

Updated analysis of vitamin D receptor gene FokI polymorphism and prostate cancer susceptibility

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Abstract

Introduction: Polymorphisms of the vitamin D receptor (VDR) gene have been investigated in various case-control studies to evaluate prostate cancer susceptibility; however, published data on the association between vitamin D receptor gene FokI polymorphism and prostate cancer risk are inconclusive.

Material and methods: To assess the impact of vitamin D receptor gene FokI polymorphism, we performed a meta-analysis of eligible studies including 9,720 patients and 9,710 control subjects.

Results: The overall results indicated no obvious association of this variant on prostate cancer risk. However, in subgroup analysis by ethnicity, positive associations existed in Caucasian descendants for allelic contrast (OR = 1.03, 95% CI: 1.00–1.06, $p_{\text{heterogeneity}} = 0.552$, $p = 0.026$) and the dominant genetic model (OR = 1.03, 95% CI: 1.00–1.05, $p_{\text{heterogeneity}} = 0.856$, $p = 0.032$). In the subgroup analysis by tumor stage, there was a significant association between this variant and advanced prostate cancer under the recessive genetic model (OR = 1.15, 95% CI: 1.01–1.32, $p_{\text{heterogeneity}} = 0.469$, $p = 0.032$). In the subgroup analysis by source of control, association of the VDR FokI polymorphism and prostate cancer susceptibility was also found in population-based studies under homozygote comparison and the recessive genetic model.

Conclusions: The VDR FokI polymorphism may contribute to the risk of developing prostate cancer in Caucasian and population-based studies. Further large, well-designed studies are warranted to confirm this conclusion in more detail.

Key words: vitamin D receptor, polymorphism, cancer risk.

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Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed solid neoplasms in the male population [1]. In the United States, prostate cancer is the second leading cause of carcinoma deaths among males, with an estimated 192,000 new cases and 27,000 deaths in 2009 [2]. In European countries, it is recognized as the most common solid tumor, with an incidence rate of 214 cases in every thousand men, outnumbering lung and colorectal cancer [3]. Although epidemiological research indicated that the incidence of prostate cancer in Asians is much lower than that in the USA and European countries, the incidence and mor-

tality rate of this disease have rapidly increased among Chinese men [4, 5]. Data from the Global Estimates of Cancer indicated that the age standardized incidence rate of PCa in China was 4.3 per 10,000 males in 2008 [6]. With the improvement of diagnostic techniques and the aging of the population, morbidity and mortality of PCa show an increasing trend. So far, many factors including lifestyle, environment and race have been demonstrated as possible contributors to the risk of PCa [1]. However, the etiology of PCa remains unclear for the reason that a complex interplay between genetic and environmental factors is involved in the development and occurrence of PCa.

The human vitamin D receptor (VDR), located on chromosome 12q12–q14, is a nuclear receptor gene with 75 kb and consists of 11 exons and 11 introns [7]. VDR acts as a ligand-dependent transcriptional factor found in various types of tissues (including the prostate) by the interaction with vitamin D [8]. It has been found that 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], the active form of vitamin D, could enhance immune regulation, promote cell differentiation and inhibit tumor invasion and metastasis via the biological effects mediated by VDR in the prostate [9–11]. Therefore, a less active VDR could be associated with either a more aggressive disease or increased susceptibility to cancer risk [12]. Studies have shown that several single-nucleotide polymorphisms (SNPs) of VDR, which potentially affect the receptor binding of 1,25(OH)₂D₃, may influence vitamin D biological activity and confer susceptibility to prostate cancer [13]. Among them, the most commonly studied SNP is the restriction fragment length polymorphism of FokI, which is detected by the endonuclease FokI. The FokI located on the coding region (exon 2) of the VDR gene results in production of a VDR protein three amino acids longer [14].

A number of epidemiological studies have been carried out to explore the association between VDR FokI polymorphism and prostate cancer risk. However, the results of these studies remain controversial rather than conclusive, possibly because of conflicting results from different case-control studies. In 2006, Berndt and his group [15] performed a meta-analysis and found no statistically significant association between the FokI polymorphism and PCa risk. Ever since, new studies have provided additional data correlating with the VDR variants. Therefore, in this meta-analysis, the most up-to-date accumulated data from all eligible studies published were utilized to obtain a summary result of the association between the VDR FokI polymorphism and PCa susceptibility [16–36].

Material and methods

Search strategy and identification of relevant studies

PubMed, Web of Science and Embase database searches were carried out using the following terms: ‘vitamin D receptor’ or ‘VDR’, ‘prostate cancer’ and ‘polymorphism’ or ‘variant’ (last search updated on August 25, 2015). References of the relevant paper and retrieved articles were also identified by a manual search. Eligible studies had to meet all the following inclusion criteria: (a) uses an unrelated case-control design; (b) includes available genotype frequencies; (c) research published in English; (d) provides sufficient data to calculate the odds ratio (OR) with 95% confidence interval (CI).

Data extraction and quality assessment

Data were collected on the genotype of VDR FokI according to prostate cancer. For each publication, the data extraction was carried out by two of the investigators independently according to the inclusion criteria above. Disagreement was to be resolved through a discussion between two authors. If they could not reach a consensus, the problem was to be discussed comprehensively by all investigators. Furthermore, eligible studies containing information about clinical stage of PCa were divided into two groups: localized and advanced (including cases with bone metastasis). Information from enrolled studies was extracted as below: first author’s name, year of publication, ethnicity of subjects, sources of controls, sample size in cases and controls, number of cases and controls with wild type and variant allele, and *p*-value for Hardy-Weinberg Equilibrium (HWE).

Statistical analysis

Odds ratios (ORs) with 95% CIs were used to assess the strength of association between the polymorphism in VDR FokI and prostate cancer risk. Five genetic contrasts were used to evaluate the association: allelic contrast (f allele vs. F allele), homozygote comparison (ff vs. FF), heterozygote comparison (Ff vs. FF), dominant genetic model (ff + Ff vs. FF) and recessive genetic model (ff vs. Ff + FF). Stratified analyses were performed by ethnicity and source of controls (hospital-based, population-based and benign prostatic hyperplasia (BPH) based). The pooled ORs for the risk were calculated using the random effects model and fixed effects model. Heterogeneity assumption was assessed by the χ^2 -based *Q* test among the studies. The data were evaluated using random-effects models (the DerSimonian and Laird method) [37] in the presence of heterogeneity

($p < 0.05$) and fixed-effects (the Mantel-Haenszel method) models [38] were performed in the absence of heterogeneity ($p > 0.05$). The HWE was calculated by the Pearson χ^2 test for goodness of fit. The Z-test was performed to evaluate the statistical significance of the summary OR; a p -value of < 0.05 was considered significant. The statistic of I^2 was also used to test the heterogeneity, with $I^2 > 75\%$, 25–75% and $< 25\%$ to represent high, moderate and low degree of inconsistency, respectively. Significance of the intercept was determined by the t -test as suggested by Egger ($p < 0.01$ represents a statistically significant publication bias) [39]. All the statistical analyses were conducted using STATA version 10.0 (Stata Corporation, College Station, TX).

Results

Study characteristics

A total of 21 articles (including 25 case-control studies) that met all the inclusion criteria were enrolled in our study (Figure 1). Characteristics of the eligible studies are summarized in Table I. In general, 9,720 prostate cancer patients and 9,710 control subjects concerning the VDR FokI polymorphism were assessed. In the subgroup of ethnicity, 14 were carried out in Caucasian descendents, three were in Asian descendents, three studies were in Arabians and three in African-Americans. Only one article was in Spanish descendents. Hospital-based controls were carried out in 18 of these studies. The classical genotyping method called polymerase chain reaction-restriction fragment length polymorphism (RFLP) was used in 13 comparisons. Five studies performed TaqMan real-time polymerase chain reaction (PCR).

Quantitative synthesis

When all the eligible studies were pooled into the meta-analysis (Table II), no obvious association was observed in the overall analysis between prostate cancer risk and the VDR FokI variant genotypes: allelic comparison (random-effects OR = 1.02, 95% CI: 0.96–1.10, $p_{\text{heterogeneity}} < 0.001$, $p = 0.498$, $I^2 = 56.6$) (Figure 2), homozygote comparison (random-effects OR = 1.08, 95% CI: 0.95–1.03, $p_{\text{heterogeneity}} = 0.020$, $p = 0.216$, $I^2 = 40.3$), heterozygote comparison (random-effects OR = 1.06, 95% CI: 0.97–1.17, $p_{\text{heterogeneity}} = 0.002$, $p = 0.211$, $I^2 = 50.7$), dominant genetic model (random-effects OR = 1.05, 95% CI: 0.95–1.16, $p_{\text{heterogeneity}} < 0.001$, $p = 0.326$, $I^2 = 57.0$) and the recessive genetic model (fixed-effects OR = 1.03, 95% CI: 0.96–1.11, $p_{\text{heterogeneity}} = 0.280$, $p = 0.406$, $I^2 = 12.8$). However, in the subgroup analysis by ethnicity, positive associations between VDR FokI polymorphism and prostate cancer risk were found in Cau-

casian descendents for allelic contrast (fixed-OR = 1.03, 95% CI: 1.00–1.06, $p_{\text{heterogeneity}} = 0.552$, $p = 0.026$, $I^2 = 0$) (Figure 3) and the dominant genetic model (fixed-effects OR = 1.03, 95% CI: 1.00–1.05, $p_{\text{heterogeneity}} = 0.856$, $p = 0.032$, $I^2 = 0$), but not in Asian descendents (allelic comparison fixed-effects OR = 0.97, 95% CI: 0.90–1.04, $p_{\text{heterogeneity}} = 0.536$, $p = 0.352$, $I^2 = 0$), Arabians (allelic comparison random-effects OR = 0.64, 95% CI: 0.37–1.11, $p_{\text{heterogeneity}} = 0.036$, $p = 0.114$, $I^2 = 69.8$) or African-Americans (allelic comparison fixed-effects OR = 0.92, 95% CI: 0.71–1.18, $p_{\text{heterogeneity}} = 0.151$, $p = 0.500$, $I^2 = 47.2$). In the subgroup analysis by tumor stage, there was a significant association between this variant and advanced prostate cancer under the recessive genetic model (fixed-effects OR = 1.15, 95% CI: 1.01–1.32, $p_{\text{heterogeneity}} = 0.469$, $p = 0.032$, $I^2 = 0$) (Figure 4). Furthermore, a significant association between the VDR FokI polymorphism and prostate cancer was also found in population-based studies under homozygote comparison (random-effects OR = 1.12, 95% CI: 1.03–1.23, $p_{\text{heterogeneity}} = 0.143$, $p = 0.010$, $I^2 = 26.7$) (Figure 5) and the recessive genetic model (fixed-effects OR = 1.09, 95% CI: 1.01–1.17, $p_{\text{heterogeneity}} = 0.669$, $p = 0.034$, $I^2 = 0$), with no association among hospital-based studies (homozygote comparison: fixed-effects OR = 0.85, 95% CI: 0.65–1.11, $p_{\text{heterogeneity}} = 0.090$, $p = 0.223$, $I^2 = 50.3$; recessive genetic model: fixed-effects OR = 0.83, 95% CI: 0.64–1.07, $p_{\text{heterogeneity}} = 0.194$, $p = 0.155$, $I^2 = 34.1$) and BPH based studies in homozygote

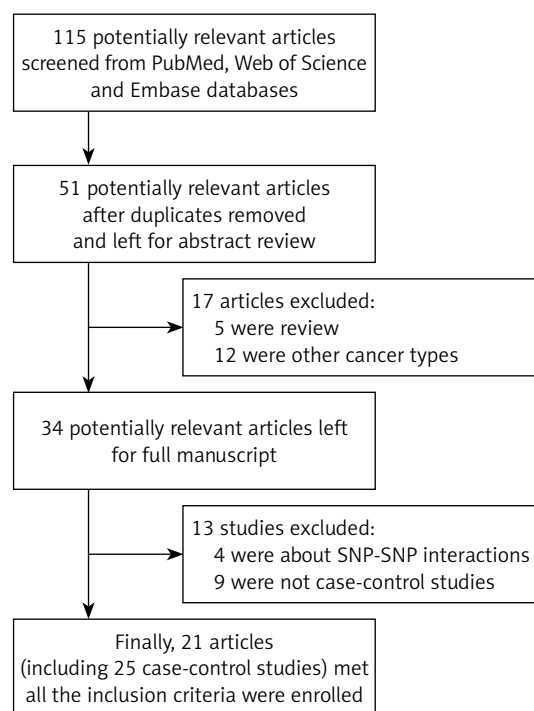


Figure 1. Study flow chart for the process of selecting the enrolled studies

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

| First author | Year | Ethnicity | Source of control | Genotyping | Sample size of case | | | Sample size of control | | | P_{HWE} | Frequency of f allele | |
|---------------|------|------------------|-------------------|----------------|---------------------|-----|-------|------------------------|-----|-------|-----------|-----------------------|-------|
| | | | | | ff | FF | Total | ff | FF | Total | | | |
| Correa | 1999 | Caucasian | Population-based | PCR-RFLP | 10 | 58 | 118 | 9 | 42 | 38 | 89 | 0.598 | 0.337 |
| Chokkalingam | 2001 | Asian | Hospital-based | PCR-RFLP | 41 | 95 | 187 | 62 | 153 | 87 | 302 | 0.725 | 0.459 |
| Tayeb | 2004 | Caucasian | Population-based | PCR-RFLP | 2 | 10 | 28 | 11 | 24 | 21 | 56 | 0.391 | 0.411 |
| Oakley-Girvan | 2004 | Caucasian | Population-based | PCR-RFLP | 27 | 120 | 232 | 26 | 77 | 68 | 171 | 0.586 | 0.377 |
| Oakley-Girvan | 2004 | African-American | Population-based | PCR-RFLP | 4 | 25 | 84 | 5 | 42 | 74 | 121 | 0.752 | 0.215 |
| Bodiwala | 2004 | Caucasian | BPH-based | PCR-RFLP | 60 | 163 | 368 | 35 | 100 | 108 | 243 | 0.137 | 0.350 |
| Cheteri | 2004 | Caucasian | Population-based | PCR-RFLP | 101 | 247 | 204 | 52 | 80 | 234 | 207 | 0.305 | 0.378 |
| Mishra | 2005 | Arabian | Hospital-based | PCR-RFLP | 5 | 45 | 78 | 128 | 16 | 69 | 62 | 0.622 | 0.344 |
| John | 2005 | Caucasian | Population-based | PCR-RFLP | 69 | 203 | 153 | 425 | 57 | 209 | 171 | 0.581 | 0.370 |
| Hayes | 2005 | Caucasian | Population-based | DGGE | 112 | 359 | 340 | 811 | 98 | 322 | 293 | 0.526 | 0.363 |
| Cicek | 2006 | Mixed | Population-based | PCR-RFLP | 71 | 191 | 77 | 339 | 77 | 202 | 200 | 0.034 | 0.372 |
| Huang | 2006 | Asian | Hospital-based | PCR-RFLP | 87 | 204 | 125 | 416 | 119 | 248 | 135 | 0.806 | 0.484 |
| Rukin | 2007 | Caucasian | BPH-based | Pyrosequencing | 166 | 203 | 61 | 430 | 135 | 141 | 44 | 0.461 | 0.642 |
| Mikhak | 2007 | Caucasian | Population-based | Taqman | 101 | 337 | 232 | 670 | 108 | 310 | 255 | 0.398 | 0.391 |
| Li | 2007 | Caucasian | Population-based | PCR-RFLP | 152 | 475 | 383 | 1010 | 206 | 655 | 571 | 0.413 | 0.373 |
| Holick | 2007 | Caucasian | Population-based | SNPlex assay | 100 | 261 | 222 | 583 | 85 | 245 | 222 | 0.204 | 0.376 |
| Torkko | 2008 | Spanish | Population-based | Taqman | 26 | 70 | 45 | 141 | 57 | 125 | 91 | 0.249 | 0.438 |
| Torkko | 2008 | Caucasian | Population-based | Taqman | 67 | 209 | 168 | 444 | 63 | 227 | 198 | 0.87 | 0.362 |
| Holt | 2009 | African-American | Population-based | SNPlex assay | 2 | 48 | 65 | 115 | 4 | 24 | 39 | 0.904 | 0.239 |
| Holt | 2009 | Caucasian | Population-based | SNPlex assay | 108 | 335 | 262 | 705 | 101 | 352 | 263 | 0.332 | 0.387 |
| Bai | 2009 | Asian | Hospital-based | PCR-RFLP | 26 | 63 | 33 | 122 | 37 | 55 | 38 | 0.08 | 0.496 |
| Rowland | 2013 | African-American | Population-based | Taqman | 24 | 161 | 236 | 421 | 10 | 90 | 134 | 0.287 | 0.235 |
| Rowland | 2013 | Caucasian | Population-based | Taqman | 193 | 598 | 406 | 1197 | 112 | 413 | 311 | 0.171 | 0.381 |
| Yousaf | 2014 | Arabian | Hospital-based | PCR-RFLP | 2 | 0 | 39 | 41 | 13 | 0 | 95 | 0 | 0.120 |
| Atoum | 2015 | Arabian | Population-based | PCR | 10 | 76 | 38 | 124 | 6 | 66 | 28 | 0 | 0.390 |

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

Table II. Stratified analyses of the vitamin D receptor gene FokI polymorphism and prostate cancer risk

| Variables | N ^a | Cases/ controls | f allele vs. F allele | | | ff vs. FF | | | ff + Ff vs. FF | | | ff vs. Ff + FF | | | | | | |
|--------------------|----------------|--------------------|-----------------------|--------------------|---------|----------------|------------------|--------------------|----------------|----------------|------------------|--------------------|---------|----------------|------------------|--------------------|-------|----------------|
| | | | OR (95% CI) | P ^b | P | I ² | OR (95% CI) | P ^b | P | I ² | OR (95% CI) | P ^b | P | I ² | OR (95% CI) | P ^b | P | I ² |
| Total | 25 | 9720/9710 | 1.02 (0.96–1.10) | < 0.001 | 0.498 | 56.6 | 1.08 (0.95–1.03) | 0.020 | 0.216 | 40.3 | 1.05 (0.95–1.16) | < 0.001 | 0.326 | 57.0 | 1.03 (0.96–1.11) | 0.280 ^c | 0.406 | 12.8 |
| Ethnicity: | | | | | | | | | | | | | | | | | | |
| Caucasian | 14 | 7573/7247 | 1.03 (1.00–1.06) | 0.552 ^c | 0.026 | 0 | 1.06 (1.00–1.13) | 0.544 ^c | 0.065 | 0 | 1.03 (1.00–1.05) | 0.856 ^c | 0.032 | 0 | 1.05 (0.98–1.13) | 0.571 ^c | 0.183 | 0 |
| Asian | 3 | 725/934 | 0.97 (0.90–1.04) | 0.536 ^c | 0.352 | 0 | 0.93 (0.80–1.08) | 0.540 ^c | 0.344 | 0 | 0.99 (0.93–1.05) | 0.548 ^c | 0.668 | 0 | 0.90 (0.75–1.08) | 0.444 ^c | 0.271 | 0 |
| Arabian | 3 | 293/355 | 0.64 (0.37–1.11) | 0.036 | 0.114 | 69.8 | 0.54 (0.21–1.39) | 0.101 ^c | 0.202 | 56.4 | 0.78 (0.55–1.13) | 0.029 | 0.189 | 71.7 | 0.61 (0.25–1.50) | 0.138 ^c | 0.279 | 49.6 |
| African-American | 3 | 649/422 | 0.92 (0.71–1.18) | 0.151 ^c | 0.50 | 47.2 | 0.89 (0.42–1.86) | 0.261 ^c | 0.749 | 25.6 | 0.92 (0.71–1.19) | 0.112 ^c | 0.531 | 54.4 | 0.91 (0.42–1.95) | 0.251 ^c | 0.801 | 27.7 |
| Spanish | 1 | 141/273 | 0.98 (0.73–1.31) | – | 0.888 | – | 0.92 (0.51–1.16) | – | 0.787 | – | 1.07 (0.69–1.65) | – | 0.771 | – | 0.86 (0.51–1.44) | – | 0.557 | – |
| Mixed | 1 | 339/479 | 1.64 (1.34–1.99) | – | < 0.001 | – | 2.40 (1.58–3.63) | – | < 0.001 | – | 2.44 (1.78–3.33) | – | < 0.001 | – | 1.38 (0.97–1.98) | – | 0.075 | – |
| Source of control: | | | | | | | | | | | | | | | | | | |
| Population-based | 17 | 8028/7958 | 1.03 (1.00–1.07) | 0.017 ^c | 0.051 | 46.3 | 1.12 (1.03–1.23) | 0.143 ^c | 0.010 | 26.7 | 1.10 (0.99–1.22) | 0.002 | 0.090 | 56.0 | 1.09 (1.01–1.17) | 0.669 ^c | 0.034 | 0 |
| Hospital-based | 5 | 894/1189 | 0.81 (0.63–1.04) | 0.022 | 0.100 | 65.1 | 0.85 (0.65–1.11) | 0.090 ^c | 0.223 | 50.3 | 0.94 (0.83–1.06) | 0.026 | 0.311 | 63.9 | 0.83 (0.64–1.07) | 0.194 ^c | 0.155 | 34.1 |
| BPH | 2 | 798/563 | 1.02 (0.90–1.15) | 0.133 ^c | 0.811 | 55.7 | 1.02 (0.84–1.23) | 0.226 ^c | 0.869 | 31.9 | 1.02 (0.93–1.13) | 0.171 ^c | 0.629 | 46.8 | 0.95 (0.81–1.11) | 0.317 ^c | 0.522 | 0.1 |

^aNumber of comparisons, ^bp-value of Q-test for heterogeneity test (P_{heter}). ^cA random-effects model was performed when P value for heterogeneity test < 0.05; otherwise, a fixed-effects model was used.

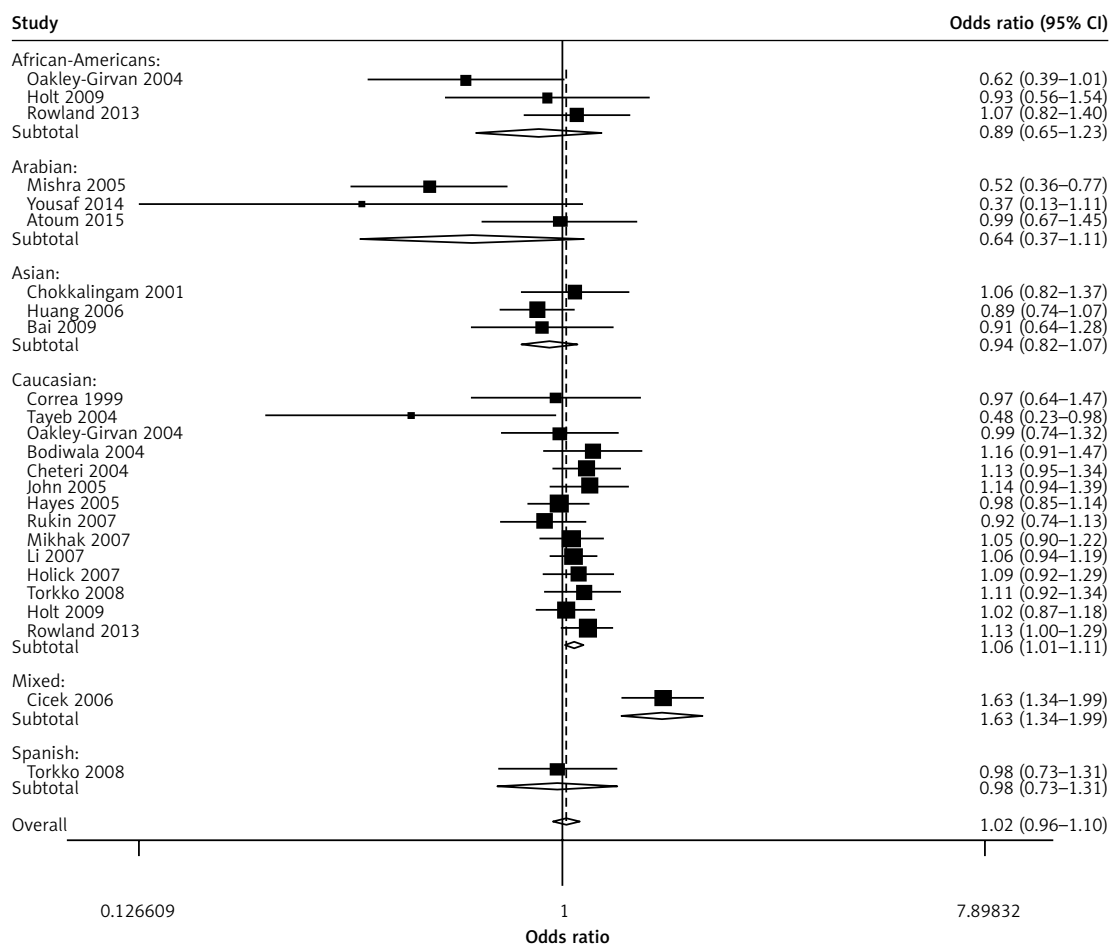


Figure 2. Forest plot of prostate cancer risk associated with the VDR FokI gene polymorphism (allelic contrast of f allele vs. F allele, random-effects)

comparison (fixed-effects OR = 1.02, 95% CI: 0.84–1.23, $p_{\text{heterogeneity}} = 0.226$, $p = 0.869$, $I^2 = 31.9$) and the recessive genetic model (fixed-effects OR = 0.95, 95% CI: 0.81–1.11, $p_{\text{heterogeneity}} = 0.317$, $p = 0.522$, $I^2 = 0.1$).

Publication bias

Egger’s test and Begg’s funnel plot were carried out to evaluate the literature’s publication bias. No obvious evidence of publication bias was found (f allele vs. F allele, $t = -2.30$, $p = 0.031$, Figure 6; ff vs. FF, $t = -1.29$, $p = 0.209$; ff vs. Ff, $t = -1.18$, $p = 0.251$; ff + Ff vs. FF, $t = -1.60$, $p = 0.251$; ff vs. Ff + FF, $t = -2.06$, $p = 0.051$).

Discussion

Genetic susceptibility of solid tumors has led to growing attention to polymorphism studies of genes involved in the pathogenesis of carcinogenesis. Accumulating data have provided evidence that a low level of vitamin D is a risk factor for prostate cancer [40–42]. The vitamin D receptor, a significant regulator of the vitamin D pathway, could regulate conversion of serum 25(OH)D into

the active hormone 1,25-dihydroxyvitamin D and mediate downstream transcription of a series of target genes [43]. Thus the FokI polymorphism of the VDR gene, encoding key proteins in vitamin D metabolism, has been chosen as a candidate polymorphism for prostate cancer susceptibility [44]. Nowadays, there is an increasing number of studies evaluating the FokI polymorphic variants of the VDR gene in prostate cancer susceptibility [45, 46]. Nevertheless, the association between this polymorphism and prostate cancer risk remains conflicting. Meta-analysis is used to combine the previous results to yield the most reliable and comprehensive conclusion because the individual research was too minor to achieve a valid conclusion [47, 48]. In this article, novel case-control studies from the last years were enrolled and a meta-analysis containing 9,720 prostate cancer patients and 9,710 controls from 25 independent case-control studies was performed.

Ethnicity is a significant biological factor which may affect the VDR functions via gene-gene interactions. When all the eligible studies were pooled into the meta-analysis, no obvious association of the VDR FokI polymorphism and prostate cancer

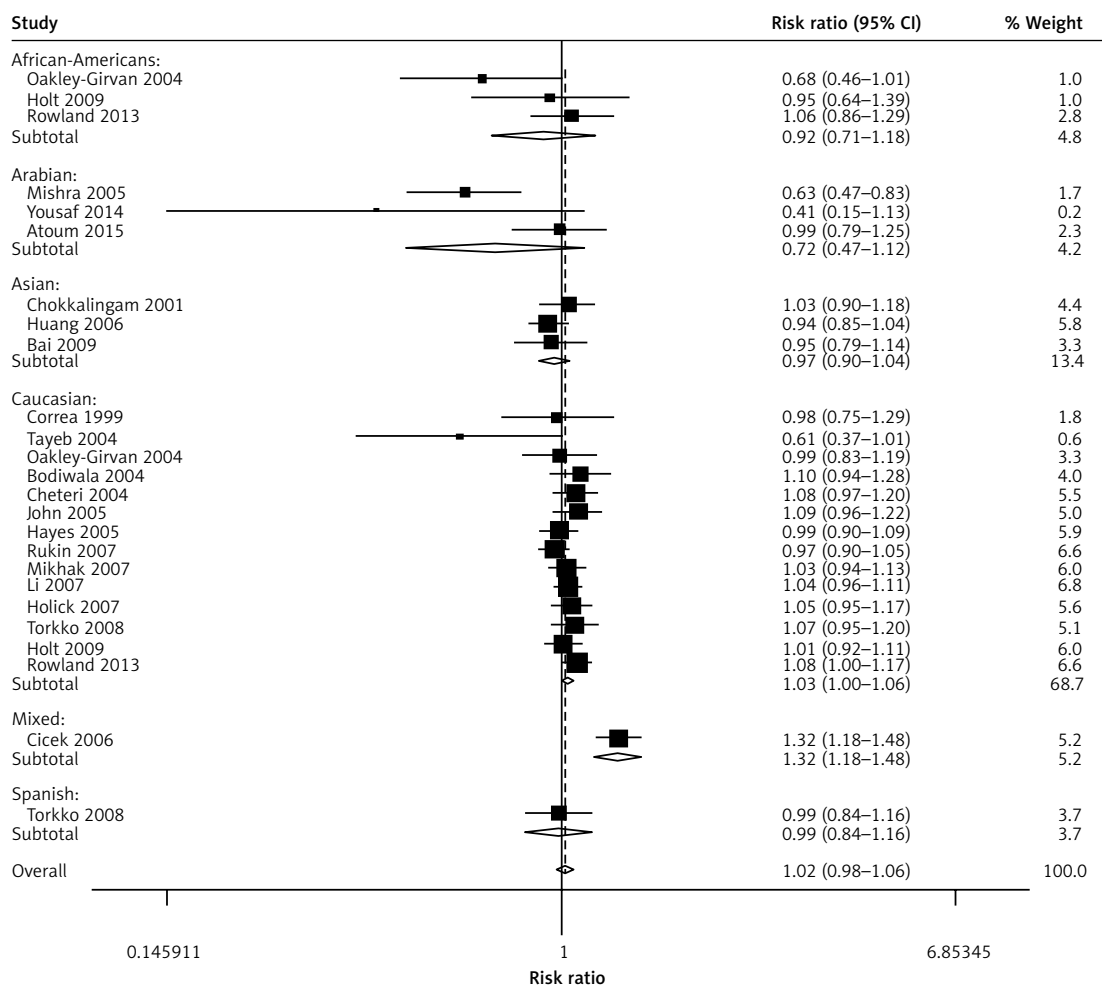


Figure 3. Forest plot of prostate cancer risk associated with the VDR FokI gene polymorphism (allelic contrast of f allele vs. F allele) in the analyses stratified by ethnicity. The squares and horizontal lines represent the study-specific OR and 95% CI. The area of the *squares* reflects the weight (inverse of the variance). The diamond corresponds to the summary OR and 95% CI. Separate details are summarized in Table I

risk was identified. However, in subgroup analysis by ethnicity, positive associations existed in Caucasian descendents (under the allelic contrast and dominant genetic model) but not in Asians, Arabians and African-Americans. Furthermore, in the analysis stratified by source of control, this VDR FokI variant was observed to increase the prostate cancer susceptibility in population-based studies (in homozygote comparison and the recessive genetic model), while no positive association was found in hospital-based and BPH-based controls. Nevertheless, some limitations of this pooled analysis ought to be addressed. The first limitation is the insufficient number of cases when specifying various ethnic backgrounds of prostate cancer. Only three studies were based on Asian [19, 34, 35] and Arabian descendents [16, 17, 28]. Second, some risk factors including age, smoking exposure, drinking, and family history were absent in this study. We tried to evaluate the gene and environment interaction effect on the susceptibility to prostate cancer. Unfortunately,

the available data were not sufficient. Third, it has been suggested that positive results tend to be published faster than those with a ‘negative’ conclusion, which may need longer time to be accepted in time-lag bias [49]. In addition, combined interaction of multiple gene polymorphisms may have a stronger association with prostate cancer susceptibility, which is beyond the detection capacity of the present analysis.

On the other hand, the present meta-analysis has some key advantages compared with individual case-control studies. First, substantial numbers of cases and control subjects were enrolled from a variety of studies, which can significantly enhance the statistical power. Second, the quality of the case-control studies in this analysis was satisfactory and met the selection criteria with a wide representation. Third, no significant publication bias was detected through the qualitative funnel plot, which indicated that the conclusions are relatively stable and publication bias may not lead to an influence on the results of the present

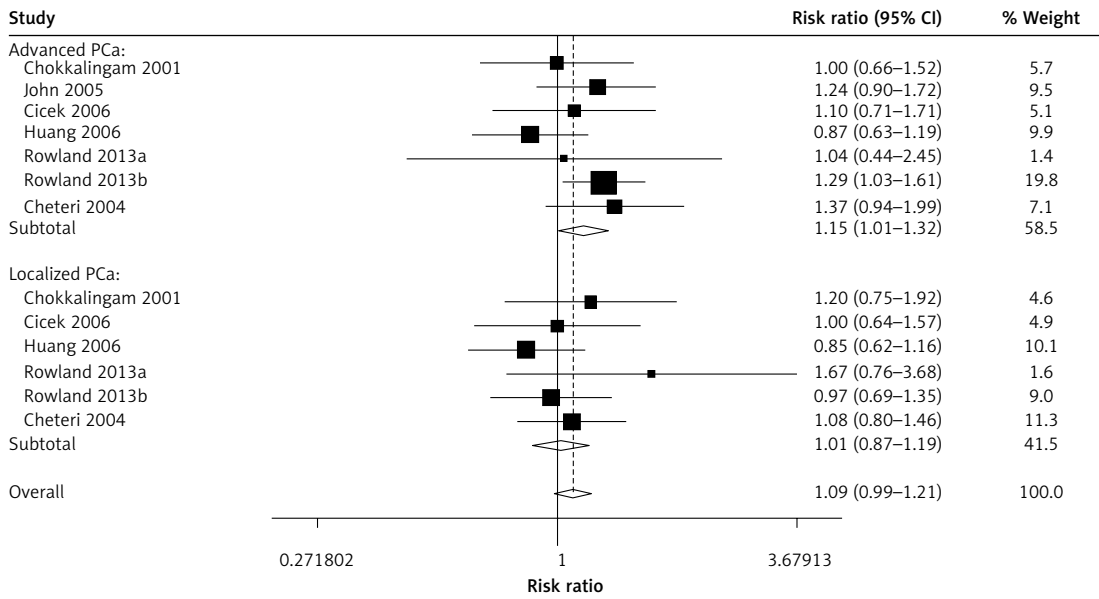


Figure 4. Association between the VDR FokI gene polymorphism and different stages of prostate cancer (PCa), evaluated under the recessive genetic model. The area of the squares reflects the weight. The squares and horizontal lines represent the study-specific OR and 95% CI. The diamond corresponds to the summary OR and 95% CI

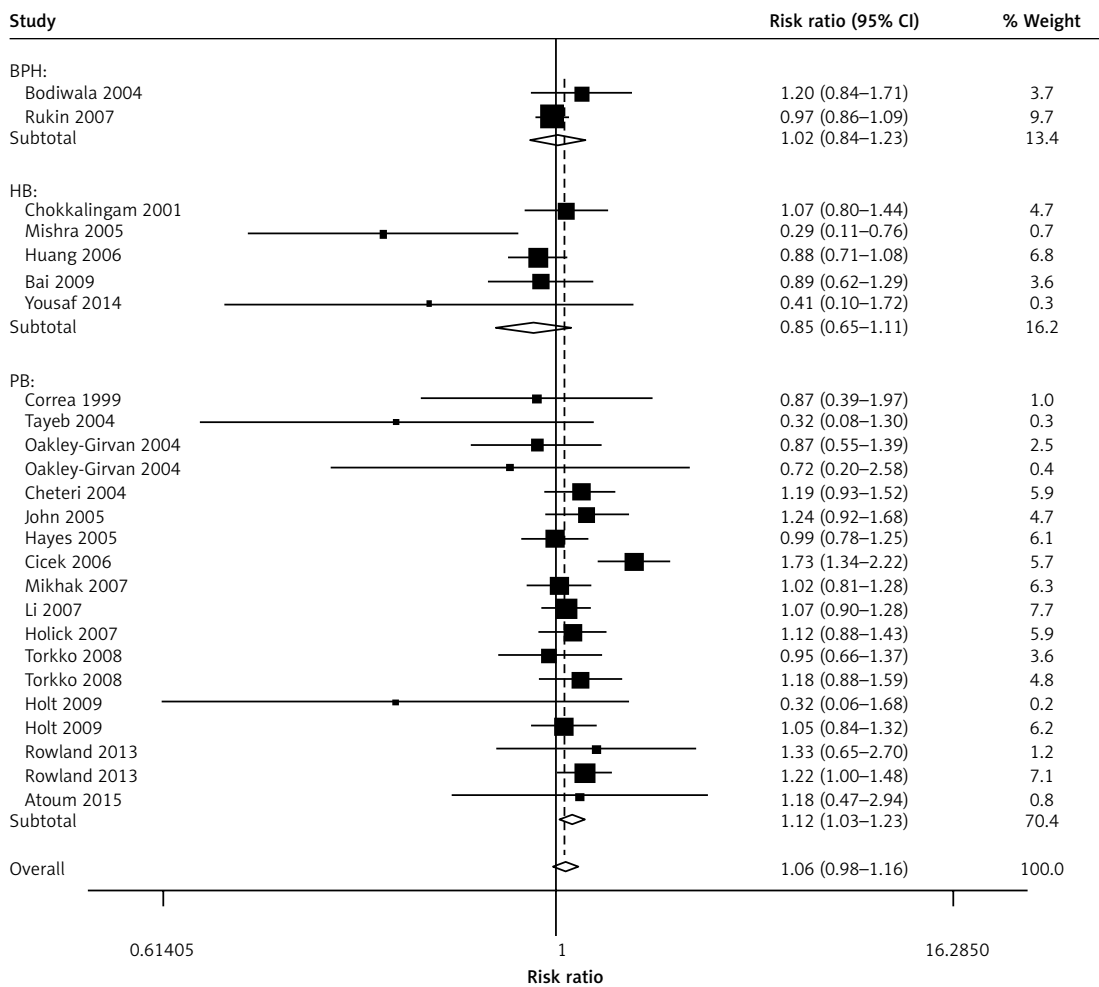


Figure 5. Association between the VDR FokI gene polymorphism and prostate cancer (PCa) in subgroup analysis by source of control (under homozygote comparison). The area of the squares reflects the weight. The squares and horizontal lines represent the study-specific OR and 95% CI. The diamond corresponds to the summary OR and 95% CI

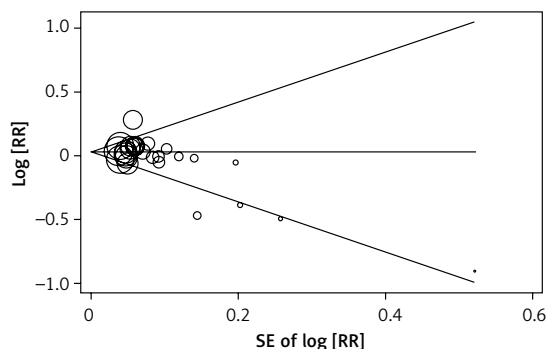


Figure 6. Begg's funnel plots to examine publication bias for allelic comparisons of VDR FokI polymorphism (f allele vs. F allele)

meta-analysis. In addition, studies using males with benign prostatic hyperplasia (BPH) as control subjects were enrolled. The reason for this inclusion was based on the assumption that BPH is a benign disease which has a similar probability for developing prostate cancer compared with normal prostate tissues. Previous epidemiological studies have provided no evidence concerning the association of increased BPH risk with VDR polymorphisms [50, 51]. Furthermore, the genotype distribution of the control population met the Hardy-Weinberg equilibrium in 23 of the studies.

In conclusion, this meta-analysis showed evidence that the VDR FokI variant may contribute to the risk for developing prostate cancer in a Caucasian population, but not with other descendents. Furthermore, there is a significant association between this variant and advanced prostate cancer. However, no association was detected in the overall analysis when all eligible studies were pooled into the analysis. Therefore, large, well-designed epidemiological studies, particularly referring to gene-environment interactions, are necessary to achieve a comprehensive conclusion of the association between VDR FokI polymorphism and prostate cancer risk.

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Yuan-Yuan Mi, Yang-Zhi Chen and Jing Chen contributed equally to this work.

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Conflict of interest

The authors declare no conflict of interest.

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