Vitamin D Receptor Gene Polymorphisms and Risk of Prostate Cancer: A Meta-analysis

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Abstract

Several polymorphisms in the vitamin D receptor (*VDR*) gene have been implicated as risk factors for prostate cancer. We performed a meta-analysis of 14 studies (17 comparisons) with *TaqI* genotyping (1870 prostate cancer cases; 2843 controls), 6 studies (8 comparisons) with poly(A) repeat genotyping (540 cases; 870 controls), 5 studies with *BsmI* genotyping (987 cases; 1504 controls), and 3 studies with *FokI* genotyping (514 cases; 545 controls). The random-effects odds ratio (OR) for the *t versus T* allele was 0.95 [95% confidence interval (CI), 0.86–1.05]. There was no suggestion of an overall effect either in recessive or dominant modeling, and the comparison of *t/t versus T/T* also showed no differential prostate cancer susceptibility (OR, 0.88; 95% CI, 0.70–1.10). No effect of *t* was seen in subjects of European descent (nine comparisons; OR, 0.97; 95% CI, 0.87–1.08), Asian descent (five comparisons; OR, 0.88; 95% CI, 0.66–1.17), or African descent (three comparisons; OR, 0.94; 95% CI, 0.41–2.17). There was no between-study heterogeneity in any of these analyses. Overall, the random effects OR was 0.94 (95% CI, 0.75–1.18; no between-study heterogeneity) for the *S versus L* allele, 0.92 (95% CI, 0.63–1.35; $P < 0.01$ for heterogeneity) for the *B versus b* allele, and 1.03 (95% CI, 0.86–1.23; no between-study heterogeneity) for the *f versus F* allele. The meta-analysis shows that these four polymorphisms are unlikely to be major determinants of susceptibility to prostate cancer on a wide population basis.

Introduction

Epidemiological studies have offered hints that low levels of vitamin D may be a risk factor for prostate cancer (1, 2). Schwartz and Hulka (1) found that mortality rates in prostate cancer are inversely correlated with UV radiation exposure, which is essential for the synthesis of vitamin D. Corder *et al.* (2) reported an association between higher serum levels of 1α,25-dihydroxyvitamin D_3, the active metabolite of vitamin D, and decreased risk of developing clinical prostate cancer. *In vitro*, vitamin D and its analogs are potential inhibitors of cell proliferation (3, 4).

The effects of vitamin D and its analogs are mediated through the vitamin D receptor (VDR), a member of the steroid hormone receptor superfamily. VDR is a ligand-dependent transcription factor that is expressed in a wide range of cell types, including normal and malignant prostatic cells (5). The human *VDR* gene (6) is located on chromosome 12, consists of nine exons with several polymorphisms, and was first investigated in studies related to bone metabolism and bone mineral density (7). A poly(A) microsatellite repeat polymorphism has been identified in the 3′-untranslated region of the *VDR* gene. This polymorphism is in linkage disequilibrium with several restriction fragment length polymorphisms located in intron 8 (*BsmI* and *ApaI*) and exon 9 (*TaqI*). A polymorphism located in the first ATG translational initiation site of the *VDR* gene (*FokI*) has also been reported (8).

Molecular epidemiological studies have presented seemingly contradictory results concerning a potential role of the *TaqI* (9–22), poly(A) microsatellite repeat (19–24), *BsmI* (10–12, 24, 25), and *FokI* (15, 21, 25) polymorphisms in prostate cancer susceptibility. Single studies may have been underpowered to detect dose–response relationships or even overall effects. Given the amount of accumulated data, a quantitative synthesis of the evidence was deemed important. In this meta-analysis, we aimed to obtain summary estimates for the strength of the postulated genetic associations as well as to quantify and explain the potential between-study heterogeneity.

Materials and Methods

Identification and Eligibility of Relevant Studies. We considered all studies that examined the association of the *TaqI*, poly(A) repeat, *BsmI*, and *FokI* polymorphisms with prostate cancer. Sources included MEDLINE and EMBASE (last search update was May 2003). The search strategy was based on combinations of "prostate cancer," "vitamin D," "*VDR*," "polymorphism," "allele," and "genetics." References of retrieved articles were also screened.

Nonfamilial case–control studies were eligible if they had determined the distribution of genotypes for any of these polymorphisms in prostate cancer cases and in a concurrent control group of prostate cancer-free subjects by a molecular method for genotyping. We accepted disease-free controls regardless of whether they had benign prostatic hyperplasia. Cases with prostate cancer were eligible regardless of whether they had a first-degree relative with prostate cancer. However, we excluded family-based studies of pedigrees with several affected cases per family because their analysis is different (based on linkage considerations).

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Data Extraction. Two investigators independently extracted data and reached consensus on all items. The following information was sought from each report: authors, journal and year of publication, country of origin, selection and characteristics of prostate cancer cases and controls, demographics, racial descent of the study population (categorized as European, African, or Asian descent), eligible and genotyped cases and controls, and number of cases and controls for each *VDR* genotype. For studies including subjects of different racial descent, data were extracted separately for each race whenever possible. We also examined whether matching had been used, whether there was specific mention of blinding of the personnel who performed the genotyping to the clinical status of the subjects, and whether the genotyping method had been validated.

Meta-analysis. The primary analysis for all four polymorphisms was based on the contrast of alleles. This analysis aims to detect overall differences. We also examined the contrast of the two groups of homozygotes, the two extreme genetic groups. Contrasts of each group of homozygotes against the remaining subjects were also performed, but none of them was formally significant, and they did not offer further insights (not shown). For the poly(A) repeat polymorphism in particular, alleles were defined as long (*L*; with ≥18 As) *versus* short (*S*; with <18 As) as proposed originally (23).

The odds ratio (OR) was used as the metric of choice. Studies with subjects of different races were split into separate race-specific comparisons. For each genetic contrast, we estimated the between-study heterogeneity across all eligible comparisons, using the χ^2-based Q statistic (26). Heterogeneity was considered significant for $P < 0.10$. Data were combined using both fixed-effects (Mantel–Haenszel) and random-effects (DerSimonian and Laird) models (26). Random effects incorporate an estimate of the between-study variance and provide wider confidence intervals when the results of the constituent studies differ among themselves. Random effects are more appropriate when heterogeneity is present (26). Subgroup analyses estimated race-specific ORs for each allele contrast.

We also performed a cumulative meta-analysis (27) and recursive cumulative meta-analysis (28, 29) to evaluate whether the summary OR for the allele contrasts changed over time as more data accumulated. We used inverted funnel plots and the Begg–Mazumdar (30) bias diagnostic (nonparametric tau correlation coefficient) to evaluate whether the magnitude of the observed association was related to the variance of each study. Finally, we evaluated whether the summary results were different when the analyses were limited to studies with rigorous selection of cases and controls (those that confirmed histologically all prostate cancer cases and specifically screened all controls to rule out prostate cancer).

Analyses were conducted in SPSS 11.0 (SPSS, Inc., Chicago, IL), StatXact (Cytel Inc., Boston, MA), and Meta-Analyst (Joseph Lau, Boston, MA). All *P*s are two-tailed.

Results

Eligible Studies

We identified 17 eligible reports (Refs. 9–25; Table 1). The number of studies with *TaqI* (9–22), poly(A) microsatellite repeat (19–24), *BsmI* (10–12, 24, 25), and *FokI* (15, 21, 25) data were 14, 6, 5, and 3, respectively. After we split the data based on racial descent in three studies (13, 19, 22), there were 17, 8, 5, and 3 available comparisons for the four polymorphisms, respectively. There was a considerable diversity of ethnic groups.

Thirteen reports (10–13, 15–22, 25) selected prostate cancer patients based on a histological diagnosis from biopsy or prostatectomy, whereas the other 4 (9, 14, 23, 24) did not clarify the exact diagnostic criteria. Three reports (10, 19, 23) mentioned positive family history of prostate cancer in 100%, 48.8%, and 16% of patients, respectively; one report (21) specifically included patients without a family history of prostate cancer, whereas the remaining did not clarify the background of family history. Controls did not have a clinical diagnosis of prostate cancer at study entry, but the extent of additional screening [with digital rectal examination, prostate-specific antigen (<4 ng/ml), needle biopsy, or prostate resection] to exclude prostate cancer differed substantially across studies (Table 1).

With three exceptions (14, 15, 21) where the mean ages of controls and cases differed by ≥3 years, the reported mean or median ages of cases and controls were very similar (difference ≤2 years) and specific matching for age was described in seven studies (11, 16–18, 22, 24, 25). Only three reports (11, 17, 25) specifically mentioned blinding of the personnel who performed the genotyping. All studies used PCR, and in one study (21) sequencing was also performed. The distribution of genotypes in control groups was consistent with Hardy–Weinberg equilibrium for all four polymorphisms in all studies, with the exception of Chokkalingam *et al.* (25), in which there was a significant excess of both homozygous genotypes for the *BsmI* polymorphism. A sensitivity analysis was thus performed excluding this study.

Meta-analysis Databases (Table 2)

***TaqI*.** The eligible studies included 1898 patients with prostate cancer and 2862 controls, of whom 1870 and 2843, respectively, had genotype data. The *t* allele was more highly represented among controls of European descent [40%; 95% confidence interval (CI), 38–42%] and African descent (37%; 95% CI, 24–50%) than in controls of Asian descent (14%; 95% CI, 12–16). Overall, the prevalence of *t*/*t* homozygosity was 17%, 18%, and 3% in control subjects of European, African, and Asian descent, respectively. The respective prevalence rates of *T*/*t* heterozygosity were 48%, 39%, and 23%.

Poly(A). The eligible studies included 569 patients with prostate cancer and 876 controls, of whom 540 and 870, respectively, had genotype data. The prevalence of the *S* allele was 41% (95% CI, 38–44%), 27% (95% CI, 13–41%), and 12% (95% CI, 9–15%) in control subjects of European, African, and Asian descent, respectively. Overall, the prevalence of *S*/*S* homozygosity was 18%, 15%, and 3% in control subjects of European, African, and Asian descent, respectively. The respective prevalence rates of *L*/*S* heterozygosity were 46%, 25%, and 18%.

***BsmI*.** The eligible studies included 1094 patients with prostate cancer and 1702 controls, of whom 987 and 1504, respectively, had genotype data. The prevalence of the *B* allele was 41% (95% CI, 38–44%) and 14% (95% CI, 12–16%) in control subjects of European and Asian descent, respectively. Overall, the prevalence of *B*/*B* homozygosity was 15% and 3% in control subjects of European and Asian descent, respectively. The respective prevalence rates of *B*/*b* heterozygosity were 51% and 22%.

***FokI*.** The eligible studies included 610 patients with prostate cancer and 755 controls, of whom 514 and 545, respectively, had genotype data. The prevalence of the *f* allele was 36% (95% CI, 32–40%) and 46% (95% CI, 42–50%) in control subjects of European and Asian descent, respectively. Overall, the prevalence of *f*/*f* homozygosity was 14% and 21% in control subjects of European and Asian descent, respectively. The respective prevalence rates of *F*/*f* heterozygosity were 44% and 51%.

Table 1 Characteristics of studies included in the meta-analyses

First author, year (Ref.)	Country	Selection/characteristics of cases and controls [age range (mean)]		Racial descent	Eligible subjects[a]	
		Prostate cancer	Controls		Prostate cancer	Controls
Taylor, 1996 (13)	United States	Prostatectomy-documented cancer	BPH[b] or impotence, without history of cancer other than nonmelanoma skin cancer	European	96	162
				African	12	8
Ingles, 1997 (23)	United States	Identified by the SEER cancer registry. Family history in 16% [51–68 (57.8) years]	Enrolled in a study of bladder cancer (58.2 years)	European	68	171
Ingles, 1998 (24)	United States	Linkage to the SEER cancer registry and the California State Cancer Registry (45–75 years)	Randomly selected from the Hawaii-Los Angeles Multiethnic Cohort [45–75 (63.9) years]	African	151	174
Kibel, 1998 (19)	United States	Men who died from metastatic prostate cancer. Family history in 48.8% (64 years)	Urology patients who participated in a screening program for prostate cancer. Normal DRE, no elevated serum PSA, and/or negative biopsy (62 years)	European	37	35
				African	4	6
Ma, 1998 (11)	United States	Review of medical records and pathology reports (40–84 years)	Physicians participating in Physicians' Health Study. Cohort with negative clinical history of cancer who returned blood samples (40–84 years)	European	372	591
Watanabe, 1999 (20)	Japan	Serological, physical, and biopsy examinations (73 years)	Most with BPH. Serological (PSA, prostatic acid phosphatase), physical, and/or histological examinations (71.1 years)	Asian	100	202
Correa-Cerro, 1999 (21)	Germany	Histologically documented cancer. No family history of prostate cancer [46–90 (68.2) years]	Normal DRE, no elevated serum PSA for 7 years. Ambiguous results were checked by ultrasound and biopsy [64–86 (71.2) years]	European	132	105
Furuya, 1999 (19)	Japan	Not clarified [57–84 (68.5) years]	Normal DRE, no elevated serum PSA, and/or negative biopsy [47–79 (67.7) years]	Asian	66	60
Habuchi, 2000 (12)	Japan	Histologically documented cancer by transrectal needle biopsy or transurethral resection of the prostate (72.1 years)	BPH on DRE without elevated serum PSA or negative transrectal biopsy (n = 209; 70.4 years); nonurological admissions without BPH on DRE and no elevated serum PSA (n = 128; 73.5 years)	Asian	222	337
Blazer, 2000 (22)	United States	Histologically documented cancer. No history of prostate surgery	Randomly selected from the Piedmont Triad community. No history of cancer other than nonmelanoma skin cancer, symptomatic BPH, prostatitis, and prostate surgery	European	70	169
				African	7	14
Chokkalingam, 2001 (25)	United States	Histologically documented cancer [50–94 (73) years]	Randomly selected from the regional population registry. Normal DRE and no elevated serum PSA levels (66%; 71.9 years)	Asian	268	495
Luscombe, 2001 (32)	United Kingdom	Histologically documented cancer (n = 190); clinically malignant prostate on DRE, positive bone scan and serum PSA > 30 ng/ml (n = 20; 70.6 years)	BPH on DRE with serum PSA in the age-related reference range. Histological confirmation of BPH (n = 123; 67 years)	European	210	155
Hamasaki, 2001 (21)	Japan	Histologically documented cancer (70.3 years)	No cancer and BPH on DRE and no elevated serum PSA (67.7 years)	Asian	115	133
Gsur, 2002 (17)	Austria	Histologically documented cancer by TRUS-guided biopsy after a suspicious finding on DRE, elevated serum PSA, or both [59–72 (65.9) years]	Patients with BPH symptoms. Prostate cancer was excluded by negative DRE and lack of elevated serum PSA, by TRUS-guided biopsy, or by transurethral resection of the prostate [60–73 (66.5) years]	European	190	190
Medeiros, 2002 (18)	Portugal	Histologically documented cancer (45–86 years)	No elevated serum PSA (41–84 years)	European	163	211
Suzuki, 2003 (10)	Japan	Histologically documented cancer. History of prostate cancer in a first-degree relative [40–88 (70.6) years]	Negative DRE, no elevated serum PSA, without history of cancer. Family history of prostate cancer [n = 2; 51–88 (71.2) years]	Asian	81	105
Tayeb, 2003 (9)	United Kingdom	Review of pathology reports	BPH patients	European	21	379

[a] All eligible subjects were genotyped with the exception of 2 controls (*TaqI*) in Ma *et al.* (11); 26 cancer patients and 10 controls (*TaqI*), 15 cancer patients and 2 controls [poly(A)], 14 cancer patients and 16 controls (*FokI*) in Correa-Cerro *et al.* (21); 1 control in Blazer *et al.* (22); 1 cancer patient and 1 control in Luscombe *et al.* (15); 1 cancer patient and 5 controls in Medeiros *et al.* (18); 11 cancer patients and 2 controls in Ingles *et al.* (23); 3 cancer patients and 1 control [poly(A)] in Kibel *et al.* (19); and 107 cancer patients and 198 controls (*BsmI*) and 81 cancer patients and 193 controls (*FokI*) in Chokkalingam *et al.* (25).

[b] BPH, benign prostatic hyperplasia; SEER, Surveillance Epidemiology, and End Results; DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

Quantitative Synthesis (Table 3)

***TaqI*.** There was no evidence that the *t* allele modified the risk of prostate cancer (Fig. 1*A*). The summary OR was 0.95 by both random and fixed effects (P = 0.3). In subgroup analyses, no differences were observed in allele distribution between prostate cancer patients and controls of European, Asian, and African descent. We also found no evidence of an association of the *t*/*t* genotype with the risk of prostate cancer relative to the *T*/*T* genotype. There was no significant between-study heterogeneity in any of these analyses.

Table 2 Distribution of *VDR* genotypes in cases and controls

TaqI polymorphism

First author, year (Ref.)	Racial descent	Genotype					
		t/t		*T/t*		*T/T*	
		Cancer (%)	Control (%)	Cancer (%)	Control (%)	Cancer (%)	Control (%)
Taylor, 1996 (13)	European	8 (8.3)	36 (22.2)	60 (62.5)	73 (45.1)	28 (29.2)	53 (32.7)
Kibel, 1998 (19)	European	5 (13.5)	7 (20)	15 (40.5)	15 (42.9)	17 (46)	13 (37.1)
Ma, 1998 (11)	European	52 (14)	86 (14.6)	186 (50)	299 (50.8)	134 (36)	204 (34.6)
Correa-Cerro, 1999 (21)	European	19 (17.9)	11 (11.6)	39 (36.8)	52 (54.7)	48 (45.3)	32 (33.7)
Blazer, 2000 (22)	European	12 (17.1)	35 (20.8)	37 (52.9)	74 (44.1)	21 (30)	59 (35.1)
Luscombe, 2001 (32)	European	29 (13.9)	30 (19.5)	110 (52.6)	67 (43.5)	70 (33.5)	57 (37)
Gsur, 2002 (17)	European	34 (17.9)	22 (11.6)	85 (44.7)	87 (45.8)	71 (37.4)	81 (42.6)
Medeiros, 2002 (18)	European	19 (11.7)	41 (19.9)	91 (56.2)	92 (44.7)	52 (32.1)	73 (35.4)
Tayeb, 2003 (9)	European	4 (19)	62 (16.4)	10 (47.6)	181 (47.7)	7 (33.3)	136 (35.9)
Watanabe, 1999 (20)	Asian	2 (2)	6 (3)	18 (18)	36 (17.8)	80 (80)	160 (79.2)
Furuya, 1999 (19)	Asian	0 (0)	1 (1.7)	25 (37.9)	18 (30)	41 (62.1)	41 (68.3)
Habuchi, 2000 (12)	Asian	2 (0.9)	3 (0.9)	44 (19.8)	81 (24)	176 (79.3)	253 (75.1)
Hamasaki, 2001 (21)	Asian	2 (1.8)	8 (6)	22 (19.1)	34 (25.6)	91 (79.1)	91 (68.4)
Suzuki, 2003 (10)	Asian	2 (2.5)	2 (1.9)	20 (24.7)	20 (19)	59 (72.8)	83 (79)
Taylor, 1996 (13)	African	1 (8.3)	1 (12.5)	8 (66.7)	6 (75)	3 (25)	1 (12.5)
Kibel, 1998 (19)	African	1 (25)	1 (16.7)	1 (25)	3 (50)	2 (50)	2 (33.3)
Blazer, 2000 (22)	African	1 (14.3)	3 (21.4)	3 (42.8)	2 (14.3)	3 (42.8)	9 (64.3)

Poly(A) microsatellite repeat polymorphism

First author, year (Ref.)	Racial descent	Genotype					
		S/S		*L/S*		*L/L*	
		Cancer (%)	Control (%)	Cancer (%)	Control (%)	Cancer (%)	Control (%)
Ingles, 1997 (23)	European	3 (5.3)	33 (19.5)	29 (50.9)	75 (44.4)	25 (43.8)	61 (36.1)
Kibel, 1998 (19)	European	5 (14.3)	7 (20.6)	16 (45.7)	13 (38.2)	14 (40)	14 (41.2)
Correa-Cerro, 1999 (21)	European	24 (20.5)	12 (11.6)	49 (41.9)	56 (54.4)	44 (37.6)	35 (34)
Blazer, 2000 (22)	European	13 (18.6)	35 (20.8)	35 (50)	75 (44.7)	22 (31.4)	58 (34.5)
Watanabe, 1999 (20)	Asian	2 (2)	6 (3)	18 (18)	36 (17.8)	80 (80)	160 (79.2)
Kibel, 1998 (19)	African	1 (33.3)	1 (16.7)	1 (33.3)	1 (16.7)	1 (33.3)	4 (66.7)
Blazer, 2000 (22)	African	1 (14.3)	2 (14.3)	4 (57.1)	4 (28.6)	2 (28.6)	8 (57.1)

BsmI polymorphism

First author, year (Ref.)	Racial descent	Genotype					
		B/B		*B/b*		*b/b*	
		Cancer (%)	Control (%)	Cancer (%)	Control (%)	Cancer (%)	Control (%)
Ma, 1998 (11)	European	52 (14)	90 (15.2)	185 (49.7)	300 (50.8)	135 (36.3)	201 (34)
Habuchi, 2000 (12)	Asian	8 (3.6)	15 (4.5)	42 (18.9)	113 (33.5)	172 (77.5)	209 (62)
Chokkalingam, 2001 (25)	Asian	4 (2.5)	7 (2.4)	17 (10.6)	31 (10.4)	140 (86.9)	259 (87.2)
Suzuki, 2003 (10)	Asian	6 (7.4)	2 (1.9)	17 (21)	20 (19)	58 (71.6)	83 (79)

FokI polymorphism

First author, year (Ref.)	Racial descent	Genotype					
		f/f		*F/f*		*F/F*	
		Cancer (%)	Control (%)	Cancer (%)	Control (%)	Cancer (%)	Control (%)
Correa-Cerro, 1999 (21)	European	10 (8.5)	9 (10.1)	58 (49.1)	42 (47.2)	50 (42.4)	38 (42.7)
Luscombe, 2001 (32)	European	32 (15.3)	24 (15.6)	92 (44)	65 (42.2)	85 (40.7)	65 (42.2)
Chokkalingam, 2001 (25)	Asian	41 (21.9)	62 (20.5)	95 (50.8)	153 (50.7)	51 (27.3)	87 (28.8)

Poly(A). The contrast of alleles did not suggest any strong genetic effect (Fig. 1*B*). The summary OR was 0.94 by random effects ($P = 0.58$) and 0.93 by fixed effects ($P = 0.49$). We also found no evidence of an association of the *S*/S genotype with the risk of prostate cancer relative to the *L*/*L* genotype. There was no significant between-study heterogeneity in any of these analyses.

***BsmI*.** There was no evidence that the *B* allele modified the risk of prostate cancer (Fig. 1*C*). The summary OR was 0.92 by random effects ($P = 0.68$) and 0.87 by fixed effects ($P = 0.075$). However, there was significant heterogeneity among the four study comparisons ($P < 0.01$ for heterogeneity). Exclusion of the one study in which Hardy–Weinberg equilibrium was violated in the controls (25) did not yield a very different genetic effect (OR, 0.91; 95% CI, 0.56–1.48; $P = 0.70$ by random effects; 0.86; 95% CI, 0.74–1.01; $P = 0.058$ by fixed effects), and there was still significant between-study heterogeneity ($P < 0.01$). No clear effect was seen, however, for the

Table 3 Summary ORs[a] and 95% CIs for various contrasts

Contrast	Comparisons (*n*)	Random-effects OR (95% CI)	Fixed-effects OR (95% CI)
t vs. T alleles	17 (9428)	0.95 (0.86–1.05)	0.95 (0.86–1.04)
European descent	9 (6484)	0.97 (0.87–1.08)	0.97 (0.87–1.08)
Asian descent	5 (2842)	0.88 (0.66–1.17)	0.86 (0.69–1.08)
African descent	3 (102)	0.94 (0.41–2.17)	0.94 (0.41–2.16)
t/t vs. T/T	17 (2799)	0.88 (0.70–1.10)	0.87 (0.70–1.08)
S vs. L alleles[b]	7 (2173)	0.94 (0.75–1.18)	0.93 (0.76–1.14)
S/S vs. L/L	8 (ND)	0.93 (0.60–1.45)	0.95 (0.64–1.42)
B vs. b alleles[b]	4 (4332)	0.92 (0.63–1.35)	0.87 (0.75–1.01)
B/B vs. b/b	5 (ND)	0.90 (0.66–1.22)	0.90 (0.66–1.22)
f vs. F alleles	3 (2118)	1.03 (0.86–1.23)	1.03 (0.86–1.23)
f/f vs. F/F	3 (554)	1.04 (0.72–1.51)	1.04 (0.72–1.52)

[a] OR, odds ratio; CI, confidence interval; ND, no data.
[b] One study (24) is not included in the primary analysis because it examines *BsmI*/poly(A) haplotypes.

B/*B* genotype compared with the *b*/*b* genotype, and there was no significant between-study heterogeneity in this comparison.

***FokI*.** The contrast of alleles did not suggest any strong genetic effect (Fig. 1*D*). The summary OR was 1.03 by both random and fixed effects ($P = 0.73$). We also found no evidence of an association of the *f*/*f* genotype with the risk of prostate cancer relative to the *F*/*F* genotype. There was no between-study heterogeneity in any of these analyses.

Bias Diagnostics

***TaqI*.** The magnitude of the summary OR had been stable over time (by random effects, summary OR for *t versus T* was 0.80 at the end of 1996, 0.91 at the end of 1998, 0.92 at the end of 2000, 0.90 at the end of 2001, 0.94 at the end of 2002, and 0.95 in 2003). The OR was not related to study size. Analyses limited to studies with rigorous selection of cases and controls yielded similar results (11 comparisons; 6178 alleles; OR, 0.95; 95% CI, 0.82–1.09; no significant between-study heterogeneity).

Poly(A). The magnitude of the summary OR was not stable over time, and it changed considerably each year with an apparent dissipation of the postulated effect (by random effects, summary OR for *S versus L* was 0.60 at the end of 1997, 0.76 at the end of 1998, 0.89 at the end of 1999, and 0.94 at the end of 2000). Analyses limited to studies with rigorous selection of cases and controls yielded similar results (four comparisons; 1200 alleles; OR, 1.04; 95% CI, 0.78–1.37; no significant between-study heterogeneity).

***BsmI* and *FokI*.** Data were too limited to apply meaningfully recursive cumulative meta-analysis and publication bias diagnostics. Analyses limited to studies with rigorous selection of cases and controls yielded similar results (three comparisons; 2406 alleles; OR, 0.96; 95% CI, 0.50–1.84; $P < 0.01$ for heterogeneity for *BsmI*; all *FokI* studies used rigorous selection criteria).

Discussion

This meta-analysis examined four well-characterized polymorphisms of the *VDR* gene and their relationship to prostate cancer susceptibility. The existing evidence does not show any increased risk conferred by these polymorphisms, and the 95% CIs are narrow enough to exclude a large genetic effect. In subgroup analyses, no differences were observed in allele distribution between prostate cancer patients and controls of European, Asian, and African descent.

The meta-analysis did not address whether these four polymorphisms may have an effect on the clinical behavior of prostate cancer or other clinicopathological attributes. A few studies have generated some relevant data, but their results have been contradictory. Taylor *et al.* (13) claimed a significantly decreased risk of prostate cancer requiring prostatectomy with the *t/t* genotype, and a trend for poor survival with the *T/T* genotype was claimed by Furuya *et al.* (14), but data were limited. Hamasaki *et al.* (16) also claimed a 2.5-fold significantly increased risk of locally advanced or metastatic disease and a significant 5.4-fold increased risk of poorly differentiated adenocarcinoma for *T/T* subjects. Conversely, two other studies (17, 22) found no significant associations for *VDR* polymorphisms with clinicopathological correlates. Gsur *et al.* (17) found no significant associations for the *TaqI* polymorphism with Gleason score and PSA levels. Similarly, Blazer *et al.* (22) found no significant associations for the *Taq*I and poly(A) polymorphisms with more advanced disease. Ingles *et al.* (24) claimed a 2-fold decrease in risk of advanced prostate cancer with the *b* allele, and a significant association of advanced disease with the *L* allele was claimed by Ingles *et al.* (23). Xu *et al.* (31) claimed that subjects with the *f/f* genotype had a lower mean percentage of Gleason grade 4/5 cancer and lower risk of PSA failure, whereas Luscombe *et al.* (32) claimed that the *f/f* genotype was associated with increased risk of metastases but not with advanced stage or tumor grade. Definitions of clinicopathological correlates varied considerably across these studies, making a comparison of their results difficult. Given the multiplicity of possible comparisons and the unavoidable flexibility of choosing and defining these correlates, associations may have been detected by chance alone. The differences among studies are consistent with spurious findings, although some genuine association cannot be totally excluded.

Our meta-analysis cannot exclude the possibility that other polymorphisms in the *VDR* gene may still be useful to pursue. Preliminary data on an *ApaI* polymorphism in subjects of Asian descent have not shown any clear association with prostate cancer (10, 12), but more evidence is required. Nevertheless, we should note that linkage studies (33, 34) based on genome scans have not identified overall any significant linkage of prostate cancer with the region of 12q12-q14, the chromosomal location of the *VDR* gene.

The biochemical evidence for a putative relationship of *VDR* polymorphisms with VDR function is also unclear. Importantly, none of these polymorphisms has been consistently shown to affect *VDR* mRNA stability (35–37). Taylor *et al.* (13) found that men who were homozygous for the *t* allele had higher levels of the active form of vitamin D. Ma *et al.* (11) claimed that the *B/B* genotype was significantly associated with higher 1,25-dihydroxyvitamin D levels. Even if the identified polymorphisms regulate VDR activity, there is no conclusive epidemiological evidence that serum vitamin D levels play an important role in the risk of prostate cancer (2, 38–42). Linkage disequilibrium with some other variants that alter VDR function is an alternative possibility to explain the biological effect, if any, of these *VDR* polymorphisms. Furthermore, several other genes have been implicated in the pathogenesis of prostate cancer, including notably genes coding for enzymes of the androgen biosynthetic and metabolic pathways (43). Polymorphisms in such genes have also been postulated as prostate cancer determinants (44), but meta-analyses of the data have yielded mostly negative results (45, 46).

Postulated genetic associations for prostate cancer need to

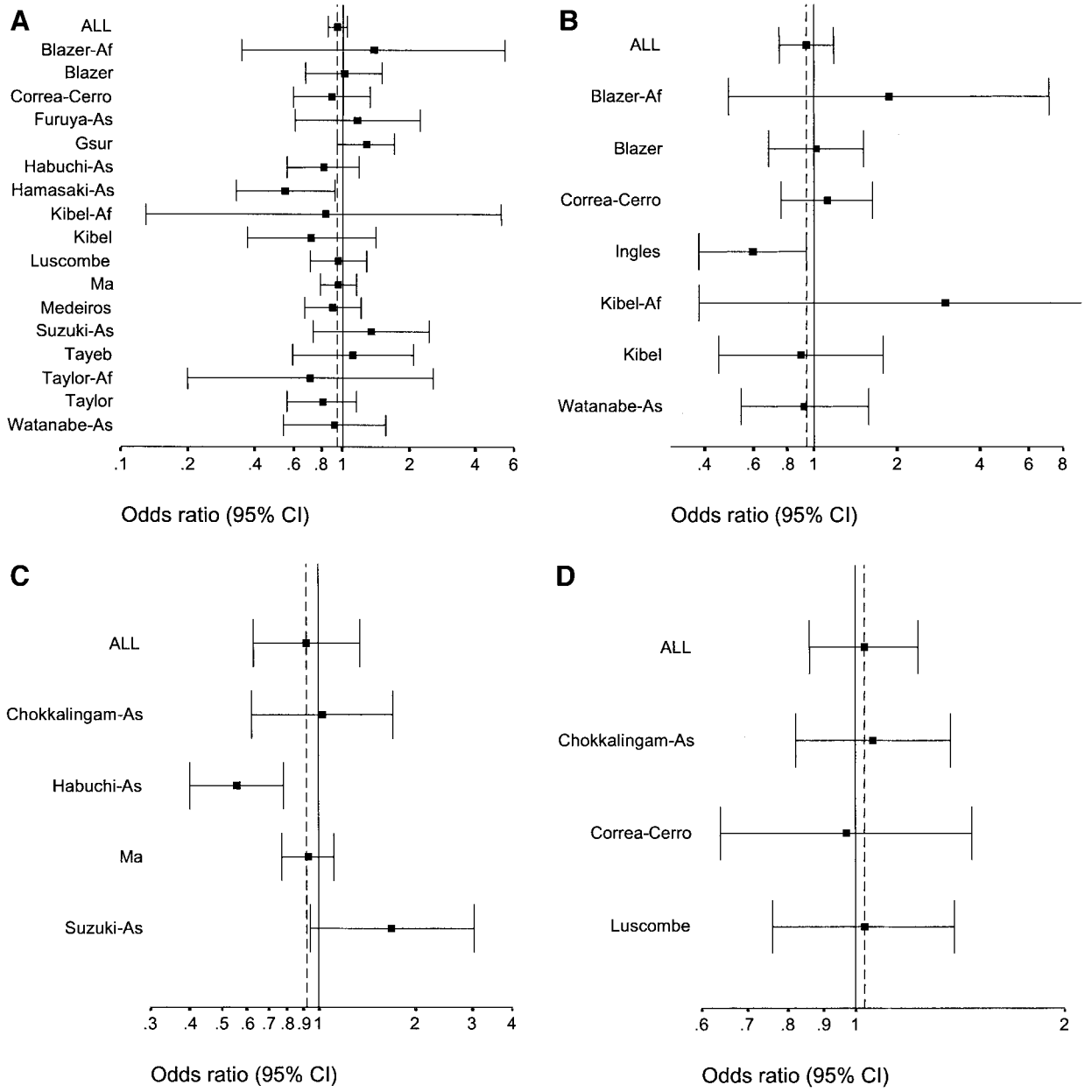

Fig. 1. *A*, effect of the *t versus T* allele on the risk of prostate cancer. Each comparison is presented by the name of the first author. *Af* signifies subjects of African descent; *As* signifies subjects of Asian descent. For each comparison, the point estimate of the odds ratio and the accompanying 95% confidence interval (*CI*) are shown. Also shown is the summary random-effects estimate for the comparison along with the respective 95% confidence interval. Values >1 denote an increased risk for prostate cancer with the *t* allele. *B*, effect of the *S versus L* allele on the risk of prostate cancer. Values >1 denote an increased risk for prostate cancer with the *S* allele. Otherwise, set up the same as *panel A*. *C*, effect of the *B versus b* allele on the risk of prostate cancer. Values >1 denote an increased risk for prostate cancer with the *B* allele. Otherwise, set up is the same as in *panel A*. *D*, effect of the *f versus F* allele on the risk of prostate cancer. Values >1 denote an increased risk for prostate cancer with the *f* allele. Otherwise, set up is the same as in *panel A*.

be carefully validated across several studies because early and small genetic association studies may come up with spurious findings (47–50). Genetic associations for such a multigenetic disease are likely to have relatively small ORs that would require large sample sizes to clarify. Some other analytical issues should also be considered. First, some nondifferential misclassification bias is possible. The majority of the considered studies could not exclude latent prostate cancer cases in the control group. Some controls may have developed prostate cancer during the subsequent years. The impact of such biases is unlikely to be large, but it may dilute small associations, if present. Furthermore, control groups included a large, often unknown proportion of subjects with benign prostatic hyperplasia. Benign prostatic hyperplasia may be also affected by these same polymorphisms. However, one would then refer to a genetic factor conferring risk for prostate enlargement rather than cancer *per se*, a hypothesis with completely different connotations. To date, three (12, 51, 52) studies do not support

this hypothesis for the *TaqI* polymorphism. Finally, this meta-analysis did not address extended haplotypes because this information was often not available. However, at least *BsmI*, *TaqI*, and poly(A) are in strong linkage disequilibrium. Concordance rates of up to 97% have been described between the *BsmI B* allele and the *TaqI t* allele (11) or the poly(A) *S* allele (23). Thus, haplotypes are unlikely to give much different results for these three polymorphisms at least.

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