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Research Article

The Relationship between 25-Hydroxyvitamin D and Homocysteine in Breast Cancer Patients

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Abstract

Background: Breast cancer is significant most common cancer, which is the leading cause of death in economically developed countries among women. Breast cancer is the second leading cause of death, not only, in India but also other developing countries. Globally, some studies have been done, to find association between homocysteine along with vitamin D in breast cancer, and only few studies were document. Hyperhomocysteinemia is an independent risk factor for cancer cell proliferation and oncogenesis. Although it is responsible for alter the gene expression and enzymatic function of homocysteine metabolism enzyme. Along this, 25-Hydroxyvitamin D [25(OH)D] may also modulate the expression of genes involved in homocysteine metabolism in breast cancer patients.

Aim: A few studies described about the relationship between homocysteine and 25(OH)D in cancer therefore, we hypothesized nonlinear association between 25(OH)D and homocysteine in breast cancer patients.

Materials and methods: A Case-control study was done from June 2015 to Jan 2020 in the Advanced Centre for Traditional and Genomic Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi. A total of 310 histopathologically confirmed new cases of breast cancer were recruited from Department of Radiotherapy & Radiation Medicine, during the same study period, were taken as cases. 190 controls were selected, were matched for age with range of ± 2 years. Subjects were interviewed using a questionnaire after obtaining written informed consent. The tHcy plasma levels and 25(OH)D were measured using ELISA Kit in 190 female controls and 310 BC patients. Data were analyzed by applying appropriate statistical tests using SPSS version 17 and other statistical online tools.

Results: Age group of the cases was 35-70 years (mean ± SD; 42.89 ± 7.2), while that of the controls was 30-70 years (mean ± SD; 42.99 ± 6.95), shows non significant whereas a significant association of breast cancer cases was found with high BMI and high fat intake. Also, differences were evident when stratified by age (≥ 50 years old), tumor stage, menopause status, tobacco and alcohol consumption and non response to chemotherapy. The observed plasma tHcy levels and serum 25(OH)D were significantly higher among the BC patients (14.10 ± 2.91 μmol/l) compared to the controls (07.17 ± 2.52 μmol/l) (p=0.019) while significantly lower among the BC patients 25.09 ± 8.55 compared to the controls (35.37 ± 5.10), respectively. There was significant negative correlation and nonlinear association between homocysteine with vitamin D in breast cancer patients.

Conclusion: Higher plasma homocysteine reduced levels of folate and possibly, also vitamin D may increase the risk of developing breast cancer. These factors are also affected by consumption of tobacco and alcohol. Along with high intake fat food increased BMI, age, menopause status etc. Achieving adequate circulating levels of folate may be particularly important for women at higher risk of developing breast cancer because of higher alcohol consumption. Although our study offers little support for an association between circulating homocysteine and vitamin D with breast cancer risk, with low folate status. Also offer the high BMI are the significant risk factors, which are modifiable and tHcy plasma levels and 25(OH)D could be a good biomarker for the progression and chemosensitivity of BC in the analyzed sample from Indian Population. Therefore, women should be encouraged to take care of all these factors.

Keywords: Plasma levels; Homocysteine; Serum vitamin D; Breast cancer; Body mass index; Menopausal; mortality; Obesity

Introduction

Cancer is an umbrella term for altogether over 100 various types of the disease, which in the early twenty-first century became the acknowledged leading cause of the deaths worldwide; contextually, breast cancer plays a major role with around two million new cases and a half of million pathology-related deaths registered annually worldwide [1]. The second foremost reason of the death is breast tumor. In UK, on an average, one woman out of nine will progress this disease in their lifespan. There are several factors associated with the breast tumor proliferation such as gender, diet, use of alcohol, body movement, family history, lifestyle and endocrine. Both non-modifiable (such as genetic ones) and modifiable risk factors contribute to the manifestation of cancerous lesions. Thereby, modifiable risk factors are clearly preventable such as environmental toxic and stress factors, unhealthy lifestyle including dietary habits, amongst others, which synergistically promote carcinogenesis and clinical onset of malignancies. Breast cancerous tissue transformation developing usually over years or even decades of life is a highly complex process involving strong stressors damaging DNA, chronic inflammation, comprehensive interaction between relevant molecular pathways, and cellular cross-talk within the neighboring tissues [1]. Only 5% to 10% of all types of cancer are basically caused by inborn

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cancer predisposition such as the so-called familial breast cancer subtype known to be related to the BRCA1 and BRCA2 mutations and other gene also [2].

Vitamin D is a natural steroid bioactive derivative, regulating concentration of calcium and phosphorus in the body and in mineralization of bone so, plays a key role in promoting bone growth [3]. Approximately, 90% Vitamin D synthesized from endogenous factors under the skin while by two mode Vitamin D produced in the two forms: D_2 (originates from dietary sources like plants and fish (ergocalciferol)) and D_3 (originates from 7-dihydroxycholesterol under the skin which is exposed to UV-B light (cholecalciferol) [4].

After hydroxylation (in the liver by mitochondrial and microsomal 24-hydroxylase (encoded by CYP24A1) to yield 25-hydroxyvitamin D (25(OH)D) known as calcidiol) Vitamin D becomes active and involved various cell function (involved in the proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis and metastasis of tumor by regulating various signaling pathways, which may affect the development and growth of tumor). Various report that shown serum vitamin D is usually determined by measuring 25(OH) D biomarker (has a half-life of about 2 to 3 weeks) [3,4]. Recently, Vitamin D Receptor (VDR) genes were reported to increase breast cancer risk and low serum vitamin D levels was linked to a higher risk of various clinical issues like colon and bladder cancer [4].

Homocysteine, a thiol-containing amino acid and that occupies a central location in the metabolic pathway of thiol compound which act as a precursor of the demethylation of methionine. It is produced through the catabolism of methionine via a multi-step process that probably occurs in every cell of the body. Excess amount of methionine, degraded homocysteine to cysteine via the transsulfuration pathway and vitamins B6, B12 and folate are essential cofactors for metabolism [5].

Hcy also plays an important role in methylation and the provision of nucleotides for DNA synthesis. However, homocysteine is remethylated to methionine in the presence of methionine synthase with vitamin B12 and methyltetrahydrofolate as a cosubstrate. Methionine is also involved to synthesized Cysteine through homocysteine and act as precursor amino acid for synthesis of proteins, glutathione, coenzyme A, and γ-glutamyl cysteinyl glycine. Through tight regulation or cellular process, it is necessary to control tissue concentration of homocysteine and cysteine. Disrupted metabolism of Hcy, elevated the level of Hcy know as hyperhomocysteinemia (Hhcy) resulting from a desert in the remethylation pathways and increased level of Cysteine in the tissue or when its catabolism affected due to stumpy cysteine dioxygenase [6].

Previous *in vitro* studies have shown that Hhcy are directly associated with proliferation rate of cells in different cancer like breast tumors and also caused oxidative damage to cells.

Recently some *in vivo* and *in vitro* studies have reported that cysteine may act as a pro-oxidant agent and causes DNA oxidative damage and ultimately produce large number of free radicals and hydrogen peroxide. They are leading to gene mutation and subsequent cancer development. Various evidence were reported that Hhcy and high level of cysteine are directly link to with several clinical metabolic disorders such as body mass index, high plasma triglyceride levels, hypertension, and abnormal oxidation of low-density lipoproteins and may act as a factor for the progression of numerous cancers including breast cancer. Conversely, different factors can affect Vitamin D and Hcy levels (deficiency of enzymes involved in the methionine to cysteine Metabolism) such as age, gender, menopause, tobacco and alcohol consumption and ethnic group. The reference ranges of Vitamin D and Hcy, in healthy individuals, are determined by standardization in each laboratory. Some studies have associated low Vitamin D and HHcy with BC with low folate levels, metastasis, and chemotherapy response. However, in the Indian Eastern Uttar Pradesh, population, these associations remain unknown. In additional, both factors low level of 25(OH)D and high level of homocysteine levels are potential risk factors for various clinical disease such as premature cardiovascular diseases and cancer. Thus, the aim of this investigation was to determine the Vitamin D and HHcy plasma levels in Indian Eastern Uttar Pradesh BC patients. We hypothesized that activated 25(OH)D may regulate the gene expression of enzymes involved in homocysteine metabolism, we hypothesized and that level of vitamin D may also have an impact on plasma homocysteine level [7].

Materials and Methods

Subject

The present study a prospective and descriptive study performed in department of Radiotherapy and Radiation Medicine, Institute of medical science, Banaras Hindu University, Varanasi, U.P.

Blood samples were collected from n=290 healthy female blood donor volunteers and n= 310 patients with clinically and histological examination confirmed Breast cancer. They were age range between 35 to 70 years old, before they were started on chemo or radiotherapy were invited to participate in this study.

After the patients signed a written informed consent, previously approved by the ethics committee Adesh University, Bhatinda Punjab (vide Ref. no. EC/MC/04/2K18/312) then we were collected blood sample. All patients were populace of Eastern Uttar Pradesh and were recruited from June 2015 to Jan 2020 [8-10].

All patients were counseled to settle on their occupational exposure and current drug regimens.

A standardized questionnaire was use to collect data from patients, including their name, age, sex, stage of breast cancer and menopausal status including the Body Mass Index (BMI). It was calculated as weight in kilogram divided by the square of height in meters. The nutritional status of adult patients was determined according to the World Health Organization Criteria (WHO expert committee).

Laboratory analyses

All cases of the breast cancer and healthy volunteers were subjected for evaluation of vitamin D and homocysteine. The above measurements were carried out by ELISA method (CALBIOTECH-VDS5047). In this case-control study blood samples were handled identically with together. Investigation was performed in the same analytical way. The blood samples were proper labeled by symbol and numerical number within each case-control pair. During the estimation process, we interspersed replicate of each samples, which were labeled to preclude their identification by the laboratory, to assess laboratory precision.

Statistical analysis

Statistical Package for Social Science (SPSS) version 19.0 software was used for statistical analysis. A p-value <0.05 was considered statistically significant. The chi-square test was used to assess the association between factor and tumor stage. This tool was to calculate p-value between percentage of case and control BMI and Education

(https://www.medcalc.org/calc/comparison_of_proportions.php). In this present study, to address the hypothesis that the association between plasma homocysteine and Vitamin D is nonlinear ,results were reported as change in plasma homocysteine levels (micromoles per liter) for each 10 ng/mL change in serum Vitamin D, p-value of 0.05 was considered statistically significant through (https://www.mathportal.org/calculators/statistics-calculator/correlation-and-regression-calculator.php).

Results

Tumor stage (Table 1A,1B) in this case control study, the age group of the cases (n=310) was 35-70 years, while that of the controls (n=190) was 36-70 years. A total of 310 patients BC with two mean age (>50 and <50) of 42.89 ± 7.2 and 57.85 ± 5.82 respectively, were evaluated. The different tumor stage of breast cancer (BC) patients data are shown in Table 1A and also Table 1B shown the different stages of tumor with different range of age of BC patients. Clinical characteristics BMI of patients in study groups of the 310 breast cancer patients, 42 (19.26%) were normal weight group, 74 (33.94%) patients were overweight, and 102 (46.78%) were obesity of under 50 years old age whereas more than 50 years old age group, 26 (11.92%) were normal weight, 31(33.69%) patients were overweight and 35 (38.04%) were obesity. Also out of 190 healthy female,76 (67.85%)were normal weight of, 36 (32.14%) patients were overweight, and 8 (7.14%)were obesity under 50 years old age group whereas more than 50 years old age group, 49 (53.97%)were normal weight, 28 (16.27%) patients were overweight and 9 (10.46%) were obesity. We then evaluated the associations between different age group of BC cancer patients and across BMI status subgroups (Table 2). Cases had higher percentage of BMI than healthy controls and showed highly significant differences. Table 2 also show that >50 years age group females were more affected by cancer. On other hand, in <50 years old age group 35 (38.04%) were affected due to high level of BMI; shows significant. Table 3 shows the comparative epidemiological data from the BC patients and the control female. The observed average age were 42.89 ± 7.2 (>50) years and 57.85 ± 5.82 (>50) years and 56.81 ± 5.44 (<50) years in the control group; non significant. Results were very similar between the total sample and among the subset used in the age group. Compared with controls, cases had little more higher education. Cases were more likely to have a higher BMI compared with healthy control and more significant. In the subgroup of BMI, obese cases (65.8%, p=0.0001) had higher effect of cancer rather than control and other subgroup of BMI.

However, the tHcy plasma levels were significantly different between the patients and controls (p=0.019), and they remained significantly different when stratified by ≥ 50 years old (p=0.049) whereas when stratified by <50 years old (p=0.035) and tobacco Consumption status (p=0.005); alcohol consumption status (p=0.048); pre-menopause status (p=0.004) menopause status (p=0.057). Similarly, the serum vitamin D levels (Table 3) were significantly different between the patients and controls (p=0.005), and they remained significantly different when stratified by ≥ 50 years old (p=0.005) whereas when stratified by <50 years old (p=0.045) and tobacco Consumption status (p=0.005); alcohol consumption status (p=0.0104); pre-menopause status (p=0.005) menopause status (p=0.005) When stratified and compared by menopause and pre-menopause status and alcohol and tobacco consumption, there were significant differences between the patients and the controls (Table 3). Significant differences were found in tHcy plasma and serum Vitamin D levels between BC patients, stratified by clinical characteristics, compared to the control group (Table 3). Significant differences in tHcy plasma and serum Vitamin D levels were found between BC groups stratified by clinical characteristics. Table 4 shows that inequity level of vitamin D and homocysteine strongly associated with the prevalence of breast cancer. Significant negative correlations between plasma Hcy levels and Vitamin D (r =-0.086, p<0.001), was determined in the study case control Singh (Table 5).

Table 1A: Showing different tumor stage of breast cancer patients with their percentage.

Tumor stage	N=310 (%)
1 stage	179 (57.74)
2 stage	85 (27.41)
3 stage	46 (14.83)

Table 1B: Association with age groups.

Age years	Tumor stage		
	1 stage	2 stage	3 stage
>50(n=218)	156(7.3%)	55(25.22%)	8(3.66%)
<50(n=92)	48(52.17%)	32(34.78%)	12(13.04%)

Discussion

Globally, BC is currently one of the leading causes of disease and death in female [1]. In the present case control study, we observed that the mean age of the BC patients was 42.89 ± 7.2 (>50 years old) years. Various studies have supported a high incidence of BC in patients who were around 50 years old [2].

Many studies have observed that modern lifestyle changes and expanded longevity likely have an influence on the increased frequency and incidence of BC in the world [2].

A number of studies has supported that high BMI were associated with different clinical issues and significantly higher among the cases than controls in cases of breast cancer patients. On the Other hand women with high BMI were at increased risk of breast cancer. Some studies has observed that high BMI association with menopausal status in breast cancer and in our study, obesity and breast cancer were found to be significantly associated in both premenopausal and menopausal women, due to hormones. Higher levels of free estrogen produced by excess aromatase activity in peripheral adipose tissue and studies supported our finding.

We also found that intake of alcohol and tabcoo consumption were associated with an increased risk for developing overall breast cancer but it is unclear whether these associations vary by a woman's familial BC risk and pathway of these factors combination.

Previous studies have suggested that tHcy metabolism associated with development and influence of breast cancer at molecular echelon which is important. Some other reports have declared that elevated tHcy in women shown deficiency of folate or folic acid. This is directly or indirectly linked to oncogenesis or related gene of breast cancer. On other hand, may affects gene expression and promotes cell proliferation in the oncogenesis of breast cells. However, the relationship between elevated tHcy and BC still not clear and under controversial. Because of ambient and environmental factors and lifestyles including diet and other toxic exposition, may involved to influence the promotion of tumoral epigenetic changes

In addition, we also found that elevated plasma Hcy and cysteine were associated with Lower folate status and an increased risk for developing breast cancer. It is likely resulting homocysteine accumulation and further conversion of cysteine, shows positive

Table 2: Distribution of patients (%) with breast cancer and control according to BMI a status-parameters, age years (<50 & >50 years old).

BMI	<25		p-value	≥ 25, <30		p-value	≥ 30		p-value
	BC (%)	Control (%)		BC (%)	Control (%)		BC (%)	Control (%)	
>50	N=218	N=112	>0.05	N=218	N=112	>0.05	N=218	N=112	>0.05
	42 (19.26)	76 (67.85)		74 (33.94)	36 (32.14)		102 (46.78)	8 (7.14)	
<50	N=92	N=86	>0.05	N=92	N=86	<0.05	N=92	N=86	>0.05
	26 (11.92)	49 (53.97)		31 (33.69)	28 (16.27)		35 (38.04)	9 (10.46)	

Table 3: General characteristics along with tHcy and Vitamin D of patients with breast cancer with control.

Characteristics	**BC patients n=310**	**Controls N=190**	**95% CI**	**p-value**
Age Years				
>50 Years old	218 (70.32%) (42.89 ± 7.2)	112(56.56%) (42.99 ± 6.95)	1.72-1.52	**0.9**
<50 Years old	92 (29.67%) 57.85 ± 5.82	86(43.43%) 56.81 ± 5.44	2.70-0.62	**0.22**
BMI, %				
<25	15.59	60.02	36.04-2.04	0.0001
≥ 25, <30	33.81	24.2	1.33-17.37	0.0232
≥ 30	65.8	8.8	49.68-3.01	0.0001
Education, %				
No formal education	3.9	4.8	2.59-5.38	0.59
Elementary school	8.6	8.4	5.28-5.03	0.91
Middle and high school	76.6	75.7	6.58-8.78	0.86
College	12.3	8.6	2.11-8.96	0.19
Plasma homocysteine (mean ± SD)				
tHcy, (µmol/l) (5-15)	14.10 ± 2.91 (n=310)	08.17 ± 2.52 (n=190)	5.42-6.43	0.019
tHcy (>50 years old)	12.36 ± 3.54 (n=218)	08.23 ± 2.64 (n=112)	3.37-4.87	0.049
tHcy, <50 years old)	14.10 ± 2.51 (n=92)	08.54 ± 2.97 (n=86)	4.79-6.32	0.035
tHcy (tobacco consumption)	12.36 ± 3.54 (n=154)	08.24 ± 2.85 (n=15)	3.16-5.07	0.005
tHcy (alcohol consumption)	12.07 ± 3.97 (n=98)	08.02 ± 2.11 (n=12)	3.10-5.00	0.048
tHcy (menopause)	14.36 ± 2.98 (n=207)	08.24 ± 2.85 (n=105)	4.32-7.97	0.057
tHcy (pre menopause)	11.54 ± 2.67 (n=103)	08.89 ± 2.97 (n=85)	1.83-3.46	0.004
Vitamin D (mean ± SD)				
Vitamin D (ng/ml) 20-50	25.09 ± 8.55 (n=310)	35.37 ± 5.10 (N=190)	11.62-.93	0.005
Vitamin-D (.50 years old)	30.80 ± 5.89 (n=218)	39.12 ± 6.87 (n=112)	9.74-6.89	0.005
Vitamin-D (<50 years old)	25.37 ± 9.55 (n=92)	36.56 ± 3.56 (n=86)	13.34-.02	0.005
Vitamin-D (tobacco consumption)	24.16 ± 9.05 (n=154)	30.56 ± 4.09 (n=15)	11.06-.73	0.0075
Vitamin-D (alcohol consumption)	24.03 ± 8.14 (n=98)	30.37 ± 5.98 (n=12)	11.15-.52	0.0104
Vitamin-D (menopause)	25.38 ± 9.78 (n=207)	30.08 ± 6.51 (n=105)	6.77-2.62	0.005
Vitamin-D (pre menopause)	24.91 ± 9.29 (n=103)	36.28 ± 3.56 (n=85)	13.47-.26	0.005

SD: Standard Deviation

Table 4: Level of tHcy and serum Vitamin D in different stages of breast cancer patients.

Groups	Average range of normal population (N=310)	95% CI of the limit of mean of average population	Stage 1 (N=179) (57.74%)	Stage 2 (N=85) (27.41%)	Stage 3 (N=46) (14.83%)	95% CI of the limit of mean in different stages		
						Stage 1	Stage 2	Stage 3
Homocysteine (µmol/l) 5 to 15	11.0 ± 5.65	7.26-12.73	16.8 ± 6.5	22.8 ± 4.8	24.8 ± 7.5	14.07-18.98	20.84-24.75	22.25-27.65
Vitamin D (ng/ml) 20 to 50	35.0 ± 8.51	34.41-36.78	28.36 ± 7.8	20.2 ± 8.5	13.11 ± 6.8	24.91-31.02	19.57-20.92	10.80-15.18

Table 5: Correlation between total homocysteine and Vitamin D.

Biological parameters	Correlation coefficient value (r value)	Significance (P value)
Vitamin D	**-0.086**	<0.001

r value is spearman's correlation coefficient; NS is non-significant

association between cysteine and breast cancer. A current study has suggested a possible causal role for Hcy in body weight regulation and also elevated Hcy levels were associated with high BMI, and low level of Vitamin D [5]. Some other studies have shown that obesity is one of the risk factor for breast cancer development in menopausal women and also some. It is a extrapolative factor for breast cancer development and mortality however, high BMI were associated with high risk of breast cancer due to elevated tHcy (hyperhomocystenamia-HHcy); these study has supported our present study finding. Although, some recent study has also suggested that the possible linkage between Vitamin D gene with oncogenesis of breast cancer which lead to association of vitamin D intake with breast cancer suspectability. Alternate, Vitamin D gene expression associated with influence the cell proliferation in the breast cancer. A few other preclinical investigations and clinical observational studies support an association between low vitamin D and high BMI which influence cell proliferation in breast cancer; higher vitamin D intake with lower breast cancer risk.

These findings support our hypothesis that high tHcy level may result decreased serum vitamin D level. Another hand, intake vitamin

D increased the level of serum 25(OH)D or greater than its rang (ng/mL) may result in decreased in homocysteine concentration and is probably needed for the primary prevention of breast cancer. The cellular and molecular mechanism responsible for the relationship between homocysteine levels and 25(OH)D status is still not clear and may include indirect or direct effects of vitamin D on homocysteine metabolism. In the mechanism, activated vitamin D is mediated through their binding to a high-affinity VDR and acts as a ligand-activated transcription factor. This modulates transcription of several genes responsible for the diverse cellular and molecular effects of vitamin D analogs.

Recent evidence has supported that activated vitamin D are able to inhibit the proliferation of lymphocytes and also diminish the production of proinflammatory.

Homocysteine is metabolized by transsulfuration and remethylation which is folate dependent pathways and linked to regulation of homocysteine, in which it is converted to cystathionine in the presence of the enzyme CBS and cofactor vitamin B6. Some other finding supported that deficiency of the CBS enzyme has been linked with Hyperhomocysteinemia (6,28) whereas a significant increase levels of CBS mRNA after incubation with activated vitamin D in murine preosteoblasts, which suggests that CBS is a target gene of Vitamin D Receptor (VDR) gene, and vitamin D may modulate homocysteine metabolism and can affect its serum concentration. Our finding of nonlinear relationship between 25(OH)D and homocysteine in healthy in breast cancer patients. Additionally, the authors further reported a correlation between vitamins D and homocysteine.

Conclusion

In the present study, high BMI due to high fat intake food and HHcy which indicate low Vitamin D were found to be significant risk factors for breast cancer and these are modifiable factors. Hence, women should be encouraged to take precaution and care of all these factors to decrease their risk of breast cancer. Therefore, this clearly shows lack of awareness regarding breast cancer among the study population. Its need of public awareness including education of this lethal disease must be developed and aids in detection of breast cancer in early stages. If cancer is detected in early stages, it is curable. In conclusion, we report an inverse relationship between levels of homocysteine and 25(OH)D independent of breast cancer risk factors.

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