Original Article

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Association of Serum Vitamin D with Risk of Breast Carcinoma: An Observational Case-control Study from Western Maharashtra, India

Oncology Section

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ABSTRACT

Introduction: Breast carcinoma is one of the most prevalent types of carcinoma and the leading cause of death among all carcinomas. Recently, vitamin D deficiency has been reported as a risk factor for breast carcinoma. Vitamin D, as an anticarcinoma agent, prevents cellular differentiation, stimulates cell death, reduces angiogenesis, tumour progression, and metastasis.

Aim: To investigate the relationship between vitamin D deficiency and the risk of breast carcinoma.

Materials and Methods: An observational study was conducted at the Armed Forces Medical College, Pune, Maharashtra, India, between November 2018 and October 2020. A total of 57 cases diagnosed with breast carcinoma and 57 healthy controls were analysed. Physical and reproductive health parameters were compared, along with vitamin D status using student's t-test and Mann-Whitney U test. Logistic regression was used to assess the risk of breast carcinoma.

Results: Out of 114 women, 57 were cases and 57 were controls with a mean age of 52 vs 48 years. The mean value of serum vitamin D levels was significantly lower (19.45 vs 27.91 ng/mL, p<0.001) than controls. The percentage of serum Vitamin D deficiency was significantly higher in cases (28 (49.1%) vs 12 (21.1%), p<0.001) compared to controls. Vitamin D concentration <20 ng/mL was significantly associated with a higher risk of breast carcinoma (OR 10.8, 95% CI 3.1-37.6). Multiparity ≥3 was associated with a decreased risk of breast carcinoma (OR 2.250, 95% CI 0.599-8.447) compared to parity ≤2 (OR 3.241, 95% CI 0.916-11.466). In luminal A and triple-negative subtypes, severe vitamin D deficiency (<20 ng/mL) was observed (p=0.045) compared to other subtypes.

Conclusion: The present study findings showed that women diagnosed with breast carcinoma had low vitamin D levels, which were linked to an increased risk and prognosis of breast carcinoma. Furthermore, multiparity lowers the risk of breast carcinoma.

Keywords: Angiogenesis, Breast carcinoma, Calcitriol, Metastasis, Multiparity, Solar ultraviolet B, Vitamin D deficiency, Vitamin D receptor

INTRODUCTION

Globally, breast carcinoma is the second most common malignancy and the leading cause of morbidity and mortality [1]. According to epidemiological studies, the expected burden of breast carcinoma will exceed two million cases by the year 2030 [2]. Incidence rates vary from 27 per 100,000 women in Middle Africa and Eastern Asia to 96 per 100,000 women in Western Europe. The mortality rates range from 6 per 100,000 in Eastern Asia to 20 per 100,000 in Western Africa.

In India, the occurrence of breast carcinoma at a young age is higher compared to Western countries. The National Carcinoma Registry data has shown a significant increase in the trend of breast carcinoma in all populations [3]. The mortality-to-incidence ratio was found to be as high as 66 in rural registries, whereas it was as low as 8 in urban registries [4]. Various risk factors like age, family history, genetic factors, and lifestyle patterns are responsible for the development of breast carcinoma. Nowadays, a deficiency of vitamin D has emerged as a risk factor for breast carcinoma. Many studies have shown an inverse association between serum Vitamin D and the incidence of several carcinomas, including breast carcinoma [5].

Worldwide, vitamin D deficiency is common and associated with serious health consequences like diabetes, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, and osteoporosis. Approximately 20 different carcinomas are inversely related to solar UV-B doses and Vitamin D concentration [5].

Vitamin D is a fat-soluble secosteroid produced in the form of D2 and D3. D2 originates from dietary sources like plants and fungi, while D3 is produced under the skin when 7-dihydroxy cholesterol is exposed to Ultraviolet (UV) B light. In the liver, both forms undergo hydroxylation to form 25-hydroxy vitamin D {25 (OH)D} or Calcidiol and are further metabolised in the kidney to produce 1,25-dihydroxy vitamin D {1,25 (OH)2D}. Vitamin D deficiency can be diagnosed by measuring circulating 25 (OH)D levels. The optimal range reported for 25 (OH)D is 25-80 ng/mL, with insufficiency defined as <30 ng/mL and deficiency as <20 ng/mL [6]. The prevalence of vitamin D deficiency is noted worldwide, with one billion people of all age groups having Vitamin D deficiency. In India, 490 million people are Vitamin D deficient [7]. Vitamin D plays an important role in calcium and bone homeostasis. However, in many experimental and animal studies, vitamin D has been found to have an anticarcinoma role in several modes of tumour development by preventing cellular differentiation, stimulating cell death, and reducing angiogenesis, tumour progression, and metastasis [8].

The aim of the present study was to analyse the Vitamin D status in women diagnosed with breast carcinoma and compare it with healthy women to find the association between vitamin D deficiency and breast carcinoma.

MATERIALS AND METHODS

This was an observational case-control study conducted at Armed Forces Medical College, Pune, Maharashtra, India. The study was approved by the Institutional Ethics Committee (IEC no. AFMC/EC/08/2018) and took place between November 2018 and October 2020. Written informed consent was obtained from all study participants.

Inclusion and Exclusion criteria: Female patients with breast carcinoma reporting to the Surgery Outpatients Department were enrolled as cases, while normal healthy females above 18 years

of age, without any type of carcinoma, who were attendants of various patients, were enrolled as controls. Females who were less than 18 years of age, pregnant, or suffering from inherent conditions causing vitamin D deficiency, or suffering from benign diseases of the breast were excluded from the study.

Study Procedure

All study participants were evaluated by clinical examination, and serum Vitamin D levels were measured using the Radio Immunoassay (RIA) method, DiaSorin S.p.A (Saluggia, Italy). Serum Vitamin D levels were evaluated using the criteria: ≥30 ng/mL was considered sufficient, 20-29 ng/mL was insufficient, and <20 ng/mL was deficient. Mammography was performed in all cases, and other imaging was done when the findings were equivocal. The diagnosis of breast carcinoma was made by histopathological examination (Core needle Biopsy) with Haematoxylin and Eosin (H&E) stain. Anatomical and histological grading of the tumour was done using the American Joint Committee Carcinoma (AJCC) manual, 8th edition [9]. The TNM grading {Primary Tumour (T), regional lymph node (N), distant Metastasis (M)}, and prognostic stage groups (I to IV) were recorded. Tissue-based Hormone receptor assay was performed to detect the expression of Oestrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2). This information was used to guide the course of treatment.

STATISTICAL ANALYSIS

Statistical analysis was conducted using MS Excel (Microsoft 365) and IBM Statistical Package for Social Sciences (SPSS) Statistics 27.0 Quantitative data are represented as Mean and Standard Deviation (SD) or Median (IQR) as appropriate. Normality was checked using the Shapiro-Wilk test. Differences were analysed using the student's t-test for normally distributed data and Mann-Whitney U test for non-normal or skewed data. One-way Analysis of Variance (ANOVA) was used to compare means of dependent variables within categories of one or more independent variables. Qualitative variables are expressed as frequency (percentage). The Chi-square test of independence of attributes was applied to check the dependency between attributes. A logistic regression model was used to assess breast carcinoma risk with different factors. Odds Ratio (OR) with 95% Confidence Levels (CI) was computed as measures of association from the logistic models. For all the tests, a p-value of <0.05 (two-tailed) was considered statistically significant.

RESULTS

Out of 114 women, 57 were cases diagnosed with breast carcinoma and 57 were controls who visited for other health issues and were not diagnosed with any type of carcinoma. Their demographic, clinical, and reproductive health information is shown in [Table/Fig-1]. Women diagnosed with breast carcinoma were older than controls, with no significant difference in their age (mean age 52 vs 48 years, p=0.242) and Body Mass Index (BMI) (24.79 vs 24.74 kg/m^2, p=0.949).

The mean value of Serum vitamin D level in women diagnosed with breast carcinoma was significantly lower than controls (19.45 vs 27.91 ng/mL, p<0.001) [Table/Fig-2]. Additionally, the authors observed that the deficiency of serum Vitamin D was significantly higher (p<0.001) in cases (28, 49.1%) than in controls (12, 21.1%).

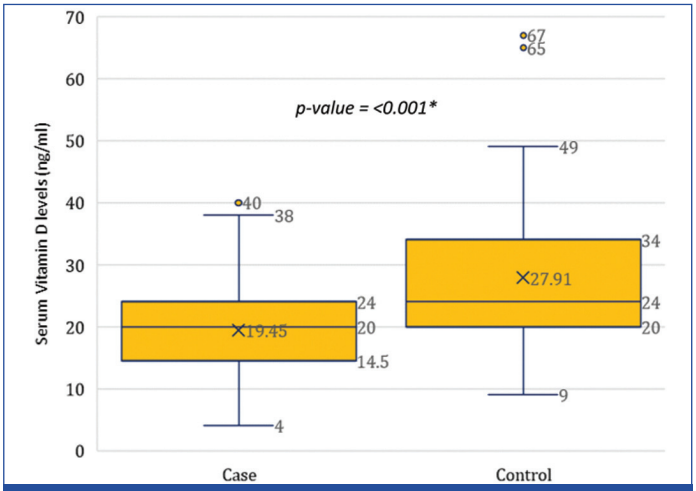
Reproductive health information mentioned in [Table/Fig-1] showed that the mean age at menarche was 14.07 years and 13.96 years in the case and control groups, respectively. Women diagnosed with breast carcinoma were younger compared to controls (mean age 21.6 vs 23.45 years) at the time of birth of their first child.

Low levels of Serum Vitamin D (<20 ng/mL) were significantly associated with a high risk of breast carcinoma {OR 10.8, CI (3.1, 37.6), p<0.001} compared to insufficient (OR 3.9, CI (1.2, 12.6), p=0.019) and adequate Vitamin D levels [Table/Fig-3]. Multiparity (≥3) was associated with a lower risk of breast carcinoma (OR 2.2, CI (0.5, 8.4)) compared to nulliparous and uniparous (OR 3.2 CI (0.9-11.4)). Pre and post-menopausal status were not associated with the risk of breast carcinoma. An overview of the diagnosis, location, and subtypes of the tumour, with respect to vitamin D status, is represented in [Table/Fig-4]. The majority of women diagnosed with stage IIA and IIB 18 (31.5%) each tumour, 11 (19.3%) with stage IIIA, 6 (10.5%) with stage IIIB, and 3 (5.3%) with stage IIIC tumour. Stage IIB onwards severe vitamin D deficiency was observed. The majority of the cases 55 (96.5%) were showing symptoms of the formation of a lump, 20 (35.1%) had pain, 19 (34.0%) had both symptoms, and 54 (94.7%) were diagnosed with Infiltrating ductal carcinoma [Table/Fig-5].

Molecular diagnosis of breast carcinoma showed that the majority of women diagnosed with luminal A subtype were 39 (68.4%),

Parameters	Case (n=57)	Control (n=57)	Total (n=114)	p-value
Age (years)	52 (44.5-58.5)	48 (41.5-55)	50.5 (43-57)	0.242
Height (meters)	1.56±0.05	1.56±0.08	1.56±0.67	0.541
Weight (kg)	58.88±8.82	60.28±9.44	60.08±9.10	0.814
BMI (kg/m^2)	24.79±3.63	24.74±4.02	24.76±3.81	0.949
Underweight/Normal (<18.5/18.5-24.9)	34 (59.6%)	27 (47.4%)	61 (53.5%)	0.388
Overweight (25-29.9)	19 (33.3%)	26 (45.6%)	45 (39.5%)	
Obese (≥30)	4 (7.0%)	4 (7.0%)	8 (7.0%)	
Sr. Vit D levels (ng/mL)#	19.45±7.66	27.91±12.17	23.68±10.98	<0.001*
Adequate ≥30	5 (8.8%)	19 (33.3%)	24 (21.1%)	0.001*
Insufficiency (20-29)	24 (42.1%)	26 (45.6%)	50 (43.9%)	
Deficiency (<20)	28 (49.1%)	12 (21.1%)	40 (35.1%)	
Menopausal status				
Premenopausal	28 (49.1%)	25 (43.9%)	53 (46.5%)	0.707
Postmenopausal	29 (50.9%)	32 (56.1%)	61 (53.5%)	
Age at menarche (years)#	14.07±1.0	13.96±1.72	14.02±1.4	0.972
Age at first child (years)#	21.6±2.01	23.45±4.22	22.47±3.35	0.059
Parity				
0	4 (7.0%)	10 (17.5%)	14 (12.3%)	0.157
1-2	35 (61.4%)	27 (47.4%)	62 (54.4%)	
> 3	18 (31.6%)	20 (35.1%)	38 (33.3%)	

[Table/Fig-1]: Demographic and prevalence data of Vitamin D deficiency in cases and controls of carcinoma of the breast.
Values displayed are mean±SD and median (IQR) for age; two-sample t-test or #Mann-Whitney U test. Categorical variables are expressed as n (%); Chi-square test. p<0.05; Statistically significant*



[Table/Fig-2]: Comparison of serum vitamin D levels between carcinoma breast cases (n=57) and controls (n=57).
*p-value derived from Mann-Whitney U test

Factors	OR (95% CI)	p-value
Sr. Vit D levels (ng/mL)*		
Adequate	1 (ref)	
Insufficiency	3.982 (1.254, 12.641)	0.019
Deficiency	10.821 (3.113, 37.619)	< 0.001
Menopausal status		
Premenopausal	1 (ref)	
Postmenopausal	0.809 (0.387, 1.691)	0.573
Parity		
0	1 (ref)	
1-2	3.241 (0.916, 11.466)	0.068
≥ 3	2.250 (0.599, 8.447)	0.23

[Table/Fig-3]: Various factors associated with carcinoma of the breast.
*Values adjusted for age and BMI

Characteristics (n=57)	n (%)	Sr. Vit D levels (ng/mL)	p-value
Stage of carcinoma breast			
IA	1 (1.8%)	21.00	0.645
IIA	18 (31.6%)	22.17±7.79	
IIB	18 (31.6%)	17.97±9.05	
IIIA	11 (19.3%)	18.18±5.51	
IIIB	6 (10.5%)	18.33±7.12	
IIIC	3 (5.3%)	18.33±7.09	
Site of carcinoma (Quadrant)			
Lower outer quadrant	10 (17.5%)	24.90±9.75	0.086
Upper inner quadrant	11 (19.3%)	20.18±5.55	
Central quadrant	2 (3.5%)	20.00±7.07	
Upper outer quadrant	28 (49.1%)	18.11±7.25	
Lower inner quadrant	6 (10.5%)	15.08±6.04	
Molecular subtypes			
Luminal A subtype (ER^+, PR^+)	39 (68.4%)	18.86±7.40	0.045*
Luminal B subtype (ER^-,PR^+)	8 (14%)	24.00±7.67	
HER2 enriched	5 (8.8%)	23.20±6.72	
Triple-negative	5 (8.8%)	13.00±6.16	

[Table/Fig-4]: Clinicopathological presentation of cases diagnosed with carcinoma breast.
Values displayed are mean±SD for Sr. Vit D levels, One-way ANOVA. p<0.05; Statistically significant*

Clinical history	n (%)	Sr. Vit D levels (ng/mL)
Lump	55 (96.5%)	19.30±7.75
Pain	20 (35.1%)	18.72±6.49
Ulcer	5 (8.8%)	18.40±5.59
Nipple discharge	3 (5.3%)	12.67±2.08
Nipple retraction	5 (8.8%)	15.20±7.56

[Table/Fig-5]: Level of serum Vitamin D for clinical history.
Values displayed are mean±SD for Sr. Vit D levels

followed by Luminal B subtype with 8 (14.0%), and 5 (8.8%) with HER2 and triple-negative subtypes. Severe vitamin D deficiency was observed in luminal A and triple-negative subtypes, which was significantly higher (p=0.045) than in luminal B and HER2-enriched subtypes.

DISCUSSION

The global burden of breast carcinoma has been rising for the past decade. The Global Cancer Observatory (GLOBOCAN) database showcased about 2.3 million new cases and 685,000 deaths from carcinoma breast in 2020 [10]. Women from less developed regions (883,000 cases) had a slightly higher number of cases compared to more developed areas (794,000) [11].

In India, although the age-adjusted incidence rate of breast carcinoma is lower (25.8 per 100,000) than in the United Kingdom (95 per 100,000), mortality rates are similar (12.7 vs 17.1 per 100,000) to the United Kingdom [12]. Accumulated data from human studies suggest that vitamin D deficiency is associated with carcinoma breast [Table/Fig-5]. Vitamin D is an essential micronutrient that plays a vital role in calcium and phosphorus homeostasis and the development of breast tissue/mammary glands. Vitamin D binds to an intracellular Vitamin D Receptor (VDR) and regulates the transcription of more than 60 genes responsible for proliferation, differentiation, metastasis, and apoptosis. Low Vitamin D levels result in neoangiogenesis and carcinogenesis. VDR knockout mice showed higher rates of preneoplastic mammary lesions [13]. A meta-analysis of 39 studies demonstrated that in human VDR polymorphism, Fok1 was associated with breast cancer [14]. Similar studies and reviews exist in literature which has studied the relationship of Vitamin D deficiency and carcinoma of breast [Table/Fig-6].

Even though India is a tropical country with plenty of sunlight, vitamin D deficiency is more common among Indians. A meta-analysis of vitamin D deficiency in South Asian adults revealed that 67% of Indians were vitamin D deficient [15]. However, according to the data, 49.1% of cases and 21.1% of controls were Vitamin D deficient (<20 ng/mL). This could be caused by a lack of food intake, supplementation, and insufficient sun exposure. A case-control study conducted on women in Australia revealed that a Vitamin D level below 30 ng/mL was associated with an increased risk of breast cancer {OR 2.5 (95% CI= 1.6-3.8)} [16]. In the present study, the authors observed that the risk of breast cancer was increased by 10.8 times (95% CI= 3.1-1.7) in women with severe vitamin D deficiency (<20 ng/mL), which is surprisingly high compared to the Western scenario.

Contradictory findings emphasised by several Western studies and meta-analyses suggest that several factors, including age, physical activity, sun exposure, obesity, vitamin D intake, and race, contribute to the development of carcinoma breast [17]. In the present study, 49.1% of women were diagnosed with carcinoma breast premenopause and 50.9% postmenopause. However, the

Author	Study design	Number of participants	Aim of study	Population	Result
Zhang K and Song L, (2014) [14]	Meta-analysis	39 studies	To clarify the association between breast cancer risk and VDR gene polymorphisms	European	The Fok1 polymorphism in the VDR gene was significantly associated with an increased risk of developing breast cancer
Bilinski K and Boyages J, (2013) [16]	Case-control	214 case and 852 controls	To examine the association between vitamin D status and risk of breast cancer in an Australian population of women	Australian	In women >50 years and obese (BMI>30) the risk of breast cancer was associated with 25(OH) D deficiency and insufficiency was higher compared to those aged <50 years
Kim Y et al., (2014) [18]	Multi-ethnic case-control study	1414	To examine the relation between plasma levels of vitamin D and the risk of postmenopausal breast cancer.	White, African American, Native Hawaiian, Japanese, and Latino	Circulating vitamin D was inversely associated with risk of carcinoma breast in white post-menopausal women who reside in latitude and not in other groups

Patel SR et al., (2020) [17]	Case-control	140 cases and 157 controls	To investigate circulatory 25(OH) D in relation to breast cancer risk and its association with various clinico-pathological parameters from Indian population	Indian	Low circulatory 25(OH) D might be associated with increased risk of breast cancer. Severe 25(OH) D deficiency was associated with poor prognostic characteristics like Estrogen negative receptor status and with triple negative breast cancer patients
Yao S et al., (2017) [21]	Prospective case-cohort	1666	To investigate a serum vitamin D status, 25-hydroxyvitamin D (25OHD) measured at the time of breast cancer diagnosis, to determine the association with prognosis	Northern California	In women with breast cancer, low serum 25(OH) D levels were associated with poorer survival and in prognostic characteristics, including TN subtype. The associations with prognostic characteristics and outcomes were independent of each other and were most prominent among premenopausal women
Siddiqee MH et al., (2021) [15]	Meta-analysis	65 studies	To address a huge knowledge gap exists about the true extent of vitamin D deficiency in different SA countries	South Asian countries	In South Asian countries, a gender-wise analysis suggested that the prevalence of vitamin D deficiency was higher in females than males

[Table/Fig-6]: Summary of literature review -studies conducted to analyse the association of Vitamin D and risk of carcinoma breast [14-17,21].

risk of carcinoma breast was not associated with their menopausal status. A literature review states that postmenopausal women with vitamin D insufficiency had a 7.5-fold increased risk of carcinoma breast compared to controls [5]. In a multiethnic nested case-control study, Kim Y et al., demonstrated that white postmenopausal women residing in latitudes where the risk of carcinoma breast was inversely associated with plasma vitamin D levels [18]. Accumulated research data shows that parity has a protective effect on breast cancer and regulates systemic hormonal changes during pregnancy (oestrogen and progesterone). Parity promotes differentiation in breast tissues and reduces the number of transforming tumour cells by inhibiting the activity of Mammary Stem Cells (MaSCs) [19]. The present study results showed similar findings: the risk of carcinoma breast decreased in multiparous (≥3 offspring) compared to uniparous and nulliparous women. The majority of women (68.4%) were diagnosed with luminal subtype A tumours. Similar findings were observed by Caldarella A et al., in a population-based study, reporting that out of 1487 patients, 70.3% were luminal A subtype, 15.6% luminal B, 8.1% triple negative, and 6.0% HER2-enriched [20]. In the present study, severe vitamin D deficiency was observed in luminal subtype A (18.86±7.40 ng/mL) and triple-negative tumours (13.0±6.16 ng/mL) compared to other subtypes. In a cohort study of 1666 women, Yao S et al., highlighted that severe vitamin D deficiency was associated with triple-negative tumours in premenopausal women [21].

Limitation(s)

There was no information available on the duration of breastfeeding, food habits, or sun exposure. Treatment modalities and outcomes regarding breast carcinoma were not discussed. Due to the Coronavirus Disease-2019 (COVID-19) pandemic and lockdown, the authors were unable to investigate more patients with breast carcinoma; therefore, the sample size was insufficient to draw any conclusions about vitamin D levels and breast carcinoma trends at the regional or national levels.

CONCLUSION(S)

It can be concluded that vitamin D deficiency is associated with the risk of carcinoma breast and prognosis. Multiparity protects against or reduces the risk of breast cancer. To fully comprehend the role of vitamin D in the progression of the disease, additional aspects such as nutrition, lifestyle, and molecular diagnosis must be examined. Since vitamin D insufficiency is common in India across all age groups and is more prevalent in women, early detection of deficiency and vitamin D supplementation can reduce the future risk of carcinoma breast. It is necessary to conduct region-specific Randomised Control Trials for the Indian population to establish the proper dosage to attain normal vitamin D status.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 29, 2023
- Manual Googling: Mar 20, 2024
- iThenticate Software: Mar 30, 2024 (19%)

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- For any images presented appropriate consent has been obtained from the subjects. NA

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