

# Association of VDR gene TaqI polymorphism with the susceptibility to prostate cancer in Asian population evaluated by an updated systematic meta-analysis

Liangliang Chen\*  
 Junjun Wei\*  
 Shuwei Zhang  
 Zhongguan Lou  
 Xue Wang  
 Yu Ren  
 Honggang Qi  
 Zhenhua Xie  
 Yirun Chen  
 Feng Chen  
 Qihang Wu  
 Xiaoxiao Fan  
 Honglei Xu  
 Shuaishuai Huang  
 Guobin Weng

Department of Urologic Surgery,  
 Ningbo Urology and Nephrology  
 Hospital, Urology and Nephrology  
 Institute of Ningbo University, Ningbo,  
 China

\*These authors contributed equally to  
 this work

Correspondence: Shuaishuai Huang;  
 Guobin Weng  
 Ningbo Urology and Nephrology  
 Hospital, Urology and Nephrology  
 Institute of Ningbo University,  
 998 North Qianhe Road, Yinzhou,  
 Ningbo, Zhejiang 315000, China  
 Tel +86 5 745 566 2926  
 Email ss.huang@aliyun.com;  
 ddwgbn@aliyun.com

**Background:** The vitamin D receptor (VDR) plays a key role in vitamin-mediated signaling pathway. Emerging evidence has suggested that the VDR polymorphism may contribute to the risk of prostate cancer (PCa). However, the existing results are not conclusive in Asian population.

**Methods:** We aim to evaluate the potential role of VDR polymorphisms on PCa of Asian population. PubMed, Scopus, Embase, Web of Science, Chinese National Knowledge Infrastructure, Wang Fang Data, and VIP Periodical were retrieved, and eligible studies (case-control or cohort study) meeting the inclusion criteria were evaluated through an updated meta-analysis using Stata13.0 software.

**Results:** A total of 1,363 cases and 2,101 controls obtained from 13 eligible publications were eventually included in this meta-analysis. Our results show that a significant association of VDR taqI polymorphism with PCa risk, especially in the Japanese population. In the clinical stage-stratified analysis, the pooled results revealed no significant difference in genetic polymorphisms between the local stage and control groups, whereas there was increased frequency of T allele and TT genotype in the advanced tumor stage group compared with local tumor stage or control groups. Similarly, no significant difference was seen in Gleason <7 and control groups, but the T allele and TT genotype were significantly higher in the Gleason  $\geq 7$  group compared with Gleason <7 or control groups.

**Conclusion:** The VDR TaqI polymorphism might be associated with PCa risk in Asian population, especially in the Japanese population. Also, PCa patients carrying the T allele or TT genotype were more likely to progress to advanced stage. These results suggest that VDR TaqI polymorphisms may be potential diagnostic biomarkers for PCa susceptibility.

**Keywords:** vitamin D receptor, polymorphism, prostate cancer, clinical stage, meta-analysis

## Background

Prostate cancer (PCa), is one of the most common malignant tumors and the second leading cause of male mortality worldwide. In the USA, a total number of 180,890 new cases and 26,120 deaths occurred in 2016.<sup>1</sup> Although the pathogenesis of PCa is not clearly elucidated, age, ethnicity, and genetic factors are believed to contribute to the occurrence of PCa.<sup>2</sup>

Some reports suggested that low levels of vitamin D in serum might be a risk factor for PCa.<sup>3</sup> The hormonally active metabolite of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub> (calcitriol), shows an anti-proliferative effect on many PCa cell lines.<sup>2,4,5</sup> The transformation of

vitamin D to calcitriol requires the binding of vitamin D receptor (VDR) and the complex of vitamin D-VDR-retinoid X receptor complex to regulate the cell proliferation, cell cycle, and apoptosis-related genes.<sup>6</sup> High levels of VDR mediate the activation of vitamin D as active vitamin D [1,25 (OH)<sub>2</sub>D<sub>3</sub>], which could inhibit the proliferation of normal prostate tissue and PCa epithelial cells, thus inhibiting the growth of PCa cells.<sup>4</sup> This discovery suggested that the variation in VDR gene affects the prognosis or risk of PCa. TaqI, one of the most extensive single-nucleotide polymorphisms located in exon 9 of VDR gene might alter VDR mRNA levels. This is through regulation of mRNA stability and the protein translation efficiency, which may be responsible for the reduction in VDR level.<sup>7-9</sup>

Currently, existing evidence is insufficient to draw robust conclusions.<sup>10,11</sup> Three previous meta-analyses have identified that there are no positive results in VDR TaqI polymorphism and PCa development,<sup>7,12,13</sup> while study of Fei et al showed an inverted result in Asian population. Regrettably, no further subgroup analysis was conducted in different countries.<sup>14</sup> The inclusion of population with benign prostatic hyperplasia (BPH) as control group is noted, and a relation of VDR TaqI polymorphism to BPH risk was also reported in some other studies. Our study considered the subjects as 1) healthy group, 2) BPH group, and 3) case group. Four new studies have provided additional data.<sup>15-18</sup> We, therefore, conducted an updated meta-analysis to investigate the role of VDR TaqI polymorphism and PCa risk.

## Methods

### Literature and research strategy

PubMed, Scopus, Embase, Web of Science, Chinese National Knowledge Infrastructure, Wang Fang data, and VIP Periodical were searched using the following terms: (“Polymorphisms”) and (“vitamin D receptor” OR “vitamin D3 receptor” OR “1,25- dihydroxyvitamin D3 receptor” OR “calcitriol receptor” OR “VDR”) and (“PCa” OR “prostate neoplasm” OR “prostate tumor” OR “prostate carcinoma” OR “prostatic neoplasm”). Articles related to the association of VDR TaqI polymorphisms and Asian PCa risk were obtained. Various combinations of the terms were also used in other databases. Literature search data were last updated on October 10, 2016. No limitations were attached.

### Inclusion and exclusion criteria

In this meta-analysis, it was a must for selected studies to meet the following criteria:

(1) Studies that performed the associations of VDR TaqI genetic polymorphisms and PCa;

- (2) Study objects belonged to the Asian population;
- (3) Local stage PCa was defined as clinical and pathological stage of T1–T2N0M0 or stage A–B; advanced PCa was defined as tumor invasion outside the prostate envelope or cancer metastasis to the lymph nodes or other organ tissue, clinical pathological stage for T3–T4NxMx or TxN1 or M1; stage C and D;
- (4) Gleason stage: low grade (Gleason <7) and high grade (Gleason ≥7);
- (5) The odds ratios (ORs) with 95% CIs could be calculated or provided through detailed genotype data in case–control, cohort groups, and GWAS studies.

Exclusion criteria:

- (1) No detailed genotype data or the raw data were available for retrieval;
- (2) Comments, review articles, editorials, and other meta-analysis;
- (3) For multiple publications from the same population/area, only the largest sample was included.

### Data extraction and synthesis

Data of eligible studies were extracted independently by 2 independent reviewers, including the following contents: name of first author, year of publication, country of origin, characteristics of cases and controls, number of cases and controls, sources of controls, pathologic diagnosis, clinical pathologic staging, Gleason score, and Newcastle–Ottawa Scale (NOS). Extracted data with discrepancies in identification were discussed to reach a consensus. A third investigator assisted by adjudicating the disagreements if dissent still existed.

### Evaluation of the eligible studies' quality

We used the NOS to evaluate each in accordance with the requirements of article quality, NOS score a total of 9 points, while each indicator score 1 point. If the score >4 points, it was considered to be a high quality article.<sup>19</sup>

### Statistical analysis

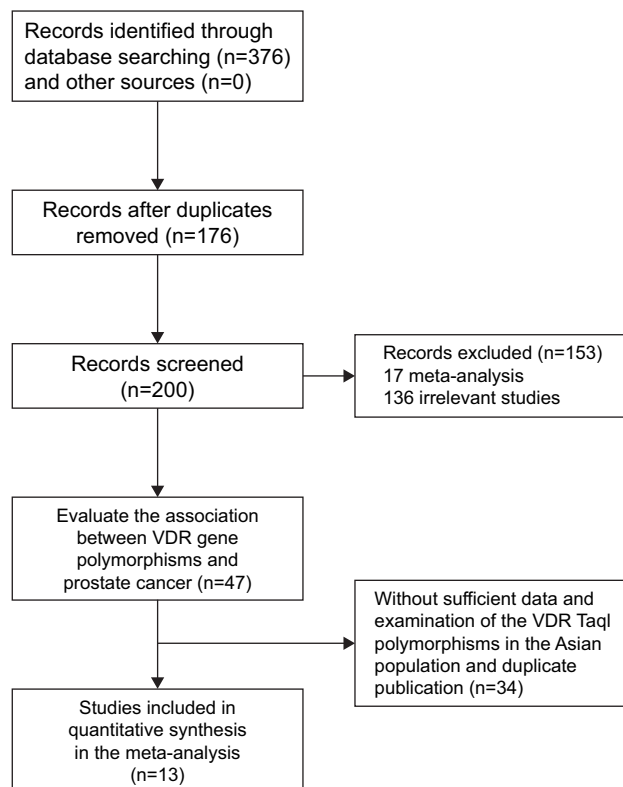
We evaluated the pooled OR and 95% CI to indicate the relationship between VDR gene TaqI polymorphism and susceptibility to PCa by Z-test, with  $P < 0.05$  considering as statistically significant. Statistical heterogeneity among studies was carried out by the  $Q$  statistic (significance level of  $P < 0.1$ ) and  $I^2$  statistic (>50% as evidence of significant inconsistency).<sup>20,21</sup> The  $Q$ -test and  $I^2$  statistic were applied to determine the effect models according to heterogeneity. When  $P$ -value of heterogeneity ( $P_H$ ) was no >0.1 ( $P_H \leq 0.1$ ), random effects model was used, and when  $P_H$  was >0.1,

fixed effects model was used.<sup>22</sup> Sensitivity analysis was also tested by removing 1 study at a time, to evaluate the effect of removal and effect of size of each study on the homogeneity of the whole. In addition, subgroup analyses were stratified by countries, cancer stages, and Gleason stages. Publication bias was investigated with Begg's funnel plots and further assessed by the Egger's regression test.<sup>23,24</sup> When an asymmetric plot was shown or Egger's test was  $P < 0.05$ , we considered it as a significant publication bias. Besides, Hardy–Weinberg equilibrium (HWE) was implemented to identify the effective records in our study. All analyses were performed with Stata 13.0 software (StataCorp, College Station, TX, USA). A 2-tailed  $P \leq 0.05$  was regarded as significant, except for specified conditions, for which a certain  $P$ -value was declared.

## Results

### Study selection and characteristics

A flow diagram of literature research and process is shown in Figure 1. Each study was retrieved and carefully reviewed according to the inclusive and exclusive criteria. Ultimately, a total of 13 articles reporting the relationship between Taq1 polymorphisms and PCa risk in Asian population were identified through both English and Chinese databases,<sup>15–18,25–33</sup>



**Figure 1** Study flowchart for the process of selecting the final 13 studies.  
**Abbreviation:** VDR, vitamin D receptor.

including 1,363 cases and 2,101 controls (including healthy and BPH). Quality of each included article was evaluated by NOS, and each had a score of  $\geq 5$ , meaning a high quality, as listed in Table 1. In addition, we found that 3 studies did not meet HWE.<sup>15,25,33</sup> We found no significant changes of the pooled results after excluding each article once.

### Association of VDR gene Taq1 polymorphism with PCa risk in Asian population

A total of 13 eligible articles, including 1,363 cases and 2,101 controls (including non-BPH and BPH) were analyzed the association between Taq1 polymorphism of VDR and PCa risk in Asian population. As is presented in Table 2, Taq1 genetic polymorphism was significantly associated with the risk of PCa (T vs t: OR [95% CI]=1.23 [1.05–1.44],  $P=0.010$ ; TT vs tt: OR [95% CI]=1.99 [1.20–3.30],  $P=0.008$ ; [TT/Tt] vs tt: OR [95% CI]=2.03 [1.24–3.34],  $P=0.005$ ); (Figure 2A, D and G). Begg's test revealed no publication bias (Figure 2B, E and H), and the sensitivity analysis was stable (Figure 2C, F and I).

Previous study suggested that the inclusion of population with BPH as control group may bias the pooled results to a varying degree.<sup>14</sup> In order to draw attention to this point, we divided the control into 2 groups, BPH and non-BPH control. As a result, a marked association was performed with Taq1 polymorphism and PCa risk in the case vs non-BPH subgroup (T vs t: OR [95% CI]=1.54 [1.20–1.98],  $P=0.001$ ; TT vs Tt: OR [95% CI]=1.41 [1.06–1.87],  $P=0.017$ ; TT vs tt: OR [95% CI]=3.53 [1.40–8.94],  $P=0.008$ ; TT vs [Tt/tt]: OR [95% CI]=1.51 [1.15–1.98],  $P=0.003$ ; [TT/Tt] vs tt: OR [95% CI]=3.15 [1.25–7.94],  $P=0.015$ ; Figure 3A, D, G, J and M), while no significant difference was found between BPH and non-BPH subgroup. The results revealed that VDR Taq1 polymorphism was not associated with BPH. Begg's test revealed no publication bias, and the sensitivity analysis was stable (Table 2 and Figure 3).

### Association of VDR gene Taq1 polymorphism with PCa risk in different Asian countries

We performed a subgroup analysis according to different Asian countries. As shown in Figure 4 and Table 3, the pooled results indicated that VDR Taq1 genetic polymorphism was closely linked with PCa risk in Japanese population (T vs t: OR [95% CI]=1.23 [1.0–1.51],  $P=0.049$ ; TT vs tt: OR [95% CI]=2.04 [1.00–4.16],  $P=0.048$ ), while no association was shown in Chinese (4 studies), Pakistan (1 study), India (1 study), and Thailand (1 study) population. Begg's test revealed no

Table 1 Characteristics of selected studies in this meta-analysis

No	Study, year	Country	Characteristics of case and controls		Genotyping method	HWE	Cancer evaluation	NOS	Total sample size		Genotype					
			Case	Controls					Case	Control	TT	Tt	TT	Tt		
1	Furiya et al, <sup>26</sup> 1999	Japan	NA	Without any tumors, no-BPH, confirmed by PCa screening	PCR-RFLP	0.384	TNM	5	66	60	41	25	0	41	18	1
2	Watanabe et al, <sup>25</sup> 1999	Japan	ALL	Without any tumors, inclusion of BPH and non-BPH, confirmed by PCa screening	PCR-RFLP	0.034	TNM	6	100	202 (202 BPH)	80	18	2	160	36	6
3	Habuchi et al, <sup>27</sup> 2000	Japan	ALL	Without any tumors, inclusion of BPH and non-BPH, confirmed by PCa screening	PCR-RFLP	0.205	NO	7	222	337 (209 BPH)	176	44	2	253	81	3
4	Hamasaki et al, <sup>28</sup> 2001	Japan	ALL	Without any tumors, no BPH, age-matched, confirmed by PCa screening	PCR-RFLP	0.061	TNM Gleason	5	115	133	91	22	2	91	34	8
5	Hamasaki et al, <sup>15</sup> 2002	Japan	ALL	Without any tumors, inclusion of BPH and non-BPH, age-matched, confirmed by PCa screening	PCR-RFLP	0.033	TNM Gleason	6	110	173 (83 BPH)	87	21	2	123	41	9
6	Suzuki et al, <sup>16</sup> 2003	Japan	ALL	Without any tumors, no BPH, confirmed by PCa screening. 2 control subjects had a family history of PCa	PCR-RFLP	0.545	TNM Gleason	6	81	105	59	20	2	83	20	2
7	Huang et al, <sup>29</sup> 2004	China	ALL	Without any tumors, no BPH, age-matched, confirmed by PCa screening	PCR-RFLP	0.332	TNM Gleason	7	160	205	146	14	0	179	26	0
8	Liu et al, <sup>17</sup> 2004	China	ALL	Without any tumors, inclusion of BPH and non-BPH, confirmed by PCa screening	PCR-RFLP, DHPLC	0.442	TNM Gleason	7	103	226 (112 BPH)	93	10	0	204	22	0
9	Chaimuangraj et al, <sup>30</sup> 2006	Thailand	ALL	Without any tumors, inclusion of BPH and non-BPH, confirmed by PCa screening	PCR-RFLP	0.871	NO	6	28	74 (30 BPH)	22	6	0	59	14	1
10	Onsory et al, <sup>31</sup> 2008	India	ALL	Without any tumors, no BPH	PCR-SSCP	0.393	NO	5	100	100	55	40	5	43	48	9
11	Bai et al, <sup>18</sup> 2009	China	ALL	Without any tumors, age matched, no BPH, confirmed by PCa screening	PCR-RFLP	0.683	TNM Gleason	8	122	130	112	10	0	121	9	0
12	Hu et al, <sup>32</sup> 2014	China	ALL	Without any tumors, no BPH, confirmed by PCa screening	PCR	0.581	TNM Gleason	7	108	242	96	10	2	219	22	1
13	Yousaf et al, <sup>33</sup> 2014	Pakistan	ALL	Without any tumors, no BPH	PCR-RFLP	0.035	NO	6	48	114	27	13	4	76	11	32

**Notes:** NA indicated as relative data were not available in original studies. ALL indicated as prostate cancer cases were confirmed by histologically diagnosis. PCa screening included PSA test and DRE, and/or TRUS, and/or prostate biopsy, NO indicated as the study is neither stratified by Gleason stage nor by TNM stage.

**Abbreviations:** BPH, benign prostatic hyperplasia; DHPLC, detected by high-performance liquid chromatography; DRE, digital rectal examination; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale; PCR, polymerase chain reaction; PCa, prostate cancer; RFLP, restriction fragment length polymorphism; SSCP, single-strand conformation polymorphism; TRUS, transrectal ultrasound.

**Table 2** Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk with different groups in Asian population

Gene	Studies	Test for overall effect			Heterogeneity		M	Publication bias	
		N	OR (95% CI)	Z-score	P-value	I <sup>2</sup>		P-value	Begg's test
Case vs all control									
T vs t	13	1.23 (1.05–1.44)	2.56	0.010	0%	0.460	F	0.127	0.092
TT vs Tt	13	1.09 (0.91–1.31)	0.96	0.330	23.4%	0.207	F	0.024	0.024
TT vs tt	13	1.99 (1.20–3.30)	2.67	0.008	0%	0.681	F	0.049	0.126
TT vs (Tt/tt)	13	1.17 (0.98–1.40)	1.77	0.076	0%	0.581	F	0.100	0.057
(TT/Tt) vs tt	13	2.03 (1.24–3.34)	2.80	0.005	0%	0.634	F	0.074	0.136
Case vs non-BPH control									
T vs t	6	1.54 (1.20–1.98)	3.42	0.001	18.8%	0.291	F	1.000	0.446
TT vs Tt	6	1.41 (1.06–1.87)	2.39	0.017	0%	0.503	F	0.707	0.479
TT vs tt	6	3.53 (1.40–8.94)	2.67	0.008	0%	0.905	F	0.734	0.606
TT vs (Tt/tt)	6	1.51 (1.15–1.98)	2.93	0.003	9.6%	0.355	F	1.000	0.493
(TT/Tt) vs tt	6	3.15 (1.25–7.94)	2.43	0.015	0%	0.933	F	0.734	0.614
BPH vs non-BPH Control									
T vs t	3 <sup>a</sup>	1.68 (0.92–3.09) <sup>a</sup>	1.68 <sup>a</sup>	0.093 <sup>a</sup>	60.6% <sup>a</sup>	0.079 <sup>a</sup>	R <sup>a</sup>	1.000 <sup>a</sup>	0.438 <sup>a</sup>
TT vs Tt	3 <sup>a</sup>	1.67 (0.80–3.47) <sup>a</sup>	1.36 <sup>a</sup>	0.173 <sup>a</sup>	62.9% <sup>a</sup>	0.068 <sup>a</sup>	R <sup>a</sup>	1.000 <sup>a</sup>	0.423 <sup>a</sup>
TT vs tt	4	2.86 (0.91–8.99)	1.80	0.073	0%	0.897	F	0.296	0.111
TT vs (Tt/tt)	3 <sup>a</sup>	1.75 (0.85–3.58) <sup>a</sup>	1.52 <sup>a</sup>	0.128 <sup>a</sup>	64.3% <sup>a</sup>	0.061 <sup>a</sup>	R <sup>a</sup>	1.000 <sup>a</sup>	0.436 <sup>a</sup>
(TT/Tt) vs tt	4	2.41 (0.77–7.54)	1.52	0.129	0%	0.853	F	0.296	0.056

**Note:** <sup>a</sup>Liu et al's<sup>17</sup> study was excluded.

**Abbreviations:** BPH, benign prostatic hyperplasia; F, fixed effects model; M, effect model of meta-analysis; OR, odds ratio; PCa, prostate cancer; R, random effects model; VDR, vitamin D receptor.

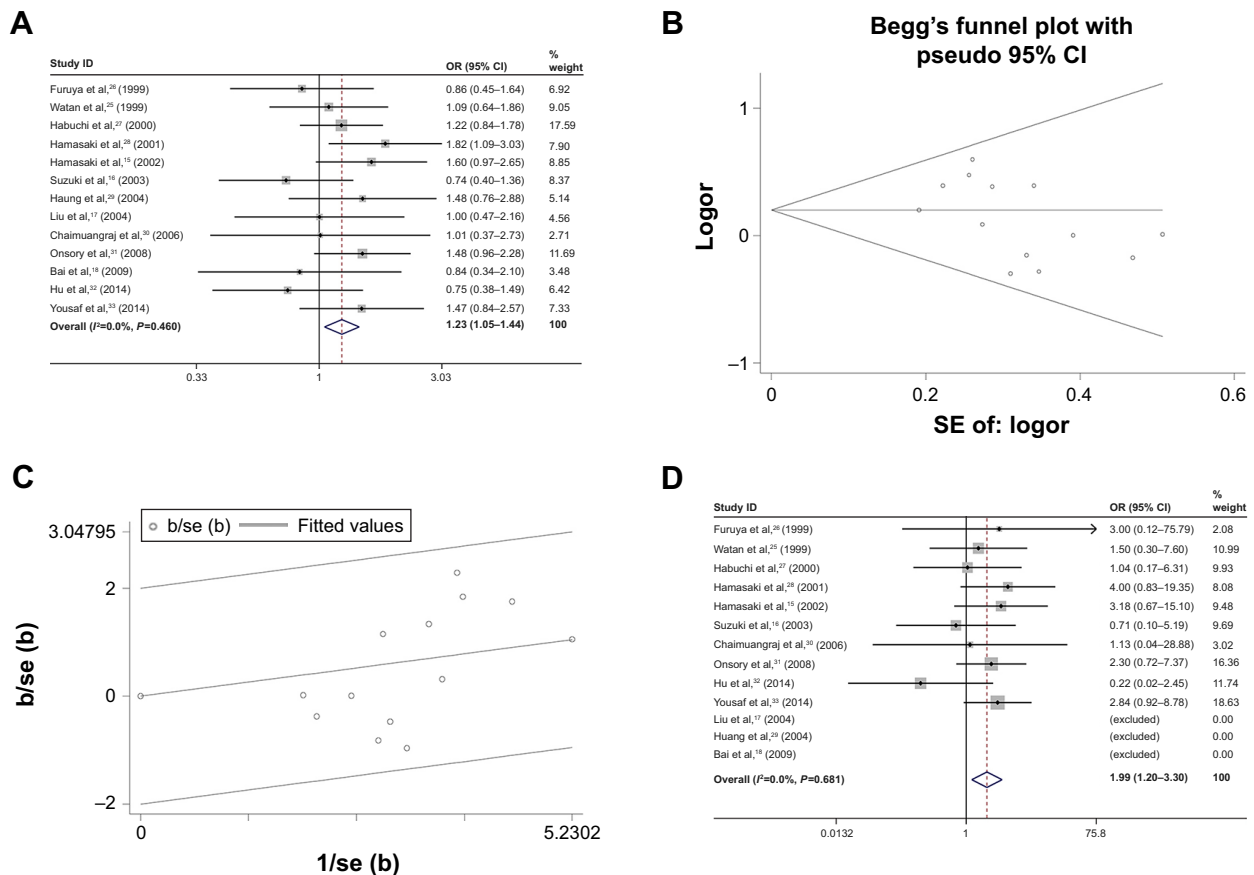


Figure 2 (Continued)

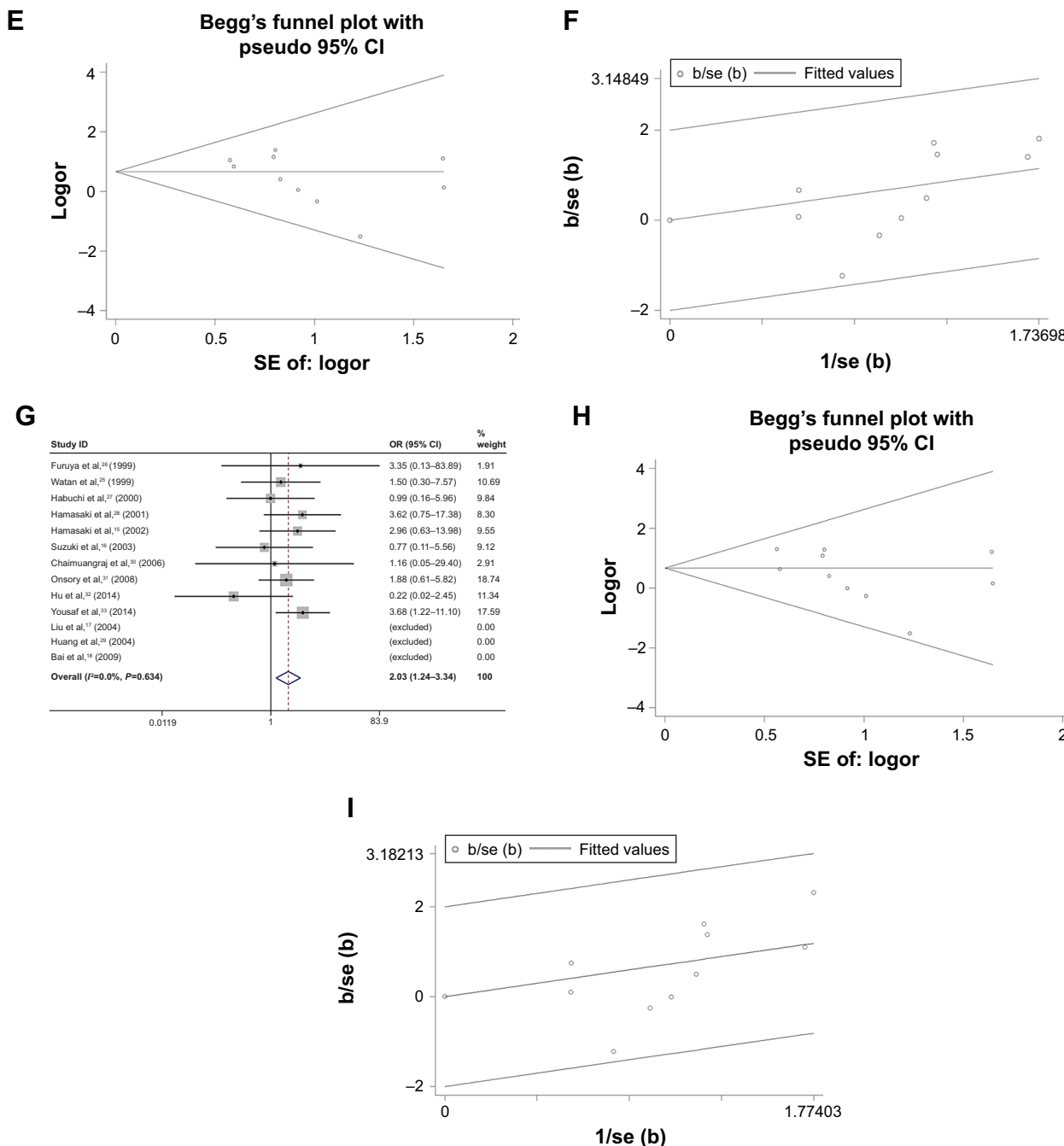


Figure 2 ORs, Begg's test and Galbraith blot test of PCa and VDR TaqI polymorphisms.

Note: T vs t (A–C), TT vs tt (D–F) and (TT/Tt) vs tt (G–I) were analyzed by fixed effects analysis.

Abbreviations: OR, odds ratio; PCa, prostate cancer; SE, standard error; VDR, vitamin D receptor.

publication bias (Figure 4B and E), and the sensitivity analysis represented a good stability (Figure 4C and F).

### Association of VDR gene TaqI polymorphism with PCa risk in different tumor and Gleason stages

According to the clinical pathological and Gleason stages, we performed a subgroup analysis to delineate the association

of VDR gene TaqI genetic polymorphism with PCa risk in more detail.

As shown in Table 4, in the clinical stage subgroup analysis, the pooled results revealed no significant association in local stage, but more frequency of T allele and TT genotype in the advanced group compared with control or local stage (advanced group vs control group: T vs t: OR [95% CI]=1.62 [1.16–2.25], P=0.004; TT vs Tt: OR

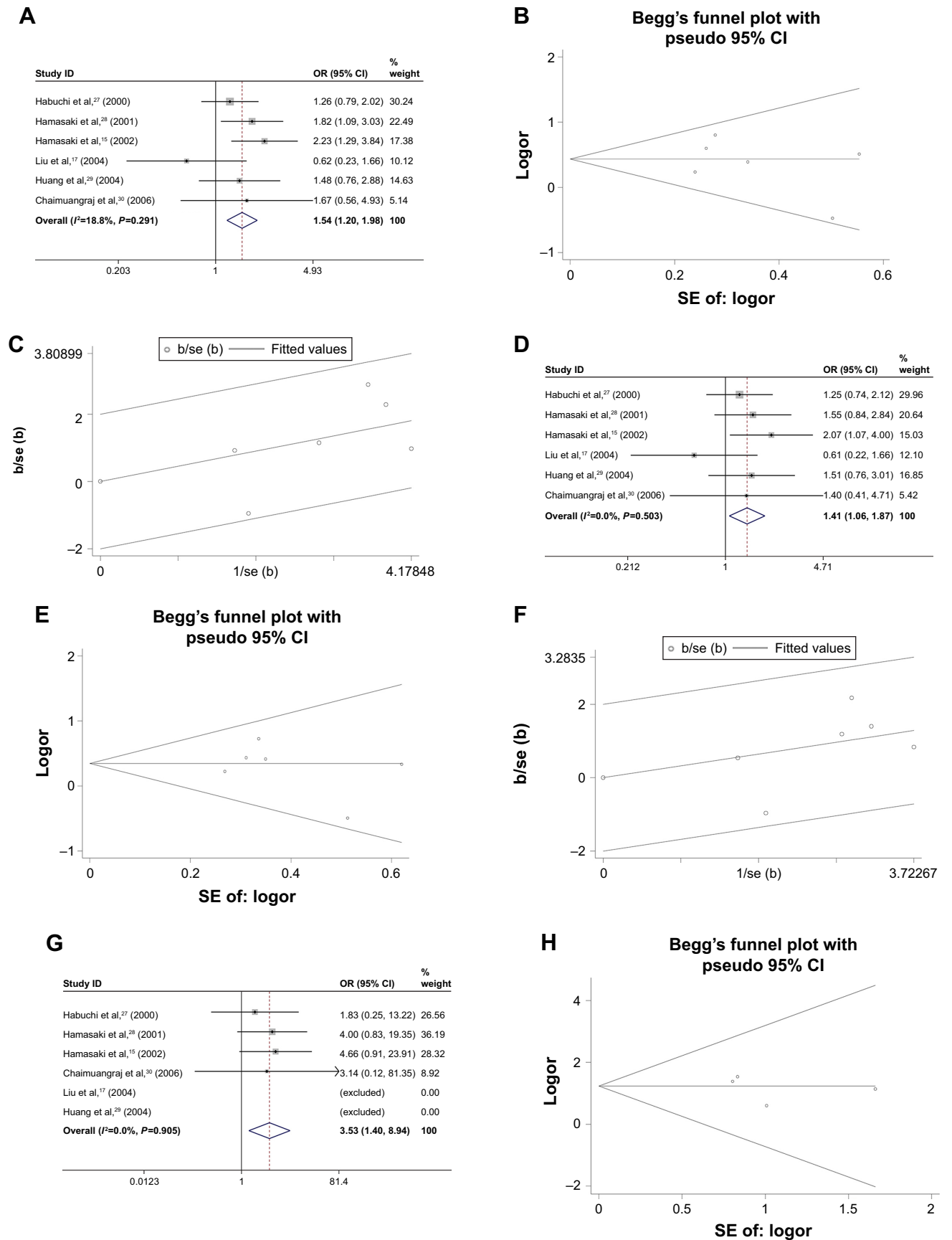
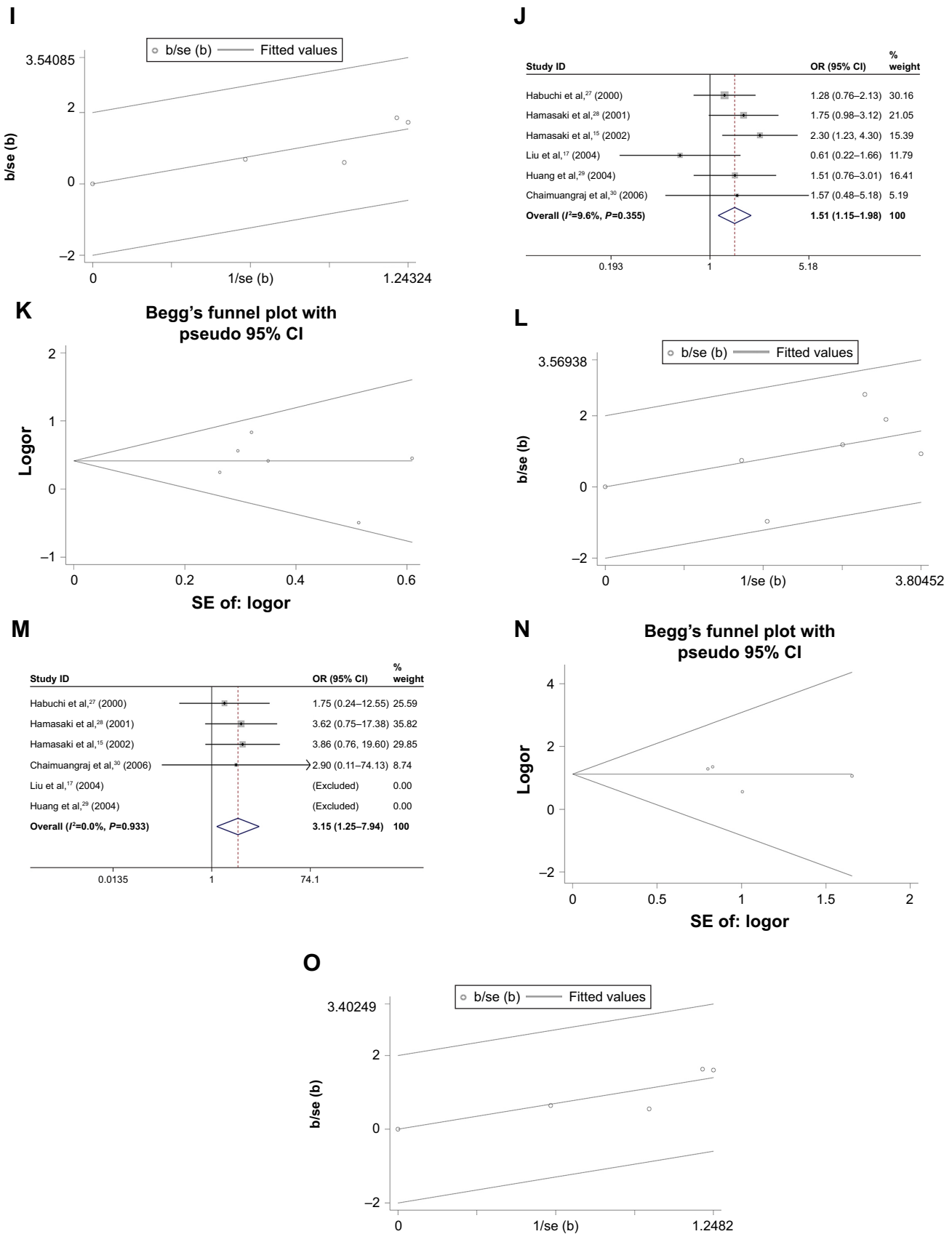


Figure 3 (Continued)



**Figure 3** ORs, Begg's test and Galbraith blot test of case vs non-BPH as control. **Note:** T vs t (A–C), TT vs Tt (D–F), TT vs tt (G–I), TT vs (TT/tt) (J–L) and (TT/Tt) vs tt (M–O) were analyzed by fixed models. **Abbreviations:** BPH, benign prostatic hyperplasia; OR, odds ratio.



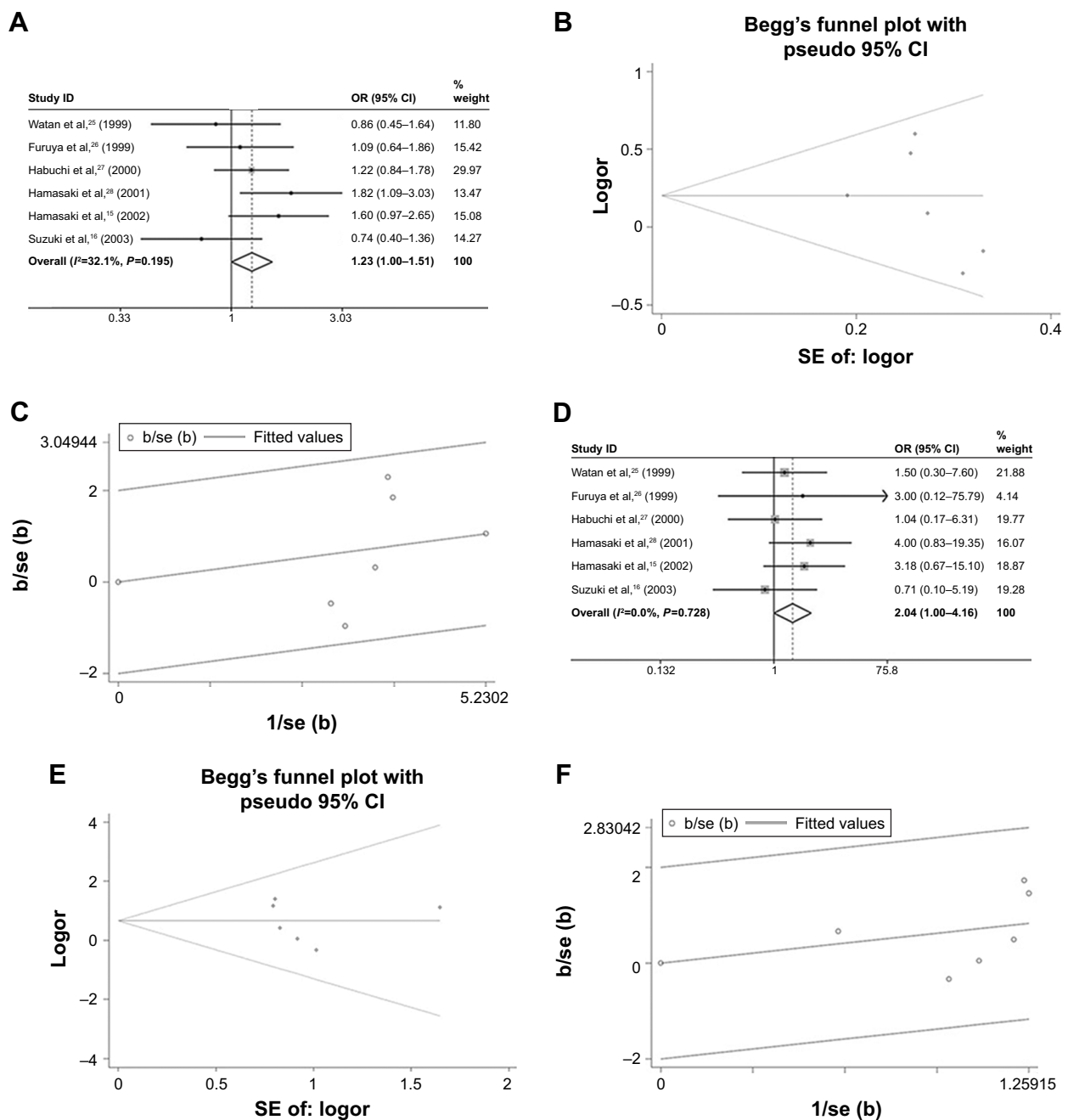


Figure 4 ORs, Begg's test and Galbraith blot test of PCa and VDR TaqI polymorphisms in Japanese population.

Note: T vs t (A–C), TT vs tt (D–F) were analyzed by fixed effects analysis.

Abbreviations: OR, odds ratio; PCa, prostate cancer; VDR, vitamin D receptor.

[95% CI]=1.59 [1.10–2.29],  $P=0.013$ ; TT vs [Tt/tt]: OR [95% CI]=1.80 [1.25–2.61],  $P=0.002$ ; advanced group vs local group: T vs t: OR [95% CI]=1.56 [1.02–2.38],  $P=0.041$ ; TT vs Tt: OR [95% CI]=2.10 [1.33–3.31],  $P=0.001$ ; TT vs [Tt/tt]: OR [95% CI]=1.68 [1.07–2.62],  $P=0.023$ ; Table 4 and Figure 5).

As shown in Table 5, in the Gleason subgroup analysis, the combined results showed no significant association between Gleason <7 vs control group, but the T allele and

TT genotype were significantly higher in Gleason  $\geq 7$  group than control group or Gleason <7 (Table 5 and Figure 6).

### Sensitivity and heterogeneity analysis

Sensitivity analysis was performed to test data stability by omitting one study at a time. The significance of all ORs was unchanged. A sensitivity analysis indicated that an independent study by Liu et al<sup>17</sup> was the principal reference for heterogeneity of TaqI polymorphism in the development of BPH.

**Table 3** Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk in Asian different countries

Gene	Studies	Test for overall effect			Heterogeneity		M	Publication bias	
		OR (95% CI)	Z-score	P-value	I <sup>2</sup>	P-value		Begg's test	Egger's test
China									
T vs t	4	1.02 (0.70–1.47)	0.09	0.929	0%	0.544	F	0.734	0.646
TT vs Tt	4	1.10 (0.75–1.63)	0.50	0.618	0%	0.720	F	0.308	0.093
TT vs tt	4	0.22 (0.02–2.45)	1.23	0.218	–	–	–	–	–
TT vs (Tt/tt)	4	1.06 (0.72–1.56)	0.30	0.762	0%	0.638	F	0.734	0.335
(TT/Tt) vs tt	4	0.22 (0.02–2.45)	1.23	0.218	–	–	–	–	–
Japan									
T vs t	6	1.23 (1.00–1.51)	1.97	0.049	32.1%	0.195	F	0.26	0.394
TT vs Tt	6	1.14 (0.90–1.44)	1.07	0.287	0.40%	0.413	F	0.26	0.190
TT vs tt	6	2.04 (1.00–4.16)	1.96	0.048	0%	0.728	F	0.26	0.708
TT vs (Tt/tt)	6	1.20 (0.95–1.50)	1.54	0.124	21.8%	0.270	F	0.26	0.287
(TT/Tt) vs tt	6	1.97 (0.97–4.02)	1.87	0.061	0%	0.777	F	0.26	0.810
India									
T vs t	1	1.48 (0.96–2.28)	1.76	0.079	–	–	–	–	–
TT vs Tt	1	1.53 (0.86–2.74)	1.45	0.147	–	–	–	–	–
TT vs tt	1	2.30 (0.72–7.37)	1.40	0.160	–	–	–	–	–
TT vs (Tt/tt)	1	1.62 (0.93–2.83)	1.69	0.090	–	–	–	–	–
(TT/Tt) vs tt	1	1.88 (0.61–5.82)	1.09	0.274	–	–	–	–	–
Thailand									
T vs t	1	1.01 (0.37–2.73)	0.02	0.984	–	–	–	–	–
TT vs Tt	1	0.87 (0.30–2.55)	0.25	0.800	–	–	–	–	–
TT vs tt	1	1.13 (0.05–28.9)	0.08	0.939	–	–	–	–	–
TT vs (Tt/tt)	1	0.89 (0.31–2.59)	0.21	0.831	–	–	–	–	–
(TT/Tt) vs tt	1	1.16 (0.05–29.4)	0.09	0.927	–	–	–	–	–
Pakistan									
T vs t	1	1.47 (0.84–2.57)	1.34	0.180	–	–	–	–	–
TT vs Tt	1	0.30 (0.12–0.75)	2.57	0.010	–	–	–	–	–
TT vs tt	1	2.84 (0.92–8.78)	1.81	0.070	–	–	–	–	–
TT vs (Tt/tt)	1	0.90 (0.44–1.83)	0.29	0.769	–	–	–	–	–
(TT/Tt) vs tt	1	3.68 (1.22–11.1)	2.31	0.021	–	–	–	–	–

Note: “–” indicates no data.

Abbreviations: F, fixed effects model; M, effect model of meta-analysis; OR, odds ratio; PCa, prostate cancer; VDR, vitamin D receptor.

**Table 4** Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk in different tumor stages

Gene	Studies	Test for overall effect			Heterogeneity		M	Publication bias	
		OR (95% CI)	Z-score	P-value	I <sup>2</sup>	P-value		Begg's test	Egger's test
Local vs control									
T vs t	5	1.02 (0.74–1.40)	0.10	0.924	0%	0.721	F	0.806	0.754
TT vs Tt	6	0.77 (0.55–1.09)	1.47	0.141	0%	0.727	F	0.707	0.291
TT vs tt	5	1.93 (0.60–6.22)	1.10	0.273	3.3%	0.376	F	0.734	0.437
TT vs (Tt/tt)	6	0.90 (0.65–1.25)	0.61	0.545	0%	0.959	F	0.707	0.580
(TT/Tt) vs tt	6	1.77 (0.63–4.93)	1.08	0.278	0%	0.521	F	0.462	0.282
Advanced vs control									
T vs t	5	1.62 (1.16–2.25)	2.86	0.004	49%	0.097	F	0.462	0.762
TT vs Tt	6	1.59 (1.10–2.29)	2.48	0.013	49.8%	0.076	F	1.000	0.901
TT vs tt	5	2.18 (0.80–5.90)	1.53	0.126	0%	0.949	F	1.000	0.412
TT vs (Tt/tt)	6	1.80 (1.25–2.61)	3.13	0.002	27.5%	0.228	F	0.133	0.111
(TT/Tt) vs tt	6	1.98 (0.80–4.83)	1.47	0.142	0%	0.994	F	0.806	0.691
Advanced vs local									
T vs t	5	1.56 (1.02–2.38)	2.04	0.041	0%	0.798	F	1.000	0.660
TT vs Tt	6	2.10 (1.33–3.31)	3.20	0.001	19.5%	0.286	F	1.000	0.901
TT vs tt	5	0.64 (0.13–3.12)	0.55	0.582	0%	0.726	F	0.296	0.028
TT vs (Tt/tt)	6	1.68 (1.07–2.62)	2.27	0.023	0%	0.557	F	0.260	0.102
(TT/Tt) vs tt	6	0.78 (0.20–2.87)	0.40	0.686	0%	0.666	F	1.000	0.387

Abbreviations: F, fixed effects model; M, effect model of meta-analysis; OR, odds ratio; PCa, prostate cancer; VDR, vitamin D receptor.

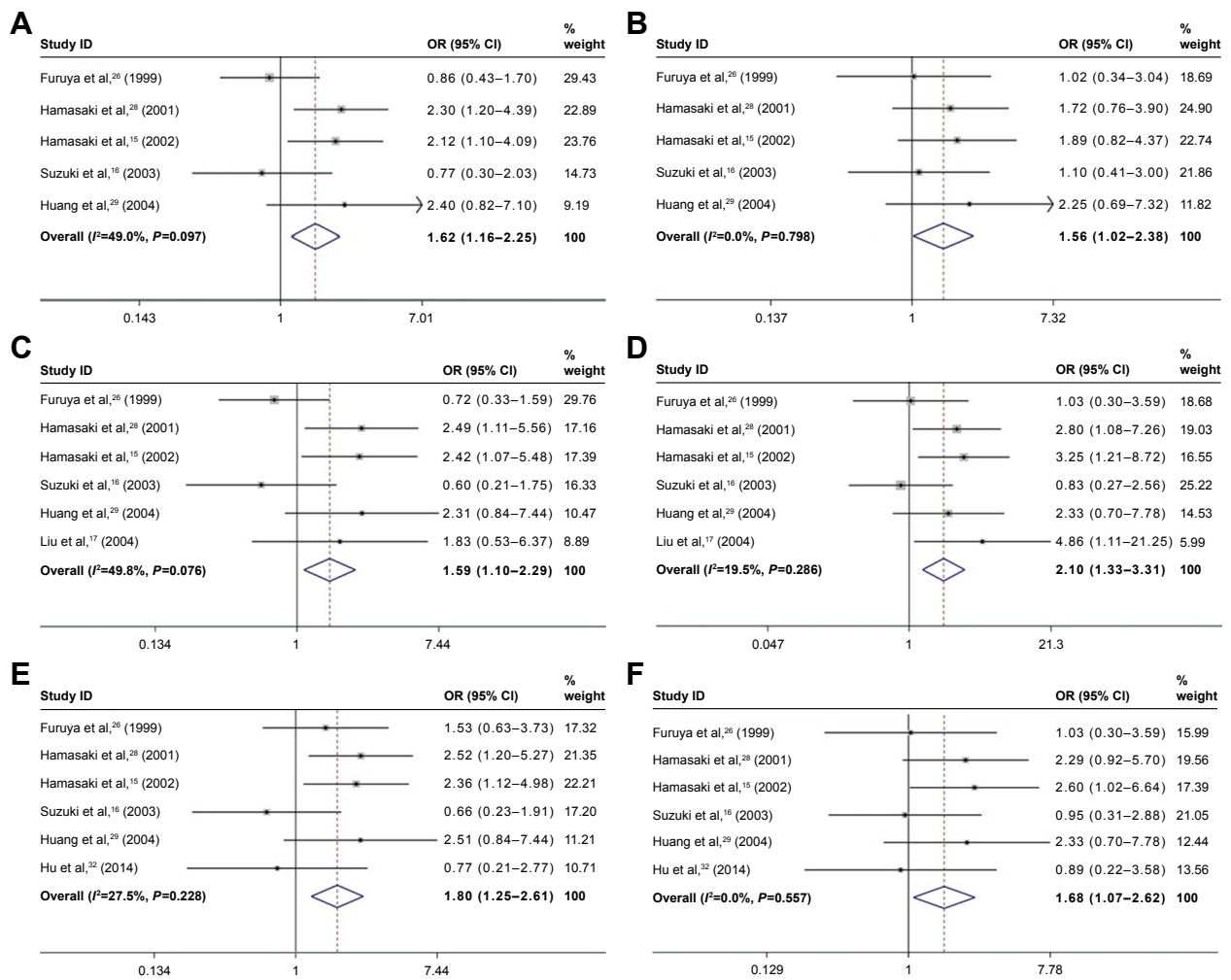


Figure 5 ORs of PCa associated with VDR TaqI polymorphisms in different tumor stages.

Notes: T vs t (A, B), TT vs Tt (C, D) and TT vs (Tt/tt) (E, F) were analyzed by fixed effects analysis. (A, C, E: Advanced vs Control; B, D, F: Advanced vs Local).

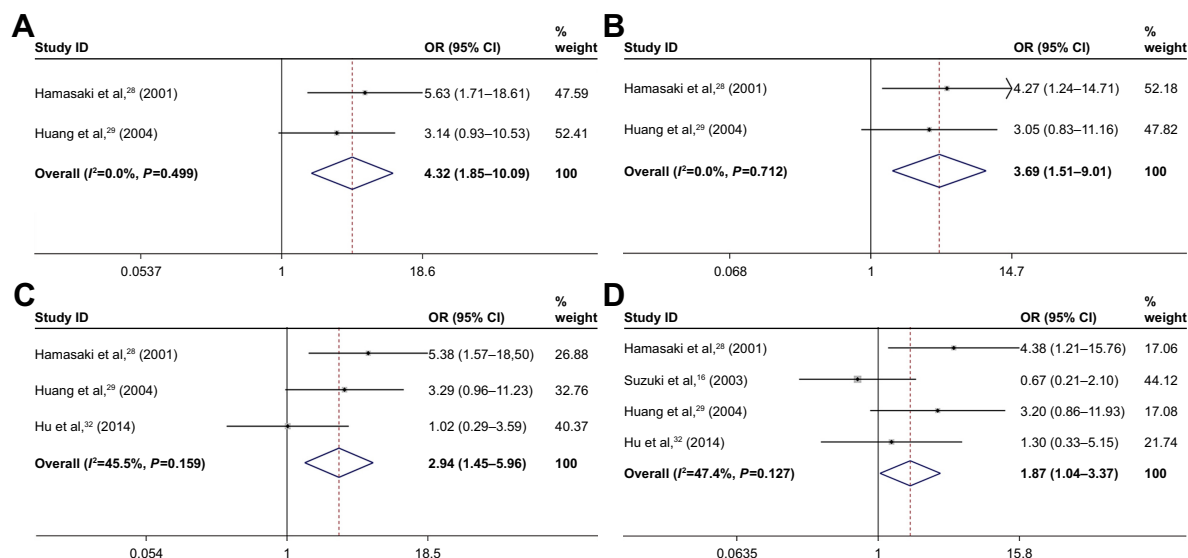
Abbreviations: OR, odds ratio; PCa, prostate cancer; VDR, vitamin D receptor.

Table 5 Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk in different Gleason stages

Gene	Studies	Test for overall effect			Heterogeneity		M	Publication bias	
		OR (95% CI)	Z-score	P-value	$I^2$	P-value		Begg's test	Egger's test
Gleason < 7 vs control									
T vs t	4	1.31 (0.96–1.78)	1.68	0.093	0%	0.617	F	0.089	0.057
TT vs Tt	5	1.14 (0.81–1.62)	0.76	0.449	0%	0.927	F	0.221	0.146
TT vs tt	4	2.20 (0.81–5.93)	1.55	0.121	0%	0.384	F	0.296	0.081
TT vs (Tt/tt)	5	1.18 (0.85–1.62)	0.99	0.322	0%	0.717	F	0.086	0.120
(TT/Tt) vs tt	4	2.10 (0.78–5.66)	1.47	0.141	0%	0.397	F	0.296	0.067
Gleason ≥ 7 vs control									
T vs t	2 <sup>a</sup>	4.32 (1.85–10.1) <sup>a</sup>	3.39 <sup>a</sup>	0.001 <sup>a</sup>	0% <sup>a</sup>	0.499 <sup>a</sup>	F <sup>a</sup>	1.000 <sup>a</sup>	–
TT vs Tt	3 <sup>a</sup>	2.21 (0.80–6.12) <sup>a</sup>	1.52 <sup>a</sup>	0.128 <sup>a</sup>	58.7% <sup>a</sup>	0.089 <sup>a</sup>	R <sup>a</sup>	0.296 <sup>a</sup>	0.066 <sup>a</sup>
TT vs tt	3	2.89 (0.51–16.6)	1.19	0.232	6.2%	0.302	F	1.000	–
TT vs (Tt/tt)	3 <sup>a</sup>	2.94 (1.45–5.96) <sup>a</sup>	2.98 <sup>a</sup>	0.003 <sup>a</sup>	45.5% <sup>a</sup>	0.159 <sup>a</sup>	F <sup>a</sup>	1.000 <sup>a</sup>	0.309 <sup>a</sup>
(TT/Tt) vs tt	3	2.61 (0.45–15.2)	1.06	0.288	0%	0.402	F	1.000	–
Gleason ≥ 7 vs Gleason < 7									
T vs t	2 <sup>a</sup>	3.69 (1.51–9.01) <sup>a</sup>	2.87 <sup>a</sup>	0.004 <sup>a</sup>	0% <sup>a</sup>	0.712 <sup>a</sup>	F <sup>a</sup>	1.000 <sup>a</sup>	–
TT vs Tt	4	1.78 (0.98–3.25)	1.89	0.059	48.3%	0.122	F	1.000	0.840
TT vs tt	3	2.71 (0.34–21.6)	0.94	0.346	0%	0.878	F	1.000	–
TT vs (Tt/tt)	4	1.87 (1.04–3.37)	2.08	0.037	47.4%	0.127	F	1.000	0.414
(TT/Tt) vs tt	3	2.63 (0.32–21.7)	0.90	0.369	0%	0.974	F	1.000	–

Notes: <sup>a</sup>Suzuki et al's<sup>16</sup> study was excluded. "–" indicates no data.

Abbreviations: F, fixed effects model; M, effect model of meta-analysis; OR, odds ratio; PCa, prostate cancer; R, random effects model; VDR, vitamin D receptor.



**Figure 6** ORs of PCa associated with VDR TaqI polymorphisms in different Gleason stages.

**Notes:** T vs t (**A, B**) and TT vs (Tt/tt) (**C, D**) were analyzed by fixed effects analysis. (**A, C:** Gleason  $\geq 7$  vs Control; **B, D:** Gleason  $\geq 7$  vs Gleason  $< 7$ ).

**Abbreviations:** OR, odds ratio; PCa, prostate cancer; VDR, vitamin D receptor.

After the exclusion of this study, we found it did not reduce the between-study heterogeneity obviously, and the outcome remained no statistical significance in the development of BPH (Table 2). In the subgroup analysis of Gleason  $\geq 7$  vs Control or Gleason  $\geq 7$  vs Gleason  $< 7$ , the sensitivity analysis indicated that an independent study by Suzuki et al<sup>16</sup> was the principal reference for heterogeneity of TaqI polymorphism in Gleason stage. After the exclusion of this study, the heterogeneity was effectively decreased or was eliminated (Table 5).

## Discussion

Studies have shown that VDR TaqI polymorphisms were associated with susceptibility to several carcinomas, such as breast cancer, oral cancer, and PCa.<sup>34–37</sup> However, the association between VDR TaqI genetic polymorphisms and PCa risk is still controversial, which may be caused by unscientific research or insufficient subjects and control numbers used in studies. In a study of Taylor et al, which included 96 cases of PCa and 162 non-BPH controls, they revealed that subjects carrying tt genotype have lower risk of PCa compared with TT/Tt genotype (OR = 0.32, 95% CI = 0.15–0.75,  $P < 0.01$ ).<sup>8</sup> Recently, similar results were also reported in studies by Liu et al,<sup>38</sup> Guo et al,<sup>39</sup> and Bonilla et al<sup>40</sup>, while 3 other studies<sup>12,41,42</sup> showed different conclusions. To evaluate the association of VDR TaqI genetic polymorphisms and susceptibility to PCa in Asian population, a comprehensive study of the previous research was performed by an updated systematic meta-analysis, which is the newest and most complete.

In the study of Fei et al,<sup>14</sup> they mentioned that inclusion of population with BPH as control may bias the results. So we divided the subjects as 1), healthy, 2), BPH, and 3), case group. Combined analysis of 4 studies suggested no significant correlation between TaqI VDR polymorphism and BPH risk. Besides, we conducted a subgroup analysis according to different Asian countries, which is an important biological factor that may affect the function of VDR by gene interaction. Interestingly, no association was shown except in the Japanese population. These inconsistent phenomena in different Asian countries may be a result of discrepant environmental conditions.

According to the different classification methods, TNM stage is based on the size of tumor diameter, lymph node metastasis, and distant metastasis staging, while Gleason stage is based on the degree of gland differentiation and tumor growth in the interstitial tissue.<sup>43</sup> These 2 methods are independent, but could be complementary to assess the risk of cancer. Fei et al's study showed the genotypes TT and TT/Tt were significantly higher in the advanced PCa group compared with the control group, indicating that T allele is riskier and easier to advanced stage,<sup>14</sup> which was consistent with our results (Table 4 and Figure 5), while no statistically significant difference was shown according to Gleason staging. But in our study, we found a higher frequency of T allele gene and TT genotype in the Gleason  $\geq 7$  stage PCa compared with Gleason  $< 7$  or Control, suggesting that PCa patients carrying T allele and TT genotype are more prone to entering an advanced stage (Table 5 and Figure 6).

Moreover, there are several limitations of this meta-analysis. 1) Observational studies are susceptible to a wide variety of biases, such as genotyping errors, allelic heterogeneity, and selection bias; 2) in some studies, lack of clear explanation for the pathologic diagnostic results of subjects. The pathogenesis of sporadic PCa differs with hereditary PCa, which may lead to inevitable selection bias; 3) the conclusions of Gleason staging subgroup analyses might be limited because of a low statistical power of the small sample size; and 4) besides genetic polymorphisms, many factors, such as occupation, diet, smoking, age, and other confounding factors might contribute to the development of PCa.

## Conclusion

Our results suggest that the VDR TaqI polymorphism might be associated with PCa risk in Asian male population, especially in the Japanese population. Moreover, PCa patients carrying T allele and TT genotype more easily progress to advanced stage. Therefore, these results indicate a high specificity and valuable biomarker to detect potential PCa in Asian population. Further steps should be taken to evaluate the gene-to-gene and gene-to-environment combined effect, and the total population and/or selected populations with different environmental background are urgently needed to conduct large scale multi-center epidemiological studies.

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## Disclosure

The authors report no conflicts of interest in this work.

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