Polymorphisms of vitamin D receptor gene TaqI susceptibility of prostate cancer: a meta-analysis

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Objective: Many studies have investigated the association of the vitamin D receptor gene TaqI polymorphism with prostate cancer (PCa) risk. However, the evidence is inadequate to draw robust conclusions. To shed light on these inconclusive findings, we conducted a meta-analysis.

Materials and methods: We searched PubMed for eligible articles. The relevant data were abstracted by two independent reviewers with the Stata 11.0 software.

Results: A total of 27 studies were included. The pooled outcomes indicated that the TaqI genetic polymorphisms were significantly associated with the risk of PCa (T vs t allele: odds ratio [OR] = 1.11, 95% confidence interval [CI] = 1.03–1.21, P = 0.008; TT vs tt: OR = 1.19, 95% CI = 1.01–1.42, P = 0.040; TT + Tt vs tt: OR = 1.18, 95% CI = 1.02–1.38, P = 0.031), especially in the Asian population (T vs t allele: OR = 1.11, 95% CI = 1.03–1.21, P = 0.008; TT/Tt vs tt: OR = 1.93, 95% CI = 1.02–3.66, P = 0.043). In the tumor stage stratified analyses, the pooled results showed no significant difference in genetic polymorphisms between the local tumor group and the control group or between the local tumor group and the advanced tumor group. However, the genotypes TT and TT/Tt were significantly higher in the advanced PCa group compared to the control group (T vs t allele: OR = 1.20, 95% CI = 1.01–1.42, P = 0.040; TT vs tt: OR = 1.34, 95% CI = 1.08–1.67, P = 0.009; TT/Tt vs tt: OR = 1.28, 95% CI = 1.05–1.56, P = 0.015).

Conclusion: The vitamin D receptor gene TaqI allele polymorphism might be associated with a PCa risk, especially in Asians, which might provide new clues for the pathogenesis research and clinical diagnosis of PCa in the future.

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

Introduction
Prostate cancer (PCa) is the second-most frequently diagnosed cancer in males around the world. It is also one of the leading causes of cancer death among men of all races.1

Its etiology has remained unclear, and few risk factors have been established for PCa other than older age, a positive family history, and race.2 Some previous epidemiological studies suggested that low serum levels of the vitamin D receptor (VDR) might be a risk factor for PCa.3,4 Such low levels could be recognized by 1 alpha, 25-dihydroxyvitamin D3 – active form of vitamin D – and its analogs, and through the interaction between these substances, the tumor cell growth cycle could be fixed in the G1 phase, leading to stagnation of the tumor cells.5 However, the mechanism responsible for reduced VDR expression is still not known.

Recently, some studies have shown that VDR gene polymorphisms have functional significance for the stability of mRNA and the protein translation efficiency and may be responsible for the reduced VDR level.6,7 The human VDR gene is located on chromosome 12q13.11 and consists of 14 exons spanning ∼75 kb.8,9 It is highly polymorphic with at least 618 variants reported, most of which are either undetectable or present
at a low frequency in the general population, according to the dbSNP database. TaqI is one of the most extensively studied SNP and is located in exon 9 of the VDR gene. Several previous studies have suggested that TaqI might alter VDR mRNA levels through regulation of mRNA stability and be associated with PCa risk. A number of case–control studies were conducted to investigate the association between the TaqI and the risk of PCa. However, existing evidence is inadequate to draw robust conclusions because the results are not consistent and most studies were generally small. Three published meta-analyses have been reported, but no positive conclusions were given. Subsequently, four new studies have provided additional data on the association between TaqI and PCa risk. Therefore, to shed light on these inconclusive findings, we used the new data to conduct a meta-analysis to revisit the association between the VDR TaqI polymorphism and the risk and characteristics of PCa.

Materials and methods

Search strategy
We searched the PubMed and Web of Science databases up to September 8, 2015, for relevant studies about the association of VDR gene TaqI polymorphism and PCa without language restrictions. The search terms included polymorphism, vitamin D receptor, vitamin D receptor, 1,25-dihydroxyvitamin D receptor, calcitriol receptor, VDR, and PCa, prostate neoplasm, prostate tumor, prostate carcinoma, or prostatic neoplasm.

Inclusion/exclusion criteria
The title, abstract, and full text of the candidate studies were independently screened by two reviewers. A study was included when all of the following criteria were met: 1) A nonfamilial case–control and cohort study that examined the association between VDR polymorphism and PCa with genotyping data for TaqI was included. 2) A study that used men with benign prostatic hyperplasia was included, but a study based on family or pedigree was excluded because of consideration of disease specificity and genetic linkage. 3) A study on localized PCa: confined within the prostate, stages T1–T2 or stages A–B; advanced PCa: extraprostatic or metastatic cancer involving lymph nodes or other organs, stages T3–T4 or stages C–D was included. 4) A study that had complete data or data that could be used to calculate an odds ratio (OR) and a 95% confidence interval (95% CI) was included. 5) A study that used men with benign prostatic hyperplasia as a control was included. 6) A case-only study or a study that had incomplete data for the control group was excluded.

Data extraction
Information was carefully extracted from all eligible publications by two independent reviewers (Fei and Liu), based on the aforementioned inclusion criteria. Any disagreements were arbitrated by discussion with a third reviewer (Wu). The following data were collected from each study: the first author’s surname, the year of publication, the study location, the ethnicity, the source of the controls, the laboratory methods used to detect VDR TaqI polymorphism, and the number of cases and controls. The ethnic groups were mainly defined as Caucasian, Asian, and African. For analysis of the risk factors associated with PCa, we divided the clinical stages and Gleason score into the following two groups: a local group and an advanced group as described previously, Gleason score <7 and ≥7 groups.

Quality assessment
We used the Newcastle–Ottawa Scale (NOS) to assess the quality of each eligible study. When an item was met, the study got one point. The NOS runs from zero to nine points. A study was considered high quality if it received more than four points.

Statistical analysis
The strength of the association between TaqI T/t polymorphism and the risk of PCa was indicated by an OR with a 95% CI. The statistical significance of the pooled OR was assessed with the Z-test and a P-value of <0.05 was considered significant. A chi-square-based Q-test was conducted to measure the heterogeneity of eligible studies, and the heterogeneity was considered significant if the P-value for heterogeneity test was <0.05. Subgroup analyses were conducted to identify the possible variables or characteristics that moderated the obtained results. A sensitivity analysis in which one study was excluded at a time was conducted to evaluate the influence of an individual study based on the results. Begg’s funnel plot and Egger’s regression test were used to evaluate the publication bias (no publication bias was indicated by a two-sided P-value ≥0.05). All analyses were conducted using the Stata version 11.0 software (StataCorp LP, College Station, TX, USA), and a two-sided P-value ≥0.05 indicated no significance.

Results

Literature search
The study selection process is shown in Figure 1. The primary literature search identified 507 studies. After the titles and abstracts were screened, 387 studies were excluded; 78 were reviews, meta-analyses, and letters. The full texts of the remaining 42 studies were evaluated further. As a result, 27 studies were included in the meta-analysis.
Characters and assessments of involved studies
The 27 eligible studies included 12,276 cases and 13,506 controls and were assessed by the NOS (Table S1). Each had a score of >4, which means that all the studies had high quality. The distribution of the VDR gene TaqI polymorphism genotype and allele is shown in Tables 1 and S2.

Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk
The pooled results of 27 relevant studies on the correlation between TaqI polymorphisms and the risk of PCa are presented in Table 2 and Figure 2. The outcome indicated that TaqI genetic polymorphism was significantly associated with the risk of PCa (T vs t allele: OR =1.11, 95% CI =1.03–1.21, P=0.008; TT/Tt vs tt: OR =1.19, 95% CI =1.01–1.42, P=0.040; TT + Tt vs tt: OR =1.18, 95% CI =1.02–1.38, P=0.031).

Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk in different populations
A previous study showed that ethnicity was a primary risk factor for PCa. In order to draw attention to this point, an stratified analysis of ethnicity was performed and the pooled results indicated that TaqI genetic polymorphism in the VDR gene was closely linked to the pathogenesis of PCa among Asian populations (T vs t allele: OR =1.11, 95% CI =1.03–1.21, P=0.008; TT/Tt vs tt: OR =1.93, 95% CI =1.02–3.66, P=0.043) (Table 3 and Figure 3). A sensitivity analyses indicated that an independent study by Jingwi et al was the principal reference for heterogeneity of TaqI polymorphism in the African population. After the exclusion of this study, the heterogeneity was effectively decreased or was eliminated, and the outcome showed that no statistical significance was found among African or Caucasian populations.

Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk in different tumor stages and Gleason score
We also performed a stratified analysis based on the tumor stage and the Gleason score to delineate the association of VDR gene TaqI polymorphism with PCa risk in more detail. As shown in Table 4 and Figure 4, in the tumor stage stratified analysis, the pooled results showed no significant difference in the genetic polymorphism between local tumor group and the control group or between the local tumor group and the advanced tumor group. However, the genotypes TT and TT/Tt were significantly higher in the advanced
PCa group compared to the control group (T vs t allele: OR = 1.20, 95% CI = 1.01–1.42, \( P = 0.040 \); TT vs tt: OR = 1.34, 95% CI = 1.08–1.67, \( P = 0.009 \); TT/Tt vs tt: OR = 1.28, 95% CI = 1.05–1.56, \( P = 0.015 \)).

In the Gleason score stratified analysis, no statistically significant difference in the distribution of the allele and genotype of TaqI polymorphism was evident (TT/Tt vs tt: OR = 1.28, 95% CI = 0.52–3.13, \( P = 0.584 \); TT vs Tt/tt: OR = 0.79, 95% CI = 0.45–1.37, \( P = 0.396 \)). However, the number of articles included was too little to draw a robust conclusion. Therefore, further relevant studies should be performed in the future.

Table 2: Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk

| Gene | Studies | Test for overall effect | \( \text{OR (95\% CI)} \) | \text{Z-score} | \text{P-value} | \text{Heterogeneity} | \( \bar{I}^2 \) | \text{P-value} | \text{Public bias} | Begg’s test | Egger’s test |
|------|---------|------------------------|--------------------------|--------------|--------------|---------------------|---------|--------------|----------------|-------------|-------------|
| T vs t | 27      | 1.11 (1.03–1.21)       | 2.64                     | 0.008        | 36.9%        | 0.029               | 0.478   | 0.423        |
| TT vs Tt | 27     | 1.07 (0.94–1.22)       | 1.05                     | 0.296        | 49%          | 0.002               | 0.835   | 0.550        |
| TT vs tt | 24    | 1.19 (1.01–1.42)       | 2.06                     | 0.040        | 34.4%        | 0.051               | 0.673   | 0.724        |
| TT vs (tt/Tt) | 26 | 1.10 (0.99–1.24) | 1.73                    | 0.084        | 41.5%        | 0.015               | 0.692   | 0.949        |
| (TT/Tt) vs tt | 24 | 1.18 (1.02–1.38) | 2.15                    | 0.031        | 31.4%        | 0.072               | 0.673   | 0.460        |

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

Sensitivity analysis
Sensitivity analyses were performed by the sequential omission of individual studies for all subjects and stratified analyses. Except for the stratified analyses of the association between TaqI polymorphism and PCa risk in an African population, the corresponding pooled ORs were not materially altered in the other stratified analyses, indicating the robustness of the results of this meta-analysis.

Publication bias assessment
Begg’s funnel plot and Egger’s test were performed to assess the publication bias in the literature. No evidence
A meta-analysis of TaqI genetic polymorphisms

Figure 2 (Continued)
Figure 2 ORs of prostate cancer associated with VDr TaqI polymorphisms.

Notes: (A) T vs t, (B) TT vs Tt, and (C) (TT/Tt) vs tt. Weights are from random effects analysis.

Abbreviations: OR, odds ratio; VDR, vitamin D receptor; CI, confidence interval.

Table 3 Meta-analysis of the association of VDr gene TaqI polymorphism with PCa risk in different populations

| Gene  | Studies | Test for overall effect | Heterogeneity | Public bias |
|-------|---------|-------------------------|---------------|-------------|
|       |         | OR (95% CI) Z-score P-value | I² P-value   | Begg's test | Egger's test |
| Caucasian |       |                         |              |             |
| T vs t | 13      | 1.06 (0.97–1.17) 1.31 0.191 | 22.9% 0.212 | 0.583 0.474 |
| TT vs Tt | 13     | 1.02 (0.86–1.21) 0.24 0.898 | 46.2% 0.034 | 0.855 0.842 |
| TT vs Tt | 13     | 1.14 (0.97–1.33) 1.55 0.122 | 2.1% 0.425 | 0.583 0.737 |
| TT vs (Tt/Tt) | 13 | 1.04 (0.90–1.21) 0.55 0.579 | 36.6% 0.090 | 0.360 0.814 |
| (TT/Tt) vs tt | 14 | 1.13 (0.94–1.35) 1.26 0.208 | 28.6% 0.150 | 0.511 0.648 |
| African |       |                         |              |             |
| T vs tt | 5       | 1.04 (0.85–1.28) 0.42a 0.676a | 0.0% 0.956 | 0.806a 0.917a |
| TT vs Tt | 5     | 0.97 (0.74–1.29) 0.18a 0.858a | 0.0% 0.558 | 0.221a 0.854a |
| TT vs Tt | 5     | 1.22 (0.75–1.97) 0.80a 0.421a | 0.0% 0.844 | 0.806a 0.935a |
| TT vs (Tt/Tt) | 5 | 1.01 (0.78–1.32) 0.08a 0.933a | 0.0% 0.805 | 0.462a 0.781a |
| (TT/Tt) vs tt | 6 | 1.32 (0.94–1.87) 1.59 0.112 | 0.0% 0.808 | 0.368 0.366 |
| Asian |       |                         |              |             |
| T vs t | 9       | 1.27 (1.06–1.52) 2.56 0.010 | 0.0% 0.527 | 0.175 0.308 |
| TT vs Tt | 9     | 1.07 (0.81–1.43) 0.49 0.627 | 39.1% 0.107 | 0.059 0.088 |
| TT vs Tt | 6     | 1.44 (0.59–3.51) 0.80 0.426 | 59.7% 0.030 | 0.452 0.969 |
| TT vs (Tt/Tt) | 8 | 1.19 (0.96–1.47) 1.58 0.115 | 0.0% 0.517 | 0.063 0.153 |
| (TT/Tt) vs tt | 6 | 1.93 (1.02–3.66) 2.02 0.043 | 11.8% 0.340 | 0.054 0.067 |

Note: Jingwi et al's study17 was excluded.

Abbreviations: VDR, vitamin D receptor; PCa, prostate cancer; OR, odds ratio; CI, confidence interval.
of publication bias was found for all analyses. Egger’s and Begg’s tests were not performed for the Gleason stratified analyses and the stage stratified analyses of TT vs tt in the comparison of local tumor group with the control group and the local tumor group with the advanced tumor group due to the small number of included studies.

Discussion

Various factors contribute to the basic pathology of PCa. Clinical diagnosis of the disease is aided by prostate-specific antigen and biopsy, but none of these methods provide a definitive diagnosis and/or a credible assessment of progression of the disease. Recently, genetic susceptibility to cancer has been a focus of research by the scientific community. The development and progression of PCa are influenced by vitamin D synthesis. Therefore, the polymorphism of genes that encode key proteins involved in vitamin D synthesis and metabolism has been chosen as primary candidate genes for PCa susceptibility. Currently, a growing number of studies that have revealed polymorphic variants of the VDR gene were associated with the etiology of PCa. In this meta-analysis, we have analyzed the role of the VDR gene TaqI polymorphism in PCa, which is located in exon 9 and is responsible for the stability of the mRNA.

A Study of publication bias was found for all analyses. Egger’s and Begg’s tests were not performed for the Gleason stratified analyses and the stage stratified analyses of TT vs tt in the comparison of local tumor group with the control group and the local tumor group with the advanced tumor group due to the small number of included studies. OR (95% CI) % weight

| Study                        | Caucasian       | African         | Asian          |
|------------------------------|-----------------|-----------------|----------------|
| Taylor et al9                | 1.24 (0.86–1.78) | 1.19 (0.19–7.46) | 1.09 (0.64–1.86) |
| Ma et al20                   | 1.04 (0.86–1.26) | 1.53 (1.18–1.97) | 0.86 (0.45–1.64) |
| Correa-Cerro et al21         | 1.12 (0.75–1.68) | 1.40 (0.39–5.00) | 1.22 (0.84–1.78) |
| Bleda et al23                | 0.99 (0.66–1.47) | 0.72 (0.18–2.82) | 1.82 (1.09–3.03) |
| Medeiros et al28             | 1.11 (0.82–1.49) | 0.98 (0.66–1.44) | 1.48 (0.76–2.99) |
| Gorf et al27                 | 0.78 (0.58–1.05) | 0.94 (0.71–1.25) | 1.01 (0.37–2.73) |
| Tayeb et al23                | 0.90 (0.48–1.68) | 0.99 (0.71–1.36) | 1.81 (0.66–5.25) |
| Tayeb et al23                | 4.54 (1.51–13.66)| 1.07 (0.85–1.35) | 1.13 (0.84–1.38) |
| Bodiwala et al31             | 1.07 (0.85–1.35) | 0.94 (0.71–1.25) | 0.98 (0.66–1.44) |
| Oakley-Girvan et al32        | 4.54 (1.51–13.66)| 1.07 (0.85–1.35) | 1.13 (0.84–1.38) |
| Andersson et al25            | 1.07 (0.85–1.35) | 4.54 (1.51–13.66)| 1.07 (0.85–1.35) |
| Onen et al27                 | 0.99 (0.71–1.36) | 0.94 (0.71–1.25) | 0.98 (0.66–1.44) |
| Rowland et al14              | 1.11 (0.97–1.26) | 1.38 (0.98–1.95) | 1.11 (0.97–1.26) |
| Subtotal (I²=22.9%, P=0.212) | 1.06 (0.97–1.17) | 6.60            |

A Study of publication bias was found for all analyses. Egger’s and Begg’s tests were not performed for the Gleason stratified analyses and the stage stratified analyses of TT vs tt in the comparison of local tumor group with the control group and the local tumor group with the advanced tumor group due to the small number of included studies. OR (95% CI) % weight

| Study                        | African         | Asian          |
|------------------------------|-----------------|----------------|
| Kibel et al19                | 1.19 (0.19–7.46) | 0.86 (0.45–1.64) |
| Jingwi et al17               | 1.53 (1.18–1.97) | 1.22 (0.84–1.78) |
| Taylor et al6                | 1.40 (0.39–5.00) | 1.82 (1.09–3.03) |
| Blazer et al23               | 0.72 (0.18–2.82) | 1.48 (0.76–2.99) |
| Oakley-Girvan et al32        | 0.98 (0.66–1.44) | 1.01 (0.37–2.73) |
| Rowland et al14              | 1.07 (0.84–1.38) | 1.81 (0.66–5.25) |
| Subtotal (I²=15.4%, P=0.315) | 1.20 (0.99–1.45) | 1.13 (0.64–1.86) |

| Study                        | Asian          |
|------------------------------|----------------|
| Watanabe et al22             | 1.09 (0.64–1.86) |
| Furuya et al23               | 0.86 (0.45–1.64) |
| Habuchi et al24              | 1.22 (0.84–1.78) |
| Hamasaki et al1              | 1.82 (1.09–3.03) |
| Huang et al23                | 1.48 (0.76–2.99) |
| Chaimuangraj et al31         | 1.01 (0.37–2.73) |
| Onsory et al38               | 1.48 (0.96–2.28) |
| Hu et al35                   | 0.75 (0.38–1.49) |
| Yousaf et al18               | 1.47 (0.84–2.57) |
| Subtotal (I²=0.0%, P=0.527)  | 1.27 (1.06–1.52) |

Overall (I²=17.8%, P=0.203) 1.12 (1.03–1.21)
We found that a variant TaqI allele (t) was significantly correlated with a reduced risk of PCa, suggesting it might be a protective factor for PCa, which was consistent with a previous meta-analysis.10

Ethnicity is an important biological factor that might influence VDR function through gene–gene interaction. In our analysis, the association of TaqI polymorphism with a PCa risk was observed in the Asian population, which was consistent with Yin et al10 Although the underlying mechanism for the observed ethnic difference in the PCa risk must still be elucidated, a tumor-protective effect of the TaqI t allele in Asians was significantly more pronounced than in the other two ethnic groups, Caucasians and Africans. In the Asian population, a tt genotype carrier had a lower risk of PCa, compared to a TT or TT/Tt genotype.

We also performed tumor stage and Gleason score stratified analyses. Differently from Yin et al’s study,10 we obtained some positive results. We found that the t allele and the tt genotype could reduce the PCa risk when compared with the T allele, TT genotype, or TT/Tt genotype, indicating that variant the TaqI t allele might indeed be associated with disease progression. However, the Gleason score stratified analysis indicated no association between TaqI polymorphism and PCa risk.
Table 4 Meta-analysis of the association of VDR gene TaqI polymorphism with PCa risk in different tumor stages

| Stage                  | Studies | Test for overall effect | Heterogeneity | Public bias | Begg’s test | Egger’s test |
|------------------------|---------|-------------------------|---------------|-------------|-------------|--------------|
|                        |         | OR (95% CI)             | Z-score       | P-value     | I²          | P-value      |              |
| local vs control       |         |                         |               |             |             |              |              |
| T vs t                 | 5       | 1.09 (0.95–1.25)        | 1.18          | 0.237       | 0.0%        | 0.939        | 0.806 0.741 |
| TT vs tt               | 2       | 1.26 (0.91–1.73)        | 1.40          | 0.160       | 0.0%        | 0.635        | – –          |
| TT vs Tt               | 5       | 0.97 (0.80–1.18)        | 0.32          | 0.752       | 0.0%        | 0.941        | 0.806 0.213 |
| TT vs (tt/Tt)          | 6       | 1.07 (0.88–1.31)        | 0.68          | 0.498       | 3.3%        | 0.395        | 1.000 0.885 |
| (TT/Tt) vs tt          | 4       | 1.16 (0.88–1.53)        | 1.07          | 0.287       | 0.0%        | 0.451        | 0.734 0.442 |
| advanced vs control    |         |                         |               |             |             |              |              |
| T vs t                 | 6       | 1.20 (1.01–1.42)        | 2.05          | 0.040       | 31.5%       | 0.199        | 0.452 0.354 |
| TT vs tt               | 4       | 1.34 (1.08–1.67)        | 0.63          | 0.009       | 0.0%        | 0.746        | 0.734 0.216 |
| TT vs Tt               | 6       | 1.15 (0.86–1.52)        | 0.93          | 0.352       | 45.6%       | 0.101        | 0.707 0.799 |
| TT vs (tt/Tt)          | 7       | 1.17 (0.89–1.54)        | 1.14          | 0.256       | 43.6%       | 0.100        | 0.368 0.941 |
| (TT/Tt) vs tt          | 6       | 1.28 (1.05–1.56)        | 2.44          | 0.015       | 0.0%        | 0.821        | 0.420 0.189 |
| local vs advanced      |         |                         |               |             |             |              |              |
| T vs t                 | 5       | 0.95 (0.82–1.10)        | 0.65          | 0.515       | 0.0%        | 0.536        | 0.462 0.191 |
| TT vs tt               | 2       | 1.02 (0.72–1.45)        | 0.13          | 0.896       | 0.0%        | 0.663        | – –          |
| TT vs Tt               | 5       | 0.76 (0.48–1.21)        | 1.14          | 0.255       | 32.9%       | 0.202        | 0.806 0.575 |
| TT vs (tt/Tt)          | 6       | 0.87 (0.62–1.21)        | 0.84          | 0.400       | 14.0%       | 0.325        | 0.260 0.805 |
| (TT/Tt) vs tt          | 4       | 1.01 (0.74–1.38)        | 0.08          | 0.938       | 0.0%        | 0.628        | 0.734 0.054 |

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

Figure 4 (Continued)
Study limitations

Although our study showed some positive results, this meta-analysis had several limitations that should be taken consideration when assessing the results. First, although we performed subgroup analyses stratified by ethnicity, tumor stage, and the Gleason score, heterogeneity of TaqI polymorphism among the studies still exists, which suggested that other potential confounding factors were present in the included studies, such as genotyping error, selection bias, population-specific gene–gene or gene–environment interaction, allelic heterogeneity, and chance.41,42 Although evidence for heterogeneity exists, the sensitivity analysis indicated that studies contributing to the heterogeneity did not significantly affect the estimate of the overall OR. Second, the overall outcomes were based on unadjusted effect estimates. Although the cases and controls were matched for age, sex, and residence in all studies, these confounding factors could slightly modify the effective estimates and a more precise evaluation would have to be adjusted for the potentially suspicious factors. Third, benign prostate hyperplasia was used as control in some included studies, which could affect the pooled results to a varying degree. Finally, in some pooled analyses such as Gleason score striated analysis, the number of included studies was too small, so further relevant studies should be performed in the future so that a stronger conclusion could be drawn.

Conclusion

In summary, a strong association was observed between VDR TaqI genetic polymorphism and PCa, and therefore, TaqI genetic polymorphism may be valuable as a biomarker, especially in Asians. Considering that the quality and quantity of the reviewed articles were limited, larger, well-designed studies should be used in the future to further confirm the association between TaqI genetic polymorphism and PCa.

Disclosure

The authors report no conflicts of interest in this work.

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### Supplementary materials

**Table S1** Characteristics and quality assessment of eligible studies in meta-analysis

| Study                  | Country | Ethnicity              | Study design        | Genotyping method     | Quality indicators from Newcastle–Ottawa Scale | H–w test |
|------------------------|---------|------------------------|---------------------|-----------------------|-----------------------------------------------|----------|
| Taylor et al<sup>6</sup> | USA     | Caucasian, African     | Hospital based      | RFLP-PCR              | 6                                              | Yes      |
| Kibel et al<sup>19</sup> | USA     | Caucasian, African     | Hospital based      | PCR-RFLP              | 7                                              | Yes      |
| Ma et al<sup>20</sup>   | USA     | Caucasian              | Nested in PHS cohort study | PCR-RFLP              | 7                                              | Yes      |
| Correa-Cerro et al<sup>21</sup> | Germany | Caucasian              | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Watanabe et al<sup>22</sup> | Japan   | Asian                  | Hospital based      | PCR-RFLP              | 6                                              | No       |
| Furuya et al<sup>23</sup> | Japan   | Asian                  | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Habuchi et al<sup>24</sup> | Japan   | Asian                  | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Blazer et al<sup>25</sup> | USA     | Caucasian, African     | Community based     | PCR-RFLP              | 8                                              | No       |
| Hamsaki et al<sup>26</sup> | Japan   | Asian                  | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Medeiros et al<sup>27</sup> | Portugal | Caucasian              | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Gsur et al<sup>28</sup>  | Austria | Caucasian              | Hospital based      | PCR-RFLP              | 7                                              | Yes      |
| Tayeb et al<sup>29</sup>  | UK      | Caucasian              | Selected from pathology database | PCR-SSCP              | 6                                              | Yes      |
| Maistro et al<sup>30</sup> | Brazil  | Caucasian, African     | Population based    | PCR-RFLP              | 6                                              | Yes      |
| Bodiwala et al<sup>31</sup> | UK      | Caucasian              | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Oakley-Girvan et al<sup>32</sup> | USA     | Caucasian, African     | Population based    | PCR-RFLP              | 6                                              | Yes      |
| Huang et al<sup>33</sup>  | Taiwan  | Asian                  | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| John et al<sup>34</sup>   | USA     | Caucasian              | Population based    | PCR-RFLP              | 6                                              | Yes      |
| Andersson et al<sup>35</sup> | Sweden  | Caucasian              | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Chaimuangraj et al<sup>36</sup> | Thailand | Asian                  | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Holick et al<sup>37</sup>  | USA     | African, Caucasian     | Population based    | PCR-SSCP              | 6                                              | Yes      |
| Onen et al<sup>38</sup>   | Turkey  | Caucasian              | Hospital based      | PCR-RFLP              | 6                                              | Yes      |
| Onsory et al<sup>39</sup>  | India   | Indian                 | Hospital based      | PCR-SSCP              | 6                                              | Yes      |
| Rowland et al<sup>40</sup> | American| African, Caucasian     | Population based    | PCR-RFLP              | 6                                              | Yes      |
| Hu et al<sup>41</sup>     | People's Republic of China | Asian               | Hospital based      | Real-time PCR         | 6                                              | Yes      |
| Yousaf et al<sup>42</sup> | Pakistan | Asian                  | Hospital based      | PCR-SSCP              | 6                                              | Yes      |
| Jingwi et al<sup>43</sup>  | American| Caucasian              | Hospital based      | Real-time PCR         | 6                                              | Yes      |

**Abbreviations:** H–w, Hardy-Weinberg; RFLP, restriction fragment length polymorphism; PCR, polymerase chain reaction; SSCP, single-strand conformation polymorphism.

**Table S2** Distribution of TaqI allele and genotype

| Study                  | Group | Allele | Genotype |
|------------------------|-------|--------|----------|
| Taylor et al<sup>4</sup> | Case  | 216    | TT       |
| Control                | 340   | 187    | T        |
| Kibel et al<sup>19</sup> | Case  | 82     | Tt       |
| Control                | 82    | 48     | t        |
| Ma et al<sup>20</sup>   | Case  | 744    | TT       |
| 204 control            | 1,178 | 707    | T        |
| Correa-Cerro et al<sup>21</sup> | Case  | 212    | TT       |
| Control                | 190   | 116    | T        |
| Watanabe et al<sup>22</sup> | Case  | 200    | TT       |
| Control                | 404   | 356    | T        |
| Furuya et al<sup>23</sup> | Case  | 132    | Tt       |
| Control                | 120   | 100    | t        |
| Habuchi et al<sup>24</sup> | Case  | 444    | TT       |
| Control                | 674   | 587    | T        |
| Blazer et al<sup>25</sup> | Case  | 154    | TT       |
| Control                | 366   | 212    | T        |
| Hamasaki et al<sup>26</sup> | Case  | 230    | TT       |
| Control                | 266   | 216    | T        |

(Continued)
| Study          | Group | Allele | Genotype |
|---------------|-------|--------|----------|
|               |       | n  |  T   |  t  |  n  | TT  | Tt  |  tt |
| Medeiros et al | Case  | 324 | 195 | 129 | 162 | 52  | 91  | 19  |
|               | Control | 412 | 238 | 174 | 206 | 73  | 92  | 41  |
| Gsur et al    | Case  | 380 | 227 | 153 | 190 | 71  | 85  | 34  |
|               | Control | 380 | 249 | 131 | 190 | 81  | 87  | 22  |
| Tayeb et al   | Case  | 42  | 24  | 18  | 21  | 7   | 10  | 4   |
|               | Control | 758 | 453 | 305 | 379 | 136 | 181 | 62  |
| Tayeb et al   | Case  | 56  | 52  | 4   | 28  | 25  | 2   | 1   |
|               | Control | 112 | 83  | 29  | 56  | 32  | 19  | 5   |
| Maistro et al | Case  | 330 | 202 | 128 | 165 | 60  | 82  | 23  |
|               | Control | 400 | 272 | 128 | 200 | 95  | 82  | 23  |
| Bodiwala et al| Case  | 736 | 444 | 292 | 368 | 133 | 178 | 57  |
|               | Control | 486 | 285 | 201 | 243 | 80  | 125 | 38  |
| Oakley-Girvan et al | Case | 690 | 418 | 272 | 345 | 124 | 170 | 51  |
|               | Control | 584 | 365 | 219 | 292 | 115 | 135 | 42  |
| Huang et al   | Case  | 320 | 306 | 14  | 160 | 146 | 14  | 0   |
|               | Control | 410 | 384 | 26  | 205 | 179 | 26  | 0   |
| John et al    | Case  | 848 | 528 | 320 | 424 | 164 | 200 | 60  |
|               | Control | 872 | 506 | 366 | 436 | 153 | 200 | 83  |
| Andersson et al| Case | 274 | 164 | 110 | 137 | 51  | 62  | 24  |
|               | Control | 352 | 212 | 140 | 176 | 67  | 78  | 31  |
| Chaimuangraj et al | Case | 56  | 50  | 6   | 28  | 22  | 6   | 0   |
|               | Control | 148 | 132 | 16  | 74  | 59  | 14  | 1   |
| Holick et al  | Case  | 1,172 | 730 | 442 | 586 | 238 | 254 | 94  |
|               | Control | 1,090 | 648 | 442 | 545 | 188 | 272 | 85  |
| Onen et al    | Case  | 266 | 180 | 86  | 133 | 62  | 56  | 15  |
|               | Control | 314 | 189 | 125 | 157 | 57  | 75  | 25  |
| Onsory et al  | Case  | 200 | 150 | 50  | 100 | 55  | 40  | 5   |
|               | Control | 200 | 134 | 66  | 100 | 43  | 48  | 9   |
| Rowland et al | Case  | 3,252 | 2,172 | 1,080 | 1,626 | 732 | 708 | 186 |
|               | Control | 2,144 | 1,376 | 768 | 1,072 | 451 | 474 | 147 |
| Hu et al      | Case  | 216 | 202 | 14  | 108 | 96  | 10  | 2   |
|               | Control | 484 | 460 | 24  | 242 | 219 | 22  | 1   |
| Yousaf et al  | Case  | 88  | 67  | 21  | 44  | 27  | 13  | 4   |
|               | Control | 238 | 163 | 75  | 119 | 76  | 11  | 32  |
| Jingwi et al  | Case  | 612 | 451 | 161 | 306 | 170 | 111 | 25  |
|               | Control | 502 | 325 | 177 | 251 | 105 | 115 | 31  |