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Original Article

Association between vitamin D receptor gene BsmI polymorphism and susceptibility to prostate cancer

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Abstract: The polymorphisms of the vitamin D receptor (VDR) gene have been hypothesized to alter the risk of prostate cancer; however, published data concerning the association between VDR gene BsmI polymorphism and prostate cancer susceptibility are somewhat inconclusive. To evaluate the impact of VDR gene BsmI polymorphism on prostate cancer risk, a meta-analysis on all eligible studies including 7,666 patients and 8,073 control subjects was carried out. No obvious association of this variant on prostate cancer risk was found in the overall results. However, in subgroup analysis by ethnicity, we indicated positive associations in Caucasian descendants for dominant genetic model (OR = 0.91, 95% CI = 0.83-1.00, $P_{heterogeneity}$ = 0.129, P = 0.042, I^2 = 33.7), but not in Asian descendants (OR = 1.07, 95% CI = 0.59-1.92, $P_{heterogeneity}$ = 0.307, P = 0.834, I^2 = 16.6) and African-Americans (OR = 1.52, 95% CI = 0.84-2.76, $P_{heterogeneity}$ = 0.066, P = 0.171, I^2 = 63.3). Furthermore, in the subgroup analysis by source of control, no obvious association was observed in neither population-based (dominant genetic model OR = 0.95, 95% CI = 0.87-1.03, $P_{heterogeneity}$ = 0.084, P = 0.224, I^2 = 36.5) or hospital-based studies (OR = 0.74, 95% CI = 0.49-1.12, $P_{heterogeneity}$ = 0.087, P = 0.157, I^2 = 48.0). In conclusion, VDR BsmI polymorphism may be related to prostate cancer in Caucasian descendants. Future well-designed and more diverse case-control populations are warranted to further evaluate this conclusion in more detail.

Keywords: Vitamin D receptor, polymorphism, cancer risk

Introduction

Prostate cancer (PCa) is one of the most common types of neoplasm in male population of the Western world [1]. In the United States, prostate cancer is the second leading cause of cancer deaths among male, with an estimation of 238,590 new cases and 29,720 deaths in 2013 and will be an estimated 1,665,540 new diagnosed cancer cases and 585,720 cancer deaths in 2014 [2, 3]. In European countries, it is recognized as the most common types of neoplasm, with an incidence rate of 214 cases in every thousand men, outnumbering the colorectal and lung cancer [4]. Although epidemiological data indicated that the incidence of PCa in Asians is much lower than that in developed world, the morbidity and mortality rate of this disease has rapidly increased among Chinese men [5, 6]. So far, there are well-established risk-factors, such as lifestyle, environment and ethnicity have been demonstrated as the possible contributors to the etiology of PCa [1]. Nevertheless, these factors may not completely explain the discrepancy between different ethnicity in PCa rates. Hence, genetic variation in PCa related genes, including human vitamin D receptor (VDR) gene, may play a role in determination of susceptibility to this disease.

The VDR gene is a nuclear receptor gene with 75 kb and consists of 11 exons and 11 introns. It acts as a ligand-dependent transcriptional factor in prostate tissues by the interaction with vitamin D [7, 8]. A series of experiments revealed that 1, 25-dihydroxyvitamin

D3[1,25(OH2)D3], the active form of vitamin D, could mediate the growth, differentiation and apoptosis of prostatic cells, which indicated that the VDR may be closely associated with prostate cancer risk [9-11]. A less active VDR could be related to either a more aggressive disease or an increased risk to cancer [12]. Previous studies have shown evidence that several single-nucleotide polymorphisms (SNPs) of VDR, which potentially influence the receptor binding of 1,25(OH2)D3 may mediate vitamin D biological activity and confer susceptibility to PCa [13]. Among them, the most commonly studied SNPs is the VDR BsmI, which is intronic and located at the 3' end of the gene. It is strongly associated with the poly (A) microsatellite repeat in 3' untranslated region and affected VDR messenger RNA stability [14].

Numerous epidemiological studies have been conducted to explore the association between VDR BsmI polymorphism and PCa risk. However, result of these researches remains controversial rather than conclusive due to conflicting results from various case-control studies. Ever since, new researches have provided additional data concerning the VDR variants. Therefore, we used the enhanced statistical power of the meta-analysis to achieve a summary conclusion on the association of VDR BsmI polymorphism and prostate cancer utilizing accumulated data from eligible studies published to date [15-34].

Materials and methods

PubMed, Web of Science and Embase databases searches were conducted utilizing the following terms: 'vitamin D receptor' or 'VDR', 'prostate cancer' and 'polymorphism' or 'variant' (last search updated on October 29, 2015). References of the identified manuscripts were also manually screened for eligibility. Eligible manuscripts should meet all of the following inclusion criteria: (a) used an unrelated case-control design; (b) contained information of genotype frequency; (c) the study was published in English; and (d) supply sufficient information to calculate the odds ratio (OR) with 95% confidence interval (CI). The major exclusion criteria are as follows: (a) the study lack of the control population; (b) genotype numbers or frequencies were not presented in the original studies; (c) abstracts or reviews; and (d) study was the duplicate.

Data extraction and quality assessment

For each eligible publication, data extraction and quality assessment was conducted by two of the co-authors independently according to the inclusion criteria above. Disagreement was resolved through a discussion between two co-authors. If the consensus could not be reached, additional co-authors should be included in the discussion until a final consensus. Furthermore, eligible studies containing data about clinical stage of prostate cancer were categorized into two groups: localized PCa and advanced PCa (including cases with bone metastasis). The following parameters from each study were recorded: first author's name, year of publication, ethnicity, the sources of controls, sample size of cases and controls, number of cases and controls with variant allele and wild type, *P* value for Hardy-Weinberg Equilibrium (HWE) respectively.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were utilized to evaluate the strength of association between the polymorphism in VDR BsmI and prostate cancer susceptibility. For this VDR BsmI variant, we investigated the relationship between genetic variants and prostate cancer risk in allelic contrast (b-allele vs. B-allele), homozygote comparison (bb vs. BB), heterozygote comparison (bB vs. BB), dominant genetic model (bb + bB vs. BB) and recessive genetic model (bb vs. bB + BB). Stratified analyses were carried out by ethnicity and source of controls [hospital-based, population-based and benign prostatic hyperplasia (BPH) based]. The pooled ORs for the risk were tested utilizing the random effects model and fixed effects model. Heterogeneity assumption was assessed by the chi-square-based *Q* test among the studies. Data were evaluated utilizing random-effects (the DerSimonian and Laird method) [35] in the presence of heterogeneity ($P<0.05$) and fixed-effects (the Mantel-Haenszel method) models [36] were performed in absence of heterogeneity ($P > 0.05$). Significant departures of allele frequencies of VDR BsmI polymorphism from expectation under HWE were evaluated in controls using the Pearson's chi-square test. *Z*-test was performed to assess the statistical significance of the summary OR, *P* value of<0.05 was considered significant. The statistic of I^2 was also uti-

Table 1. Characteristics of studies of the vitamin D receptor (VDR) BsmI gene polymorphism included in this meta-analysis

First author	Year	Ethnicity	Source of control	Genotyping	Sample size of case				Sample size of control				P_{HWE}	Frequency of b allele
				Method	bb	Bb	BB	Total	bb	Bb	BB	Total		
Ingles	1998	African-Americans	Population-based	PCR-RFLP	112	37	2	151	135	38	1	174	0.333	0.885
Ma	1998	Caucasian	Population-based	PCR-RFLP	135	185	52	372	201	300	90	591	0.203	0.594
Habuchi	2000	Asian	BPH-based	PCR-RFLP	172	42	8	222	64	59	5	128	0.054	0.73
Chokkalingam	2001	Asian	Population-based	PCR-RFLP	140	17	4	161	259	31	7	297	0	0.924
Suzuki	2003	Asian	Hospital-based	PCR-RFLP	58	17	6	81	83	20	2	105	0.545	0.886
Nam	2003	Mixed	BPH-based	PCR-RFLP	114	174	195	483	130	203	215	548	0	0.422
Oakley-Girvan	2004	Caucasian	Population-based	PCR-RFLP	70	122	40	232	59	79	33	171	0.479	0.576
Oakley-Girvan	2004	African-Americans	Population-based	PCR-RFLP	56	45	12	113	58	51	12	121	0.872	0.69
Huang	2004	Asian	Hospital-based	PCR-RFLP	147	11	2	160	173	27	5	205	0.005	0.91
Cheteri	2004	Caucasian	Population-based	PCR-RFLP	207	216	120	543	170	210	130	510	0	0.539
Hayes	2005	Caucasian	Population-based	DGGE	144	373	295	812	130	351	232	713	0.891	0.428
Cicek2006	2006	Mixed	Population-based	PCR-RFLP	174	196	69	439	168	224	85	477	0.492	0.587
Chaimuangraj	2006	Asian	Hospital-based	PCR-RFLP	79	13	3	95	23	4	3	30	0.004	0.833
Mikhak	2007	Caucasian	Population-based	Taqman	242	280	124	646	249	314	106	669	0.673	0.607
Li	2007	Caucasian	Population-based	PCR-RFLP	381	480	173	1034	575	747	244	1566	0.957	0.606
Holick	2007	Caucasian	Population-based	SNPlex assay	90	279	221	590	84	280	177	541	0.121	0.414
Onen	2008	Caucasian	Hospital-based	PCR-RFLP	53	66	14	133	50	90	17	157	0.012	0.605
Holt	2009	African-Americans	Population-based	SNPlex assay	57	47	7	111	27	26	13	66	0.155	0.606
Holt	2009	Caucasian	Population-based	SNPlex assay	239	339	106	684	255	331	115	701	0.664	0.6
Bai	2009	Asian	Hospital-based	PCR-RFLP	114	8	0	122	108	21	1	130	0.985	0.912
Szendroi	2011	Caucasian	Hospital-based	PCR-RFLP	52	101	51	204	53	35	14	102	0.048	0.691
Jingwi	2015	Caucasian	Population-based	Taqman	22	117	139	278	11	33	27	71	0.862	0.387

HWE: Hardy-Weinberg equilibrium of controls, RFLP: restriction fragment length polymorphism; BPH: benign prostatic hyperplasia.

lized to calculate the heterogeneity, with I^2 > 75%, 25-75% and <25% to represent high, moderate and low degree of inconsistency, respectively. Significance of the intercept was determined by t-test as suggested by Egger (P<0.01 represent a statistically significant publication bias) [37]. All the statistical analyses were carried out by STATA version 11.0 (Stata Corporation, College Station, TX).

Results

Study characteristics

A total of 20 articles (including 22 case-control studies) met all the inclusion criteria and were enrolled in our study. Study characteristics of the eligible publications are summarized in **Table 1**. In general, 7,666 prostate cancer patients and 8,073 control subjects correlate with the VDR BsmI polymorphism were assessed. In the subgroup of ethnicity, 11 were carried out in Caucasian descendants, 6 were in Asian descendants. Population-based controls were carried out in 14 of these studies. The classical genotyping method called polymerase chain reaction-restriction fragment length polymorphism (RFLP) was performed in 16 comparisons. 2 studies performed TaqMan real-time polymerase chain reaction (PCR).

Quantitative synthesis

Using the pooled data (**Table 2**), no obvious association was observed in the overall analysis between prostate cancer risk and the VDR BsmI variant genotypes: allelic comparison (random-effects OR = 1.03, 95% CI = 0.93-1.14, $P_{heterogeneity}$<0.001, P = 0.597, I^2 = 73.1), the homozygote comparison (random-effects OR = 0.97, 95% CI = 0.83-1.15, $P_{heterogeneity}$ = 0.005, P = 0.746, I^2 = 49.0), heterozygote comparison (fixed-effects OR = 0.92, 95% CI = 0.85-1.01, $P_{heterogeneity}$ = 0.442, P = 0.216, I^2 = 1.3), dominant genetic model (fixed-effects OR = 0.94, 95% CI = 0.86-1.02, $P_{heterogeneity}$ = 0.073 P = 0.129, I^2 = 32.4) and the recessive genetic model (random-effects OR = 1.07, 95% CI = 0.92-1.24, $P_{heterogeneity}$<0.001, P = 0.390, I^2 = 71.0). However, in the subgroup analysis by ethnicity, positive associations between VDR BsmI polymorphism and prostate cancer risk were

Table 2. Stratified analyses of the vitamin D receptor gene BsmI polymorphism on prostate cancer risk

Variables	N[a]	Cases/ Controls	b-allele vs. B-allele				bb vs. BB				Bb vs. BB				bb+Bb vs. BB				bb vs. Bb+BB			
			OR (95% CI)	P^b	*P*	I^2	OR (95% CI)	P^b	*P*	I^2	OR (95% CI)	P^b	*P*	I^2	OR (95% CI)	P^b	*P*	I^2	OR (95% CI)	P^b	*P*	I^2
Total	22	7666/ 8073	1.03 (0.93-1.14)	<0.001	0.597	73.1	0.97 (0.83-1.15)	0.005	0.746	49.0	0.92 (0.85-1.01)	0.442[c]	0.216	1.3	0.94 (0.86-1.02)	0.073[c]	0.129	32.4	1.07 (0.92-1.24)	<0.001	0.390	71.0
Ethnicity																						
Caucasian	11	5528/ 5792	0.94 (0.85-1.04)	0.001	0.219	68.2	0.90 (0.75-1.08)	0.008	0.251	57.8	0.91 (0.82-1.00)	0.502[c]	0.051	0	0.91 (0.83-1.00)	0.129[c]	0.042	33.7	0.94 (0.80-1.10)	0.001	0.429	67.0
Asian	6	841/ 895	1.54 (0.93-2.55)	0.001	0.096	77.2	1.20 (0.66-2.18)	0.247[c]	0.550	25.0	0.72 (0.38-1.37)	0.487[c]	0.321	0	1.07 (0.59-1.92)	0.307[c]	0.834	16.6	1.66 (0.94-2.93)	0.001	0.082	76.8
African-Americans	3	375/ 361	1.12 (0.87-1.44)	0.075[c]	0.369	61.4	1.57 (0.84-2.92)	0.067[c]	0.156	62.9	1.44 (0.76-2.70)	0.107[c]	0.260	55.3	1.52 (0.84-2.76)	0.066[c]	0.171	63.3	1.07 (0.78-1.45)	0.328[c]	0.691	10.2
Mixed	2	922/ 1025	1.05 (0.92-1.19)	0.216[c]	0.446	34.7	1.08 (0.85-1.38)	0.274[c]	0.521	16.5	0.99 (0.79-1.24)	0.579[c]	0.939	0	1.02 (0.83-1.25)	0.364[c]	0.846	0	1.10 (0.91-1.34)	0.330[c]	0.328	0
Source of control																						
Population-based	14	6166/ 6668	0.99 (0.94-1.04)	0.074[c]	0.772	38.0	1.00 (0.86-1.16)	0.085[c]	0.986	36.4	0.93 (0.85-1.02)	0.241[c]	0.134	19.5	0.95 (0.87-1.03)	0.084[c]	0.224	36.5	1.02 (0.95-1.11)	0.528[c]	0.538	0
Hospital-based	6	795/ 729	1.16 (0.65-2.06)	<0.001	0.619	86.1	0.91 (0.34-2.45)	0.004	0.852	70.6	0.84 (0.53-1.33)	0.623[c]	0.455	0	0.74 (0.49-1.12)	0.087[c]	0.157	48.0	1.14 (0.56-2.32)	<0.001	0.710	85.7
BPH	2	705/ 676	1.52 (0.62-3.76)	<0.001	0.364	94.4	1.00 (0.74-1.36)	0.366[c]	0.986	0	0.91 (0.69-1.19)	0.225[c]	0.482	32.0	0.96 (0.75-1.22)	0.825[c]	0.739	0	1.82 (0.54-6.15)	<0.001	0.334	94.9

[a]Number of comparisons. [b]*P* value of Q-test for heterogeneity test (P_{heter}). [c]Random effects model was performed when *P* value for heterogeneity test <0.05; otherwise, fixed effects model was used.

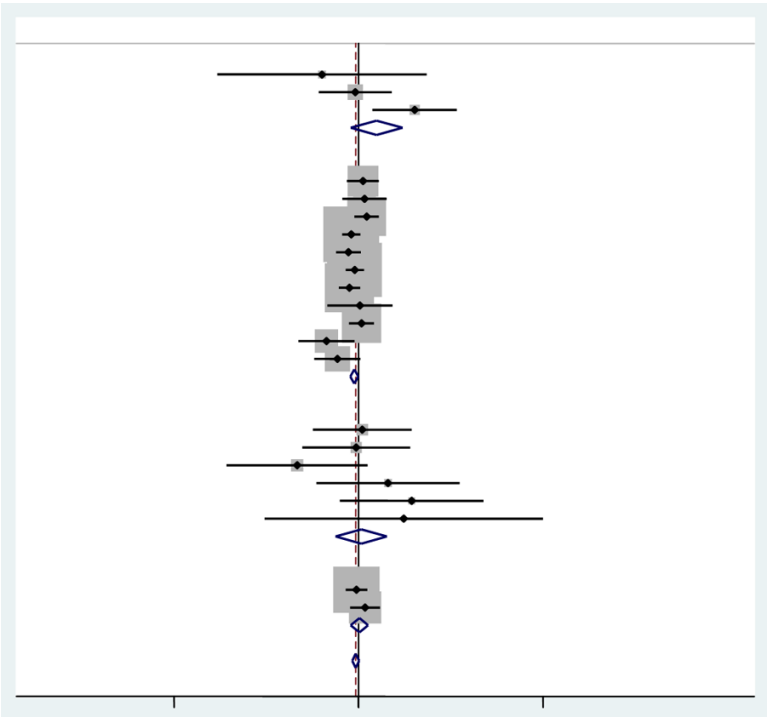

Figure 1. Forest plot of prostate cancer risk associated with the VDR BsmI gene polymorphism (allelic contrast of b-allele vs. B-allele) in the stratified analyses by ethnicity. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The area of the *squares* reflects the weight (inverse of the variance). The *diamond* corresponds to the summary OR and 95% CI. Separate details were summarized in **Table 1**.

found in Caucasian descendants for dominant genetic model (fixed-OR = 0.91, 95% CI = 0.83-1.00, $P_{heterogeneity}$ = 0.129, P = 0.042, I^2 = 33.7) (**Figure 1**), but not in Asian descendants (fixed-effects OR = 1.07, 95% CI = 0.59-1.92, $P_{heterogeneity}$ = 0.307, P = 0.834, I^2 = 16.6), African-Americans (fixed-effects OR = 1.52, 95% CI = 0.84-2.76, $P_{heterogeneity}$ = 0.066, P = 0.171, I^2 = 63.3) and Mixed descendents (fixed-effects OR = 1.02, 95% CI = 0.83-1.25, $P_{heterogeneity}$ = 0.364, P = 0.846, I^2 = 0). Furthermore, in the subgroup analysis by source of control, no obvious association was observed in population-based (dominant genetic model fixed-effects OR = 0.95, 95% CI = 0.87-1.03, $P_{heterogeneity}$ = 0.084, P = 0.224, I^2 = 36.5), hospital-based studies (dominant genetic model fixed-effects OR = 0.74, 95% CI = 0.49-1.12, $P_{heterogeneity}$ = 0.087, P = 0.157, I^2 = 48.0) and BPH based studies (dominant genetic model fixed-effects OR = 0.96, 95% CI = 0.75-1.22, $P_{heterogeneity}$ = 0.825, P = 0.739, I^2 = 0) (**Figure 2**). 7 studies contains information about clinical stage of PCa (1 was carried out in Caucasian descendants, 4 were in Asian descendants, 1 was in African-Americans and 1 was in mixed descendants), in the subgroup analysis by tumor stage, there is a positive association between this variant and localized prostate cancer under allelic comparison (fixed-effects OR = 1.18, 95% CI = 1.03-1.35, $P_{heterogeneity}$ = 0.164, P = 0.021, I^2 = 34.6) and recessive genetic model (fixed-effects OR = 1.23, 95% CI = 1.02-1.48, $P_{heterogeneity}$ = 0.642, P = 0.034, I^2 = 0), but not in advanced prostate cancer (allelic comparison: random-effects OR = 1.07, 95% CI = 0.73-1.57, $P_{heterogeneity}$ = 0.003, P = 0.731, I^2 = 70.0; recessive genetic model: random-effects OR = 1.10, 95% CI = 0.69-1.75, $P_{heterogeneity}$ = 0.005, P = 0.685, I^2 = 67.9).

Publication bias

The Egger's test and Begg's funnel plot were performed to evaluate the literatures' publication bias. The shape of the funnel plots seemed asymmetrical in allelic comparison for VDR BsmI polymorphism, suggesting no publication bias (**Figure 3**). Egger's test was also carried out to assess the publication bias to provide statistical evidence of funnel plot symmetry, and result did not reveal evidence of publication bias (**Table 3**).

Discussion

Genetic susceptibility of cancers has led to growing attention to polymorphisms in genes involved in the pathogenesis of carcinogenesis. Accumulating evidence demonstrates that low level of vitamin D was a risk factor for prostate cancer and the development and progression of PCa were affected by vitamin D synthesis [38-40]. The vitamin D receptor, the significant regulator in vitamin D pathway, could mediate conversion of serum 25(OH)D into the active hormone 1,25-dihydroxyvitamin D and regulate the downstream transcription of various target

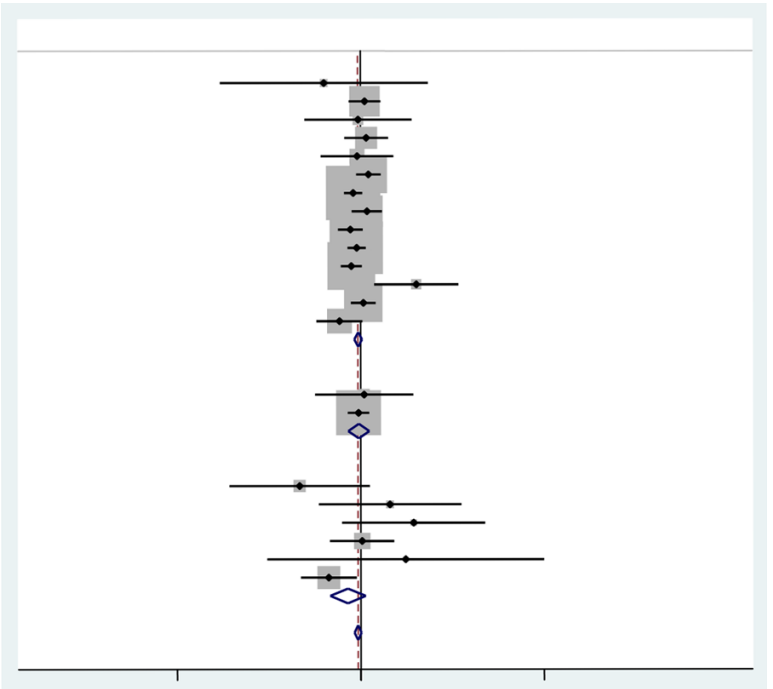

Figure 2. Association between the VDR BsmI gene polymorphism and prostate cancer (PCa) in subgroup analysis by source of control (under homozygote comparison). The area of the *squares* reflects the weight. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The *diamond* corresponds to the summary OR and 95% CI.

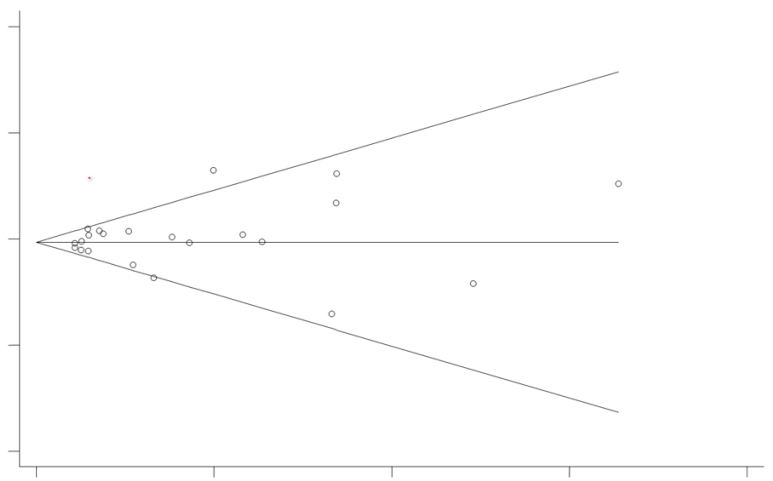

Figure 3. Begg's funnel plot for publication bias test (b-allele vs. B-allele). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size.

genes [41]. Therefore, polymorphism of the VDR BsmI, encoding key proteins in vitamin D metabolism, have been considered as candidate gene for prostate cancer susceptibility [42]. Nowadays, there is a growing number of publications evaluate the polymorphic variants of VDR BsmI gene in prostate cancer susceptibility [43, 44]. Nevertheless, the association between this variant and prostate cancer risk is still inconclusive. The goal of the meta-analysis was to combine results from previous research to achieve summary conclusions, which is useful when individual studies may have been too small to yield a valid conclusion. In addition, our meta-analysis revealed new information regarding the association of VDR BsmI polymorphism with prostate cancer.

Ethnicity is a significant biological factor, which may influence the VDR functions by gene-gene interactions. When all the eligible manuscripts pooled into meta-analysis, no obvious association of the VDR BsmI polymorphism and prostate cancer risk was indicated. However, in subgroup analysis by ethnicity, positive association was observed in Caucasian descendants (under dominant genetic model) but not in Asian descendants African-Americans and mixed descendants. Furthermore, no obvious association was observed in population-based, hospital-based and BPH-based studies. In addition, in the subgroup analysis by tumor stage, there is a positive association between this variant and localized prostate cancer under allelic comparison and recessive genetic model, which indicated that VDR BsmI polymorphism may play different role in various races. Nevertheless, some challenges may limit the generalization of these results. First, the diversity of ethnic backgrounds was limited with only one publication included information on clinical stage in Caucasian descendants. Second, some other risk factors including

Table 3. Publication bias tests (Begg's funnel plot and Egger's test) for VDR BsmI polymorphism in prostate cancer

Compared genotype model	Begg's test		Egger's test	
	z-value	*p*-value	t-value	*p*-value
Allelic contrast	1.47	0.143	1.03	0.317
Homozygote comparison	1.07	0.284	0.81	0.429
Heterozygote comparison	1.24	0.215	0.93	0.365
Dominant genetic model	1.07	0.284	0.90	0.378
Recessive genetic model	0.79	0.430	0.96	0.351

smoking exposure, age, drinking, and family history were absent in the present study. Although we attempted to evaluate the effect of VDR BsmI polymorphism on the susceptibility in different risk factors of prostate cancer, the available data were too limited. Third, positive findings tend to be published more quickly than 'negative' findings, which creating a time-lag bias [45]. Fourth, combined interaction of multiple gene or environmental factors may predominate in the development or metastasis of prostate cancer, which is beyond the detection capacity of present analysis.

Despite the limitations, the pooled analysis involves some key advantages while compared with individual case-control studies. First, the substantial number of cases and control subjects were extracted from various studies, which can significantly increase the statistical power. Second, the quality of case-control studies in this analysis was satisfactory based on the selection criteria. Third, no significant publication bias was observed through qualitative funnel plot, suggesting that the conclusions are relatively stable and did not influence the results of the previous analysis. In addition, studies using male with benign prostatic hyperplasia (BPH) as controls were enrolled. The reason was based on the assumption that BPH is a benign disease with a similar probability for developing prostate cancer compared with normal prostate tissues. Previous published studies have identified no evidence concerning the association of increased BPH risk with this variant [46, 47]. Furthermore, the genotype distribution of control population met Hardy-Weinberg equilibrium in 15 of all the studies.

In conclusion, this meta-analysis demonstrated that VDR BsmI variant may contribute to the risk of developing prostate cancer in the Caucasian population, but not with other descendants. However, no association was identified in the overall analysis when all eligible studies were pooled into analysis. Therefore, future well-designed large studies, particularly referring to gene-environment interactions, are warranted. These studies should lead to a more comprehensive conclusion of the association between VDR BsmI polymorphism and prostate cancer susceptibility.

Disclosure of conflict of interest

None.

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