



# International Journal of Surgery Science

E-ISSN: 2616-3470  
P-ISSN: 2616-3462  
© Surgery Science  
[www.surgeryscience.com](http://www.surgeryscience.com)  
2020; 4(2): 275-279  
Received: 22-02-2020  
Accepted: 25-03-2020

**Dr. Satish Deshmukh**  
MBBS, MS General Surgery,  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

**Dr. Sushrut Fulare**  
MBBS, MS General Surgery,  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

**Dr. Sanjeev Chowksey**  
MBBS, MS General Surgery,  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

**Dr. Angir Soitkar**  
MBBS, MS General Surgery,  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

**Dr. Akshay Nagre**  
MBBS, MS General Surgery,  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

**Dr. Jyoti Gupta**  
Resident, General Surgery  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

**Corresponding Author:**  
**Dr. Sushrut Fulare**  
MBBS, MS General Surgery,  
NKP Salve Institute of Medical  
Sciences, Nagpur, India

## Association of vitamin D level with breast lumps: A cross-sectional analytical study

**Dr. Satish Deshmukh, Dr. Sushrut Fulare, Dr. Sanjeev Chowksey, Dr. Angir Soitkar, Dr. Akshay Nagre and Dr. Jyoti Gupta**

DOI: <https://doi.org/10.33545/surgery.2020.v4.i2d.427>

### Abstract

**Introduction:** Breast Cancer is the second most common cause of death (1.38 million, 10.9%) out of all cancer worldwide after lung cancer. A study conducted in 2017 ranked breast cancer as the second most common cancer among Indian females with age adjusted rate of 25.8 per 100000 women and mortality of 12.7 per 100,000 women. The relation between Vitamin D level and various breast lumps, both benign and malignant remain unclear. But multiple studies have reported the association of breast cancer with vitamin D deficiency. In India, the prevalence of vitamin D deficiency ranges from 50-84%.

**Methodology:** The study was conducted in Department of Surgery, NKPSIMS & LMH between the period of September 2017 to October 2019. A total of 90 patients with breast lumps were included in the study after taking informed consent and ruling out the exclusion criterion. Blood Vitamin D level were estimated before the commencement of treatment. After surgery, the specimen was sent for histopathological study.

**Result:** A total of 90 patients were enrolled in this study, 56 patients with benign breast lump and 34 patients with malignant breast lump. Out of 56 patients with benign breast lump, 44 had Vitamin D deficiency. Out of 34 patients with malignant breast lump, 32 had vitamin D deficiency. The p-value was 0.04 which is significant.

**Conclusion:** Vitamin D deficiency is highly prevalent among Indian females. This problem could be addressed by adequate sun exposure and dietary supplementation. Most of the vitamin D studies support the direct association between vitamin D deficiency and breast cancer risk. Further researches will strengthen this association of vitamin D deficiency and breast cancer.

**Keywords:** Vitamin D, deficiency, Breast cancer, neoplasm

### Introduction

Vitamin D is a group of fat soluble vitamin mainly responsible for intestinal absorption of calcium, magnesium and phosphate and thus helping in mineral homeostasis and proper formation of bones. It also plays a vital role in immune, cardiovascular and reproductive system functions. Sunlight, fortified foods and cereals, some types of fish, algae and fungi are significant sources of vitamin D. In 2011, the National Academy of Medicine, formerly known as Institute of Medicine has quantified an optimal range of Vitamin D between 20-150 ng/ml. Vitamin D deficiency has detrimental health consequences and can result in serious diseases like osteoporosis, rheumatoid arthritis, diabetes, Alzheimer's and Parkinson disease. Studies indicate that Vitamin D inhibits cell proliferation and promotes apoptosis and cell differentiation, providing biological grounds for study of this relationship.

Breast Cancer is the second most common cause of death (1.38 million, 10.9% of all cancer) worldwide after lung cancer. A study conducted in 2017 ranked breast cancer as the most common cancer among Indian females with age adjusted rate of 25.8 per 100000 women and mortality of 12.7 per 100,000 women. In 2018, 1,62,468 new cases and 87,090 deaths for breast cancer were reported in India.

### Aims and Objective

Considering the burden of Breast cancer and recent studies showing inverse association of Vitamin D level and breast cancer risk, this study is conducted to determine the association of Vitamin D deficiency in breast cancer. Also, to determine the proportion of vitamin D deficiency in relation to tumour size, lymph node status, histological type and receptor status.

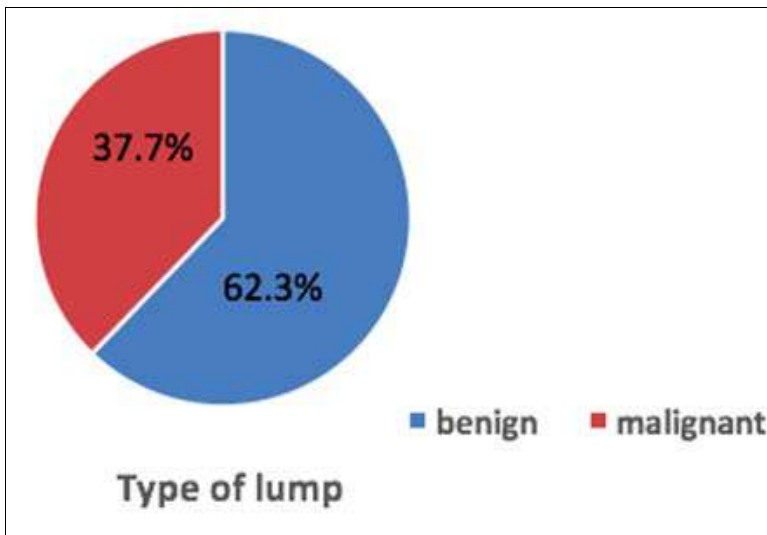
**Material and Method**

This cross sectional analytical study was conducted in NKPSIMS, Lata Mangeshkar Hospital, Nagpur from September 2018 to October 2018. Patients attending the Out Patient Department with lump in breast were evaluated by clinical examination, radiological imaging (Mammography, MRI) and pathological assessment (FNAC, biopsy) to establish a diagnosis of various benign breast diseases and carcinoma breast. Patients between age group of 16 years to 80 years were included in this study. Patients who received Vitamin D supplements in last 1 year were excluded from the study. A written and informed consent was taken before inclusion and those denying consent were excluded from the study. A detailed history of the patients including demographic details, BMI, socioeconomic status was

taken. Baseline general examination and local examination of breast was done by “dial of clock” method and bilateral axillary and supraclavicular lymph nodes were examined. Mammography and FNAC of breast lump were done. After surgery the specimen of breast lump was sent for histopathological examination. The blood serum level of vitamin D3 was assessed before initiation of treatment. Statistical analysis was done by Student T Test for continuous data, for categorical data Chi Square test and Fisher Test was applied. All the data was studied using epi info 7 (version 6) software.

**Result**

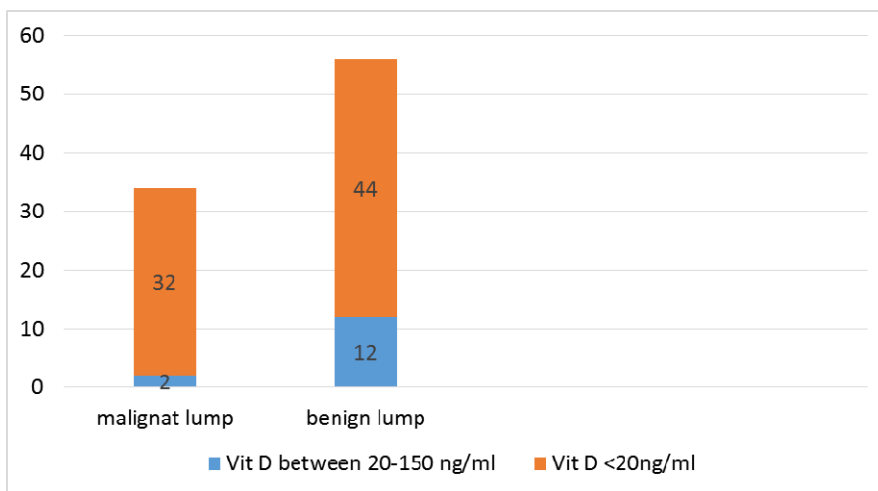
A total of 90 women were enrolled in this study, 56 women with benign breast lump and 34 women with malignant breast lump.



**Graph 1:** Out of 90 women enrolled in study, 56 had benign breast lump and 34 women had malignant breast lump

In patients with benign breast lump, mean age was 28±9.6 years and mean serum vitamin D level was 18.2 ± 7 ng/ml. In patients with malignant breast lump, mean age was 47±12 years and mean serum vitamin D level was 13.6 ± 5 ng/ml.

Out of 56 patients with benign breast lump, 44 had Vitamin D deficiency. Out of 34 patients with malignant breast lump, 32 had vitamin D deficiency. The p-value was 0.04.



**Graph II:** 44 out of 56 patients with benign breast lump and 32 out of 34 patients with malignant breast lump had vitamin D deficiency. The p-value was 0.04.

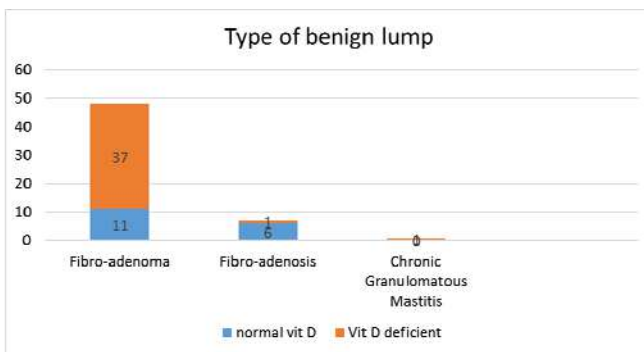
Out of 56 patients with benign breast lump, 38 were nulliparous, 27 amongst whom had vitamin D deficiency and 17 out of 18 parous woman had vitamin D deficiency. All of the patients with

benign breast lump were pre-menopausal. 39 out of 56 patients were urban dwellers amongst whom 33 had vitamin D deficiency, rest 17 patients were rural-dweller out of whom 11

had Vitamin D deficiency. 9 out 11 women with BMI less than 18.5 were Vitamin D deficient, 31 out 38 woman with BMI between 18.5 and 24.9 were Vitamin D deficient, 4 out of 7 woman with BMI between 25.0 to 29.9 were Vitamin D deficient.

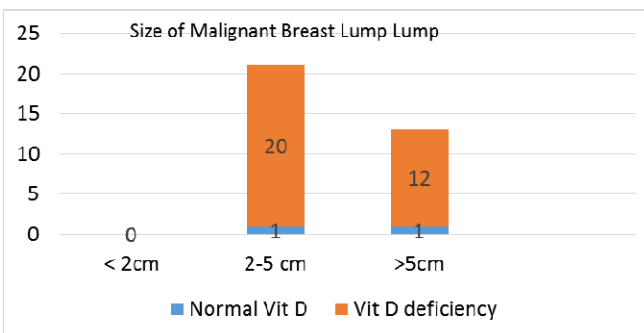
Out of 34 patients with malignant breast lump, all of them had parity of more than 1, out of whom 32 had vitamin D deficiency. 11 out of 13 woman who were pre-menopausal had vitamin D Deficiency whereas all 21 post-menopausal woman were vitamin D deficient. 23 out of 34 patients were urban dwellers amongst whom all had vitamin D deficiency, rest 11 patients were rural-dweller out of whom 9 had Vitamin D deficiency. 21 out of 22 woman with BMI between 18.5 and 24.9 were Vitamin D deficient, 9 out of 9 woman with BMI between 25.0 to 29.9 were Vitamin D deficient. 2 out of 3 woman with BMI > 30 were vitamin D deficient.

48 out of 56 women with benign breast lump had a histopathological finding of fibro-adenoma, amongst whom 37 were vitamin D deficient. 7 had histopathological finding of fibro-adenosis, out of whom 6 were vitamin D deficient. 1 patient had histopathological finding of chronic granulomatous mastitis who was vitamin D deficient.



**Graph III:** In pts with benign breast lump, 37 out of 48 pts with histopathological diagnosis of fibro adenoma, 6 out of 7 pts. With HP diagnosis of fibroadenosis and 1 pt with HP diagnosis of chronic granulomatous mastitis had vitamin D deficiency.

No patient with malignant lump had tumour size less than 2 cm. 21 out of 34 patients had tumour size between 2-5cm, amongst whom 20 were vitamin D deficient. 13 patients had tumour size > 5cm, out of whom 12 were vitamin D deficient. No patient included in this study had tumour fixity to skin, chest wall, pectoralis muscle or ulceration of lump.

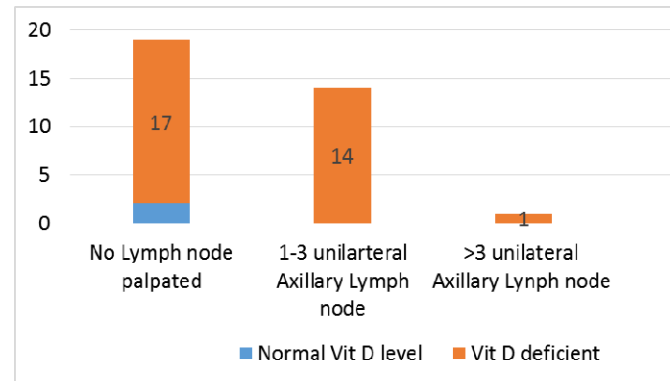


**Graph IV:** 20 out of 21 pts of malignant breast tumour of size 2-5cm had vitamin D deficiency. 12 out of 13 pts with malignant tumour size >5cm had vitamin D deficiency.

In 19 patients regional lymph node could not be palpated out of whom 17 were vitamin D deficient. In 14 patients 1-3 unilateral axillary lymph node could be palpated, all of whom were vitamin D deficient. 1 patient had more than 3 axillary lymph node palpable who was vitamin D deficient. No patient had contra-lateral axillary lymph nodes, infra-clavicular or supra-clavicular lymph node palpable.

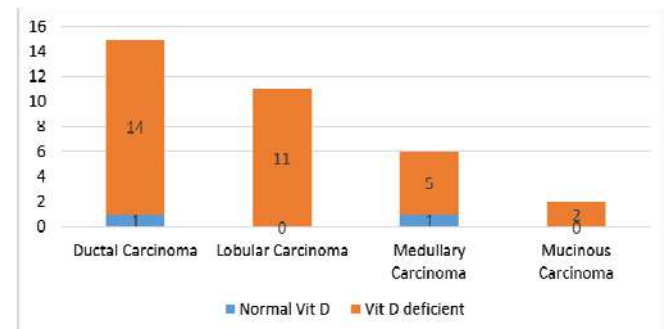
No patients in this study had distant metastases.

**Lymph Node Status of Malignant Breast Lump**



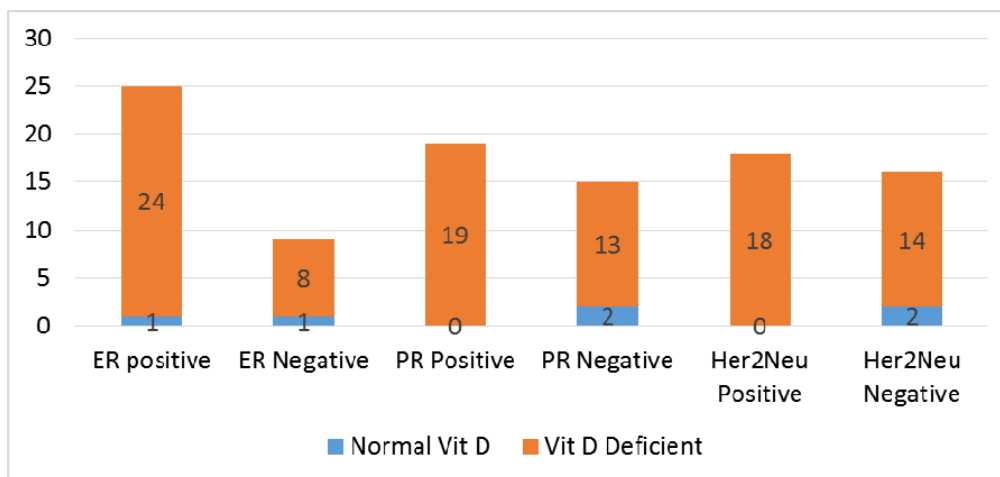
**Graph V:** 17 out of 19 pts with no regional lymph node palpable, 14 out of 14 pts with 1-3 unilateral axillary LN and 1 pt with more than 3 unilateral axillary LN palpable were Vitamin D deficient

17 out of 34 women with had histo-pathological finding of ductal carcinoma in situ, amongst whom 16 were vitamin D deficient. 6 had histo-pathological finding of lobular carcinoma in situ and all of them were vitamin D deficient. 11 patient had histopathological finding of amongst whom 10 were vitamin D deficient.



**Graph VI:** 16 out of 17 pts with HP diagnosis of ductal carcinoma, all 11 pts with HP diagnosis of lobular Carcinoma, 5 out of 6 pts with medullary carcinoma, all 2 pts with mucinous carcinoma were Vitamin D deficient.

25 out of 34 patients were ER status positive, amongst whom 24 were vitamin D deficient. 19 out of 34 patients were PR status positive, amongst whom all 19 were vitamin D deficient. 13 out of 34 patients were ER status positive, amongst whom 11 were vitamin D deficient.



**Graph VII:** 25 out of 34 pts with ER positive status, 8 out of 9 pts with ER negative status, all 19 pts with PR positive status, 13 out of 15 pts with PR negative status, 18 pts with Her2Neu positive and 14 out of 16 pts with Her2Neu negative status were Vitamin D deficient.

**Discussion**

Breast cancer is a heterogenous, multifarious disease with its diagnosis rising steadily each year. It is the most commonly occurring cancer amongst female’s worldwide and second most common cancer amongst females in India. Many risk factors associated with breast cancer include early age at menarche and late menopause, nulliparity and later age at first pregnancy, menstrual irregularity, hormone replacement therapy and other oral contraceptives, alcohol consumption, cigarette smoking, obesity and physical inactivity. Familial predisposition, mutation in tumour suppressor gene BRCA1/ BRCA2 and occasionally in BRCA3 or p53 gene is also involved with high risk of breast cancer.

Vitamin D is a fat-soluble steroid hormone produced mainly in two forms: Vitamin D2 and Vitamin D3. Vitamin D2, also known as ergo-calciferol, originates from dietary sources such as plants and fish (salmon, herring, Cod liver oil). Vitamin D3, also known as cholecalciferol, is produced from 7-dihydro-cholesterol under the skin that is exposed to UV-B light. Both forms produce 25-hydroxy-vitamin D, also known as calcidiol after undergoing hydroxylation in the liver under the influence

of mitochondrial enzyme 24-hydroxylase (encoded by CYP24A1). The 25-hydroxy Vitamin D is then transported in the circulation by vitamin D-binding protein and further metabolized in kidneys to produce 1, 25 di-hydroxy-vitamin D or calcitriol under the influence of 1 $\alpha$ -hydroxylase enzyme that is encoded by CYP27B1. Vitamin D protein receptor gene (VDR), first identified in 1979, is a gene lying on the long arm of chromosome 12 (12q12-14) having more than 200 single nucleotide polymorphism. It has an intra-cellular hormone response that binds to 1, 25 di-hydroxy-vitamin D and interacts with VDR response elements of target genes. It is found in epithelial cells of breast, prostate and colon. Vitamin D receptor gene plays an important role in mammary gland through regulation of calcium transport during lactation, milk production and hormone differentiation. In later years after subsequent research, VDR was also identified in human breast tumour tissues hence concluding that it increases risk of breast cancer.

Many studies examined the association between vitamin D level and breast cancer risk, which generally show an inverse association:

**Table I:** previous studies conducted to show association between vitamin D level and breast cancer risk.

Author (year)	Design	Sample Size(N)	Outcome	Result
Yao et al, 2017	Case-control and case series study	579 women with primary incident breast cancer, 574 controls	Vitamin D levels in form of 25 OHD obtained from blood samples via phlebotomy, prior to any treatment	Higher serum levels of 25OHD were associated with reduced risk of breast cancer, with associations strongest for high grade, ER negative or triple negative cancers in pre-menopausal women
Goodwin et al, 2017	Prospective inception study	512 women with early breast cancer	25OHD levels taken from plasma which was collected before initiation of systemic therapy	Low vitamin D levels had an increased risk of distant recurrence and death
Jacobs et al, 2015	Prospective cohort study and control study	3085 women	Vitamin D intake by a questionnaire outlining their daily eating habits, which included foods consumed, their quantity and frequency. Serum Vitamin D level by blood sample was drawn at beginning of study.	No relationship between breast cancer recurrence and vitamin D level was noted in overall population. However, in pre-menopausal women, a significant inverse relationship between vitamin D levels and recurrence was noted.
Hoe Jeong Kim et al, 2014	Descriptive Study	310 cases	Clinico-pathological data were examined to determine the prognostic effects of serum Vitamin D. Expression of Estrogen receptor, Progesterone receptor, Her2Neu receptor were measured using tissue microarrays	Vitamin D deficiency may be associated with poor outcomes in patients with luminal type breast cancer
Abbas et al, 2011	Population based Case-	944 cases, 666 controls	Participants completed a food frequency questionnaire(FFQ) to assess the	Strongly suggested a protective effect for post-menopausal breast cancer.

	control Study		association of dietary vitamin D, calcium and pre-menopausal breast cancer risk	
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In our study, a total of 90 women were enrolled, 56 women with benign breast lump and 34 women with malignant breast lump. In patients with benign breast lump, mean serum vitamin D level was  $18.2 \pm 7$  ng/ml and in patients with malignant breast lump mean serum vitamin D level was  $13.6 \pm 5$  ng/ml. Out of 56 patients with benign breast lump, 44 had Vitamin D deficiency. Out of 34 patients with malignant breast lump, 32 had vitamin D deficiency. The p-value was 0.04 which is significant showing vitamin D deficiency was more prevalent among women with breast cancer and thus Vitamin D deficiency is associated with increased breast cancer risk. In our study, no significant correlation could be found between tumour staging, type, ER, PR and HER2Neu status.

### Conclusion

Vitamin D deficiency is highly prevalent among Indian females. This problem could be addressed by adequate sun exposure and dietary supplementation. Most of the vitamin D studies support the direct association between vitamin D deficiency and breast cancer risk. Further researches will strengthen this association of vitamin D deficiency and breast cancer.

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