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Original Article

Vitamin D receptor genetic polymorphisms and prostate cancer risk: a meta-analysis of 36 published studies

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Abstract: To update data on the role of vitamin D receptor (VDR) single nucleotide polymorphisms (SNPs) in susceptibility to prostate cancer, we performed a meta-analysis of 36 eligible publications on the association of *TaqI*, *ApaI*, *BsmI*, *FokI* and *CDX2* SNPs of the *VDR* gene with prostate cancer risk. Our study suggested that the *TaqI t* and *BsmI B* alleles were associated with reduced prostate cancer risk among all study populations. Stratified analysis by ethnicity revealed that the *ApaI a* allele was associated with reduced prostate cancer risk only among Asian populations, whereas the *FokI f* allele showed a trend of increased prostate cancer risk only among Caucasian populations in a dominant model, independent of tumor stage (local or advanced). These results suggest that *VDR* polymorphisms may be potential biomarkers for prostate cancer susceptibility.

Key words: Prostate cancer, Genetic polymorphism, Meta-analysis, Molecular Epidemiology

Introduction

Prostate cancer is the most common type of cancer among men in the United States, with an estimation of 186,320 new cases and 28,660 deaths in 2008 [1]. Although the etiology of prostate cancer is not well elucidated, both genetic and environmental factors are believed to play a role. Previous epidemiological studies suggested that low serum levels of vitamin D might be a risk factor for prostate cancer [2]. Laboratory investigations also demonstrated that the active form of vitamin D, 1, 25-dihydroxy-vitamin D_3, could inhibit normal and malignant prostate epithelial cell proliferation *in vitro* [3, 4], whereas some ecological studies supported an inverse correlation between prostate cancer mortality and UV radiation exposure [5], an essential environmental factor for Vitamin D synthesis. Therefore, an adequate level of serum vitamin D may protect against prostate cancer in humans.

Vitamin D exerts its biological effects through binding to and thereby activating the intracellular vitamin D receptor (VDR), a member of the steroid hormone receptor superfamily, which acts as a ligand-dependent transcriptional factor found in many types of tissues, including the prostate [6]. When the cell exposed to 1, 25-dihydroxyvitamin D_3, VDR is translocated to the nucleus and regulates expression of VDR-responsive genes, which further induce cell differentiation and suppress proliferation [7, 8]. Therefore, polymorphisms of the *VDR* gene, which potentially affect the receptor binding of 1, 25-dihydroxyvitamin D_3, may modify vitamin D biological activity and confer different susceptibility to prostate cancer.

The human *VDR* gene is located on chromosome 12q13.11 [9], consisting of 14 exons and spanning approximately 75 kb long [10]. It is highly polymorphic with at least 618 variants reported to date, most of which are either not detectable or at a low frequency in the general population, according to the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?chooseRs=all&go=Go&locusId=7421, June 4th, 2009). Previous

studies had primarily focused on four common variants that were hypothesized to influence the expression and/or function of the VDR protein, including three single nucleotide polymorphisms (SNPs) located in the intron 8 (*ApaI* and *BsmI*) and exon 9 (*TaqI*), in addition to a mononucleotide repeat (*polyA*) in the 3'-untranslated region (3'-UTR). There is a fifth polymorphism, known as *FokI* (*F/f*), corresponding to a C>T substitution in exon 2 of the *VDR* gene [11]. The absence of the *Fok* I restriction site, designated *F*, is associated with a short VDR protein with a greater luciferase reporter gene activity, compared with the *f* allele [12]. A recently reported new functional SNP of G>A substitution in the promoter region of the *VDR* gene interacts with the caudal related homeodomain transcription factor (CDX2), and the common *CDX2 G* allele has 70% of the transcriptional activity, compared with the *A* allele [13].

The association between *VDR* genetic polymorphisms and prostate cancer risk has been extensively studied but reported with mixed results [14, 15]. Two published meta-analyses failed to conclude any positive associations [16, 17]. Ever since, new studies have provided additional data on the association between *VDR* polymorphisms and prostate cancer risk. Therefore, we used the most updated data and performed a quantitative analysis to revisit the association between *VDR* variants (i.e., *TaqI*, *BsmI*, *ApaI*, *FokI* and *CDX2*) and prostate cancer risk.

Materials and methods

Identification and Eligibility of Relevant Studies

We searched for relevant papers published before December 2008 by using the electronic MEDLINE database with the following terms "prostate cancer", "vitamin D", "VDR", "polymorphism" AND "variant". References of retrieved articles were also screened for any missing original study not shown in the search. We included all non-familial case-control and cohort studies that examined the associations between *VDR* polymorphisms and prostate cancer risk with genotyping data for at least one of the five variants, *TaqI*, *BsmI*, *ApaI*, *FokI* and *CDX2*. Studies using men with benign prostatic hyperplasia (BPH) were included, whereas studies based on family or pedigree were excluded for considerations of disease-specificity and genetic linkage.

Data Extraction

We extracted the following information from each manuscript: author, year of publication, country of origin, selection and characteristics of cancer cases and controls, demographics, ethnicity, histological types and genotyping information. For studies including subjects of different ethnicities, data were extracted separately and categorized as Asians, Caucasians (European descendents), Africans and Indians. However, if the authors did not provide specific ethnicity information or we could not separate them according to the genotypes, the term "mixed" was used.

Meta-analysis

We performed a meta-analysis to estimate risks (odds ratios, ORs) of prostate cancer associated with different *VDR* polymorphisms. In addition to comparison among all subjects, the studies were also categorized by the ethnicity and tumor stage (local or advanced) for subgroup analyses. We assumed study subjects to be Caucasians, if Caucasians comprised of > 90% of the subjects without other detailed ethnicity information. We investigated the between-study heterogeneity by using the Cochran's Q test, and the heterogeneity was considered significant, if $P < 0.05$ [18]. Values from single studies were combined using models of both random effects (DerSimonian Laird) and fixed effects (Mantel-Haenszel) [19]. We also did cumulative meta-analysis to evaluate whether the summary OR for the allele contrasts was changed over time as more data accumulated [20]. Inverted funnel plots and the Egger's test were used to examine the influence of publication bias (linear regression analysis) [21]. All *P* values were two-sided with a significance level of $P < 0.05$, and all analyses were done in Statistical Analysis System software (v.8.0; SAS Institute, Cary, NC) and Review Manager (v.5.0; Oxford, England).

For quality control, one person (first author) did a thorough search for eligible articles, collected the actual articles, and abstracted the data, and the second person (second author) checked for completion of inclusion of the published articles and accuracy of the data pool used for analysis.

Results

Meta-analyses Database

We identified a total 36 eligible studies and established a database according to the extracted information from each article (**Table 1**). There were 23 case-control studies of *TaqI* polymorphism, 6 studies of *ApaI*, 14 studies of *BsmI*, 16 studies of *FokI* and 4 studies of *CDX2*. We compared the data pool of current analysis with those of two previous meta-analyses [16, 17] and found a little difference. The study by Luscombe *et al.* was excluded from the current analysis, because it did not contain normal controls [22], whereas the study by Suzuki *et al.* was excluded because it was family-based [23]. We also examined the data quality of published results and excluded the data of the *BsmI* polymorphism in the article by Chaimuangraj *et al.* [24], because the description of genotype frequencies of this polymorphism was not consistent. Therefore, the final data pool of the *BsmI* polymorphism included 13 studies.

There was a considerable diversity of study designs in these reports, including 21 hospital-based case-control studies, 5 cohort-nested studies, 1 study established on pathology database and 10 population/community-based studies. Most of the prostate cancer patients were diagnosed by a histological examination from biopsy or prostatectomy, whereas the others were confirmed by self report or review of medical records, except for the study by Furuya *et al.*, which did not clarify the diagnostic criteria [25]. All controls did not have a clinical diagnosis of prostate cancer at study entry, but BPH commonly existed. All studies also had different screening examinations, such as digital rectal examination, prostate-specific antigen (PSA), and needle biopsy, to rule out prostate cancer. Most studies indicated that the frequency distributions of genotypes in the controls were consistent with the Hardy-Weinberg equilibrium (HWE), whereas deviations from HWE were also observed in two studies of *TaqI* [26, 27], one of *ApaI* [28], and five of *BsmI* [24, 28-31].

Quantitative Synthesis

TaqI. The eligible studies included 4,054 cases and 5,069 controls. There were significant differences in the *t* allele frequencies among three major ethnicities [Caucasians, 39.5%; 95% confidence interval (CI), 37.0-41.9; Africans, 36.0%; 95% CI, 24.1-47.9; Asians, 12.9%; 95% CI, 8.3-17.5; $P < 0.001$; **Figure 1**]. Comparison within groups revealed that the difference existed between Caucasians and Asians, Africans and Asians, but not Caucasians and Africans. In the model of random effects, individuals carrying the *t* allele did not have an altered cancer risk, compared with individuals with the *T/T* genotype, in homozygote, dominant or recessive models (**Figure 2** and **Table 2**). This null association was also observed in subgroups stratified by ethnicity (**Table 3**). In the model of fixed effects, individuals with the *t* allele appeared to have a lower prostate cancer risk in the overall population in both the homozygote (*t/t* versus *T/T*: OR, 0.87; 95% CI 0.75-1.00; $P = 0.366$ for heterogeneity, $I^2 = 7\%$) and dominant (*t/t* + *T/t* versus *T/T*: OR, 0.91; 95% CI 0.83-1.00; $P=0.039$ for heterogeneity, $I^2 = 37\%$) models (**Table 2**). To investigate if the influence of *VDR* polymorphisms on prostate cancer risk was tumor-stage dependent, we stratified prostate cancer patients into two groups of either a local or an advanced disease. Our analysis failed to reveal any association between *TaqI* polymorphism and risk of advanced prostate cancer (**Table 4**), which was consistent with two current individual studies with tumor stage of prostate cancer [26, 28].

ApaI. The eligible studies included 1,053 cases and 1,266 control subjects. There were significant differences in the *a* allele frequencies among three major ethnicities [Caucasians, 41.6%; 95% CI, 33.3-50.0; Africans, 37.1%; 95% CI, 32.5-41.7; Asians, 66.2%; 95% CI, 62.8-69.6; $P < 0.001$; **Figure 1**]. Similarly, comparison within groups showed differences in the *a* allele frequencies between Caucasians and Asians, Africans and Asians, but not Caucasians and Africans. There was no evidence that the *ApaI* polymorphism modified prostate cancer risk among the overall population, because individuals carrying the *a* allele did not have an altered cancer risk, compared with individuals with the *A/A* genotype, in homozygote, dominant or recessive models (**Figure 2** and **Table 2**). However, subgroup analysis by ethnicity showed that the *a* allele was associated with a reduced prostate cancer risk in Asian populations in the homozygote (*a/a* versus *A/A*: OR, 0.69; 95% CI 0.47-0.99 by random effects; $P = 0.647$ for heterogeneity, $I^2 = 0\%$) and dominant (*a/a* + *A/a* versus *A/A*: OR,

0.61; 95% CI 0.43-0.87 by random effects; P = 0.574 for heterogeneity, I^2 = 0%) models. In terms of tumor stage, there was only one study available, which reported a null association of the *A* allele with risks of local or advanced prostate cancer [28].

BsmI. The eligible studies included 5,378 cases and 6,103 control subjects. There were no differences in the *B* allele frequencies among three major ethnicities (P = 0.290). However, the *B* allele frequency of the Asian subjects by Nam *et al.* [30] was significantly different from those of the other four Asian populations. After deletion of the study by Nam *et al.*, there were significant differences in the *B* allele frequencies among three major ethnicities [Caucasians, 43.3%; 95% CI, 38.8-47.7; Africans, 43.3%; 95% CI, 0-86.8; Asians, 10.2%; 95% CI, 0-22.6; P < 0.001; **Figure 1**]. Comparison within groups showed differences of *B* allele frequencies only between Caucasians and Asians. The *BsmI* polymorphism did not appear to contribute to prostate cancer risk in either the overall population (**Table 2**) or subgroups stratified by ethnicity (**Table 3**), except that the *BsmI B/B* genotype was associated with significantly reduced prostate cancer risk in the dominant model in the overall population (*B/B* + *B/b* versus *b/b*: OR, 0.87; 95% CI 0.77-0.98 by random effects; P = 0.035 for heterogeneity, I^2 = 46%) (**Figure 2**). Further analysis by tumor stage did not reveal any significant association between the *B/B* genotype and risks of local or advanced prostate cancer (**Table 4**).

FokI. The eligible studies included 6,736 cases and 7,325 control subjects. Since there was only one *FokI* study by Oakley-Girvan *et al.* with African ethnicity [32], the comparison of *f* allele frequencies was done between Caucasians and Asians, which did not show any significant difference [Caucasians, 39.7%; 95% CI, 34.1-45.3; Africans, 21.5%; Asians, 47.4%; 95% CI, 44.0-50.9; **Figure 1**]. There was no evidence that the *FokI* polymorphism modified prostate cancer risk in the overall population in homozygote, dominant or recessive models (**Figure 2** and **Table 2**). This null association was also observed in subgroups stratified by tumor stage (**Table 4**). When stratified by ethnicity, the *FokI f* allele tended to be associated with an increased prostate cancer risk in Caucasians in the dominant model (*f/f* + *f/F* versus *F/F*: OR, 1.08; 95% CI 1.00-1.17 by random effects; P = 0.798 for heterogeneity, I^2 = 0%) (**Table 3**)

CDX2. The eligible four studies included 2,058 cases and 2,128 control subjects. The comparison of *A* allele frequencies among three major ethnicities was not performed, because the study pool consisted of only three Caucasian studies and one other study without clear description of ethnicity information [33]. The data did not support an association between the *CDX2* polymorphism and prostate cancer risk in the overall population (**Figure 2** and **Table 2**) or Caucasians in homozygote, dominant or recessive models (**Table 3**). There was only one study that investigated the association of the *CDX2* polymorphism with advanced prostate cancer risk, which, however, did not yield positive findings [34].

Sensitivity analyses

Sensitivity analyses indicated that two independent studies by Maistro *et al* [35] and Tayeb *et al.* [36] were the main origin of heterogeneity for the *TaqI* polymorphism in the overall population. The heterogeneity was effectively decreased or removed after exclusion of these two studies (*t/t* + *T/t* versus *T/T*: P = 0.372 for heterogeneity, I^2 = 7%). Although the genotype distribution in the studies by Blazer *et al.* [26] and Watanabe *et al.* [27] did not follow HWE, the corresponding pooled ORs were not substantially altered with or without including these studies (data not shown).

The between-study heterogeneity for the *BsmI* polymorphism in the dominant model in the overall population mainly resulted from the study by Habuchi *et al.* [37], exclusion of which slightly elevated the OR (*B/B* + *B/b* versus *b/b*: OR, 0.92; 95% CI 0.84-1.00 by random effects; P = 0.410 for heterogeneity, I^2 = 4%). Exclusion of the five studies, whose genotype distributions deviated from HWE [24, 28-31], abrogated the significant association of the *BsmI* polymorphism with cancer risks by random effects (*B/B* + *B/b* versus *b/b*: OR, 0.89; 95% CI 0.76-1.04), but not by fixed effects (*B/B* + *B/b* versus *b/b*: OR, 0.91; 95% CI 0.83-0.99). No single study influenced the pooled OR qualitatively, as indicated by sensitivity analyses.

Bias Diagnostics

TaqI. The magnitude of the summary ORs had

Table 1. Characteristics of studies included in the meta-analysis

References	Country	Race	Study design	Characteristics of cases and controls		SNPs	Genotyped No.	
				Cases	Controls		Cases	Controls
Taylor, 1996 (58)	United States	Caucasian, African	Hospital based	Patients under prostatectomy	BPH or impotence patients	*TaqI*	108	170
Ingles, 1998 (55)	United States	African	Nested in cohort study HLAM	Identified by SEEER and California State cancer registry	Randomly selected from the non-diseased of HLAM Cohort study	*Poly A, BsmI*	151	174
Kibel, 1998 (53)	United States	Caucasian, African	Hospital based	Metastatic prostate cancer	Urology patients without prostate cancer	*TaqI*	41	41
Ma, 1998 (49)	United States	Caucasian	Nested in PHS cohort study	Confirmed by medical records	Selected from the the cohort study without history of prostate cancer	*TaqI, BsmI*	372	589, 591
Watanabe, 1999 (27)	Japan	Asian	Hospital based	Histologically confirmed	Urology patients without prostate cancer	*TaqI*	100	202
Correa-Cerro, 1999 (54)	Germany	Caucasian	Hospital based	Histologically confirmed	Free of prostate cancer, confirmed by DRE and PSA	*TaqI, FokI*	106, 118	95, 89
Furuya, 1999 (25)	Japan	Asian	Hospital based	Not stated	Urology patients without prostate cancer	*TaqI*	66	60
Habuchi, 2000 (37)	Japan	Asian	Hospital based	Histologically confirmed	BPH and non-BPH individuals, confirmed by DRE and PSA	*TaqI, BsmI, ApaI*	222	337
Blazer, 2000 (26)	United States	Caucasian, African	Community based	Histologically confirmed	Randomly selected from Piedmont Triad community	*TaqI*	77	183
Chokkalingam, 2001 (59)	China	Asian	Polulation based	Histologically confirmed	Randomly selected from regional population, confirmed by DRE and PSA	*BsmI, FokI*	161, 187	297, 302
Hamasaki, 2001 (47)	Japan	Asian	Hospital based	Histologically confirmed	No prostate cancer and BPH, confirmed by DRE and PSA	*TaqI*	115	133
Gsur, 2002 (60)	Austria	Caucasian	Hospital based	Histologically confirmed	Patients with BPH symptoms, confirmed by DRE and PSA	*TaqI*	190	190
Medeiros, 2002 (61)	Portugal	Caucasian	Hospital based	Histologically confirmed	Confirmed by PSA	*TaqI*	162	206
Tayeb, 2003 (62)	United Kingdom	Caucasian	Selected from pathology database	Histologically confirmed	BPH	*TaqI*	21	379
Liu, 2003 (63)	China	Asian	Hospital based	Histologically confirmed	Healthy individuals, free of prostate cancer, confirmed by DRE and PSA	*BsmI*	103	106
Nam, 2003 (30)	Canada	Caucasian, African, Asian	Hospital based	Histologically confirmed	Selected from community, confirmed by DRE and PSA	*BsmI*	483	548
Bodiwala, 2004 (64)	United Kingdom	Caucasian	Hospital based	Histologically confirmed	BPH	*TaqI, FokI, CDX2*	368	243
Cheteri, 2004 (29)	United States	Caucasian	Population-based	Histologically confirmed	Selected from randomly-digit dialing	*Poly A, BsmI, FokI*	558, 543, 552	523, 510, 521
Huang, 2004 (28)	Taiwan	Asian	Hospital based	Histologically confirmed	Healthy individuals, free of prostate cancer, confirmed by DRE and PSA	*TaqI, BsmI, ApaI*	160	205
Maistro, 2004 (35)	Brazil	Caucasian, African	Population based	Histologically confirmed	Selected from community, confirmed by DRE and PSA	*TaqI, ApaI*	165	200
Oakley-Girvan	United States	Caucasian,	Population based	Histologically confirmed	Free of prostate cancer, confirmed by DRE	*TaqI, BsmI,*	345	282

2004 (32)		African				*ApaI, FokI*		
Tayeb, 2004 (36)	United Kingdom	Caucasian	Hospital based	Histologically confirmed	BPH	*TaqI, FokI*	28	56
Yang, 2004 (65)	China	Asian	Hospital based	Histologically confirmed	Prostate cancer-free individuals	*FokI*	80	96
Hayes, 2005 (15)	Australia	Caucasian	Population based	Histologically confirmed	Randomly selected from the State Electoral Roll	*BsmI, FokI*	812	713
Mishra, 2005 (66)	India	Indian	Hospital based	Histologically confirmed	Free of prostate cancer, confirmed by PSA	*FokI*	128	147
John, 2005 (34)	United States	Caucasian	Population based	Identified by SEEER cancer registry, advanced stage	Selected from randomly-digit dialing	*TaqI, FokI, CDX2*	424, 425, 417	436, 437, 435
Chaimuangraj, 2006 (24)	Thailand	Asian	Hospital based	Histologically confirmed	BPH and outpatients without urinary syndromes, confirmed by PSA	*TaqI, ApaI*	28	74
Huang, 2006 (67)	Taiwan	Asian	Hospital based	Pathologically confirmed	BPH and non-BPH individuals, confirmed by PSA	*FokI*	416	691
Rukin, 2006 (68)	United Kingdom	Caucasian	Community based	Histologically confirmed; clinically malignant+positive bone scan and PSA	BPH	*FokI*	430	320
Andersson, 2006 (69)	Sweden	Caucasian	Hospital based	Histologically confirmed	Randomly selected from DNA bank	*TaqI*	137	176
Li, 2007 (40)	United states	Mixed	Nested in PHS cohort study	Self report,review of medical documents and/or pathological confirmation	Selected from prostate cancer-free indiviuals	*BsmI, FokI*	1034, 1010	1566, 1432
Mikhak, 2007 (48)	United states	Mixed	Nested in HPFS cohort study	Self report and review of medical documents	Free of prostate cancer, confirmed by PSA	*BsmI, FokI, CDX2*	646, 670, 688	669, 673, 689
Holick, 2007 (14)	United States	Mixed	Population based	Histologically confirmed	Randomly selected from King community. No prostate cancer history and normal DRE	*TaqI, BsmI, FokI*	586, 590, 583	545, 541, 552
Onen, 2008 (31)	Turkey	Caucasian	Hospital based	Pathologically confirmed	Examined by DRE, PSA and transrectal ultrasound	*TaqI, BsmI, ApaI*	133	157
Torkko, 2008 (33)	United States	Mixed	Nested in SABOR cohort study	Histologically confirmed	PSA<2.5 ng/mL, normal DRE	*FokI, CDX2*	585	761
Onsory, 2008 (70)	India	Indian	Hospital based	Histologically confirmed	Select from patients for minor treatment	*TaqI*	100	100

Note: DRE, digital rectal examination; PSA, prostate-specific antigen; Li, 2007: mostly Caucasian; Mikhak, 2007: mostly Caucasian; Holick, 2007: Caucasian 95.9% and African American 4.1%; Torkko, 2008: NHW 56% and HW 44%, excluding African Americans.

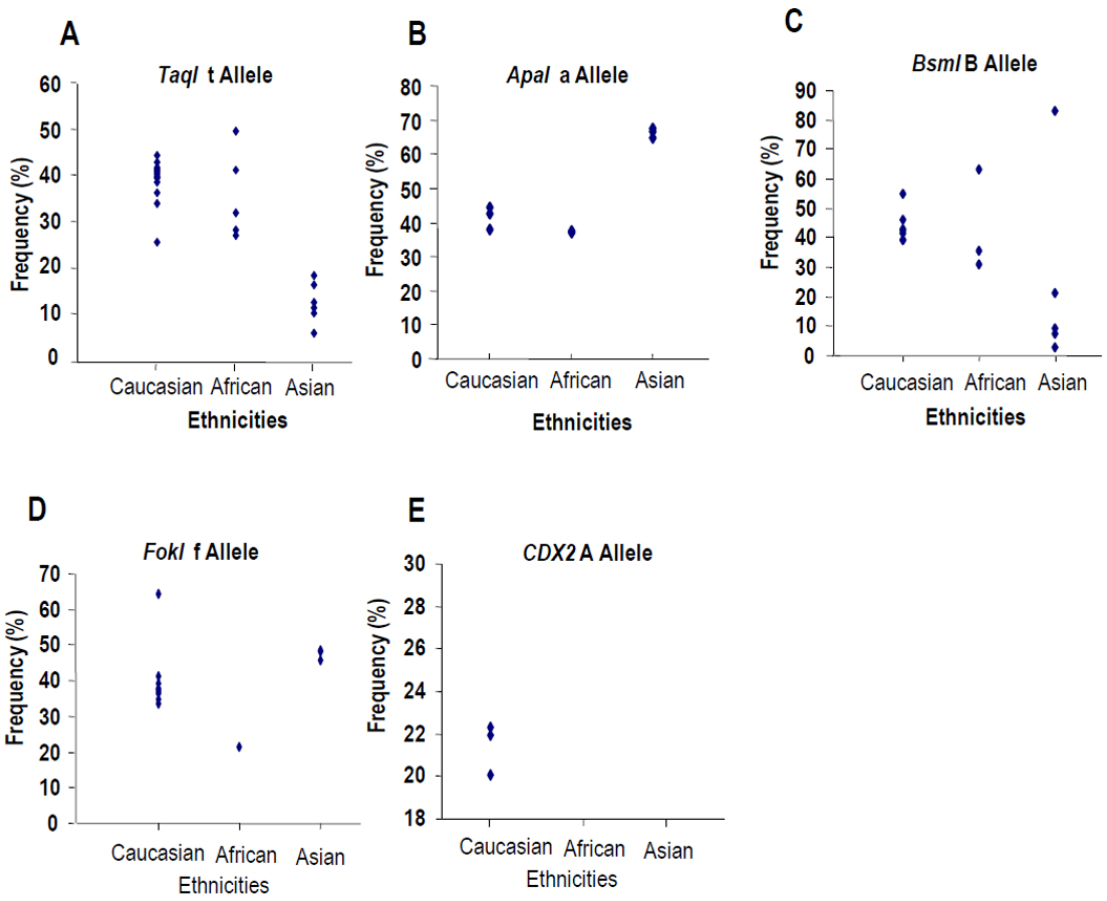


Figure 1. Minor allele frequencies of *TaqI, ApaI, BsmI, FokI* and *CDX2* polymorphisms among control subjects by different ethnicities. Each data point represents an individual study for the indicated association.

been fluctuating around 0.9 in the past years (in random effect model, summary OR for *t/t* versus *T/T*: 0.85 at the end of 2002, 0.95 at the end of 2004, 0.91 at the end of 2006, and 0.87 till the end of 2008). In the funnel plot analysis of publication bias (contrast of homozygous genotype plotted against the precision), the shape of the funnel plot seemed asymmetrical, with three studies located in the left corner of the plot (**Figurer 3**). However, an Egger's test did not show any publication bias ($P = 0.217$).

ApaI and *CDX2*. Data were too limited to apply recursive cumulative meta-analysis. The shape of the funnel plot seemed symmetrical for both *ApaI* and *CDX2* (**Figure 3**), which was confirmed by an Egger's test ($P = 0.805$ for *ApaI*; $P = 0.846$ for *CDX2*).

BsmI. The magnitude of the summary ORs had been stable in the past years (in random effect model, summary OR for *B/B* versus *b/b*: 0.85 at the end of 2002, 0.88 at the end of 2004, 0.88 at the end of 2006, and 0.95 at the end of 2008). In the funnel plot analysis, the shape seemed symmetrical (**Figure 3**), and an Egger's test did not show any publication bias ($P = 0.210$).

FokI. The magnitude of the summary ORs had been fluctuating around 1.0 in the past years (in random effect model, summary OR for *f/f* versus *F/F*: 0.98 at the end of 2004, 0.96 at the end of 2006, and 1.02 at the end of 2008). In the funnel plot analysis, the shape seemed asymmetrical, with three studies located at the left corner (**Figure 3**). An Egger's test proved that there was a significant publication bias in the association between the *FokI* polymorphism and prostate cancer risk ($P = 0.011$).

Table 2. Summary ORs and 95% CIs for various models in the overall population

Model	Studies No. (Participants)	Random-effects OR [95% CI]	Fixed-effects OR [95% CI]
TaqI (*t vs. T* allele)			
Homozygote	23 (5,288)	0.87 [0.75-1.02]	0.87 [0.75-1.00]
Dominant	23 (9,123)	0.91 [0.81-1.03]	0.91 [0.83-1.00]
Recessive	23 (9,123)	0.88 [0.75-1.03]	0.88[0.78-1.01]
ApaI (*a vs. A* allele)			
Homozygote	6 (1,309)	0.97 [0.68-1.39]	0.96 [0.76-1.22]
Dominant	6 (2,319)	0.98 [0.67-1.43]	1.04 [0.86-1.25]
Recessive	6 (2,319)	1.05 [0.87-1.27]	1.05 [0.87-1.27]
BsmI (*B vs. b* allele)			
Homozygote	13 (6,725)	0.95 [0.85-1.07]	0.95 [0.85-1.07]
Dominant	13 (11,481)	0.87 [0.77-0.98]	0.89 [0.82-0.96]
Recessive	13 (11,481)	1.01 [0.91-1.12]	1.01 [0.91-1.12]
FokI (*f vs. F* allele)			
Homozygote	16 (7,572)	1.02 [0.91-1.16]	1.03 [0.93-1.14]
Dominant	16 (14,061)	1.02 [0.94-1.12]	1.03 [0.96-1.11]
Recessive	16 (14,061)	1.00 [0.92-1.10]	1.00 [0.91-1.09]
CDX2 (*A vs. G* allele)			
Homozygote	4 (2,841)	1.07 [0.81-1.41]	1.07 [0.81-1.40]
Dominant	4 (4,186)	1.04 [0.90-1.20]	1.04 [0.92-1.18]
Recessive	4 (4,186)	1.05 [0.80-1.38]	1.05 [0.80-1.38]

Discussion

In the present meta-analysis, we examined five well-characterized SNPs of the *VDR* gene for their associations with prostate cancer risk. Our study demonstrated that there was significant difference in the minor allele frequencies between Asians and the other two ethnicities (Caucasians and Africans). Different from the conclusions of previous two meta-analyses [16, 17], we provided some new evidence to support an association between *VDR* polymorphisms and prostate cancer risk. The *TaqI t* allele and *BsmI B* allele seemed to be associated with reduced prostate cancer risk in the overall population, whereas the *ApaI a* allele was associated with a reduced prostate cancer risk only in Asian populations. In contrast, the *FokI f* allele was associated with a trend of increased prostate cancer risk only in Caucasian populations in the dominant model. We also examined the association between *VDR* polymorphisms and prostate cancer risk by tumor stage (local or advanced), but we failed to find any significant findings, suggesting that these variants may be indeed associated with risk of developing the disease rather than disease progression.

Prostate cancer is a multifactorial disease that results from complex interactions between genetic and environmental factors [38, 39]. The associations of serum vitamin D and *VDR* polymorphisms with prostate cancer risks have been explored for decades without conclusive results [40, 41], partly because of small sizes of the published studies. This may be also true that previous two meta-analyses of prostate cancer failed to find any association in the examined *VDR* polymorphisms, including *TaqI*, *ApaI*, *BsmI*, *FokI*, and *polyA*. In the present meta-analysis with a much larger number of subjects included, we observed an association of variant *TaqI t*, *BsmI B* and *ApaI a* alleles with reduced prostate cancer risk and the *FokI f* allele with increased prostate cancer risk. These findings are partly supported by another recent systemic evaluation of *BsmI* and *FokI VDR* polymorphisms with skin cancer risks [42]. Considering the relative weak association

Table 3. Summary ORs and 95% CIs for various models stratified by ethnicity (Random effects)

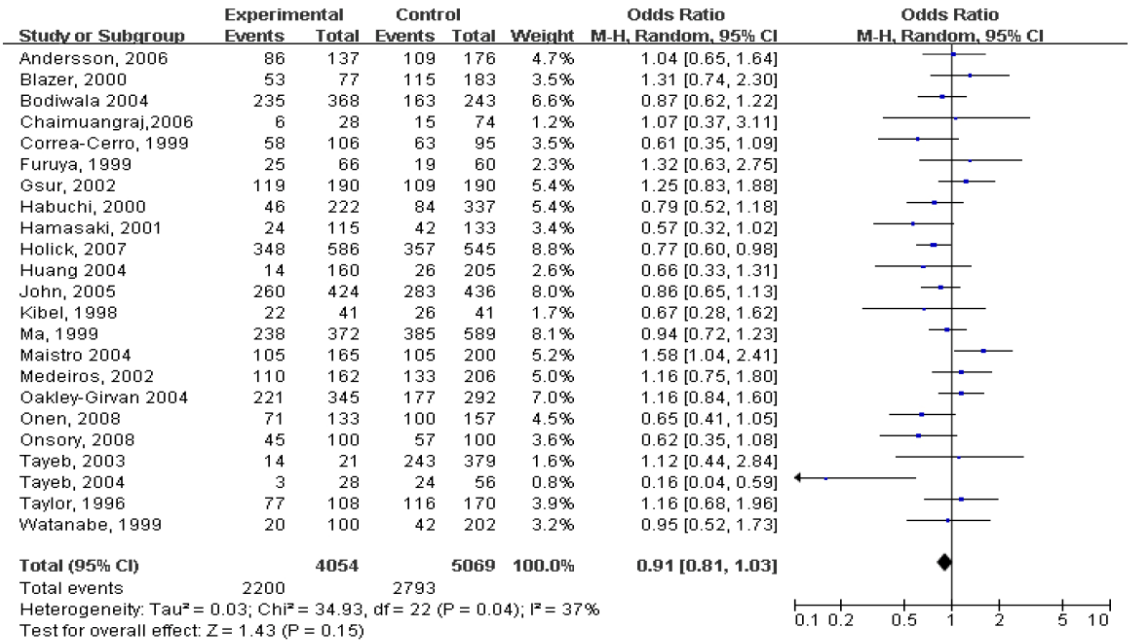
Model	Caucasian	African	Asian
TaqI (t vs. T allele)			
No. studies	16	5	6
Homozygote	0.86 [0.74-1.01]	1.30 [0.64-2.62]	0.52 [0.21-1.25]
Dominant	0.93 [0.81-1.06]	1.33 [0.68-2.59]	0.81 [0.63-1.03]
Recessive	0.88 [0.74-1.04]	1.18 [0.61-2.29]	0.51 [0.22-1.22]
ApaI (a vs. A allele)			
No. studies	3	2	3
Homozygote	1.32 [0.82-2.11]	0.78 [0.34-1.78]	0.67 [0.47-0.99]
Dominant	1.31 [0.89-1.93]	1.12 [0.73-1.74]	0.61 [0.43-0.87]
Recessive	1.11 [0.80-1.54]	0.72 [0.38-1.38]	1.06 [0.82-1.36]
BsmI (B vs. b allele)			
No. studies	8	3	5
Homozygote	0.98 [0.87-1.10]	0.93 [0.56-1.55]	0.72 [0.38-1.36]
Dominant	0.92 [0.84-1.01]	0.91 [0.66-1.26]	0.69 [0.44-1.08]
Recessive	1.03 [0.93-1.15]	1.04 [0.67-1.63]	0.78 [0.43-1.41]
FokI (f vs F allele)			
No. studies	11	1	3
Homozygote	1.09 [0.97-1.23]		0.86 [0.66-1.14]
Dominant	1.08 [1.00-1.17]		0.90 [0.73-1.12]
Recessive	1.03 [0.93-1.15]		0.91 [0.72-1.15]
CDX2 (A vs. G allele)			
No. studies	3	N/A	N/A
Homozygote	0.96 [0.69-1.34]		
Dominant	1.05 [0.85-1.30]		
Recessive	0.93 [0.67-1.29]		

of *VDR* polymorphisms with prostate cancer risks, different conclusions of current and previous meta-analyses could be due to improved statistical power in the present analysis, because previous analyses did show similar ORs that did not reach a statistical significance.

So far, the influence of *VDR* polymorphisms on VDR protein function and signaling is largely unknown. The polymorphisms for *TaqI, BsmI* and *ApaI* are probably nonfunctional because they are either located within intron (*BsmI* and *ApaI* in intron 8), which will be removed during mRNA post-transcriptional modification, or result in no amino acid sequence change (*TaqI* in exon 9). Therefore, their linkage disequilibrium (LD) with other unidentified functional polymorphisms elsewhere in the *VDR* gene is likely to explain the observed associations. Since these three polymorphisms are located in the 3'-UTR of the *VDR* gene, some investigators suggested that they might alter *VDR* mRNA levels through regulation of mRNA stability [43]. Although our data indicated that *TaqI, BsmI* and *ApaI* polymorphisms were individually associated with prostate cancer risk, they could have a synergistic effects, such as haplotypes [44]. In terms of the *FokI* polymorphism, the association of *FokI f* allele with increased prostate cancer risk was consistent with previous reports, which showed a reduced luciferase activity, compared with the *F* allele. In this case, the tumor counteracting activity of vitamin D in the *f* allele carriers may be reduced due to decreased transcription of the VDR-responsive genes [12].

Ethnicity is an important biological factor, which may influence VDR functions through gene-gene interactions. In our analysis, the association of *ApaI* and *FokI* polymorphisms with prostate cancer risk was observed in

A. *TaqI*



B. *ApaI*

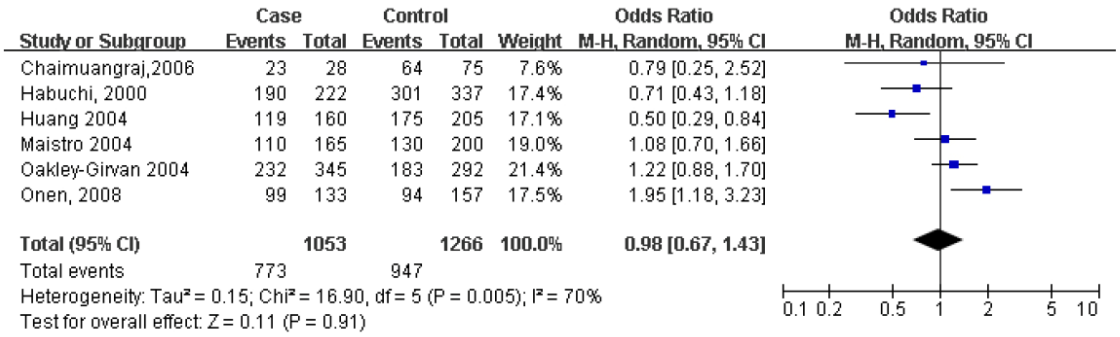


Figure 2. A and B. ORs of prostate cancer associated with *VDR* polymorphisms under dominant model by random effects. Comparison of minor allele *vs.* common allele.

Asian and Caucasian populations, respectively. Although the underlying mechanisms for the observed ethnical difference in prostate cancer risk need to be elucidated, the more pronounced tumor protecting effect of the *ApaI a* allele in Asian populations may be probably because the *a* allele frequency among Asians was significantly higher (66.2%) than that of the other two ethnic groups (Caucasians, 41.6% and Africans, 37.1%). Regarding to the *FokI* polymorphism, although Asians showed a similar *f* allele frequency to that of Caucasians (Caucasian, 39.7%; Asian, 47.4%), the Asian study sample size (3 studies in Asians *versus* 11 studies in Caucasians) may be too small to capture potential differences.

Despite the new findings from this analysis, we still cannot exclude the possibility that current significant results may be detected by chance alone, because multiple factors could have influenced our analysis, which might mask or exaggerate the true associations and thus require confirmation from additional analysis with more published studies in the future. First, a large proportion of studies included

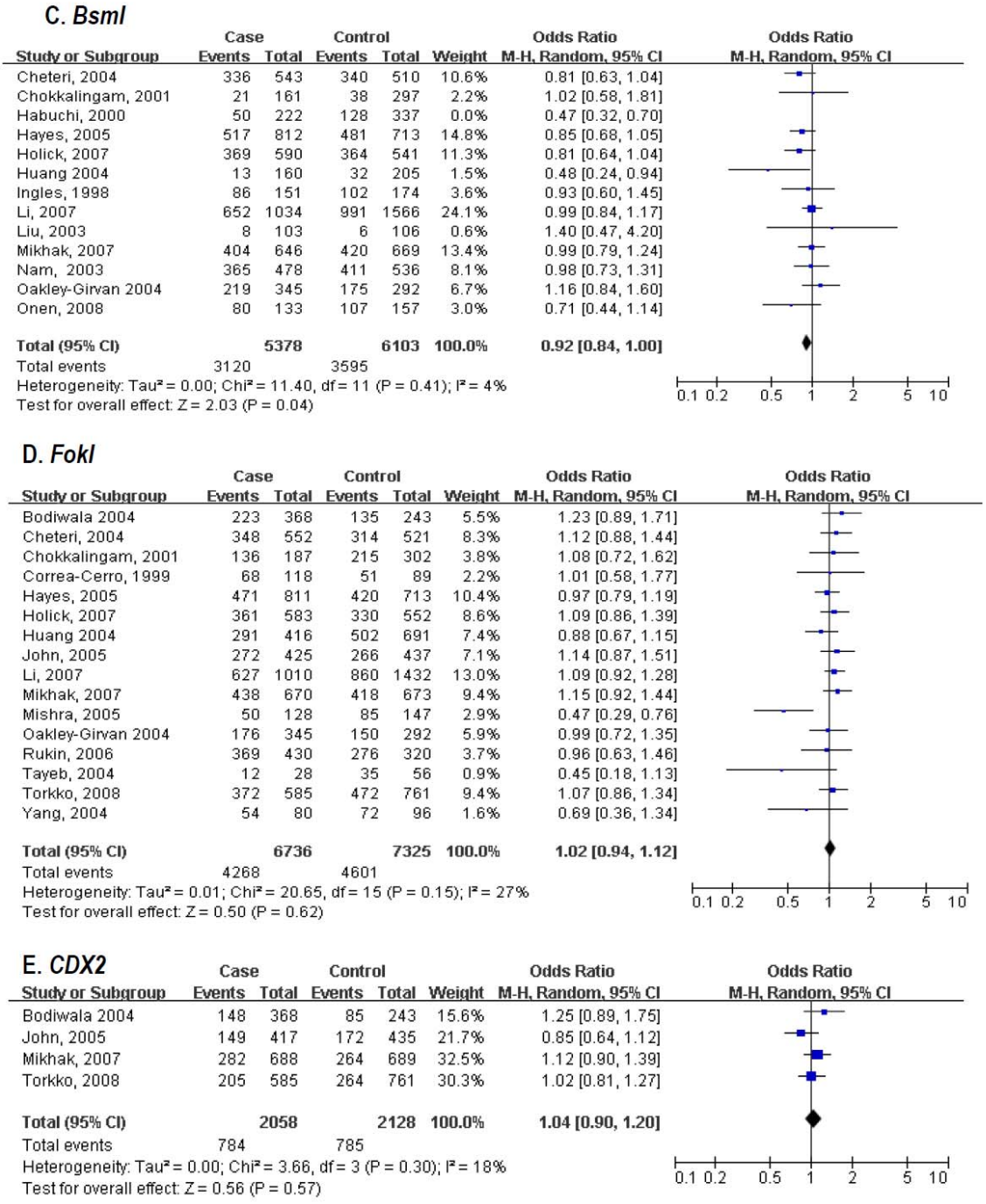


Figure 2. C, D and E. ORs of prostate cancer associated with *VDR* polymorphisms under dominant model by random effects. Comparison of minor allele *vs.* common allele.

BPH as their controls, which is characterized as prostatic stromal and epithelial cell hyperplasia, a risk factor for prostate cancer. The rationale for such an inclusion is based on the assumption that BPH is a benign disease that has a similar probability of developing prostate cancer to that of normal prostate tissues. Furthermore, some epidemiological studies did not support an association of increased BPH risk with *VDR* polymorphisms,

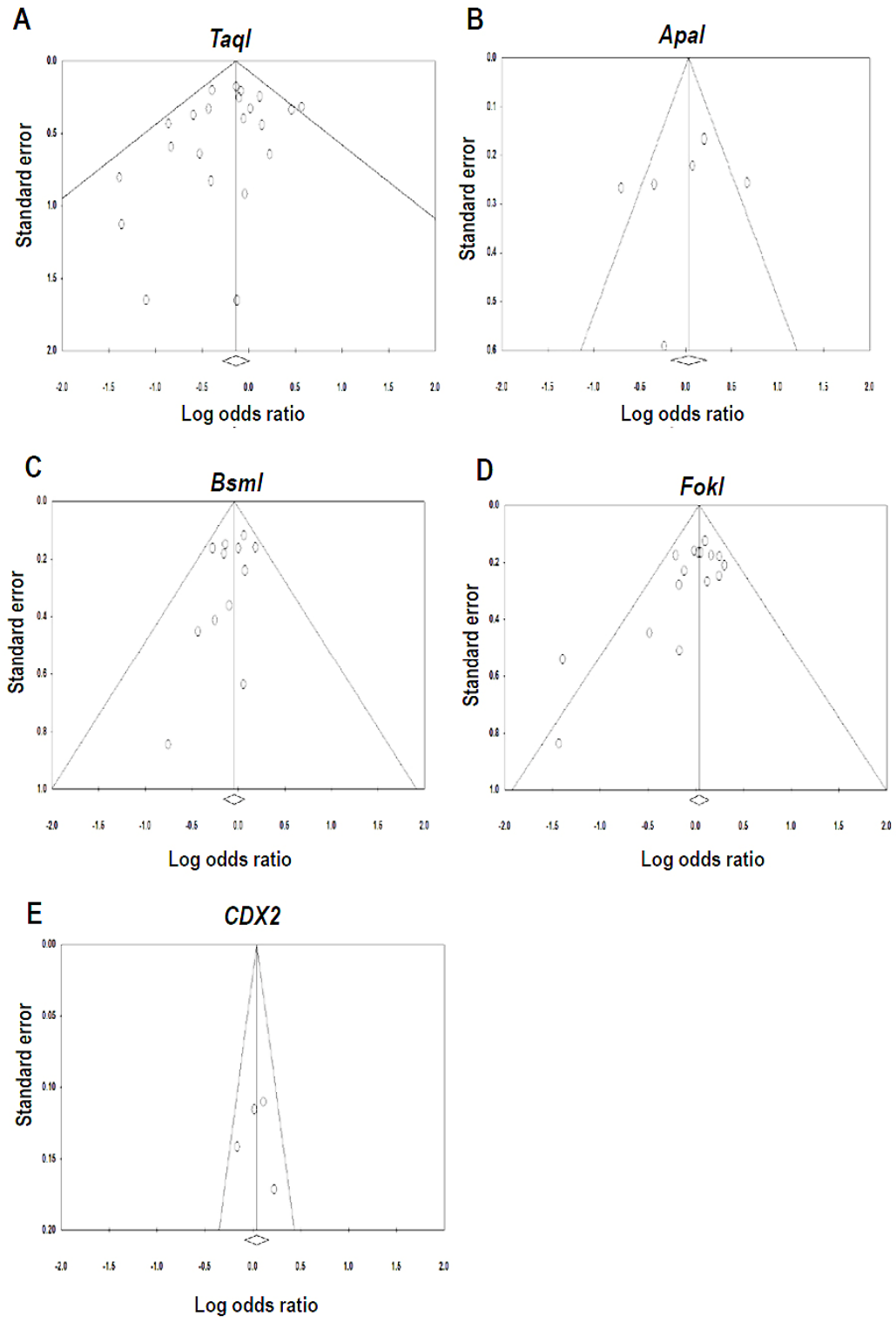


Figure 3. Funnel plot analysis to detect publication bias. Each point represents an individual study for the indicated association.

compared with normal controls [45, 46], although other investigations did observe antiproliferative effect of 1,25-dihydroxy-vitamin D_3 on primary culture of human prostatic cells [3] and an increased risk of BPH with *VDR* polymorphisms [37, 47]. In our meta-

Table 4. Summary ORs and 95% CIs for various models stratified by tumor stage (Random effect)

Models	Local	Advanced
TaqI (*t vs. T* allele)		
No. studies	2	5
homozygote	0.94 [0.43-2.06]	0.89 [0.49-1.63]
Dominant	0.95 [0.49-1.86]	0.89 [0.68-1.16]
Recessive	0.75 [0.37-1.50]	0.90 [0.48-1.66]
ApaI (*a vs. A* allele)		
No. studies	1	1
BsmI (*B vs. b* allele)		
No. studies	3	3
homozygote	1.03 [0.36-2.91]	0.77 [0.48-1.24]
Dominant	0.80 [0.63-1.03]	0.73 [0.40-1.34]
Recessive	1.10 [0.40-3.03]	0.84 [0.55-1.28]
FokI (*f vs F* allele)		
No. studies	3	4
homozygote	1.04 [0.77-1.40]	1.20 [0.93-1.55]
Dominant	1.05 [0.86-1.29]	1.07 [0.89-1.29]
Recessive	1.00 [0.79-1.28]	1.18 [0.93-1.48]
CDX2 (*A vs. G* allele)		
No. studies	N/A	1

analysis, we included BPH patients in the control groups because the data were too limited to reach any meaningful results, if BPH patients were used as an additional comparison group.

Second, it remains unclear how vitamin D may impact prostate cancer risk. It is known that tumor suppressor genes mainly work in the initial stage of tumor development, and multiple mutations in oncogenes will drive tumor growth and progression. If *VDR* polymorphisms did modify antitumor activity of vitamin D in prostate cancer development, it is more likely to occur in populations with high level of circulating vitamin D and in the very early stage of prostate carcinogenesis. Although our analysis did not support an association of *VDR* polymorphisms with prostate cancer progression, further analysis based on more detailed tumor information, such as the TNM stage and Gleason scores, may provide more valuable information. In terms of vitamin D status, data from individual studies supported the notion that high plasma 1,25-dihydroxyvitamin D_3 interacted with *VDR* polymorphisms and thus modified prostate cancer risks [40, 48, 49]. It has been hypothesized that vitamin D exerts its antitumor activity through its cytoplasm receptor, VDR [50]. However, recent reports have shown various VDR-independent effects of vitamin D, including regulation of calcium [51] and, more importantly, inhibition of cancer cell proliferation [52]. Given these, further mechanistic investigations are necessary to examine the antitummor activity of vitamin D in VDR-knockout prostate cancer cell lines.

Third, single genetic polymorphism described here may have a weak association with prostate cancer risks, which is beyond detection capacity of our current analysis. However, combined analysis of multiple polymorphisms may be more informative than a single-locus analysis to identify individuals at high risk of prostate cancer. Indeed, there was LD among the polymorphisms of *TaqI*, *ApaI*, *BsmI* and *polyA* [26, 53, 54]. The *BL* haplotype (BsmI-polyA) was reported to be associated with increased risk of advanced prostate cancer risk [55] and the four-locus *FBAt* haplotype (FokI-BsmI-ApaI-TaqI) had an inverse

association with the disease [56]. Without detailed individual genotyping information, we could not examine such haplotypes for their impact on prostate cancer risk.

Although considerable efforts have been made to test possible associations between *VDR* polymorphisms and prostate cancer risk, there are serious limitations inherited from the published studies. First, different study design and selection criteria for the cases and controls may have significant heterogeneity among studies. In addition, the genotype distributions among control subjects did not meet HWE in several studies of *TaqI, ApaI* and *BsmI* polymorphisms. Second, demographic parameters were not well matched or statistically adjusted in a few studies. Third, although Egger's test and funnel plots are commonly used to detect publication bias in the meta-analyses, the appearance of the funnel plots is influenced dramatically by effect size and the scale on the y-axis, whereas the power of Egger's test to detect bias is low using small numbers of studies. In our analysis, the Egger's test revealed significant publication bias in the *FokI* polymorphism, which was mainly caused by small studies, as suggested by the Funnel plot, as well as some unpublished studies, but this publication bias may also be explained by studies of lesser quality, resulting in an exaggerated association effect. To reduce the impact of publication bias, we further performed an adjusted meta-analysis for *FokI* polymorphism, using the trim and fill method described by Duval and Tweedie [57]. However, the corresponding pooled ORs were not substantially altered after adjustment of the missing studies on the right of the funnel plot (data not shown). Fourth, in addition to ethnicity and tumor stage, previous studies had examined prostate cancer risk associated with *VDR* polymorphisms in the presence of multiple environmental or clinicopathological factors, such as age, sun exposure, alcohol consumption, PSA levels and estrogen receptor status. However, we were unable to make a systemic evaluation based on these stratification factors, because definitions of these factors varied considerably across the studies, and the number of reports for individual factors, such as PSA, was small. Fifth, it should be noted that random and fixed effects models test different research questions. A random effects model assumes that each individual study is estimating its own OR, whereas a fixed effects model assumes that every study is estimating the same OR (a single common effect that underlies every study in the meta-analysis). Therefore, our results should be interpreted cautiously.

Overall, our meta-analysis found statistical evidence that supports an association of *VDR* polymorphisms of *TaqI, ApaI, BsmI* and *FokI*, but not *CDX2*, with prostate cancer risk. Larger studies of different ethnic populations, especially with detailed information about tumor characteristics, such as tumor stage and Gleason scores, are needed to confirm our findings.

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