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Prevalence of low levels of vitamin D in patients with breast cancer who live in Northern latitudes 21-22º

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Summary

Objective: Vitamin D has been involved in various diseases, including cancer. Several studies have linked vitamin D levels with breast cancer. The aim of our study was to establish the importance of adequate vitamin D concentrations to prevent breast cancer.

Materials and methods: The study included 76 patients. Dietary habits, sun exposure, body mass index (BMI), and skin type were evaluated. Vitamin D determination in serum was measured by liquid chromatography. Vitamin D receptor pleomorphism was analyzed by immunohistochemistry.

Results: Vitamin D ingestion was deficient in 18 patients and 22 controls; and sufficient in 6 patients and 30 controls, odds ratio of 4.09, confidence interval 95% 1.04-11.0, (p=0.016). Sun exposure was present in 9 patients and 15 controls; 15 patients and 37 controls had less sun exposure or used protection. Two patients and 13 controls had normal levels of vitamin D (30-60), two patients and 26 controls had low levels (20-30), and 18 patients and 12 controls had very low levels (<20). Odds ratio for patients with vitamin D serum levels of 20 ng/mL or less, or higher was 9, CI 95% 2.95-27.5, (p<0.001). These levels were independent from BMI.

Conclusion: Low concentrations of vitamin D are strongly related to breast cancer in a region with high solar exposure. More studies are needed to confirm this relationship.

Key words: *breast cancer, vitamin D, risk factor, sun exposure, diet, skin type.*

Introduction

Vitamin D's importance in maintaining bone mineralization has been recognized for decades. Currently, 30 to 60 ng/mL plasma concentrations of vitamin D have been associated with improvement in other conditions such as hypertension, cardiovascular disease, diabetes, autoimmune diseases and cancer[1].

Breast cancer is the leading cause of cancer death in women in the world[2]. In 2012 an estimated 1.67 million new cases were diagnosed worldwide[3]. This is a significant increase if compared with the 12,433 new breast cancer cases in women aged 40 to 59 years, according to Mexico's National Register of Malign Tumors in 2003. The rate of the disease in Mexico is 18.7 per 100,000 women aged 25, an increase of 49.5% over the past 20 years[4].

Due to the global impact of breast cancer, numerous efforts have been made to identify risk factors and thus develop preventive measures.

A recent study of 44,778 pairs of twins with cancer identified a contribution of approximately 5% of inheritable genetic factors in cancer development. This study suggested that between one and two thirds of cancer cases could be prevented with dietary factors[5]. So efforts have been made to link low vitamin D levels with low sun exposure and particularly breast cancer in women living in Northern latitudes[6-8]. Other epidemiological studies have even shown that high levels of metabolites of vitamin D are consistently associated with decreased risk of breast cancer[9], while low concentrations were significantly associated with negative characteristics of breast tumors, such as tumor size or higher grade[1]. Besides epidemiological findings have demonstrated that breast tissue contains receptors for vitamin D, and several polymorphisms of the gene encoding this receptor have been associated with worse prognosis[10,11].

For most people, between 80 and 90% of circulating vitamin D reserves are derived from accidental exposure to radiation solar[12], which is limited in areas where such radiation is low. That inadequate sun exposure is also due to cultural habits, such as clothing and public health recommendations which are aimed at preventing neoplastic growths such as skin cancer, for example[13]. It is also worth considering that, despite the existence of vitamin D enriched milk, fatty fish and cod liver oil, food sources containing this vitamin are limited, and in many countries, dairy products are not fortified with vitamin D[13].

To confirm the link between low levels of vitamin D and breast cancer, we conducted a case-control study in women living in a region that receives high doses of UVB radiation throughout the year. We tried to eliminate confounding variables by evaluating vitamin D intake, body mass index, family history, hormonal history and the circulating level of vitamin D receptor. Our hypothesis was that vitamin D concentrations would be significantly lower in women diagnosed with breast cancer than in those of the control group.

Material and methods

Study population

We designed a case-control study with information on the population of Aguascalientes, a state in Mexico, located between 21 and 22° north latitude with an average temperature of 19.2°C and receiving a daily dose of between 6 to 7 kWh/m^2 of solar energy[14]. In 2010, the population of Aguascalientes was 1,184,996 inhabitants (National Institute of Statistics, Geography and History of Mexico, INEGI), and in 2012, 150 new cases were diagnosed and treated for breast cancer[15].

The protocol was submitted to the Institutional Ethics Committee on 22 December 2011, adopted on 26 January 2012, and registered with the Federal Commission for the Protection against Sanitary Risk of the Mexican Health Ministry (COFEPRIS) on 19 December 2012 (CAS/OR/01/CAS123300410D0034-3789/2012). All the study procedures were carried out in accordance with the Declaration of Helsinki. All the study participants signed informed consent forms.

Patients in the case group were included if they had breast cancer confirmed by histopathological diagnosis prior to systemic therapy between March 2012 and March 2013. We included two controls for each woman, those who had negative mammogram results (BIRADS 0-2 confirmed by a central radiologist) or benign biopsy, they were matched by age and place of residence in the previous three years. Patients and women in the control group were referred by Oncology Services Advanced Medical Hospital with Central Medical Surgical Area General Hospital Number 1 of the Aguascalientes Delegation of the Mexican Social Security Institute; General Hospital Institute of Health and Social Security Workers in Aguascalientes State; and the Women's Hospital. All patients participating in the study were evaluated between 7 and 15 days after cancer diagnosis through a complete medical history, including eating habits skin type and sun exposure. For all participants, records of vitamin D (25-OH) in serum were taken. Two patients declined to participate in the study. None of the controls refused to participate in the study.

Exclusion criteria for both groups were: previous diagnosis of hyperparathyroidism, intake of vitamin D supplements prescribed or over the counter, existence of previous burn injury have needed a skin graft, intestinal malabsorption, hormone replacement therapy thyroid, neoplasia other and patients with altered levels of serum calcium, phosphorus and magnesium.

All cases and controls were given two separate interviews, one to evaluate the risk factors of breast cancer and sun exposure habits, and the second for a nutritional intake survey of vitamin D. Risk factors for cancer breast are included in the breast Cancer Risk Assessment Tool[16], but in our study we excluded people of color because this model is designed only for white women.

Habits solar radiation were evaluated by a questionnaire on the use of sunscreen, clothing

with long sleeves, radiation exposure by occupation or recreation (or both), and the time and duration of exposure to solar radiation.

In our study we determined the serum levels of calcium, phosphorus and magnesium, and vitamin D (25-hydroxy vitamin D_3) and vitamin D receptor (VDR). The role of vitamin D in calcium homeostasis was assessed using biomarkers as levels of parathyroid hormone, calcium absorption and bone mineral density[17].

As it has shown that adequate intake of calcium and vitamin D reduces significantly bone loss[18], a DXA bone density scan of the lumbar spine and proximal femur was carried out in all patients to determine chronicity in vitamin D deficiency.

Tumor tissue samples were taken from cancer patients to be examined by one pathologist (ARP).

All participants (cases and controls) were interviewed by one of the researchers (RGF/SPJ) who notified the women of the test results. Those who had abnormal levels of vitamin D or bone density diagnosis of osteopenia or osteoporosis were referred to their primary care physician to prescribe treatment.

Determination of vitamin D and its receptor

Measurement of 25 (OH) vitamin D was carried out using liquid chromatography. Pleomorphism receptor Vitamin D was analyzed by immunohistochemistry. The VDR gene polymorphisms (Bsm-1, Fork-1) was formed by cells taken from peripheral venous blood genomic DNA (5 ml blood stored in tubes containing ethylenediaminetetraacetic acid).

The DNA was extracted by Lahiri and Numberger method[19]. Genomic DNA (100 ng) was amplified by PCR technique under standard conditions: 1.5 mM MgCl2, 20 µM dNTPs, Taq DNA polymerase 1 IU, final volume of 50 µl.

Statistic analysis

The odds ratio was used to estimate the association between low levels of vitamin D and breast cancer as study participants were selected based on the presence or absence of breast cancer, and not for their vitamin D levels. To quantify the accuracy of the association, a confidence interval of 95% was calculated, and to assess the risk weighted in the presence of confounding variables we used the Cochran-Mantel-Haenzel test.

Results

Between March 2012 and March 2013, a total of 76 women were included in the study. All of them met the inclusion criteria and none were excluded because of serum electrolyte abnormalities.

Of these, 24 had confirmed breast cancer aged 22-79 years (median 50.5 and 53.6 average), and were included in the case group diagnosis. The remaining 52 women, aged between 24 and 67 years (median 51 and average of 51.09), were assigned to the control group.

The risk of breast cancer was analyzed by modifying the Breast Cancer Risk Assessment Tool (with ethnicity factor removed); the 5-year risk was similar in both groups.

Sun exposure, at least 30 minutes a day, was present in 9 patients and 15 controls; while 15 patients and 37 controls had less sun exposure or used adequate protection (odds ratio=1.48; confidence interval (CI) 95%: 0.53 to 4.11; p=0.625) (Table 1).

Vitamin D intake was evaluated and classified as deficient in 18 patients and 22 controls, and sufficient in 6 patients and 30 controls (odds ratio=4.09; 95% CI 1.04 to 11.0; p=0.016) (Table 1).

Six patients and 20 controls had normal BMI (18.5 to 24.9), 6 patients and 21 controls were overweight (BMI 25 to 9.9); 12 patients and 10 controls were classified as obese (BMI of 30 or more) (odds ratio=4.42; 95% CI 1.51 to 13.1; p=0.01) (Table 1).

Two patients and 13 controls had normal levels of vitamin D (30-60 ng/mL); 2 patients and 26 controls had low levels (20-30 ng/mL); and 18 patients and 12 controls had very low levels (<20 ng/mL) (Figure 1). Looking at the distribution, we calculated the odds ratio for patients with serum levels of vitamin D of ≤20 ng/mL compared to those with levels above 20 ng/mL, with 9 (95% CI: 2.95 to 27 5; p<0.001) (Table 1).

Bone densitometry was normal in 40.4% of women in the control group, while they were only 20.8% of patients with breast cancer; 16.7% of cancer patients and only 9.6% of the control group were classified as osteoporotic. These findings suggest that there were low levels of vitamin D for a long period of time; however, bone mineral density was not related to current vitamin D levels.

The BSM-1 receptor polymorphism of circulating vitamin D in blood was positive in 4 cases and 5 controls, but was not associated with circulating levels of vitamin D; while Fork-1 polymorphism was positive in 3 control and in one case, and it was not related to circulating levels of vitamin D.

In assessing the risk factors analyzed and breast cancer in our patients we found a positive association. In other words, the risk of breast cancer is 1.48 times higher in women with less than 30 minutes of daily sun exposure, compared with women with sun exposure of 30 minutes or more. Similarly, the risk of breast cancer is 4.09 times higher in women with deficient intake of vitamin D, compared to those in whom it was determined that the intake of vitamin D was sufficient. The risk was 4.42 times higher in women with obesity or overweight and 9 times higher in patients with serum vitamin D levels less than or equal to 20 ng/mL. All these associations, except less sun exposure 30 minutes a day, were statistically significant according to the Chi-square test.

To avoid confusion, we performed a multivariate analysis using the Cochran-Mantel-Haenzel test. The Chi-square with one degree of freedom was significant with a value of 18,863 (p=0.000014), indicating that the association of breast cancer with low levels of vitamin D was independent of the other variables analyzed.

Discussion

Evidence of the relationship between vitamin D and breast cancer has significantly increased in recent years. Garland and Garland suggested the importance of exposure to solar radiation to explain the geographical variation in the frequency of breast cancer[20]. Although several recent studies identified a low or no relationship between sun exposure and breast cancer in women living in regions with low sun exposure, they also found that lower risk is greater in regions with high solar and intermediate irradiation areas with intermediate sun exposure[8]. Similarly, Ingraham emphasizes that in Norway a positive effect on survival in women with breast cancer diagnosed in summer or autumn has been found, when vitamin D levels are higher[21].

These findings concur with those which have demonstrated decreased synthesis of vitamin D in the winter in regions with low sun exposure in the United States[8]. Therefore, it is noteworthy that in our population we found that very low vitamin D levels (<20 ng/mL) are closely related to breast cancer in a region with considerable sun exposure throughout the year, which contrasts sharply with the control group. In our population, this association was independent of BMI, skin type, exposure habits/sunscreen or intake of vitamin D.

This finding confirms the hypothesis that low levels of vitamin D are associated with the development of breast cancer, but does not explain the cause of these serum levels[22]. Another study in Mexican women, which found a 47% reduction in the risk of developing breast cancer in those with serum vitamin D above 30 mg/mL, attributed low levels of vitamin D to limited sun exposure due to the indoor work activity, to lack of outdoor recreational activity, hyperpigmentation of the skin and because they actively avoided sun exposure[23].

One significant aspect for confirming vitamin D's potential role in the development of breast cancer is that aging and estrogen deficiency are also associated with low vitamin D levels. The former reduces the production of skin cholecalciferol, while the latter decreases the metabolic activation of vitamin D. Therefore, postmenopausal women, predominantly white, with breast cancer are at higher risk of vitamin D deficiency, compared with younger women[24], but equally in this study we found no significant difference related to menopausal status.

Two important findings are expressed in VDR breast tissue and there is a greater disease-free period in women with breast tumors with positive VDR, compared to those with tumors negative VDR[25]. The ligand VDR is the metabolite 1,25-hydroxyvitamin D3 (1,25 $(OH)_2D$), which has important effects on cell growth and differentiation. Laboratory studies have shown that 1,25 $(OH)_2$ D and its analogs inhibit cell proliferation and promote apoptosis in cell culture and animal models of breast cancer, causing delay in tumor development and regression of mammary tumors diagnosed previously[25].

Several polymorphisms of the gene encode the ligand VDR. One of them, identified by restriction enzyme Fokl produces RVD proteins differing in three amino acids. This polymorphism has been associated with increased risk of breast cancer in Afro-American women[10].

Other alterations that generate restrictions on BSML, ApaI and TaqI sites have been associated with alterations in receptor UTR region 3C is important in the control of post transcriptional gene expression. Polymorphisms in this region have also been linked to breast cancer; so that associations are confirmed between breast cancer risk and Apal polymorphism and progression of breast cancer and absence of TaqI genotype BSML with increased risk of metastasis[11].

In our study, we did not find any differences in the detection of the Fokl polymorphism among the two groups, nor did we monitor any prognosis in patients in which this mutation was shown. The number of patients with the mutation was limited and the possible conclusions obtained would not be reliable.

In 2010, the US Institute of Medicine defined as sufficient levels of vitamin D 20 ng/mL; deficiency considered concentrations 12 ng/mL or less and insufficient 12-19 ng/ml[26]. If we rely on these figures, none of our patients would have required any intervention and, as we found a correlation between levels of vitamin D equal to or less than 20 ng/mL with breast cancer. In this respect we agree with Manson et al. that this definition should be revised[27].

Bauer et al.[28] conducted a meta-analysis of prospective studies in which they analyzed the association and ranked them by menopausal status. They hypothesized that differences in condition and a non-linear dose-response relationship could be responsible for the discrepancies[1]. The meta-analysis included 9 prospective studies (published between 1996 and 2011) with 11 databases that evaluated circulating vitamin D levels in patients with breast cancer. 5,206 cases and 6,450 controls were included. Through a complex statistical analysis, they found a boundary relationship between circulating levels of vitamin D and breast cancer (RR for 5 ng/mL=0.99) in postmenopausal women, but not in premenopausal. They also found a flattening of the association at lower levels (27 ng/mL) or higher (35 ng/mL). The decreased risk in the range of 27-35 ng/mL in postmenopausal women was such that increments of 5 ng/mL in vitamin D levels were associated with decreased risk of breast cancer by 12% (RR=0,88 5 ng/mL).

With this study, the authors demonstrated the ability to determine an optimal range of vitamin D plasma levels (27-35 ng/mL) to decrease the risk of breast cancer in postmenopausal women. These findings should now be validated in studies incorporating individual-level data.

Another metanalysis evaluated a dose-response association[29]. This study included data from 15 publications that analyzed the relationship of breast cancer calcium intake in the diet. Seven studies

Table 1. Summary of results

Sun exposure less than 30 minutes a day				
	<30 min/day	>30 min/day		
Breast cancer	9	15	Prevalence in cases	0.63
Controls	15	37	Prevalence in controls	0.71
			Chi-squared=0.24	p=0.625
			Odds ratio	**1.48**
			CI 95%	**0.53-4.11**
			Population attributable risk	0.12
			Attributable risk in exposed	0.81
Deficient vitamin D intake				
	Deficient	Sufficient		
Breast cancer	18	6	Prevalence in cases	0.75
Controls	22	30	Prevalence in controls	0.42
			Chi-squared=5.79	p=0.016
			Odds ratio	**4.09**
			CI 95%	**1.04-11.9**
			Population attributable risk	2.81
			Attributable risk in exposed	3.33
Overweight/obesity				
	BMI >25	BMI 18-24.9		
Breast cancer	18	6	Prevalence in cases	0.75
Controls	21	31	Prevalence in controls	0.59
			Chi-squared=6.55	p=0.01
			Odds ratio	**4.42**
			CI 95%	**1.51-13.1**
			Population attributable risk	3.09
			Attributable risk in exposed	4.12
Very low levels of vitamin D				
	≤20 ng/mL	>20 ng/mL		
Breast cancer	18	6	Prevalence in cases	0.75
Controls	13	39	Prevalence in controls	0.25
			Chi-squared=14.99	p=<0.001
			Odds ratio	**9.0**
			CI 95%	**2.95-27.5**
			Population attributable risk	6.64
			Attributable risk in exposed	0.88

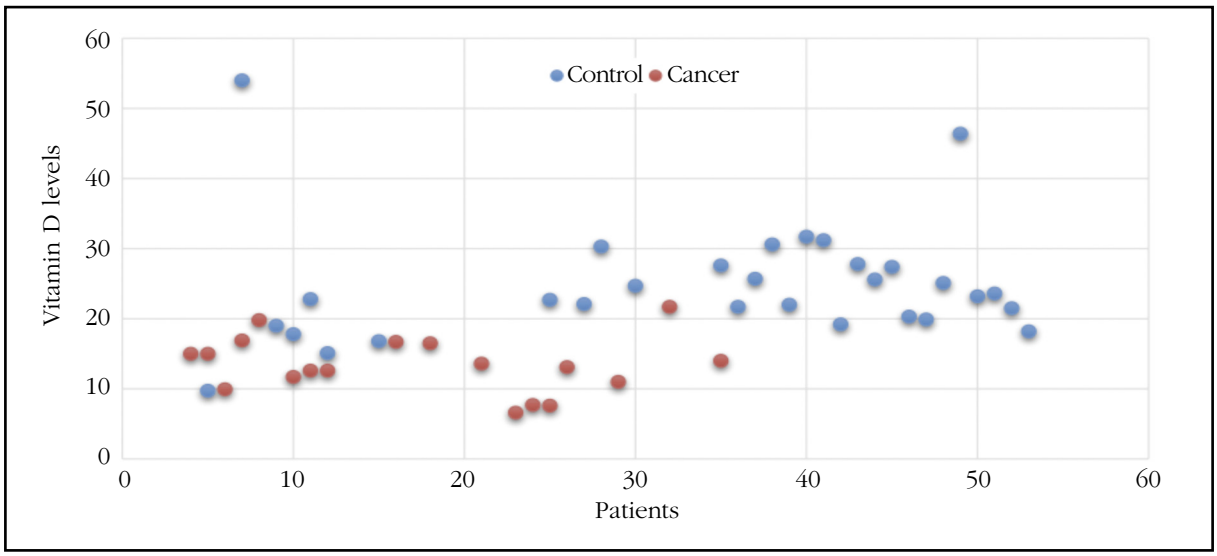
BMI: body mass index; 95% CI: confidence interval of 95%.

examined the association of breast cancer with serum levels of vitamin D and 11 reports where the relationship of this cancer with vitamin D intake were studied showed a linear association between calcium intake, a nonlinear relationship between vitamin D levels or vitamin D intake with the risk of breast cancer.

Chen et al.[29] suggest that women with a high intake of calcium, high vitamin D intake or those with adequate vitamin D serum levels present a lower risk of developing breast cancer.

Whether or not these data are conclusive concerning the association of low levels of vitamin D and breast cancer in all women, the benefits for

Figure 1. Levels of vitamin D in cases and controls



bone health and protection against other chronic diseases associated with adequate vitamin D levels are equally important. We must encourage patients to practice healthy lifestyle habits that help increase levels of vitamin D, such as maintaining healthy weight, avoid smoking, increase physical activity, and appreciate the importance of vitamin D supplements in adults who do not observe these changes in lifestyle.

Competing interests: The authors declare no conflicts of interest.

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