a negative association between sunlight exposure and increased risk of breast cancer incidence (Engel et al., 2013). Next findings focused on the protective role of sunlight exposure and its inverse association with breast density pattern in premenopausal women (Wu et al., 2013). Above study suggested that sunlight exposure may be associated with reduced risk of breast cancer without any clear evidence of modification by the vitamin D receptor (VDR) variant which is a crucial mediator for the cellular effects of vitamin D (Wu et al., 2013) and later studies didn't show any association between VDR BsmI polymorphism and increased risk of breast cancer (Du et al., 2013; Huang et al., 2014). In line with our findings, dressing style with body coverage has recently been shown to be important for vitamin D levels and breasat cancer in Turkey (Alco et al., 2014).

In our study the total sunlight exposure was not significantly different between cases and controls in the meanwhile the both groups were vitamin D deficient but the major difference between two groups was personal protection against sun with special emphasis to dressing style. Nearly all cases (98.33%) didn't have any sun exposure because of dressing style and total body coverage. This situation was considered in 85.3% of controls as well but the dressing style was impressively different and protected them from any type of sunlight exposure. (p=0.007, OR=10.131, CI 98% 0.314-78.102).

Since studies have demonstrated a higher prevalence of vitamin D deficiency in women with breast cancer we showed here dramatic data about vitamin D deficiency in more than 95% of young Iranian women ,therefore correction of vitamin D deficiency in these women represents a reasonable, but as yet untested, strategy to delay recurrence and extend survival of breast cancer as recently described (Laporta and Welsh, 2013).

In summary, we believe that the data presented here will shed some light on a possible association between vitamin D deficiency according to dietary resources and sunlight exposure by living even in unpolluted areas and increased risk of premenopausal breast cancer. It seems that these factors should be strongly considered as a possible risk factor for early breast cancer and could be considered anywhere else despite of geographical differences.

In conclusion, we reported for the first time these environmental risk factors of early breast cancer in this province of Iran and their contribution to the extent of serum levels of vitamin D. Our study contributes to the understanding of the effects of vitamin D serum levels as well as women's health and point out possible risk factors for the development and growth breast tumors in high risk vitamin D deficient normal women. It seems that incidence of early breast cancer could be the result of interactions between hormonal and environmental factors. Further studies are necessary to find the possible interactions between Vitamin D and other hormonal factors and their possible contribution in premenopausal breast cancer.

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