GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Racial disparities in the association between diabetes mellitus-associated polymorphic locus rs4430796 of the *HNF1β* gene and prostate cancer: a systematic review and meta-analysis

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Genet. Mol. Res. 13 (3): 6582-6592 (2014)
Received January 11, 2013
Accepted July 10, 2013
Published August 28, 2014
DOI http://dx.doi.org/10.4238/2014.August.28.3

ABSTRACT. Polymorphism 17q12 rs4430796 within *HNF1β* is a genetic variant associated with both diabetes mellitus and prostate cancer, but findings on the correlations of rs4430796 with prostate cancer risk specifically are not in agreement, especially among diverse populations. To shed some light on the contradictory findings, therefore, we carried out a meta-analysis by pooling the odds ratios (ORs) with corresponding 95% confidence intervals (CIs) of all currently available case-control studies located within PubMed and Embase databases up to December 2012. A total of 16 studies comprising 30 datasets that collectively involved 25,535 prostate cancer patients and 25,726 controls were ultimately included in this analysis. The meta-analysis of all the studies revealed that the rs4430796 polymorphism was significantly associated

with an increased risk of prostate cancer in all contrast models (OR_{A} *vs* $_{G}$ = 1.25, 95%CI = 1.21-1.30, $P_{OR} < 0.001$; OR_{AA} *vs* $_{GG}$ = 1.53, 95%CI = 1.45-1.62, $P_{OR} < 0.001$; OR_{AG} *vs* $_{GG}$ = 1.24, 95%CI = 1.16-1.34, $P_{OR} < 0.001$; OR_{AA} *vs* $_{AG+GG}$ = 1.36, 95%CI = 1.30-1.42, $P_{OR} < 0.001$; OR_{AA+AG} *vs* $_{GG}$ = 1.37, 95%CI = 1.30-1.44, $P_{OR} < 0.001$). After subgroup analyses stratified by ethnicity, however, the rs4430796 polymorphism was significantly associated with prostate cancer in both Caucasians and Asians but not in African-Americans. In conclusion, our meta-analysis identified a significant association between the 17q12 rs4430796 polymorphism and prostate cancer risk, although the degree of this association and frequency of the causative allele varied among men of different races.

Key words: *HNF1β*; Genetic polymorphisms; Prostate cancer; Diabetes mellitus; Meta-analysis

INTRODUCTION

In men from industrialized countries, prostate cancer is the most frequently diagnosed malignancy (Jemal et al., 2011). Among American men specifically, it accounts for 29% of all cancer cases and is the second most common cause of death by cancer (Jemal et al., 2010). In 2012, an estimated 241,740 men will be diagnosed with prostate cancer, and 28,170 of those will die of it (Siegel et al., 2012). There is, therefore, a clear need for the identification of potential risk factors of prostate cancer development and progression, in order to develop prostate cancer interventions subsequently. In recent years, research has paid great attention to the role of genetics in the development, progression, and treatment of prostate cancer. Genome-wide linkage scans have been widely used to detect variants with effects on prostate cancer risk. The chromosome 8q24 region and the *HNF1β* (formerly TCF2) locus at chromosome 17q12 are the two main loci that have been reported to be strongly associated with prostate cancer risk (Amundadottir et al., 2006; Gudmundsson et al., 2007a,b).

Diabetes mellitus is another serious public health problem. Epidemiologic research suggests that diabetes mellitus is associated with reduced prostate cancer risk (Wynder et al., 1971; Baradaran et al., 2009) and three meta-analysis studies have confirmed this association (Bonovas et al., 2004; Kasper and Giovannucci, 2006; Zhang et al., 2012). Although the detailed mechanism behind the relationship remains unclear, several genome-wide association studies suggest that shared genetic risk factors for diabetes mellitus and prostate cancer exist. Indeed, the most common allelic variants of the *HNF1β* and *JAZF1* genes are associated with both type II diabetes mellitus (Gudmundsson et al., 2007b; Winckler et al., 2007; Zeggini et al., 2008) and prostate cancer (Gudmundsson et al., 2007a; Thomas et al., 2008; Sun et al., 2008b), with opposite effects described for these two phenotypes. Of these variants, the G to A 17q12 rs4430796 polymorphism in *HNF1β*, the one most often associated with both prostate cancer and diabetes mellitus, has been investigated in an increasing number of studies, including several that evaluated its relationship with prostate cancer risk. Molecular epidemiological studies, however, have yielded contradictory results concerning the potential role of polymorphism rs4430796 in prostate cancer, especially among diverse populations (Gudmundsson et al., 2007b; Thomas et al., 2008; Sun et al., 2008a,b; Levin et al., 2008; Waters et al., 2009; Penney et al., 2009; Yamada et al., 2009; Helfand et al., 2009, 2010; Hooker et al., 2010; Zhou et al., 2011; Liu et al., 2011; Kim et al., 2011; Lange et al., 2012; Chan et al., 2012).

Some of these reports evaluated this association in a variety of races including American white (AW), European white (EW), African-American (AA), Latin-American (LA), and Asian (A). These studies suggest that single nucleotide polymorphism genotype frequencies of 17q12 rs4430796 may vary by race and, therefore, may at least partially account for observed racial differences in prostate cancer risk.

The evaluation of the magnitude that polymorphism rs4430796 affect the development and progression of prostate cancer is thus required to provide insight into the detailed mechanism behind the association between diabetes mellitus and prostate cancer and, consequently, a greater understanding of these two diseases. This meta-analysis study was, therefore, performed to determine how strongly polymorphism rs4430796 within the *HNF1β* gene is associated with prostate cancer susceptibility in men.

MATERIAL AND METHODS

Search strategy and selection criteria

We conducted a comprehensive literature search within PubMed and Embase databases up to December 1, 2012 using the following search terms: prostate cancer, prostate carcinoma; polymorphism, polymorphisms; 17q12, rs4430796. There restrictions were placed on time periods, sample sizes, or types of reports. The references all eligible articles cited were also checked for relevance. Studies were included in the meta-analysis if they met the following selection criteria: 1) case-control studies determining the association between the 17q12 rs4430796 polymorphism and prostate cancer risk; 2) prostate cancer was confirmed histologically or pathologically in all prostate cancer patients, while controls were selected from individuals without cancer; 3) data on the genotype frequency of the 17q12 rs4430796 polymorphism or odds ratios (ORs) and their 95% confidence intervals (CIs) were provided. Case-only studies and review papers were excluded. If two or more studies contained overlapping cases or controls, only the study with the largest sample size was included into the meta-analysis.

Data extraction

All data were independently extracted by two investigators (Y.Z. Xiang and S.B. Jiang) according to the pre-specified selection criteria. The first author's surname, publication year, country of origin, ethnicity of the study population, source of controls, result of Hardy-Weinberg equilibrium (HWE) test for controls, number of cases and controls of different genotypes (AA, AG, GG), and total number of cases and controls with corresponding ORs were collected. Ethnicity was categorized as AW, EW, AA, LA, or A. For studies that included subjects of additional ethnic groups, data were extracted separately for each ethnic group whenever possible. Consensus was mostly achieved between separate data collections. A third investigator (X.B. Jin) settled any data collection discrepancies.

Quality assessment

The quality of included studies was attributed mainly to the HWE finding for the genotypic distribution of the 17q12 rs4430796 polymorphism in controls (Su et al., 2011). Studies with data that departed from the HWE in controls were defined as low-quality studies. Alternatively, studies with a control 17q12 rs4430796 polymorphism genotypic distribution in agreement with the HWE ($P > 0.05$) were defined as high-quality studies.

Meta-analysis

The strength of the association between the 17q12 rs4430796 polymorphism and prostate cancer risk was assessed by the pooled OR with its 95%CI. We investigated the association between the 17q12 rs4430796 polymorphism and prostate cancer risk using both the allele contrast model (A *vs* G) and the genotype contrast model (AA *vs* GG, AG *vs* GG, AA *vs* AG + GG and AA + AG *vs* GG). Two models of meta-analysis for dichotomous outcomes were employed: the random-effects model and the fixed-effects model. The random-effects model was conducted using the DerSimonian and Laird's (1986) method, while the fixed-effects model was conducted using the Mantel-Haenszel (1959) method. Both the chi-square-based Q-statistic test (Cochran's Q-statistic) that assesses the between-study heterogeneity and the I^2 statistic that quantifies the proportion of the total variation due to heterogeneity were calculated (Higgins et al., 2003). Severe heterogeneity existed when the I^2 value was greater than 50% or the P value of Cochran's Q-statistic was less than 0.05 and the random-effects model was used to pool the results. The fixed-effects model was used to pool results when I^2 value was less than 50% with a P value more than 0.05. The significance of the pooled OR was determined with the Z-test; a result with a P value of less than 0.05 was considered to be significant. To validate the credibility of outcomes obtained with this meta-analysis, sensitivity analysis was subsequently performed by sequentially omitting individual studies or by omitting studies with low quality. Sensitivity analysis was also performed by adding previously excluded studies containing controls not in the HWE (Salanti et al., 2005). Subgroup analyses were conducted by ethnicity. Publication bias was investigated by funnel plot, in which the standard error of log OR of each study was plotted against its log OR; an asymmetric plot was suggestive of a risk of publication bias (Stuck et al., 1998). Furthermore, the asymmetry of the funnel plot was assessed using the Egger linear regression test. All analyses were performed with STATA version 11.0 (StataCorp. LP, College Station, TX, USA). Results with a $P < 0.05$ were considered to be statistically significant.

RESULTS

Characteristics of reviewed studies

A total of 28 records were identified with a computerized literature search, and, following the exclusion of 12 records that did not meet eligible criteria, 25,535 prostate cancer cases and 25,726 controls in total were ultimately included into this meta-analysis. Summaries of the 16 final studies (Gudmundsson et al., 2007b; Thomas et al., 2008; Sun et al., 2008a,b; Levin et al., 2008; Waters et al., 2009; Penney et al., 2009; Yamada et al., 2009; Helfand et al., 2009, 2010; Hooker et al., 2010; Zhou et al., 2011; Liu et al., 2011; Kim et al., 2011; Lange et al., 2012; Chan et al., 2012), comprised of 30 datasets collectively, are presented in Table 1. Ethnic groups among these datasets were distributed as follows: within 12 datasets 12,038 cases and 11,938 controls were AW; within 7 datasets 8916 cases and 9401 controls were EW; within 6 datasets 2188 cases and 2477 controls were A; and within 3 datasets 1678 cases and 1229 controls were AA. Only one study included LA and native Hawaiian populations. A allele frequencies in controls exhibited significant deviation from the HWE ($P = 0.01$) in only one study, denoting possible selection bias and necessity for sensitivity analysis. Overall, the quality of these included studies was good. According to quality assessment criteria, there were 29 datasets with high quality and one with low quality.

Table 1. Characteristics of included studies about the *HNF1β* polymorphism rs4430796 and its association with prostate cancer risk.

References	Country/study	Ethnicity	HWE	Subjects		RAF		Case			Control			A *vs* G	AG *vs* GG	AA *vs* GG	AA *vs* AG+GG	AA+AG *vs* GG
				Case	Control	Case	Control	AA	AG	GG	AA	AG	GG	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Gudmundsson et al. (2007b)	Iceland	EW	Yes	1474	1860	0.558	0.512	467	709	298	466	930	464	1.20 (1.05-1.38)	1.12 (0.97-1.29)	1.40 (1.19-1.64)	1.39 (1.19-1.62)	1.31 (1.11-1.55)
Gudmundsson et al. (2007b)	Netherlands	EW	Yes	983	1442	0.568	0.508	305	502	176	387	688	367	1.27 (1.08-1.50)	1.52 (1.23-1.88)	1.64 (1.30-2.08)	1.23 (1.03-1.47)	1.57 (1.28-1.92)
Gudmundsson et al. (2007b)	Spain	EW	Yes	451	1073	0.469	0.454	101	220	130	209	556	308	1.07 (0.86-1.33)	0.94 (0.73-1.21)	1.15 (0.84-1.57)	1.19 (0.91-1.56)	1.00 (0.78-1.27)
Gudmundsson et al. (2007b)	USA	AW	No	531	500	0.563	0.477	156	285	90	127	222	151	1.41 (1.11-1.81)	2.15 (1.57-2.95)	2.06 (1.45-2.93)	1.22 (0.93-1.61)	2.12 (1.58-2.85)
Thomas et al. (2007)	PLCO	AW	Yes	1121	1048	0.55	0.5	345	522	254	262	529	257	1.22 (1.03-1.45)	1.00 (0.81-1.23)	1.33 (1.05-1.69)	1.33 (1.10-1.61)	1.11 (0.91-1.35)
Thomas et al. (2007)	FPCC	EW	Yes	620	618	0.56	0.49	163	308	149	148	309	161	1.32 (1.06-1.65)	1.08 (0.82-1.42)	1.19 (0.87-1.63)	1.13 (0.88-1.47)	1.11 (0.86-1.44)
Thomas et al. (2007)	HPFS	AW	Yes	581	591	0.54	0.5	179	289	113	138	300	153	1.18 (0.94-1.48)	1.30 (0.97-1.75)	1.76 (1.26-2.44)	1.46 (1.13-1.90)	1.45 (1.10-1.91)
Thomas et al. (2007)	ATBC	EW	Yes	901	902	0.68	0.61	419	395	87	335	431	136	1.36 (1.12-1.65)	1.43 (1.06-1.94)	1.96 (1.44-2.65)	1.47 (1.22-1.78)	1.66 (1.25-2.21)
Thomas et al. (2007)	ACS-CPSII	AW	Yes	1716	1718	0.58	0.53	516	843	357	434	850	434	1.22 (1.07-1.40)	1.21 (1.02-1.43)	1.45 (1.20-1.75)	1.27 (1.10-1.48)	1.29 (1.10-1.51)
Levin et al. (2008)	USA (PCGP)	AW	NA	542	473	0.59	0.53	NA	NA	NA	NA	NA	NA	1.28 (0.99-1.64)	NA	NA	NA	NA
Sun et al. (2008b)	Sweden (CAPS)	EW	Yes	2874	1708	0.61	0.56	1073	1355	446	509	883	316	1.23 (1.09-1.39)	1.09 (0.92-1.29)	1.49 (1.25-1.79)	1.40 (1.23-1.60)	1.24 (1.05-1.45)
Sun et al. (2008b)	USA (JHH)	AW	Yes	1521	479	0.58	0.51	488	779	254	120	253	106	1.33 (1.08-1.63)	1.28 (0.98-1.68)	1.70 (1.25-2.30)	1.41 (1.12-1.78)	1.42 (1.10-1.83)
Sun et al. (2008b)	USA	AW	NA	1563	576	0.58	0.52	NA	NA	NA	NA	NA	NA	1.27 (1.05-1.54)	1.36 (1.05-1.75)	1.66 (1.25-2.20)	NA	NA
Sun et al. (2008b)	USA	AA	NA	364	353	0.38	0.33	NA	NA	NA	NA	NA	NA	1.25 (0.92-1.70)	1.43 (1.04-1.96)	1.47 (0.91-2.37)	NA	NA
Levin et al. (2008)	UK	EW	Yes	1613	1798	0.58	0.49	547	773	293	450	880	468	1.44 (1.26-1.65)	1.40 (1.18-1.67)	1.94 (1.60-2.35)	1.20 (1.01-1.43)	1.59 (1.35-1.87)
Waters et al. (2009)	USA (MEC)	AA	NA	860	575	0.35	NA	NA	NA	NA	NA	NA	NA	0.99 (0.84-1.16)	1.02 (0.80-1.28)	0.96 (0.68-1.37)	NA	NA
Waters et al. (2009)	USA (MEC)	AW	NA	468	419	0.48	NA	NA	NA	NA	NA	NA	NA	1.44 (1.18-1.74)	1.30 (0.92-1.83)	2.05 (1.39-3.02)	NA	NA
Waters et al. (2009)	USA (MEC)	LA	NA	603	572	0.57	NA	NA	NA	NA	NA	NA	NA	1.26 (1.07-1.50)	1.42 (1.02-1.99)	1.66 (1.17-2.36)	NA	NA
Waters et al. (2009)	USA (MEC)	Janpanese	NA	725	684	0.64	NA	NA	NA	NA	NA	NA	NA	1.04 (0.89-1.22)	1.32 (0.93-1.86)	1.21 (0.86-1.72)	NA	NA
Waters et al. (2009)	USA (MEC)	NH	NA	112	109	0.7	NA	NA	NA	NA	NA	NA	NA	1.23 (0.79-1.90)	0.72 (0.27-1.92)	1.13 (0.42-3.06)	NA	NA
Penney et al. (2009)	USA (PHS)	AW	Yes	1300	1394	0.55	0.5	366	687	247	343	700	351	1.22 (1.05-1.42)	1.40 (1.15-1.69)	1.52 (1.22-1.89)	1.40 (1.23-1.60)	1.44 (1.19-1.72)
Penney et al. (2009)	USA (FHCRC)	AW	Yes	1254	1250	0.57	0.5	412	602	240	312	633	305	1.33 (1.13-1.55)	1.20 (0.98-1.48)	1.68 (1.34-2.10)	1.47 (1.24-1.75)	1.36 (1.13-1.65)
Yamada et al. (2009)	Japan	Janpanese	Yes	311	1025	0.72	0.63	166	116	29	399	497	129	1.51 (1.14-2.00)	1.04 (0.66-1.63)	1.85 (1.19-2.88)	1.80 (1.39-2.32)	1.40 (0.92-2.14)
Helfand et al. (2009)	USA	AW	NA	687	777	0.568	0.51	240	300	147	NA	NA	NA	1.26 (1.03-1.55)	NA	NA	1.33 (1.07-1.66)	1.61 (1.26-2.07)
Hooker et al. (2010)	USA	AA	NA	454	301	0.37	0.31	NA	NA	NA	NA	NA	NA	1.31 (0.96-1.79)	NA	NA	NA	NA
Zhou et al. (2011)	China	Chinese	Yes	105	78	0.724	0.705	59	34	12	38	34	6	1.10 (0.57-2.10)	0.50 (0.17-1.49)	0.78 (0.27-2.24)	1.35 (0.75-2.43)	0.65 (0.23-1.80)
Liu et al. (2011)	Japan	Janpanese	Yes	518	323	0.693	0.63	252	214	55	129	149	45	1.34 (1.00-1.79)	1.60 (0.97-2.66)	1.60 (1.02-2.50)	1.41 (1.06-1.87)	1.37 (0.90-2.09)
Kim et al. (2011)	Korea	Korean	NA	240	223	0.726	0.666	NA	NA	NA	NA	NA	NA	1.31 (0.88-1.95)	NA	NA	NA	NA
Lange et al. (2012)	USA	AW	NA	754	2713	0.571	0.499	NA	NA	NA	NA	NA	NA	1.34 (1.14-1.58)	NA	NA	NA	NA
Chan et al. (2012)	Singapore	Chinese	Yes	289	144	0.756	0.7	169	99	21	67	63	11	1.31 (0.84-2.04)	0.82 (0.37-1.82)	1.32 (0.60-2.89)	1.56 (1.04-2.33)	1.08 (0.51-2.31)

HWE = Hardy-Weinberg equilibrium; NA = not available; RAF = Risk allele frequencies; EW = European white; AW = American white; AA = African-American; LA = Latin-American; NH = native; OR = odds ratio; 95%CI = confidence interval at 95%; PLCO = Prostate, Lung, Colon, Ovarian Trial; ACS-CPSII = American Cancer Society Cancer Prevention Study II; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CAPS = Cancer of Prostate in Sweden; FHCRC = Fred Hutchinson Cancer Research Center King County; FPCC = French Prostate Case-Control Study; HPFS = Health Professionals Follow-up Study; MEC = Multiethnic Cohort; PHS = Physicians' Health Study; JHH = Johns Hopkins Hospital; PCGP = Prostate Cancer Genetics Program.

Results of the meta-analysis

Overall, meta-analysis of all 16 included studies revealed that the 17q12 rs4430796 polymorphism was significantly associated with an increased risk of developing prostate cancer in both the allelic model and the genotypic contrast model (OR_{A} *vs* $_{G}$ = 1.25, 95%CI = 1.21-1.30, I^2 = 0%; OR_{AA} *vs* $_{GG}$ = 1.53, 95%CI = 1.43-1.65, I^2 = 33.3%; OR_{AG} *vs* $_{GG}$ = 1.24, 95%CI = 1.16-1.34, I^2 = 46.5%; OR_{AA} *vs* $_{AG+GG}$ = 1.36, 95%CI = 1.30-1.42, I^2 = 0%; OR_{AA+AG} *vs* $_{GG}$ = 1.37, 95%CI = 1.27-1.48, I^2 = 49.0%) (Figure 1). Sensitivity analysis conducted by sequentially omitting individual studies did not significantly influence the results above (data not shown).

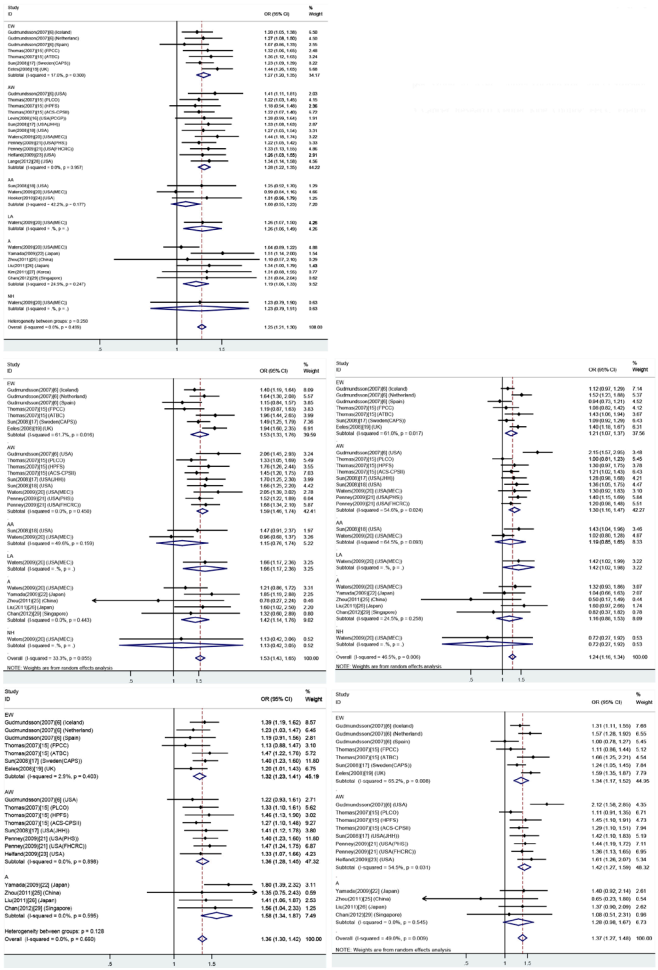

Figure 1. Forest plots of odds ratios [95% confidence interval (CI)] of individual studies and meta-analyses for the variant allele at rs4430796 under five models stratified by ethnicity. EW = European white; AW = American white; AA = African-American; LA = Latin-American; NH = native; OR = odds ratio; PLCO = Prostate, Lung, Colon, Ovarian Trial; ACS-CPSII = American Cancer Society Cancer Prevention Study II; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CAPS = Cancer of Prostate in Sweden; FHCRC = Fred Hutchinson Cancer Research Center King County; FPCC = French Prostate Case-Control Study; HPFS = Health Professionals Follow-up Study; MEC = Multiethnic Cohort; PHS = Physicians' Health Study; JHH = Johns Hopkins Hospital; PCGP = Prostate Cancer Genetics Program.

In subgroup analysis done by ethnicity and with the five genetic models, the pooled ORs were clearly significant in Caucasians (AW or EW), whereas they were only significant with three genetic models in A, and were not significant with any genetic models in AA (Table 2).

Table 2. Summary of 17q12 rs4430796 allele frequencies and meta-analyses by race.

	American whites [(12,038 PC) (11,938 C)]	European whites [(8916 PC) (9401 C)]	Asians [2188 PC) (2477 C]	African-Americans [(1678 PC) (1229 C)]
Mean variant allele				
Frequency of PC	0.566	0.588	0.693	0.362
Frequency of C	0.507	0.517	0.643	0.321
A *vs* G				
OR (95%CI)	1.28 (1.22-1.35)	1.27 (1.20-1.35)	1.19 (1.06-1.49)	1.08 (0.95-1.23)
P value for homogeneity	0.96	0.3	0.25	0.18
AA *vs* GG				
OR (95%CI)	1.59 (1.46-1.74)	1.53 (1.33-1.76)	1.42 (1.14-1.76)	1.15 (0.76-1.74)
P value for homogeneity	0.45	0.02	0.44	0.16
AG *vs* GG				
OR (95%CI)	1.30 (1.16-1.47)	1.21 (1.07-1.37)	1.16 (0.88-1.53)	1.19 (0.85-1.65)
P value for homogeneity	0.02	0.02	0.26	0.09
AA *vs* AG+GG				
OR (95%CI)	1.36 (1.28-1.45)	1.32 (1.23-1.41)	1.58 (1.34-1.87)	NA
P value for homogeneity	0.9	0.4	0.6	NA
AA+AG *vs* GG				
OR (95%CI)	1.42 (1.27-1.59)	1.34 (1.17-1.52)	1.28 (0.98-1.67)	NA
P value for homogeneity	0.03	0.008	0.55	NA
No. of datasets	12	7	6	3

PC = prostate cancer cases; C = controls; OR = odds ratio; 95%CI = confidence interval at 95%; NA = not available.

Publication bias

Sensitivity analysis results revealed that the corresponding pooled ORs were not altered by recalculation with a random-effects model or after the exclusion of any single study (data not shown), indicating that our results were statistically significant. The shape of the funnel plots did not reveal any obvious asymmetry (Figure 2). Moreover, Begg and Egger tests suggested the absence of significant publication bias; corresponding P values are listed in Table 3. Evidence of significant publication bias was also not observed when publication bias tests were conducted in subgroups with more than two studies (when possible) (Table 3).

DISCUSSION

Previously published results suggest that single nucleotide polymorphisms are the most common sources of human genetic variation, and that they may be associated with an individual's increased risk of cancer development (Wu et al., 2009). In recent years, the study of genetic polymorphisms involved in tumorigenesis has led to a growing interest in the genetic susceptibility to cancers. Since the identification of the 17q12 rs4430796 polymorphism in the *HNF1β* gene, an increasing number of studies have suggested that it plays an important role in the development of prostate cancer. These studies, however, have reported conflicting results, especially among different races. Some of the studies we reviewed were limited in sample size, and consequently suffered from having a power that was too low to detect any underlying effects that may have existed. Pooled ORs generated from much larger populations can increase

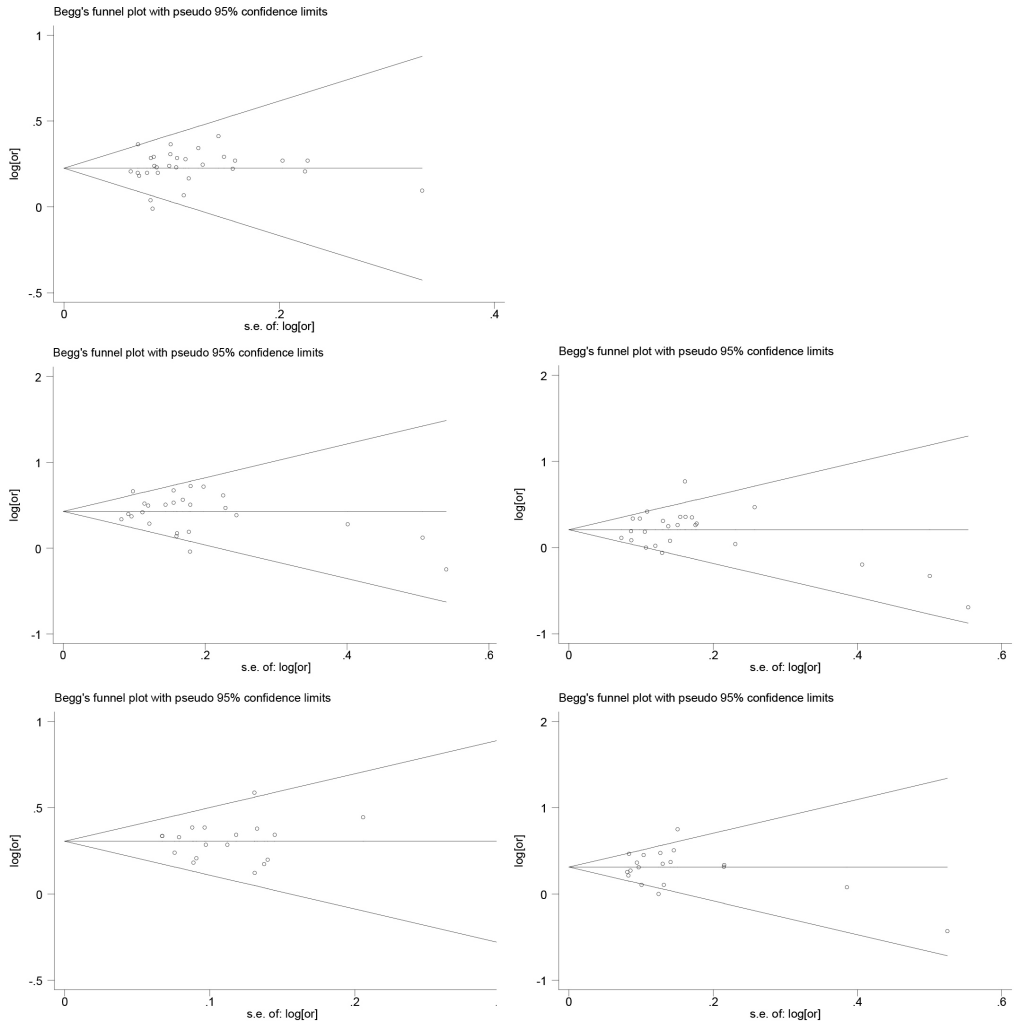

Figure 2. Begg's funnel plot at rs4430796 of the *HNF1β* gene for the five models for all studies. A *vs* G; AA *vs* GG; AG *vs* GG; AA *vs* AG+GG; AA+AG *vs* GG.

Table 3. Begg and Egger test P values of diverse ethicity groups and genetic models.

Group or model	N	Begg test P	Egger test P
American white	12	0.304	0.309
European white	7	1	0.756
Asian	6	0.348	0.253
African-American	3	0.117	0.06
A *vs* G	30	0.498	0.48
AA *vs* GG	25	0.691	0.626
AG *vs* GG	25	0.944	0.953
AA *vs* AG+GG	19	1	0.902
AA+AG *vs* GG	19	0.944	0.859

the statistical power. Further, combining data from several studies have the advantage of reducing random error (Ioannidis et al., 2008). In order to provide a comprehensive and reliable conclusion, therefore, we performed the present meta-analysis using 16 independent case-control studies, which collectively included 25,535 prostate cancer cases and 25,726 controls.

Indeed, through this meta-analysis on all eligible previously published studies we found that the rs4430796 polymorphism is a significant risk factor for prostate cancer, as determined with various genetic models including the allelic and genotypic contrast models consisting of the homozygous model, heterogeneous model, dominant model, and recessive model. Significant associations, however, were only identified in some models for A and no models for AA, suggesting an ethnic influence on genetic backgrounds stemming from the environments in which the populations lived. However, there are many factors that could affect results, such as variability among populations, the existence of selection factors, etc. Considering the limited number of studies available on the topic and the total population numbers of AA and A included in this meta-analysis, our results should be interpreted with caution.

Heterogeneity is also a potential concern when interpreting the results of the present meta-analysis. In the overall analysis, significant differences were found using the heterogeneity model and recessive model comparison. After subgroup analysis was performed by ethnicity, heterogeneity was effectively removed in A and AA. Variability in genetic backgrounds and environment, therefore, may have existed among different ethnicities.

Limitations of this meta-analysis should be acknowledged. First, because only published and English articles were included in the meta-analysis, publication and potential English language biases occurred, although not formally determined with statistical tests. Second, in the subgroup analysis, the number of A and AA was relatively small, resulting in an insufficient statistical power that would not enable the exploration of a true association. Additional studies and participants of A and AA decent will be needed in future analyses, so that a more precise conclusion on the association between the rs4430796 polymorphism and prostate cancer risk can be determined. Third, our results were based on unadjusted estimates, while a more accurate analysis would be conducted with the availability of individual data values, allowing for an adjustment estimate with confounding factors.

In conclusion, a significant association was detected between rs4430796 and the risk of prostate cancer development in the overall study population, Caucasians (AW or EW), and A, but not AA. These findings suggest that 17q12 rs4430796, which is associated with both diabetes mellitus and prostate cancer, should be the basis of further future investigations. Due to the limitations of this analysis, it is crucial that larger, well-designed multicenter studies be conducted to confirm these results.

ACKNOWLEDGMENTS

Research supported by the China Scholarship Council (#2009622110) and the National Science Fund for Distinguished Young Scholars (#81202016).

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