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THE SERUM VITAMIN D LEVELS AND BREAST CANCER : IS THERE ANY ASSOCIATION?

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ABSTRACT:
Breast cancer has emerged as a significant public health concern in India, with its incidence rising steadily over the past few decades. As the most common cancer among women in the country, it poses substantial challenges to the healthcare system and profoundly affects the lives of countless individuals and families (1) According to the GLOBOCAN 2020 data, breast cancer accounted for 27.7% of all new cancer cases and 23.5% of all cancer 1 related deaths among women in India. The age-standardized incidence rate of breast cancer in India is estimated to be 25.8 per 100,000 women, lower than in many Western countries but steadily increasing (2).

INTRODUCTION
The complex interplay of genetic, environmental, and lifestyle factors contributing to breast cancer development and progression necessitates a multifaceted approach to research, prevention, and treatment. In recent years, there has been growing interest in the potential roles of various biomarkers in breast cancer pathogenesis, diagnosis, and prognosis. Among these, serum ferritin and vitamin D have garnered considerable attention due to their involvement in crucial physiological processes and their potential implications in cancer biology(3). The potential role of vitamin D in cancer has been a subject of intense research in recent years. Several mechanisms have been proposed to explain the potential anti cancer effects of vitamin D, including cell cycle regulation, promotion of cell differentiation, induction of apoptosis, inhibition of angiogenesis, immune modulation, and anti-inflammatory effects. In the context of breast cancer, numerous studies have investigated the relationship between vitamin D status and various aspects of the disease, including risk, prognosis, and treatment response(4). This comprehensive study aims to investigate the relationship between vitamin D levels in breast cancer patients in India.

METHODOLOGY
Our study was prospective observational study conducted at tertiary care center at Udaipur, Rajasthan from Janauary 2024 to Jan 2025. Patients were informed regarding the aims and objectives of the study and detailed informed written consents were taken prior to inclusion into this study. The data was collected in a specially designed standardized proforma containing details of clinical history, clinical examination, laboratory investigations, radiological findings and type of management. A prospective observational study will be done indoor admitted patients of breast cancer in tertiary care hospital, after obtaining approval from I.E.C (RNT/ACAD/IEC/2024/73). Data analysis done using Stata version 15.0

INCLUSION CRITERIA:
1) Patients of diagnosed Carcinoma Breast.

EXCLUSION CRITERIA:
1. Patients receiving any oncology treatment including hormone therapy, chemotherapy, radiotherapy and surgery.
2. History of chronic or rheumatic diseases and other malignancies 25
3. History of acute inflammation
4. Patients on medications such as iron, levothyroxine and vitamin D supplement a few months before.

Sampling and Processing Methods:
Under all aseptic condition, blood sample were drawn by venipuncture method and collected in a clean plan blood vial. The blood sample was sent to biochemistry laboratory where vitamin D was estimated by spectrophotometrically using their diagnostic kits.
Diagnostic methods used for vitamin D: The ectrochemiluminescence for vitamin D. Normal value of serum vitamin D according to this method is 20-32 ng/ml.

RESULTS:

The mean age of presentation was 50.56±4.81 years. The age of females in the study was in the range of 26 to 80 years, with majority belonging to age group 51-60 years (33.75%), followed by 30% of females between 41- 50 years, about 16.2% of females presented between 31-40 years and 10% of females between age 61-70 years.

All the patients included in this study attained menarche by 15 years of age. A majority of females (n=64, 80%) gained menarche by 13 years of age. Out of these 64 patients, thirty six females reached menarche by 12 years of age. Only a small proportion of females (n=16, 20%) had gained menarche between 13 to 15 years. Out of eighty patients, fifty females had attained menopause (62.5%), and the remaining thirty were premenopausal (37.5%).

Only a small population (5%) presented at extremes of age (21- 30 years and 71 years). Out of eighty cases fifty one (63.75%) had lump in left breast and twenty nine (36.25%) had lump on right side. All the patients in this study had complaints of lump in the breast; next common complaint was lump in breast with pain. A large number of patients also presented with history of lump in breast with skin changes and retraction of nipple. Some patients also complained of discharge from nipple and weight loss.

Most of the patients presented with a mass in the upper outer quadrant (n=41. 51.25%). Out of eighty, sixteen cases (20%) had involvement of multiple quadrants. Fifteen patients had mass in the upper inner quadrant; four patients had mass in the lower outer quadrant and rest four in the lower inner quadrant.

The serum Vitamin D levels distribution among 80 breast carcinoma patients. A significant majority, 53 patients (66.25%), exhibited low Vitamin D levels below 20 ng/mL. Only 27 patients (33.75%) had normal Vitamin D levels between 20-32 ng/mL. These findings suggest that Vitamin D deficiency is prevalent in this group of breast cancer patients, with two-thirds of the study population showing below-normal levels.

Table 1 **Distribution of serum Vitamin D level in breast carcinoma patients**

Sr. VITAMIN D	NO. OF CASES	%
NORMAL (20-32ng/ml)	27	33.75%
LOW (<20ng/ml)	53	66.25%
Total	80	100%

DISSCUSION:

Breast cancer has emerged as a significant public health concern in India, with its incidence rising steadily over the past few decades. As the most common cancer among women in the country, it poses substantial challenges to the healthcare system and profoundly affects the lives of countless individuals and families(1). The complex interplay of genetic, environmental, and lifestyle factors contributing to breast cancer development and progression necessitates a multifaceted approach to research, prevention, and treatment.

Vitamin D, the other key biomarker examined in this study, is a fat-soluble steroid that plays a crucial role in calcium homeostasis and bone metabolism. However, its biological functions extend far beyond skeletal health, with increasing evidence suggesting its involvement in various physiological processes and disease states, including cancer.13 Vitamin D can be obtained through diet, supplements, or synthesized in the skin upon exposure to UVB radiation(5). The potential role of vitamin D in cancer has been a subject of intense research in recent years. Several mechanisms have been proposed to explain the potential anti cancer effects of vitamin D, including cell cycle regulation, promotion of cell differentiation, induction of apoptosis, inhibition of angiogenesis, immune modulation, and anti-inflammatory effects. In the context of breast cancer, numerous studies have investigated the relationship between vitamin D status and various aspects of the disease, including risk, prognosis, and treatment response(4).

However, the relationship between vitamin D and breast cancer is complex and may be influenced by various factors, including genetic polymorphisms in vitamin D metabolism pathways, body mass index, and other 3 lifestyle factors(6,7). Factors such as skin pigmentation, cultural practices affecting sun exposure, dietary habits, and the high prevalence of vitamin D deficiency in India may influence vitamin D status and its potential associations with breast cancer in ways that differ from Western populations(8).

Estebanej et al (Spain, 2018) conducted a meta-analysis based on published observational studies to evaluate the association of vitamin D intake and blood vitamin D levels with breast cancer susceptibility. PubMed, EMBASE, and Web of Science databases were searched up to January 2019. The pooled odds ratio (OR) and 95% confidence intervals (CIs) were extracted to estimate the risk. We identified 70 relevant studies on blood vitamin D levels (50 studies) and vitamin D intake (20 studies), respectively. Linear and nonlinear trend analyses were performed and showed that an increase in blood vitamin D levels by 5 nmol/l was associated with a 6% decrease in breast cancer risk (OR = 0.94, 95% CI = 0.93–0.96). Similar results were obtained for premenopausal (OR = 0.96, 95% CI = 0.93–0.99) and postmenopausal women (OR = 13 0.96, 95% CI = 0.94–0.98). The pooled OR of breast cancer

risk for a 400IU/day increase in vitamin D intake was 0.97 (95% CI = 0.92–1.02). In conclusion, we found that breast cancer risk was inversely related to blood vitamin D levels; however, no significant association was observed in vitamin D intake(9).

Vaibhav et al (Uttar Pradesh, 2020) 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. 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. 15 This 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 etiogenesis 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(10).

V. A. Belgaumkar et al (Maharashtra, 2021) A cross-sectional study was conducted on 100 adult non-pregnant women with CTE to document serum ferritin, B12 and vitamin D levels in an attempt to validate their role as biochemical markers using Statistical package for social sciences (SPSS) version 25:0 and Fisher's exact test. Mean ferritin level was 31.17 ng/dL. 23% patients had serum ferritin levels lower than the normal range (13- 150 ng/dL). Vitamin D levels (normal range 5.2-60.4 ng/ml, mean 21.41 ng/ml) were low (deficiency range) in 2%. Vitamin B12 levels (normal range 191-663 pg/ml, mean 239.79) were low in 35.7% patients. Other parameters like duration, family history, past history of treatment did not demonstrate any statistically significant correlation. This study detected low levels of serum ferritin and vitamin B12 in approximately one-fourth and a third of females with chronic telogen effluvium respectively with vitamin D deficiency found in only a small proportion. Although a statistically significant correlation could not be established between these nutrients and participant age or other parameters; we concur with most authors who recommend that all females with diffuse hair loss deserve a thorough screening for nutritional deficiencies to facilitate prompt recognition and timely supplementation(11).

Pedram Fadavi et al (Iran, 2021) This study consisted of two groups, the first group comprising patients diagnosed with breast cancer before undergoing any treatment and the second group as control were healthy people. Serum ferritin and vitamin D levels were measured. Pathological information of the patient's tumour, including ER, HER2, KI67, lymph vascular invasion, and disease stage, were collected as well. Data were analysed by IBM SPSS advanced statistics version 23.0 (SPSS Inc., Chicago, IL). P-value of ≤0.05 was considered significant. Eighty-eight subjects were enrolled in this study, 29 (33%) breast cancer patients and 59 (67%) healthy women. In breast cancer patients, serum ferritin levels were 106.55±111.25, which were higher than healthy women's serum ferritin 52.71±36.95 (p=0.083). Furthermore, 18 (66.7%) of breast cancer patients and 55 (93.2%) of healthy women had low serum ferritin levels (p=0.001), 3 (11.1%) patients in the cancer group had serum vitamin D deficiency, while all subjects in the control group had serum vitamin D higher than 10 ng/dl (p=0.009). In conclusion, this study showed that there is a significant relationship between breast cancer and increased ferritin, but no significant relationship was found with vita- min D plus ferritin levels in pathological tumour parameters such as tumour stage, LVI, ER, HER2, and KI67, also vitamin D deficiency was more in the breast cancer group. Future studies with more cases are highly recommended(12).

. Ziyi Li et al (Taiwan, 2021) MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, and abstracts of three major conferences were searched (up to December 8, 2020). Parallel randomized controlled trials (RCTs) examining the efficacy of vitamin D 17 supplementation on risk of breast cancer or change of mammography compared with placebo in females were included. Data were meta-analysed using a random-effects model. Bayesian meta-analysis was conducted to synthesize the results using data from observational studies as priors. Seven RCTs were identified for effect of vitamin D on risk of breast cancer, with 19,137 females included for meta-analysis. No statistically significant effect of vitamin D on risk of breast cancer was found in classical random-effects meta-analysis (risk ratio = 1.04, 95% confidence interval: 0.84–1.28, p = 0.71). When Bayesian meta analyses were conducted, results remained non-significant. There was no statistically significant effect of vitamin D on mammography density observed: mean difference = 0.46, 95% confidence interval: −2.06 to 2.98, p = 0.72. There is insufficient evidence to support the efficacy of vitamin D supplementation in breast cancer risk and change in mammography density. The protective effect of vitamin D on the risk of breast cancer from previous observational studies may be overestimated(13).

Miriam et al (Spain, 2024) This was an integrative review of the medical literature on the impact of vitamin D and its supplementation in the prevention of breast cancer. It generated a minimum serum vitamin D level by focusing on five published studies (three case-control studies, a combination of randomized clinical trials and prospective cohort, and a meta-analysis) on vitamin D levels influencing breast cancer prevention and computing a simple mean and standard deviation (using the square root of the mean). Vitamin D serum levels of ≥ 40.26 ± 14.19 ng/mL may exert a protective effect against breast cancer. 18 This value is double the standard level of vitamin D deficiency (< 50 nmol/L or 20 ng/mL). Overall, 30% of adults are estimated to have vitamin D deficiency. A randomised trial of > 35,000 women over a 20-year period has found that supplementation with a

minimum of vitamin D (400 IU) and calcium (1000 mg) vs placebo reduces the risk for ductal carcinoma in situ of the breast.

CONCLUSION:

In our study, the serum Vitamin D levels were distributed among 80 breast carcinoma patients. A significant majority, 53 patients (66.25%), exhibited low Vitamin D levels below 20 ng/mL. Only 27 patients (33.75%) had normal Vitamin D levels between 20-32 ng/mL. These findings suggest that Vitamin D deficiency is prevalent in this group of breast cancer patients, with two-thirds of the study population showing below-normal levels.

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