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# Vitamin D status and gene receptor polymorphisms related to breast cancer risks

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**ABSTRACT**

Breast cancer is the most common cancer in women worldwide. It has many causes and one of these is genetic, as many genes are implicated in the generation of this type of cancer. The vitamin D3 receptor is one of these genes and has been shown to be involved in the development of breast cancer through a polymorphism. It is in this context that we conducted our study in which we investigated the relationship between the Fok1 and Taq1 polymorphisms, breast cancer and plasma vitamin D concentrations in Moroccan patients. Our study included 98 women, 53 of whom were ill and 45 healthy. We tested for two types of VDR polymorphisms, Taq1 and Fok1, by real-time PCR. Vitamin D status was assessed by the electrochemiluminescence method. Our work concluded that there is no correlation between Fok1 and disease stage and a probable Fok correlation. It was shown that there is a significant correlation between vitamin D and Fok1. In conclusion, vitamin D deficiency appears to be related to the Taq1 polymorphism which may increase the risk of developing breast cancer in Moroccan women.



## 1. INTRODUCTION

Breast cancer is the most frequent malignancy among women worldwide [1] that is the second leading cause in low and middle income countries [2]. Many genes have proven to play a role in the inherited genetic risk for breast cancer and the discovery of new breast cancer susceptibility genes has become inevitable to improve risk assessment and to provide insight toward disease mechanisms [3].

The genetic factors known to be involved in breast cancer risk comprise about many genes some of which

are considered as high penetrance genes and other as low penetrance genes [4]. The vitamin D-3 receptor (VDR) is a member of the nuclear receptor family of transcription factors. This receptor modulates gene expression through binding with its ligand 1-α,25-dihydroxycholecalciferol [1,25(OH)2-D3], whi1ch is the biologically active form of vitamin D-3 [5]. VDR has been shown to be involved in insulin-like growth factor (IGF) signaling, in inflammation and estrogen-related pathways, in the activation and regulation of vitamin D and calcium, and lastly in breast cancer risk [6].

VDR gene has been suspected to be implicated in the risk and progression of breast carcinoma through single nucleotides polymorphism (SNP). Two of the most studied SNP for this gene in association with cancers are the Fok1 and Taq1 polymorphisms [7], [8]. To the best of our knowledge our study is the first to analyze both SNPs polymorphisms in breast cancer Moroccan patients, However many studies worldwide have analyzed both polymorphisms in breast cancer [9- 11].

Moreover, Vitamin D (1, 25-dihydroxyVitamin D3) which is the VDR receptor ligand has been shown experimentally to have anti-carcinogenic effects and is thought to inhibit breast Cancer [12]. Vitamin D is hypothesized to lower the risk of breast cancer by inhibiting cell proliferation via the nuclear vitamin D receptor (VDR) [13].

Tell date there are limited studies on the relationship between VDR gene polymorphisms and breast cancer characteristics [14]. Therefore, we conducted a study in which we investigated the correlation between both Fok1 and Taq1 polymorphisms with Breast cancer and D vitamines levels in Moroccan patients.

## 2. Methods

### *2.1 Patients*

This retrospective study was approved by the ethical committee of Hassan II University. In a cross-control study, 53 Breast Cancer case and 45 control women were chosen. The controls did not have any relationship with patients and had no history of cancer. Complete clinical, pathological and follow-up data. Informed consent was obtained from all recruited cases in our cohort permitting the use of their collected blood samples and clinic-pathological data for research purposes.

### *2.2 Vitamin D status evaluation*

Venous blood samples were obtained from each participant. 25-hydroxyvitamin D levels were measured by chemiluminescence using the VIDAS 3 automate according to the manufacturer's instructions. The standards doses were between 30 and 150 µg / l regardless of the age and gender. The severity of vitamin D deficiency was evaluated according to the vitamin D status [16]: vitamin D deficiency is defined as < 12 ng/ml, vitamin D insufficiency as ≥12 -< 30 ng/ml and vitamin D sufficiency as ≥30 ng/ml. Vitamin is considered toxic for serum concentration ≥150 ng/ml.

### *2.3 VDR Genotype Analysis*

▪ DNA extraction

Genomic DNA was extracted using Invitrogen PureLink™ Genomic DNA Mini Kit according to the manufacturer's guidelines. Both DNA concentration and quality were assessed using the NanoVue Plus spectrophotometer from Biochrom.

▪Real Time PCR

Real time-PCR method was used for analysis of rs 2228570, and rs 731236 of the VDR gene. Genotyping

was performed using the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) for both the *VDR* SNPs *Taq-I* (rs731236) and *Fok-1* (rs2228570). This assay contain a predesigned mix of unlabeled polymerase chain reaction (PCR) primers and the TaqMan® minor groove binding group (MGB) probe (FAM™ and VIC® dye-labeled) and it was used in combination with TaqMan® Universal PCR MasterMix that contains DNA polymerase, dNTPs and optimized mix components and uses the same thermal conditions.

These assays were applied using The Agilent AriaMx Real Time PCR system. The real time PCR experiments were performed according to the manufacturer's guidlines with a final reaction volume of 10 µl that contained 1 µl of genomic DNA (20 ng), 8.5 µl of TaqMan Genotyping Master Mix (2 ×) (Applied Biosystems, USA) and 0.5 µl of assay mix (20 ×). The Real Time PCR thermal conditions were as follows:

**Table1:** Real Time PCR thermal profile.

| Step | Temperature | Time | Cycles |
|---|---|---|---|
| Initial denaturing | 95 °C | 20 s | 1 Cycle |
| Denaturing | 96 °C | 3 s | 40 cycles |
| Annealing/Extension | 60 ° | 30 s | |

For quality control, 5% of samples were re-genotyped in a blinded fashion with positive, negative controls and blanks.

### *2.4 Statistical Analysis*

We used the processing and analysis software Stata (version stata 14), to conduct the different statistical tests and estimations of ANOVA, CHI-DEUX and Linear Regression. The logistic regression analyses were assessed by computing the odds ratio (OR) and 95% confidence intervals (CI) for association between genotypes and breast cancer. Also, a p-value < 0.05 was considered to be statistically significant.

## 3. Results

The allele and genotype frequencies of both analyzed *VDR* gene SNPs *Fok-1* (rs2228570) and *Taq-I* (rs731236) in our Moroccan cohort are shown in Table 2 and Table 3. Out of the 98 subjects analyzed for *Fok-1* (rs2228570) and *Taq-I* (rs731236), the following genotypic frequencies were obtained: AA 14.4%, AG 29.3%, GG 56.2% and AA 13.9%, AG 43.2%, GG 41.8% respectively.

▪ Correlation with breast cancer

From the 98 successfully analyzed proband in our cohort 53 had breast cancer while 45 were healthy 0. From the 53 patients 10.2% had AA genotype, 30.6% had AG genotype and 59.1% had GG genotype for the Fok-1 (rs2228570) SNP. While for Taq-I (rs731236) polymorphism % harbored AA genotype, 48.9% harbored AG genotype and 28.5% harbored 18.3% GG genotype statistical analysis results revealed the absence of any correlation between both SNPs and breast cancer risk in the Moroccan population p-value 0.63 and 0.13 respectively.

**Table 2:** *Fok-1* (rs2228570) genotype distribution

| **rs2228570** | **G/G** | **G/A** | **A/A** |
|---|---|---|---|
| breast cancer | 27 | 13 | 5 |
| Healthy | 19 | 12 | 14 |
| Totale Population | 46 | 25 | 19 |

**Table 3:** *Taq-I* (rs731236) genotype distribution

| rs731236 | G/G | G/A | A/A |
|---|---|---|---|
| breast cancer | 16 | 26 | 11 |
| Healthy | 19 | 20 | 6 |
| Totale Population | 35 | 46 | 17 |

## 4. Discussion

Recently, many studies have proven that vitamin D receptor (VDR) genes were implicated in an increased breast cancer risk [14] Several Vitamin D receptor genes operated by vitamin D have important roles in the mammary gland through regulation of calcium transport during lactation, hormone differentiation, and milk production [15]. Many efforts and enormous research have been directed toward identifying vitamin D as a breast cancer risk factor to be targeted for cancer prevention. This is because circulating vitamin D levels (levels ≥45 ng/mL) may protect against breast cancer [16].

The VDR gene lies on the long arm of chromosome 12 (12q12-14), with more than 200 single-nucleotide polymorphisms verified in it [17]. The most common studied allelic variants within VDR were as follows: FokI (T/C) in exon II, BsmI (A/G) and ApaI (C/A) between exon VII and IX, TaqI (T/C) variant in exon IX, and poly(A) [17]. Reports show which of these polymorphisms associated with breast cancer are inconsistent. Iqbal and Khan in their systematic meta-analysis showed that VDR gene polymorphisms, Bsm1, Apa1, poly(A), Fok1, and Apa1, were associated with the breast cancer, whereas Cdx2, Bgl1, and Taq1 polymorphisms did not show any association. In another meta-analysis conducted by [18] for 125 951 persons from 135 populations, Fok1 VDR polymorphism was associated with increased breast cancer risk (OR = 0.96; 95% CI = 0.93-0.99. Another meta-analysis of 8 studies did not show any significant association between Fok1, Bsm1, Taq1, Apa1, VDR polymorphism, and breast cancer risk [19]. The VDR polymorphism case-control studies showed different associations between different VDR polymorphisms and breast cancer risk among different populations: ApaI and TaqI confer high breast cancer susceptibility among Egyptian women [20], Taq1 among Jordanian women [21], Bsma1 among Pakistani women [22], and poly(A) microsatellite among Iranian women. BsmI but not Fok1 was associated with the risk of breast cancer among Iranian women [23]. However, [24] in their mini review compare the impact of VDR gene polymorphisms, Fok1, Bsm1, Taq1, Apa1, and poly(A), on the development of breast cancer and showed inconsistent results, with no conclusive statements about the significance of the VDR genotype on breast carcinoma development.

The FokI polymorphism, either singly or in combination with other VDR polymorphisms, has been extensively investigated in breast cancer risk assessment studies [25], [26]. For example, [29] reported that the FokI variant allele together with other VDR polymorphisms, amplified breast cancer risk in a Caucasian population in the United Kingdom [27]. On the other hand, two other studies found that women with the variant genotype were more susceptible to breast cancer than those with the variant genotype [28], [29], while another study did not observe any correlation between the FokI polymorphism and increased breast cancer risk in postmenopausal women [30]. Our study results join the latter from 97 successfully analyzed cases no correlation was observed between FOK1 and breast cancer.

These conflicting conclusions are often derived due to small sample sizes, compounding variables and selection biases in patient populations for each study. However, more recently, two reports with meta-analyses of multiple studies with large sample sizes provide evidence for a positive association between the FokI variant genotype and an augmented predisposition to the disease [31], [32]. However, these reports do not provide any conclusive evidence linking VDR variant to breast cancer risk or responsiveness to vitamin D. Therefore, it is necessary to evaluate functional differences between polymorphic alleles experimentally in breast cancer cells.

Regarding VDR TaqI polymorphism this study showed no significant association between it genotypes or allelic frequencies among breast cancer patients and controls. Similar results were reported by [33], [34] among both population in Taiwan (China) and Caucasian breast cancer women. The same results were also reported by the meta-analysis from pooling 39 studies that showed no significant associations between VDR TaqI polymorphisms and breast cancer risk [35].

On the other hand, regarding vitamin D levels This study showed that most breast cancer participants were Vitamin D deficient (66.4%) and this result is consistent with the previous study that is carried out by [36] Vitamin D deficiency might be attributed to other contributing factors including the use of sun blocks as well as avoiding performing activity in sunny areas and the dietary regimen.

This study showed a significant difference between Vitamin D level among VDR TaqI different genotypes and within breast cancer patients and control groups (P-value=0,03), in which the rare genotype (tt) had the highest Vitamin D level compared to the other patterns, followed by the heterozygous genotype (Tt). Meanwhile, the wild-type genotype (TT) scored the lowest Vitamin D level which is compatible with results that were found by [37]. While for VDR FOK1 different genotypes no correlation with vitamin D levels was observed our results join those of [38- 40].

## 5. Conclusion

Our work has highlighted the correlation between vitamin D deficiency and the Tak 1 polymorphism of the VDR receptor, which may be incriminated in the genesis of breast cancer. It would be desirable to carry out other randomized studies, with a larger sampling, before introducing vitamin D supplementation in the therapeutic strategy of breast cancer in Moroccan women.

## 6. Competing interests

The authors declare no competing interests.

## 7. Ethics approval and consent to participate

Agreement of the Ethics Committee of Biomedical Research in Morocco code: (n°3/2018/April 30/2018-Morocco).

## 8. Authors contributions

HA: participated in the project design, experimental analysis, and Statistical analysis and drafted the manuscript. FJ: participated in the experimental analysis; MN: participated in the project design and review of the final manuscript; FE: participated in the project design and review of the final manuscript; SAF: participated in statistical analysis; JF: participated in the project design and review of the final manuscript; MME: participated in the design and coordination of the project and review of the final manuscript coordinate all project. All authors have reviewed and approved the manuscript.

All co-authors gave final approval for the submitted manuscript.

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