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Review Article

Cytochrome P1B1 4326C/G gene polymorphism correlation to prostate cancer: a meta-analysis

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Abstract: Background: Human cytochrome P1B1 (CYP1B1) gene polymorphism is correlated with the risk of various cancers, but it is unclear whether this polymorphism is correlated with the risk of prostate cancer. Therefore, this study systematically explored the relationship between genetic polymorphism of CYP1B1 4326C/G and the corresponding susceptibility to prostate cancer. Methods: We conducted a comprehensive and detailed search of PubMed, Cochrane Library, CNKI, EMBASE, and WanFang databases to examine the relationship of CYP1B1 4326C/G polymorphism with the susceptibility to prostate cancer, and the strength of this association was assessed using odds ratios (ORs) with 95% confidence intervals (CIs). Results: In total, 16 case-control studies were included in the current study. The results revealed no correlation between CYP1B1 4326C/G polymorphism and the risk of prostate cancer in the overall population. Subgroup analysis of different races determined that Asian people carrying the G allele were associated with an increased risk of prostate cancer, but no statistical correlation was observed. The analysis of subgroups of different control group sources revealed that compared with the population carrying the C allele, the community population carrying the G allele showed a positive correlation with the risk of prostate cancer (homozygous model: OR = 1.34, 95% CI = 1.01-1.77, P = 0.044). Conclusions: This study revealed no significant association between genetic polymorphism of CYP1B1 4326C/G and prostate cancer susceptibility. However, analysis of different control sources showed that the CYP1B1 GG genotype may have increased prostate cancer susceptibility in the general population.

Keywords: Prostate cancer, polymorphism, susceptibility, CYP1B1, meta-analysis

Introduction

Prostate cancer (PC) is the most commonly diagnosed tumor in men worldwide, as well as the most common malignant tumor in the male reproductive system in the Western Hemisphere. Among cancers in male patients in the United States, prostate cancer shows the highest incidence (about 174650 new cases per year), thus posing a serious threat to the health of male patients [1, 2]. The pathogenic factors of prostate cancer have not been fully elucidated. Multitudinous epidemiological studies have demonstrated that the incidence of prostate cancer may be associated with age, race, heredity, eating habits, and lifestyle [3]. Therefore, it is particularly important to clarify the pathogenic mechanism of prostate cancer to provide a reference for early diagnosis and initiate effective treatment for prostate cancer.

Cytochrome P450 (CYP450) is a type of heme-mercaptan protein required for the synthesis and decomposition of diverse molecules and chemicals in cells [4, 5]. CYP450 plays a role in the metabolism of many endogenous substances, including steroids, vitamin D, cholesterol, neurotransmitters, and bile acids [6, 7]. The superfamily of human CYP450 isozymes comprises 57 CYP genes and 58 pseudogenes, which are divided into 18 families and 43 sub-families [8]. CYP1B1, a core member of the CYP450 super-family, is located on chromosome 2 (2p21-22) and contains two introns and three exons [9, 10]. CYP1B1 is usually overexpressed in human malignant tumors and is involved in the hydroxylation of estrogen and activation of other carcinogenic compounds, including aromatic amines, heterocyclic amines, polycyclic aromatic hydrocarbons, and other carcinogens [11, 12]. In most cases,

CYP1B1 can catalyze the production of more toxic intermediate metabolites. Tokizane et al. [13] found that hypomethylation of the promoter/enhancer region can lead to overexpression of the CYP1B1 gene in prostate cancer cells. In animal models, it has been confirmed that CYP1B1-catalyzed metabolites can induce prostate cancer [14]. Based on these findings, it is clear that the CYP1B1 gene plays a vital part in the occurrence, development and prognosis of prostate cancer and is a potential molecular marker for its diagnosis and prognosis.

Numerous studies have reported the association between genetic polymorphism of human CYP1B1 4326C/G and the susceptibility to prostate cancer; however, the results remain controversial [15-28]. Therefore, to elucidate the exact association between genetic polymorphism of CYP1B1 4326C/G and prostate cancer susceptibility, we included all eligible case-control studies to conduct this meta-analysis.

Materials and methods

Literature search

Searches were carried out in PubMed, Cochrane Library, CNKI, EMBASE, and WanFang databases using the following key words: "genotype OR variant OR polymorphism OR mutation OR single nucleotide polymorphisms OR SNP" and "CYP1B1 OR cytochrome P450 1B1 OR cytochrome P-450 1B1 OR C4326G OR rs1056836" and "prostate tumor OR prostate neoplasm OR prostate cancer OR prostate carcinoma". The endpoint of literature retrieval was November 2019.

Inclusion and exclusion criteria

We identified studies that met the following criteria: (i) estimated the correlation between genetic polymorphism of CYP1B1 4326C/G and prostate cancer susceptibility, (ii) contained sufficient genotypic data to assess the odds ratios (ORs) and its corresponding 95% confidence interval (CI), and (iii) was a case-control study. The exclusion criteria included: (i) animal experiments; (ii) conference abstracts, case reports, and reviews; and (iii) studies that did not provide the required data or repetitive literature with little data.

Data extraction and quality evaluation

According to the previously established inclusion and exclusion criteria, two independent researchers extracted the following data from eligible articles into an Excel table: first author name, country, publication year, race of the study population, frequency of genotypes of cases and controls in each study, source of the control group, gene detection methods, and Hardy-Weinberg equilibrium (HWE) in the control group. In cases where disagreements occurred during data extraction, a consensus was reached through consultation with a third researcher. The included study quality was assessed by two independent authors based on the improved Newcastle-Ottawa scale. The included articles with Newcastle-Ottawa scale scores of more than six stars were deemed to be high-quality studies.

Statistical analysis

The association between genetic polymorphism of CYP1B1 4326C/G and prostate cancer susceptibility were evaluated via ORs and 95% CI. In the current study, the assessment of the between-study heterogeneity was tested using the Labbe plot, Cochrane's Q test, and I^2. $I^2 > 50\%$ or $P < 0.1$ indicated remarkable heterogeneity among the studies, in which case the random-effect model (DerSimonian-Laird) was used for pooled analysis [29]. Furthermore, $I^2 < 50\%$ or $P > 0.1$ implied no remarkable heterogeneity; hence, the fixed-effect model (Mante-Hazenszel) was used for pooled analysis [30]. By eliminating each included study one-by-one and then pooling the results, the reliability and robustness of the meta-analysis results were tested. The potential publication bias was detected by Begg's funnel plot and Egger's test [31, 32]. All statistical analyses were carried out by Stata 15.1 software.

Results

Literature search

Using the PubMed, Cochrane Library, CNKI, EMBASE, and WanFang databases; 256 possible related articles were preliminarily searched. In total, 79 articles were excluded by reading titles and abstracts: 38 articles were not related to gene polymorphisms, 18 articles

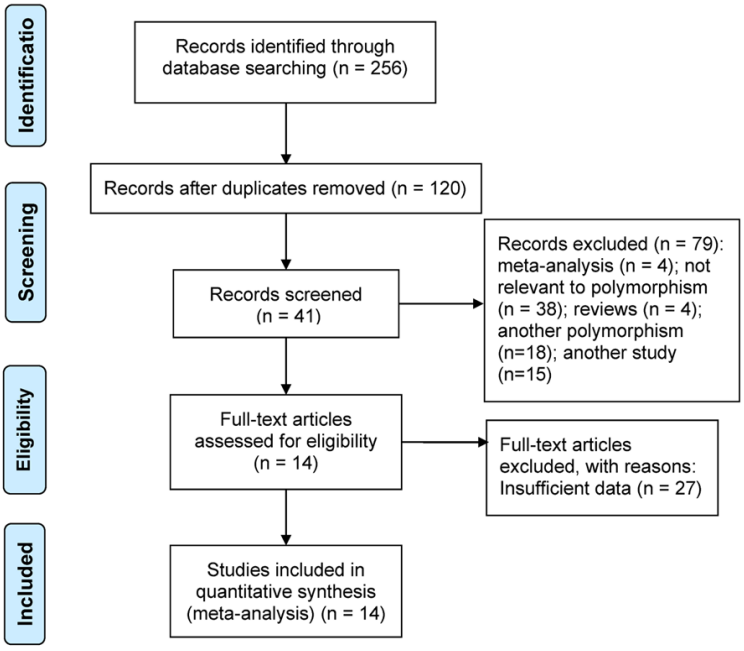

Figure 1. Flow diagram of the current study.

discussed gene polymorphisms other than CYP1B1 4326C/G, 15 articles were not related to prostate cancer, four articles were reviews, and four were meta-analyses [33-36]. Then, by carefully reading the full text and applying the above-mentioned criteria, 27 studies were excluded due to insufficient genotype data to assess the OR with its 95% CI. Ultimately, 14 articles (16 studies) were included in the current study [15-28]. The detailed screening process of literature is shown in **Figure 1**.

The description of included studies

A total of 16 case-control studies, which involved 7859 patients and 7428 controls, were included to assess the relationship between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer. Among them, two studies investigated two different populations, so they could be regarded as two independent studies [16, 17]. The sample size of cases in these articles ranged from 50 to 1419 patients, while that of the control group ranged from 50 to 1235 patients. Of all included studies, four studies (including 1368 patients and 1607 controls) were conducted in Asian populations [22, 25, 26, 28], and 10 studies (including 5885 patients and 5134 controls) were conducted in Caucasian populations [15, 16, 18-21, 23, 24, 27]. Two studies, which involved 606 patients and 687 controls, were conducted in mixed populations [17]. With regard to the source of the control group, eight studies used the hospital patients [15, 16, 19-22, 24], and the other eight studies used the general population [17, 18, 23, 25-28]. Genotypes were detected by MassARRAY nucleic acid mass spectrometry, polymerase chain reaction (PCR), TaqMan determination, and PCR-restriction fragment length polymorphism. The gene frequency distribution of all the included studies was in accordance with HWE, and the quality of the studies was greater than 6 points. The basic characteristics of the included articles are shown in **Table 1**.

Meta-analysis results

The results of this meta-analysis revealed no statistical correlation between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer in the overall population (allele model: OR = 1.05, 95% CI = 0.94-1.16; homozygous model: OR = 1.08, 95% CI = 0.88-1.33; heterozygous model: OR = 1.03, 95% CI = 0.96-1.11; dominant model: OR = 1.06, 95% CI = 0.93-1.21; recessive model: OR = 1.04, 95% CI = 0.89-1.21), as shown in **Figure 2** and **Table 2**. Subgroup analyses of populations of different races revealed that Asian individuals carrying the G allele were correlated with increased risk of prostate cancer, but there was no statistical correlation (allele model: OR = 1.28, 95% CI = 0.83-1.96; homozygous model: OR = 1.66, 95% CI = 0.60-4.59; heterozygous model: OR = 1.17, 95% CI = 0.81-1.70; dominant model: OR = 1.26, 95% CI = 0.81-1.96; recessive model: OR = 1.53, 95% CI = 0.61-3.84), and similar results were found among the Caucasian population, as shown in **Table 2** and **Figure 3**. Subgroup analysis based on different control group sources indicated that, compared with the population carrying the C allele, the community population carrying the G allele showed a positive correlation with prostate cancer risk (homozygous model: OR = 1.34, P = 0.044), whereas the genetic

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Control source	Genotyping method	Case	Control	HWE	NOS
Catsburg	2012	USA	Caucasian	PB	Taqman	1419	756	0.002	8
Berndt	2007	USA	Caucasian	HB	Taqman	486	611	0.493	9
Cicek	2005	USA	Caucasian	HB	PCR-RFLP	439	479	0.005	8
Chang	2003	USA	Caucasian	HB	MassARRAY	310	182	0.21	8
Fukatsu	2004	Japan	Asian	HB	PCR-RFLP	136	255	0.1518	7
Beuten	2008	USA	Hispanic caucasian	HB	Taqman	142	237	0.1448	8
Beuten	2008	USA	non-Hispanic Caucasian	HB	Taqman	491	496	0.3446	8
Tanaka	2002	Japan	Asian	PB	PCR-RFLP	117	200	0.0018	8
Sobti	2006	India	Asian	PB	PCR-RFLP	100	100	0.2331	7
Kachakova	2016	Bulgaria	Caucasian	HB	PCR-RFLP	239	251	0.7214	7
Brureau1	2016	French	Mixed	PB	PCR-RFLP	456	548	0.3912	8
Brureau2	2016	French	Mixed	PB	PCR-RFLP	150	139	0.4412	8
Holt	2013	USA	Caucasian	PB	PCR-RFLP	1256	1235	0.4482	9
Cussenot	2007	French	Caucasian	HB	Taqman	1053	837	0.8621	8
Tang	2000	USA	Caucasian	PB	PCR-RFLP	50	50	NA	7
Gu	2018	China	Asian	PB	Taqman	1015	1052	0.0645	7

Abbreviations: HWE, hardy-Weinberg equilibrium; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; NOS, Newcastle-Ottawa Scale; NA, not available.

polymorphism of CYP1B1 4326C/G was not correlated with prostate cancer susceptibility in the hospital patients, as shown in **Table 2** and **Figure 4**.

Heterogeneity and sensitivity analysis

In the heterogeneity analysis of the results of 16 studies, the summary analysis of most genetic models showed moderate heterogeneity (allele model: I^2 = 72.9%, P < 0.001; dominant model: I^2 = 63.7%, P < 0.001; homozygous model: I^2 = 65.3%, P < 0.001; recessive model: I^2 = 53.6%, P = 0.006) (**Figure 5**), so the results of this meta-analysis were pooled using a random-effect model. By eliminating each included study one-by-one, the effect sizes of the OR values were combined, and the changes in OR values were observed to detect the reliability and robustness of the combined results. Sensitivity analysis revealed no significant change after excluding any included studies, as shown in **Figure 6**.

Publication bias

The Begg's funnel plot and Egger's test were employed for the estimation of the potential publication bias. As shown in **Figure 7**, there was no significant asymmetry in the shape of the funnel plot. Moreover, the Egger linear regression test showed no publication bias in the genetic comparison models (allele model: P = 0.628; homozygous model: P = 0.873; heterozygous model: P = 0.591; recessive model: P = 0.934; dominant model: P = 0.402), as shown in **Table 2**.

Discussion

The occurrence of tumors is an extremely complex multi-stage process. Genetic studies have shown that the occurrence and development of prostate cancer may be the result of a combination of environmental and genetic factors, which determine the susceptibility of a patient, and single-nucleotide polymorphisms (SNPs) show a particularly significant impact [37]. From a theoretical point of view, genetic polymorphisms among a biological population usually contain two or more discontinuous variants, genotype, and allele phenomenon. SNPs are genotypes, or alleles. As the most common type of genetic variation in the human genome, SNPs are caused by a single-nucleotide differences in the DNA sequence [38, 39]. SNPs occur randomly throughout the genome and are more likely to occur in the non-coding regions of DNA [39].

CYP1B1 is a member of the family of CYP450 genes and is a primary enzyme involved in estrogen hydroxylation, which is a key res-

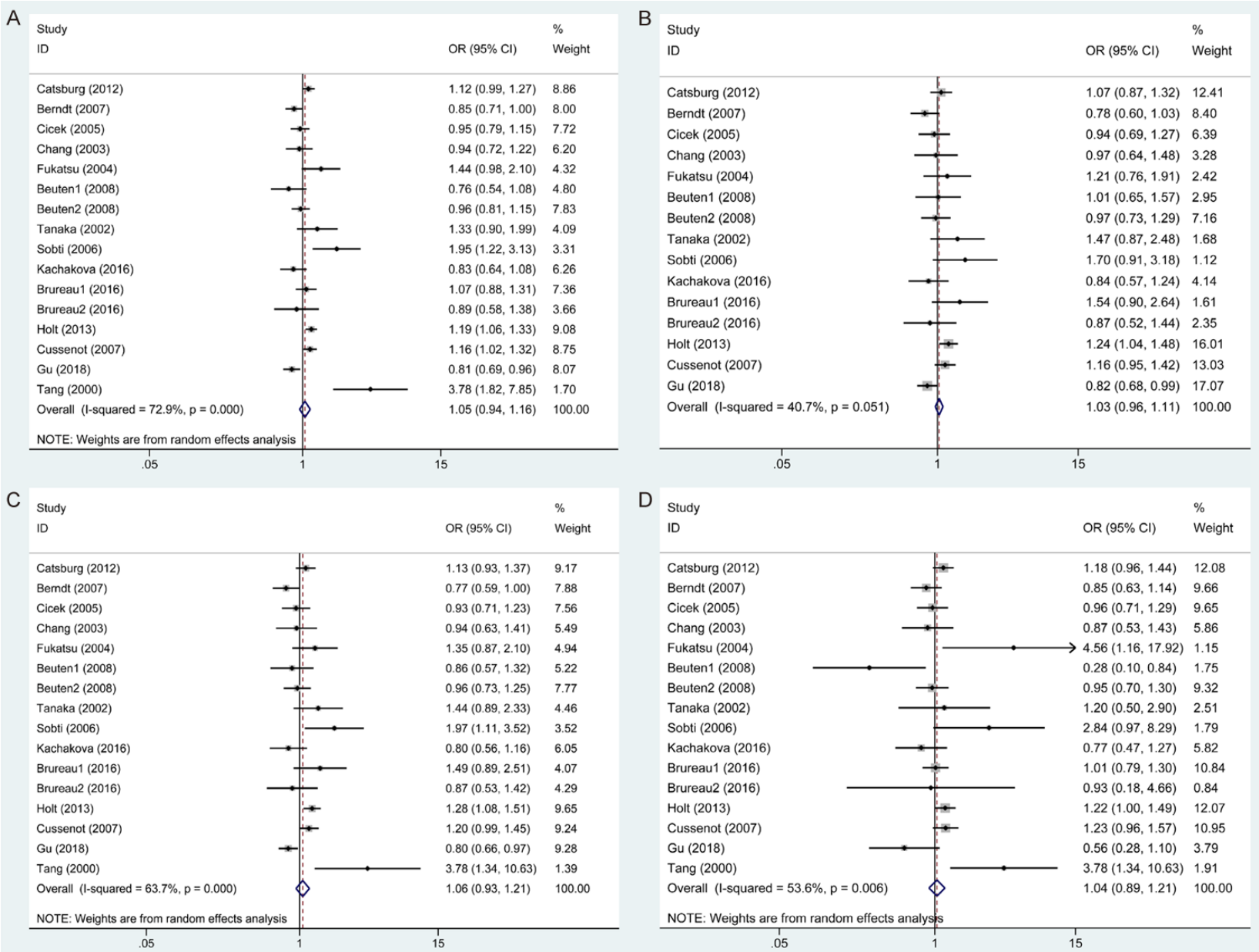

Figure 2. Meta-analysis for the association between CYP1B1 4326C/G polymorphism and prostate cancer in the overall populations. A. G *vs.* C; B. CG *vs.* CC; C. CG + GG *vs.* CC; D. GG *vs.* CC + CG.

Table 2. Association between CYP1B1 4326C/G polymorphism and prostate susceptibility

Comparison	Subgroup	Studies	Heterogeneity test		Association test		Model	Publication bias	
			p-value	I^2	OR (95% CI)	*p*-value		Begg	Egger
G vs. C	Overall	16	< 0.001	72.90%	1.05 (0.94-1.16)	0.38	R	0.26	0.628
	PB	8	< 0.001	79.00%	1.17 (0.98-1.40)	0.075	R		
	HP	8	0.02	58.1	0.97 (0.86-1.09)	0.559	R		
	Caucasian	10	< 0.001	74.1	1.02 (0.91-1.15)	0.759	R		
	Asian	4	< 0.001	84.60%	1.28 (0.83-1.96)	0.259	R		
	Mixed	2	0.443	0.00%	1.04 (0.87-1.25)	0.678	R		
GC vs. CC	Overall	15	0.051	40.7%%	1.03 (0.96-1.11)	0.409	F	0.166	0.591
	PB	7	0.015	62.1%%	1.13 (0.93-1.37)	0.237	R		
	HP	8	0.467	0	0.99 (0.89-1.10)	0.83	R		
	Caucasian	9	0.215	25.70%	1.03 (0.93-1.14)	0.576	R		
	Asian	4	0.026	67.7%%	1.17 (0.81-1.70)	0.399	R		
	Mixed	2	0.129	56.6%%	1.14 (0.65-2.01)	0.639	R		
GG vs. CC	Overall	16	< 0.001	65.30%	1.08 (0.88-1.33)	0.677	R	0.893	0.873
	PB	8	0.039	52.60%	1.34 (1.01-1.77)	0.044	R		
	HP	8	0.006	64.60%	0.91 (0.69-1.20)	0.51	R		
	Caucasian	10	0.001	68.80%	1.02 (0.82-1.27)	0.829	R		
	Asian	4	0.004	77.10%	1.66 (0.60-4.59)	0.327	R		
	Mixed	2	0.564	0.00%	1.40 (0.84-2.31)	0.193	R		
GG + GC vs. CC	Overall	16	< 0.001	63.70%	1.06 (0.93-1.21)	0.354	R	0.137	0.402
	PB	8	< 0.001	74.00%	1.23 (0.98-1.54)	0.077	R		
	HP	8	0.117	39.30%	0.97 (0.84-1.11)	0.617	R		
	Caucasian	10	0.005	61.40%	1.03 (0.89-1.18)	0.726	R		
	Asian	4	0.002	79.40%	1.26 (0.81-1.96)	0.297	R		
	Mixed	2	0.137	54.90%	1.13 (0.66-1.93)	0.649	R		
GG vs. CC + CG	Overall	16	0.006	53.60%	1.04 (0.89-1.21)	0.602	R	0.822	0.934
	PB	8	0.058	48.70%	1.16 (0.94-1.45)	0.166	R		
	HP	8	0.033	54.20%	0.94 (0.76-1.17)	0.599	R		
	Caucasian	10	0.013	57.20%	1.03 (0.87-1.21)	0.724	R		
	Asian	4	0.012	72.80%	1.53 (0.61-3.84)	0.366	R		
	Mixed	2	0.913	0.00%	1.01 (0.79-1.29)	0.928	R		

Abbreviations: OR, odds ratio; CI, confidence interval; R, random-effect model; F, fixed-effect model.

ponse to hormone carcinogenesis [40, 41]. Therefore, CYP1B1 is usually associated with hormone-mediated tumors, such as breast cancer, ovarian cancer, prostate cancer, and endometrial cancer. CYP1B1 is highly expressed in these cancers and is responsible for hormone metabolism and the formation of toxic metabolites from endogenous and exogenous molecules [40, 41]. Multitudinous studies have examined the relationship between CYP proteins and their SNPs as well as their role in the occurrence and development of prostate cancer. A single study may be insufficient to fully demonstrate this complex genetic correlation due to a relatively small sample size and low statistical efficiency. Therefore, to determine the exact association between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer, we included all eligible case-control studies in the current study.

This study included 16 case-control studies consisting of 15,287 participants to assess the relationship between genetic polymorphism of human CYP1B1 4326C/G and the susceptibility to prostate cancer. The results revealed no correlation between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer. Subgroup analy-

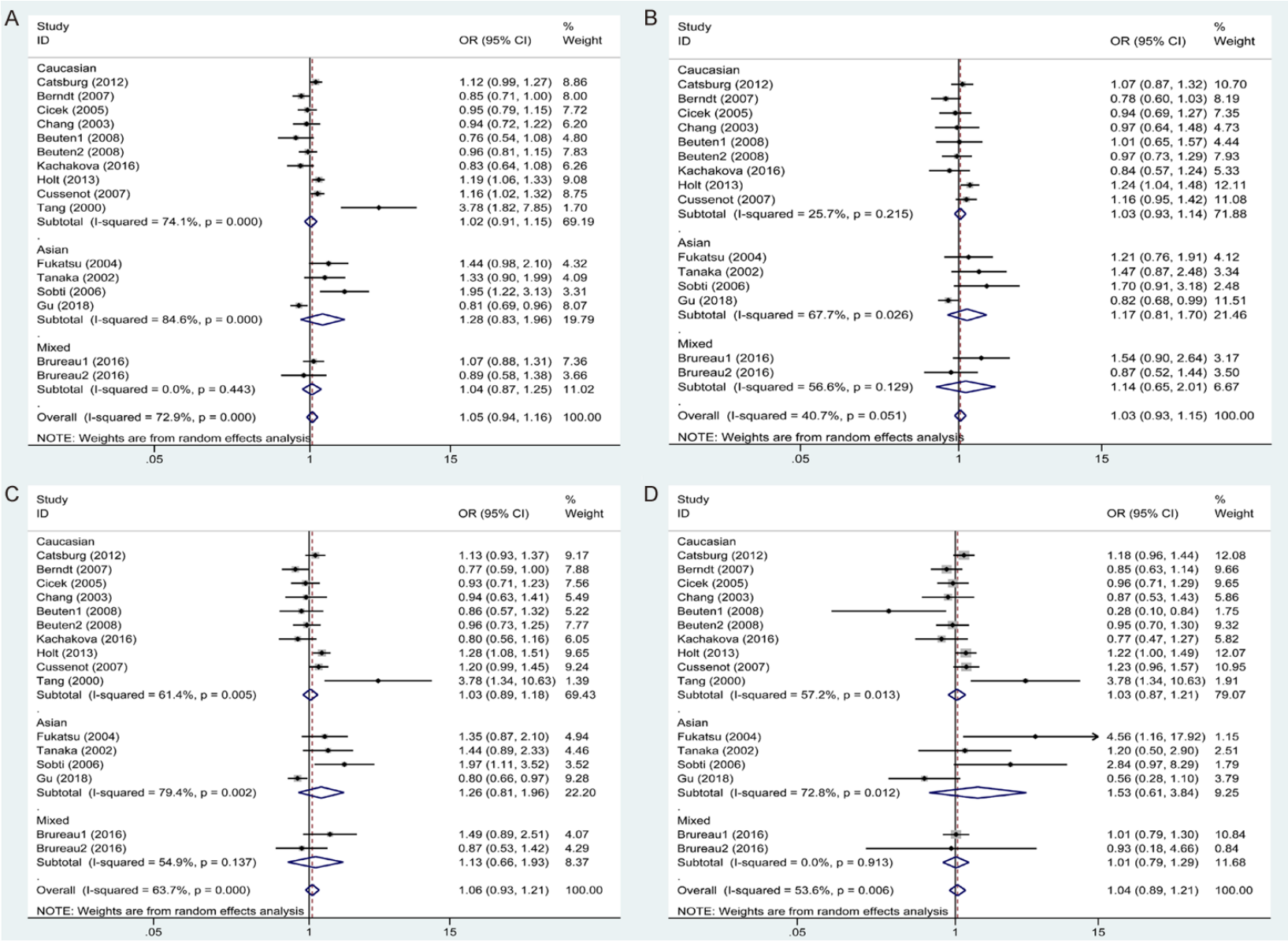

Figure 3. Meta-analysis for the association between CYP1B1 4326C/G polymorphism and prostate cancer in the different ethnicity populations. A. G *vs.* C; B. CG *vs.* CC; C. CG + GG *vs.* CC; D. GG *vs.* CC + CG.

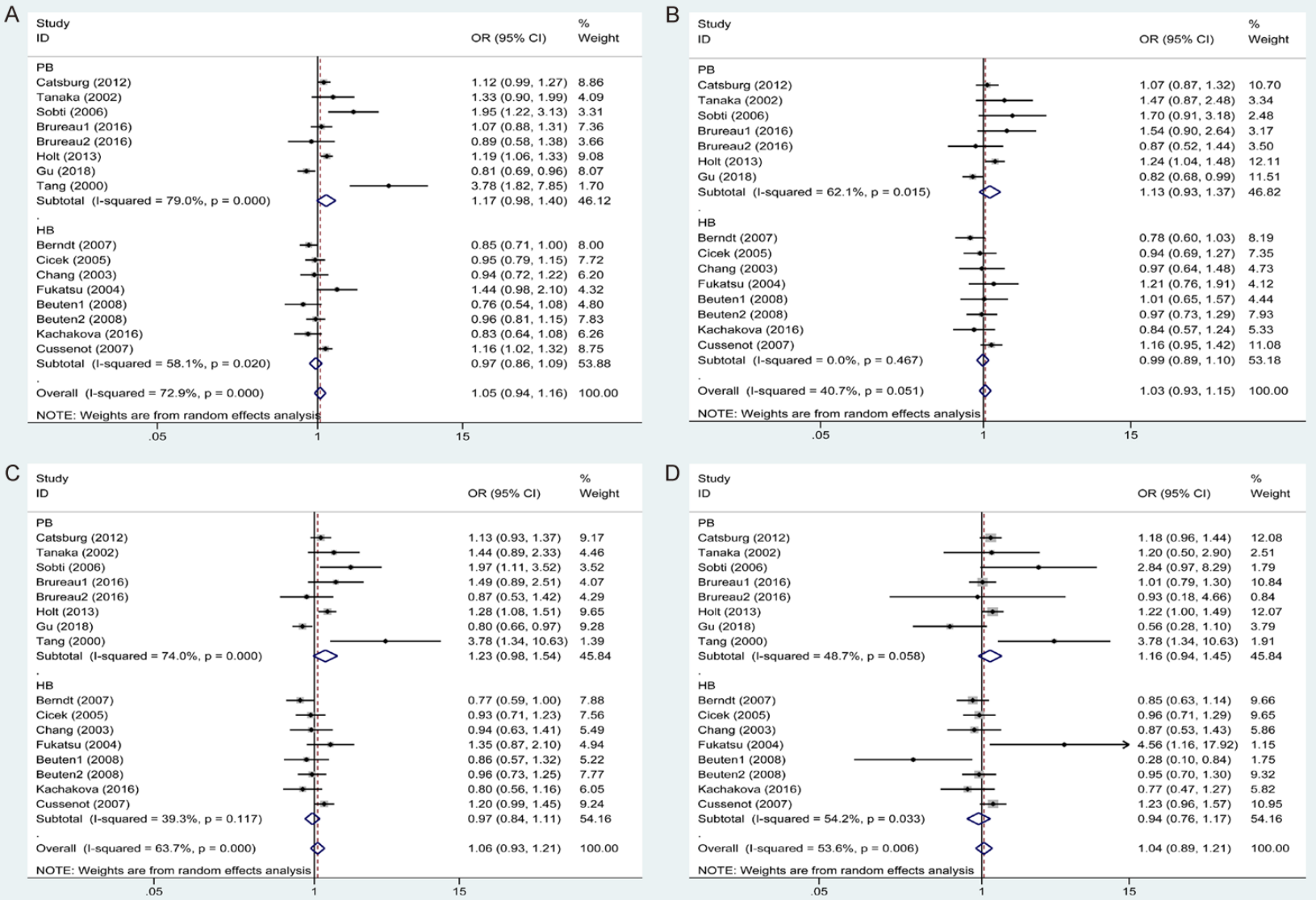

Figure 4. Meta-analysis for the association between CYP1B1 4326C/G polymorphism and prostate cancer in the different control sources. A. G *vs.* C; B. CG *vs.* CC; C. CG + GG *vs.* CC; D. GG *vs.* CC + CG.

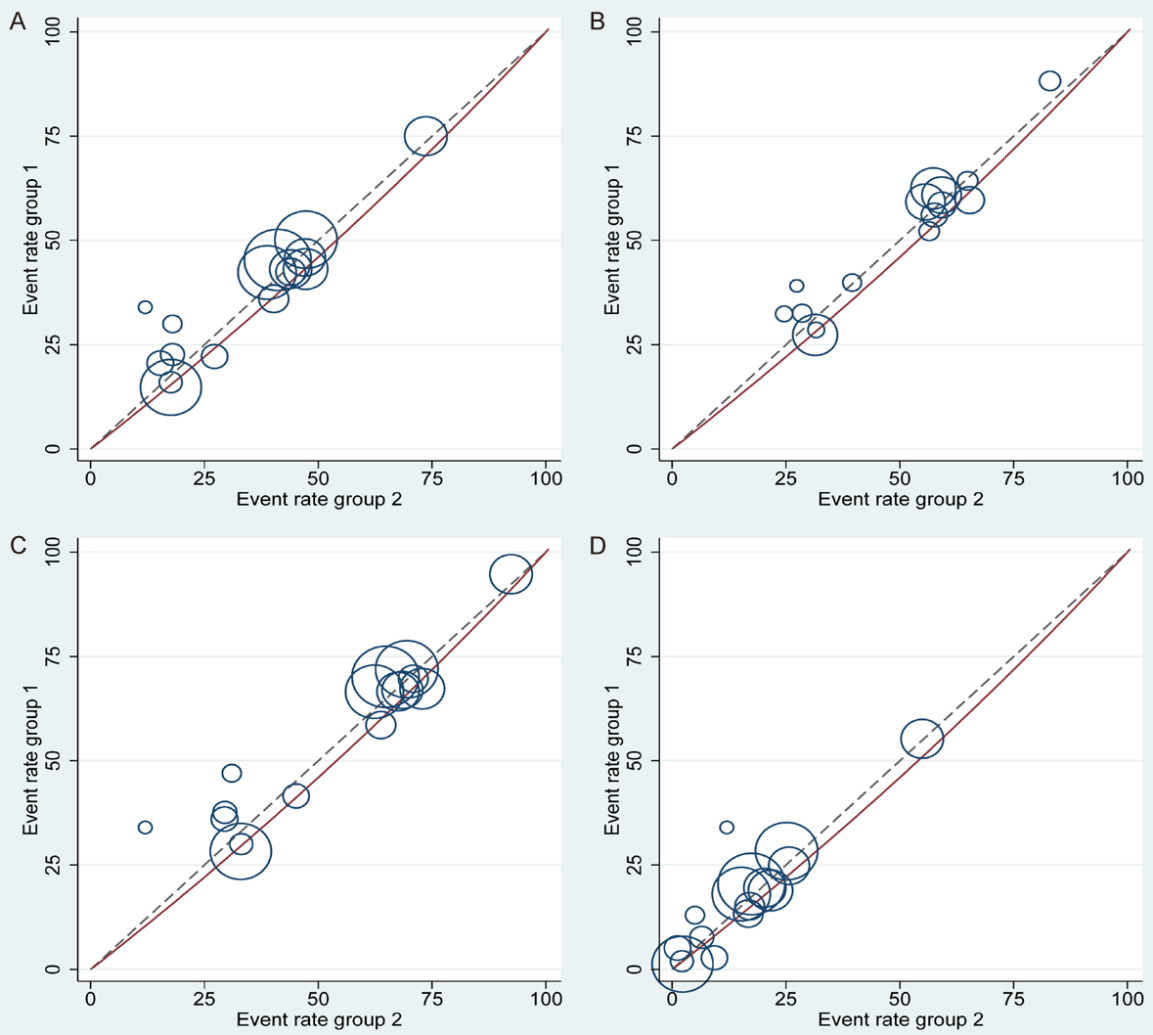

Figure 5. Labbe plot analysis to examine between-study heterogeneity. A. G *vs.* C; B. CG *vs.* CC; C. CG + GG *vs.* CC; D. GG *vs.* CC + CG.

ses based on different races detected no relationship between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer in Asian and Caucasian men. Upon conducting subgroup analysis of different control group sources, it was found that compared with the population with the C allele, the community population with the G allele showed a positive correlation with the susceptibility to prostate cancer. The effect of the polymorphism on prostate cancer susceptibility is affected by race. It is reported that African-Americans have the highest incidence of prostate cancer, which not only emphasizes the ethnic background of the disease, but also confirms the interaction of genetic and environmental factors in prostate cancer [42]. The interaction of genetic and lifestyle factors, including dietary fat intake, obesity, and sexual factors, can explain these differences to some extent. Undoubtedly, a larger study will provide further insight into the relationship between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer among different ethnic backgrounds, especially among African-Americans.

The present study has certain limitations: (i) most included studies examined Caucasian people, which may limit the generalizability of our research conclusions to some extent; (ii) due to limited data in the literature, this study was unable to conduct subgroup analyses of patients' age, sex, family history, lifestyle, and other factors; therefore, it was not possible to determine whether these factors are risk

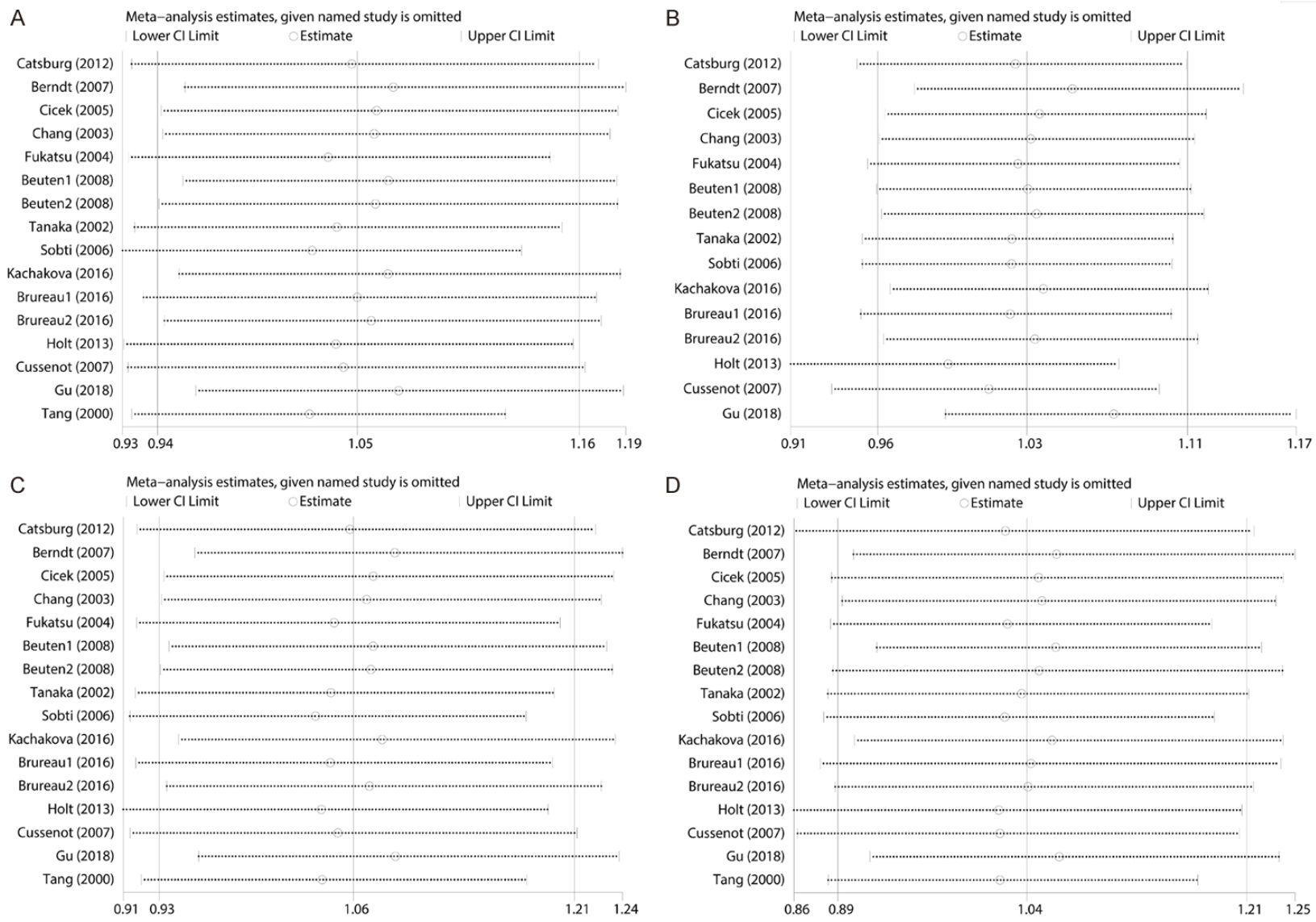

Figure 6. Sensitivity analysis on the association between CYP1B1 4326C/G polymorphism and prostate cancer. A. G *vs.* C; B. CG *vs.* CC; C. CG + GG *vs.* CC; D. GG *vs.* CC + CG.

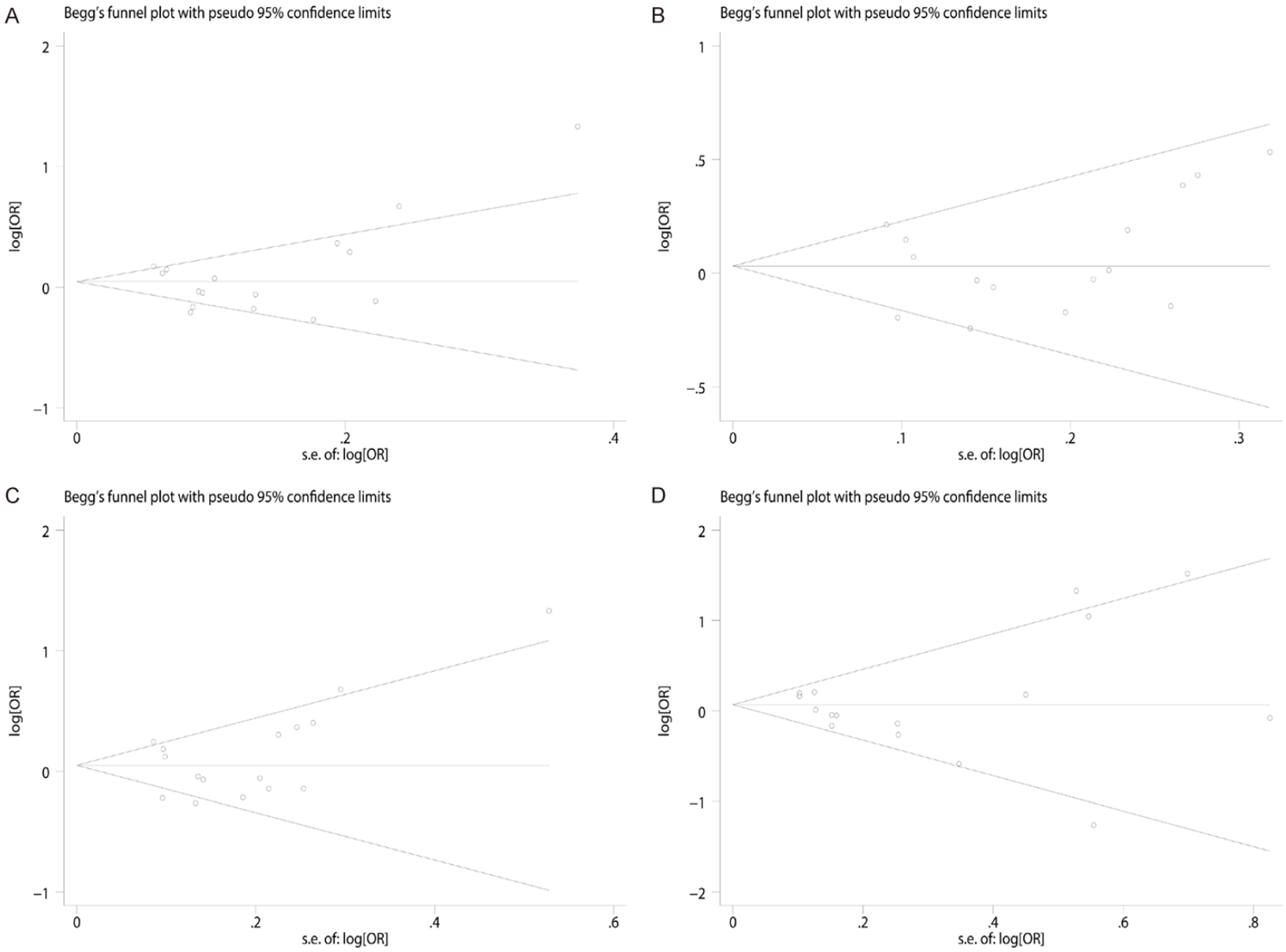

Figure 7. Begg's funnel plot analysis to examine publication bias. A. G *vs.* C; B. CG *vs.* CC; C. CG + GG *vs.* CC; D. GG *vs.* CC + CG.

factors for the incidence and prognosis of prostate cancer; and (iii) the included studies did not provide the relevant original data, and the meta-analysis did not elaborate on interactions among genes or between genes and environments.

In conclusion, the results demonstrated that there is no significant correlation between genetic polymorphism of CYP1B1 4326C/G and the susceptibility to prostate cancer; however, based on the analyses of different races and control group sources, CYP1B1 GG genotypes may increase the risk of prostate cancer in Asians as well as the general population.

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

[3] Pernar CH, Ebot EM, Wilson KM and Mucci LA. The epidemiology of prostate cancer. Cold Spring Harb Perspect Me 2018; 8.

[4] Ortiz de Montellano PR. Hydrocarbon hydroxylation by cytochrome P450 enzymes. Chem Rev 2010; 110: 932-48.

[5] Nebert DW and Russell DW. Clinical importance of the cytochromes P450. Lancet 2002; 360: 1155-62.

[6] Rendic S and Guengerich FP. Survey of human oxidoreductases and cytochrome P450 enzymes involved in the metabolism of xenobiotic and natural chemicals. Chem Res Toxicol 2015; 28: 38-42.

[7] Rendic SP and Guengerich FP. Human cytochrome P450 enzymes 5-51 as targets of drugs and natural and environmental compounds: mechanisms, induction, and inhibition - toxic effects and benefits. Drug Metab Rev 2018; 50: 256-342.

[8] Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM and Nebert DW. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenetics 2004; 14: 1-18.

[9] Shimada T, Hayes CL, Yamazaki H, Amin S, Hecht SS, Guengerich FP and Sutter TR. Activation of chemically diverse procarcinogens by human cytochrome P-450 1B1. Cancer Res 1996; 56: 2979-2984.

[10] Buters JT, Sakai S, Richter T, Pineau T, Alexander DL, Savas U, Doehmer J, Ward JM, Jefcoate CR and Gonzalez FJ. Cytochrome P450 CYP1B1 determines susceptibility to 7, 12-dimethylbenz[a]anthracene-induced lymphomas. Proc Natl Acad Sci U S A 1999; 96: 1977-1982.

[11] Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol 2008; 21: 70-83.

[12] Zhou SF, Liu JP and Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev 2009; 41: 89-295.

[13] Tokizane T, Shiina H, Igawa M, Enokida H, Urakami S, Kawakami T, Ogishima T, Okino ST, Li LC, Tanaka Y, Nonomura N, Okuyama A and Dahiya R. Cytochrome P450 1B1 is overexpressed and regulated by hypomethylation in prostate cancer. Clin Cancer Res 2005; 11: 5793-5801.

[14] Williams JA, Martin FL, Muir GH, Hewer A, Grover PL and Phillips DH. Metabolic activation of carcinogens and expression of various cytochromes P450 in human prostate tissue. Carcinogenesis 2000; 21: 1683-1689.

[15] Berndt SI, Chatterjee N, Huang WY, Chanock SJ, Welch R, Crawford ED and Hayes RB. Variant in sex hormone-binding globulin gene and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2007; 16: 165-8.

[16] Beuten J, Gelfond JA, Byrne JJ, Balic I, Crandall AC, Johnson-Pais TL, Thompson IM, Price DK and Leach RJ. CYP1B1 variants are associated with prostate cancer in non-Hispanic and Hispanic Caucasians. Carcinogenesis 2008; 29: 1751-7.

[17] Brureau L, Moningo D, Emeville E, Ferdinand S, Punga A, Lufuma S, Blanchet P, Romana M and Multigner L. Polymorphisms of estrogen metabolism-related genes and prostate cancer risk in two populations of african ancestry. PLoS One 2016; 11: e0153609.

[18] Catsburg C, Joshi AD, Corral R, Lewinger JP, Koo J, John EM, Ingles SA and Stern MC. Polymorphisms in carcinogen metabolism enzymes, fish intake, and risk of prostate cancer. Carcinogenesis 2012; 33: 1352-9.

[19] Chang BL, Zheng SL, Isaacs SD, Turner A, Hawkins GA, Wiley KE, Bleecker ER, Walsh PC, Meyers DA, Isaacs WB and Xu J. Polymorphisms in the CYP1B1 gene are associated with increased risk of prostate cancer. Br J Cancer 2003; 89: 1524-9.

[20] Cicek MS, Liu X, Casey G and Witte JS. Role of androgen metabolism genes CYP1B1, PSA/KLK3, and CYP11alpha in prostate cancer risk and aggressiveness. Cancer Epidemiol Biomarkers Prev 2005; 14: 2173-7.

[21] Cussenot O, Azzouzi AR, Nicolaiew N, Fromont G, Mangin P, Cormier L, Fournier G, Valeri A, Larre S, Thibault F, Giordanella JP, Pouchard M, Zheng Y, Hamdy FC, Cox A and Cancel-Tassin G. Combination of polymorphisms from genes related to estrogen metabolism and risk of prostate cancers: the hidden face of estrogens. J Clin Oncol 2007; 25: 3596-602.

[22] Fukatsu T, Hirokawa Y, Araki T, Hioki T, Murata T, Suzuki H, Ichikawa T, Tsukino H, Qiu D, Katoh T, Sugimura Y, Yatani R, Shiraishi T and Watanabe M. Genetic polymorphisms of hormone-related genes and prostate cancer risk in the Japanese population. Anticancer Res 2004; 24: 2431-7.

[23] Holt SK, Kwon EM, Fu R, Kolb S, Feng Z, Ostrander EA and Stanford JL. Association of variants in estrogen-related pathway genes with prostate cancer risk. Prostate 2013; 73: 1-10.

[24] Kachakova D, Mitkova A, Popov E, Beltcheva O, Vlahova A, Dikov T, Christova S, Mitev V, Slavov C and Kaneva R. Polymorphisms in androgen metabolism genes AR, CYP1B1, CYP19, and SRD5A2 and prostate cancer risk and aggressiveness in Bulgarian patients. Turk J Med Sci 2016; 46: 626-40.

[25] Sobti RC, Onsory K, Al-Badran AI, Kaur P, Watanabe M, Krishan A and Mohan H. CYP17, SRD5A2, CYP1B1, and CYP2D6 gene polymorphisms with prostate cancer risk in North Indian population. DNA Cell Biol 2006; 25: 287-94.

[26] Tanaka Y, Sasaki M, Kaneuchi M, Shiina H, Igawa M and Dahiya R. Polymorphisms of the CYP1B1 gene have higher risk for prostate cancer. Biochem Biophys Res Commun 2002; 296: 820-6.

[27] Tang YM, Green BL, Chen GF, Thompson PA, Lang NP, Shinde A, Lin DX, Tan W, Lyn-Cook BD, Hammons GJ and Kadlubar FF. Human CYP1B1 Leu432Val gene polymorphism: ethnic distribution in African-Americans, Caucasians and Chinese; oestradiol hydroxylase activity; and distribution in prostate cancer cases and controls. Pharmacogenetics 2000; 10: 761-766.

[28] Gu CY, Li GX, Zhu Y, Xu H, Zhu Y, Qin XJ, Bo D and Ye DW. A single nucleotide polymorphism in CYP1B1 leads to differential prostate cancer risk and telomere length. J Cancer 2018; 9: 269-274.

[29] DerSimonian R and Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45: 139-45.

[30] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-48.

[31] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

[32] Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-101.

[33] Jiang W, Sun G, Xiong J, Xi X and Shi Z. Association of CYP1B1 L432V polymorphism with urinary cancer susceptibility: a meta-analysis. Diagn Pathol 2014; 9: 113.

[34] Yang J, Xu DL, Lu Q, Han ZJ, Tao J, Lu P, Wang C, Di XK and Gu M. Prostate cancer risk and aggressiveness associated with the CYP1B1 4326C/G (Leu432Val) polymorphism: a meta-analysis of 2788 cases and 2968 controls. Asian J Androl 2012; 14: 560-5.

[35] Zhang H, Li L and Xu Y. CYP1B1 polymorphisms and susceptibility to prostate cancer: a meta-analysis. PLoS One 2013; 8: e68634.

[36] Zhu W, Liu H, Wang X, Lu J, Zhang H, Wang S and Yang W. Associations of CYP1 polymorphisms with risk of prostate cancer: an updated meta-analysis. Biosci Rep 2019; 39: BSR20181876.

[37] Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A and Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343: 78-85.

[38] The International HapMap Consortium. The international HapMap project. Nature 2003; 426: 789-796.

[39] Ahmed M and Eeles R. Germline genetic profiling in prostate cancer: latest developments and potential clinical applications. Future Sci OA 2015; 2: FSO87.

[40] Singh PB, Ragavan N, Ashton KM, Basu P, Nadeem SM, Nicholson CM, Krishna RK, Matanhelia SS and Martin FL. Quantified gene expression levels for phase I/II metabolizing enzyme and estrogen receptor levels in benign prostate from cohorts designated as high-risk (UK) versus low-risk (India) for adenocarcino-

ma at this organ site: a preliminary study. Asian J Androl 2010; 12: 203-14.

[41] Aprikian AG, Bazinet M, Plante M, Meshref A, Trudel C, Aronson S, Nachabe M, Péloquin F, Déssureault J, Narod S, et al. Family history and the risk of prostatic carcinoma in a high risk group of urological patients. J Urol 1995; 154: 404-6.

[42] Hsing AW and Devesa SS. Trends and patterns of prostate cancer: what do they suggest? Epidemiol Rev 2001; 23: 3-13.