Association between Single Nucleotide Polymorphisms rs3757318 and Vitamin D Deficiency in Iraqi Breast Cancer Patients

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Abstract

Background: Multiple single-nucleotide polymorphisms (SNPs) located in the intergenic region between estrogen receptor 1 and *CCDC170* (especially at rs3757318) are thought to be associated with breast cancer risk. ADditionally, the serum level of vitamin D is believed to be linked to different aspects of breast carcinogenesis. **Objectives:** To assess the potential association between rs3757318 SNP and breast cancer pathogenicity, specifically in relation to serum vitamin D levels. **Materials and Methods:** For addressing this issue, 100 subjects were enrolled in this work, including 50 female patients diagnosed with breast cancer recruited from the Oncology Hospital, Baghdad, Iraq and 50 apparently healthy women with no malignancies as a control group. The serums level of vitamin D was measured for breast cancer patients and healthy controls groups, whereas, *CCDC170* rs3757318 SNP genotypes were assessed using TaqMan SNP genotyping and utilizing genomic DNA extracted from the participants. **Results:** Vitamin D levels were shown to be significantly reduced ($P < 0.001$) in breast cancer patients than that of the healthy controls (6.604 vs. 22.268, respectively). In respect to the *CCDC170* gene rs3757318 SNP genotypes frequency, the mutant genotype (AA) was only identified in the investigated breast cancer patients (O.R. (C.I.) = 1.69 (0.86–2.07)) and this seems to confer the increased risk of breast cancer susceptibility. **Conclusion:** Overall, the findings of the present study suggest an association between the reduced vitamin D levels and *CCDC170* gene rs3757318 SNP genotypes frequency in breast carcinogenesis.

Keywords: Breast cancer, *CCDC170* (rs3757318) polymorphism, vitamin D

Introduction

Researchers are still investigating why the breast is the most affected organ with cancer in women's body. Efforts have focused on understanding the underlying biological alterations in attempt to solve this puzzle.[1-3] At the molecular level, cancer is believed to be a very heterogeneous disease.[4,5] However, several lines of evidence have highlighted that certain single nucleotide polymorphism (SNP, refers to mutations manifest upon a single nucleotide "A, T, C, or G" in the genome is altered) are associated with different aspects of breast cancer pathogenicity. Taking into account their ubiquitous distribution throughout the human genome, SNPs are the most commonly studied molecular markers for their association with various aspects of cancer biology. Depending on their genomic location, SNPs mapping to the coding regions of the genome are potentially employed as molecular markers in genetic disease research. SNPs could have key biological influence on gene's function as they can modify the encoded amino acids. In these cases, they have the potential to alter promoter accessibility, messenger RNA, and protein configuration (stability), and hence cause illness.[6] Gene expression abnormalities have recently been explored as being potential molecular predictors for malignancy

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progression in breast cancer patients[7-11] as well as other malignant diseases.[12-14]

Although many SNPs do not affect cell biology, some can predispose individuals to particular diseases, impact their immunological response to drugs, which is why they are used as biomarkers for disease susceptibility.[15] Some of the reported SNPs have been linked to breast cancer vulnerability and treatment responses. Genome-wide association (GWA) studies have been adapted as an approach for identifying genetic variants linked to cancer development. Since the first GWA study about breast cancer was reported in 2007,[16] several GWA studies have reported a number of SNPs associated with breast cancer pathogenicity. Of these, rs3757318 that is, located at 6q25.1, in proximity to the estrogen receptor 1 gene (*ESR1*), and maps ~200 kb upstream in an intron of coiled-coil domain containing 170 (*CCDC170*). *CCDC170* has been linked to estrogen resistance which increases the risk of breast cancer development.[17-19] Also a number of GWA studies have engaged the genomic region located around this gene in regulating bones' mineral content.[20] Although there were many statistical evidences, including some meta-analysis studies,[21] that mutated rs3757318 confer breast cancer risk, however, conflicting findings have emerged in respect to the rs3757318 involvement in breast cancer susceptibility, especially among the different studied ethnic groups.[21] Locally, in Iraq, where breast cancer accounts for the most common women-affecting malignancy,[22] yet no previous study has investigated rs3757318 association with this disease.

On the other hand, other factors, such as vitamin D level, affect the breast cellular microenvironment and have the potential to modulate the immune system activity.[23,24] Vitamin D deficiency appears to be attendant with multiple types of cancer, including thyroid cancer,[25] colorectal,[26] and breast cancer.[27,28] Plethora of evidence have revealed an inverse relation between vitamin D levels and cancer mortality,[29,30] whereas others have considered its level as a potential cancer risk factor.[31,32] Additionally, *in vitro* and *in vivo* preclinical studies have demonstrated significant impact of vitamin D in modulating key breast cancer associated-cellular processes including proliferation, apoptosis, autophagy and the epithelial mesenchymal transition.[33,34] Interestingly, the metabolism of cancer stem cells, that represents the root of cancer initiation and progression, seems to be profoundly affected by vitamin treatment.[35] Additionally, several epidemiological studies have demonstrated an association between low levels of vitamin D and the increased risk of breast cancer development.[36] However, studies have often conflicting discourses emerged largely failed to confirm the association between SNPs in genes related with lower serum vitamin D levels and breast cancer risk.[34,37] All the above mentioned evidences that are supporting the involvement of rs3757318 and vitamin D in breast cancer pathogenicity constitute the rationale behind conducting this study due to the scarcity of studies addressed the association of these potential biomarkers (rs3757318 and vitamin D) with Iraqi breast cancer patients.

Materials and Methods

Subjects

Peripheral blood samples were taken from 50 women diagnosed with breast cancer (mean age 47.64 years range 43–69 years) and 50 age-matched women with no malignancies who designated as apparently healthy controls. The inclusion criteria that have been followed for recruiting cases in this study were involving female patients newly diagnosed with stages I-III breast primary tumors aged 30–70 years. On the other hand, control individuals involved women who were apparently healthy with almost similar age range mentioned above. However, female patients with breast secondary cancers and those out of the age range mentioned above as well as males were excluded. Breast cancer patients were recruited from the Oncology Hospital, Baghdad, Iraq and the patients' clinical data were obtained from the hospital records including age, family history, and tumor stage. All breast cancer patients in this study were selected on the basis of clinical and laboratory examination and diagnosed by specialist doctors in Oncology hospital.

Vitamin D total assay (cobas e411)

Vitamin D serum levels were measured utilizing vitamin D total assay (Roche Diagnostics GmbH, Mannheim, Germany) employing vitamin D binding protein (VDBP) to capture both 25-hydroxyvitamin D3 and D2. This assay is intentional for the quantitation of total vitamin D (25-OH) in human serum using cobas e411 automated system. According to the manufacturing protocol, serum samples were taken from the refrigerator and allowed to reach to room temperature for 30 min. A total of 500 µL of breast cancer patients' serum were drawn using a micropipette, into the sample cobas e411 system well, also 500 µL of serum samples of control were drawn using a micropipette, into the sample cobas e411 well. Vitamin D levels were considered sufficient when 25-(OH)D concentration was ≥30 ng/mL, insufficient when it was between 20 and 29 ng/mL, and deficient when it was below 20 ng/mL.

DNA extraction and *CCDC170 rs3757318 SNP* polymorphisms using TaqMan SNP genotyping

Genomic DNA extraction from the whole fresh blood samples was directly performed using blood DNA extraction kit, Cat. 46300-Norgen®, Canada, according to the manufacturing protocol, whereas the sequence of *CCDC170* rs3757318 was amplified using TaqMan fluorescent oligonucleotide forward: AAATGTGTTGTTTGGCAGAG, and reverse: TCTTGTTCTCAATGACTGCA primers. Primers were

designed using NCBI designing tool and lyophilized primer were manufactured by Macrogen® (Korea).

For this assay, DNA samples both for breast cancer patients and healthy controls were genotyped for the above mentioned SNP. The RT-PCR reaction mixture total volume was 25 µL composed of 12.5 µL of TaqMan master (PROBE), 0.5 µL of each fluorescence probes, 0.5 µL from each forward and reverse primer (10 µM), 5 µL of template DNA, and 5.5 µL nuclease-free water. RT-PCR amplification reaction was accomplished using a programmed thermocycler with one hold cycle of 95°C for 15 min, 45 cycles of 95°C for 5 s, 60°C for 20 s and 72°C for 15 s, followed by one cycle of 72°C for 5 min.

Ethical approval

This investigation was conducted in compliance with the ethical principles originated by the Helsinki Declaration of. All patients gave informed consent to participate in the study. The study protocol, the subject information and consent form were reviewed and approved by the Biomedical Research Ethics Committee of the National Cancer Research Center, University of Baghdad approved this study (Reference no. NCRCEC/01/002).

Statistical analysis

Data analysis was performed using IBM® SPSS® statistical software (Version 27.0; IBM SPSS, Armonk, New York). Spearman's rank correlation was used to assess the correlation between the investigated parameters. Mann–Whitney *U* test was used to compare significance between means, whereas Chi-square test was used to compare the observed results of the variables in this study. All measures were obtained from three replicates and presented as a mean ± SD; $P < 0.05$ cut off was taking into account for significant differences.

Results

The study found that breast cancer patients had significantly lower levels of vitamin D compared to healthy controls (6.604 ± 2.523 vs. 22.268 ± 5.811, respectively). The mean level of vitamin D in the investigated breast cancer patients was reduced by 70.34% in comparison to healthy controls. Interestingly, the serum vitamin D levels were able to clearly distinguish between breast cancer patients and healthy controls [Figure 1].

As for the *CCDC170* gene rs3757318 SNP genotypes frequency, the results showed that wild genotype (GG) was the predominant pattern in the healthy individuals, where 72% (36/50) showed to have the aforementioned genotype. However, none of the investigated breast cancer patients appeared to have the wild genotype (GG) for the assessed SNP [Figure 2].

This is a quite interesting finding as the genomic variance in this region could differentiate breast cancer patients from healthy counterparts. However, large scale studies are needed to validate such findings.

Additionally, the mutant genotype (AA) is only identified in the investigated set of breast cancer patients. In contrast,

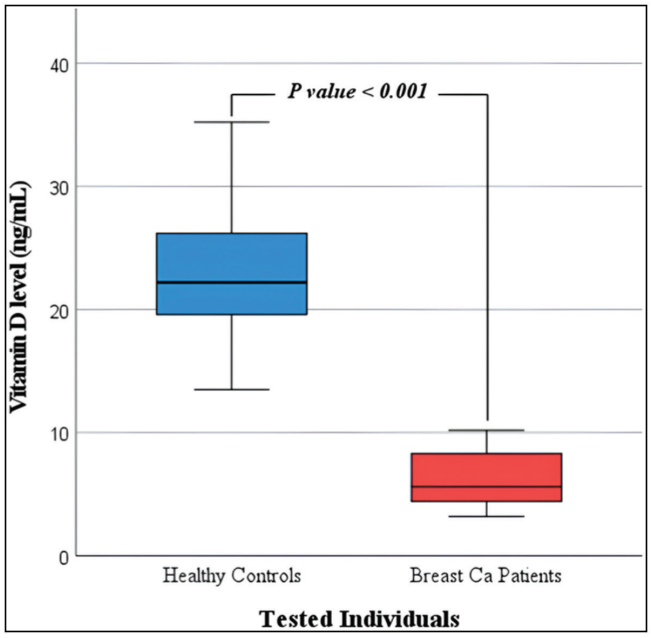

Figure 1: Comparison between the vitamin D levels (ng/mL) in blood samples of breast cancer patients and individuals with no malignancies (healthy controls). The boxplot elucidates that the vitamin D levels are significantly decreased ($P < 0.001$) in blood samples of the patients with breast cancer compared with the healthy controls. The *P* value is derived from Mann–Whitney test

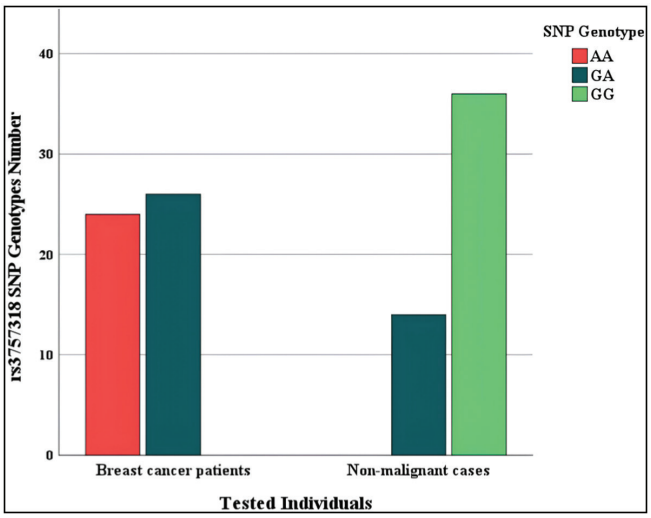

Figure 2: Bar-chart depicting SNPs genotypes of *CCDC170* gene rs3757318 among the studied breast cancer patients and non-malignant cases. The bar-chart shows that the wild type (GG) was the dominant pattern in the healthy individuals, whereas the mutant genotype (AA) is only detected in the breast cancer patients. On the other hand, the heterozygous genotype (GA) is more prevalent in the patients than non-malignant cases

Table 1: Genotype and allele frequency of at rs3757318 (G>A) SNP Polymorphisms gene in control and breast cancer groups

Genotype	Group		χ^2	*P*-value	OR (CI)
	Control ($N = 50$)	Patients ($N = 50$)			
GG: Wild	36 (72.00%)	0 (0.00%)	10.027	0.0001**	1
GA: Hetero.	14 (28.00%)	26 (52.00%)	1.80	0.179^{NS}	0.577 (0.29–1.33)
AA: Mutant	0 (0.00%)	24 (48.00%)	8.934	0.0025 **	1.69 (0.86–2.07)
Alleles		Frequencies			
G	0.84	0.26	-		
A	0.14	0.74	-		

NS: non-significant
** $P \leq 0.01$

Table 2: The correlation between Vitamin D levels (ng/mL) and both SNPs rs3757318 pattern "AA" of *CCDC170* gene and the age the recruited breast cancer patients and individuals with no malignancies

			SNPs of rs3757318	Vit. D level (ng/mL)
Spearman's rank correlations rho (ρ)	Vit. D level (ng/mL)	Correlation coefficient	**-0.672****	
		Sig. (2-tailed)	**<0.001**	
	Age	Correlation coefficient	0.316**	**-0.573****
		Sig. (2-tailed)	**0.001**	**<0.001**

** Correlation is significant at the $P \leq 0.01$ level (2-tailed)
Bold value indicates $P \leq 0.001$

the heterozygous genotype (GA) is more pronounced in the breast cancer patients than non-malignant cases. This is obvious where it frequency was approximately two folds higher in the breast cancer patients' group than that of their healthy counterparts [Table 1]. Considering the odd ratio value of obtained results, mutant genotype (AA) seems to confer increased the risk of breast cancer susceptibility. While the heterozygous genotype (GA) indicates a protective effect [Table 1].

In respect to the relation between the assessed *CCDC170* gene rs3757318 SNP and the investigated vitamin D levels, the present study results showed inverse significant correlation between vitamin D levels (ng/mL) and the SNP rs3757318 pattern "AA" of *CCDC170* gene (rho = -0.672, $P < 0.001$) of the recruited breast cancer patients and individuals with no malignancies. Similarly, *CCDC170* gene rs3757318 SNP "AA" seemed to be negatively correlated (rho = -0.573, $P < 0.001$) with the age of the assessed participants but with lower correlation coefficient rate (rho = 0.316) [Table 2]. Nevertheless, there was no significant correlation between the vitamin D levels identified in the breast cancer patient and progressing TNM stages histologically scored in their malignant breast tissues (rho = -0.1, $P = 0.49$).

Discussion

A number of SNPs which are associated with breast cancer risk have been reported by recent GWA studies. However, it is often uncertain how these SNPs are related to breast cancer. Analysis of associations between SNPs and phenotypic variations of key cellular components may be important in determining the potential mechanisms of action, including carcinogenesis. Thus, vitamin D deficiency has been proposed to be linked to a number of serious health issues including cancer. Our study results showed a significant reduction in the vitamin D serum of breast cancer patients in comparison to the healthy control group. The lower serum levels of vitamin D were able to discriminate between the two assessed groups. This quite interesting observation seems to be consistent with proposed involvement of vitamin D deficiency in different forms of autoimmune diseases related cancer.[32] Indeed, a recent finding of meta-analyses based on randomized controlled trials have confirmed a substantial drop in cancer-related mortality by almost 30,000 cancer deaths per year in Germany owing to vitamin D supplementation.[38] Tumor invasiveness and tendency to metastasize are believed to be decreased in those with higher serum vitamin D levels at diagnosis, leading to reduced cancer mortality.[39]

In respect to the investigated *CCDC170* gene rs3757318 SNP, our study findings indicate that A allele of rs3757318 correlates with breast cancer susceptibility, especially the homozygous genotype (AA) that occurs only in the breast cancer patients but not in the non-malignant cases. Although no pervious local study has addressed the association between *CCDC170* gene rs3757318 SNP and breast carcinogenesis, yet, the results of the present study seem to be in line with that recently reported international studies that are linked rs3757318 SNP to breast

cancer.[40,41] Recent evidences also showed that *CCDC170* affects breast cancer apoptosis through inositol-requiring enzyme 1 (*IRE1*) pathway suggesting a key role for SNP in the intergenic region between *ESR1* and *CCDC170* with breast cancer risk.[42]

Additionally, as *CCDC170* rs3757318 SNP "AA" genotype was shown to be negatively correlated with age in breast cancer patients, this could be explore further for its potential utility in the predication of the disease occurrence at early ages. In the same vein, a number of genetic variations have been linked to different types of malignancies.[43-45]

Overall, these findings suggest the involvement of both *CCDC170* gene rs3757318 and vitamin D in breast carcinogenesis. These potential biomarkers can be useful tools in breast cancer risk assessment and management; highlighting the need of large-scale studies to validate the findings of present investigation.

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Conflicts of interest
There are no conflicts of interest.

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