

Original Research Article

Association of level serum 25-hydroxy vitamin D in benign and malignant breast disease in a tertiary care center in North India

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ABSTRACT

Background: The study was to compare 25-hydroxy vitamin D levels in women with benign and malignant breast disease patients to the age-matched controls in a tertiary care center in North India.

Methods: This was a prospective study carried out in the Department of Surgery, S.R.N. Hospital associated with M.L.N. Medical College, Allahabad. The levels of vitamin D are measured by electrochemiluminescence and the serum levels divided into normal, mild, moderate, and severe vitamin D deficiency.

Results: Overall 60 patients were included. 30 was having malignant breast disease and 30 having benign breast disease. On comparing the mean value of serum vitamin D level between malignant breast disease and controls, the serum vitamin D level was found to be lesser in the former group and the difference was highly significant. On comparing the mean value of serum vitamin D level between benign breast disease and controls, the serum vitamin D level was found to be elevated in the former group, the difference was nonsignificant.

Conclusions: Our study supports the hypothesis that vitamin D deficiency is an important risk factor in the development of malignant breast disease. The study was also concluded that vitamin D is not associated with the etiology of benign breast diseases. There is also a possibility of using 25-hydroxy vitamin D as an adjuvant therapy during the treatment of breast malignancy.

Keywords: 25- hydroxy vitamin D, Breast cancer, Vitamin D

INTRODUCTION

Breast cancer is the most common cancer in women worldwide as well as in India. In Indian females with an age-adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. In India during periods 2020 suggests the number of breast cancer patients to go as high as 1,797,900. Proper health awareness and breast cancer screening programs availability and treatment facilities would result in a positive clinical picture in the country.¹ Factors associated with breast cancer are genetic mutation, breast density, age, and nutritional risk factors, family history, reproductive factors, etc.

In India, vitamin D deficiency ranges between 70% and 100%. This review aimed to present the association of vitamin D deficiency with Breast cancer. Given the high prevalence of vitamin D deficiency and a higher incidence of breast cancer in India, interventional possibilities to increase vitamin D status should be done.² In India, the majority of the population is vegetarian and the food items rich in vitamin D are of animal origin. Milk a common source of vitamin D for vegetarians and content of vitamin D in unfortified milk is significantly low (2 IU/100 ml). A recent research study revealed that more than 90% of women with Breast cancer were suffering from vitamin D deficiency. The higher risk of

BC was found to be associated with low serum 25-hydroxy vitamin D levels.

Vitamin D receptor (VDR) is a regulator of bone and calcium homeostasis. It is also associated with cellular differentiation and replication in different target tissues. Association between vitamin D receptor gene polymorphisms and Breast cancer has been investigated by some studies. Studies indicate that VDR poly-A polymorphism is significantly related to Breast Cancer risk in north Indians especially with early-onset disease. Analysis of VDR gene polymorphisms in breast cancer in the Indian population has revealed that some VDR gene polymorphisms (Taq 1 genotypes) are associated with Breast cancer risk. Another study to analyze androgen and vitamin D receptor levels in human (IDC) and benign breast tumors with clinical findings of Breast cancer found no significant correlation between nuclear androgen and VDR expression of the IDC or benign tumors. The possible reason was a high degree of variability in tumor heterogeneity.²

We compared 25-hydroxy vitamin D levels in women with benign and malignant breast disease patients to evaluate the association between the serum 25-hydroxy-vitamin D with benign and malignant breast disease.

METHODS

This was a prospective study carried out in the Department of Surgery, S.R.N. Hospital associated with M.L.N. Medical College, Allahabad from September 2018 to October 2019. All the patients with benign and malignant breast disease aged 18-65 years are part of the study.

The levels of vitamin D are measured by electrochemiluminescence and the serum levels of >35 ng/dl, 25-35 ng/dl, 12.5-25 ng/dl and <12.5 ng/dl is considered as normal, mild, moderate and severe vitamin D deficiency. Serum samples were taken by the laboratory technician from all the patients and refrigerated in -40 degrees centigrade before undertaking the test. No sample was kept for more than four weeks. Levels of vitamin D were measured by the electrochemiluminescence method in all samples in one laboratory.³

Exclusion criteria include the patient who has used any form of vitamin D in the last 2 years, the patient who underwent treatment for osteopenia, osteoporosis, patients with a history of any other cancer, patients with a history of renal failure.

Results are tabulated, analyzed, and subjected to statistical analysis using SPSS version 21. Paired t-test is used to compare the vitamin D deficiency among the 3 study groups. P<0.05 is considered statistically significant.

RESULTS

A total of 60 patients (30 having malignant breast disease and 30 having benign breast disease) who satisfied the inclusion criteria are included in our study and compared with 30 controls.

Table 1: Age distribution.

Age distribution (in years)	No. of cases	Percentage (%)
16 to 30	32	35.56
31 to 40	10	11.11
41 to 50	15	16.66
>50	33	36.67
Total	90	100

On comparing the mean value of serum vitamin D level between malignant breast disease and controls, the serum vitamin D level was found to be lesser in the former group and the difference was highly significant.

Table 2: Serum vitamin D levels (malignant group).

	Mean	SD	P value
Patients	13.20	5.43	0.003
Controls	15.84	9.17	

The mean serum vitamin D levels in the case of malignant breast disease were 13.20 ng/dl while in the case of controls it was 15.84 ng/dl.

On comparing the mean value of serum Vitamin D level between benign breast disease and controls, the serum vitamin D level was found to be elevated in the former group, the difference was nonsignificant.

Table 3: Serum vitamin D levels (benign group).

	Mean	SD	P value
Patients	15.96	7.34	0.28
Controls	15.84	9.17	

The mean serum vitamin D levels in the case of benign breast disease were 15.96 ng/dl while in controls it was 15.84 ng/dl.

On comparing the mean serum vitamin D levels in malignant and benign breast disease the levels were found to be less in the case of the former group.

The mean serum vitamin D levels in the case of malignant breast disease were 13.20 ng/dl while in the case of benign breast disease is 15.96 and the difference is significant (p value is 0.013).

The prevalence of vitamin D deficiency in the study groups is shown in Table 4.

Table 4: Prevalence of vitamin D deficiency in the study groups.

Study group	Severe	Moderate	Mild	Normal	Total
	N (%)	N (%)	N (%)	N (%)	
Malignant	21 (70)	7 (23.33)	2 (6.66)	0	30
Benign	16 (53.33)	10 (30.33)	4 (13.33)	0	30
Control	18 (60)	7 (23.33)	3 (10)	2 (6.66)	30

We also studied the prevalence of vitamin D deficiency in pre and postmenopausal groups including the cases and controls.

Table 5: Prevalence of vitamin D deficiency in pre and postmenopausal group.

Status	Mean vitamin D level (ng/dl)
Premenopausal (n=51)	14.80
Postmenopausal (n=39)	15.23

DISCUSSION

This study is carried out in 60 patients out of which 30 were suffering from malignant breast disease and 30 were having benign breast disease who met the inclusion criteria. In this study we compared the serum 25-hydroxy vitamin D level between malignant group and matched controls, benign group and matched controls as well as malignant group and benign group. We also compared the levels of vitamin D between premenopausal and postmenopausal women including the cases and controls to get the idea of vitamin D deficiency burden among Indian women in north India.

In this study we found out that the value of serum vitamin D level was different than that of matched controls. We found out that the levels of serum vitamin D in malignant cases was lower than the controls and that the study is highly statistically significant ($p < 0.003$).

Yao et al measured the circulating vitamin D levels in 579 patients affected by breast cancer and 574 controls at their institute.⁴ They showed an inverse relationship for breast cancer risk in regard to vitamin D levels.

Chen et al meta-analysis of vitamin D, calcium, and the prevention of breast cancer. In this study data from 11 studies on vitamin D intake, 7 studies on circulating 25-hydroxy vitamin D levels, 3 studies of circulating 1a,25(OH)2D levels, and 15 studies on calcium intake and breast cancer risk were included in this analysis.⁵ Five case-control and six cohort studies were identified that had examined the association between vitamin D intake and breast cancer risk. Of these reports, one study of premenopausal women reported a significant inverse association between vitamin D intake and breast cancer risk, with a p trend value of 0.02. A second study also found a significant inverse association in the pre-

menopausal subgroup ($p \text{ trend} = 0.01$), but no significant association was found in the post-menopausal women when the highest quantile for total dietary vitamin D intake was compared with the lowest quantile.

Four case-control studies and three nested case-control studies examined the relationship between the circulating of 25-hydroxy vitamin D level and breast cancer. Of these seven studies, three examined the circulating 25-hydroxy vitamin D level in pre or peri-menopausal women and five studied the circulating 25-hydroxy vitamin D level and breast cancer risk in postmenopausal women. A significant inverse relationship between circulating 25-hydroxy vitamin D levels and breast cancer risk was found based on the fixed effects model ($OR = 0.66$, 95% $CI = 0.50 - 0.88$) but not under the random-effects model ($OR = 0.69$, 95% $CI = 0.42 - 1.11$), with moderate heterogeneity among the pooled studies ($Q = 5.25$, $df = 2$, $p = 0.0723$; $I^2 = 61.9\%$) in the pre or peri-menopausal women. A marginal inverse association for circulating 25-hydroxy vitamin D levels was found for the post-menopausal women ($OR = 0.60$, 95% $CI = 0.35 - 1.03$), although there was significant heterogeneity among the pooled studies ($Q = 35.7$, $df = 4$, $p = 0.0001$; $I^2 = 88.8\%$).

Bauer et al, plasma vitamin D levels, menopause, and risk of breast cancer dose-response meta-analysis of prospective studies.⁶ A total of 9 prospective studies were included, comprising 5206 cases and 6450 controls. Data were pooled using dose-response random-effects meta-regression models. Identifying nonlinear effects, spline models were optimized for thresholds. The relationship between circulating 25-hydroxy vitamin D and breast cancer risk differed by menopausal status ($p = 0.05$ for effect modification). While no association was found in premenopausal women, dose-response modeling revealed a nonlinear inverse association among postmenopausal women. Notably, a flat association was observed in the lowest range of 25-hydroxy vitamin D levels < 27 ng/ml ($RR = 1.01$ per 5 ng/ml; 95% confidence interval [CI], 0.98-1.04). In contrast, postmenopausal breast cancer risk decreased with 25-hydroxy vitamin D levels 27-35 ng/ml ($p = 0.02$ for nonlinear risk change), where a 5 ng/ml increase in 25 hydroxy vitamin D was associated with a 12% lower risk of breast cancer ($RR = 0.88$ per 5 ng/ml; 95% CI , 0.79-0.97), with suggestive flattening at higher doses 935 ng/ml. The significant inverse association did not appear to vary across strata of invasive or in-situ cases, body mass index adjustment, region, postmenopausal hormone use, or assay method. In

summary, this dose-response meta-analysis of prospective studies of plasma 25-hydroxy vitamin D suggested a breast cancer risk differential by menopause, whereby a step-wise inverse association was observed beyond a threshold of 27 ng/ml, but with flattening of effects above 35 ng/ml, in postmenopausal women. These findings help resolve prior inconsistent findings and may carry important clinical and public health implications.

Mohr et al, serum 25-hydroxy vitamin D and prevention of breast cancer: pooled analysis.⁷ A PubMed search for all case-control studies on risk of Breast cancer by 25-hydroxy vitamin D concentration identified 11 eligible studies. Data from all 11 studies were combined to calculate the pooled odds ratio of the highest vs. lowest quantile of 25-hydroxy vitamin D across all studies.

The present study supports the hypothesis that higher serum 25-hydroxy vitamin D levels reduce the risk of breast cancer. According to the review of observational studies, a serum 25-hydroxy vitamin D level of 47 ng/ml was associated with a 50% lower risk of breast cancer.

Bilinski et al, the results of this observational case-control study conducted in Australia indicate that a 25-hydroxy vitamin D concentration below 75 nmol/l at diagnosis was associated with a significantly higher risk of breast cancer.⁸ These results support previous research which has shown that lower 25-hydroxy vitamin D concentrations are associated with increased risk of breast cancer.

Shaukat et al, this case-control study included 94 female patients aged 20-75 years of any marital status and parity.⁹ Newly diagnosed 42 breast cancer patients who presented to surgical OPD of Dow University Hospital from January 2016 to June 2016 were included in the study as-cases after informed consent. Vitamin D deficiency is very common as shown in their results that 55.8% of controls and 88.7% of breast cancer patients are vitamin D deficient. This study suggests that vitamin D deficiency is associated with the risk of breast cancer.

Comparison of serum 25-hydroxy vitamin D levels between benign breast disease and controls was done in this study. We found out that the value of serum vitamin D level was different than that of matched controls. We found out that the levels of serum vitamin D in benign cases were elevated than the controls and that the study is not statistically significant ($p < 0.28$).

Rohan et al, experimental evidence provides strong support for anti-carcinogenic effects of calcium and vitamin D for breast cancer.¹⁰ Observational epidemiologic data also provide some support for inverse associations with risk. They tested the effect of calcium plus vitamin D supplementation on the risk of benign proliferative breast disease, a condition that is associated with increased risk of breast cancer. They used the Women's health initiative randomized controlled trial.

The 36,282 participants were randomized either to 500 mg of elemental calcium as calcium carbonate plus 200 IU of vitamin D3 (GlaxoSmithKline) twice daily ($n=18,176$) or to placebo ($n=18,106$). Regular mammograms and clinical breast exams were performed. They identified women who had had a biopsy for benign breast disease and subjected histologic sections from the biopsies to standardized review. After an average follow-up period of 6.8 years, 915 incident cases of benign proliferative breast disease had been ascertained, with 450 in the intervention group and 465 in the placebo group. Calcium plus vitamin D supplementation was not associated with altered risk of benign proliferative breast disease overall (hazard ratio=0.99, 95% CI=0.86-1.13), or by histologic subtype. Risk varied significantly by levels of age at baseline, but not by levels of other variables. Daily use of 1,000 mg of elemental calcium as calcium carbonate plus 400 IU of vitamin D3 for almost 7 years by postmenopausal women did not alter the overall risk of benign proliferative breast disease.

CONCLUSION

In this study we found out that there is a severe deficiency of vitamin D among the patients with malignant breast disease this suggests that Serum 25-hydroxy vitamin D is associated with malignant breast disease. So, it may be concluded that Vitamin D may be having some role in the etiology of breast carcinoma and that there is an inverse association of vitamin D levels and malignant breast disease. Our study supports the hypothesis that vitamin D deficiency is an important risk factor in the development of malignant breast disease.

We also concluded that vitamin D is not associated with the etiology of benign breast diseases. There is also a possibility of using 25-hydroxy vitamin D as an adjuvant therapy during the treatment of breast malignancy.

More research is needed to confirm these findings to understand the role of vitamin D in carcinogenesis and also using it as a treatment modality in the management of breast malignancy in the future.

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