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Vitamin D receptor genetic variations in association to the susceptibility to prostate cancer: a case-control study in a Moroccan population

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Abstract

Aim: It has been shown that the vitamin D receptor (*VDR*) gene and its biological functions can be affected by genetic alterations in the *VDR* gene. These genetic alterations particularly (rs1544410), (rs7975232), and (rs731236) polymorphisms, and deficiency of vitamin D are suggested to contribute to predisposition to prostate cancer (PCa). Our case-control study investigates the association between *VDR* gene polymorphisms and PCa risk, in relation to clinicopathological features, within the Moroccan population. Assess the relationship between *VDR* polymorphisms (rs1544410), (rs7975232), and (rs731236) and PCa risk in Moroccan men and their association with clinicopathological characteristics.

Methods: A total of 100 men patients (mean age of 69.8 years) with different stages of PCa were genotyped for three *VDR* gene polymorphisms, (rs1544410), (rs7975232), and (rs731236), as well as 100 healthy controls using the PCR-RFLP using restriction enzymes (*BsmI*, *ApaI,* and *TaqI*). The evaluation of the association between *VDR* genetic polymorphisms and clinicopathological features was carried out by the chi-square test (χ^2) and the odds ratios (OR) with 95% confidence intervals (CI).

Results: Significant associations were found between the *ApaI* (p = 0.045) and *TaqI* (p = 0.029) polymorphisms and the risk of PCa. The haplotypes AA (42%) of *ApaI* and Tt (45%) of *TaqI* were more frequent in PCa patients, suggesting an increased risk. The *BsmI* polymorphism was significantly associated

with PSA levels (p = 0.045). Additionally, the *ApaI* polymorphism was linked to smoking status in PCa patients (p = 0.023), and *TaqI* was associated with pathological T stage (p = 0.042) and surgical history (p = 0.013).

Conclusions: Our findings indicate that the *ApaI* (rs7975232) and *TaqI* (rs731236) polymorphisms of the *VDR* gene are significantly associated with an increased risk of PCa in the Moroccan population. Moreover, *ApaI* was linked to smoking, while *TaqI* showed an association with tumor stage and surgical history, suggesting that these variants may influence both genetic predisposition and cancer progression.

Keywords

Vitamin D, vitamin D receptor, single nucleotide polymorphisms, prostate cancer, Moroccan population

Introduction

Prostate cancer (PCa) is the fifth most common cause of death worldwide and the second most common cancer in men [1, 2]. As well as it remains the second leading cause of cancer death worldwide and the most frequently diagnosed type of cancer in men [3]. It was reported that 1,414,259 men were diagnosed with PCa and 375,304 died of PCa worldwide in 2020 [4]. In Morocco, PCa is the most common cancer in men aged over 50, with a proportion of 12.4% after lung cancer, according to the cancer registry [5]. It remains the most important cancer in terms of incidence and mortality, it represents the leading cause of cancer mortality in men aged over 70 [6]. Genetic factors and many other risk factors are associated with a higher risk of developing PCa [7]. Alcohol consumption and smoking are considered well-established environmental risk factors for this cancer [8]. The causality of PCa is still not well explained, although genetic polymorphisms may play an important role in the genesis of this disease.

Vitamin D, the active form of which is 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], has been indicated as an important prohormone involved in the risk of PCa and in several actions, including its antiangiogenic, antiproliferative, and apoptotic effects [9, 10]. Previous studies have discovered that normal and malignant prostate cells contain vitamin D receptors (VDR) that initiate the antiproliferative action of $1,25(OH)_2D_3$ [11, 12]. Thus VDR, coded by the *VDR* gene located on chromosome 12q13.1 has been considered as a ligand-dependent transcription factor [13, 14]. It has also been shown that serum levels of $1,25(OH)_2D_3$ can affect the proliferation and differentiation of prostate tumor cells [15, 16]. VDR has been studied in relation to the pathogenesis of PCa. High VDR expression in clinical PCa samples is linked to a lower risk of fatal cancer. This suggests that the vitamin D pathway plays an anti-oncogenic role in the progression of PCa [17]. Consequently, any modification of the VDR can cause an increase in the incidence of PCa [18], the *VDR* gene includes several allelic variations that have been epidemiologically associated with the etiology of PCa [19]. The most common single nucleotide polymorphisms (SNPs), including *BsmI* and *TaqI*, have been identified as impacting the expression and function of VDR protein, which has been linked to PCa [20–22]. *VDR* genetic polymorphisms have also been linked to PCa progression [23]. Environmental and physiological factors are also involved in the metabolism of the vitamin D, including levels of exposure to ultraviolet light, skin color, and genes involved in the synthesis and metabolism of vitamin D, which may be involved in the risk of PCa [24, 25].

Genetic variety is crucial for promoting the development of more sophisticated genes, safeguarding existing populations, advancing evolutionary processes, and enabling adaptation to changing conditions in the natural environment [26, 27]. Conversely, the identification of gene polymorphisms is crucial in the process of detecting and treatment of diseases [28, 29]. On the other hand, determination of gene polymorphism is important in characterizing of various populations [30] in order to define genotypes of individuals and their associations with immune system, resistance, or susceptibility to cancers [31]. Genetic studies have analysed the relationship between PCa risk and *VDR* polymorphisms [22, 32, 33], several of which have suggested statistically remarkable associations [22, 33], and others have detected the absence of association [21]. Others have reported an association between VDR SNPs and prostate-specific antigen (PSA) level, Gleason score, and consequently PCa risk in men [20]. Additionally, polymorphisms in the 3'

untranslated region (UTR), including the *ApaI* and *TaqI* sites, have been shown to affect gene transcription and mRNA stability [18]. It is assumed that the differential carriage of these SNPs has an effect on the transcriptional activity of the VDR and on the risk of cancer. Which normally manifests itself following the activation of target genes via the vitamin D responsive element (VDRE) when the active metabolite $1,25(OH)_2D_3$ binds to the *VDR*. Although numerous studies have explored the relationship between *VDR* gene polymorphisms and PCa risk, the findings have been inconsistent across different populations [20–22]. While some studies have reported significant associations between *ApaI, BsmI, and TaqI* polymorphisms and PCa, others have found no correlation [23]. Moreover, most of these studies have been conducted in European and Asian populations, with limited data available on African and North African populations, including Morocco. Additionally, while previous research has largely focused on the association between *VDR* polymorphisms and PCa risk, few studies have investigated their potential impact on clinicopathological features such as PSA levels, tumor stage, Gleason score, and smoking status. Our research addresses this knowledge gap by providing the first comprehensive analysis of *VDR* gene polymorphisms (*ApaI*, *BsmI*, and *TaqI*) in Moroccan men with PCa, assessing not only their potential role in cancer susceptibility but also their associations with clinicopathological characteristics.

This case-control study aimed to evaluate the association between the investigated *VDR* polymorphisms (*BsmI*, *ApaI*, *TaqI*) in PCa patients in the Moroccan population in association to clinicopathological features.

Materials and methods

Collection of samples

The Department of Urology of Mohammed V Military Teaching Hospital in Rabat recruited 100 men diagnosed with PCa (mean age 69.8 years). A total of 100 age-matched controls with no family history of cancer were recruited. The Ethics Committee for Biomedical Research of the Faculty of Medicine and Pharmacy of Casablanca, Morocco (No. 3/2018/April 30, 2018) approved the ethics of this study. The subject's peripheral blood samples were collected in sterile tubes containing EDTA anticoagulant sodium salt and stored at 4°C.

Inclusion and exclusion criteria

The inclusion criteria for this study required PCa patients to have a confirmed histopathological diagnosis, be aged 40 years or older, and have no previous history of other malignancies.

Healthy control participants were age-matched individuals with no history of PCa or other malignancies and no clinical signs suggestive of PCa.

Exclusion criteria included a history of other cancers, chronic diseases affecting vitamin D metabolism (such as severe kidney or liver disease), and ongoing hormonal or chemotherapy treatment for PCa.

DNA extraction and amplification

DNA was extracted from whole blood using the PureLink Genomic DNA Kit (Invitrogen Genomic DNA Mini Extraction Kit, Thermo Scientific) according to the manufacturer's instructions at the Laboratory of Virology, Oncology, Biosciences, Environment and New Energies (LVO BENE) in the Faculty of Science and Technology at Mohammedia, Morocco. The extracted DNA was eluted in 30 µL and stored at 20°C until further use. To evaluate the quality and integrity of the extracted DNA, all samples were subjected to *β-globin* gene amplification by PCR using the specific primers GH20/PCO4 primer set indicated in Table 1. DNA concentration and quality were obtained using the NanoDrop spectrophotometer 2000 (Thermo Scientific) by absorbance measurements at 260/280 nm. The *BsmI*, *ApaI*, and *TaqI* polymorphisms of the *VDR* gene were detected by PCR followed by restriction enzyme digestion (PCR-RFLP). The PCR reaction consisted of a total volume of 25 µL containing 2 µL of genomic DNA (8 ng), 12.5 µL of the master mix kit (Taq PCR), 2 µL × 2 of primers (Table 1) with 6.5 µL of distilled water. PCR amplification was carried out according to the following protocol: an initial denaturation step at 94°C for 3 minutes, followed by 35

denaturation cycles at 94°C for one minute, annealing at 56°C (for *BsmI*) and 66°C (for *ApaI*, *TaqI*) for one minute, elongation at 72°C for one minute, and a final elongation at 72°C for 10 minutes. The size of the PCR products was confirmed by electrophoresis on a 2% agarose gel for 1.5 h at 70°C.

Table 1. Primers used for detection of *β-globin* and *VDR* gene polymorphisms

Genes	Primers	Sequences	Annealing temperature (°C)	Amplified fragment size (bp)	Reference
β-globin gene	PC04	5'-CAACTTCATCCACGTTCACC-3'	54	268	[34]
	GH20	5'-GAAGAGCCAAGGACAGGTAC-3'			
VDR gene SNP (rs1544410) restricted by *BsmI*	Forward	5'-CAACCAAGACTACAAGTACCGCGTCAGTGA-3'	56	825	[35]
	Reverse	5'-AACCAGCGGGAAGAGGTCAAGGG-3'			
VDR gene SNP (rs7975232)/(rs731236) restricted by *ApaI/TaqI*	Forward	5'-CAGAGCATGGACAGGGAGCAA-3'	66	740	[36]
	Reverse	5'-GCAACTCCTCATGGCTGAGGTCTC-3'			

VDR: vitamin D receptor; SNP: single nucleotide polymorphism

Single nucleotide identification polymorphisms

After amplification, the PCR products were digested with *ApaI* and *BsmI* enzymes (at 37°C) and a *TaqI* enzyme (at 65°C). The final PCR-RFLP product was electrophoresed on a 2% agarose gel. PCR products digested with *BsmI* reveal genotypes (after treatment with the enzyme) denoted BB (825 bp), Bb (825, 650, and 175 bp), bb (650 and 175 bp), *ApaI* AA (740 bp) genotypes, Aa (740, 530, and 210 bp), aa (530 and 210 bp) and the *TaqI* genotypes TT (495 and 245 bp), Tt (495, 290, 245, and 205 bp), tt (290, 245, and 205 bp).

Statistical analysis

Mean values were first assessed for normality using the Kolmogorov-Smirnov test, confirming that the data followed a normal distribution. Mean values were then compared using Student's *t*-test to assess the significance of the difference in mean PSA levels and age between the case and control groups. The chi-square test (χ^2) was used to compare the genotype frequencies between the case and control groups. A *p*-value < 0.05 was considered statistically significant. The association between different genotypes and PCa risk was assessed by calculating odds ratios (OR) and 95% confidence intervals (CI). All statistical analyses were performed using SPSS version 20.0.

Results

Our results show that the average age was 69.8 ± 9.08 and 69.4 ± 9.01 years in PCa patients and control subjects, respectively. Additionally, the average PSA level among cancer patients was significantly higher compared to that in the controls (1.8 ± 1.4 ng/mL), $p = 0.037$ (Table 2).

Table 2. Clinical data of PCa patients and controls

Clinical data	Case Mean ± SD	Control Mean ± SD	*p*-value
Age	69.8 ± 9.08 years	69.4 ± 9.01 years	0.755
PSA	318 ± 150.7 ng/mL	1.8 ± 1.4 ng/mL	0.037

PSA: prostate-specific antigen; SD: standard deviation

Table 3 presents the genotypes and their frequencies according to the Hardy-Weinberg equation of the alleles of the polymorphisms of the *VDR* gene digested by (*BsmI*, *ApaI*, *TaqI*) enzymes in participants with PCa and in controls. A significant association was observed between the *ApaI* and *TaqI* polymorphisms and the risk of PCa ($p = 0.045$ and $p = 0.029$, respectively), while no association was found for the *BsmI* polymorphism ($p = 0.927$).

Table 3. Association of *VDR* genotype frequencies in PCa and control participants

SNPs	Genotypes/ Alleles	Cancer cases *N* (%)	Controls *N* (%)	*p*-value (χ^2)	OR (95% CI)
rs1544410 *BsmI*	BB	16 (16%)	30 (30%)	0.927	1 (Reference)
	Bb	38 (38%)	28 (28%)		OR = 0.556; $p = 0.446$ (95% CI: 0.122–2.54)
	bb	46 (46%)	42 (42%)		OR = 0.952; $p = 0.947$ (95% CI: 0.226–4.01)
	B	35%	44%		
	b	65%	56%		
rs7975232 *ApaI*	AA	42 (42%)	41 (41%)	0.045*	1 (Reference)
	Aa	44 (44%)	33 (33%)		OR = 1.67; $p = 0.3$ (95% CI: 0.632–4.39)
	aa	14 (14%)	26 (26%)		OR = 5.33; $p = 0.024$ (95% CI: 1.16–24.6)
	A	64%	57.5%		
	a	36%	42.5%		
rs731236 *TaqI*	TT	41 (41%)	54 (54%)	0.029*	1 (Reference)
	Tt	45 (45%)	27 (27%)		OR = 1.98; $p = 0.037$ (95% CI: 1.05–8.47)
	tt	14 (14%)	19 (19%)		OR = 4.63; $p = 0.031$ (95% CI: 1.09–19.7)
	T	63.5%	67.5%		
	t	36.5%	32.5%		

SNPs: single nucleotide polymorphisms; OR: odds ratios; CI: confidence intervals; * statistically significant. Two OR are reported for each genotype. The first OR corresponds to the comparison between BB and Bb (AA and Aa) (TT and Tt) genotypes, and the second OR compares BB and bb (AA and aa) (TT and tt) genotypes. Each OR is accompanied by its *p*-value and 95% CI

The BB genotype of *BsmI* SNP was present in 16% of PCa patients compared to 30% of healthy controls, whereas the bb genotype was found in 46% of PCa patients and 42% of controls. The estimated OR for PCa occurrence compared to controls for the BsmI polymorphism was 0.952 (95% CI: 0.226–4.01, $p = 0.947$).

The *ApaI* polymorphism showed a significant association, with the aa genotype being less frequent in PCa patients (14%) compared to controls (26%), and an OR of 5.33 (95% CI: 1.16–24.6, $p = 0.024$). Similarly, for the *TaqI* polymorphism, the tt genotype was present in 14% of PCa patients and 19% of controls, and the Tt genotype was 45% among the cases and 27% in the control group, with an OR of 4.63 (95% CI: 1.09–19.7, $p = 0.031$).

Table 4 illustrates the association between patient demographic and behavioral parameters with *VDR* genotypes. A significant relationship was found between the *ApaI* polymorphism and smoking status in PCa patients ($p = 0.023$). However, no SNPs showed associations with alcohol consumption in PCa patients.

Further analysis examined the correlation between *VDR* genotypes and clinicopathological features in PCa patients (Table 5). A significant association was observed between the *BsmI* SNP and PSA levels ($p = 0.045$), where 67% of cases had PSA levels higher than 10 ng/mL, including 31 (46.3%) with the bb genotype. The Gleason score was significantly associated with the *ApaI* polymorphism ($p = 0.049$), as 31 (42.5%) of the study population had a Gleason score > 7, with 48.4% of them carrying the Aa and Tt genotypes. A total of 21 patients presented with advanced pathological stage T (T3 and T4), distributed respectively 8% and 13%, and most of them carried the TT genotype. The *TaqI* polymorphism was significantly associated with pathological T stage ($p = 0.042$), with most patients carrying the TT genotype. Additionally, a strong association ($p = 0.013$) was found between surgical history and the *TaqI* SNP, with the majority (38.5%) of patients carrying the TT genotype.

Table 4. Association between patient demographic and behavioral parameters with *VDR* genotypes

SNPs		*N*	*BsmI*			*ApaI*			*TaqI*		
			BB *N* = 16	Bb *N* = 38	bb *N* = 46	AA *N* = 42	Aa *N* = 44	aa *N* = 14	TT *N* = 41	Tt *N* = 45	tt *N* = 14
Age at diagnosis	< 60 years	15	2 (13.3%)	6 (40%)	7 (46.7%)	8 (53.3%)	6 (40%)	1 (6.7%)	8 (53.3%)	4 (26.7%)	3 (20%)
	≥ 60 years	85	14 (16.5%)	32 (37.6%)	39 (45.9%)	34 (40%)	38 (44.78%)	13 (15.3%)	33 (38.8%)	41 (48.2%)	11 (12.9%)
	p-value	0.952				0.527			0.297		
Smoking	Smoker	55	10 (18.2%)	22 (40%)	23 (41.8%)	18 (32.7%)	31 (56.4%)	6 (10.9%)	23 (41.8%)	23 (41.8%)	9 (16.4%)
	Non-smoker	45	6 (13.3%)	16 (35.6%)	23 (51.1%)	24 (53.3%)	13 (28.9%)	8 (17.8%)	18 (40%)	22 (48.9%)	5 (11.1%)
	p-value	0.620				0.023*			0.676		
Alcohol consumption	Alcoholic	32	4 (12.5%)	16 (50%)	12 (37.5%)	14 (33.3%)	13 (29.5%)	5 (35.7%)	12 (37.5%)	17 (53.1%)	3 (9.4%)
	Non-alcoholic	68	12 (17.6%)	22 (32.4%)	34 (50%)	28 (66.7%)	31 (70.5%)	9 (64.3%)	29 (42.6%)	28 (41.2%)	11 (16.2%)
	p-value	0.237				0.885			0.461		

SNPs: single nucleotide polymorphisms; * statistically significant

Table 5. Correlation between genotype frequencies of *VDR* gene polymorphisms and clinicopathological characteristics in PCa patient group

SNPs		*BsmI N* (%)			*ApaI N* (%)			*TaqI N* (%)		
		BB	Bb	bb	AA	Aa	aa	TT	Tt	tt
PSA (ng/mL)	< 4	5 (50%)	2 (20%)	3 (30%)	4 (40%)	5 (50%)	1 (10%)	2 (20%)	5 (50%)	3 (30%)
	4–10	3 (14.3%)	7 (33.3%)	11 (52.4%)	8 (38.1%)	9 (42.9%)	4 (19%)	9 (42.9%)	10 (47.6%)	2 (9.5%)
	> 10	8 (11.9%)	28 (41.8%)	31 (46.3%)	29 (43.3%)	29 (43.3%)	9 (13.4%)	29 (43.3%)	29 (43.3%)	9 (13.4%)
	p-value	0.045*			0.951			0.492		
Pathological Gleason score	< 7	1 (6.7%)	7 (46.7%)	7 (46.7%)	4 (26.7%)	8 (53.3%)	3 (20%)	6 (40%)	8 (53.3%)	1 (6.7%)
	7 (3 + 4)	2 (15.4%)	4 (30.8%)	7 (53.8%)	5 (38.5%)	8 (61.5%)	0 (0%)	8 (61.5%)	4 (30.8%)	1 (7.7%)
	7 (4 + 3)	2 (14.3%)	4 (28.6%)	8 (57.1%)	10 (71.4%)	1 (7.1%)	3 (21.4%)	6 (42.9%)	4 (28.6%)	4 (28.6%)
	> 7	7 (22.6%)	11 (35.5%)	13 (41.9%)	13 (41.9%)	15 (48.4%)	3 (9.7%)	11 (35.5%)	15 (48.4%)	5 (16.1%)
	p-value	0.808			0.049*			0.411		
Pathological T-stage	T1	4 (10.5%)	16 (42.1%)	18 (47.4%)	13 (34.2%)	20 (52.6%)	5 (13.2%)	10 (26.3%)	24 (63.2%)	4 (10.5%)
	T2	6 (16.2%)	11 (29.7%)	20 (54.1%)	17 (45.9%)	13 (35.1%)	7 (18.9%)	20 (54.1%)	12 (32.4%)	5 (13.5%)
	T3	1 (12.5%)	3 (37.5%)	4 (50%)	4 (50%)	3 (37.5%)	1 (12.5%)	4 (50%)	1 (12.5%)	3 (37.5%)
	T4	5 (38.5%)	4 (30.8%)	4 (30.8%)	7 (53.8%)	6 (46.2%)	0 (0%)	5 (38.5%)	6 (46.2%)	2 (15.4%)
	p-value	0.354			0.522			0.042*		

Table 5. Correlation between genotype frequencies of *VDR* gene polymorphisms and clinicopathological characteristics in PCa patient group (*continued*)

SNPs		*BsmI N* (%)			*ApaI N* (%)			*TaqI N* (%)		
		BB	Bb	bb	AA	Aa	aa	TT	Tt	tt
Medical background	Yes	9 (23.7%)	13 (34.2%)	16 (42.1%)	15 (39.5%)	18 (47.4%)	5 (13.2%)	15 (39.5%)	17 (44.7%)	6 (15.8%)
	No	7 (11.3%)	25 (40.3%)	30 (48.4%)	27 (43.5%)	26 (41.9%)	9 (14.5%)	26 (41.9%)	28 (45.2%)	8 (12.9%)
	p-value	0.260			0.868			0.916		
Surgical history	Yes	8 (30.8%)	8 (30.8%)	10 (38.5%)	10 (38.5%)	11 (42.3%)	5 (19.2%)	10 (38.5%)	8 (30.8%)	8 (30.8%)
	No	8 (10.8%)	30 (40.5%)	36 (48.6%)	32 (43.2%)	33 (44.6%)	9 (12.2%)	31 (41.9%)	37 (50%)	6 (8.1%)
	p-value	0.058			0.666			0.013*		

SNPs: single nucleotide polymorphisms; PSA: prostate-specific antigen; * statistically significant

Discussion

Vitamin D deficiency is common in the general population worldwide. The metabolically active form $1,25(OH)_2D_3$ of vitamin D exerts its actions through interaction with the VDR. Severe vitamin D deficiency with a 25(OH)D concentration below < 30 nmol/L (or 12 ng/mL) dramatically increases the risk of excess mortality [37]. Moreover, a low vitamin D status is associated with an increased risk of various cancers, including PCa [37]. It was the anticancer effects of vitamin D that drew attention to investigate the *VDR* gene polymorphism. Studies on the relationship between *VDR* mutations and PCa conducted in several populations have yielded conflicting results, ranging from statistically significant associations to no correlation [32, 38–40]. Many other studies have linked common genetic variations in the *VDR* gene (*ApaI*, *BsmI*, *FokI*, and *TaqI*) to increased risk of PCa. *VDR* SNPs at the 3' end of the gene were associated with a 3- or 4-fold increased risk of PCa in two preliminary studies [40]. *ApaI*, *BsmI*, *FokI*, and *TaqI* polymorphisms could influence *VDR* expression by altering mRNA stability; they are located in the 3' UTR region of the *VDR* gene with strong linkage disequilibrium, which explains why they are sometimes studied together in haplotype analysis [41, 42].

Our research revealed significant associations between the *ApaI* and *TaqI* polymorphisms of the *VDR* gene and the risk of PCa ($p = 0.024$; OR = 5.33; 95% CI: 1.16–24.6), ($p = 0.031$; OR = 4.63; 95% CI: 1.09–19.7), on the other hand, the *BsmI* polymorphism does not show any significant association. This finding is compatible with a number of previous research conducted in a population of African men, which found that PCa risk was strongly correlated with the *TaqI* (rs731236) and *ApaI* (rs7975232) SNPs ($p < 0.05$) [43]. Also the *BsmI* SNP is associated with the PSA level ($p < 0.05$) which also agrees with our results ($p = 0.045$), which is consistent with a study showing that decreased vitamin D status correlates with PSA levels in men with PCa [44], and that there is no correlation between the two parameters in healthy men [45]. Similarly, a recent meta-analysis revealed that *TaqI* polymorphism of *VDR* in the Asian population may be related to PCa risk [46]. Nevertheless, a meta-analysis of 17 studies investigating *TaqI*, *BsmI*, *poly-A*, and *FokI* polymorphisms in exon 2 concluded that none of these variants was likely to be a significant predictor of cancer risk of the prostate [47]. These associations suggest that these two polymorphisms (*ApaI* and *TaqI* of the *VDR* gene) may play a role in the genetic predisposition to PCa. More specifically, the Aa genotype of the *ApaI* polymorphism and the Tt genotype of the *TaqI* polymorphism were more frequent in patients with PCa, with significant OR, suggesting an increased risk of cancer associated with these genotypes, located in exon 9, which encodes the ligand-binding domain of *VDR*. These observations are consistent with other studies that have also suggested links between *VDR* gene polymorphisms and PCa risk [48]. However, other work has revealed no correlation between these SNPs and cancer risk of prostate [49, 50].

Our results found associations between *BsmI* and *TaqI* polymorphisms with clinical features of PCa, such as PSA level, Gleason score, and pathological T stage. These associations suggest that *VDR* gene polymorphisms may have an influence on the progression and clinical presentation of PCa. The strong association between *TaqI* polymorphism and patients' surgical history is also notable ($p = 0.013$), this could indicate that this polymorphism is linked to a clinical course that requires surgical intervention. Additionally, *ApaI* polymorphism was significantly associated with tumor Gleason score ($p = 0.049$), which is an indicator of PCa severity. The significant association ($p = 0.023$) between the *ApaI* polymorphism and smokers within the PCa group raises interesting questions about the interaction between genetic and environmental factors in the development of PCa. This highlights the importance of considering behavioral risk factors in conjunction with genetic variations.

Nevertheless, this investigation is subject to numerous limitations. The small sample size is one of the main limitations, which could have impacted the statistical power of our findings. Furthermore, the study's focus on genetic profiling of *VDR* polymorphisms, while informative, did not delve deeply into the underlying biological mechanisms. Additional mechanistic research is required to explore how these polymorphisms affect VDR expression and its downstream effects in PCa cells.

Conclusions

Our investigation revealed a significant association between the *TaqI* (rs731236) and *ApaI* (rs7975232) polymorphisms of the *VDR* gene and the risk of PCa in Moroccan men. The AA genotype of *ApaI* (42%) and the Tt genotype of *TaqI* (45%) were more prevalent in PCa patients, suggesting that these variants may contribute to genetic susceptibility to the disease. Additionally, the *BsmI* polymorphism was significantly associated with PSA levels ($p = 0.045$), *ApaI* was linked to smoking status in PCa patients ($p = 0.023$), and *TaqI* was associated with tumor stage ($p = 0.042$) and surgical history ($p = 0.013$). These findings suggest that *VDR* polymorphisms may not only influence PCa risk but also impact disease progression and clinical presentation.

While our study provides new insights into the genetic predisposition of Moroccan men to PCa, further large-scale studies are needed to confirm these associations and explore the functional mechanisms underlying *VDR* gene variations in PCa development. Understanding these genetic markers may contribute to better risk assessment, early diagnosis, and potential therapeutic targets in PCa management.

Abbreviations

$1,25(OH)_2D_3$: 1,25-dihydroxyvitamin D_3

CI: confidence intervals

OR: odds ratios

PCa: prostate cancer

PSA: prostate-specific antigen

SNPs: single nucleotide polymorphisms

UTR: untranslated region

VDR: vitamin D receptor

Declarations

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Author contributions

KN: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft. AL: Resources, Writing—review & editing. IT: Data curation, Investigation. KAT: Investigation, Methodology. MM and AA: Resources. KE: Data curation, Resources. MB: Supervision, Writing—review & editing. MME: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study protocol was approved by the Ethics Committee for Biomedical Research of the Faculty of Medicine and Pharmacy of Casablanca, Morocco (No. 3/2018/April 30, 2018).

Consent to participate

The informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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