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A STUDY OF CORELATION OF SERUM VITAMIN D AND VITAMIN B12 LEVELS IN PATIENTS WITH CARCINOMA BREAST

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Abstract
Background: Numerous studies have shown that vitamins reduce the risk of cancers, but the relationship between serum vitamin levels of vitamin D and B12 in breast cancer is still controversial. In this study, we evaluated serum levels of vitamin D and B12 in Haryana, India among patients with carcinoma breast and investigated their association with clinical and laboratory parameters. **Aims and Objectives**: The study aimed to estimate and correlate the serum vitamin D and vitamin B-12 levels in patient with diagnosed carcinoma breast and in control subjects. **Materials and Method:** The present study comprises 60 subjects of both pre and post menopause women whom 30 are healthy controls and 30 are clinically confirmed cases of Breast Cancer, with an age group ranging from 38 to 70 years. Serum Vitamin D and B12 were estimated by ELISA Method. **Results:** The levels of vitamin D in serum was significantly ($P > 0.05$) low in clinically diagnosed breast Cancer patients (9.96 ± 2.45ng/dl) as compared to age and gender-matched healthy control subjects (24.54 ± 6.22ng/dl) and Serum vitamin B12 was significantly ($P > 0.05$) high in clinically diagnosed breast Cancer patients (1163.83 ± 135.77ng/dl) as compared to healthy control subjects (645.43 ± 134.22ng/dl). **Conclusion:** Many studies have shown that vitamin deficiency can be the primary cause of breast cancer. The current cogitation proved that raised serum Vitamin D and B12 are linked with the pathogenesis of autoimmune abnormal masses in Breast. It seems that Vitamin B12 level was no significant High and vitamin D levels are significantly low in the cases of Breast cancer.

KEY WORDS: Breast Carcinoma, Vitamin D, Vitamin B12

Introduction

Breast cancer has been considered the most common type of cancer among women in 161 countries, and the most common cause of cancer deaths, within 98 countries.[1] The known and well-established risk factors for breast cancer include age, family history, the density of breast tissue, parity, overweight, alcohol intake, and genetic risk factors such as BRCA mutations.[2] Breast cancer is the most common female cancer worldwide representing nearly a quarter (23%) of all cancers in women [3,4]. The global burden of breast cancer is expected to cross 2 million by the year 2030, with growing proportions from developing countries [5].

Although age-standardized incidence rates in India are lower than in the United Kingdom (UK) (25.8 versus 95 per 100,000), mortality rates are nearly as high (12.7 versus 17.1 per 100,000, respectively)

as those of the UK [3]. Breast cancer incidence rates within India display a 3–4-fold variation across the country, with the highest rates observed in the Northeast and in major metropolitan cities such as Mumbai and New Delhi [6]. Reasons for this variation include differences in demographic (e.g., education), reproductive (e.g., age at first child and number of children), anthropomorphic (e.g., adipose) and lifestyle factors (e.g., tobacco smoking and alcohol use).However, studies have suggested that vitamin D supplementation significantly reduces the mortality rate of cancer, but does not reduce the overall cancer incidence[7]. Breast cancer is the most common cancer in the world, and its occurrence, development and prognosis prediction are also closely related to multivitamins . Women with low vitamin D levels in their bodies have a higher risk of breast cancer. The higher the vitamin D level, the better the prognosis of breast cancer patients and the lower the risk of death[8].

Vitamins B are also closely related to breast cancer, but the conclusions on the relationship with breast cancer are inconsistent. Studies have shown that appropriate supplementation of folic acid and vitamin B12 has a protective effect on BRCA - related breast cancer, especially in BRCA1 mutation carriers[9]. However, in a nested case study, it was found that plasma vitamin B12 compared with the highest quintile and lowest quintile breast cancer, the risk of breast cancer increased by 64% (95% CI 1.17-2.29, P value = 0.02), the higher the level of vitamin B12 in plasma, the higher the risk of breast cancer.

The association between elevated B12, D and Breast cancers is of great value, because it could be used as biological marker for screening for breast cancers. This requires that this association be independent of other causes of elevated B12. The main objective of our study was to confirm the association between elevated B12, D and Breast cancers.

Materials and Method

The study was conducted in NCMCH, Department of General Surgery. Ethical clearances were obtained and written informed consent was taken from all the cases and controls, before carrying out the study.

Subject Selection

The present study comprises 60 subjects of both pre and post-menopause women whom 30 are healthy controls and 30 are clinically confirmed cases of Breast Cancer, with an age group ranging from 35 to 70 years. We included breast cancers from stage 0 to stage 4 based on TNM classification. The patients under treatment were also included as cases. Patients with renal failure and other malignancies have been excluded from this study.

Sample Collection

Overnight fasting 5 ml of blood was drawn from the antecubital vein of all the study participants.

Sample Analysis

Serum separated from 5 ml blood in a plain vial after centrifuging at 3000 rpm. The ELISA Reader method analyzed serum Vitamin D and B12 parameters using standard kits.

Statistics Analysis

Mean ± SD was calculated for all the parameters of interest and were differentiated by Student's t-test using SPSS 16. P-values considered significant were as follows: – $P < 0.05$– a Significant and $P > 0.001$ –a highly Significant.

Results

The table shows the difference in the mean level of Serum vitamin D was significantly ($P > 0.05$) deficient in clinically diagnosed breast Cancer patients (9.96 ± 2.45ng/dl) as compared to age-matched healthy control subjects (24.54 ± 6.22ng/dl) and Serum vitamin B12 was significantly ($P > 0.05$) raise in clinically diagnosed breast Cancer patients (1163.83 ± 135.77ng/dl) as compared to age-matched healthy control subjects (645.43 ± 134.22ng/dl) found to be statistically significant.

Table No. Comparison of serum Vitamin D and B12 levels between controls and patients.

Parameter	Control subject (n=110) Mean ±SD	Breast Cancer subject (n=90) Mean ± SD	P- value

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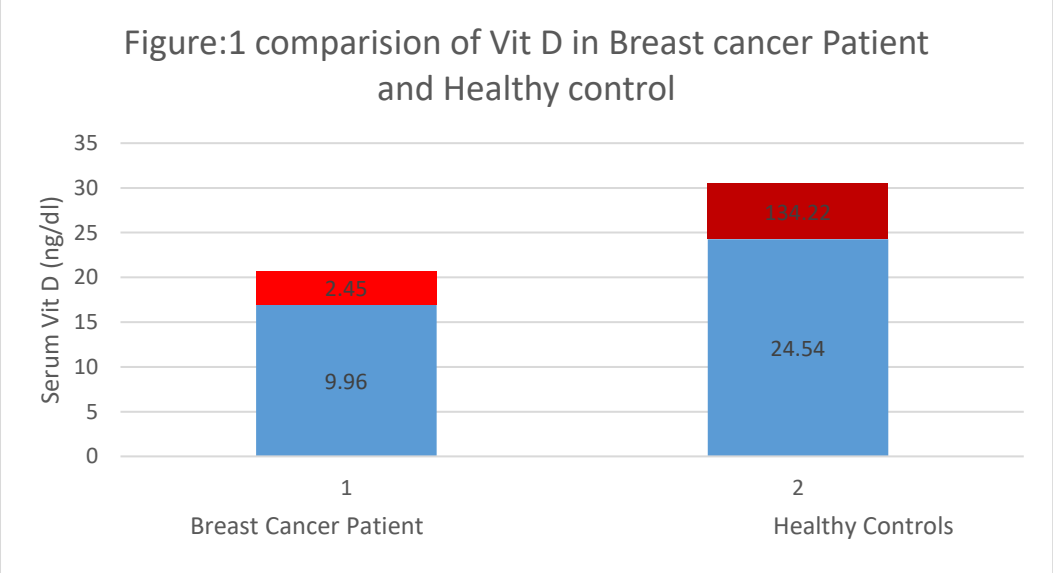
Vitamin D (ng/ml)	24.56 ± 2.45	24.54 ± 6.22	0.000
Vitamin B12	645.93 ± 134.22	1163.83 ± 135.77	0.000

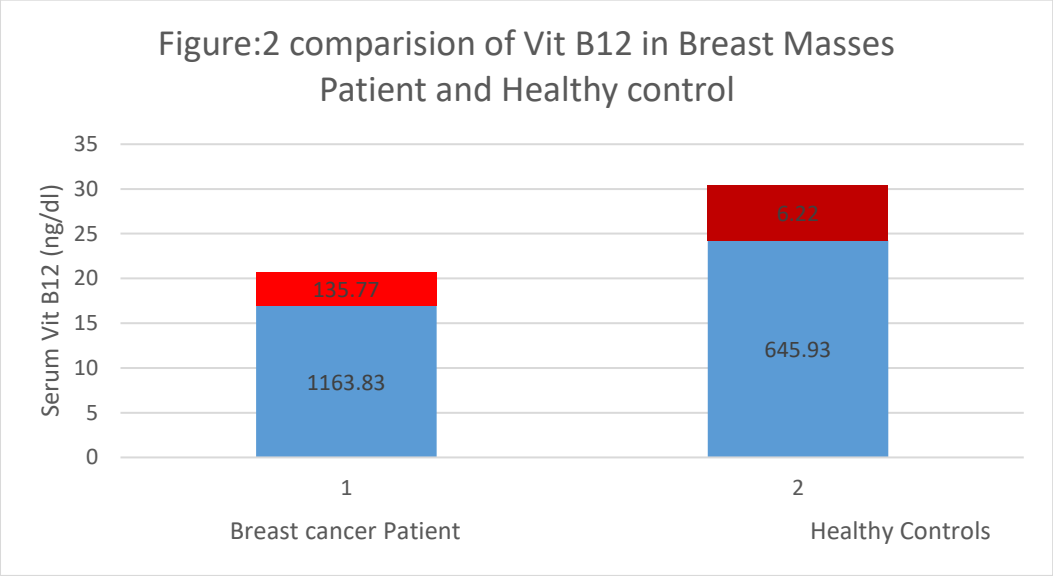
One-Sample Test

	Test Value = 0					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
vitamin D case	22.202	29	.000	9.96333	9.0455	10.8812
vitamin D control	21.608	29	.000	24.54667	22.2232	26.8701

One-Sample Test

	Test Value = 0					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
case	46.949	29	.000	1163.83333	1113.1330	1214.5337
control	26.358	29	.000	645.93333	595.8132	696.0535





The table showing the Vitamin B12 level is significantly higher in Breast Cancer patients who were suffering from the disease and Vitamin D level is significantly lower in Breast Cancer patient.

DISCUSSION

This comparative study was done to analyze the Vitamin D and B12 in Breast cancer patients and compare with that of controls. In this cross-sectional study, a total of 60 subjects were taken, of which 30 were diagnosed breast Cancer patients and 30 were age, pre and post menopausal matched controls. A comparative study showing that Serum vitamin D was significantly ($P > 0.05$) deficient in clinically diagnosed breast Cancer patients (9.96 ± 2.45) as compared to age matched healthy control subjects (24.54 ± 6.22) and Serum vitamin B12 was significantly ($P > 0.05$) raise in clinically diagnosed breast Cancer patients (1163.83 ± 135.77) as compared to age matched healthy control subjects (645.43 ± 134.22).

Breast cancer is the most common female cancer worldwide including India, where advanced stages at diagnosis, and rising incidence and mortality rates, make it essential to understand cancer literacy in women. We conducted a literature review to evaluate the awareness levels of risk factors for breast cancer among Indian women and health professionals

In this study, we measured serum levels of vitamins in Indian female patients with breast cancer or benign breast disease, and in healthy controls. The present study is one of only a few studies to investigate serum levels of multiple vitamins and to examine the association between serum levels of vitamins and breast cancer in an Indian population. As previously reported, our study results showed that patients with breast cancer were considered to be more frequently obese than healthy controls or patients with benign breast disease. Obesity increases the risk of postmenopausal breast cancer since adipose tissue enhances the mammary estrogen signaling pathway. In addition, several studies found that adipose tissue sequesters vitamin D and leads to relatively low serum vitamin D levels in obese people. However, the consistency of the role of vitamin D as a mediator on the link between obesity and cancer is still low [10]. The relationship between obesity, vitamin D, and cancer risk needs to be further studied. Numerous studies have proposed that vitamins have protective effects against breast carcinogenesis, but results have been inconsistent. Results of previous research into the roles of vitamins in breast cancer are summarized in Table.

A summary of previous studies of vitamin status in patients with breast cancer.

Study of vitamin	Region	No. Of cases	observation	References
Vitamin D	USA	701/724	High levels of vitamin D were associated with lower BC risk, but this was not statistically significant (25(OH)D, RR = 0.73, 95% CI = 0.49–1.07, N.S.; 1,25(OH)2D, RR = 0.76, 95% CI = 0.52–1.11, N.S.).	Bertone-Johnson, 2005

Vitamin D	USA	1005/1005	No inverse association between vitamin D levels and BC risk (25(OH)D, RR = 1.04, 95% CI = 0.75–1.45, N.S.; 1,25(OH)2D, RR = 1.23, 95% CI = 0.91–1.68, N.S.).	Freedman, 2008
Vitamin D	USA	1026/1075	Mean vitamin D levels were significantly lower in BC patients than in controls ($p < 0.0001$). There was an inverse association between vitamin D and BC risk in a concentration-dependent manner ($p = 0.002$).	Crew, 2009
Vitamin D	Germany	1394/1365	Vitamin D Germany 1394/1365	Abbas, 2008
Vitamin D	Pakistan	90/90	Significantly lower vitamin D levels in BC patients than in controls ($p < 0.001$). However, no significant association between tumor characteristics and vitamin D levels among BC patients.	Imtiza, 2012
Vitamin D	Korea	310 b	Vitamin D deficient individuals (<20 ng/mL) had increased risk of recurrence compared with those with sufficient vitamin D levels (30–150 ng/mL) ($p = 0.002$). Inverse association between vitamin D levels and prognosis of BC in luminal A ($p = 0.012$) and luminal B subtypes ($p = 0.023$), but no association with prognosis of BC in HER2(+) or TN subtypes.	Kim, 2011
Vitamin D	USA	194/194	Significantly lower vitamin D levels in BC patients than in controls ($p = 0.02$). Patients with sub optimal vitamin D levels (<32 ng/mL) had significantly higher risk of having ER(-) (OR = 2.59, 95% CI = 1.08–6.23) and TN (OR = 3.15, 95% CI = 1.05–9.49) BC than those with optimal vitamin D levels (≥32 ng/mL). BC patients with a basal-like subtype had lower vitamin D levels than BC patients with a luminal subtype ($p = 0.04$).	Peppone, 2012

Vitamin D is the most widely investigated vitamin in terms of breast cancer. The importance of vitamin D in breast cancer patients has been emphasized because calcitriol, the active metabolite of vitamin D, is known to have anti proliferative effects by activating apoptotic pathways and inhibiting pathogenesis. vitamin D receptor (VDR) genes were reported to increase breast cancer risk.[11] Several molecular breast cancer subtypes have been identified: luminal A and B (accounting for 50%-60% of breast cancer cases), basal-like or triple-negative (10%-20% of breast cancer cases) and human epidermal growth factor receptor 2 (HER2)-enriched (10%- 15% of cases).[12] Vitamin D receptor genes operated by vitamin D have important roles in the mammary gland through the regulation of calcium transport during lactation, hormone differentiation, and milk production.[13] Many efforts and enormous research have been directed toward identifying vitamin D as a breast cancer risk factor to be targeted for cancer prevention. This is because circulating vitamin D levels (levels ≥45ng/mL)]may protect against breast cancer [14]

Many studies examined the association between vitamin D level and breast cancer risk, which generally show an inverse association. The meta-analysis conducted by Chen et al11 revealed that women with the highest quartile of circulating 25(OH)D was associated with a 45% (odds ratio [OR]=0.55, 95% confidence interval [CI]=0.38-0.80) decrease in breast cancer risk when compared with those women with
the lowest quartile of blood 25(OH)D. Another meta-analysis of nested case-control studies found a step-wise inverse association beyond a threshold of 27ng/ml, but with flattening of effects above 35ng/ml, in postmenopausal women but not in premenopausal. The meta-analysis conducted by Ordóñez-Mena et al showed increased breast cancer risk with higher 25(OH)D concentrations. The different finding of this study from the previous other meta-analysis studies may be explained by different settings, different enrolled populations, and differences in the adjusted levels. The study by Ordóñez Mena et al enrolled cohort data from European population based cohort studies, whereas the previous studies enrolled nested case-control studies conducted in the United States with different adjustments for con-founders. The inverse association between vitamin D level and breast cancer risk was also shown in pooled and review studies. Mohr et al reported in their pooled analysis of case-control studies that individuals in the highest quintile versus the lowest quintile of 25(OH)D concentrations had a reduction in breast cancer risk, in which serum 25(OH)D level of 47ng/ml was associated with a 50% lower risk of breast cancer.

Similar inverse association was also reported by Stoll et al in their systematic review of 37 studies. They suggested that elevated serum 25(OH)D through the sun exposure and dietary intake more than 400 IU per day vitamin D supplementation decreased breast cancer risk and recurrence. Similar findings were also reported by Shekarriz-Foumani et al in their systematic review who reviewed [16] studies and found that serum 25(OH)D deficiency has been very prevalent among breast cancer neoplasms.
For breast cancer–controlled studies, case-control studies consistently find an inverse correlation between 25(OH)D and breast cancer risk.[17,18] Bilinski et al showed that 25(OH)D concentration below 75nmol/L at diagnosis was associated with a significantly higher risk of breast cancer. Compared with subjects with sufficient 25(OH)D concentration, the ORs of breast cancer were 2.3 (95% CI = 1.3-4.3), 2.5 (95% CI = 1.6- 3.9), and 2.5 (95% CI =1.6-3.8) for subjects categorized as severely deficient, deficient, or insufficient vitamin D status, respectively Other studies have found similar reduction in the risk for breast cancer. Park et al16 found that serum 25(OH) D less than 20ng/mL was associated with 27% increased risk of breast cancer. Similar results have been reported by Colagar et al and Bertrand et al Reimers et al and Kim et al The prevalence of vitamin D deficiency in breast cancer population has ranged from 23% to 95.6%.4 Jamshidinaeini et al found that women in the fourth quartile of serum 25(OH)D level had 3 times lower risk of developing breast cancer compared with those in the first quartile. Inverse association was only seen in premenopausal women (OR=0.25; 95% CI =0.094-0.687). They also found that dietary intake of vitamin D was inversely associated with breast cancer risk (OR fourth quartile versus first quartile= 0.39; 95% CI =0.196-0.784), and this inverse association remained significant after adjusting for the confounding factors.18 Similar results were reported by Shaukat et al who studied 42 newly diagnosed breast cancer cases and 52 controls. They found that serum vitamin D levels were significantly lower in cases (85.7%) compared with controls (55.8%). The unadjusted and adjusted ORs for breast cancer in cases and controls showed a statistically significantly increased risk of breast cancer. After adjustment for age, parity, body mass index, sun exposure, economic status, and education status, the OR (95% CI) for breast cancer risk was 7.8 (1.99- 30.58) for women with vitamin D concentrations less than 20ng/mL.

In our study, plasma vitamin B12 ≥ 1000 ng/L was observed in patients. This confirmed that the incidental finding of elevated B12 is not uncommon, even in departments with no specific recruitment of patients with liver or malignant diseases. This finding was slightly lower than that reported in previous studies, including among inpatients with frequencies ranging from 10 to 15% [35,36]. Lower prevalence of elevated B12 was observed in the general population: 3.5% of the population had a B12 > 813 ng/L in the British registry [19], and 6.6% of the population had a B12 > 1084 ng/L in the Danish registry [20]. The differences between these studies may be explained by variations in the recruitment (mean age, inpatients or outpatients, studied departments) and the threshold defining the status of elevated B12.

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In our study, we evaluated this association at highly significant. We showed that the association with cancers, especially metastatic ones, tended to increase with increasing B12 levels. The prognostic value of elevated B12 in breast cancers was already emphasized, and a one-year survival rate was reported in patients with breast cancer of 62.3% in cases with B12 levels between 200 and 600 pmol/L, 49.6% between 600 and 800 pmol/L and 35.8% above 800 pmol/L ($p < 0.0001$) [40]. While the patho physiological explanation of an elevated B12 for breast cancers is not elucidated, some authors think that B12 elevation could be secondary to the inflammation induced by the anti tumor immune response, with plasma haptocorrin release (trans coalmines I and III) by the inflammatory cells [21,22,23]. However, a direct link with tumor mass is not excluded. In the absence of a consensus on the threshold that findings an abnormal elevated B12, we chose the symbolic value of 1000 ng/L, defined as the upper normal limit of our test.

High serum vitamin B12 levels *vs* low levels were not significantly associated with the risk of breast cancer and no significant association was found in the subgroup analysis by menopausal status. Only one study (Lin et al, 2008) provided the association of serum vitamin B12 levels with the risk of breast cancer by ER status and PR status; thus, the subgroup analysis by ER status and PR status was not conducted. Among the four studies included, one study (Lin et al, 2008) adjusted for the most known risk factors of breast cancer, and women in the highest quintile relative to those in the lowest quintile had multivariate RR of 1.29 (0.92–1.82). The result from the other three studies indicated an obvious protection of serum vitamin B12 levels on risk of breast cancer (0.61 (0.41–0.92), P=0.02, $I2$=22.3%).. It would be therefore interesting to assess the association between breast cancers and elevated B12 based on persistent elevated B12 levels. In the absence of therapeutic cancer management, increases in B12 would persist in cases of underlying cancer. The retrospective character of our study limited the interpretation of the time sequence of events, especially the causality link between so breast cancers and elevated B12.Our research provides basic results for future research to further prove the role of B12 vitamins in the occurrence and development of breast cancer.

Conclusion

In conclusion, we assessed serum concentrations of multiple vitamins or vitamin biomarkers in Indian breast cancer patients, benign breast disease patients, and healthy controls using established methodologies. Patients with breast cancer as well as patients with breast Cancer disease had lower concentrations of vitamins D and higher frequencies of vitamin B12 than healthy controls. Moreover, tumor sub types known to develop more aggressively and have poorer outcomes were associated with reduced levels of vitamin D, suggesting potential sub type-specific roles and impacts of vitamins in breast cancer. Our study provides important background information regarding the potential effects of vitamins in breast cancer.

Conflict of interest:

No existence of conflict of interest among the authors of the study.

Strength and Limitations of the Present Study

There are a few limitations of the study. In the present study, only 38–70 years ages subjects participated in the research. Hence, in the feature, we would like to include an increase in a number of participants to reach a concrete conclusion. The present study was given an impact to understand about the increased concentration of the deficiency of vitamin D and toxicity of vitamin B12 is involved in the Breast Carcinoma.

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