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Role of vitamin D receptor FokI (rs10735810) variant in breast cancer susceptibility

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Abstract: Breast cancer (BC) has a significant morbidity and death rate and accounts for a disproportionate percentage of healthcare costs. It affects one of every eight women during her lifetime. BC has various genetic mutation disorders, including the VDR FokI polymorphism. The aim of this study was to evaluate the association of VDR FokI polymorphisms in Egyptian women with breast cancer. As well as to look into the relationship between FokI polymorphisms and a variety of patient characteristics. The study included 100 women with breast cancer and 100 healthy volunteers in the control group. Genotype analysis was performed using ARMS-PCR technique. The genetic research of FokI rs10735810 revealed significant associations among BC patients and a higher percentage of co-dominant, dominant, recessive, and allelic models ($p < 0.001$ for all). Pathological categories (IDC and ILC) reveal a significant difference for the FokI variant ($p=0.03$). Otherwise, no significant correlation was detected between FokI genotype and molecular classification ($p > 0.05$) or tumor size ($p = 0.68$) in the examined instances. In conclusion, our results suggest that FokI rs10735810 polymorphism may be associated with breast cancer development in Egyptian women and could be used as a prognostic factor for breast cancer.

Keywords: FokI; breast cancer; genetic mutations.

1. Introduction

Cancer remains a serious public health issue, with rising incidence and mortality rates. Breast cancer (BC) has recently become the most common cancer among women worldwide. In 2022, there were 9.7 million cancer-related fatalities and 20 million new cases of cancer globally [1]. According to the 2012 WHO classification, BC are largely classified as carcinomas and sarcomas [2]. Breast carcinomas are classed as in situ or invasive due to their high diversity. Invasive ductal carcinoma (IDC) is the most frequent kind of invasive carcinoma (about 80% of all BC), subsequently followed by invasive lobular carcinomas (ILC), which are responsible for 10-15% of all BC [3]. BC is produced by a complex interaction of controllable and uncontrollable elements. The fact that a woman's chance of acquiring breast cancer rises within one or two generations after moving from a low-risk to a high-risk location implies that the risk of developing BC is influenced by both genetic and environmental variables [4][5], such as age [6], food, body mass index (BMI), sensitive to hormones (especially estrogen and progesterone) [7], reproductive history [8], common oncogenes, breast density [9], family history [10], and inadequate vitamin supplementation [11].

Importantly, vitamin D is a steroid in structure, and its biological chemical component, 1,25 $(OH)_2D_3$, is required for both phosphorus and calcium metabolism. Preclinical studies have demonstrated that 1,25

$(OH)_2D_3$ can inhibit the growth of BC cells while encouraging differentiation and apoptosis [12]. Prior meta-analyses have supported a negative association between vitamin D status/intake and BC incidence, as well as a correlation between low levels of vitamin D and greater risk of recurrence and death in BC patients [13]. It appears inappropriate to recommend that each patient take the same dose of vitamin D because vitamin D's biological activity is based on binding to the receptor, and the vitamin D receptor (VDR) expression differs between patients. The mammary gland's epithelial, stromal, and immune cells express VDR, which is regulated in the epithelial compartments during hormonal alterations such as puberty and pregnancy. Vitamin D supports differentiation and passiveness in the breast epithelium by interacting with VDR in the same site or in adjacent cells [13]. Research indicates that VDR levels in breast cancer tissue are linked to better prognosis [14]. The VDR receptor gene is located on the longer arm of chromosome 12 (12q12-q14). It has no less than 11 exons that span 60 kb of DNA and five promoter regions[15]. The VDR gene harbors more than 900 allelic variants [16]. A portion of this is thought to interfere with Vitamin D function. FokI (rs10735810) variant, (ACG–ATG) located in exon 2, is a significant and well-studied single nucleotide polymorphism (SNP) of VDR [17]. Several studies have been conducted to investigate this mutation, finding conflicting results. Many studies have found that the FokI polymorphism rs10735810 is linked to an increased risk of breast cancer across multiple populations. But another research investigation found that distinct studies have not identified a link. However, FokI modifies the elevated risk of other VDR SNPs, resulting in an increased breast cancer risk [18], [19], [20], [21]

Consequently, the present study aims to determine whether VDR FokI polymorphism is associated with breast cancer susceptibility in Egyptian women using a case-control study in patients and matched controls, which is preferable in terms of assessing risk factors regarding this mutation in breast cancer susceptibility while taking into account confounding factors such as age differences between healthy and breast cancer patients and histopathological subtypes among breast cancer patients.

2. Materials and methods

The proposal was submitted to the Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB) for approval (ethical code: MS.23.02.2295, date: March 26, 2023). Both patients as well as controls signed informed agreement forms. In this comparative study, 100 histologically proven breast cancer cases diagnosed at Mansoura University Oncology Center between May 2023 and March 2024 were examined and matched with 100 age-matched normal female participants. The age of the examined individuals is greater than 20 years old at the time of being diagnosed with breast cancer in cases and sampling in controls. Matched healthy controls will be selected based on the absence of both clinical indicators and a family history of breast cancer. There were no additional cancers or autoimmune disorders in any trial group. Cases in which extraintestinal illnesses or other characteristics of the underlying tumour were excluded. Nobody in the healthy group smokes, has a history of complicated disease, or takes medications on a regular schedule. Patients with end-stage renal failure, liver disease, or malabsorption syndrome, which hinders vitamin D absorption, have also been excluded. The TNM, stage, tumour histology, and grade were all evaluated. The molecular testing for genetic changes was performed in the laboratory.

Blood sampling

Extraction of Genomic DNA

3 ml of whole blood was drawn from all participants into an EDTA tube. DNA was isolated from whole blood samples using a commercial extraction kit (QIAamp DNA Extraction Kit, Catalog No. #51106, QIAGEN, Hilden, Germany), extraction kit, Catalog No. #51106, QIAGEN, Hilden, Germany), according to the manufacturer's

VDR-FOKI (rs10735810) ARMS-PCR:

The VDR-FokI genotype variant was identified using ARMS-PCR method [22]. Sequences of specific and control primers, for ARMS-PCR assay are shown in Table 1. Each sample applied in two tubes in total volume 25

µl. Each tube contains 4 µl of C allele or T allele primer, 4 µl of common primer, 4 µl DNA and 13 µl of Master Mix (cat. no. BM311). Samples were amplified using a professional thermocycler (Biometra, Germany). The PCR assay conditions were as follows: initial denaturation at 95°C for 2 minutes for one cycle; 29 cycles, including denaturation at 95°C for 25 seconds; annealing at 58°C for 30 seconds; 72°C for extension for 1 minute; and final extension at 72°C for 5 minutes in one cycle; then soak at 4°C. The products of PCR were electrophoresed on 2.5 % agarose gel and visualized under UV yielding an expecting 77 bp amplicon for both C and T allele [22].

Table (1): Primers utilized for screening the FOKI (rs10735810) mutation via ARMS-PCR

Mutation		Size
FokI (rs10735810)	FokI/Common primer: 5'-AGCTGGCCCTGGCACTGA 3'	
	FokI/T: 5'-TGGCCGCCATTGCCTCCG 3'	77 bp
	FokI/C: 5'-TGGCCGCCATTGCCTCCA 3'	77 bp

The data collected were analyzed and lobulated with the SPSS software tool (IBM Corp. version 26). Chicago: SPSS, Inc. In terms of the study population's demographic and clinical characteristics, categorical variables such as age are presented as frequencies with percentages, with a 95% confidence interval and an odds ratio (OR) conferred by potential correlations between FoKI gene polymorphisms and the risk and progression of breast cancer. A significance criterion was specified as a probability level (P) less than 0.05.

3. Result and discussion:

The Hardy-Weinberg equation indicated that the population's frequencies do not match those expected for the studied gene, as significant variations were discovered among observed and predicted numbers (p = 0.008 and 0.001 for BC and controls, respectively). The results presented here compare selected data of all investigated parameters between cases of cancer patients and control persons. The average (±SD) ages of 100 patients were (52.73 ±12.85) years. The average age (±SD) of 100 controls was (54.43 ± 9.45) years.

There did not appear to be a significant association between patients and age-matched healthy controls (P = 0.28) Table (2).

Table (2). Comparison of the age among studied groups

Age (years)	BC patients *n=100*	Volunteers *n=100*	*p-value*
mean ± SD	*52.73 ± 12.85*	*54.43 ± 9.45*	*t=1.06 p=0.28*
median (range)	52 (25 - 88)	54 (36 - 72)	

SD, standard deviation; Numerical data are expressed as mean and SD, Student t-test was applied.

Table (3) shows a very statistically significant difference in FOKI (rs10735810) genotype polymorphisms from controls. The homozygous TT genotype was more common in patients (58%) than in controls (20%). Heterozygous TC was more common in healthy volunteers than BC patients (49 vs. 42), although not statistically significant (p = 0.98). The CC genotype was discovered in 31 controls but not in BC subjects. Regarding the FOKI co-dominant model, TC and CC genotypes show a highly significant difference in decrease with BC patients (OR 0.29, p < 0.001). dominant and recessive models investigate a significant correlation as p < 0.001 for each and OR < 1. The allelic model investigates a significant relationship among studied groups. Breast cancer patients have been shown to have a higher incidence of the T allele **Figure (1)**

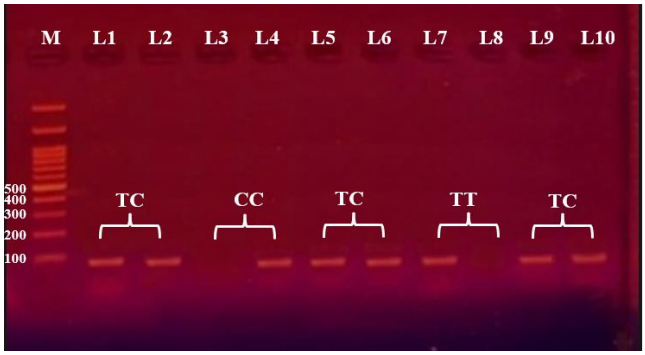

Figure (1): Gel electrophoretic pattern of ARMS-PCR of Foki gene polymorphism. Each sample is indicated by two lanes. M represent (100 bp) DNA ladder. Lanes (1, 3, 5, 7, and 9) included T allele at 77 bp; lanes (2, 4, 6, 8, and 10) indicate C mutant alleles as amplicon 77 bp

can appear. Lanes (1, 2, 5, 6, 9, and 10) indicated TC heterozygous genotype. Lanes (3 and 4) appeared the CC mutant homozygous genotype. Lanes (7 and 8) indicate TT wild homozygous genotype

Table (3). Comparison of FOKI rs10735810 genotypes frequency and alleles between BC cases and healthy volunteers.

Models		BC (n=100)		Control (n=100)		P-value	OR (95 % CI)
		n	%	n	%		
Co-dominant	TT	58.0	58%	20.0	20%	*MC=91.2 p<0.001*	1.0 (reference)
	TC	42.0	42%	49.0	49%		0.29 (0.15 – 0.57)
	CC	0.0	0%	31.0	31%		-
Dominant	TT	58.0	58%	20.0	20%	*p*<0.001 *FET=25.2*	1.0 (reference)
	TC+ CC	42.0	42%	80.0	80%		0.18 (0.09 – 0.34)
Recessive	TT+TC	100.0	100%	69.0	69%	*FET=85.7 p<0.001*	1.0 (reference)
	CC	0.0	0%	31.0	31%		-
Allelic	T-allele	158.0	79%	89.0	44.5%	*p*<0.001 χ^2=50.4	1.0 (reference)
	C-allele	42.0	21%	111.0	55.5%		0.21 (0.14 – 0.33)

Parameters were expressed as frequency (percentage). OR: Odds ratio, CI: Confidence Interval, (OR>1 is considered risky; OR<1 is considered protective). Chi-Square, FET, and monte carlo tests were applied. * Significant (if *p<0.05*)

We investigated the correlation of several variables and the FokI mutations. No significant association was found regarding FoKI with age among all studied BC patients (P= 0.97). The histology and grading of the malignant cells should be used to select instances for investigation. Of the 100 individuals studied, (94.0%) had invasive ductal carcinoma, while (6%) had Invasive lobular carcinoma form of BC. In terms of the staging, 17% of cases were classified as the 3rd grade and the majority (83%) were in the secondary grade. The majority of cases (72%) were not investigated for BC metastases to other organs in the body, and 28% of the cases had the highest stage of BC M1. The pathological types (IDC and ILC) show significant difference for FokI variant with (p=0.03). Chi-square testing χ found no significant relationship with molecular classification (p > 0.05) or tumor size (p=0.68) regarding FoKI genotypes. No significantly association was seen regarding FoKI genotypes with Tumor grading or TNM staging among all studied cases. **Table (4).** Regression analysis was performed to predict susceptibility to BC employing age and FoKI rs10735810 as factors. In both univariable and multivariable analyses, reduced FokI dominant variation polymorphisms were associated with a higher risk of BC (p < 0.001 for each, OR= 0.1, 0.18, respectively). Age was not considered a risk factor for BC illness (p = 0.31).

Table (4): Association of FOKI genotypes with different variables among all BC cases.

FOKI		TTn (%)	TCn (%)	*p-value*
		n=58	n=42	
Age (years)		53.74 ± 12.4	51.33 ± 13.46	p=0.97F=0.02
Tumor size	small	13 (22.4%)	8 (20%)	p=0.68χ2=0.16
	large	45 (77.6%)	34 (80%)	
Pathological type	*IDC*	*52 (89.6%)*	*42 (100%)*	*p=0.03χ2=4.6*
	ILC	6 (10.4%)	0 (0%)	
T	0	1 (1.7%)	3 (7.2%)	p=0.4MC=2.8
	1	12 (20.7%)	10 (23.8%)	
	2	31 (53.4%)	23 (54.7%)	
	3	14 (24.2%)	6 (14.3%)	
N	0	12 (20.6%)	13 (30.9%)	p=0.92χ2=0.5
	1	24 (41.4%)	11 (26.2%)	
	2	8 (13.8%)	7 (16.7%)	
	3	14 (24.1%)	11 (26.2%)	
M	0	40 (69%)	32 (76.2%)	p=0.42χ2=0.63
	1	18 (31%)	10 (23.8%)	
Tumor grade	II	48 (82.7%)	35 (83.3%)	p=0.93χ2=0.006
	III	10 (17.3%)	7 (16.7%)	

Parameters were expressed as frequency (percentage), Chi-square, FET a, and Monte Carlo tests were applied. Significant if $p<0.05$

Discussion:

The prevalence rate of BC amongst Egyptian women is approximately 48.8 per 100,000 [23]. Developing countries have the greatest mortality rates from breast malignant carcinoma [24]. It has been shown to be heavily influenced by gene alterations affecting hormone metabolism. Previous studies showed that the expression of vitamin D receptor is lower in cancerous breast cells as compared to regular breast cells [25]. In the present study, women with breast cancer are more likely to develop invasive ductal carcinoma, grade II cancer, and larger tumors. The same frequencies were found in a prior study at Egyptian [26]

and southern Pakistani women [27]. In research conducted in Egypt, breast cancer women with ductal carcinoma and grade I tumor were more prevalent [23]. In our study, breast cancer patients were analyzed for VDR gene Fok-I polymorphisms. The allele frequencies of the VDR FokI SNP were obtained. The distribution of co-dominant genotypes shows a significant difference among the studied subjects ($P < 0.001$). Also, the (TC+CC) show a very statistically significant difference from controls ($P < 0.001$) compared to the TT reference dominant model. Moreover, the allelic C model correlates significantly with low BC incidence ($P < 0.001$, $OR = 0.21$). Several studies have shown that the FokI variations, namely the CC genotype, are linked to an increased risk of BC. This relationship is seen in a variety of populations, including French, Canadians, Caucasians, and Pakistani women [18], [28],[29], [30]. Furthermore, a meta-analysis of twenty-one case-control research studies with Fok1, Bsm1, Apa1, and Taq1 mutations found that the Fok1 polymorphism was associated with an increased risk of developing breast cancer [31]. A prior Egyptian study indicated a considerably higher risk of breast cancer with the Fok-I TC genotype [23]. Some researchers discovered no significant link between the FokI polymorphism and breast cancer risk, although it can impact the increased risk for additional VDR genotypes, such as the BsmI C allele, that leads to breast cancer [32]. Another study among the UK Caucasian community showed similar outcomes, with no association between Fok1 and breast cancer [21]. Taking all of these factors into account, the preceding investigations revealed an ambiguous connection between Fok1 and breast cancer. Historical genetic bottlenecks, founder effects, and environmental aspects can affect these variations. Further research is needed to clarify the findings based on the Fok1 polymorphism's connection with that cancer.

To analyze the association between FokI genotype frequencies and different clinicopathological features, statistical analysis did not show a significant association of FokI genotype frequency distribution regarding the age of patients ($p=0.97$). The FokI mutation differs significantly across pathological kinds (IDC and ILC) ($p = 0.03$). While the FokI polymorphism in the VDR gene has been associated with an increased risk of breast cancer, the precise relationship between this polymorphism and the pathological types of breast cancer (IDC and ILC) remains unknown. Some evidence suggests that the C allele is associated with more aggressive tumour features, which are common in IDC [28]. In conclusion, the current study sought to determine VDR FokI genotypic frequency distribution in the Egyptian population across several variables. A deeper awareness of the tumor's biology and the most predominant genetic mutation in the FOKI gene associated with Egyptian society allows for disease prediction before critical stages and the provision of targeted treatments that promise to increase the chances of survival from breast cancer

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