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ORIGINAL ARTICLE

The Role of Vitamin D Deficiency as a Potential Risk Factor for Breast Cancer: A Case-Control Study

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ABSTRACT
Objective: To determine the role of vitamin D deficiency as a risk factor for carcinoma breast.
Study Setting: Khyber Teaching Hospital Peshawar in Khyber Pakhtunkhwa.
Study Duration: Minimum of 6 months after approval of synopsis.
Study Design: Case-control study
Material and Methods: After taking approval from the hospital ethical committee, 256 patients were included in the study, between August 2022 and January 2023, divided equally into 2 groups as cases (breast cancer) and controls (breast diseases other than cancer). Vitamin D levels along with other variables were collected in Microsoft excel sheet and shifted to SPSS data base for analysis and the results shown in tables and charts.
Results: The mean age for cases was 47.8 ± 11.6 SD and for controls was 33.7 ± 12.7 SD. The mean BMI for cases was 27.9 kg/m^2 ± 3.3 and for controls was 26.6 kg/m^2 ± 3.4. Other biological variables did not show much variation between both groups. The adjusted OR for cases showed significant association between low vitamin D levels {OR 1.25 with 95% CI (0.74-2.12), p value 0.01} and higher BMIs {OR 1.63 with 95% CI (0.96-2.75), p-value 0.05} with increased risk of breast cancer. Adjustment for age, sun exposure and use of vitamin D supplements did not show any significant association with risk of developing breast cancer.
Conclusion: Since Vitamin D was found deficient in most of our study subjects, it can be considered as an independent risk factor in progression of breast cancer disease.
Keywords: Vitamin D, breast cancer, risk factor.

INTRODUCTION
Carcinomas of the breast are one of the most prevailing types of cancers among females, more prevalent in the Western communities as compared to East Asian countries. Recent surveys have reported an increase in the number of cases globally and at an alarming rate[1]. For reasons more related to environmental factors rather than genetics, this disease is more frequent in developed parts of the world[2]. In India, it is customary to find breast cancer in urban populations compared to rural areas, average 30%[3] and this disease has also affected southern and northern regions in Pakistan as well[4].

The role of vitamin D as a significant nutritional element in protection against various diseases has been studied for decades. Not only does it regularize calcium metabolism and homeostasis in our body to maintain strength in our bones, surprisingly, this nutrient has some anticancer functioning as well, specifically in organ systems such as hepatobiliary, colorectal and the breast[5]. Revelations from histological studies have shown that breast cells contain cellular mechanisms similar to those found in the kidney and intestine, allowing these cells to synthesis their own vitamin D from circulating precursors. This finding has theoretically proven the effect of vitamin on breast cancer as biologically plausible[6].

The naturally active form of vitamin D is calcitriol and research has shown that calcitriol has affinity for an intracellular receptor found in the parenchymal cells of mammary glands[9,10], called the vitamin D receptor (VDR)[7,8]. Microbiological experts say that VDR has the potential to standardize extracellular calcium proportions and, in addition, has some role in activating a cascade of genes related to cell growth, cell cycle and apoptosis as well[11]. Example of an important oncogene affected by VDR is Ki67[12] and VDR increases activity of some tumor suppressor genes such as p21 and p27[13,14] and E-cadherin[15]. This property of VDR enables breast cells to live in a relatively anticancer environment.

There is ample literature available on various risk factors associated with breast cancer, which have been discovered over the course of many years of research. Of all these causes, low levels of vitamin D has also been postulated to be connected with poor prognosis in breast cancer[16-19]. However, some scholars e.g., Huss L et al[8] suggest that higher levels of vitamin D can also induce death in breast cancer patients but the data available is limited. An analysis conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan illustrated below optimum levels of vitamin D in 95.6% breast cancer patients and about 77% in the other group[20]. Our nation commonly experiences low vitamin D levels, and if we can prove a link between the two, we will be able to provide remedies and try to lower the prevalence of breast cancer specifically in our society and that is basically the objective behind conducting this study.

METHADOLOGY AND STUDY DESIGN
This following case control study was conducted in department of surgery Khyber teaching hospital Peshawar from August 2022 to January 2023 comprising of 256 patients selected through non probability consecutive sampling.

The hospital's ethics and scientific committee gave its clearance before the study could be carried out. Through OPD, all patients who met the inclusion requirements were added to the trial and then admitted to the ward for additional evaluation. All participants in the study had their goals and advantages outlined to them, and if they agreed, formal informed consent was obtained. All patients underwent thorough clinical and historical evaluations before undergoing the requisite preoperative baseline tests.

The patients were allocated into two groups. Group A, Cases, (patients presenting with diagnosed breast cancer), and group B, control group, (patients presenting with pathologies other than breast cancer. The ELISA technique was used to examine serum vitamin D levels in blood samples obtained from the study population at their initial presentation, and the results were recorded in ng/ml. Vitamin D deficiency was categorized at serum levels less than 20 ng/ml and optimal levels were considered more than 20 ng/ml. Proformas were filled and all the information was transferred to Microsoft excel sheet for convenience.

Data was analyzed by using the statistical software SPSS version 23.0. Continuous variables i.e., BMI, height and vitamin D levels were calculated as Means ± Standard deviation. Categorical variables i.e., age, number of cases and controls were calculated as frequencies and percentages. The relation of vitamin D deficiency with cases and control groups was determined by using the odds ratio at 95% confidence interval in a 2*2 contingency table. A p-value of < 0.05 was considered significant and the results were presented in the form of tables and charts.

RESULTS

Data on 253 patients, 126 cases and 127 controls were included in the study for analysis. For cases, the mean along with standard deviation for various variables is as follows: mean age was 47.8 ± 11.6, height 156 cm ± 6.9, weight 144.3 pounds ± 12.1, BMI 27.9 kg/m^2 ± 3.3 and vit D3 levels 13.17 ng/ml ± 8.4. As far as sun exposure is concerned, average being at least 30 mins/day for 6 months, 67 patients (53.2%) were habitual of going out into the open while 59 patients (46.8%) were almost totally confined to their homes. Exactly 8 patients (6.3%) gave drug history of using vitamin D supplements while the remaining 118 (93.7%) did not use them at all. In terms of disease presentation, 72 (57.1%) patients had left sided carcinomas while 54 (42.9%) patients had right sided carcinomas. Levels of vitamin D were analyzed and it was found that 109 patients (86.5%) had blood levels of vitamin D less than 20 ng/ml and only 17 patients (13.5%) had levels over a range of 20 to 50ng/ml.

Similarly for controls, the mean along with standard deviation for various variables is as follows: mean age was 33.7 ± 12.7, height 155 cm ± 5.8, weight 138.1 pounds ± 15.9, BMI 26.6 kg/m^2 ± 3.4 and vit D3 levels 13.6 ng/ml ± 8.3. As far as sun exposure is concerned, 67 patients (53.2%) were habitual of going out into the open while 59 patients (46.8%) were totally confined to their homes. Precisely 14 patients (11%) gave drug history of using vitamin D supplements while the remaining 113 (89%) did not use them at all. Controls included diseases such as breast abscess, cysts, galactoceles, mastitis, ectasia, fibroadenoma and accessory breast tissues as depicted in the table 3. Levels of vitamin D were analyzed and it was found that 107 patients (84.9%) had blood levels of vitamin D less than 20 ng/ml and only 20 patients (15.1%) had levels over a range of 20 to 50 ng/ml.

Table 1: Descriptive statistics of demographic variables

Variable	Cases Mean (SD)	Controls Mean (Sd)
Age	47.8 (11.6)	33.7 (12.7)
Height (cm)	156 (6.9)	155 (5.8)
Weight (pounds)	144.3 (12.1)	138.1 (15.9)
BMI kg/m^2	27.9 (3.3)	26.6 (3.4)
Vitamin D3 levels	13.17 (8.4)	13.6 (8.3)

Table 2: Frequency and percentages of demographic variables.

Variable		Number (%)
1.	Groups	
	Cases	126 (49.8%)
	Controls	127 (51.2%)
2.	Vitamin D deficiency (<20ng/ml)	
	Cases	109 (86.5%)
	Controls	107 (84.9%)
3.	Vitamin D adequate levels (>20ng/ml)	
	Cases	17 (13.5%)
	Controls	20 (15.1%)
4.	Sun exposure (at least 30mins/day for 6 months)	
	Cases	67 (53.2%)
	Controls	67 (52.3%)
5.	Vitamin d supplements	
	Cases	8 (6.3%)
	Controls	14 (11%)
6.	BMI (cases)	
	18 to 24.9	19 (15.1%)
	25 to 30.9	18 (64.3%)
	31 to higher levels	26 (20.6%)
7.	BMI (controls)	
	18 to 24.9	34 (27%)
	25 to 30.9	78 (61.9%)
	31 to higher levels	41 (11.1%)

Serum Vit D levels did not show any notable difference among the cases and controls. The adjusted OR for cases showed significant association between low vitamin D levels {OR 1.25 with 95% CI (0.74-2.12), p value 0.01} and higher BMIs {OR 1.63 with 95% CI (0.96-2.75), p-value 0.05} with increased risk of breast cancer. Adjustment for age (p-value 0.473), sun exposure (p-value 0.918), and use of vitamin D supplements (p-value 0.292) did not show any significant association with risk of developing breast cancer.

Table 3: Type of disease (cases)

	Frequency	Percentage	Cumulative Percentage
Fibroadenoma	13	10.2	10.2
Galactocele	5	3.9	14.2
Left accessory breast	3	2.4	16.5
Left breast abscess	18	14.2	30.7
Left breast cyst	27	21.3	52.0
Left duct ectasia	9	7.1	59.1
Mastitis	5	3.9	63.0
Post MRM DD	4	3.1	66.1
Right accessory breast	2	1.6	67.7
Right breast abscess	18	14.2	81.9
Right breast cyst	18	14.2	96.1
Right duct ectasia	5	3.9	100.0
Total	127	100.0	

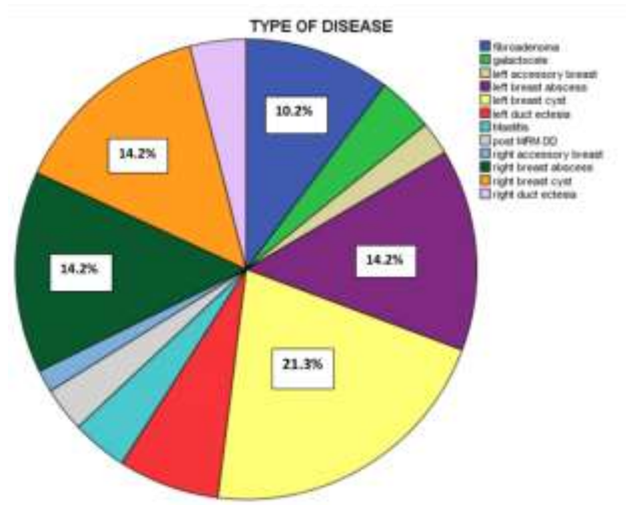

Chart 1: Type of disease (cases)

Table 4: Association of variables with cases (using chi square test)

Variable	Left sided breast CA N (%)	Right sided breast CA N (%)	OR (95% CI)	P-value
Age Groups(total)	72 (100%)	54 (100%)	0.76 (0.356-1.614)	0.473
< 40 years	21 (29.1%)	19 (35.2%)	0.89 (0.63-1.25)	
> 40 years	51 (70.9%)	35 (64.8%)	1.17 (0.77-1.77)	
BMI Groups	61 (100%)	46 (100%)	0.44 (0.19-1.02)	0.05
Underweight	34 (55.7%)	34 (73.9%)	0.72 (0.53-0.99)	
Overweight	27 (44.3%)	12 (26.1%)	1.63 (0.96-2.75)	
Sun exposure	72 (100%)	54 (100%)	1.04 (0.51-2.10)	0.918
< 30 mins/day	34 (47.2%)	25 (46.3%)	1.02 (0.75-1.38)	
> 30 mins/day	38 (52.8%)	29 (53.7%)	0.98 (0.65-1.47)	
Vit D supplements	72 (100%)	54 (100%)	0.42 (0.08-2.18)	0.292
Yes	6 (9.1%)	2 (3.7%)	0.75 (0.48-1.15)	
No	66 (90.9%)	52 (96.3%)	1.76 (0.52-5.96)	
Vit D deficiency	72 (100%)	54 (100%)	1.60 (0.57-4.46)	0.01
< 20 ng/ml	64 (88.9%)	45 (83.3%)	1.25 (0.74-2.12)	
> 20 ng/ml	8 (11.1%)	9 (16.7%)	0.78 (0.47-1.29)	

Table 5: Correlation of vit D among cases with other variables (using student T test and independent samples T test)

Vit D levels (CASES)			Mean	SD	P-VALUE
1.	Age		47.8	11.6	<0.01
2.	BMI		27.9	3.3	<0.01
3.	Sun exposure	Yes	15.7	9.22	0.02
		No	10.3	5.51	
4.	Vit D supplements	Yes	23.0	12.2	0.05
		N0	12.5	7.4	

Table 6: Correlation of vit D among controls with other variables (using student T test and independent samples T test)

Vit D levels (CONTROLS)			Mean	SD	P-VALUE
1.	Age		33.7	12.7	<0.01
2.	BMI		26.6	3.4	<0.01
3.	Sun exposure	Yes	16.4	10.02	<0.01
		No	10.5	4.30	
4.	Vit D supplements	Yes	23.2	15.4	<0.01
		N0	12.4	6.2	

DISCUSSION

Although Vitamin D deficiency is a prevalent global health problem[22] but its more common in regions of south east Asia[23] and stats are available on the Pakistani population as well[24.] A national nutritional survey conducted in Pakistan in 2011 depicted an average vitamin D deficiency of 68% among Pakistani women both non pregnant and expecting mothers[25] and a regional evaluation in Karachi females showed a deficiency of 84%[26]. In the following study, serum vitamin D levels of both premenopausal and postmenopausal women was collected along with some other demographic factors such as solar exposure and vitamin D supplementation.

The mean concentration of serum vitamin D in our study population was 13.17 ng/ml (SD + 8.4 ng/ml) for cases and 13.6 ng/ml (SD + 8.3 ng/ml) for controls which is comparable to the laboratory results found at Agha khan university Karachi in 2011[22]. These values are slightly lower than the average values calculated by a group of researchers at Ayub teaching hospital Abbottabad (mean serum vitamin D level was 25.15±18.97 ng/ml with a minimum and maximum value of 9.60 ng/ml and 98.0 ng/ml respectively)[27] and another study done at Karachi in 2007 which showed a mean value of 15.65 ± 9.91 SD[28]. Compared to south east Asia, surveys have shown better vitamin D status in countries like Canada[29], America[30] and the UK[31]. This difference can be attributed to various reasons: the fact that the population in south east Asia, specifically Pakistan, is predominantly Muslim where most women are house wives and wearing complete clothing for religious reasons is a common cultural norm. Similarly, poverty can be considered as the main cause for deficient nutritional intake of vitamin D related products.

The main outcome of this study was to find the relationship between blood levels of vitamin D and breast cancer. Previous review studies have accepted the inverse relationship between these two variables, in fact multiple retrospective and prospective designs have proclaimed that low vitamin D levels increases the risk of breast cancer[32-33]. The findings in our study showed that patients with decreased levels of vitamin D are 1.6 times more at risk for developing breast cancer (OR 1.6 with a 95% CI between 0.57-4.46 and a p-value of <0.01) and this is comparable to the analysis conducted by Lowe LC et.al[34], Chlebowski et.al[35] and Freedman et al.[36] in their respective studies.

The results of further case control trials are given in tabulated form for convenience (table.6)[37].

Table.6:

Study	Description	n cases/controls	Comparison (ng/mL)	OR (95% CI)
Abbas et al. (2008) [50]	Population-based case–control study in Germany, 2002–2005	1,394/1,365 (postmenopausal women only)	≥30 versus <12	0.31 (0.24–0.42)
Abbas et al. (2009) [51]	Population-based case–control study in Germany, 1992–1995	285/595 (premenopausal women only)	≥24 versus <12	0.45 (0.29–0.70)
Bertone-Johnson (2007) [52]	Nested case–control study within the Nurses' Health Study cohort, 1989–1990	701/724	≥40 versus ≤20	0.73 (0.49–1.07)
Chlebowski et al. (2008) [53]	Nested case–control study within the Women's Health Initiative clinical trial, 1995–2005	1,067/1,067	≤13 versus ≥27	1.22 (0.89–1.67)
Crew et al. (2009) [54]	Population-based case–control study in New York, 1996–1997	1,026/1,075	≥40 versus ≤20	0.56 (0.41–0.78)
Engel et al. (2010) [55]	Nested case–control study within the French E3N cohort, 1993–1995	636/1,272	>27 versus <19.8	0.73 (0.55–0.96)
Freedman et al. (2008) [56]	Nested case–control study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1993–2001	1,005/1,005 (postmenopausal women only)	≥33.7 versus <18.3	1.04 (0.75–1.45)
Lowe (2005) [57]	Hospital-based case–control study in the U.K., 1996–2003	179/179	<20 versus >60	5.83 (2.31–14.7)

To make the study more compulsive, some other variables were also considered such as BMI, vitamin D supplementation and sun basking as part of demographic factors. For both cases and controls, it was discovered that patients with occasional and habitual sun exposure along with use of vitamin D related drugs had relatively better serum levels of vitamin D in their bodies theoretically leading to a protective effect against breast cancer. Even though trials by Rollison et al[38] and Rossi et al[39] support this theory, however, the findings in our study were not convincing enough to prove this association. The study also depicted positive correlation between body mass index and breast cancer as people who were overweight were found to have a 1.63 times higher risk of developing breast cancer, OR 1.63 with 95% CI (0.96-2.75) and a p-value of 0.05. An analysis by Kang Liu et al. has stated that every 5 kg/m^2 increase in BMI corresponded to a 2% increase in breast cancer risk[40]. There are some other cohort designs that also support this association[41-43].

Some limitations of the study included vague assumptions and estimations regarding sun exposure and the use of vitamin D supplements. Also, this was a single institution-based study therefore It cannot be applied completely to the population outside the study center. However, full effort was done to decrease the selection bias among the cases and controls.

CONCLUSION AND RECOMMENDATION STATEMENT

The results of the study depict that although vitamin D deficiency can act as a remarkable nutritional risk factor in breast cancer progression however this deficiency is so routine in our population, courtesy of nutritional deficiency and decreased sun exposure, that other reliable risk factors such as family history, genetics and hormonal status should be considered first as far as risk assessment is concerned. Nonetheless, the government and higher authorities should prioritize this nutritional deficiency as an important health issue and create public awareness among the Pakistani woman population to take necessary steps to revert back this limitation. As a result, we can expect this initiative to decrease the incidence of breast cancer in Pakistan.

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