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ORIGINAL RESEARCH

Lack of association between the risk of prostate cancer and vitamin D receptor *Bsm I* polymorphism: a meta-analysis of 27 published studies

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Background: The association between vitamin D receptor gene *Bsm I* (rs1544410) polymorphism and prostate cancer (PCa) risk has been investigated by numerous previous studies, which yielded inconsistent results. We conducted this meta-analysis to derive a relatively precise description of this association.

Methods: All studies published up to December 2017 were identified via a systematic search of PubMed, Embase, and China National Knowledge Infrastructure databases. Pooled odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated to describe the strength of the relationship between *Bsm I* and PCa risk.

Results: In this meta-analysis, 27 studies with 9,993 cases and 9,345 controls were included. The pooled results revealed that *Bsm I* polymorphism was not associated with PCa risk in the overall analysis. Moreover, no significant relationship was found in the subgroup analyses by ethnicities, genotyping methods, Hardy–Weinberg equilibrium status, and Gleason score. In the stratified analysis by the source of controls and clinical stages, controls of benign prostatic hyperplasia (BPH) seemed to be in the particular groups in which the association of PCa risk with *Bsm I* polymorphism was significant (Bb vs. bb: OR=0.643, 95% CI=0.436–0.949, p=0.026; BB/Bb vs. bb: OR=0.627, 95% CI=0.411–0.954, p=0.029; B vs. b: OR=0.715, 95% CI=0.530–0.965, p=0.029).

Conclusion: Our results suggest that *Bsm I* polymorphism is weakly associated with PCa risk, and hence, it cannot be considered as a predictor of the occurrence and development of PCa in clinical practice. Future studies with a larger number of samples are needed to verify our results.

Keywords: *Bsm I*, prostate cancer, vitamin D receptor, polymorphisms, meta-analysis

Introduction

According to a recent report published in the *CA: A Cancer Journal for Clinicians* in January, 164,690 new prostate cancer (PCa) cases and 29,430 PCa-related deaths were estimated in Americans in 2015.[1] PCa has risen to the first place among new cancer cases, and become the second leading cause of cancer-related deaths in males.[1] To make matters worse, the global prevalence rate of PCa is rising rapidly. It is forecasted that by 2030, the number of newly diagnosed PCa cases and deaths will rise up to more than 1.8 million and 0.5 million, respectively.[2] Existing evidence suggests that PCa risk might increase due to multiple factors, including aging, genetic factors, pathological changes, diet, hormonal level, as well as ethnicity and environment.[3] However, the pathophysiological mechanism of PCa remains largely unclear.

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In a laboratory investigation, prostate cell division and growth was reported to be affected by vitamin D.[4] Thus, low plasma levels of vitamin D were hypothesized to be one of the important contributors to PCa.[4] The clinical trial also found that pre-diagnostic serum levels of vitamin D >85 nmol/L may improve survival in men with PCa.[5] The action of vitamin D is mediated by vitamin D receptor (*VDR*).[6] 1,25-Dihydroxy vitamin D3 ($1,25(OH)_2D_3$), which is one of the active forms of vitamin D, would combine with *VDR* to form a heterodimer complex. Subsequently, the complex binds to vitamin D response element inducing reduced transcriptional levels of many genes which then stimulates tumor cell growth and differentiation.[7,8]

In recent years, the association between PCa risk and some single-nucleotide polymorphisms of *VDR* gene has become the focus of research attention.[9] We also conducted a meta-analysis on *Taq I* and *Fok I* polymorphisms and their relationships with PCa risk.[7] *Bsm I* polymorphism (rs1544410) is one of the most frequently researched variants. It is a restriction site located in intron 8 of *VDR* gene, which does not affect the amino acid sequence during VDR protein expression.[10] However, mutations in the intron region might be able to lower the stability of mRNA and affect the mRNA levels. Numerous research has revealed that *Bsm I* mutation might play a significant role in the development or progression of PCa.[11–14] However, some other studies do not support this association.[15–18] These results are inconsistent and worth further exploration. In addition, previous meta-analyses[10,19–22] seemed to be out of date due to availability of new data.[3,9,14,23,24] Therefore, we performed a new meta-analysis with the aim of obtaining more accurate and updated results.

Methods

Literature retrieval strategy

PubMed, Embase, and China National Knowledge Infrastructure (CNKI) electronic databases were searched for eligible studies published till December 2017. The terms "*VDR*/vitamin D receptor", "prostate cancer/tumor/carcinoma", and "polymorphism/mutation/variant" were used for searching titles or abstracts. Full search expressions were "vitamin D receptor [Title/Abstract] AND ((polymorphism [Title/Abstract] OR mutation [Title/Abstract]) OR variant [Title/Abstract]) AND prostate cancer [Title/Abstract]" for PubMed, "'vitamin d receptor':ab,ti AND 'polymorphism':ab,ti AND 'prostate cancer':ab,ti" for Embase, and "vitamin D receptor AND polymorphism AND prostate cancer" in Chinese for CNKI. In addition, we read the original or review reports carefully and searched manually for more eligible literature based on their references.

Study selection

Candidate studies were evaluated by two authors independently (Lei Wang and Jian Liu) for the following inclusion criteria: (1) studies in nonfamilial case–control or nested case–control design conducted on human beings; (2) studies that assessed the relationship between *Bsm I* polymorphism and risk or progression of PCa; (3) studies in which the distribution frequency of genotype and allelic profile of participants could be acquired or calculated; (4) studies in which no significant difference was reported between cases and controls in the aspect of baseline characters; (5) studies that scored more than 5 points on the Newcastle–Ottawa Scale (NOS).

Data extraction

Two investigators (Lei Wang and Jian Liu) collected the following information independently: first author's name, publication year, population information, genotyping methods, the number of participants, genotype and allelic profile, as well as the source of controls. Cases and controls were classified into different subgroups by ethnicity, source of controls, and genotyping method, respectively. The subjects were also divided into group with Gleason score <7 and group with Gleason score ≥7 by pathological grade, and localized group and aggressive group by clinical stages, respectively. Any controversial content was discussed and evaluated by a third reviewer (Yansheng Zhao) to reach an agreement on all the items.

Statistical analyses

The heterogeneity was evaluated by using χ^2-test based on Cochran's Q-test and I^2 statistics. If I^2>50% and p<0.05, the heterogeneity between studies was significant and the random-effects model was used to combine the values from single studies;[25] otherwise, in the absence of heterogeneity, the fixed-effects model was chosen. The pooled odds ratios (ORs), together with 95% confidence intervals (CIs), were calculated to assess the strength of the relationship. The statistical significance of ORs was determined with Z-test. Five genetic comparison models were calculated in our analysis, including homozygote model (BB vs. bb), heterozygous model (Bb vs. bb), dominant model (BB vs. Bb/bb), recessive model (BB/Bb vs. bb), and allele genetic model (B vs. b allele). Begg's funnel plot and Egger's linear regression were used to evaluate the potential publication

bias. Sensitivity analysis was performed to evaluate the stability of pooled results. Moreover, the Hardy–Weinberg equilibrium (HWE) status of controls was recalculated with the goodness-of-fit χ^2-test; $p<0.05$ indicated that the genotype frequency of controls was not consistent with HWE.

For each outcome, we also conducted subgroup analyses by ethnicity, the source of controls, genotyping method, and clinical stages. *p*-values were two-sided, and $p<0.05$ was considered statistically significant. All analyses were done using the STATA package version 12.0 (Stata Corp, College Station, TX, USA).

Results

Characteristics of studies

A total of 87 studies were identified to be potentially related to the topic through our search strategy. Following our inclusion criteria, 27 studies[3,9,11–17,23,24,26–41] published between the years 1998 and 2017 were finally included to evaluate the association (Figure 1). As shown in Table 1, out of the 27 studies, 25 explored the relationship of PCa risk with *Bsm I*, and nine were about the association between PCa progression and *Bsm I*. The number of participants in the case group and control group varied from 28 to 1,034, and 30 to 1,566, respectively. For all studies, except five, the genotype distribution frequency of *Bsm I* polymorphism in the control groups conformed to the HWE. All the studies scored more than 5 on the NOS, and were considered to be of high quality (Table 1).

Heterogeneity

Obvious heterogeneity between the studies was found in overall analysis for some genetic comparison models (Bb vs. bb: $p=0.000$, $I^2=59.2\%$; BB/Bb vs. bb: $p=0.000$, $I^2=65.9\%$; and B vs. b: $p=0.000$, $I^2=65.8\%$) (Tables 2–6). Thus, the random-effects model was chosen for data analysis in these comparison models. Meanwhile, in the recessive model, no heterogeneity was detected (BB vs. Bb/bb: $p=0.285$, $I^2=12.5\%$), and the fixed-effects model was used. Similar results were found in the subgroup analyses.

Pooled results in terms of PCa risk with Bsm I polymorphism

The results of the overall analysis obtained by pooling all the 25 studies are shown in Table 2 and Figure 2. These results indicate that *Bsm I* mutation does not increase the risk of PCa under different comparison models (BB vs. bb: OR=0.977, 95% CI=0.889–1.074, $p=0.634$; Bb vs. bb: OR=0.940, 95% CI=0.825–1.072, $p=0.357$; BB/Bb vs. bb: OR=0.951, 95% CI=0.832–1.087, $p=0.462$; BB vs. Bb/bb: OR=1.002, 95% CI=0.923–1.087, $p=0.963$; B vs. b: OR=0.969, 95% CI=0.883–1.065, $p=0.516$) (Table 2).

In the subgroup analyses conducted for a more detailed evaluation of the relationship, the results did not reveal any association by different ethnicities (Table 3), different genotyping methods (Table 4), or different HWE statuses of control groups (results not shown).

As shown in Figure 3 and Table 5, in the stratified analysis by the source of control groups, the PCa risk was significantly

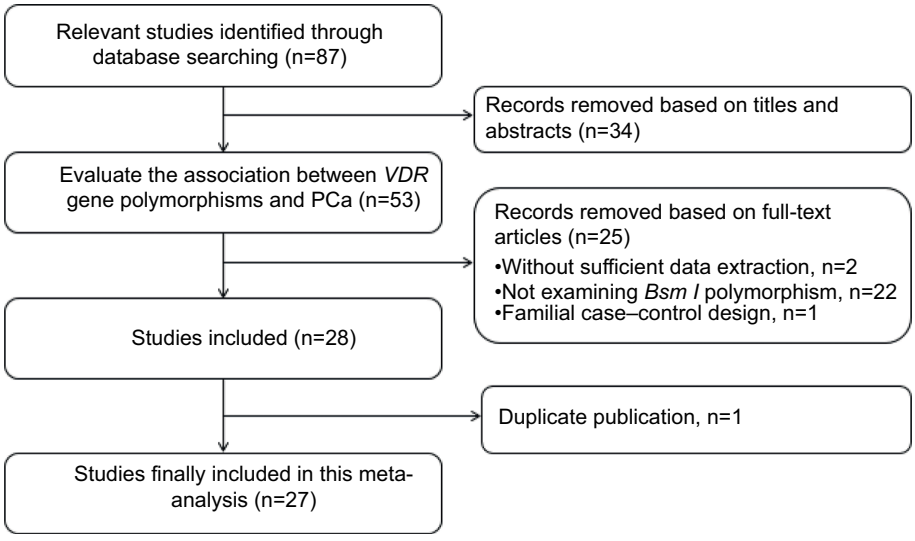

Figure 1 Flowchart showing the process of selection of the final 27 studies.
Abbreviation: PCa, prostate cancer.

Table 1 Characteristics and quality assessment of the studies included in this meta-analysis

Author	Year	Country	Ethnicity	Genotyping method	Source of controls	Sample size (cases/controls)	HWE	NOS
Bai et al[11]*	2009	People's Republic of China	Asian	PCR-RFLP	HB	122/130	Y	6
Chaimuangraj et al[15]	2006	Thailand	Asian	PCR-RFLP	HB/BPH	28/30/44	N/N	5
Chen et al[26]	2001	People's Republic of China	Asian	PCR-RFLP	HB	95/103	Y	5
Cheteri et al[27]*	2004	USA	Caucasian	PCR-RFLP	PB	543/510	N	6
Chokkalingam et al[16]*	2001	People's Republic of China	Asian	PCR-RFLP	PB	161/297	N	6
Cicek et al[28]*	2006	USA	Mixed	PCR-RFLP	PB	493/479	Y	7
El Ezzi et al[24]	2014	Lebanon	Asian	PCR-RFLP	BPH	50/68	N	5
El Ezzi et al[23]	2017	Lebanon	Asian	PCR-RFLP	PB	50/79	Y	6
Habuchi et al[12]	2000	Japan	Asian	PCR-RFLP	PB/BPH	222/326/209	Y/Y	8
Hayes et al[17]	2005	Australia	Caucasian	PCR-RFLP	PB	812/713	Y	8
Holick et al[29]	2007	USA	Caucasian	SNPlex	PB	590/541	Y	8
Holt et al[30]	2009	USA	Mixed	SNPlex	PB	795/767	Y	8
Huang et al[13]*	2004	People's Republic of China	Asian	PCR-RFLP	PB	160/205	N	6
Jingwi et al[9]	2015	USA	African	TaqMan	HB	278/71	Y	7
Li et al[31]	2007	USA	Caucasian	PCR-RFLP	PB	1034/1566	Y	8
Liu et al[32]	2003	People's Republic of China	Asian	HPLC	PB	103/106	Y	7
Ma et al[33]	1998	USA	Caucasian	PCR-RFLP	PB	372/591	Y	7
Mikhak et al[34]	2007	USA	Caucasian	TaqMan	PB	646/669	Y	7
Nam et al[35]	2003	Canada	Mixed	PCR-RFLP	HB/BPH	483/548/256	N/Y	7
Nunes et al[14]*	2016	Brazil	Caucasian	PCR-RFLP	PB/BPH	132/169/41	Y/Y	7
Oakley-Girvan et al[36]	2004	USA	Mixed	PCR-RFLP	PB	345/292	Y	7
Oh et al[3]	2014	South Korea	Asian	SNPlex	BPH	272/173	Y	6
Onen et al[37]	2008	Turkey	Caucasian	PCR-RFLP	PB	133/157	Y	7
Suzuki et al[38]*	2003	Japan	Asian	PCR-RFLP	HB	81/105	Y	6
Szendroi et al[39]	2011	Hungary	Caucasian	PCR-RFLP	PB	204/102	Y	7
Chen et al[40]*	2009	UK	Caucasian	TaqMan	HB	Gleason score <7/≥7 1104/449 Localized/Advanced 1356/197	Y	7
Williams et al[41]*	2004	USA	Mixed	TaqMan	HB	Gleason score <7/≥7 159/267 (Caucasian) and 102/208 (African)	Y	7

Note: *These studies evaluated the association between *Bsm I* and PCa progression by different clinical stage or Gleason score. In the Sample size column the three numbers were case/HB/BPH as it has two control groups.
Abbreviations: HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa Scale; HB, hospital-based; BPH, benign prostate hyperplasia; PB, population-based; N, non-HWE; Y, HWE.

increased in patients with bb genotype or b genotype specifically in the subgroup of benign prostatic hyperplasia (BPH) controls (Bb vs. bb: OR=0.689, 95% CI=0.534–0.890, p=0.004; BB/Bb vs. bb: OR=0.627, 95% CI=0.411–0.954, p=0.029; B vs. b: OR=0.715, 95% CI=0.530–0.965, p=0.029). However, the results for the other two control groups revealed no significant association (Table 5).

Pooled results in terms of Bsm I polymorphism with PCa progression

Stratified analyses, according to the clinical stages and Gleason score of patients, were also performed. As shown in Table 6, the pooled results for the patients with Gleason score <7 and Gleason score ≥7 did not reveal any relationship between the *Bsm I* variant and PCa risk in various genetic models compared to controls. Similarly, the subgroup of PCa cases with localized stage and aggressive stage showed no association.

In the inter-patient comparisons by different clinical stages and Gleason score statuses, a weak influence of *Bsm I* polymorphism on PCa progression was detected in patients with Gleason score ≥7 compared to the group with Gleason score <7 (BB/Bb vs. bb: OR=1.176, 95% CI=1.008–1.373, p=0.04). However, no effect of *Bsm I* polymorphism on the clinical stages was detected (Figure 4 and Table 6).

Publication bias and sensitivity analysis

The funnel plots for publication bias analysis did not show any significant asymmetry in the overall analysis (Figure 5).

Table 2 Results of the association between *Bsm I* polymorphism and PCa risk in the whole population

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	*Z*-score	*p*-value	I^2 (%)	*p*-value	Begg's test	Egger's test
BB vs. bb	25	0.977 (0.889–1.074)	0.48	0.634	48.5	0.005	0.874	0.901
Bb vs. bb	25	0.940 (0.825–1.072)	0.92	0.357	59.2	0	0.126	0.013
BB/Bb vs. bb	25	0.951 (0.832–1.087)	0.74	0.462	65.9	0	0.229	0.042
BB vs. Bb/bb	25	1.002 (0.923–1.087)	0.05	0.963	12.3	0.293	0.853	0.824
B vs. b	25	0.969 (0.883–1.065)	0.65	0.516	65.8	0	0.913	0.229

Abbreviations: PCa, prostate cancer; OR, odds ratio; CI, confidence interval.

Table 3 Results of the association between *Bsm I* polymorphism and PCa risk by different ethnicities

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	*Z*-score	*p*-value	I^2 (%)	*p*-value	Begg's test	Egger's test
Asian								
BB vs. bb	11	1.075 (0.625–1.850)	0.26	0.793	26.7	0.207	1	0.945
BB vs. bb	11	0.884 (0.592–1.320)	0.6	0.546	65.9	0.001	0.484	0.253
BB/Bb vs. bb	11	0.913 (0.612–1.362)	0.45	0.656	69.9	0	0.392	0.371
BB vs. Bb/bb	11	1.125 (0.756–1.675)	0.58	0.562	0.0	0.618	0.677	0.987
B vs. b	11	0.957 (0.686–1.334)	0.26	0.794	70.0	0	0.938	0.481
Caucasian								
BB vs. bb	11	0.975 (0.812–1.172)	0.26	0.791	58.2	0.008	0.815	0.875
Bb vs. bb	11	0.970 (0.840–1.120)	0.42	0.675	60.0	0.005	0.186	0.215
BB/Bb vs. bb	11	0.975 (0.839–1.134)	0.33	0.743	67.8	0.001	0.392	0.366
BB vs. Bb/bb	11	0.995 (0.904–1.094)	0.11	0.913	31.7	0.146	0.938	0.835
B vs. b	11	0.981 (0.887–1.085)	0.37	0.711	67.2	0.001	0.938	0.649
African								
BB vs. bb	3	1.131 (0.316–4.055)	0.19	0.85	83.1	0.003	0.117	0.137
Bb vs. bb	3	1.131 (0.544–2.349)	0.33	0.742	71.3	0.031	0.602	0.212
BB/Bb vs. bb	3	1.155 (0.509–2.622)	0.34	0.731	79.7	0.007	0.602	0.273
BB vs. Bb/bb	3	1.021 (0.670–1.555)	0.1	0.924	63.7	0.064	0.602	0.578
B vs. b	3	1.015 (0.592–1.738)	0.05	0.957	80.6	0.006	0.117	0.228

Abbreviations: PCa, prostate cancer; OR, odds ratio; CI, confidence interval.

Table 4 Results of the association between *Bsm I* polymorphism and PCa risk by different genotyping methods

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	*Z*-score	*p*-value	I^2 (%)	*p*-value	Begg's test	Egger's test
PCR-RFLP								
BB vs. bb	16	0.979 (0.730–1.313)	0.14	0.877	60.7	0.001	0.528	0.742
BB vs. bb	16	0.976 (0.784–1.215)	0.22	0.826	68.1	0	0.528	0.758
BB/Bb vs. bb	16	0.987 (0.789–1.235)	0.11	0.91	73.7	0	0.510	0.513
BB vs. Bb/bb	16	0.987 (0.861–1.132)	0.19	0.853	35.7	0.077	0.510	0.513
B vs. b	16	0.995 (0.842–1.176)	0.06	0.951	74.4	0	0.510	0.569
TaqMan								
BB vs. bb	3	1.041 (0.867–1.250)	0.43	0.668	0.0	0.71	0.117	0.126
Bb vs. bb	3	0.957 (0.838–1.093)	0.65	0.518	0.0	0.948	0.117	0.016
BB/Bb vs. bb	3	0.972 (0.859–1.100)	0.45	0.656	0.0	0.84	0.117	0.48
BB vs. Bb/bb	3	1.031 (0.893–1.191)	0.42	0.677	0.0	0.689	0.117	0.48
B vs. b	3	0.998 (0.918–1.084)	0.06	0.954	0.0	0.696	0.117	0.316
SNPlex								
BB vs. bb	4	0.960 (0.786–1.171)	0.41	0.685	13.1	0.327	0.497	0.501
Bb vs. bb	4	0.852 (0.671–1.082)	1.31	0.19	54.9	0.064	0.497	0.492
BB/Bb vs. bb	4	0.854 (0.677–1.078)	1.33	0.184	57.0	0.054	0.624	0.427
BB vs. Bb/bb	4	0.990 (0.857–1.143)	0.14	0.888	0.0	0.861	0.624	0.513
B vs. b	4	0.918 (0.796–1.060)	1.17	0.243	50.5	0.089	0.070	0.126

Abbreviations: PCa, prostate cancer; OR, odds ratio; CI, confidence interval.

Table 5 Results of the association between *Bsm I* polymorphism and PCa risk by different sources of controls

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	*Z*-score	*p*-value	I^2 (%)	*p*-value	Begg's test	Egger's test
Population-based								
BB vs. bb	17	0.963 (0.809–1.147)	0.42	0.675	48.5	0.016	0.653	0.737
Bb vs. bb	17	0.910 (0.779–1.065)	1.18	0.24	69.5	0	0.510	0.599
BB/Bb vs. bb	17	0.920 (0.787–1.075)	1.05	0.294	73.0	0	0.742	0.656
BB vs. Bb/bb	17	1.004 (0.909–1.109)	0.08	0.937	14.0	0.293	0.928	0.961
B vs. b	17	0.950 (0.850–1.062)	0.9	0.368	71.9	0	1	0.968
Hospital-based								
BB vs. bb	6	0.951 (0.505–1.790)	0.15	0.877	43.1	0.118	0.573	0.973
BB vs. bb	6	1.016 (0.600–1.721)	0.06	0.953	70.6	0.005	0.573	0.782
BB/Bb vs. bb	6	1.026 (0.607–1.732)	0.1	0.924	75.0	0.001	0.851	0.858
BB vs. Bb/bb	6	1.015 (0.806–1.279)	0.13	0.879	30.9	0.204	0.573	0.969
B vs. b	6	1.035 (0.666–1.607)	0.15	0.879	78.1	0	0.851	0.906
BPH								
BB vs. bb	6	0.515 (0.239–1.108)	1.7	0.09	67.7	0.015	0.624	0.287
Bb vs. bb	6	**0.689 (0.534–0.890)**	2.86	0.004	42.8	0.12	0.573	0.325
BB/Bb vs. bb	6	**0.627 (0.411–0.954)**	2.18	0.029	56.7	0.042	0.573	0.27
BB vs. Bb/bb	6	0.842 (0.649–1.093)	1.29	0.197	28.6	0.231	1	0.385
B vs. b	6	**0.715 (0.530–0.965)**	2.19	0.029	59.1	0.032	0.573	0.379

Note: Bold values indicate statistical significance.
Abbreviations: PCa, prostate cancer; OR, odds ratio; CI, confidence interval; BPH, benign prostatic hyperplasia.

Moreover, Begg's and Egger's tests also revealed no publication bias in overall analysis as well as subgroup analyses (Tables 2–6). Sensitivity analysis for the positive results suggested that no obvious change in the pooled results was detected by omitting each individual study for the subgroup analysis of BPH controls, while the results were unstable in the comparison of PCa cases in terms of Gleason scores (Figure 6).

Discussion

Polymorphisms of *VDR* gene and their relationships with PCa susceptibility have drawn a lot of attention in recent years. *Bsm I* polymorphism is one of the "star biomarkers". Even though *Bsm I* polymorphism is located in the noncoding regions of *VDR* gene, it is frequently considered to be associated with PCa risk by numerous studies.[9,11,12,39] Meanwhile, some studies support the opposite conclusion.[15,16,30,34] Five meta-analyses conducted by Yin et al,[19] Zhang et al,[20] Guo et al,[21] Xu et al,[22] and Liu et al,[10] including 14, 19, 19, 15, and 6 primary studies, respectively, also yielded conflicting results. Moreover, some new data were reported.[3,9,14,23,24] Therefore, a new meta-analysis is necessary to clarify this issue. In the present study, data of 27 independent studies including 9,993 cases and 9,345 controls, which is higher compared to the previous meta-analyses, were pooled. Therefore, our updated results will be more convincing and stringent.

According to our results, no association between PCa risk and *Bsm I* polymorphism was detected in the overall population, which was similar to the results reported by Guo et al,[21] Liu et al,[10] and Xu et al,[22] but different from the other two meta-analyses.[19,20] As we mentioned above, the results of previous meta-analyses might be suspect due to outdated data or inclusion of incomplete studies. Ethnicity might be an important biological factor for the genetic difference.[42] The genotype frequency distribution of *Bsm I* was found to be different between Asians, Caucasians and Africans, but in each subgroup by ethnicity, no association was found. In addition, subgroup analyses by the genotyping method and HWE status both revealed no influence of *Bsm I* on PCa risk, suggesting that these two variables would not change the negative result of the overall analysis either.

An interesting finding was that according to the results of the subgroup analysis by different sources of controls, *Bsm I* mutation increased the risk of PCa in BPH controls in the heterozygote model, recessive model, and allele model. Moreover, this result was proved to be robust by sensitivity analysis, and the heterogeneity was found to be acceptable as well. Based on this result, for individuals with BPH, the bb genotype or b might increase the risk of PCa, however, this result was suspicious and difficult to explain. Age was reported to be a risk factor for the relationship between *Bsm I* mutation and PCa risk.[26,35] We intended to perform a subgroup meta-analysis by age, but the age classification in the included studies was too ambiguous to be pooled.

Similar to overall analysis, subgroup analyses by clinical stage and Gleason score revealed no relationship between

Table 6 Results of the association between *Bsm I* polymorphism and PCa risk by different tumor stages

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	*Z*-score	*p*-value	I^2 (%)	*p*-value	Begg's test	Egger's test
Gleason score <7 (cases vs. controls)								
BB vs. bb	6	1.095 (0.490–2.449)	0.22	0.824	74.8	0.001	0.851	0.4
Bb vs. bb	6	1.051 (0.848–1.304)	0.46	0.649	28.6	0.22	0.573	0.072
BB/Bb vs. bb	6	0.942 (0.612–1.450)	0.27	0.787	69.4	0.006	0.348	0.147
BB vs. Bb/bb	6	1.097 (0.572–2.106)	0.28	0.78	66.8	0.01	0.851	0.426
B vs. b	6	0.957 (0.635–1.443)	0.21	0.835	81.1	0	0.573	0.193
Gleason score ≥7 (cases vs. controls)								
BB vs. bb	6	0.873 (0.607–1.253)	0.74	0.46	0.0	0.429	0.573	0.899
Bb vs. bb	6	0.787 (0.609–1.017)	1.83	0.067	55.3	0.048	0.348	0.15
BB/Bb vs. bb	6	0.742 (0.470–1.171)	1.28	0.2	63.1	0.019	0.039	0.191
BB vs. Bb/bb	6	0.920 (0.662–1.279)	0.48	0.621	0.0	0.483	0.851	0.874
B vs. b	6	0.793 (0.540–1.163)	1.19	0.235	69.2	0.006	0.091	0.253
Localized (cases vs. controls)								
BB vs. bb	6	0.855 (0.632–1.158)	1.01	0.312	47.9	0.088	0.851	0.478
Bb vs. bb	6	0.793 (0.627–1.003)	1.93	0.053	0.0	0.78	0.188	0.19
BB/Bb vs. bb	6	0.818 (0.661–1.012)	1.85	0.065	0.0	0.504	0.348	0.216
BB vs. Bb/bb	6	0.923 (0.701–1.215)	0.57	0.567	45.7	0.101	0.851	0.443
B vs. b	6	0.874 (0.748–1.022)	1.69	0.092	42.8	0.12	0.188	0.22
Aggressive (cases vs. controls)								
BB vs. bb	6	0.709 (0.461–1.092)	1.56	0.118	0.0	0.637	0.573	0.339
Bb vs. bb	6	0.753 (0.559–1.014)	1.87	0.062	54.7	0.051	0.348	0.466
BB/Bb vs. bb	6	0.693 (0.416–1.155)	1.41	0.159	54.9	0.05	0.851	0.799
BB vs. Bb/bb	6	0.785 (0.530–1.164)	1.20	0.229	0.0	0.685	0.851	0.323
B vs. b	6	0.711 (0.459–1.101)	1.53	0.127	56.7	0.042	0.573	0.603
Gleason score ≥7 vs. <7								
BB vs. bb	8	1.207 (0.962–1.514)	1.63	0.103	53.8	0.043	0.548	0.632
Bb vs. bb	8	1.166 (0.989–1.375)	1.82	0.068	18.0	0.288	0.266	0.684
BB/Bb vs. bb	8	**1.176 (1.008–1.373)**	2.06	0.040	39.3	0.117	0.536	0.763
BB vs. Bb/bb	8	1.131 (0.919–1.392)	1.16	0.246	51.1	0.056	1	0.833
B vs. b	8	1.163 (0.928–1.457)	1.31	0.191	59.9	0.015	0.536	0.901
Aggressive vs. localized								
BB vs. bb	7	0.946 (0.692–1.295)	0.34	0.731	22.0	0.268	0.133	0.054
Bb vs. bb	7	0.971 (0.765–1.231)	0.806	0.25	23.0	0.254	0.368	0.338
BB/Bb vs. bb	7	0.984 (0.790–1.226)	0.14	0.887	4.0	0.396	0.035	0.031
BB vs. Bb/bb	7	0.966 (0.727–1.284)	0.24	0.812	23.7	0.256	0.133	0.071
B vs. b	7	0.981 (0.839–1.147)	0.24	0.808	26.9	0.224	0.035	0.001

Note: Bold values indicate statistical significance.
Abbreviations: PCa, prostate cancer; OR, odds ratio; CI, confidence interval.

PCa risk and *Bsm I*. Moreover, we conducted inter-patient analysis to assess the relationship of *Bsm I* polymorphism with PCa progression by comparing cases with aggressive stage and Gleason score ≥7 to cases with localized stage and Gleason score <7, respectively. Almost all the results were negative, except for the comparison between cases with Gleason score ≥7 and <7 in the recessive model. However, the only positive result was not stable in sensitivity analysis. Therefore, we have ignored the weak relationship.

Regrettably, we failed to perform a subgroup analysis by vitamin D intake, because only two primary studies have a detailed description of the effect of plasma vitamin D levels on the association between *Bsm I* and PCa risk. Ma et al reported that in patients with low levels of 25-D, which is one of the vitamin D metabolites, the PCa risk would be significantly increased by carrying bb genotype.[33] Meanwhile, in the group with high levels of 25-D, the relationship was not significant. Similar results were reported by Ahn et al in 2009.[18] These studies suggest that plasma levels of 25-D might influence our pooled result, and a stratified analysis by vitamin D intake or 25-D levels is warranted in the future.

Significant heterogeneity between studies was detected in both overall analysis and subgroup analyses under multiple comparison models. We noted that the BB genotype in the Asian group was quite rare but very commonly detected in Caucasians and Africans. It may contribute to this heterogeneity.

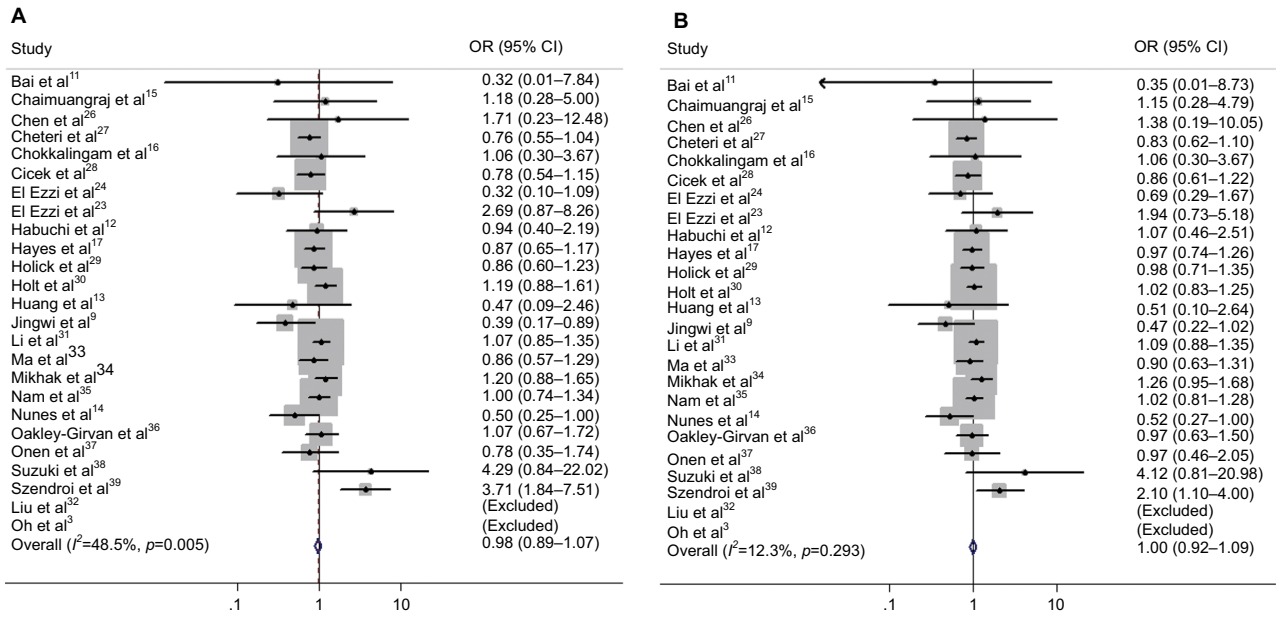

Figure 2 Forest plots to estimate the association of *VDR Bsm I* polymorphism with PCa in the overall analysis. (**A**) Homozygote model (BB vs. bb). (**B**) Recessive model (BB vs. Bb/bb).
Abbreviations: PCa, prostate cancer; OR, odds ratio; CI, confidence interval.

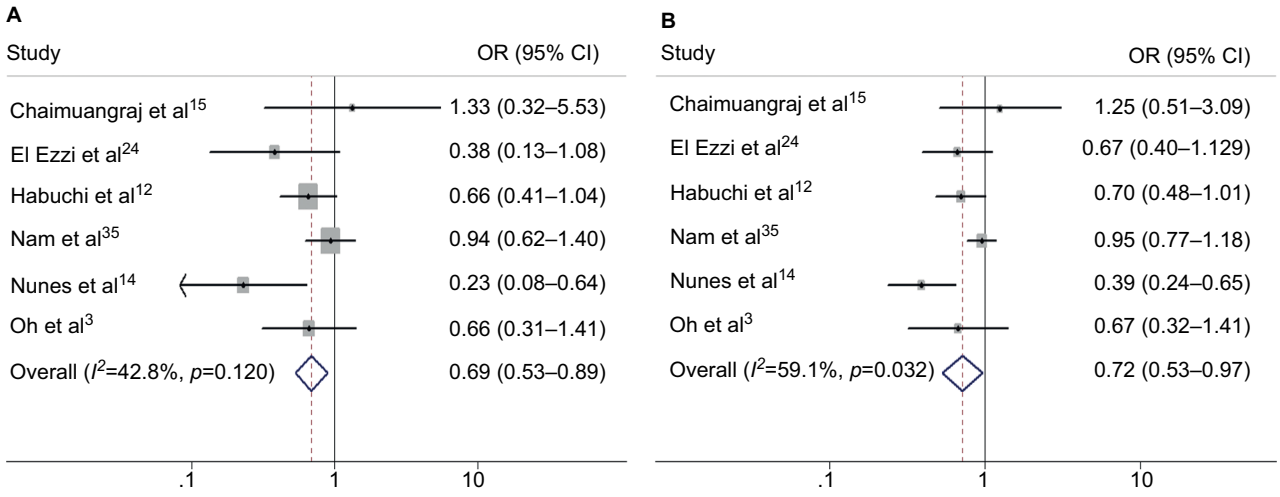

Figure 3 Forest plots to estimate the association of *VDR Bsm I* polymorphism with PCa in the subgroup of BPH controls. (**A**) Heterozygote model (Bb vs. bb). (**B**) Allelic frequency model (B vs. b).
Abbreviations: PCa, prostate cancer; BPH, benign prostatic hyperplasia; OR, odds ratio; CI, confidence interval.

However, no obvious publication bias was found and the sensitivity analysis supported the stability of our results. Overall, the present analysis was credible and statistically valid for the studied population.

However, some limitations of our meta-analysis should be acknowledged. First of all, some reports with a small number of cases and controls were included in our analysis, which increases the statistical power but introduces potential bias and heterogeneity as well. Second, our pooled outcomes were based on the initial results of the included studies, which were not adjusted by patient characteristics and other potential factors, such as age, gender, smoking, alcohol, sunshine, vitamin D intake, and so on. Therefore, a more precise analysis is required, in which the results should be adjusted by some related parameters. Besides, heterogeneity was obviously detected in some pooled results, which cannot be eliminated by subgroup analyses.

In conclusion, the present pooled analysis might be the largest one so far to evaluate the relationship between PCa susceptibility and *Bsm I* polymorphism of *VDR* gene. No increased risk of PCa was detected to be associated with *Bsm I* mutant in the overall analysis, and similarly in different

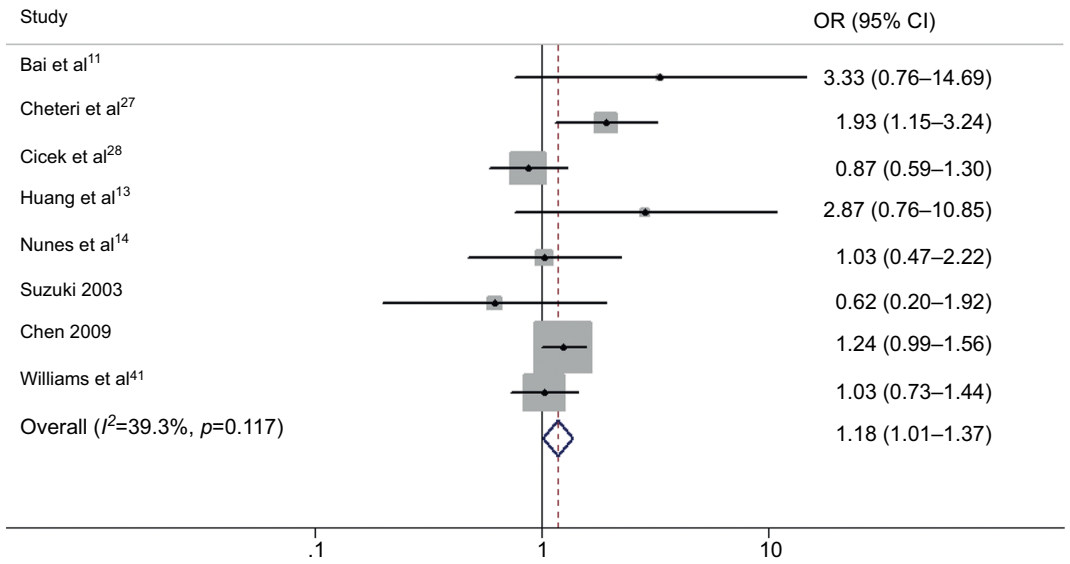

Figure 4 Forest plot to estimate the association of *VDR Bsm I* polymorphism with cases with Gleason score >7 and cases with Gleason score <7 in the dominant model (BB/Bb vs. bb).
Abbreviations: OR, odds ratio; CI, confidence interval.

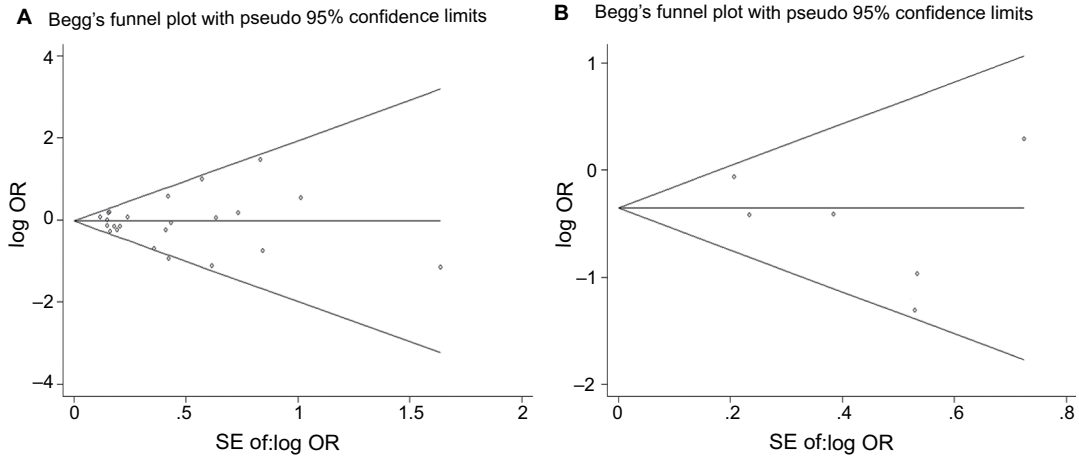

Figure 5 Begg's funnel plots to examine publication bias for reported comparisons of *VDR* gene *Bsm I* polymorphism for the homozygote model in the (**A**) overall analysis and (**B**) the subgroup analysis of BPH controls.
Abbreviations: BPH, benign prostatic hyperplasia; OR, odds ratio.

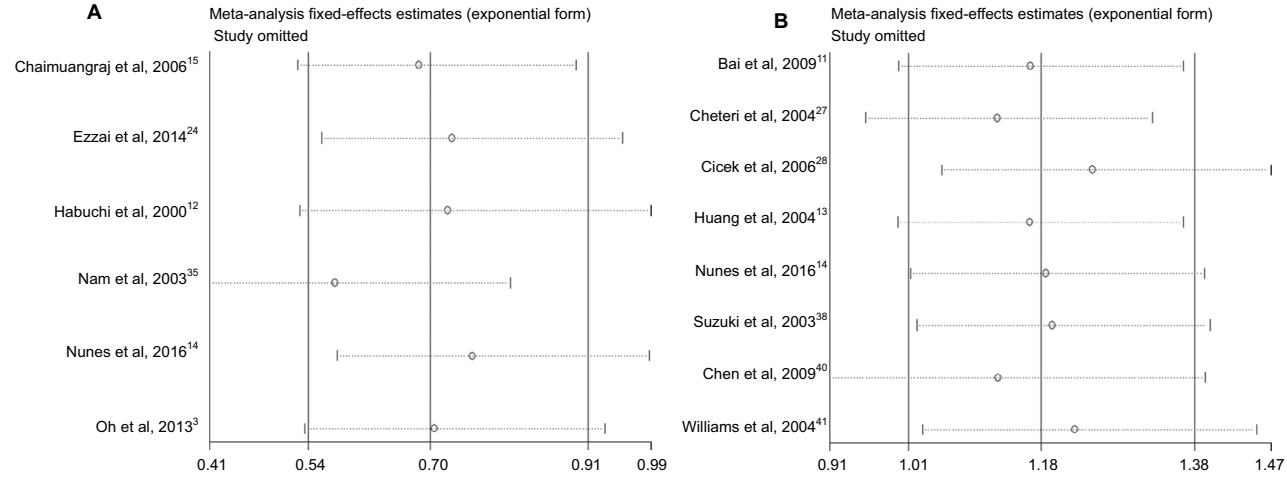

Figure 6 Sensitivity analysis of the (**A**) comparison of PCa cases with BPH controls (Bb vs. bb) and (**B**) comparison of PCa cases with Gleason score >7 vs. <7 (BB/Bb vs. bb).
Abbreviations: PCa, prostate cancer; BPH, benign prostatic hyperplasia.

subgroup analyses by race, genotyping methods, HWE status of controls, and clinical stage and Gleason score of cases. The association between PCa progression and *Bsm I* was also negative. Individuals with BPH, carrying bb genotype and b, seemed to have an increased risk of PCa. More large-scale and well-designed studies are needed in future to demonstrate the weak influence of *Bsm I* mutant on PCa risk and progression.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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