Meta-Analysis

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Association of *VDR* polymorphisms (*Taq* I and *Bsm* I) with prostate cancer: a new meta-analysis

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Abstract

Objective: Prostate cancer is a malignant tumour that poses a serious risk to human health. Epidemiological studies suggest that it may be associated with vitamin D receptor gene (*VDR*) polymorphisms. Previous work investigated potential risks between *Taq* I (rs731236) and *Bsm* I (rs1544410) *VDR* polymorphisms with prostate cancer in humans; however, results are inconsistent.

Methods: We conducted a meta-analysis to retrieve genetic association analyses of rs731236 and rs1544410 polymorphisms with prostate cancer from studies published between 2006–2016. Pooled odds ratios with 95% confidence intervals were used to assess genetic associations, and heterogeneity was assessed by Q and I^2statistics.

Results: Our findings suggest a significant association between rs731236 and prostate cancer risk in Asians and African Americans, but rs1544410 was not associated with prostate cancer under three genetic models.

Conclusion: Future studies including larger sample sizes and the analysis of gene functions are needed to help develop prostate cancer treatment.

Keywords

VDR, polymorphisms, *Taq* I, *Bsm* I, meta-analysis, prostate cancer

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Introduction

Prostate cancer originates from epithelial cells and is a serious threat to human health. Its incidence in China was reported to be 9.92/10 million in 2012, representing the sixth most common male malignant tumour. Similar incidences were also seen in the United States, where 192,000 new cases of

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prostate cancer were reported in 2009 according to the American Cancer Society.[1] In recent years, numerous medical studies have made important progress in the field. Clinical studies showed that the incidence of prostate cancer increases with age, with a high incidence of disease concentrated in individuals 70–80 years of age. However, patients with familial hereditary prostate cancer are usually less than 50 years old.[2] An increased disease incidence is also related to frequent sexual activity, a high-fat diet,[3] race, and regional location.

Molecular biology and epidemiological studies results suggest that the pathogenesis of prostate cancer may be associated with single nucleotide polymorphisms (SNPs) in several genes.[4–8] For example, polymorphisms of the vitamin D receptor gene (*VDR*) are closely associated with prostate cancer. *VDR* is located on human chromosome 12 and encodes the nuclear hormone receptor for vitamin D3.[9,10] VDR is a ligand-dependent nuclear transcription factor, which plays an important role in maintaining calcium metabolism, and regulating cell proliferation and differentiation.[11] Several SNPs have been identified in *VDR* that appear to influence the risk of cancer and other disease,[12,13] including bone mineral density, hyperparathyroidism, and osteomalasia.[14–16] In normal and malignant prostate cells, VDR expression mediates the biological actions of 1,25(OH)2D,[17–19] and polymorphisms in different regions of *VDR* cause different effects. The *Bsm* I (rs1544410) restriction site is in intron 8 of *VDR*; this polymorphism does not affect the amino acid sequence of VDR, but many studies have suggested that it is closely related to prostate cancer risk.[20–23] The *Taq* I (rs731236) polymorphism is a synonymous mutation located in *VDR* exon 9, which is also associated with prostate cancer risk.[20,24–29]

Several studies have investigated the potential risk of *Taq* I (rs731236) and *Bsm* I (rs1544410) polymorphisms on prostate cancer worldwide. However, the results are inconsistent.[30–32] Therefore, we conducted a new meta-analysis to assess the effect of these two SNPs on the risk of prostate cancer.

Materials and methods

Search strategy and data extraction

We carried out a search of the literature to retrieve association analyses of *Taq* I (rs731236) and *Bsm* I (rs1544410) polymorphisms with prostate cancer published between 2006–2016. We searched PubMed, Springer, and ScienceDirect databases using the search terms '*Taq* I (or rs731236)', '*Bsm* I (or rs1544410)', 'prostate cancer', and 'association analysis'. For data extraction, we paid attention to the publication time, country of publication, population information, genetic models used, case and control sample size, and polymorphism genotype and allele frequencies.

Statistical analysis and meta-analysis

We detected allele frequencies by Hardy–Weinberg equilibrium (HWE) using the χ^2 test. Ideally, allele frequencies were stable and unchanged ($P > 0.05$). Heterogeneity was tested for using Q and I^2 statistics, with $P < 0.05$ indicating significant difference. In the absence of heterogeneity, the fixed-effects model was used to calculate the odds ratio (OR) of each study; otherwise the random-effects model was used. The strength of association between *Taq* I (rs731236), *Bsm* I (rs1544410), and prostate cancer was accessed by calculating pooled ORs and 95% confidence intervals (CIs) under additive, dominant, and recessive genetic models. Publication bias was tested by Begg's test and Egger's linear regression. STATA software (version 12.0) was used for statistical analysis.

Results

Data statistics

A total of eight case–control studies about the *Taq* I (rs731236) polymorphism and the relationship between prostate cancer were identified.[30–37] These included a total of 1,720 prostate cancer patients (502 Asians, 829 Caucasians, and 389 African Americans) and 1,729 controls (730 Asians, 866 Caucasians, and 133 African Americans). A total of six case–control studies about the *Bsm* I (rs1544410) polymorphism and the relationship between prostate cancer were identified.[30,32–35,37] These included a total of 1,555 prostate cancer patients (350 Asians, 816 Caucasians, and 389 African Americans) and 1,376 controls (369 Asians, 870 Caucasians, and 137 African Americans). In these studies, the *Bsm* I (rs1544410) allele frequency was in line with the HWE (χ^2 test, $P > 0.05$) (Table 1).

Meta-analysis and publication bias

The results of the associations between *Taq* I (rs731236) and *Bsm* I (rs1544410) polymorphisms with prostate cancer and heterogeneity are shown in Table 2 and Figures 1–3. Our meta-analysis suggested that *Taq* I (rs731236) is associated with prostate cancer in the Asian population (dominant model: OR = 1.618, 95% CI 1.071–2.445, $P = 0.022$) and African American population (recessive model: OR = 1.668, 95% CI 1.115–2.496, $P = 0.013$) under the dominant model and recessive model, respectively. However, *Bsm* I (rs1544410) was not associated with prostate cancer under any of the three genetic models (additive model, OR = 1.005, 95% CI 0.746–1.353, not significant (NS); dominant model, OR = 1.237, 95% CI 0.753–2.031, NS; recessive model, OR = 0.906, 95% CI 0.623–1.316, NS).

We used Begg's test and Egger's linear regression to estimate the publication bias.

Table 1. Sample information and *VDR* polymorphism (*Taq* I and *Bsm* I) genotyping data in the current meta-analysis.

Ethnicity (country)	Author	Year of publication	rs731236 (*Taq* I)					rs1544410 (*Bsm* I)				
			Case/control genotype				Hardy–Weinberg	Case/control genotype				Hardy–Weinberg
			CC	CT	TT		*P*-value	GG	AG	AA		*P*-value
Asians (Lebanon)	Ezzi et al.	2014	23/26	38/48	7/5		0.006	18/9	43/41	7/29		NS
Asians (China)	Bai et al.	2009	0/0	10/9	112/121		NS	0/1	8/21	114/108		NS
Asians (China)	Hu et al.	2014	2/1	10/22	96/219		NS	–	–	–		–
Asians (Pakistan)	Yousaf et al.	2014	4/32	13/11	27/76		1.01E-17	–	–	–		–
Asians (India)	Manchanda et al.	2010	16/30	52/60	92/70		0.011	42/56	102/79	16/25		NS
Caucasians (America)	Nunes et al.	2016	10/23	62/75	60/71		NS	14/28	63/70	55/71		NS
Caucasians	Holt et al.	2009	106/108	349/328	242/261		NS	239/255	339/331	106/115		NS
African Americans	Holt et al.	2009	11/7	45/27	58/29		NS	57/27	47/26	7/13		NS
African Americans	Jingwi et al.	2015	19/10	99/33	157/27		NS	22/11	117/33	139/27		NS

NS, No statistically significant differences ($P \geq 0.05$)

Table 2. Summary of ORs and 95% CIs under different genetic models and heterogeneity estimates.

SNP	Genetic model	Population	Pooled odds ratio [95% confidence interval] *P*-value	Heterogeneity		Begg's test *P*-value	Egger's test *P*-value
				I^2	*Q*-test (*P*-value)		
rs731236 (TaqI)	Additive (T/C)	Asians	1.224 [0.899–1.666] NS	38.40%	NS	NS	NS
		Caucasians	1.035 [0.812–1.319] NS	47.60%	NS	NS	–
		African Americans	1.487 [0.948–2.330] NS	54.00%	NS	NS	–
		Total	1.217 [0.988–1.499] NS	58.40%	0.014	–	–
	Dominant (CT + TT/CC)	Asians	**1.618 [1.071–2.445] 0.022**	60.20%	0.057	NS	NS
		Caucasians	1.110 [0.847–1.456] NS	54.70%	NS	NS	–
		African Americans	1.694 [0.898–3.195] NS	0.00%	NS	NS	–
		Total	**1.288 [1.040–1.594] 0.020**	48.30%	NS	–	–
	Recessive (TT/CC + CT)	Asians	1.259 [0.929–1.708] NS	20.80%	NS	NS	NS
		Caucasians	0.932 [0.765–1.135] NS	0.00%	NS	NS	–
		African Americans	**1.668 [1.115–2.496] 0.013**	43.80%	NS	NS	–
		Total	1.095 [0.940–1.276] NS	47.70%	NS	–	–
rs1544410 (BsmI)	Additive (A/G)	Asians	0.969 [0.408–2.301] NS	89.00%	0	NS	NS
		Caucasians	0.971 [0.845–1.115] NS	0.00%	NS	NS	–
		African Americans	1.043 [0.400–2.722] NS	90.30%	0.001	NS	–
		Total	1.005 [0.746–1.353] NS	79.80%	0	–	–
	Dominant (AA + AG/GG)	Asians	1.420 [0.347–5.814] NS	89.10%	0	NS	NS
		Caucasians	1.054 [0.826–1.346] NS	0.00%	NS	NS	–
		African Americans	1.424 [0.249–8.139] NS	89.80%	0.002	NS	–
		Total	1.237 [0.753–2.031] NS	80.00%	0	–	–
	Recessive (AA/AG + GG)	Asians	1.109 [0.324–3.794] NS	76.00%	0.016	NS	NS
		Caucasians	0.846 [0.582–1.230] NS	33.90%	NS	NS	–
		African Americans	0.867 [0.273–2.750] NS	81.60%	0.02	NS	–
		Total	0.906 [0.623–1.316] NS	60.90%	0.018	–	–

NS, no statistically significant differences ($P \geq 0.05$)

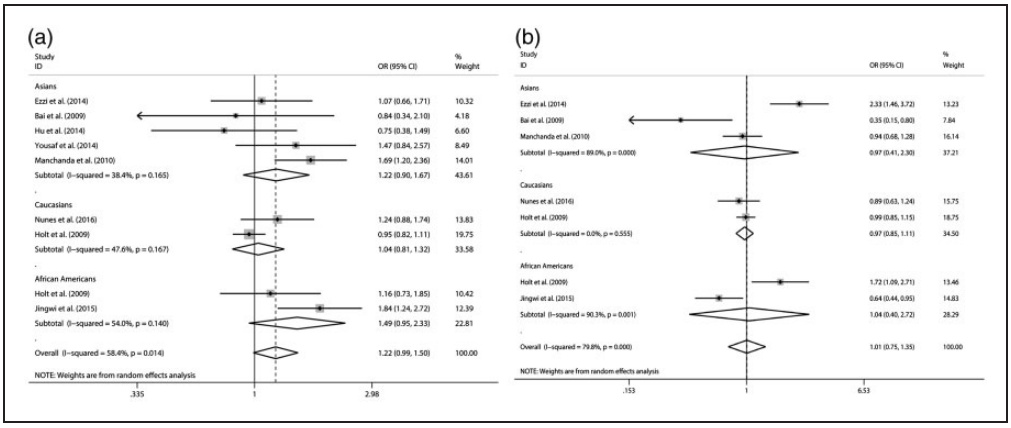

Figure 1. Forest plot of odds ratios for prostate cancer (additive model) a: *Taq* I (rs731236); b: *Bsm* I (rs1544410).

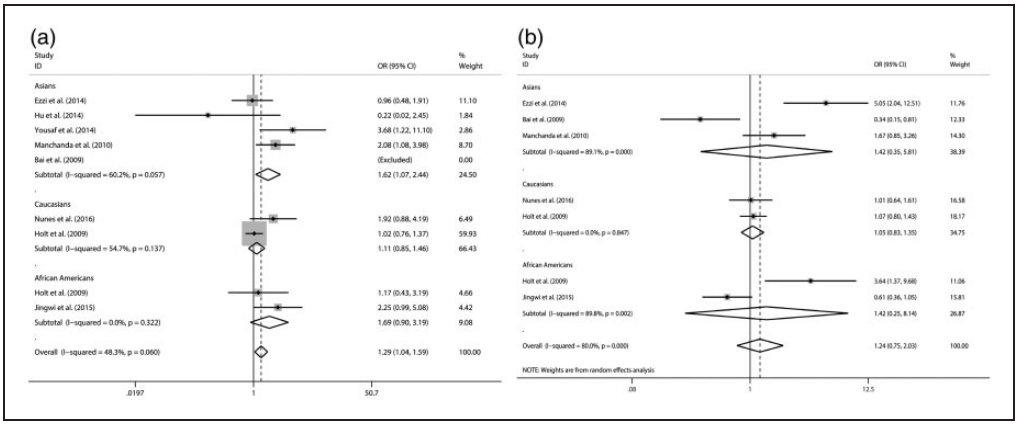

Figure 2. Forest plot of odds ratios for prostate cancer (dominant model) a: *Taq* I (rs731236); b: *Bsm* I (rs1544410).

As shown in Table 2, the results provided statistical evidence of no publication bias ($P > 0.05$) in case–control studies of Asians, Caucasians, and African Americans.

Discussion

Several previous studies have reported an association of the *Taq* I (rs731236) and *Bsm* I (rs1544410) polymorphisms with prostate cancer.[20–29] However, other investigations reached the opposite conclusion.[30–32] In the present study, we conducted a meta-analysis of recently published genetic association analyses. The results suggested that *Bsm* I (rs1544410) was not associated with prostate cancer under the additive, dominant, or recessive genetic models. These negative association results could be explained by our method of identifying studies from the literature, or could reflect the fact that we did not analyse other prostate cancer risk factors

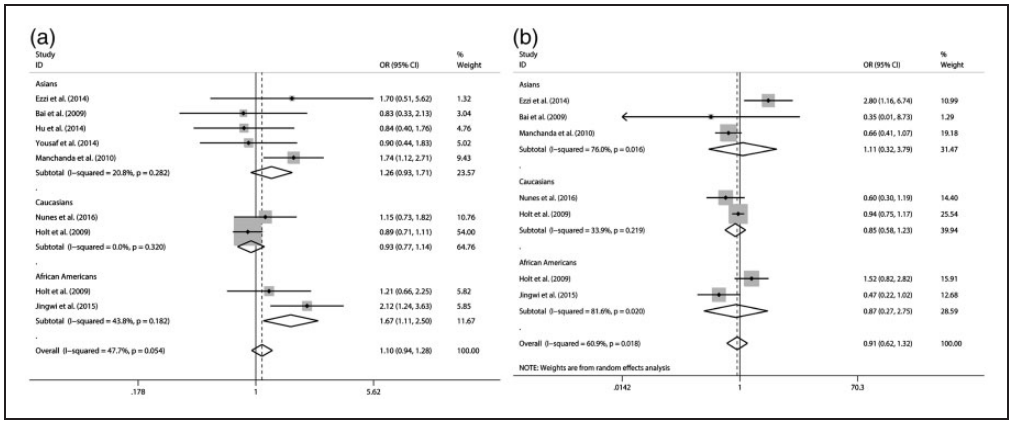

Figure 3. Forest plot of odds ratios for prostate cancer (recessive model) a: *Taq* I (rs731236); b: *Bsm* I (rs1544410).

such as atmospheric pollution, autoimmune diseases, and dietary factors. Moreover, the observed heterogeneity may also explain why no association was detected between *Bsm* I (rs1544410) and prostate cancer risk.

We did reveal a significant association between the *Taq* I (rs731236) polymorphism and prostate cancer risk in both Asian and African American populations (Table 2 and Figures 2–3). In 1994, Morrison et al.[38] reported that the *Taq* I (rs731236) polymorphism affects *VDR* transcriptional activity and mRNA stability, thus altering the abundance of VDR protein, and in turn affecting vitamin D levels. Low vitamin D levels have been shown to increase the risk of prostate cancer,[39] which agrees with our meta-analysis findings and previous epidemiological studies and gene function research.

By extension, our results show that genetic association analysis between susceptibility loci and disease involving small sample sizes does not provide solid evidence. Increasing the sample size would avoid the false-positive results obtained from local samples. Larger investigations should therefore be conducted together with molecular function studies of susceptibility genes and loci. This will ultimately provide an important theoretical basis for the development of prostate cancer clinical treatment.

Contributors

All authors have reviewed the final version of this manuscript and approved its submission for publication.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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