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Nutritional risk factors and status of serum 25(OH)D levels in patients with breast cancer: A case control study in India

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ABSTRACT

To study the nutritional risk factors and status of serum 25(OH)D levels in patients with breast cancer. A total of 100 women (cases) with confirmed breast cancer (BC) matched with equal number of healthy females (controls) of similar age and socioeconomic status (SES) were included in study. Controls included were nonbreast cancer patients who accompanied the patients to a tertiary care hospital. All the subjects (cases and controls) were administered a questionnaires to collect data on socioeconomic status, dietary pattern and the frequency of food consumption using a validated food frequency questionnaire. Anthropometric assessment was done for waist and hip circumference to calculate waist to hip ratio (WHR). Non fasting blood samples were collected for serum 25-hydroxyvitamin D [25(OH)D] levels estimation using chemiluminescent immunoassay technique and total serum calcium levels by colorimetric assay technique. Serum 25(OH)D and total calcium levels were expressed in ng/ml and mg/dl. Vitamin D deficiency was defined as per the guidelines set by United States Endocrine Society. The mean age of cases and controls was 45 ± 9 and 46 ± 10 years respectively. On multivariate analysis, an inverse association with BC was found for less frequency of fruits consumption with an adjusted (ORs, 95% CI) (2.7, 0.5–15.7) respectively. Mushroom intake was inversely associated with risk of BC (ORs, 95% CI) (5.6, 1.9–16.6). Saturated fat intake and high WHR were significantly associated with high risk of BC with adjusted ORs, 95% CI of (3.4, 1.4–8.1) and (5, 1.4–17). A significant association ($p < 0.05$) was found between low serum 25(OH)D levels and the risk of BC with adjusted ORs, 95% CI of (2.5, 0.9–7.4). Majority of the patients with BC were suffering from vitamin D deficiency. Dietary intake of mushrooms containing vitamin D naturally was found to be associated with decreased risk of breast cancer. A significant association was found between low serum 25(OH)D levels (<20 ng/ml) with the risk of BC. Obesity as a consequence of nutritional risk factors determined by higher WHR was found to be significantly associated with the risk of BC.

1. Introduction

Cancer is a major public health problem and cause of death worldwide. According to WHO, cancer accounted for 7.6 million deaths in 2008, which is projected to rise with an estimated 13.1 million deaths in 2030. Breast cancer (BC) is the most common cancer among women, accounting for 25% of all new cancer cases [1]. In India, BC is the leading cancer diagnosed in women overtaking cervical cancer [2]. A number of risk factors are associated with BC like age, family history, genetic mutation, breast density, reproductive factors, nutritional status, obesity, alcohol use and socioeconomic status (SES). Epidemiological and clinical evidence supports that nutrition in its broadest sense, plays a role in BC [3,4]. Evidence suggests that vitamin D intake (ergocalciferol and cholecalciferol) in association with calcium may be protective against BC [5–7]. Women with 25(OH)D concentrations ≥40 ng/ml have a significantly lower risk of cancer (~70%) compared with concentrations <20 ng/ml [8].

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Vitamin D has been shown to have anti-carcinogenic properties like effects on cell proliferation and differentiation [9]. Synthesis of 1,25-dihydroxyvitamin D in breast tissue may contribute to maintenance of normal cell function, which could be impaired in vitamin D deficiency. A large number of Indian women are affected with BC. The literature available on the nutritional risk factors in BC has provided mixed results [10]. Hence, the present case control study aimed to investigate the nutritional factors and status of serum 25(OH)D levels and the risk of BC was conducted.

2. Materials and methods

A hospital based case control study was conducted. Women (cases) with confirmed diagnosis of BC attending a tertiary health care hospital located at latitude of 28.56N and longitude of 77.21E in the national capital territory of India were enrolled. Patients were referred to the current hospital from peripheral hospitals, clinics or physicians in private practices.

Considering average serum 25(OH) levels in cases as 9.5 ± 6.5 ng/ml and controls as 15 ± 13 ng/ml [11] Power of 90 with alpha equal to 5%, the required estimated sample size was seventy seven (77), we recruited a total of 100 cases and 100 controls of similar age.

Controls were healthy females of similar age and socioeconomic status (SES) who accompanied the nonbreast cancer patients to hospital. The case to control ratio was maintained as 1:1. The inclusion criteria adopted was i) confirmed BC by histopathological and fine needle aspiration cytology (FNAC) reports ii) No history of specific treatment for BC, iii) absence of any chronic disease like diabetes or crohn's disease that may affect the dietary intake iv) written consent to participate in the study. Exclusion criteria adopted was i) any vitamin, protein or mineral supplement intake during last one year, ii)corticosteroid therapy, iii) use of antiepileptic drugs, iv) suffering from hepatic disorders v) severe malnutrition vi) non ambulatory patient. The study was conducted from November 2014 till December 2015.

We had a total of (n = 100) cases who fulfilled the inclusion criteria. A semi structured questionnaire was used to record data on parameters like age and socio economic status. Socio economic status was determined by using modified Kuppuswamy's SES scale [12]. Dietary consumption pattern for different food items was done by using a validated food frequency questionnaire method for selected food groups. Waist and Hip circumference to calculate Waist to Hip Ratio (WHR) was done by using standard tools and the cut offs used were adopted from the guidelines set by World Health Organization [13]. The approval for the study was obtained from the Institutional ethics board.

Non fasting blood sample collection was done for the biochemical estimation of serum 25(OH)D and total calcium (Ca) levels. The season for blood with draw was similar for cases and controls. Three milliliters of blood was withdrawn from the median cubital vein of cases. The serum separation was carried out within 2 h after collection by centrifugation at 2100 revolutions per minute (rpm) for seven minutes. Serum samples were stored at minus 80 °C till biochemical analysis was done. Serum 25(OH)D and total calcium levels were estimated by chemiluminescent immunoassay (chemiluminescence) and colorimetric assay (Roche Cobas) technique. The values were documented in ng/ml for 25 (OH)D and mg/dl for serum calcium levels. Vitamin D deficiency was defined as per the criteria of United States Endocrine Society [14]. Cases and controls were subjected to similar investigations. Internal and external quality control was maintained throughout the assay.

2.1. Measurement of serum 25(OH)D levels by chemiluminescence technique principle

25(OH)D levels in serum was measured as a standard procedure at the department of biochemistry at an apex healthcare institute. The LIAISON® 25-hydroxyvitamin D Assay (DiaSorin) uses chemiluminescent immunoassay technology. The lower limit of Quantitation of the assay was 4.0 ng/ml [15]. Specific antibody to vitamin D is used for coating magnetic particles (solid phase) and vitamin D is linked to an isoluminol derivative. During the incubation, 25(OH)D was dissociated from its binding protein and competes with labelled vitamin D for binding sites on the antibody. After the incubation, the unbound material was removed with a wash cycle. Subsequently, the starter reagents were added and a flash chemiluminescent reaction was initiated. The light signal was measured by a photomultiplier as relative light units and was inversely proportional to the concentration of 25(OH)D present in samples. Internal and external quality control was maintained by running a sample of known concentration of 25(OH)D along with the samples for analysis. The coefficient of variance calculated for low QC was 8% and high QC was 13% which was found to be similar to recent research study for measurement of 25(OH)D assays [16].

2.2. Measurement of serum calcium levels by colorimetric assay (Roche cobas) technique

Serum total calcium estimation was done on an automated analyzer, COBAS INTEGRA 400 Plus. Calcium ions react with O-cresolphthelein under alkaline conditions to form a violet colored complex. The addition of 8- hydroxyl quinoline prevents interference by magnesium and ferric ions. The color intensity of the complex formed was directly proportional to the calcium concentration [17]. It is determined by measuring the increase in absorbance at 552 nm. The value is expressed in mg/dl.

2.3. Statistical analysis

Categorical and continuous data were presented as frequency (%) and mean ± sd respectively. To see the comparison of a continuous variable between two independent groups, student's *t*-test/Wilcoxon rank sum test was used and to see the association between two categorical variables, Chi-square/Fisher's exact test was applied. Bivariate and multivariate logistic regression analysis was done for unadjusted and adjusted odds ration with its 95% CI, respectively. To select the variables in the final model, any variable whose bivariate test had a p-value <0.25 along with all other variables of known biological/theoretical importance was considered as a covariate for the backward stepwise multivariate logistic regression model with probability of entry as 0.05 and probability of removal as 0.10. All the p-values less than 0.05 were taken as significant. All the data analysis was done using software Stata 12.1.

3. Results

A total of 100 cases with confirmed BC matched with equal number of healthy controls of similar age and SES were included in this study. The mean age of cases and controls was 45 ± 9 and 46 ± 10 years respectively. Baseline characteristics of cases and controls are shown in Table 1. It was found that a high percentage of women (69%) with BC were in the age group of 28–48 years. On the basis of American Joint Committee on Cancer (AJCC) classification for staging of BC, it was found that (83%) of the patients were diagnosed with BC stage II and III respectively. The unadjusted and adjusted odds ratio for BC according to the presence of risk factors is depicted in Table 2. It was found that

Table 1
Baseline characteristics of the cases and controls (N = 100).

Characteristics	Cases N (%)	Controls N (%)
Age (years)		
28–38	30 (30%)	31 (31%)
39–48	39 (39%)	39 (39%)
49–58	17 (17%)	16 (16%)
≥59	14 (14%)	14 (14%)
Type of family		
Nuclear	63 (63%)	58 (58%)
Joint	37 (37%)	42 (42%)
Religion		
Hindu	81 (81%)	95 (95%)
Muslim	15 (15%)	3 (3%)
Others	4 (4%)	2 (2%)
Educational Status		
Graduate and above	30 (30%)	31 (31%)
Intermediate (11th and 12th)	12 (12%)	30 (30%)
Primary to High school	23 (23%)	17 (17%)
Illiterate	35 (35%)	22 (22%)
Socio-economic status		
Upper	15 (15%)	15 (15%)
Upper middle	29 (29%)	29 (29%)
Middle	37 (37%)	37 (37%)
Lower	19 (19%)	19 (19%)
Histologic grade		
Grade I	13 (13%)	NA[a]
Grade II	52 (52%)	NA[a]
Grade III	31 (31%)	NA[a]
Grade IV	4 (4%)	NA[a]

[a] Not Applicable.

mushroom consumption containing vitamin D naturally was inversely associated with risk of BC ($p < 0.05$).

Saturated fat consumption was significantly associated ($p < 0.05$) with risk of BC and the risk increased to more than three times after adjusting for other variables (OR = 3.4, 95% CI: 1.1, 1.4, 8.1) (Table 2). Similarly, subjects with lower intake of fruits had an increased risk of BC (OR = 2.7, 95% CI: 0.5–15.7). Subjects with higher Waist to Hip Ratio (WHR > 0.85) had five times increased risk of BC (OR = 5, 95% CI: 1.4–17). Serum calcium levels were found to be in the normal range for both cases and controls. Serum 25 (OH)D levels were less than 20 ng/ml in more than 90% of patients. A significant association was found between low serum levels of 25 (OH)D and risk of BC.

4. Discussion

The results of the present study revealed that majority (69%) of BC cases were in the age group of 28–48 years. In Asia, BC incidence peaks among women in their 40s which are around 20 years earlier compared to women from western countries [18]. Breast cancer at younger age has been linked to genetic/hereditary factors [19]. However there is no strong evidence to support it. Our study had majority (62%) of cases from middle and lower SES with primary or no level of education. A recent study from India documented women from low socio-economic strata experience higher death rates due to diagnosis of breast and other cancers at late stages [20].

Low SES with less education and awareness is negatively associated with prevalence of health outcome. This explains the lack of awareness and preventive measures against various diseases including BC [21].

Nutrition in early life can affect height and age at menarche, established risks factors for BC. There exists increasing evidence that dietary factors can play an important role in both the development and prevention of BC [22]. Foods like fish, fish oils, eggs, mushroom, milk, red meat, poultry fat contain vitamin D naturally. However, lack of accessibility and vegetarian dietary practices reduces dietary intake of vitamin D. In our study, we found that other than mushroom, consumption of vitamin D containing foods was not associated with risk of BC. Similar results were found in a recent research study where no association was found between dietary vitamin D or calcium intake and BC risk [23].

Saturated fat consumption in comparison to unsaturated fat was significantly associated ($p < 0.05$) with risk of BC. The odds of having BC increased to more than three times (OR, 95% CI: 3.4, 1.4–8.1). This was in accordance with the studies conducted earlier where high intake of low-fat dairy foods, especially skim/low-fat milk was associated with reduced risk of BC [24,25].

Similarly, subjects with lower intake of fruits had an increased risk of BC (OR = 2.7, 95% CI: 0.5–15.7). Recent research studies have documented an inverse relationship of high fruits and vegetable intake with BC risk [26,27]. The possible mechanism for a protective effect of fruit and vegetable consumption could possibly be the antioxidant and negligible fat properties of fruits and vegetables.

WHR, a measure of central adiposity, is gaining increased use as a measure of etiologically significant obesity and is thought to be more closely related to BC [28]. WHR is associated with an increased risk of both pre- and postmenopausal BC. Obesity as a consequence of higher WHR is also associated with significant hormonal changes such as decreased serum estradiol and sex hormone binding globulin (SHBG) levels, increased peripheral fat conversion of estrogens to progesterone and increased serum testosterone levels that may be associated with an increased risk of BC [29]. Subjects with higher Waist to Hip Ratio (WHR > 0.85) had five times increased risk of BC (OR = 5, 95% CI: 1.4–17). Research studies have also found an association between WHR and the risk of BC especially in postmenopausal women [30,31].

Preclinical and clinical findings support the hypothesis that low levels of vitamin D are linked to an increased risk of BC. Vitamin D has been implicated in proliferative, apoptotic, anti-angiogenic, and pro-differentiative processes [32]. In our study, a higher percentage of cases (93%) were suffering from vitamin D deficiency (serum vitamin D levels <20 ng/ml) as compared to controls (83%). Similar results were observed in another study where invariably almost all patients with BC were vitamin D deficient [33]. Scientific research concluded that lower level of vitamin D may be associated with higher incidence and worse prognosis in terms of overall survival and distant disease free survival particularly in postmenopausal women [34,35].

In the present study, serum 25(OH)D levels were less than 20 ng/ml in more than 90% of patients. This is in accordance with the recent studies where 77.2% [36] and 68% [37] patients with BC were suffering from vitamin D deficiency. The present study revealed a significant association between low serum levels of 25(OH)D with risk of BC (OR, 95% CI: 2.5, 0.9–7.4). Similar results were documented in a recent research study on 120 BC patients. The adjusted ORs (95% CIs) for invasive BC was found to be 6.1 (2.4, 15.1) for women with a serum 25(OH)D concentration less than10 ng/ml and 4.0 (1.6, 10.4) for women with a serum concentration in the range of 10 to less than 20 ng/ml [11]. Another study found similar results where an inverse association was found between circulating vitamin D levels and BC risk among pre- and postmenopausal women [38].

Specifically, case-control studies have generally shown a statistically significant reduction in risk for BC associated with higher circulating concentrations of 25(OH)D [11,39,40]. The present case control study is in accordance with the results documented by earlier research studies. Serum calcium levels were found in normal

Table 2
Unadjusted and Adjusted Odds Ratio (95%CI) for predictors of Breast Cancer.

Parameter	Cases N = 100	Controls N = 100	p-value	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)					
28–38	30	31	0.997	1.0	–
39–48	39	39		1.1 (0.5, 2.0)	
49–58	17	16		1.1 (0.4, 2.5)	
≥ 59	14	14		1.1 (0.4,2.5)	
Poultry					
3/wk–1/wk	8	14	0.275	1.0	–
Twice–once/Mo	18	18		2.0 (0.6, 6.5)	
Occ/Never	74	68		2.1 (0.8, 5.7)	
Fish					
3/wk–1/wk	7	9	0.76	1.0	–
Twice–once/Mo	8	9		1.1 (0.2, 4.0)	
Occ/Never	85	82		1.3 (0.4, 3.7)	
Eggs					
Daily–1/wk	17	30	0.091	1.0	–
Twice–once/Mo	10	8		2.5 (0.7 to 8.4)	
Occ/Never	72	62		2.0 (1.0, 3.9)	
Mushroom					
3/wk–1/wk	2	7	0.007	1.0	1.0
Twice–once/Mo	3	13		0.8 (0.1, 6.03)	2 (0.13, 8.9)
Occ/Never	95	80		4.1 (0.8, 20.5)	5.6 (1.9, 16.6)
Type of Fat					
Unsaturated	25	90	0.005	1.0	1.0
Saturated	75	10		3 (1.3, 6.6)	3.4 (1.4, 8.1)
Consumption of Fruits					
Daily–4/wk	18	27	0.165	1.0	1.0
3/wk–1/wk	33	39		1.2 (0.6, 2.7)	1.9 (0.3, 10.8)
Twice–once/Mo	13	10		1.9 (0.7, 5.4)	2.5 (2.4, 13.1)
Occ/Never	36	24		2.2 (1.0, 4.9)	2.7 (0.5, 15.7)
Waist to hip ratio					
< 0.85	41	52	0.119	1.0	1.0
≥ 0.85	59	48		1.5 (0.9, 2.7)	5 (1.4, 17.0)
Serum calcium levels (mg/dl)					
8.5 to 10.5	98	92	0.101	1.0	1.0
≥ 10.5	2	8		0.27 (0.1, 1.3)	0.2 (0.04, 1.2)
Serum 25 (OH) D levels (ng/ml)					
≥ 20	6	17	0.024	1.0	1.0
< 20	94	83		2.9 (1.1, 8.0)	2.5 (0.9, 7.4)

range for both cases and controls (8.5 mg/dl–10.5 mg/dl). Although the nutritional risk factors like consumption of saturated fat was found to be positively associated with BC. In addition to this, less consumption of fruits and higher WHR were also found to be significantly associated with increases risk of BC. Our case-control study suggests that, serum 25(OH)D concentrations had an association with the risk of BC. High frequency of vitamin D deficiency in the Indian population with its unfavorable impact on bone health and further intolerance to various systemic cancer treatments makes it important for the health specialists to recognize, treat and prevent vitamin D deficiency. However, nutritional risk factors like consumption of saturated fat, fruits and less dietary intake of vitamin D have a positive association with BC. More scientific evidence is needed to strengthen the findings of our study.

5. Limitations to the study

The potential confounding variables such as reproductive risk factors, physical activity, breast density, genetic factors, body mass index, smoking status, and education level were not included in the analysis. Since the primary focus was on nutritional risk factors with status of vitamin D and calcium. It is possible that the effect of these factors might have masked the effect of association of nutritional risk factors with BC.

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