Original Article

Vitamin D Deficiency in Breast Cancer Patients and its Association with Histopathological Tumor Characteristics

Sadaf Fatima, Asma Rafique and Fatima Tehsin

ABSTRACT

Objective: To determine the prevalence of vitamin D deficiency in women with breast carcinoma and to determine the association of vitamin D levels with histopathological tumor characteristics.
Study Design: Observational Study.
Place and Duration of Study: This study was conducted at the Oncology Department, Nishtar Medical College / Hospital Multan from April 2016 to October 2016.
Materials and Methods: Ninety female patients with diagnosis of breast cancer on histopathology reporting were selected. A specialized Proforma was used to get information about their personal life e.g. marital status, menopause history, age, BMI, educational status and daily life style. Vitamin D levels were measured in all females. Information regarding tumor grade, stage, type of carcinoma and hormonal receptor status was extracted from pathology, histology and hematology reports of patients.
Results: The mean age of study participants was 46.64±10.64 Years. All of the participants were married. 48 (53.3%) patients were in post-menopausal period. 74 (82.2%) were urban residents. Mean vitamin D levels in study participants were 17.78±14.66 ng/ml. There were 56 (62.2%) patients with deficient vitamin D levels, 18 (20.0%) with sub-optimal and 16 (17.8%) patients with optimal vitamin D levels. We did not found any strong association of vitamin D levels with tumor grades, stage and expression of tumor PR and HER-2 receptors. However in our study, tumor ER receptors expression was significantly high in patients in deficient and optimal vitamin D levels as compared to the patients with suboptimal vitamin D levels.
Conclusion: There is high prevalence of vitamin D deficiency in breast cancer patients. We did not found any association of vitamin D levels with tumor characteristics.
Key Words: Breast Cancer, Vitamin D, menopausal state

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INTRODUCTION

Breast cancer is a leading cause of death in women globally.[1] In Pakistan every 5th women with cancer have diagnosis of breast cancer.[2] Literature have suggested that vitamin D levels are inversely related with the development of many types of epithelial cancers including the breast cancer.[3] It has also been shown that sun-light exposure significantly reduces the risk of breast cancer by 25% to 65%, because sun-light is a direct source of vitamin D production.[4,5] About 90% of total body vitamin D is produced by skin in response to ultra-violet B sun-light radiations, while remaining 10% is obtained from different dietary sources.

In spite of maintaining bone and mineral homeostasis vitamin D has also its role in carcinogenesis. It exerts its anti-proliferative properties by binding to specific vitamin D receptors present in many cells and tissues of the body. Some human genes also contain vitamin D sensitive DNA sequences that are very important for proper cell proliferation, differentiation as well as angiogenesis.[6,7] Deficient levels of vitamin D impair these activities resulting in abnormal cell growth, impaired angiogenesis and thus cancer development. Vitamin D receptors are also present in nuclei of human breast cells and it is hypothesized that polymorphism of these vitamin D receptor genes increases the likelihood of breast cancer in women.[8,9]

Vitamin D is metabolized to 25-hydroxyvitamin D (25OHD) in the liver, 25OHD levels are used to measure Vitamin D levels in the body. Recent data have documented increased risk of reoccurrence of breast cancer and death in women with deficient levels of vitamin D and in those who have early diagnosis of breast cancer.[10-12] Little data have been from Pakistan and also from East Asia regarding prevalence of vitamin D deficiency in female patients with breast carcinoma. So in present study we evaluated the prevalence of vitamin D deficiency in women with breast carcinoma and to determine the association of vitamin D levels with histopathological tumor characteristics.

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MATERIALS AND METHODS

This observational study was conducted in oncology ward of Nishtar Hospital Multan (NHM). Ninety female patients with diagnosis of breast cancer on histopathology reporting were selected in a period of seven months from April 2016 to October 2016. Patients of breast cancer who have received any type of vitamin D supplementation from last one year were excluded from analysis. This study had approval from IRB of hospital.

A specialized Proforma was used to get information about their personal life e.g. marital status, menopause history, age, BMI, educational status and daily life style. Blood samples for vitamin D levels were taken in anti-coagulant free tubes from all participants and 25-OHD levels were measured using chemiluminescence technique using Abbott architect immunodiagnostics system manufactured by Abbott laboratories USA. 25-OHD levels < 20 ng/ml were labelled as deficient, 20-30 ng/ml as suboptimal and >30 were considered as optimal vitamin D levels. Information regarding tumor grade, stage, type of carcinoma and hormonal receptor status was extracted from pathology, histology and hematology reports of patients.

Analysis was done using computer software SPSS v23. Chi-square test was used to see the association between vitamin D levels status and stage of tumor, grade of cancer and hormonal receptor status. Mean vitamin D levels between pre-menopausal and post-menopausal women were compared using independent sample t-test.

RESULTS

Ninety female patients with diagnosis of breast cancer were recruited for this study. The mean age of study participants was 46.64±10.64 Years. All of the participants were married. 42 (46.7%) were with pre-menopausal status and 48 (53.3%) were with post-menopausal status. 74 (82.2%) were urban residents. 66 (73.3%) patients were poor and only 2 (2.2%) patients were rich. 56 (62.2%) females were illiterate. Positive family history of breast cancer was found in 35.6% patients. 84 (93.3%) females were house wives. Mean vitamin D levels in study participants were 17.78±14.66 ng/ml. There were 56 (62.2%) patients with deficient vitamin D levels, 18 (20.0%) with sub-optimal and 16 (17.8%) patients with optimal vitamin D levels.

Regarding association of vitamin D with tumor characteristics, there were 60.7% patients with deficient vitamin D levels who have Tumor Grade I, while most of the patients with sub-optimal and optimal vitamin D levels (66.7% and 62.5% respectively) were with tumor grade II. But this difference was not statistically significant (p-value 0.10).

Regarding stages of tumor, most of the patients with deficient vitamin D levels (50.0%) were with tumor stage III, there were 24.0% patients with suboptimal vitamin D levels in tumor stage III and 62.5% with optimal vitamin D levels (p-value 0.67).

Over expression of tumor estrogen receptor (ER) was found in 71.4% patients with deficient vitamin D levels, in 44.4% patients with sub-optimal vitamin D levels and in 87.5% patients with optimal vitamin D levels with p-value 0.54. Over-expression of progesterone receptors (PR) was found 67.9% patients with deficient levels, in 55.6% patients with sub-optimal and 75.0% patients with optimal vitamin D levels with insignificant p-value of 0.54. over-expression of HER-2 receptor was found in 46.4% patients with deficient vitamin D levels, in 55.6% patients with sub-optimal and in 50.0% patients with optimal vitamin D levels (p-value 0.79).

Table No.1: Baseline Characteristics of Patients.

Variable	Value
Age	46.64±10.64
BMI	27.21±6.67
Marital Status	
Married**(%)**	90 (100)
Unmarried**(%)**	0 (0.0)
Menopause State	
Pre-menopausal**(%)**	42 (46.7)
Post-menopausal**(%)**	48 (53.3)
Residential Status	
Rural**(%)**	16 (17.8)
Urban**(%)**	74 (82.2)
Socio-economic Status	
Poor**(%)**	66 (73.3)
Middle Income**(%)**	22 (24.4)
Rich**(%)**	2 (2.2)
Educational Level	
Illiterate**(%)**	56 (62.2)
Literate**(%)**	34 (37.8)
Family History of Breast Cancer	
Yes**(%)**	32 (35.6)
No**(%)**	58 (64.4)
Occupational Status	
House Wife**(%)**	84 (93.3)
Working Women**(%)**	6 (6.7)
Vitamin D Levels	17.78±14.66
Vitamin D status	
Deficient**(%)**	56 (62.2)
Sub-optimal**(%)**	18 (20.0)
Optimal**(%)**	16 (17.8)

Tumor metastasis was found in 4 (7.1%) patients with deficient vitamin D levels, and in 12.5% patients with optimal vitamin D levels but there was no patients with suboptimal vitamin D levels with insignificant difference p-value 0.61.

We also compared mean vitamin D levels in post and pre-menopausal females and we did not found any significant difference in mean vitamin d levels between these patients; mean vitamin D levels 16.00±14.04 ng/ml and 19.33±15.14 respectively. Mean vitamin D levels were little high in pre-menopausal females with p-value 0.28 (table 3).

Table No.2: Association of Vitamin D status with Tumor Characteristics.

		Vitamin D Status			P-value
		Deficient (<20 ng/ml) N= 56	Sub-optimal (20-29.9 ng/ml) N=18	Optimal (>30 ng/ml) N=16	
Grades of Tumor	Grade I (%)	34 (60.7)	6 (33.3)	6 (37.5)	0.10
	Grade II (%)	20 (35.7)	12 (66.7)	10 (62.5)	
	Grade III (%)	2 (3.6)	0 (0.0)	0 (0.0)	
Stages of Tumor	Stage I (%)	10 (17.9)	2 (11.1)	2 (12.5)	0.67
	Stage II (%)	6 (10.7)	2 (11.1)	0 (0.0)	
	Stage III (%)	28 (50.0)	12 (24.0)	10 (62.5)	
	Stage IV (%)	12 (21.4)	2 (11.1)	4 (25.0)	
Tumor Estrogen Receptor (ER)	Positive (%)	40 (71.4)	8 (44.4)	14 (87.5)	0.02
	Negative (%)	16 (28.6)	10 (55.6)	2 (12.5)	
Tumor Progesterone Receptor (PR)	Positive (%)	38 (67.9)	10 (55.6)	12 (75.0)	0.54
	Negative (%)	16 (28.6)	8 (44.4)	4 (25.0)	
Tumor epidermal growth factor receptor-2 (HER-2)	Positive (%)	26 (46.4)	10 (55.6)	8 (50.0)	0.79
	Negative (%)	30 (53.6)	8 (44.4)	8 (50.0)	
Extent of Disease Spread	Early stage (%)	8 (14.3)	4 (22.2)	2 (12.5)	0.61
	Locally advanced (%)	44 (78.6)	14 (77.8)	12 (75.0)	
	Metastasis (%)	4 (7.1)	0 (0.0)	2 (12.5)	

Table No.3: Comparison of vitamin D levels between pre-menopausal and post-menopausal women.

	Vitamin D Levels		P-value
	Mean	Standard Deviation	
Pre-menopausal women	19.33	15.14	0.28
Post-menopausal Women	16.00	14.04	

DISCUSSION

Vitamin D deficiency have now become a major public health issue. In Pakistan the reported prevalence of vitamin D deficiency have been reported to be from 70 to 97% more than twice the incidence reported from western countries.[13] A study published from Denmark have revealed that immigrants from Pakistan have very low vitamin D levels.[14] In our study, the mean vitamin D levels were 17.78±14.66 ng/ml. In the study by Imtiaz et al. mean vitamin D levels in breast cancer women were 9.6±5 ng/ml.[15]The levels reported by them were very less as compared to our study. Napoli et al. reported mean vitamin D levels in breast cancer women were 13.4±0.5 ng/ml.[16]Many other investigators have also found decreased vitamin D levels in breast cancer patients.[10,17,18]

In our study, there were 62.2% patients with deficient vitamin D levels, 20.0% with sub-optimal vitamin D levels and 17.8% patients with optimal vitamin D levels. In the study by Imtiaz et al. there were 99% patients with deficient or sub-optimal vitamin D levels and only 1.0% patients with optimal vitamin D levels. In a study by Acevedo et al. 70.47% female having breast cancer with deficient vitamin D levels, 22.85% patients with sub-optimal vitamin D levels and 6.7% patients with optimal vitamin D levels.[19] These results were similar to the results of our study.

In our study, most of women (82.2%) who presented with breast cancer were living in urban areas. Another study conducted in Pakistan have also found a high prevalence (91.7%) of urban population who present with breast cancer.[20]

In our study, mean vitamin D levels were little less in post-menopausal women as compared to pre-menopausal women. Other studies have also revealed similar results. Vrieling et al. concluded that low vitamin D levels is associated with higher risk of metastasis and poor survival in BC patients.[21] In our study, there were 6 patients with metastasis, out of which 4 patients were with deficient vitamin D levels.

In our study, we did not found any strong association of vitamin D levels with tumor grades, stage and expression of tumor PR and HER-2 receptors. However in our study, tumor ER receptors expression was significantly high in patients in deficient and optimal vitamin D levels as compared to the patients with suboptimal vitamin D levels. Imtiaz et al. also did not found any significant association of vitamin D levels with tumor characteristics.[15] However, Thanasitthichai et al found significant association of vitamin D levels with clinic-pathological features of patients with breast cancer. Hatse et al. found significant association of vitamin D levels with improved operative outcomes.[22] Recent meta-analysis reports have also concluded improved survival in patients with high levels of vitamin D.[23,24]

CONCLUSION

There is high prevalence of vitamin D deficiency in breast cancer patients. We did not found any

association of vitamin D levels with tumor characteristics.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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