

Original Research Article

Analysis of serum level of 25-hydroxycholecalciferol, calcium and lipid profile in carcinoma breast

Sanjeev Saha, Bipin Kumar Singh, Kirti Singh, Rahul Khanna, Ram Niwas Meena*

Department of General Surgery, Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India

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***Correspondence:**

Dr. Ram Niwas Meena,

E-mail: drramniwasmeena@gmail.com

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ABSTRACT

Background: Breast cancer (BC) is one of the major surgical problems in India, particularly in younger females. There are conflicting reports regarding the association between the serum lipid profiles, vitamin D, calcium and BC. The objective of the study was to measure the serum vitamin D, calcium and lipid profile levels in BC, benign breast diseases (BBD) and healthy control (HC), and compared these variables with clinico-pathological parameters in BC patients.

Methods: Forty histologically confirmed invasive BC, 20 BBD patients and 20 healthy individuals taken as controls were enrolled for estimation of serum lipid profile, calcium and vitamin D. The study variables were compared with all three groups. In BC group, the levels were also compared with clinico-pathological parameters.

Results: The mean age of subjects in BC, BBD and HC group was 48.88 ± 11.33 , 31.10 ± 3.93 and 36.30 ± 5.97 years respectively. The levels of serum cholesterol, triglyceride, HDL, LDL, VLDL and calcium was significantly increased and vitamin D was significantly decreased in BC patients as compared with BBD and HC group ($p < 0.001$). On comparing lipid profile, calcium and vitamin D in receptor positive BC patients and triple negative BC patients, only serum HDL and serum calcium was significantly high in receptor positive BC patients ($p = 0.047$ and $p = 0.041$).

Conclusions: Our findings suggest that lower vitamin D level and higher calcium and lipid profile level could be an important etiopathological factor in the causation of BC. Correction of these factors could be used as a prophylactic and preventive strategy in the population against BC.

Keywords: 25-hydroxycholecalciferol, Calcium, Lipid profile, Breast cancer

INTRODUCTION

India has been facing a cancer epidemic. It was estimated that over 100,000 new breast cancer (BC) patients are diagnosed annually in India.^{1,2} By 2020 it is estimated that 1/5th of the world's cancer cases will be in India.³ The exact cause of BC is not completely known, but presumably it represents a complex relationship of genetic susceptibility and environmental factors.^{4,5} Various studies have suggested that the relative risk of BC is directly linked with the increase in dietary fat intake.⁶ The association between lipids and BC is

undistinguished. Until now, inconsistent results have been reported on the relationship between lipids and risk of BC in women. Several studies found that the dietary fat increases BC risk. These studies have been strongly supported by international data collected among developed countries during the past few decades. Population aggregates with higher lipid intake have tended to report higher BC prevalence and mortality.⁷

Interestingly, some laboratory data suggests that calcium can reduce the progression of mammary tumors in mice.⁸ However, several epidemiologic studies have provided

various evidence for an inverse relationship between dietary calcium intake and BC risk.^{9,10} Additionally, calcium regulates vitamin D and parathyroid hormone, both of which have been proposed to influence BC risk.^{11,12} Almquist et al reported that serum calcium levels were inversely related with BC risk among premenopausal women, whereas a positive relationship was observed among overweight postmenopausal women.¹³

Vitamin D deficiency has been reported in BC patients during adolescence, pregnancy and/or lactation and after menopause, even in sunny climates.¹⁴ Women with raised vitamin D status, including those who are commonly exposed to sunlight and consumers of comparatively higher amounts of vitamin D, had significantly lesser incidence rates of BC.¹⁵ Case-control studies with measurement of 25(OH) D after BC diagnosis suggests an inverse relationship among serum 25(OH) D and the risk of BC, while low vitamin D levels were associated with a 73% increased risk of death from BC.^{15,16}

Some previous studies have found associations between increase calcium intake and increase vitamin D intake and reduced BC risk in postmenopausal women, but the results have not been consistent.¹⁷⁻²⁰ The aim of the present study is to investigate serum vitamin D, calcium and lipid profile levels in BC patients, BBD patients and healthy control subjects of matched age group and compare these with clinico-pathological parameters such as stage, menopausal status, hormone receptor status of breast cancer patients.

METHODS

The study was carried out in the Department of General Surgery in collaboration with Department of Pathology and Biochemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi. The study was done after ethical approval from Institutional Ethics Committee, period ranging from July 2015 to June 2017.

This study was undertaken on 40 histological confirmed invasive BC patients, 20 BBD patients and 20 healthy controls. Patients who have received chemo or radiotherapy prior to presentation, previous history of malignancy or any disease affecting calcium metabolism (parathyroid, pancreatic, liver diseases etc.) and pregnant and lactating women were excluded from the study.

After obtaining the informed consent a detailed history, physical examination, laboratory investigations and chest and abdominal X-ray was done in all the patients. 2 ml of blood was taken from peripheral vein and transferred to sterile plane vial. The estimation of serum lipid profile (total cholesterol, triglyceride, HDL, LDL and VLDL), calcium and vitamin D was done in all the subjects. The statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 16.0 statistical analysis software. The values were represented in number (%) and mean±standard deviation (SD). For categorical variable

Chi-square test and Fisher Exact test was used. Student's t test was used for comparing two groups of mean and one-way ANOVA test was used for more than two groups. The critical value of 'p' indicating the probability of significant difference was taken as <0.05 for comparison.

RESULTS

The mean age of subjects in BC, BBD and HC group was 48.88±11.33, 31.10±3.93 and 36.30±5.97 years respectively with age range from 26 to 80 years. There was statistically significant age difference was found between BC versus BBD group (p<0.001) and BC versus HC group (p<0.001). No significant difference was found between BBD versus HC group (p=0.198). At time of presentation, 24 (60%) patients have initiation of symptoms after 6-12 months followed by <6 months in 10 (25%) patients and >12 months in 6 (15%) patients respectively.

Table 1: Demographic characteristics of BC patients.

	n=40
Age (years)	48.88±11.33
Duration of symptoms (months)	9.07±7.09
Age of menarche	N (%)
<15 year	33 (82.5)
>15 year	7 (17.5)
Menstrual history	
Premenopausal	18 (45.0)
Postmenopausal	22 (55.0)
Family history of breast cancer	7 (17.5)
Parity	
No child	2 (5.0)
1-3 child	34 (85.0)
>3 child	4 (10.0)
Breast pain	4 (10.0)
Nipple discharge	6 (15.0)
Ulceration of breast	9 (22.5)
Axillary swelling	33 (82.5)

Among BC group, family history of breast cancer was present in 7 (17.5%) patients. BC was found to be relatively common in patient who attended early menarche 33(82.5%), post-menopausal females 22 (55%) and had 2-3 child (Table 1). All the patients in BC group had T3 and T4 stage. In 30 (75%) patients had T4 stage followed by T3 stage in 10 (25%). Nodal involvement was seen in 37/40 (92.5%) patients with nodal status N1 in 29 (72.5%), N2 in 6 (15%) and N3 in 2 (5%) patients. In radiographic evidence of distant metastasis was seen only in 3 patients while most of the patients had no distant metastasis. Out of 40 cases of BC, 11 (27.5%) patients had triple negative while ER, PR, HER-2/neu status was positive in 12 (30%), 13 (32.5%) and 22 (55%) patients respectively. Infiltrating ductal carcinoma was the most common tumor type found in 37 (92.5%) patients followed by adenocarcinoma in 3 (7.5%) patients.

Table 2: Comparison of various parameters between carcinoma breast, benign breast disease and healthy control.

	Breast cancer Mean±SD (n=40)	Benign breast disease Mean±SD (n=20)	Healthy control Mean±SD (n=20)	BC group vs. BBD group (p value)	BC group vs. HC group (p value)	BBD group vs. HC group (p value)
Cholesterol	200.18±24.23	181.55±21.17	172.30±36.11	0.042	0.001	0.329
TG	188.88±18.45	159.78±24.37	131.58±40.81	0.001	<0.001	0.011
HDL	50.52±4.45	45.21±10.56	40.06±9.63	0.045	<0.001	0.115
LDL	183.28±7.43	152.50±39.42	115.30±35.99	<0.001	<0.001	0.003
VLDL	49.55±9.00	46.01±15.89	27.81±7.7	0.716	<0.001	<0.001
Calcium	11.43±0.82	10.12±0.50	9.86±1.12	<0.001	<0.001	0.349
Vitamin-D	16.74±2.13	26.02±1.63	25.57±1.84	<0.001	<0.001	0.418

Table 3: Laboratory parameters among 40 breast cancer patients as per their menstrual status

	Premenopausal (n=18) Mean±SD	Postmenopausal (n=22) Mean±SD	t-value	P value
Cholesterol	198.58±18.40	200.86±26.61	-0.269	0.790
TG	188.25±18.38	189.14±18.81	-0.138	0.891
HDL	50.08±3.91	50.71±4.72	-0.406	0.687
LDL	183.92±6.25	183.00±7.98	0.353	0.726
VLDL	47.91±5.43	50.25±10.17	-0.746	0.460
Calcium	11.35±0.89	11.47±0.81	-0.391	0.698
Vitamin-D	16.89±2.19	16.68±2.14	0.27	0.784

Table 4: Receptor positive vs. triple negative breast carcinoma.

	Receptor positive breast carcinoma (n=29) Mean±SD	Triple negative breast carcinoma (n=11) Mean±SD	t-value	P value
Cholesterol	218.20±28.23	197.60±22.91	1.831	0.075
TG	190.40±15.01	188.65±19.06	0.195	0.846
HDL	54.20±3.19	50.00±4.39	2.052	0.047
LDL	188.40±7.12	182.5±7.28	1.685	0.100
VLDL	53.80±9.12	48.94±8.96	1.132	0.265
Calcium	12.14±0.61	11.33±0.81	2.112	0.041
Vitamin-D	15.82±1.70	16.88±2.17	1.041	0.304

On comparing serum lipid profile, calcium and vitamin D in BC, BBD and HC group. The levels of mean serum cholesterol, triglyceride, HDL, LDL and calcium was significantly high and vitamin D level was significantly low in BC group as compared with BBD ($p=0.042$, $p=0.001$, $p=0.045$, $p<0.001$, $p<0.001$, $p<0.001$) and HC group ($p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). Serum VLDL was comparable in both BC and BBD group but statistically significant difference was found between BC and HC group (Table 2). On comparing all these study variables in BBD and HC group, the level of serum triglyceride, LDL and VLDL was significantly high in BBD group and serum total cholesterol, HDL, calcium and vitamin D was comparable in both the groups (Table 2).

Out of 40 patients of BC, 18 (45%) had premenopausal and 22 (55%) had postmenopausal. On comparing serum lipid profile (serum cholesterol, triglyceride, HDL, LDL, VLDL), calcium and vitamin D in premenopausal and postmenopausal patients we found there was no statistically significant difference was observed between premenopausal and postmenopausal BC patients (Table 3).

Of 40 BC patients we found 29 (72.5%) patients receptor positive and 11 (27.5%) had triple negative BC patients. On comparing serum lipid profile (serum cholesterol, triglyceride, HDL, LDL, VLDL), calcium and vitamin D in receptor positive and triple negative BC patients, we found serum HDL and serum calcium was significantly raised in receptor positive cases and serum cholesterol,

triglyceride, LDL, VLDL and vitamin D was comparable (Table 4).

DISCUSSION

Women who have early menarche and late menopause have a slightly higher risk of BC. This may be related to a higher lifetime exposure to the hormones.^{21,22} Various factors such as lipid profile, calcium and vitamin D levels have been implicated in correlation of BC and may be useful in treatment of these patients. Serum calcium, serum lipid profile and serum vitamin D are few of the parameters which affect the prognosis of BC patients. Patients suffering from breast carcinoma have a poor prognosis because of the lack of effective treatment strategies. Detection and identification of parameters such as level of serum lipid profile, calcium, and vitamin D may be helpful for predicting therapeutic response among BC treatment.

This study was carried out with an aim to measure the serum vitamin D, calcium and lipid profile levels in BC, BBD and HC subjects and also compared these with clinico-pathological parameters in BC patients.

In this study, the mean age of subjects in BC, BBD and HC group was 48.88±11.33, 31.10±3.93 and 36.30±5.97 years respectively with age range from 26 to 80 years. There was statistically significant difference in age of subjects enrolled in the study. The reason for this difference among groups could be the fact that in Indian women diagnosis of BC is late and about 70% of patients diagnosed, belong to clinically advanced disease.²³ On the other hand, benign breast disease can be diagnosed at any age. Sangma et al found in his study the age of BBD patients was seen to range from 8 to 68 years with a mean age at presentation being 28.4 years.²⁴ In an Indian study conducted by Dixit et al similar to our study found the mean age of subjects in malignant, benign and control group was 45.71±10.04, 24.91±6.83 and 35.60±12.42 years, respectively.²⁵ They also found the significant difference in age of subjects.

In our study, all the patients in BC group advanced stage (T3 and T4). Nodal involvement was seen in 37/40 (92.5%) patients. In radiographic evidence of distant metastasis was seen only in 3 patients while most of the patients had no distant metastasis. In this study, 11(27.5%) patients had triple negative while ER, PR, HER-2/neu status was positive in 12 (30%), 13 (32.5%) and 22 (55%) patients respectively.

In respect to lipid levels, many studies have indicated the correlation of lipids and lipoproteins with the risk of breast cancer.²⁶ The exact mechanisms by which lipids, lipoproteins contribute to carcinogenesis are not clearly understood. Previous study reported that lipids may primarily affect the gonads, and consequently higher estradiol secretion could influence the development of

malignancies in the mammary glands and lymphoid system.²⁷

In the present study, significantly increased serum cholesterol, triglyceride, HDL and LDL levels were observed among the BC group as compared to that of BBD group ($p=0.042$, $p=0.001$, $p=0.045$, $p<0.001$, $p<0.001$, $p<0.001$) and HC group ($p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). Serum VLDL was comparable in both BC and BBD group but statistically significant difference was found between BC and HC group.

Previous studies also reported elevated TC and TG levels in breast cancer.^{26,28} It is suggested that cholesterol may apparently stimulate cell proliferation and induce fibrosarcomas in mice.²⁷ Report also suggests that higher concentration of TG may lead to the decreased level of sex hormone-binding globulin, resulting in higher amount of free estradiol, which may likely to increase breast cancer risk.²⁹ Our results also propose that higher concentrations of TC and TG may either play a role in carcinogenesis or are responsible for higher incidence of breast cancer. Previous studies reported decreased serum HDL-C concentration with higher TG levels in cancer.³⁰ In contrast, significantly higher serum HDL-C concentration has also been reported in breast cancer patients.³¹

Ray and Hussain et al examined the association between lipids, lipoproteins, vitamins and it was found that Breast cancer patients had a higher level of serum cholesterol, triglycerides and LDL-C than healthy controls.³² Similarly higher levels of all components of lipid profile were found among breast cancer patients compared to healthy control subjects in our study as well. These parameters were by and largely similar among benign breast disease and healthy control subjects as compared to carcinoma breast where these levels were high. Higher level of serum triglycerides and lower level of HDL-C among breast cancer patients compared to healthy control shown by Chang et al; Furberg et al; Kucharska-Newton et al in contrast to our study in which levels of HDL were also high.³³⁻³⁵

There are limited studies mimicking the design used by us, where comparisons have been made among controls, benign breast disease, and malignant patients. Dixit et al who conducted such study found mean serum cholesterol levels in malignant, benign and healthy controls did not show a significant difference, however, mean TG levels of malignant cases were significantly higher as compared to that of benign and healthy controls.²⁵ Mean serum HDL levels were significantly higher in benign group as compared to healthy controls. However, mean serum LDL levels were maximum in healthy controls and minimum in benign breast disease group. Another study by Shah et al found the mean TG levels was significantly higher in malignant patients and controls as compared to benign cases.³⁶ However, in their study HDL and TG

levels were found to be significantly different between malignant and benign cases.

Some authors have attempted to evaluate the lipid levels in patients with different stages of breast cancer and have found significant differences for different stages.²⁶ In our study, no such association could be seen as all the cases were of advanced stage of cancer.

In our study the serum vitamin-D level in carcinoma breast patient was 16.74 and in benign breast disease was 26.02 and in healthy control was 25.57 which shows significant difference ($p < 0.001$). This could be attributed to the fact that level of serum vitamin-D is significantly lesser in breast cancer patients compared to benign breast diseases and healthy control female. There was a weak inverse association between 25 (OH) D levels and breast cancer risk shown by Lappe et al and WHI trial as consistent with our study.³⁷

In our study the mean serum calcium in carcinoma breast patient was 11.43 and in benign breast disease was 10.12 and in healthy control was 9.86 which shows significant difference ($p < 0.001$). This could be attributed to the fact that level of serum calcium increases in Breast cancer patients compared to benign breast diseases and Healthy normal female which is inverse result to the most of studies done. Low Serum calcium levels were positively associated with breast cancer risk in premenopausal and/or overweight women.³⁸ Calcium is required for optimal activity of vitamin D and has been found to participate in regarding apoptosis, cell proliferation and differentiation. We found that serum calcium level was slightly higher among breast cancer patients compared to healthy controls (11.43 ± 0.82 versus 9.86 ± 1.12). The more likely explanation for this difference will be that breast cancer patients were mostly peri or postmenopausal on our study and serum calcium level is known to rise with menopause. This is explained by the fact that the estrogen levels decline in menopausal women and the bones became more sensitive to parathyroid hormone resulting in higher serum calcium levels. A study by Martin et al found that serum calcium levels were positively associated with breast cancer risk in premenopausal women although the exact mechanism was not explained.³⁸

In our study we also found that vitamin D level lower in breast cancer patients (16.74 ± 2.13 ng/ml) compared to healthy control (25.57 ± 1.84 ng/ml). On the other hand, vitamin-D level in benign breast disease (26.02 ± 1.63 ng/ml) found nearly similar to healthy control (25.57 ± 1.84 ng/ml) and higher than that of breast cancer patients (16.74 ± 2.13 ng/ml). Similar to our study Garland et al also found individuals with a higher serum level of 25(OH)D (> 52 ng/ml), which is the major circulating metabolite of vitamin D and the marker for determination of a patient's vitamin D status showed a 50% decrease of breast cancer risk compared to those with low levels of 25(OH)D (< 13 ng/ml).³⁹

In this study we found 29 (72.5%) patients receptor positive and 11 (27.5%) had triple negative BC patients. On comparing serum lipid profile, calcium and vitamin D in receptor positive and triple negative BC patients and we found serum HDL and serum calcium was significantly raised in receptor positive cases and serum cholesterol, triglyceride, LDL, VLDL and vitamin D was comparable.

In view of these limitations, the present study in general supports the finding that lipid levels might vary in breast cancer; however, their role in benign breast disease might entirely vary. Further studies on a larger sample size with a design that can take care of confounding effect of different variables are recommended.

CONCLUSION

We postulate that lower serum vitamin-D level and higher calcium and lipid profile level could be an important etiopathological factor in the causation of breast cancer. Correction of these factors could be used as prophylactic and preventive strategy in the population against breast cancer.

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