World Cancer Research Journal
WCRJ 2025; 12: e2950
DOI: 10.32113/wcrj_202511_2950

ASSOCIATION BETWEEN VITAMIN D RECEPTOR GENE POLYMORPHISMS AND PROSTATE CANCER RISK: A META-ANALYSIS

I. BOUSSAKRI[1], A. EL MAATAOUI[1,2]

[1]Biochemistry Department, Ibn Zohr University, Faculty of Medicine and Pharmacy, Agadir, Morocco
[2]Clinical Chemistry Department, Souss Massa Teaching Hospital, Agadir, Morocco

Corresponding Author
Aissam El Maataoui, MD; e-mail: a.elmaataoui@uiz.ac.ma

ABSTRACT – *Objective:* Studies on the relationship between vitamin D receptor (VDR) polymorphisms and Prostate Cancer (PCa) have shown conflicting results. Therefore, we conducted a meta-analysis of case-control studies to investigate a possible association between VDR (single-nucleotide polymorphisms) SNPs and PCa risk.

Materials and Methods: Our aim was to evaluate separately how the 6 known VDR gene SNPs TaqI (T>C), FokI (C>T), BsmI (G>A), Cdx2 (G>A), ApaI (G>T) and Poly-A (L/S) affect PCa in the general population and in ethnic subgroups of prostate cancer patients. Databases including Medline, Scopus, and Web of Science were searched. Studies meeting the inclusion criteria were reviewed in an updated meta-analysis using Revman 5.4.1 and Stata 16.0 software. The methodological quality of each study was assessed using the Newcastle-Ottawa scale. Fixed or random effect models were used to summarize odds ratios (ORs) with 95% CIs according to heterogeneity. Sensitivity analyses and meta-regression analyses were performed to identify potential sources of heterogeneity.

Results: A total of 65 studies fulfilled the inclusion criteria. The overall results indicated a positive association between Poly-A polymorphism and PCa risk, especially in the Caucasian population. However, in subgroup analysis by ethnicity, TaqI polymorphism was associated with increased risk of PCa in the Caucasian and Arab subgroups under the contrasting allelic and dominant genetic models. For ApaI polymorphism, our results show a significant positive association with PCa risk in Caucasian and Asian men under additive and recessive genetic models, respectively. Notably, the recessive, dominant and contrasting allelic models of the FokI polymorphism show a higher risk of developing PCa in Caucasian and mixed men, respectively. Conversely, the Cdx2 and BsmI polymorphisms showed no apparent association with PCa risk either in the overall results or in the subgroup analysis by ethnicity.

Conclusions: The results suggest that the VDR gene TaqI (T>C), FokI (C>T), ApaI (G>T), and Poly-A (L/S) SNPs are associated with PCa risk. Further large and well-designed studies are needed to confirm this conclusion.

KEYWORDS: Vitamin D receptor, Polymorphisms, Prostate cancer, Ethnicity.

INTRODUCTION

The human vitamin D receptor (VDR) gene is located on chromosome 12[1], which contains 618 reported variants, most of which are either undetectable or occur at a low frequency in the general population[2,3]. The role of the most common VDR single-nucleotide polymorphisms (SNPs) influencing the VDR expression in prostate cancer has not been established[4,5].

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License

This gene has at least five promoter regions, six untranslated exons, and eight protein-coding exons, which are alternatively spliced into BsmI, FokI, ApaI, and TaqI[6]. BsmI and ApaI are situated on the ninth intron of the 3' terminal; TaqI is located on the ninth exon of the 3' terminal and FokI is established on the promoter of the 5' terminal.

Scholars have reported that BsmI and TaqI SNPs are not involved in altering the protein structure of the VDR gene. They have been suggested to play a role in the translation proficiency and stability of the corresponding mRNA, which may be responsible for the reduction in VDR level[7]. Cdx2 SNP has been recorded to diminish the transcriptional activity of the VDR promoter by 30%[8]. Also, variations in the length of Poly-A may potentially influence the expression of the VDR gene through post-transcriptional regulation[9].

The most frequently studied polymorphisms (TaqI (rs731236), FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232), Cdx2 (rs11568820), and Poly-A (rs17878969) are found to be associated with several cancers[10]. Nevertheless, this relationship between these SNPs and PCa risk has yielded contradictory findings.

Studies have found positive associations; in Lebanon, a study reported that the f allele of the VDR FokI polymorphism was associated with an increased risk of PCa[11]. Kambale et al[12] demonstrated that their analysis showed significantly decreased incidence of Tt and Aa genotype of TaqI, ApaI polymorphisms in PCa patients as compared to healthy non-relative controls. Nonetheless, Akgül et al[13] reported that the BsmI Bb genotype, ApaI Aa genotype, and TaqI Tt genotypes were more frequently observed in Turkish patients with metastatic PC. El-Attar et al[14] suggested that the VDR ApaI SNP may be a diagnostic and prognostic marker for prostate cancer in Egyptian men. In Japan, PCa patients with the TT genotype were more likely to progress to the advanced stage, which suggests that VDR TaqI polymorphism may be a potential diagnostic biomarker for PCa susceptibility[15].

On the other hand, other studies have found no associations. Braczkowski et al[16] and Martínez-Nava[17] did not find any associations between PCa and VDR gene polymorphisms FokI, BsmI, and TaqI. Studies conducted by Cheteri et al[18] and Deschasaux et al[19] found no associations between VDR gene polymorphisms Cdx2 and Poly-A SNPs and PCa risk. These discrepancies can be attributed in part to statistical weakness, heterogeneity, publication bias, and ethnicity. As a result, we conducted this meta-analysis of all relevant case-control studies to evaluate the effect of VDR FokI, BsmI, ApaI, TaqI, Cdx2, and Poly-A polymorphisms in prostate cancer risk.

MATERIALS AND METHODS

Literature search

This study was conducted in accordance with the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[20]. We identified publications from January 1998 to August 2023 using the three largest medical databases, Medline, Scopus, and Web of Science. We used the following keywords to search the databases: "vitamin D receptor", "polymorphism", and "prostate cancer".

The inclusion criteria of the studies were as follows: case-control study evaluating the association between VDR gene SNPs and PCa, articles investigating at least one of the 6 polymorphic SNPs of VDR, articles published between 1998 and 2023, studies had to be independent and not duplicate results published in another article. The exclusion criteria were as follows: studies with insufficient data, case reports, reviews, and editorial studies (Figure 1).

Data Extraction and Quality Assessment

Data extracted from the articles included the first author's name (reference), year of publication, number of cases and controls, Hardy-Weinberg equilibrium, source of controls, genotyping methods, polymorphic sites, and ethnicity as subgroups of the studies.

To reduce the risk of selection bias due to individual studies, data extraction from all included articles was performed by the first author in a predefined database and then revised by the second co-author. In addition, the Newcastle-Ottawa Scale (NOS) score was used as a tool to assess the methodological quality of each study to independently assess the risk of bias by the two previous investigators[21].

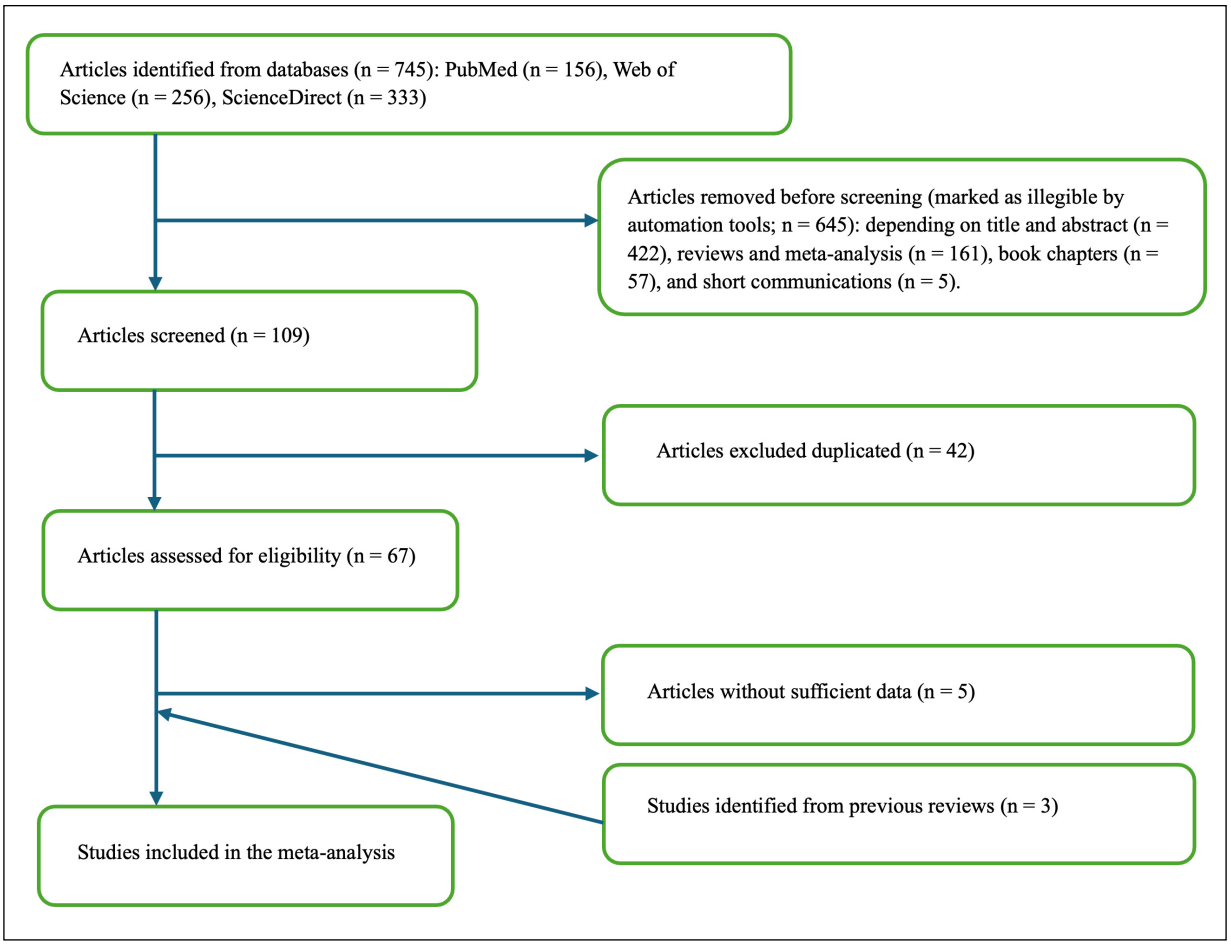

Figure 1. Process of article selection.

The primary search yielded 745 studies. Of these, 645 studies were excluded for various reasons (as shown in Figure 1). Of the remaining 109 studies, 42 were duplicates. Finally, 65 studies were included for quantitative analysis, but five studies that had insufficient information to estimate the ORs for the association between polymorphisms (SNPs) and prostate cancer (PCa) *via* genotyping frequencies were excluded; three additional studies were identified from previous reviews.

Statistical Analysis

For each VDR polymorphism, we estimated the association with PCa risk under specific genotypic models, namely, allelic, additive, recessive, and dominant. Pooled ORs were used to estimate the strength of the associations. Cochran's Q statistic was used to measure the degree of heterogeneity using the I-squared (I^2) test (a p-value < 0.10 was considered significant). In the presence of heterogeneity (Q statistic p<0.10 and I^2>50%), the random effect model (R) was used; otherwise, the fixed effect model (F) was used. In addition, the risk of publication bias was assessed using Begg's and Egger's tests. Furthermore, the influence of individual studies on the pooled OR was assessed by a sensitivity analysis by sequentially excluding each study in turn (leave one study out). However, to assess sources of heterogeneity among the included studies, a meta-regression analysis was performed based on year of population, genotyping methods, source of controls, and ethnicity. Statistical analyses were performed using REVMAN® UK v.5.4.1 and STATA® v.16.0 USA, Software.

RESULTS

A total of 754 potentially relevant citations were reviewed, and only 65 studies with 19,937 PCa cases and 22,469 controls met the inclusion criteria (Table 1).

Table 1. Characteristics of the studies included in the meta-analysis on the association between VDR gene polymorphisms and prostate cancer risk.

Author and reference	Country	Ethnicity	Source of controls	SNPs	Genotype method	Cases n.	Controls n.	HWE	NOS
Taylor et al[43]	UK	Caucasians/ African-American	BPH	TaqI	PCR-RFLP	96	162	YES	6
Ma et al [44]	USA	Caucasian	Population	TaqI	PCR-RFLP	372	589	YES	7
Kibel et al[45]	USA	Caucasians/ African-Americans	Hospital	TaqI, Poly-A	PCR-RFLP	41	41	YES	6
Furuya et al[4]	Japan	Asians	Hospital	TaqI	PCR-RFLP	66	60	YES	6
Watanabe et al[69]	Japan	Asian	BPH and non-BPH	TaqI, Poly-A	PCR-RFLP	100	202	NO	6
Correa-Cerro et al[47]	France	Caucasian	Population	FokI, TaqI, Poly-A	Nested PCR	132	105	YES	7
Blazer et al[49]	USA	Caucasians/ African-American	Population	TaqI, Poly-A	PCR-Polyacrylamide	77	183	YES	7
Habuchi et al[48]	Japan	Asian	Hospital	ApaI, BsmI	PCR-RFLP	222	128	YES	8
Chokkalingam[72]	China	Asian	Population	FokI, BsmI	PCR-RFLP	191	304	YES	6
Hamasaki et al[50]	Japan	Asians	Hospital	TaqI	PCR-RFLP	115	133	YES	5
Hamasaki et al[51]	Japan	Asians	Hospital	TaqI	PCR-RFLP	110	90	YES	6
Gsur et al[52]	Austria	Caucasian	BPH	TaqI	PCR-RFLP	190	190	YES	6
Medeiros et al[53]	Portugal	Caucasian	Hospital	TaqI	PCR-RFLP	162	206	YES	6
Tayeb et al[54]	UK	Caucasians	BPH	TaqI	PCR-RFLP	21	379	YES	6
Ahn et al[22]	USA	Caucasian	Population	BsmI	TaqMan	749	781	NO	7
Szendroi et al[88]	Hungary	Caucasian	Hospital	BsmI	PCR-RFLP	204	102	NO	6
Ingles 1998[91]	USA	African-American	Population	BsmI, Poly-A	PCR-Polyacrylamide	151	174	YES	7
Nam et al[89]	Canada	African-American/Asian/ Caucasian	Hospital	BsmI	PCR-RFLP	483	804	YES	6
Suzuki et al[81]	Japan	Asian	Hospital	ApaI, BsmI, TaqI	PCR-RFLP	81	105	YES: BsmI, TaqI NO: ApaI	6
Tayeb et al[55]	UK	Caucasians	BPH	TaqI, FokI	PCR-RFLP	28	56	YES	6
Maistro et al[55]	Brasil	Mixed	Hospital	ApaI, TaqI	PCR-RFLP	165	200	YES	6
Yang et al[74]	China	Asian	Hospital	FokI	PCR-RFLP	80	96	YES	6
Cheteri et al[71]	USA	Caucasian	BPH	FokI, BsmI, Poly-A	nested PCR	559	523	YES: Poly-A, FokI NO: BsmI	6
Huang et al[75]	Taiwan	Asian	Hospital	ApaI, BsmI, TaqI	PCR-RFLP	160	205	YES: TaqI NO: ApaI, BsmI	7

Continued

Table 1 *(continued)*. Characteristics of the studies included in the meta-analysis on the association between VDR gene polymorphisms and prostate cancer risk.

Author and reference	Country	Ethnicity	Source of controls	SNPs	Genotype method	Cases n.	Controls n.	HWE	NOS
Bodiwala et al[57]	UK	Caucasian	BPH	TaqI, FokI	PCR-RFLP	368	243	YES	6
Oakley-Girvan et al[41]	USA	African-American/Caucasian	Population	ApaI, FokI, BsmI, TaqI, Poly-A	PCR-Polyacrylamide	345	290	YES: ApaI, TaqI,BsmI NO: Poly-A/	6
Liu et al[58]	China	Asians	Hospital	BsmI, TaqI, ApaI	PCR-RFLP, DHPL	112	171	YES	7
Hayes[83]	Australia	Caucasian	Population	FokI, BsmI	DGGE	812	713	YES	7
Mishra[76]	India	Asian	Hospital	FokI	PCR-RFLP	128	147	YES	6
Forrest et al[73]	UK	Caucasian	Population	TaqI	Mini sequencing	288	700	YES	7
John et al[59]	USA	Caucasian	Population	FokI TaqI	TaqMan	450	455	YES	6
Moon et al[60]	USA	Caucasians	BPH	FokI, TaqI, Cdx2	Pyrosequencing + PCR-RFLP (Cdx2)	430	310	YES	7
Andersson et al 2006[61]	Sweden	Caucasian	Population	TaqI	PCR-RFLP	137	176	YES	7
Chaimuangraj et al[62]	Thailand	Asian	Hospital	ApaI, BsmI, TaqI	PCR-RFLP	95	30	YES	6
Holick et al[63]	USA	Caucasian	Population	FokI, BsmI, TaqI	SNPlex	586	545	YES	6
Cicek et al[35]	USA	Mixed	Population	ApaI, FokI, BsmI, Cdx2, TaqI, Poly-A	PCR-RFLP	439	479	YES: BsmI, ApaI, FokI, Cdx2, NO: FokI	7
Onen et al[37]	Turkey	Caucasian	Hospital	ApaI, BsmI, TaqI	PCR-RFLP	133	157	YES: TaqI, ApaI NO: BsmI	6
Onsory et al[90]	India	Asians	Population	TaqI	PCR-SSCP	100	100	YES	6
Holt et al[65]	USA	African-American	Population	FokI, BsmI, TaqI	SNPlex assay	827	787	YES	6
Bai et al[36]	China	Asian	Population	ApaI, FokI, BsmI, TaqI	PCR-RFLP	122,5	130,5	YES: ApaI, BsmI, Taq, NO: FokI	8
Rowland et al[39]	USA	African-American	Population	FokI, Cdx2, TaqI	TaqMan	414	223	YES: TaqI, FokI 41NO: Cdx2	7
Hu et al[66]	China	Asian	Hospital	TaqI	PCR	108	242	YES	7

Continued

Table 1 *(continued)*. Characteristics of the studies included in the meta-analysis on the association between VDR gene polymorphisms and prostate cancer risk.

Author and reference	Country	Ethnicity	Source of controls	SNPs	Genotype method	Cases n.	Controls n.	HWE	NOS
Yousaf et al[70]	Pakistan	Asians	Hospital	ApaI, TaqI	PCR-RFLP	47	134	NO	6
Jingwi et al[5]	USA	African-American	Hospital	ApaI, BsmI, TaqI	TaqMan	310	254	YES	7
Gilbert et al [38]	UK	Caucasian/African American	Hospital/BPH	ApaI, FokI, BsmI, Cdx2, TaqI	TaqMan	954	895	YES: Cdx2, FokI, BsmI, NO: ApaI/	7
Nunes et al[67]	Brasil	Mixed	Hospital	ApaI, FokI, TaqI, BsmI	PCR-RFLP	132	169	YES	6
Kambale et al[12]	India	Asian	Hospital	ApaI, FokI, TaqI	PCR-RFLP	120	120	YES	7
El Ezzi et al[11]	Lebanon	Asians	Hospital	ApaI, FokI, BsmI, TaqI	PCR-RFLP	69	69	YES	6
Braczkowski et al[16]	Poland	Caucasian	Hospital	FokI, bsmI, TaqI	TaqMan	72	72	YES	6
Martínez-Nava et al[79]	Mexico	Hispanic	Population	FokI, TaqI	PCR-RFLP	370	759	YES	7
Akgül et al[13]	Turkey	Caucasians	Population	ApaI, FokI, BsmI, TaqI	PCR-RFLP	72	72	YES	7
Dafalla et al[68]	Sudan	African-Arabs	Population	ApaI, FokI, BsmI, TaqI	PCR-RFLP	42	45	YES	7
Huang et al[93]	Taiwan	Asian	Hospital	FokI	PCR-RFLP	416	502	YES	6
Li et al[64]	USA	Caucasian	Population	FokI, BsmI	PCR-RFLP	1066	1618	YES	8
Atoum et al[77]	Jordan	Asians	Population	FokI	TaqMan	124	100	YES	6
Mikhak et al[42]	USA	Caucasian	Population	FokI, BsmI, Cdx2	PCR-SSCP	688	689	YES	7
Deschasaux et al[78]	France	Caucasian	Population	FokI, BsmI, Cdx2	TaqMan	129	167	YES	7
Amiri et al [80]	Pakistan	Asians	Population	FokI, BsmI	PCR-RFLP	111	150	YES	7
Rukin et al[85]	UK	Caucasian	BPH	FokI	Pyrosequencing	430	320	YES	6
Torkko et al[86]	USA	Caucasian/ African-American	Population	Cdx2, BsmI	TaqMan	1,081/444	1,075/425	YES	7
El Attar et al[14]	Egypte	African-Arabs	Population	ApaI	PCR-RFLP	50	50	YES	7
Veronique-Baudin et al[31]	France	Mixed	Population+ Hospital	Poly-A	PCR-RFLP	126	127	-	6
Ingles et al[91]	USA	Caucasian	Population	Poly-A	PCR-Polyacrylamide	57	169	YES	7

Abbreviations: NOS: Newcastle-Ottawa Scale score; HWE: Hardy–Weinberg equilibrium; BPH: Benign Prostatic Hyperplasia; SNPlex assay: Single Nucleotide Polymorphism multiplex; DGGE: Denaturing Gradient Gel Electrophoresis; DHPLC: Denaturing High-Performance Liquid Chromatography; PCR stands for Polymerase Chain Reaction- RFLP stands for Restriction Fragment Length Polymorphism; (-): not reported.

VDR Polymorphisms and Prostate Cancer

TaqI polymorphism and prostate cancer risk

For the association between TaqI SNP and PCa risk, 42 studies with 9,693 cases and 12,438 controls were included in the analyses[22-67]. As heterogeneity was observed for the total studies according to Q and I^2 tests under all four genetic models (Table 2), the random effect model was used. The pooled results showed no significant association between the TaqI SNP and PCa risk under all four genetic models. For ethnicity subgroup analysis (Table 3), Arabic subgroup showed a positive association with PCa risk under three genetic models (recessive: p=0.02; OR=4.04 [1.21, 13.46]); dominant: (p<0.0001; OR=4.49 [2.26, 8.94]) and allele contrast model: (p<0.00001; OR=0.37 [0.26, 0.54]). The Asian subgroup also showed a statistically positive association between TT genotype and increased risk of PCa in the allele-contrast model (p=0.008; OR=1.23 [1.06, 1.44]) (Table 3). Among these 42 studies, there were one study that deviated from HWE[68,69], so we excluded the study and then obtained another result. In addition, after these exclusions, we found that they did not significantly reduce the heterogeneity between studies, and the result remained non-statistically significant in the development of PCa. However, other ethnic subgroups showed no significant correlation in all four genetic models (Table 2 and Supplementary Figure 1). Egger's and Begg's tests for publication bias showed no bias in the overall analysis under the recessive, additive, and allelic contrast models. For the dominant model, publication bias was found only by Egger's test (Table 2). To adjust for this bias, the trim-and-fill method was used, and statistically similar data were obtained after trimming. The detected asymmetry of the funnel plot was attributed to heterogeneity rather than publication bias (data not shown).

FokI Polymorphism and Prostate Cancer Risk

Among the 65 studies reviewed, 33 studies involved 12,156 cases and 12,439 controls associated with the FokI SNP[11-13,16,24,29,35,36,39,47,63,68-80.]. The pooled OR revealed a significant association between PCa risk and the FokI SNP in the additive model (p=0.04; OR=1.10 [1.00, 1.20]) (Table 2). However, the OR of this model was found to be sensitive to the removal of individual studies. Consequently, the exclusion of the two studies[35,36] in which controls were not in HWE, resulted in a change in the pooled OR for the additive model towards the null (p=0.12; OR=1.07 [0.98, 1.17]) (Table 2). Consequently, no association was observed between the FokI SNP and PCa risk (Table 2 and Supplementary Figure 2). Heterogeneity was evident across these 33 studies in all genetic models. Therefore, the DerSimonian and Laird method for a random-effect model was employed in the subgroup analysis. Furthermore, a significant relationship between the FokI SNP and PCa risk was identified in the Caucasian population under the recessive model (p = 0.01; OR = 0.92 [0.87, 0.98]). Furthermore, an association was observed using the dominant model (p=0.04; OR=2.31 [0.52, 0.98]) and allele-contrast model (p=0.009; OR=1.45 [1.10, 1.92]) in the mixed population. Among the 33 studies, two deviated from HWE[35,36], so they were excluded, and then a contrast result was obtained in the dominant model when examining the mixed population. However, this result was not obtained in other genetic models. Publication bias was assessed by Egger's and Begg's tests. The results of the aforementioned models indicated that there was no evidence of publication bias for FokI SNPs (Table 2).

BsmI Polymorphism and Prostate Cancer Risk

A total of 19 studies were included in this analysis, with 11,141 cases and 12,233 controls[5,11,13,29,35,36,51,52,53,63,74,81-88] .The Q test of heterogeneity was almost always significant, prompting the decision to conduct analyses using a random-effects model. No significant relationship was observed between the BsmI SNP and PCa risk under all four genetic models. This was true for the dominant model (p=0.90; OR=1.01 [0.90, 1.13]), the recessive model (p=0.20; OR=1.08 [0,96, 1.21]), the additive model (p=0.20; OR=0.94 [0.86, 1.03]), and the allele-contrast model (p=0.69; OR=1.02 [0,93, 1.11]) (Table 2). Furthermore, the findings of stratified analyses by ethnicity indicated a significant association in an Arabian population under recessive (p=0.003; OR=4.44 [1.69, 11.68]), allele-contrast model (p=0.02; OR=0.33 [0.13, 0.86]), and additive models (p=0.02; OR=0.33 [0.13, 0.86]) (Table 2 and Supplementary Figure 3). Moreover, it appears that there is no correlation between prostate cancer risk and the BsmI genotypes in other ethnic groups (Table 3). Among the 19 studies, six deviated from the Hardy-Weinberg equilibrium (HWE)[26,27,28,31,30]. These studies were excluded, and a new result was obtained. To assess publication bias, Egger's and Begg's tests were employed for different analysis models. The results in Table 2 indicated that there was no bias.

Table 2. Overall significant summary odds ratios for the association of VDR polymorphisms with the tests of publication bias.

Genetic model	Test of association			Test of heterogeneity		Public bias		Effect model
	OR (95%CI)	Z-score	*p*	I^2 (%)	P*h*-value	Begg's test (pB)	Egger's test (pE)	
TaqI polymorphism								
Recessive	0.89 [0.68, 1.15]	0.91	0.36	89%	0.000	1.9200	0.7064	R
Dominant	0.91 [0.77, 1.06]	1.20	0.23	81%	0.000	0.3239	**0.0139**	R
Additive	1.00 [0.87, 1.13]	0.06	0.95	76%	0.000	0.6124	0.3635	R
Allelic	1.08 [0.92, 1.26]	0.97	0.33	91%	0.000	0.1524	0.1983	R
ApaI polymorphism								
Recessive	1.04 [0.88, 1.22]	0.41	0.68	51%	0.0004	0.2171	0.3774	R
Dominant	0.97 [0.87, 1.07]	0.65	0.52	42%	0.03	0.2423	0.8510	F
Additive	0.94 [0.78, 1.14]	0.60	0.55	72%	0.000	1.0000	0.4549	R
Allelic	1.02 [0.95, 1.09]	0.50	0.62	19%	0.22	0.9482	0.7969	F
Cdx2 polymorphism								
Recessive	1.11 [0.96, 1.29]	1.38	0.17	0%	0.51	1.5723	0.4200	F
Dominant	0.97 [0.90, 1.04]	0.90	0.37	29%	0.15	0.5830	0.7257	F
Additive	0.97 [0.89, 1.04]	0.89	0.37	26%	0.19	0.8548	0.9040	F
Allelic	1.01 [0.95, 1.08]	0.45	0.65	28%	0.16	0.6693	0.7302	F
BsmI polymorphism								
Recessive	1.08 [0,96, 1.21]	1.28	0.20	51%	0.0004	0.6292	0.4929	R
Dominant	1.01 [0.90, 1.13]	0.13	0.90	66%	0.000	0.1914	0.2390	R
Additive	0.94 [0.86, 1.03]	1.30	0.20	51%	0.0002	1.4106	0.3334	R
Allelic	1.02 [0,93, 1.11]	0.40	0.69	71%	0.000	0.9095	0.4748	R
FokI polymorphism								
Recessive	0.97 [0.85, 1.10]	0.46	0.64	78%	0.000	0.2943	0.6238	R
Dominant	1.07 [0.90, 1.27]	0.81	0.42	79%	0.000	0.0620	0.6007	R
Additive	1.10 [1.00, 1.20] #1.07 [0.98, 1.17]	2.03 #1.56	**0.04** #0.12	62% 57%	0.000	0.2360	0.4150	R
Allelic	1.00 [0.90, 1.12]	0.06	0.96	87%	0.000	1.7301	0.6346	R
Poly-A polymorphism								
Recessive	1.18 [0.96, 1.45] #1.27 [1.02, 1.58]	1.58 #2.18	0.11 **#0.03**	43% #33%	0.05 #0.13	0.5830	0.3858	F
Dominant	1.16 [1.00, 1.34] #1.22 [1.04, 1.43]	1.98 #2.42	**0.05** #0.02	0% #0%	0.59 #0.73	1.7003	0.9001	F
Additive	0.92 [0.81, 1.05]	1.27	**0.20**	12%	0.32	0.6693	0.5462	F
Allelic	0.98 [0.80, 1.20] #0.90 [0.81, 1.00]	0.19 #2.04	0.85 **#0.04**	69% #8%	0.000 #0.37	0.2997	0.2652	R

 # Sensitivity analysis; Abbreviations: OR: Odds ratio; CI: Confidence intervals; F: Fixed-effect model; F: Random-effect model

ApaI Polymorphism and Prostate Cancer Risk

The heterogeneity test indicated a significant degree of heterogeneity in the additive and recessive models of the total 19 studies evaluated for the ApaI polymorphic site, with 3,652 cases and 3,989 controls[5,11-14,35,36,39,40,42,48,55,57,61,63,67,68]. Consequently, the random-effect model was employed. As demonstrated in Table 2, there was no significant correlation between the VDR ApaI SNP and PCa risk in the pooled analysis of eligible studies, regardless of the genetic model employed. In the stratified analyses by ethnicity, the results indicated a positive and significant association between the FokI SNP and PCa risk in Asians across the recessive model, as well as in Caucasians under the additive model (p=0.02; OR=1.50 [1.08, 2.08]) and (p=0.02; OR=1.19 [1.02, 1.39]) respectively (Table 3 and Supplementary Figure 4). Among the 19 studies associated with the ApaI SNP, four studies deviated from the Hardy-Weinberg equilibrium (HWE)[38,39,40,70]. We excluded these studies and obtained a new result that was identical to the prior one for the association of the ApaI SNP with PCa in the overall population, except in the dominant model, which remained associated with PCa risk (p=0.01; OR=0.84 [0.74, 0.97]). No evidence of publication bias was observed for the ApaI SNP in any genetic model (Table 2).

Cdx2 Polymorphism and Prostate Cancer Risk

A total of 8 eligible studies were included in the analysis, with 6,166 cases and 5,692 controls[35,39,41,59,61,85-87]. The results of the overall and subgroup analyses by ethnicity revealed no significant heterogeneity according to the Q test and I^2 in terms of the VDR Cdx2 SNP and PCa risk. Consequently, the Mantel-Haenszel method for the fixed-effect model was employed for all data analyzed in this study. Additionally, the summary risk estimate demonstrated that this SNP was not associated with PCa risk in any of the genetic models, including the recessive, dominant, additive, or allele-contrast models, in the pooled results (p=0). The OR for the recessive model was 1.11 (95% CI: 0.96, 1.29), with a p-value of 0.37. The OR for the dominant model was 0.97 (95% CI: 0.90, 1.04), with a p-value of 0.37. The OR for the additive model was 0.97 (95% CI: 0.89, 1.04), with a p-value of 0.65. The OR for the allele contrast model was 1.01 (95% CI: 0.95, 1.08), with a p-value of 0.65. These results are presented in Table 2 and Supplementary Figure 5. Furthermore, the results of the subgroup analysis by ethnicity indicate that no correlation exists under any genetic model (Table 3). In contrast, one study deviated from the Hardy-Weinberg equilibrium (HWE)[39]. An alternative approach was taken, whereby the data set was excluded, resulting in a new result that was consistent with the overall study results. The Egger's and Begg's tests, which were employed to provide statistical evidence of publication bias, indicated that no evidence of publication bias existed in the overall analysis (Table 2).

Meta-analysis: Poly-A Polymorphism and Prostate Cancer Risk

Among the 11 studies with 1,953 cases and 2,280 controls examining the Poly-A microsatellite SNP[35,40,48,61,68,70,72,75,77,81,87,88,91,92], there was evidence of statistical heterogeneity under the allele-contrast model only (Table 2). Consequently, the DerSimonian and Laird method for a random-effect model was employed in the subgroup analysis for this model. Moreover, no specific association was identified between the Poly-A SNP and PCa risk under any of the four genetic models: recessive (p = 0.11; OR = 1.18 [0.96, 1.42]), dominant (p = 0.05; OR = 1.16 [1.00, 1.34]), additive (p = 0.20; OR = 0.92 [0.81, 1.05]), and allele-contrast model (p = 0.85; OR = 0.98 [0.80, 1.20]) (Table 2). The results of the subgroup analysis indicated that there was no significant association between the Poly-A SNP and PCa risk under any of the four genetic models: recessive (p = 0.11; OR = 1.18 [0.96, 1.45]), dominant (p = 0.05; OR = 1.16 [1.00, 1.34]), additive (p = 0.20; OR = 0.92 [0.81, 1.05]), and allele-contrast model (p = 0.85; OR = 0.98 [0.80, 1.20]) (Table 2). However, the results were found to be sensitive to the removal of individual studies in the three genetic models, with the exception of the additive model. This demonstrated that the pooled ORs of these three models were significantly influenced by the exclusion of each eligible study (Supplementary Figure 6). Upon the removal of the studies of[19,22,87] from the recessive, dominant, and allele-contrast models, the pooled ORs remained statistically significant, with p-values of 0.03, 0.02, and 0.04, respectively, and ORs of 1.27 (1.02, 1.58), 1.22 (1.04, 1.43), and 0.90 (0.81, 1.00). The aforementioned results were obtained from Table 2. However, given that the controls in two studies[89,90] were not in Hardy-Weinberg equilibrium (HWE), the results should be interpreted with caution.

Table 3. Subgroup analyses based on ethnicity under the four genetic models.

Genetic model	Test of association			Test of heterogeneity	
Ethnicity	**OR (95%CI)**	**Z-score**	***p***	**I^2 (%)**	**P*h*-value**
			TaqI polymorphism		
			Recessive		
African-Americans	0.94 [0.70, 1.26]	0.42	0.68	4%	0.39
Caucasians	0.90 [0.69, 1.16]	0.83	0.42	86%	0.000
Asians	0.73 [0.93, 1.36]	0.99	0.32	40%	0.09
Arabians	4.04 [1.21, 13.46]	2.27	**0.02**	65%	0.09
Hispanic	0.97 [0.74, 1.28]	0.20	0.84	-	-
Mixed	0.53 [0.08, 3.60]	0.65	0.51	98%	-
			Dominant		
African-Americans	0.75 [0.50, 1.12]	1.40	0.16	44%	0.12
Caucasians	0.90 [0.76, 1.07]	1.24	0.21	76%	0.000
Asians	0.82 [0.66, 1.03]	1.73	0.08	36%	0.09
Arabians	4.49 [2.26, 8.94]	4.29	**0.0001**	0%	0.87
Hispanic	0.93 [0.51, 1.70]	0.24	0.81	-	-
Mixed	0.89 [0.21, 3.80]	0.16	0.88	97%	-
			Additive		
African-Americans	0.83 [0.67, 1.04]	1.58	0.11	0%	0.75
Caucasians	0.99 [0.88, 1.12]	0.12	0.91	58%	0.0004
Asians	0.93 [0.68, 1.27]	0.44	0.66	66%	0.0003
Arabians	1.16 [0.53, 2.51]	0.37	0.71	52%	0.15
Hispanic	1.01 [0.76, 1.36]	0.09	0.93	-	-
Mixed	1.70 [0.80, 3.63]	1.38	1.17	93%	0.000
			Allelic		
African-Americans	1.13 [0.83, 1.55]	0.78	0.43	59%	0.03
Caucasians	1.08 [0.93, 1.26]	1.00	0.32	87%	0.000
Asians	1.23 [1.06, 1.44]	2.67	**0.008**	7%	0.38
Arabians	0.37 [0.26, 0.54]	5.19	**0.0001**	0%	0.82
Hispanic	1.03 [0.82, 1.31]	0.26	0.79	-	-
Mixed	1.45 [0.34, 6.11]	0.50	0.62	99%	0.000

Continued

Table 3 *(continued).* Subgroup analyses based on ethnicity under the four genetic models.

Genetic model	Test of association			Test of heterogeneity	
Ethnicity	**OR (95%CI)**	**Z-score**	***p***	**I^2 (%)**	**P*h*-value**
			ApaI polymorphism		
			Recessive		
African-Americans	0.82 [0.65, 1.04]	1.65	0.10	0%	0.80
Caucasians	0.82 [0.62, 1.08]	1.41	0.16	40%	0.17
Asians	1.50 [1.08, 2.08]	2.42	**0.02**	37%	0.14
Arabians	1.18 [0.32, 4.41]	0.25	0.80	80%	0.02
Mixed	0.98 [0.80, 1.21]	0.16	0.88	0%	0.61
			Dominant		
African-Americans	0.79 [0.56, 1.10]	1.38	0.17	64%	0.06
Caucasians	1.10 [0.92, 1.32]	1.02	0.31	31%	0.23
Asians	0.99 [0.83, 1.18]	0.14	0.89	40%	0.11
Arabians	0.57 [0.25, 132]	1.32	0.19	79%	0.03
Mixed	0.86 [0.67, 1.09]	1.24	0.21	0%	0.59
			Additive		
African-Americans	1.08 [0.86, 1.37]	0.67	0.51	0%	0.48
Caucasians	1.19 [1.02, 1.39]	2.26	**0.02**	0%	0.73
Asians	0.84 [0.55, 1.30]	0.76	0.44	78%	0.000
Arabians	0.65 [0.06, 7,23]	0.36	0.72	93%	0.000
Mixed	0.92 [0.75, 1.12]	0.85	0.40	0%	0.54
			Allelic		
African-Americans	1.18 [0.99, 1.40]	1.89	0.06	72%	0.28
Caucasians	1.02 [0.92, 1.14]	0.40	0.69	58%	0.07
Asians	0.89 [0.78, 1.01]	1.78	0.08	0%	0.62
Arabians	1.04 [0.68, 1.60]	0.20	0.84	0%	0.66
Mixed	1.06 [0.92, 1.22]	0.82	0.41	0%	0.57

Continued

Table 3 *(continued)*. Subgroup analyses based on ethnicity under the four genetic models.

Genetic model	Test of association			Test of heterogeneity	
Ethnicity	**OR (95%CI)**	**Z-score**	***p***	**I^2 (%)**	**P*h*-value**
			Cdx2 polymorphism		
Recessive					
African-Americans	1.22 [0.90, 1.67]	1.26	0.21	0%	0.54
Caucasians	1.14 [0.95, 1.37]	1.40	0.16	0%	0.48
Hispanic white	0.52 [0.19, 1.43]	1.26	0.21	-	-
Mixed	0.91 [0.57, 1.44]	0.42	0.68	-	-
			Dominant		
African-Americans	1.67 [0.95, 2.94]	1.77	0.08	0%	0.84
Caucasians	0.97 [0.90, 1.05]	0.77	0.44	33%	0.15
Hispanic white	0.77 [0.50, 1.19]	1.17	0.24	-	-
Mixed	0.91 [0.70, 1.18]	0.73	0.47	-	-
			Additive		
African-Americans	0.95 [0.69, 1.31]	0.32	0.75	0%	0.57
Caucasians	0.97 [0.89, 1.06]	0.62	0.53	48%	0.05
Hispanic white	0.87 [0.56, 1.38]	0.58	0.58	-	-
Mixed	0.93 [0.71, 1.22]	0.51	0.61	-	-
			Allelic		
African-Americans	1.26 [0.98, 1.62]	1.80	0.07	0%	0.58
Caucasians	1.02 [0.52, 1.09]	0.55	0.58	22%	0.25
Hispanic white	0.75 [0.52, 1.09]	1.50	0.13	-	-
Mixed	0.92 [0.75, 1.14]	0.77	0.44	-	-

Continued

Table 3 *(continued).* Subgroup analyses based on ethnicity under the four genetic models.

Genetic model	Test of association			Test of heterogeneity	
Ethnicity	**OR (95%CI)**	**Z-score**	***p***	**I^2 (%)**	**P*h*-value**
			BsmI polymorphism		
Recessive					
African-Americans	1.00 [0.49, 2.04]	0.00	1.00	61%	0.04
Caucasians	1.04 [0.96, 1.14]	1.01	0.31	18%	0.24
Asians	1.19 [0.58, 2.43]	0.46	0.64	69%	0.002
Arabians	4.44 [1.69, 11.68]	0.02	**0.003**	0%	0.64
Mixed	0.90 [0.68, 1.19]	0.71	0.47	-	-
			Dominant		
African-Americans	1.25 [0.80, 1.98]	0.98	0.33	62%	0.03
Caucasians	1.02 [0.92, 1.13]	0.32	0.75	53%	0.004
Asians	0.83 [0.49, 1.42]	0.67	0.50	79%	0.000
Arabians	1.51 [0.62, 3.71]	0.91	0.36	-	-
Mixed	1.09 [0.56, 2.15]	0.26	0.80	-	-
			Additive		
African-Americans	1.20 [0.93, 1.54]	1.42	0.16	0%	0.69
Caucasians	0.98 [0.92, 1.04]	0.78	0.43	5%	0.39
Asians	0.66 [0.43, 1.02]	1.85	0.06	71%	0.000
Arabians	0.33 [0.13, 0.86]	2.26	0.02	-	-
Mixed	0.95 []0.76, 1.19]	0.43	0.66	0%	0.51
			Allelic		
African-Americans	1.12 [0.77, 1.62]	0.60	0.55	71%	0.008
Caucasians	1.03 [0.96, 1.10]	0.83	0.40	50%	0.000
Asians	0.90 [0.52, 1.54]	0.39	0.70	87%	0.000
Arabians	0.33 [0.13, 0.86]	2.26	**0.02**	-	-
Mixed	0.95 [0.75, 1.22]	0.38	0.71	42%	0.19

Continued

Table 3. Subgroup analyses based on ethnicity under the four genetic models.

Genetic model	Test of association			Test of heterogeneity	
Ethnicity	**OR (95%CI)**	**Z-score**	***p***	**I^2 (%)**	**P*h*-value**
			FokI polymorphism		
			Recessive		
African-Americans	1.15 [0.76, 1.73]	0.65	0.52	53%	0.12
Caucasians	0.92 [0.87, 0.98]	2.54	**0.01**	0%	0.70
Asians	1.04 [0.73, 1.47]	0.19	0.85	67%	0.003
Arabians	0.45 [0.07, 2.99]	0.83	0.41	92%	0.0005
Hispanic	2.47 [0.37, 16.49]	0.93	0.35	97%	0.000
Mixed	0.56 [0.29, 1.09]	1.69	0.09	83%	0.01
			Dominant		
African-Americans	1.11 [0.50, 2.47]	0.26	0.80	28%	0.25
Caucasians	0.97 [0.89, 1.05]	0.84	0.40	1%	0.44
Asians	1.19 [0.96, 1.47]	1.61	0.11	7%	0.38
Arabians	0.58 [0.23, 1.51]	1.11	0.27	0%	0.33
Hispanic	2.31 [0.40, 13.27]	0.94	0.35	98%	0.000
Mixed	2.31 [0.52, 0.98]	2.07	**0.04**	0%	0.88
			Additive		
African-Americans	0.89 [0.57, 1.38]	0.53	0.60	57%	0.10
Caucasians	1.06 [1.00, 1.12]	1.82	0.07	0%	0.07
Asians	1.10 [0.84, 1.44]	0.71	0.48	60%	0.02
Arabians	0.57 [0.24, 1.35]	1.28	0.20	61%	0.11
Hispanic	1.69 [0.85, 3.39]	1.49	0.14	88%	0.005
Mixed	1.42 [0.87, 2.31]	1.40	0.16	72%	0.06
			Allelic		
African-Americans	0.89 [0.65, 12.3]	0.69	0.49	47%	0.15
Caucasians	1.04 [0.99, 1.08]	1.68	0.06	0%	0.84
Asians	0.93 [0.76, 1.15]	0.67	0.50	65%	0.003
Arabians	1.84 [0.51, 6.69]	0.93	0.35	90%	0.001
Hispanic	0.49 [0.13, 1.89]	1.04	0.30	98%	0.000
Mixed	1.45 [1.10, 1.92]	2.62	**0.009**	55%	0.14

Continued

Table 3 *(continued).* Subgroup analyses based on ethnicity under the four genetic models.

Genetic model	Test of association			Test of heterogeneity	
Ethnicity	**OR (95%CI)**	**Z-score**	***p***	**I^2 (%)**	**P*h*-value**
			Poly-A polymorphism		
			Recessive		
African-Americans	0.79 [0.47, 1.32]	0.91	0.36	0%	0.91
Caucasians	1.66 [1.12, 2.45]	2.53	**0.01**	43%	0.14
Asians	1.50 [0.30, 7.57]	0.49	0.62	-	-
Mixed	1.27 [0.93, 1.72]	1.51	0.13	80%	0.02
			Dominant		
African-Americans	1.04 [0.68, 1.58]	0.18	0.86	25%	0.26
Caucasians	1.24 [1.01, 1.52]	2.05	**0.04**	0%	0.69
Asians	1.05 [0.58, 1.91]	0.16	0.87	-	-
Mixed	1.44 [0.96, 2.17]	1.74	0.08	0%	0.41
			Additive		
African-Americans	0.83 [0.60, 1.16]	1.10	0.27	0%	0.41
Caucasians	0.93 [0.78, 1.10]	0.86	0.39	43%	0.12
Asians	1.01 [0.54, 1.89]	0.04	0.97	-	-
Mixed	0.95 [0.75, 1.20]	0.44	0.66	31%	0.23
			Allelic		
African-Americans	1.01 [0.79, 1.29]	0.05	0.96	0%	0.56
Caucasians	0.89 [0.76, 1.05]	1.36	0.17	14%	0.32
Asians	**# 4.53 [2.46, 8.34]**	**Watanabe et al 1999 was excluded by sensitivity analysis**			
Mixed	0.80 [0.58, 1.11]	1.36	0.18	64%	0.10

 # Sensitivity analysis; Abbreviations: OR: Odds ratio; CI: Confidence intervals; (-): not estimated

Evaluation of the Heterogeneity and Publication Bias

The results of the publication bias test indicated that there was no evidence of publication bias for the overall population of FokI, BsmI, ApaI, BsmI, and Poly-A SNPs. However, a publication bias was identified in the recessive model of the TaqI SNP. Furthermore, heterogeneity was identified in both the overall and subgroup analyses, with the exception of the Cdx2 and Poly-A SNPs (Table 2).

In the sensitivity analysis, each eligible study was sequentially removed to assess the influence of individual data on the pooled ORs. In this meta-analysis, the pooled results were not significantly affected by any single study in the dominant, recessive, and allele-contrast models for TaqI, ApaI, Cdx2, and BsmI SNPs (Table 2), indicating that the combined results of our meta-analysis were statistically robust. Nevertheless, the Poly-A and FokI were found to be materially altered by the exclusion of studies in which controls were not in HWE, with positive associations between Poly-A and FokI SNPs and the risk of PCa. This indicates that the pooled results were more reliable and should be treated with caution. It is interesting to note that studies lacking in Hardy-Weinberg equilibrium may have resulted in erroneous outcomes.

Meta-Regression Analyses

The potential sources of heterogeneity among the included studies were estimated by meta-regression analyses (Table 4). The findings indicated that ethnicity (p=0.013; p=0.004) and source of controls (p=0.029; p=0.006) were the sources of heterogeneity for the association between VDR gene polymorphisms and the risk of PCa in the TaqI SNP under either the recessive or the allele-contrast models, respectively. Additionally, the meta-regression identified ethnicity as a source of heterogeneity for the relationship between the FokI SNP and PCa risk (p=0.025 and p=0.009) under the dominant and the additive genetic models, respectively. Moreover, none of the other anticipated sources of heterogeneity were identified as the source of heterogeneity in the other polymorphisms under any genetic models.

DISCUSSION

Prostate cancer (PCa) is a complex disease that can be diagnosed only by histological testing, which is usually conducted through a prostate biopsy[23]. It is, however, important to note that the biopsy test did not prove to be an optimal method for the early detection of PCa. Consequently, there is a need for the development of a new diagnostic method that can illustrate an individual's susceptibility to prostate cancer. The advent of new genetic technology may facilitate the identification of a genetic biomarker that could serve as an effective tool for early PCa detection, as evidenced by current studies[87].

Alternatively, numerous epidemiological studies have demonstrated a potential correlation between VDR gene polymorphisms (SNPs) and PCa risk, which represents one of the genetic biomarkers of interest[1-22,35,36,68,69,89]. Although the results of these studies have yielded inconclusive findings, the prevalence of these SNPs varies among different ethnic groups, which is an important biological factor for the decline of VDR function[24]. This decline appears to act as a modifier in the context of cancer risk[10]. Consequently, the development of a novel genetic biomarker, such as VDR gene SNPs, for the diagnosis of PCa remains a challenging topic[69].

In order to produce an evidence-based analysis, we conducted a comprehensive search of all epidemiological papers for findings on the association between VDR gene single-nucleotide polymorphisms (SNPs) and prostate cancer (PCa) risk. In comparison to prior studies, our meta-analysis included the six main variants of the VDR gene, as well as ethnicity subgroup analyses. Furthermore, for each polymorphic site, we employed the dominant, recessive, additive, and allele-contrast models, thereby ensuring that the present meta-analysis represents the most comprehensive and critical synthesis of available data investigating the associations between VDR Fok1 (rs2228570), Bsm1 (rs1544410), Taq1 (rs731236), Apa1 (rs7975232), Cdx2 (rs11568820), and Poly-A (rs17878969) SNPs. The outcomes of the study demonstrated that, with the exception of the Poly-A SNP, there was no association between the VDR gene TaqI, ApaI, BsmI, FokI, and Cdx2 SNPs and the risk of PCa in the overall population. It is also important to consider the issue of heterogeneity, which is a significant factor in interpreting the results of this meta-analysis. Significant heterogeneity is notably evident in the overall comparison for both TaqI and FokI SNPs. This heterogeneity can be explained by ethnicity and source of control in either contrast-allele and recessive models for the TaqI SNP and in dominant and additive models for the FokI SNP.

Table 4. Meta-regression analysis of potential source of heterogeneity.

Genetic model	Heterogeneity factor	Coefficient	SE	*t-test*	*p*	95% (CI)	
						UL	LL
TaqI polymorphism							
Recessive	Publication year	.0151053	.0108152	1.40	0.170	-.0067205	.0369312
	Genotyping method	.0044018	.0362176	0.12	0.904	-.0686883	.077492
	Source of controls	.1754534	.0773898	2.27	**0.029**	.0192745	.3316323
	Ethnicity	-.1884565	.0730589	-2.58	**0.013**	-.3358953	-.0410176
Dominant	Publication year	.0025637	.0086263	0.30	0.768	-.0148449	.0199723
	Genotyping method	.0115758	.028306	0.41	0.685	-.0455481	.0686997
	Source of controls	.1165155	.0598775	1.95	0.058	-.0043223	.2373532
	Ehnicity	-.1055769	.0641789	-1.65	0.107	-.2350951	.0239413
Allelic	Publication year	-.006506	.0056972	-1.14	0.260	-.0180035	.0049915
	Genotyping method	-.0087645	.0191904	-0.46	0.650	-.0474924	.0299634
	Source of controls	-.1157103	.0402416	-2.88	**0.006**	-.1969212	.0344995
	Ethnicity	.1234973	.0405069	3.05	**0.004**	.041751	.2052436
Additive	Publication year	-.0038553	.0076073	-0.51	0.615	-.0192075	.0114968
	Genotyping method	-.0088646	.0257751	-0.34	0.733	-.0608809	.0431517
	Source of controls	-.0690432	.0531351	-1.30	0.201	-.1762742	.0381878
	Ethnicity	.0857905	.0541	1.59	0.120	-.0233877	.1949687
ApaI polymorphism							
Recessive	Publication year	.0022576	.0130282	0.17	0.865	-.0255113	.0300265
	Genotyping method	-.036316	.1592869	-0.23	0.823	-.3758279	.303196
	Source of controls	.013051	.0893722	0.15	0.886	-.1774412	.2035433
	Ethnicity	.0661884	.0756568	0.87	0.395	-.0950704	.2274471
Additive	Publication year	-.0067772	.0117204	-0.58	0.572	-.0317585	.0182042
	Genotyping method	.0400211	.1275799	0.31	0.758	-.2319091	.3119512
	Source of controls	.0136507	.080499	0 .17	0.868	-.1579289	.1852302
	Ethnicity	-.0519068	.0682126	-0.76	0.458	-.1972985	.0934849
BsmI polymorphism							
Recessive	Publication year	-.0040235	.0092991	-0.43	0.668	-.0230147	.0149678
	Genotyping method	.0375299	.0442108	0.85	0.403	-.0527606	.1278204
	Source of controls	.0566873	.0577918	0.98	0.334	-.0613392	.1747139
	Ethnicity	.0475812	.1011637	0.47	0.642	-.1590227	.2541851

Continued

Table 3 *(continued)*. Meta-regression analysis of potential source of heterogeneity.

Genetic model	Heterogeneity factor	Coefficient	SE	*t-test*	*p*	95% (CI)	
						UL	LL
BsmI polymorphism							
Dominant	Publication year	.0052241	.0085018	0.61	0.544	-.0121389	.0225871
	Genotyping method	.0199535	.042521	0.47	0.642	-.0668859	.106793
	Source of controls	.0375374	.0566332	0.66	0.513	-.0781231	.1531979
	Ethnicity	-.0822772	.096887	-0.85	0.402	-.2801468	.1155924
Additive	Publication year	.0058642	.0069751	0.84	0.407	-.0083808	.0201092
	Genotyping method	-.0092582	.0354526	-0.26	0.796	-.0816621	.0631457
	Source of controls	.0029944	.0453802	0.07	0.948	-.0896844	.0956731
	Ethnicity	-.0997153	.0760268	-1.31	0.200	-.2549827	.0555522
Allelic	Publication year	.0021266	.0051476	0.41	0.682	-.0083861	.0126393
	Genotyping method	-.0143392	.0254619	-0.56	0.578	-.0663394	.0376609
	Source of controls	.0338492	.0332973	1.02	0.317	-.0341529	.1018513
	Ethnicity	-.0187531	.0573987	-0.33	0.746	-.135977	.0984707
FokI polymorphism							
Recessive	Publication year	-.0000132	.000024	-0.55	0.587	-.0000622	.0000358
	Genotyping method	.0015249	.0257771	0.06	0.953	-.0510478	.0540976
	Source of controls	.022801	.0552285	0.41	0.683	-.0898382	.1354402
	Ethnicity	.0150397	.0423161	0.36	0.725	-.0712646	.1013439
Dominant	Publication year	-.0000134	.0000353	-0.38	0.707	-.0000855	.0000586
	Genotyping method	-.001357	.0350043	-0.04	0.969	-.0727488	.0700348
	Source of controls	-.0216488	.0728049	-0.30	0.768	-.1701353	.1268378
	Ethnicity	.1319726	.0559541	2.36	**0.025**	.0178534	.2460919
Additive	Publication year	6.44e-06	.0000233	0.28	0.784	-.0000412	.000054
	Genotyping method	-.0012842	.0244922	-0.05	0.959	-.0512364	.048668
	Source of controls	-.0612885	.0517048	-1.19	0.245	-.1667411	.0441641
	Ethnicity	.1091636	.0393995	2.77	**0.009**	.0288078	.1895194
Allelic	Publication year	.1895194	.0000171	0.60	0.551	-.0000246	.0000452
	Genotyping method	.0002037	.0180026	0.01	0.991	-.036513	.0369203
	Source of controls	.0124693	.0378718	0.33	0.744	-.0647708	.0897093
	Ethnicity	-.0558727	.0288267	-1.94	0.062	-.1146651	.0029197
Poly-A polymorphism							
Allelic	Publication year	-.0212412	.0260367	-0.82	0.438	-.081282	.0387995
	Genotyping method	-.1000443	.1252159	-0.80	0.447	-.3887928	.1887041
	Source of controls	.0483762	.1482505	0.33	0.753	-.2934901	.3902426
	Ethnicity	-.0239312	.1515316	-0.16	0.878	-.3733638	.3255014

Abbreviations: SE: Standard Error; CI: Confidence intervals; LL: Lower Limit; UL: Upper Limit

Unfortunately, the heterogeneity of ApaI and BsmI has not yet been elucidated, indicating that other factors should be taken into consideration. In this context, a significant contributing factor to heterogeneity may be the inadequate homogeneity of cases and controls, which was a consequence of the diversity of the genotype distributions of the VDR BsmI and ApaI SNPs in the included studies. Ideally, all cases and controls should be matched with respect to sex, smoking status, or other relevant factors. Additionally, the limited sample size of some studies investigating these SNPs is a further limitation.

Previous studies have yielded similar results. For instance, the Gnagnarella et al[10] meta-analysis reported that the pooled results indicated that VDR Fok1, Bsm1, Taq1, Apa1, and Cdx2 SNPs are not associated with PCa risk in the overall population. In summary, the meta-analysis conducted by Guo et al[93] found no evidence to support an association between any of the BsmI and FokI SNPs and PCa risk. Similarly, Wang et al[94] indicate that the VDR Cdx2 and ApaI SNPs are not associated with PCa risk in the overall population . In contrast with our findings, the previous meta-analysis performed by Huang et al[40] suggested that the poly-A SNP is not associated with increased or decreased risk of PCa.

Conversely, the analysis of data for subgroups by ethnicity revealed the existence of positive associations in multiple ethnic groups. Upon analysis of the TaqI SNP, a statistically significant positive correlation was observed between TaqI genotypes and PCa risk. In the Asian subgroup, the TT genotype was found to significantly elevate the risk of PCa in the allele-contrast model. Similarly, the same results were observed in three meta-analyses published by Zhang et al[23] under both dominant and recessive models; by Liu et al[91] under the dominant model, and by Chen et al[15] under the TT genotype. In contrast, a negative correlation was observed in both Caucasian and African-American populations. Conversely, Liu et al[34] observed a positive correlation in the African-American group. Moreover, the Arab descendants exhibited a positive correlation in the dominant, recessive, and allele-contrast models. Despite the limited number of studies on this group, it is not possible to rule out a relationship between the TaqI SNP and PCa risk due to the high degree of homogeneity observed between studies (I^2 = 0%) in Arabs.

The data obtained for the ApaI SNP yielded conflicting results in the ethnic subgroups. In the Asian and Caucasian subgroups, respectively, the ApaI SNP demonstrated a positive association with PCa risk in both recessive and additive models, with no evidence of between-study heterogeneity. Gnagnarella et al[10] also reported a significant association between the Apa1 SNP and PCa risk, with a reduction in risk. In contrast, Wang et al[94] did not identify a significant relationship in any subgroup analysis based on ethnicity in the ApaI SNP.

Moreover, no heterogeneity was observed among studies investigating the VDR Cdx2 SNP in our meta-analysis. Moreover, the relationship between this SNP and PCa risk in prior studies was attributed to limited case and control sizes. Therefore, a larger sample size is necessary for subgroup analysis of various ethnic populations.

When BsmI was stratified by ethnicity, no such relationship was detected, with the exception of a modest association with the Arab group under the recessive, additive, and allele contrast models. As this result was presented by only one study, it should be interpreted with caution. Our findings are consistent with those of the previously published meta-analysis by Guo et al[93]. This phenomenon has been observed in Asian, Caucasian, and African populations, as well as in a study conducted by Liu et al[34] the same ethnic groups were observed under the three genetic models. In contrast, a significant reduction was observed in the Caucasian population, as reported by Raimondi et al[95] in which a comparison was made between the BsmI Bb genotype and the bb genotype. It is important to note that significant heterogeneity was detected, which may have an impact on the interpretation of the results.

In subgroup analysis by ethnicity, the FokI polymorphism was negatively correlated with PCa risk in Caucasians and Arabs under the recessive model, and in mixed populations under the dominant and allelic contrast models. However, this was not the case in Asians, Hispanics, or African-Americans. Similarly, Zhang et al[29] indicated a negative correlation. Consequently, the FF genotype may confer a protective effect in Caucasians. Conversely, positive associations were observed in Caucasian descendants under the allelic contrast and dominant genetic model, but not in Asians or African Americans.

Upon analysis of the Poly-A variable, the results indicated that Poly-A was a significant factor, as previously described. Consequently, a statistically significant negative correlation was identified between PCa risk and the FF genotype in Caucasian men under both dominant and recessive genetic models.

These results were partly inconsistent with previous meta-analysis conducted by Berndt et al[26] and Huang et al[41], which indicated that no association between this SNP and PCa risk was observed when their results were stratified by ethnicity.

Vitamin D and its receptor present oncoprotective actions through modulation of inflammation, cell proliferation, cell differentiation, angiogenesis, invasive and metastatic potential, apoptosis, miRNA expression regulation, and modulation of the Hedgehog signaling pathway[96]. Androgens comprise the

primary driver of prostate cancer cells' growth, acting through the androgen receptor (AR). Vitamin D promotes inactivation of androgens by inducing phase I monooxygenases and phase II transferases[28].

In conclusion, it is important to note that the current meta-analysis should be interpreted with caution due to certain limitations that may influence the final results. Firstly, the findings of this study may be limited by the fact that only six polymorphic sites that have been most extensively studied in prostate cancer (PCa) were analysed. Consequently, further studies are required to ascertain whether any association exists between other single-nucleotide polymorphisms (SNPs) in the vitamin D receptor (VDR) gene and the risk of prostate cancer (PCa). Secondly, there was a significant degree of heterogeneity in the data, and the results were based on unadjusted parameters or matching criteria. Therefore, it would be beneficial to include further analysis based on factors, including age and diet, in order to adjust the outcomes. Third, prostate cancer (PCa) is a multifactorial disease that is influenced by both environmental and genetic factors. However, the interaction between the VDR gene and certain gene-environmental factors, such as vitamin D concentration or vitamin D supplements, was not considered in our analysis. Conversely, the present meta-analysis possesses several notable advantages when compared with individual studies or previous meta-analyses. First, the meta-analysis included 65 studies, which included both case and control subjects.

Furthermore, the analysis was stratified by ethnicity, a key subgroup. Finally, a well-designed search method was employed, comprising the NOS, sensitivity analysis, and weighted meta-regression. This was conducted in order to increase the statistical power of the meta-analysis and attenuate the effect of possible heterogeneity factors.

CONCLUSIONS

The present meta-analysis represents the most comprehensive synthesis of available data investigating the associations between VDR Fok1 (rs2228570), Bsm1 (rs1544410), Taq1 (rs731236), Apa1 (rs7975232), Cdx2 (rs11568820), and Poly-A (rs17878969) polymorphisms and prostate cancer risk in the overall population and by ethnicity. Moreover, our findings indicate that these SNPs exert varying effects across different populations, suggesting the influence of ethnicity and opening the door to the impact of environmental factors and their interactions. For future studies, it is recommended that a more rigorous selection of patients and controls be employed, along with a larger sample size, to validate the associations identified in the current meta-analysis, despite the heterogeneity of the source controls. Moreover, additional approaches, such as haplotypic analysis, can provide more valuable data than single genotype-based articles. Furthermore, the penetrance of the SNPs is dependent on interactions with other SNPs as well as exposure to specific environmental factors, which may result in different phenotypes. Accordingly, as Wang et al[6] have indicated, gene-gene and gene-environment interactions may influence the results of our study. Consequently, these parameters must also be taken into account in future studies investigating the association between the VDR gene and prostate cancer, particularly in relation to genotype-phenotype alterations.

Conflicts of interest:
We have no conflicts of interest and there has been no financial support for this work that could have influenced its outcomes.

Ethical Approval:
Not applicable due to the type of study.

Funding:
Not applicable.

Availability of Data and Materials:
Data available upon reasonable request.

Authors' Contributions:
The project conception was developed by A.E., I.B., and A.E. wrote the main manuscript text, and I.B. prepared figures. I.B. and A.E. reviewed the manuscript.

REFERENCES

1. Miyamoto K, Kesterson RA, Yamamoto H, Taketani Y, Nishiwaki E, Tatsumi S, Inoue Y, Morita K, Takeda E, Pike JW. Structural organization of the human vitamin D receptor chromosomal gene and its promoter. Mol Endocrinol 1997; 11: 1165-1179.
2. Labuda M, Fujiwara TM, Ross MV, Morgan K, Garcia-Heras J, Ledbetter DH, Hughes MR, Glorieux FH. Two hereditary defects related to vitamin D metabolism map to the same region of human chromosome 12q13-14. J Bone Miner Res 1992; 7: 1447-1453.
3. Crofts LA, Hancock MS, Morrison NA, Eisman JA. Multiple promoters direct the tissue-specific expression of novel N-terminal variant human vitamin D receptor gene transcripts. Proc Natl Acad Sci U S A 1998; 95: 10529-10534.
4. Yin M, Wei S, Wei Q. Vitamin D Receptor Genetic Polymorphisms and Prostate Cancer Risk: A Meta-analysis of 36 Published Studies. Int J Clin Exp Med 2009; 2: 159-75.
5. Jingwi EY, Abbas M, Ricks-Santi L, Winchester D, Beyene D, Day A, Naab TJ, Kassim OO, Dunston GM, Copeland RL, Kanaan YM. Vitamin D receptor genetic polymorphisms are associated with PSA level, Gleason score and prostate cancer risk in African-American men. Anticancer Res 2015; 35: 1549-1558.
6. Nejentsev S, Godfrey L, Snook H, Rance H, Nutland S, Walker NM, Lam AC, Guja C, Ionescu-Tirgoviste C, Undlien DE, Rønningen KS, Tuomilehto-Wolf E, Tuomilehto J, Newport MJ, Clayton DG, Todd JA. Comparative high-resolution analysis of linkage disequilibrium and tag single nucleotide polymorphisms between populations in the vitamin D receptor gene. Hum Mol Genet 2004; 13: 1633-1609.
7. Zhou TB, Jiang ZP, Huang MF, Su N. Association of vitamin D receptor Fok1 (rs2228570), TaqI (rs731236) and ApaI (rs7975232) gene polymorphism with the risk of chronic kidney disease. J Recept Signal Transduct Res 2015; 35: 58-62.
8. Arai H, Miyamoto KI, Yoshida M, Yamamoto H, Taketani Y, Morita K, Kubota M, Yoshida S, Ikeda M, Watabe F, Kanemasa Y, Takeda E. The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene. J Bone Min Res 2001; 16: 1256-1264.
9. Whitfield GK, Remus LS, Jurutka PW, Zitzer H, Oza AK, Dang HT, Haussler CA, Galligan MA, Thatcher ML, Encinas Dominguez C, Haussler MR. Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. Mol Cell Endocrinol 2001; 177: 145-159.
10. Gnagnarella P, Raimondi S, Aristarco V, Johansson H, Bellerba F, Corso F, De Angelis SP, Belloni P, Caini S, Gandini S. Ethnicity as modifier of risk for Vitamin D receptors polymorphisms: Comprehensive meta-analysis of all cancer sites. Crit Rev Oncol Hematol 2021; 158: 103-202.
11. El Ezzi AA, Boyko VG, Baker MT, Zaidan WR, Hraiki KM, El Saidi MA, Kuddus RH. Association of Some Polymorphisms in the VDR Gene, CYP17 Gene and SRD5A2 Gene and Prostate Cancer among Lebanese Men. Asian Pac J Cancer Prev 2017; 18: 93-100.
12. Kambale PR, Haldar D, Kabi BC, Kambale KP. Study of Vitamin D Receptor Gene Polymorphism (FokI, TaqI and ApaI) Among Prostate Cancer Patients in North India. J Clin Diagn Res 2017; 11: BC05-BC08.
13. Akgül M, Üren N, Yaman A, Baykan Ö, Ergül E, Haklar G, Tinay İ. The Relationship Between Vitamin D Gene Polymorphisms and the Diagnosis of Prostate Cancer in Patients with High Prostate-Specific Antigen Value. Bull Urooncol 2020; 19: 191-195.
14. El-Attar AZ, Hussein S, Salama MFA, Ibrahim HM, AlKaramany AS, Elsawi MK, Hemeda M, Algazeery A. Vitamin D receptor polymorphism and prostate cancer prognosis. Curr Urol 2022; 16: 246-255.
15. Chen L, Wei J, Zhang S, Lou Z, Wang X, Ren Y, Qi H, Xie Z, Chen Y, Chen F, Wu Q, Fan X, Xu H, Huang S, Weng G. Association of VDR gene TaqI polymorphism with the susceptibility to prostate cancer in Asian population evaluated by an updated systematic meta-analysis. Onco Targets Ther 2018; 11: 3267-3280.
16. Braczkowski RS, Kwiatkowski R, Danikiewicz A, Górczyńska-Kosiorz S, Trautsolt W, Braczkowska B, Grzeszczak W. Vitamin D receptor gene polymorphisms and prostate cancer. J Biol Regul Homeost Agents 2018; 32: 1245-1248.
17. Martínez-Nava GA, Gómez R, Burguete-García AI, Vázquez-Salas RA, Ventura-Bahena A, Torres-Sánchez L. BRCA1 and VDR gene polymorphisms are associated with prostate cancer risk in Mexican men. Mol Carcinog 2020; 59: 629-639.
18. Cheteri MBK, Stanford JL, Friedrichsen DM, Peters MA, Iwasaki L, Langlois MC, Feng Z, Ostrander EA. Vitamin D receptor gene polymorphisms and prostate cancer risk. Prostate 2004; 59: 409-418.
19. Deschasaux M, Souberbielle JC, Latino-Martel P, Sutton A, Charnaux N, Druesne-Pecollo N, Galan P, Hercberg S, Le Clerc S, Kesse-Guyot E, Ezzedine K, Touvier M. A prospective study of plasma 25-hydroxyvitamin D concentration and prostate cancer risk. Br J Nutr 2016; 115: 305-314.
20. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.
22. Ahn J, Albanes D, Berndt SI, Peters U, Chatterjee N, Freedman ND, Abnet CC, Huang WY, Kibel AS, Crawford ED, Weinstein SJ, Chanock SJ, Schatzkin A, Hayes RB; Prostate, Lung, Colorectal and Ovarian Trial Project Team. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis 2009; 30: 769-776.
23. Zhang Q, Shan Y. Genetic polymorphisms of vitamin D receptor and the risk of prostate cancer: a meta-analysis. J BUON 2013; 18: 961-969.
24. O Neill V, Asani FF, Jeffery TJ, Saccone DS, Bornman L. Vitamin D Receptor Gene Expression and Function in a South African Population: Ethnicity, Vitamin D and FokI. PLoS One 2013; 8: e67663.
25. Huang J, Yang J, Wang H, Xiong T, Zhang H, Ma Y, Wang X, Huang J, Du L. The association between the poly(A) polymorphism in the VDR gene and cancer risk: A meta-analysis. Tumor Biology 2013; 34: 1833-1838.
26. Berndt SI, Dodson JL, Huang WY, Nicodemus KK. A systematic review of vitamin D receptor gene polymorphisms and prostate cancer risk. J Urol 2006; 175: 1613-1623.
27. Bandera Merchan B, Morcillo S, Martin-Nuñez G, Tinahones FJ, Macías-González M. The role of vitamin D and VDR in carcinogenesis: Through epidemiology and basic sciences. J Steroid Biochem Mol Biol 2017; 167: 203-218.
28. Onen IH, Ekmekci A, Eroglu M, Konac E, Yesil S, Blrl H. Association of genetic polymorphisms in vitamin D receptor gene and susceptibility to sporadic prostate cancer. Exp Biol Med 2008; 233: 1608-1614.

29. Zhang Q, Shan Y. Genetic polymorphisms of vitamin D receptor and the risk of prostate cancer: a meta-analysis. J BUON 2013; 18: 961-969.
30. Hessels D, Verhaegh GW, Schalken JA, Witjes JA. Applicability of biomarkers in the early diagnosis of prostate cancer. Expert Rev Mol Diagn 2004; 4: 513-526.
31. Veronique-Baudin J, Dieye M, Kouyoumdjian JC, Vacheron F, Draganescu C, Azaloux H. Case-control study of the genes of receptors of the androgens of vitamin-D and of 5-alphareductase in a population of Afro-Caribbean population with prostate cancer. Prog Urol 2006; 16: 303-310..
32. Raimondi S, Johansson H, Maisonneuve P, Gandini S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. Carcinogenesis 2009; 30: 1170-1180.
33. Berndt SI, Dodson JL, Huang WY, Nicodemus KK. A systematic review of vitamin D receptor gene polymorphisms and prostate cancer risk. J Urol 2006; 175: 1613-1623.
34. Liu S, Cai H, Cheng W, Zhang H, Pan Z, Wang D. Association of VDR polymorphisms (Taq I and Bsm I) with prostate cancer: a new meta-analysis. J Int Med Res 2017; 45: 3-10.
35. Cicek MS, Liu X, Schumacher FR, Casey G, Witte JS. Vitamin D receptor genotypes/haplotypes and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2006; 15: 2549-2552.
36. Bai Y, Yu Y, Yu B, Ge J, Ji J, Lu H, Wei J, Weng Z, Tao Z, Lu J. Association of vitamin D receptor polymorphisms with the risk of prostate cancer in the Han population of Southern
37. Onen IH, Ekmekci A, Eroglu M, Konac E, Yesil S, Biri H. Association of genetic polymorphisms in vitamin D receptor gene and susceptibility to sporadic prostate cancer. Exp Biol Med 2008; 233: 1608-1614.
38. Gilbert R, Bonilla C, Metcalfe C, Lewis S, Evans DM, Fraser WD, Kemp JP, Donovan JL, Hamdy FC, Neal DE, Lane JA, Smith GD, Lathrop M, Martin RM. Associations of vitamin D pathway genes with circulating 25-hydroxyvitamin-D, 1,25-dihydroxyvitamin-D, and prostate cancer: a nested case-control study. Cancer Causes Control 2015; 26: 205-218.
39. Rowland GW, Schwartz GG, John EM, Ingles SA. Protective Effects of Low Calcium Intake and Low Calcium Absorption Vitamin D Receptor Genotype in the California Collaborative Prostate Cancer Study. Cancer Epidemiol Biomarkers Prev 2013; 22: 16-24.
40. Huang SP, Chou YH, Wayne Chang WS, Wu MT, Chen YY, Yu CC, Wu TT, Lee YH, Huang JK, Wu WJ, Huang CH. Association between vitamin D receptor polymorphisms and prostate cancer risk in a Taiwanese population. Cancer Lett 2004; 207: 69-77.
41. Oakley-Girvan I, Feldman D, Eccleshall TR, Gallagher RP, Wu AH, Kolonel LN, Halpern J, Balise RR, West DW, Paffenbarger RS Jr, Whittemore AS. Risk of early-onset prostate cancer in relation to germ line polymorphisms of the vitamin D receptor. Cancer Epidemiol Biomarkers Prev 2004; 13: 1325-1330. China. BMC Med Genet 2009; 10: 125.
42. Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Hollis BW, Giovannucci E. Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk. Prostate 2007; 67: 911-923.
43. Taylor JA, Hirvonen A, Watson M, Pittman G, Mohler JL, Bell DA. Association of prostate cancer with vitamin D receptor gene polymorphism. Cancer Res 1996; 56: 4108-4110.
44. Ma J, Stampfer MJ, Gann PH, Hough HL, Giovannucci E, Kelsey KT, Hennekens CH, Hunter DJ. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. Cancer Epidemiol Biomarkers Prev 1998; 7: 385-390.
45. Kibel AS, Isaacs SD, Isaacs WB, Bova GS. Vitamin D receptor polymorphisms and lethal prostate cancer. J Urol 1998; 160: 1405-1409.
46. Furuya Y, Akakura K, Masai M, Ito H. Vitamin D receptor gene polymorphism in Japanese patients with prostate cancer. Endocr J 1999; 46: 467-470.
47. Correa-Cerro L, Berthon P, Häussler J, Bochum S, Drelon E, Mangin P, Fournier G, Paiss T, Cussenot O, Vogel W. Vitamin D receptor polymorphisms as markers in prostate cancer. Hum Genet 1999; 105: 281-287.
48. Habuchi T, Suzuki T, Sasaki R, Wang L, Sato K, Satoh S, Akao T, Tsuchiya N, Shimoda N, Wada Y, Koizumi A, Chihara J, Ogawa O, Kato T. Association of vitamin D receptor gene polymorphism with prostate cancer and benign prostatic hyperplasia in a Japanese population. Cancer Res 2000; 60: 305-308.
49. Blazer DG, Umbach DM, Bostick RM, Taylor JA. Vitamin D receptor polymorphisms and prostate cancer. Mol Carcinog 2000; 27: 18.
50. Hamasaki T, Inatomi H, Katoh T, Ikuyama T, Matsumoto T. Clinical and pathological significance of vitamin D receptor gene polymorphism for prostate cancer which is associated with a higher mortality in Japanese. Endocr J 2001; 48: 543-549.
51. Hamasaki T, Inatomi H, Katoh T, Ikuyama T, Matsumoto T. Significance of vitamin D receptor gene polymorphism for risk and disease severity of prostate cancer and benign prostatic hyperplasia in Japanese. Urol Int 2002; 68: 226-231.
52. Gsur A, Madersbacher S, Haidinger G, Schatzl G, Marberger M, Vutuc C, Micksche M. Vitamin D receptor gene polymorphism and prostate cancer risk. Prostate 2002; 51: 30-34.
53. Medeiros R, Morais A, Vasconcelos A, Costa S, Pinto D, Oliveira J, Lopes C. The role of vitamin D receptor gene polymorphisms in the susceptibility to prostate cancer of a southern European population. J Hum Genet 2002; 47: 413-418.
54. Tayeb MT, Clark C, Haites NE, Sharp L, Murray GI, McLeod HL. CYP3A4 and VDR gene polymorphisms and the risk of prostate cancer in men with benign prostate hyperplasia. Br J Cancer 2003; 88: 928-932.
55. Tayeb MT, Clark C, Haites NE, Sharp L, Murray GI, McLeod HL. Vitamin D receptor, HER-2 polymorphisms and risk of prostate cancer in men with benign prostate hyperplasia. Saudi Med J 2004; 25: 447-451.
56. Maistro S, Snitcovsky I, Sarkis AS, da Silva IA, Brentani MM. Vitamin D receptor polymorphisms and prostate cancer risk in Brazilian men. Int J Biol Markers 2004; 19: 245-249.
57. Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RC. Polymorphisms in the vitamin D receptor gene, ultraviolet radiation, and susceptibility to prostate cancer. Environ Mol Mutagen 2004; 43: 121-127.
58. Liu JH, Li HW, Wang JQ, Li M, Xin DQ, Na X, Zhang M, Ye SY, Na YQ. Vitamin D receptor gene Bsm I polymorphism and the susceptibility to prostate cancer in northern Chinese Han population. Zhonghua Nan Ke Xue 2003; 9: 413-416.
59. John EM, Schwartz GG, Koo J, Van Den Berg D, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. Cancer Res 2005; 65: 5470-5479.

60. Moon S, Holley S, Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RC. Associations between G/A1229, A/G3944, T/C30875, C/T48200 and C/T65013 genotypes and haplotypes in the vitamin D receptor gene, ultraviolet radiation and susceptibility to prostate cancer. Ann Hum Genet 2006; 70: 226-236.
61. Andersson P, Varenhorst E, Söderkvist P. Androgen receptor and vitamin D receptor gene polymorphisms and prostate cancer risk 2006. Eur J Cancer; 42: 2833-2837.
62. Chaimuangraj S, Thammachoti R, Ongphiphadhanakul B, Thammavit W. Lack of association of VDR polymorphisms with Thai prostate cancer as compared with benign prostate hyperplasia and controls. Asian Pac J Cancer Prev 2006; 7: 136-139.
63. Holick CN, Stanford JL, Kwon EM, Ostrander EA, Nejentsev S, Peters U. Comprehensive association analysis of the vitamin D pathway genes, VDR, CYP27B1, and CYP24A1, in prostate cancer. Cancer Epidemiol Biomarkers Prev 2007; 16: 1990-1999.
64. Li H, Stampfer MJ, Hollis JB, Mucci LA, Gaziano JM, Hunter D, Giovannucci EL, Ma J. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLoS Med 2007; 4: e103.
65. Holt SK, Kwon EM, Peters U, Ostrander EA, Stanford JL. Vitamin D pathway gene variants and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2009; 18: 1929-1933.
66. Hu J, Qiu Z, Zhang L, Cui F. Kallikrein 3 and vitamin D receptor polymorphisms: potentials environmental risk factors for prostate cancer. Diagn Pathol 2014; 9: 84.
67. Nunes SB, de Matos Oliveira F, Neves AF, Araujo GR, Marangoni K, Goulart LR, Araújo TG. Association of vitamin D receptor variants with clinical parameters in prostate cancer. Springerplus 2016; 5: 364.
68. Dafalla AM, Abuidris D, Abakar AD, Khallafalah AS, Dafalla AM, Mergani A, Gadallah M, Mohammed YA. Vitamin D Receptors Gene Polymorphisms among Sudanese Patients with Prostate Cancer. Sudan Med Lab J 2022; 2: 9-22.
69. Watanabe M, Fukutome K, Murata M, Uemura H, Kubota Y, Kawamura J, Yatani R. Significance of vitamin D receptor gene polymorphism for prostate cancer risk in Japanese. Anticancer Res 1999; 19: 4511-4514.
70. Yousaf N, Afzal S, Hayat T, Shah J, Ahmad N, Abbasi R, Ramzan K, Jan R, Khan I, Ahmed J, Siraj S. Association of vitamin D receptor gene polymorphisms with prostate cancer risk in the Pakistani population. Asian Pac J Cancer Prev 2014; 15: 10009-10013.
71. Cheteri MB, Stanford JL, Friedrichsen DM, Peters MA, Iwasaki L, Langlois MC, Feng Z, Ostrander EA. Vitamin D receptor gene polymorphisms and prostate cancer risk. Prostate 2004; 59: 409-418.
72. Chokkalingam AP, McGlynn KA, Gao YT, Pollak M, Deng J, Sesterhenn IA, Mostofi FK, Fraumeni JF Jr, Hsing AW. Vitamin D receptor gene polymorphisms, insulin-like growth factors, and prostate cancer risk: a population-based case-control study in China. Cancer Res 2001; 61: 4333-4336.
73. Forrest MS, Edwards SM, Houlston R, Kote-Jarai Z, Key T, Allen N, Knowles MA, Turner F, Ardern-Jones A, Murkin A, Williams S, Oram R, Bishop DT, Eeles RA; CR-UK/BPG UK prostate cancer study collaborators. Association between hormonal genetic polymorphisms and early-onset prostate cancer. Prostate Cancer Prostatic Dis 2005; 8: 95-102.
74. Yang Y, Wang S, Ye Z, Yang W. Association of single nucleotide polymorphism of vitamin D receptor gene start codon and the susceptibility to prostate cancer in the Han nationality in Hubei area. Zhonghua Nan Ke Xue 2004; 10: 411-414.
75. Huang SP, Huang CY, Wu WJ, Pu YS, Chen J, Chen YY, Yu CC, Wu TT, Wang JS, Lee YH, Huang JK, Huang CH, Wu MT. Association of vitamin D receptor FokI polymorphism with prostate cancer risk, clinicopathological features and recurrence of prostate specific antigen after radical prostatectomy. Int J Cancer 2006; 119: 1902-1907.
76. Mishra DK, Bid HK, Srivastava DSL, Mandhani A, Mittal RD. Association of Vitamin D Receptor Gene Polymorphism and Risk of Prostate Cancer in India. Urol Int 2005; 74: 315-318.
77. Atoum MF, AlKateeb D, Mahmoud SAA. The Fok1 Vitamin D Receptor Gene Polymorphism and 25(OH) D Serum Levels and Prostate Cancer among Jordanian Men. Asian Pac J Cancer Prev 2015; 16: 2227-2230.
78. Deschasaux M, Souberbielle JC, Latino-Martel P, Sutton A, Charnaux N, Druesne-Pecollo N, Galan P, Hercberg S, Le Clerc S, Kesse-Guyot E, Ezzedine K, Touvier M. A prospective study of plasma 25-hydroxyvitamin D concentration and prostate cancer risk. Br J Nutr 2016; 115: 305-314.
79. Martínez-Nava GA, Gómez R, Burguete-García AI, Vázquez-Salas RA, Ventura-Bahena A, Torres-Sánchez L. BRCA1 and VDR gene polymorphisms are associated with prostate cancer risk in Mexican men. Mol Carcinog 2020; 59: 629-639.
80. Huang J, Yang J, Wang H, Xiong T, Zhang H, Ma Y, Wang X, Huang J, Du L. The association between the poly(A) polymorphism in the VDR gene and cancer risk: A meta-analysis. Tumor Biology 2013; 34 :1833-1838.
81. Amiri M, Elieh Ali Komi D, Vaisi-Raygani A, Kiani A, Moradi M, Aliyari M, Rahimi Z, Mohammadi-Noori E, Bashiri H. Association Between Vitamin D Binding Protein Gene Polymorphism (rs7041), Vitamin D Receptor, and 25-Hydroxyvitamin D Serum Levels With Prostate Cancer in Kurdish Population in West of Iran. Pathol Oncol Res 2022; 28: 1610246. Oncol Res 2022; 28: 1610246.
82. Suzuki K, Matsui H, Ohtake N, Nakata S, Takei T, Koike H, Nakazato H, Okugi H, Hasumi M, Fukabori Y, Kurokawa K, Yamanaka H. Vitamin D receptor gene polymorphism in familial prostate cancer in a Japanese population. Int J Urol 2003; 10: 261-266.
83. Ingles SA, Coetzee GA, Ross RK, Henderson BE, Kolonel LN, Crocitto L, Wang W, Haile RW. Association of prostate cancer with vitamin D receptor haplotypes in African-Americans. Cancer Res 1998; 58: 1620-1623.
84. Chokkalingam AP, McGlynn KA, Gao YT, Pollak M, Deng J, Sesterhenn IA, Mostofi FK, Fraumeni JF Jr, Hsing AW. Vitamin D receptor gene polymorphisms, insulin-like growth factors, and prostate cancer risk: a population-based case-control study in China. Cancer Res 2001; 61: 4333-4336.
85. Hayes VM, Severi G, Padilla EJ, Eggleton SA, Southey MC, Sutherland RL, Hopper JL, Giles GG. Genetic variants in the vitamin D receptor gene and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2005; 14: 997-999.
86. Rukin NJ, Luscombe C, Moon S, Bodiwala D, Liu S, Saxby MF, Fryer AA, Alldersea J, Hoban PR, Strange RC. Prostate cancer susceptibility is mediated by interactions between exposure to ultraviolet radiation and polymorphisms in the 5' haplotype block of the vitamin D receptor gene. Cancer Lett 2007; 247: 328-335.
87. Torkko K, Till C, Tangen CM, Goodman PJ, Song X, Schenk JM, Lucia MS, Peters U, van Bokhoven A, Thompson IM, Neuhouser ML. Vitamin D Pathway and Other Related Polymorphisms and Risk of Prostate Cancer: Results from the Prostate Cancer Prevention Trial. Cancer Prev Res (Phila) 2020; 13: 521-530.
88. Nam RK, Zhang WW, Trachtenberg J, Jewett MA, Emami M, Vesprini D, Chu W, Ho M, Sweet J, Evans A, Toi A, Pollak M, Narod SA. Comprehensive assessment of candidate genes and serological markers for the detection of prostate cancer. Cancer Epidemiol Biomarkers Prev 2003; 12: 1429-1437.

89. Hessels D, Verhaegh GW, Schalken JA, Witjes JA. Applicability of biomarkers in the early diagnosis of prostate cancer. Expert Rev Mol Diagn 2004; 4: 513-526.
90. Szendroi A, Speer G, Tabak A, Kosa JP, Nyirady P, Majoros A, Romics I, Lakatos P. The role of vitamin D, estrogen, calcium sensing receptor genotypes and serum calcium in the pathogenesis of prostate cancer. Can J Urol 2011; 18: 5710-5716.
91. Onsory K, Sobti RC, Al-Badran AI, Watanabe M, Shiraishi T, Krishan A, Mohan H, Kaur P. Hormone receptor-related gene polymorphisms and prostate cancer risk in North Indian population. Mol Cell Biochem 2008; 314: 25-35.
92. Ingles SA, Ross RK, Yu MC, Irvine RA, La Pera G, Haile RW, Coetzee GA. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. J Natl Cancer Inst 1997; 89: 166-170.
93. Guo Z, Wen J, Kan Q, Huang S, Liu X, Sun N, Li Z. Lack of association between vitamin D receptor gene FokI and BsmI polymorphisms and prostate cancer risk: An updated meta-analysis involving 21,756 subjects. Tumor Biol 2013; 34: 3189-3200.
94. Wang K, Wu G, Li J, Song W. Role of vitamin D receptor gene Cdx2 and Apa1 polymorphisms in prostate cancer susceptibility: a meta-analysis. BMC Cancer 2016; 16: 674.
95. Raimondi S, Johansson H, Maisonneuve P, Gandini S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. Carcinogenesis 2009; 30: 1170-1180.
96. Ahn J, Park S, Zuniga B, Bera A, Song CS, Chatterjee B. Vitamin D in Prostate Cancer. Vitam Horm 2016; 100: 321-355.