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Lack of association between the cyclooxygenase 2 -765G>C polymorphism and prostate cancer risk: a meta-analysis

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ABSTRACT. The aim of this study was to investigate the association between the cyclooxygenase 2 (*COX2*) -765G>C (rs20417) polymorphism and prostate cancer (PC) risk using meta-analysis. A systematic literature search was performed using the PubMed, Embase, Cochrane Library, and Google Scholar databases by using the terms “cyclooxygenase-2/COX-2/PTGs2”, “polymorphism” or “variation”, and “prostate” and “cancer” or “carcinoma” to identify relevant articles up to June 14, 2014. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were assessed for PC risk associated with *COX2* -765G>C polymorphism using fixed- and random-effect models. We identified a total of nine publications, including 5952 cases and 5078 controls, to investigate the effect of *COX2* -765G>C on PC risk, and found no significant association in any genetic model tested (CC *vs* GG: OR = 0.993, 95%CI = 0.923-1.068; GC+CC *vs* GG: OR = 1.041, 95%CI = 0.931-1.103; CC *vs* GC+GG: OR = 0.858, 95%CI = 0.689-1.067; CC

vs GG: OR = 0.871, 95%CI = 0.689-1.086; GC *vs* GG: OR = 1.032, 95%CI = 0.945-1.127). Power analysis and tests for publication bias ensured the reliability of our results. This meta-analysis suggested that the functional *COX2* -765G>C polymorphism, located in the *COX2* gene promoter, is unlikely to be associated with PC risk. However, additional larger, well-designed studies are still required to reach a conclusive result on this issue.

Key words: *COX2* -765G>C; Polymorphism; Prostate cancer; Meta-analysis

INTRODUCTION

Prostate cancer (PC) is one of the most prevalent malignancies in men and the second most frequent cause of male cancer-related death (Siegel et al., 2012). It is a clinically heterogeneous disease and the incidence is increasing. PC is also a major public health burden in many countries, and seriously impacts patient quality of life.

Cyclooxygenase (COX), also known as prostaglandin-endoperoxide synthase (PTGS), is a rate-limiting enzyme produced during the production of prostaglandins (Wang et al., 2007). There are two forms of COX proteins, COX-1 and COX-2; COX-1 may have a role as a housekeeping enzyme involved in cell signaling, whereas COX-2 is absent from many cell types unless induced by tumor promoters, growth factors, or cytokines (Kawata et al., 1995). More importantly, COX-2 is also involved in mechanisms of carcinogenesis such as apoptosis (Ding et al., 2000; Li et al., 2001), invasiveness (Sheng et al., 2001), adhesion (Chen et al., 2001), and angiogenesis (Masferrer et al., 2000).

The single nucleotide polymorphism (SNP) *COX2* -765G>C (rs20417) is a functional, extensively studied polymorphism that consists of a guanine (G) to cytosine (C) conversion at position -765 of the *COX2* promoter region, altering the transcriptional activity of the *COX2* gene. Over the last decade, numerous molecular epidemiological case-control studies have been conducted in diverse ethnic backgrounds to explore the association between the *COX2* -765G>C polymorphism and risks of various cancers, including breast cancer (Piranda et al., 2010), colorectal carcinoma (Daraei et al., 2012), esophageal (Bye et al., 2011) and gastric cancers (Li et al., 2012), hepatocellular carcinoma (He et al., 2012), leukemia (Zheng et al., 2011), lung cancer (Coskunpinar et al., 2011), lymphoma (Monroy et al., 2011), ovarian (Agachan Cakmakoglu et al., 2011), head and neck (Peters et al., 2009), pancreatic (Zhao et al., 2009), skin (Cocoş et al., 2012), and cervical cancers (Pandey et al., 2010), among others. However, due to the relatively small sample sizes, the results obtained from these studies have been inconclusive or even controversial. In 2010, a meta-analysis was conducted with the aim to assess the exact relationship of the *COX2* -765G>C polymorphism with PC susceptibility (Murad et al., 2009), and demonstrated that it was associated with increased risk of PC. However, there were some limitations of this meta-analysis, such as a relatively small number of studies included (only two in addition to the author's own study) and incorrectly extracted data.

In consideration of the small sample sizes utilized in previous studies, we performed this meta-analysis to systematically summarize the published data to assess the association between *COX2* -765G>C and PC.

MATERIAL AND METHODS

Publication search

A systematic literature search was performed using the PubMed, Embase, Cochrane Library, and Google Scholar databases by using the terms “cyclooxygenase-2/COX-2/PTGs2”, “polymorphism” or “variation”, and “prostate” and “cancer” or “carcinoma” to identify relevant articles up to June 14, 2014. We evaluated all associated publications to retrieve the most eligible literature. In addition, the reference lists in each database were hand-searched to find other relevant publications. Articles were limited to English language papers.

Inclusion and exclusion criteria

Studies were selected if they met the following criteria: 1) published in peer-reviewed journals, 2) about the *COX2* -765G>C polymorphism and risk of PC, and 3) contained useful genotype frequencies. The exclusion criteria were: 1) non-case-control studies, 2) control population included malignant tumor patients, 3) the genotype frequencies of the control group departed from Hardy-Weinberg equilibrium (HWE), and 4) duplicated publications.

Data extraction

Two investigators (Y.Q.F. and Y.L.) reviewed and extracted information from all eligible publications independently, according to the inclusion and exclusion criteria listed above. An agreement was reached by discussion between the two reviewers whenever there was a conflict. The following items were collected from each study: first author’s surname, year of publication, country of origin, ethnicity of participants, source of controls used for assessment of *COX2* -765G>C genotypes, and total number of cases and controls as well as numbers of cases and controls with C/C, G/C, and G/G genotypes.

Statistical analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association between the *COX2* -765G>C polymorphism and PC risk. The pooled ORs were performed for homozygote comparison (CC *vs* GG), and dominant (CC + GC *vs* GG), recessive (CC *vs* CG + GG), and codominant models (CC *vs* GG, CG *vs* GG). Stratified analyses were performed based on the source of controls, the specimens used for determining *COX2* -765G>C genotypes, and racial descent. A chi-square-based Q-test was performed to check the heterogeneity (Cochran, 1954). If $P \geq 0.1$ was obtained in the heterogeneity test, ORs were pooled according to the fixed-effect model (the Mantel-Haenszel model) (Mantel and Haenszel, 1959), otherwise the random-effect model (the DerSimonian and Laird model) was used (DerSimonian and Laird, 1986). One-way sensitivity analyses were performed to evaluate the stability of the meta-analysis results. Potential publication bias was estimated using Begg’s funnel plot and the Egger test; $P < 0.05$ was considered to be statistically significant for publication bias (Begg and Mazumdar, 1994; Egger et al., 1997). If publication bias existed, the Duval and Tweedie non-parametric “trim-and-fill” method was used to adjust the results accordingly (Duval and Tweedie, 2000). All statistical tests were performed with the STATA software, version 12.1 (Stata Corporation; College Station, TX, USA).

RESULTS

Study characteristics

The initial search yielded 78 studies; 61 were excluded after review of the title or abstract. After screening the full text of the remaining 16 studies, and from the extraction of data, five articles that were not case-control studies, and one review article were excluded. One study (Dossus et al., 2010) was excluded because the genotype frequencies of controls deviated from HWE. Thus, a total of 9 case-control studies [Panguluri et al., 2004; Cheng et al., 2007; Murad et al., 2009; Balistreri et al., 2010; Wu et al., 2011; Catsburg et al., 2012; Joshi et al., 2012; with Panguluri et al. (2004) and Cheng et al. (2007) including two studies], involving 5078 cases and 5952 controls, were included in the present meta-analysis. Figure 1 provides a summary of the selection process. Patient data were compiled from six Caucasian studies (Panguluri et al., 2004; Cheng et al., 2007; Murad et al., 2009; Balistreri et al., 2010; Catsburg et al., 2012; Joshi et al., 2012), 2 African studies (Panguluri et al., 2004; Cheng et al., 2007), and 1 Asian study (Wu et al., 2011).

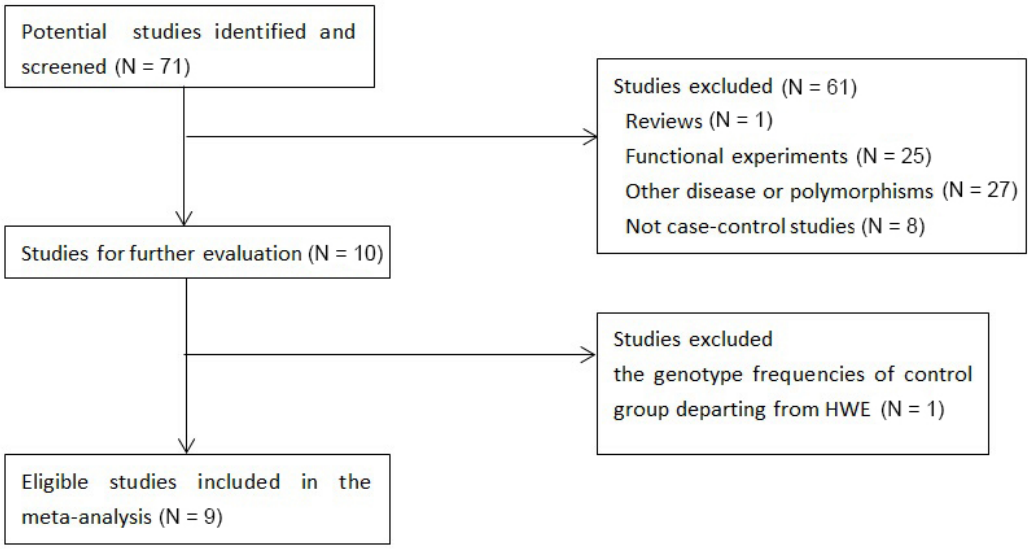

Figure 1. Study identification, inclusion, and exclusion for meta-analysis.

The characteristics of the nine eligible case-control studies are summarized in Table 1. The sample size of the nine studies ranged from 177 to 4620 in total, and a total of 5078 patients with PC and 5952 controls were included in the meta-analysis. The distribution of *COX2* -765G>C genotype frequencies among patients with PC and controls from the 9 studies are shown in Table 2. Five studies's control group are from hospital which were patients who did not have PC, another 4 studies' control group are from normal people which were chosen randomly.

Table 1. Main characteristics of studies included in the meta-analysis.

First author (year)	Country	Ethnicity	Source of controls	Sample size (case/control)	HWE
Balistreri et al. (2010)	Italy	Caucasian	HB	50/125	Y
Cheng et al. (2007)	US	Caucasian	HB	416/417	Y
Cheng et al. (2007)	US	African	HB	89/88	Y
Murad et al. (2009)	UK	Caucasian	HB	1592/3028	Y
Catsburg et al. (2012)	US	Caucasian	PB	1431/756	Y
Wu et al. (2011)	China	Asian	HB	218/436	Y
Joshi et al. (2012)	US	Caucasian	PB	935/756	Y
Panguluri et al. (2004)	Nigeria	Caucasian	PB	87/90	Y
Panguluri et al. (2004)	Nigeria	African	PB	260/256	Y

HWE = Hardy-Weinberg equilibrium; US = United States; UK = United Kingdom; HB = hospital-based; PB = population-based.

Table 2. Distribution of *COX2* -765G>C genotypes among patients with prostate cancer and controls.

First author (year)	Patients (N)			Controls (N)		
	GG	GC	CC	GG	GC	CC
Balistreri et al. (2010)	31	15	4	65	46	14
Cheng et al. (2007)	294	115	7	293	113	11
Cheng et al. (2007)	38	42	9	38	38	12
Murad et al. (2009)	1104	451	37	2137	819	72
Catsburg et al. (2012)	892	469	70	481	237	38
Wu et al. (2011)	198	20	0	365	71	0
Joshi et al. (2012)	595	304	36	481	237	38
Panguluri et al. (2004)	86	1	0	88	2	0
Panguluri et al. (2004)	202	52	6	205	42	9

Meta-analysis results

All nine studies included, with a total of 5952 patients and 5078 controls, were pooled to explore the association between *COX2* -765G>C and the susceptibility to PC. Detailed results are summarized in Table 3. Overall, there was no significant heterogeneity in any of the genetic models, and a fixed-effect model was applied to estimate the ORs. We did not find a statistical association of *COX2* -765G>C with PC risk in the allelic model (CC *vs* GG: OR = 0.993, 95%CI = 0.923-1.068) (Figure 2A). Similar results were observed in the other models (GC+CC *vs* GG: OR = 1.041, 95%CI = 0.931-1.103; CC *vs* GC+GG: OR = 0.858, 95%CI = 0.689-1.067; CC *vs* GG: OR = 0.871, 95%CI = 0.689-1.086; GC *vs* GG: OR = 1.032, 95%CI = 0.945-1.127) (Figure 2B-E). In subgroup analysis by ethnicity and source of control group, nearly all of the genetic models demonstrated non-significant results. Although the homozygote comparison (CC *vs* GG) and the dominant model (GC+CC *vs* GG) analyses from the Asian studies appeared to show that the C allele conferred a higher PC risk than did the GG genotype (OR = 0.519, 95%CI = 0.307-0.878), this result was based on a small sample size (218 patients and 436 controls), and discrepancy with the other models made it difficult to have confidence in the reliability of this finding.

Evaluation of study quality

A single study involved in the meta-analysis was deleted in successive iterations to reflect the effects of individual data sets on the pooled ORs; most of the corresponding pooled ORs were not materially altered (data not shown).

Table 3. Results of meta-analysis for the *COX2* -765G>C polymorphism and prostate cancer risk.

Study groups	N	Sample size (case/control)	CC *vs* GC			GC + CC *vs* GG			CC *vs* GC + GG			CC *vs* GG			GC *vs* GG		
			OR (95% CI)	[a]P	[b]P	OR (95% CI)	[a]P	[b]P	OR (95% CI)	[a]P	[b]P	OR (95% CI)	[a]P	[b]P	OR (95% CI)	[a]P	[b]P
Overall	9	5078/5952	0.993 (0.923-1.068)	0.846	0.379	1.014 (0.931-1.103)	0.755	0.331	0.858 (0.689-1.067)	0.168	0.919	0.871 (0.698-1.086)	0.900	0.219	1.032 (0.945-1.127)	0.487	0.321
Source of controls																	
PB	4	2713/1858	1.005 (0.902-1.120)	0.921	0.862	1.039 (0.914-1.181)	0.58	0.863	0.852 (0.636-1.141)	0.282	0.633	0.869 (0.647-1.167)	0.350	0.637	1.067 (0.933-1.221)	0.342	0.818
HB	5	2365/4094	0.982 (0.889-1.085)	0.724	0.100	0.994 (0.888-1.114)	0.92	0.085	0.864 (0.622-1.202)	0.386	0.781	0.873 (0.625-1.218)	0.424	0.728	1.006 (0.895-1.130)	0.474	0.093
Ethnicity																	
Caucasian	6	4511/5172	1.008 (0.933-1.088)	0.846	0.723	1.030 (0.942-1.126)	0.755	0.788	0.880 (0.699-1.108)	0.276	0.822	0.889 (0.705-1.122)	0.322	0.761	1.047 (0.954-1.148)	0.334	0.873
African	2	478/344	1.004 (0.755-1.335)	0.980	0.980	1.107 (0.784-1.563)	1.563	0.740	0.684 (0.343-1.364)	0.281	0.894	0.715 (0.350-1.460)	0.357	0.888	1.203 (0.834-1.735)	0.322	0.745
Asian	1	218/436	0.993 (0.923-1.068)	0.019	-	0.519 (0.307-0.878)	0.015	-	-	-	-	-	-	-	0.519 (0.307-0.878)	0.015	-

N = number of comparisons; OR = odds ratio; CI = confidence interval; [a]P value for association; [b]P value for heterogeneity; a random-effect model was used when [b]P < 0.1, otherwise a fixed-effect model was used.

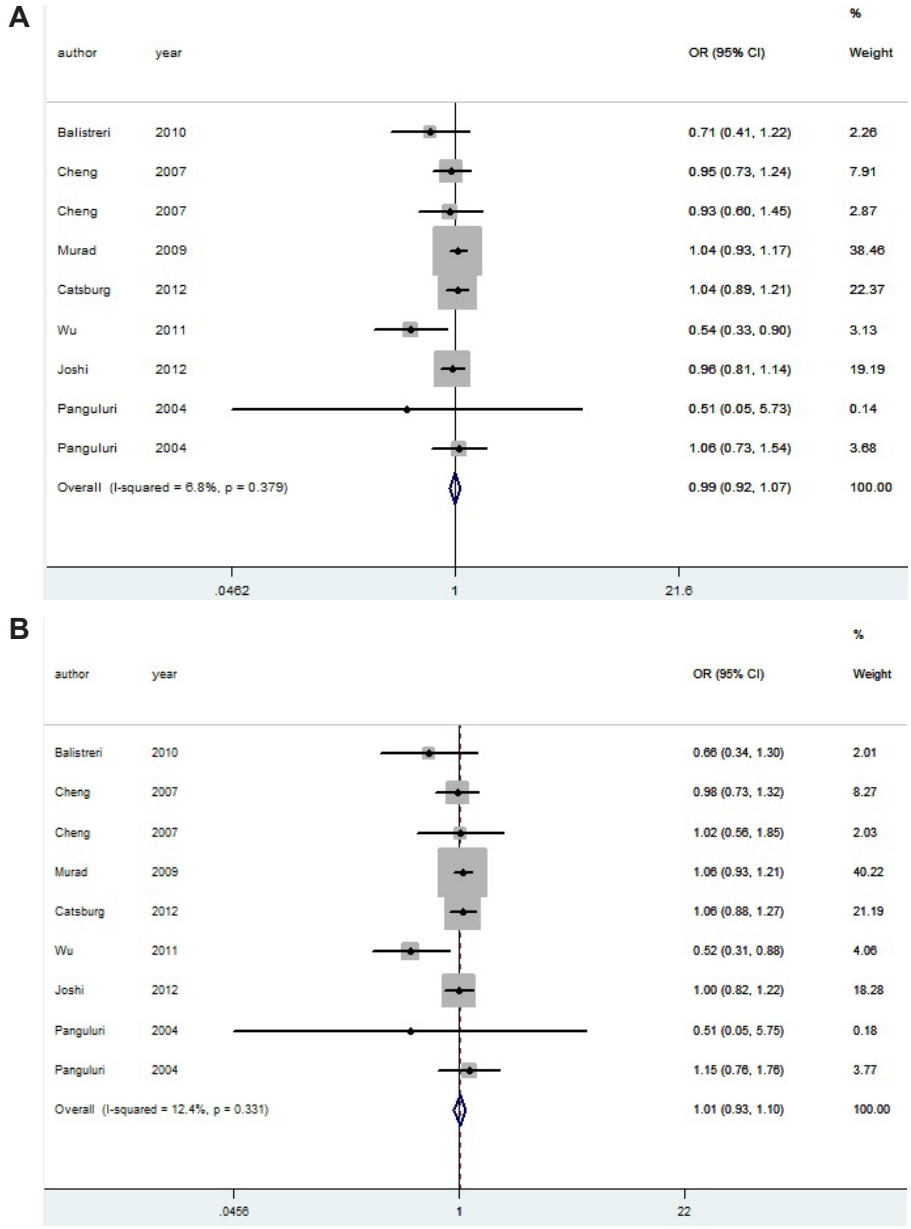

Figure 2. Forest plots of the relationships between the *COX2*-765G>C polymorphism and prostate cancer risk in studies included. **A.** Homozygote comparison (CC *vs* GG). **B.** Dominant model (CC + GC *vs* GG). **C.** Recessive model (CC *vs* CG + GG). **D. E.** Codominant model (CC *vs* GG, CG *vs* GG, respectively). The first author surname and year of publication are given in the left side of each figure. The size of the grey square corresponding to each study is proportional to the sample size. The center of each square represents the odds ratio (OR) and the horizontal line shows the corresponding 95% confidence interval (CI). The pooled OR was obtained using a fixed-effect model and is represented by an open diamond, with the center indicating the OR and the ends corresponding to the 95%CI.

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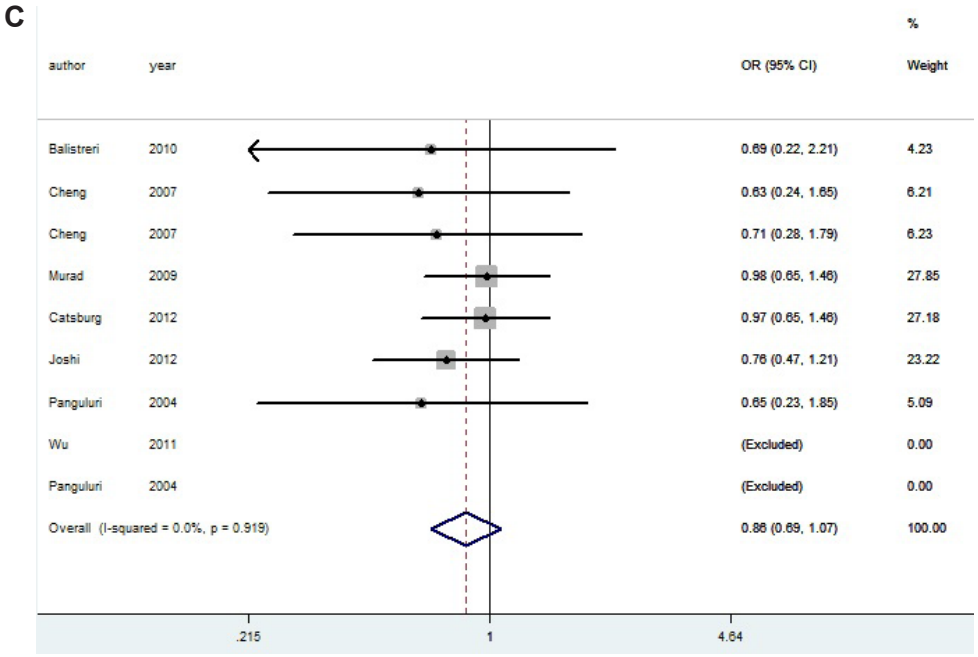

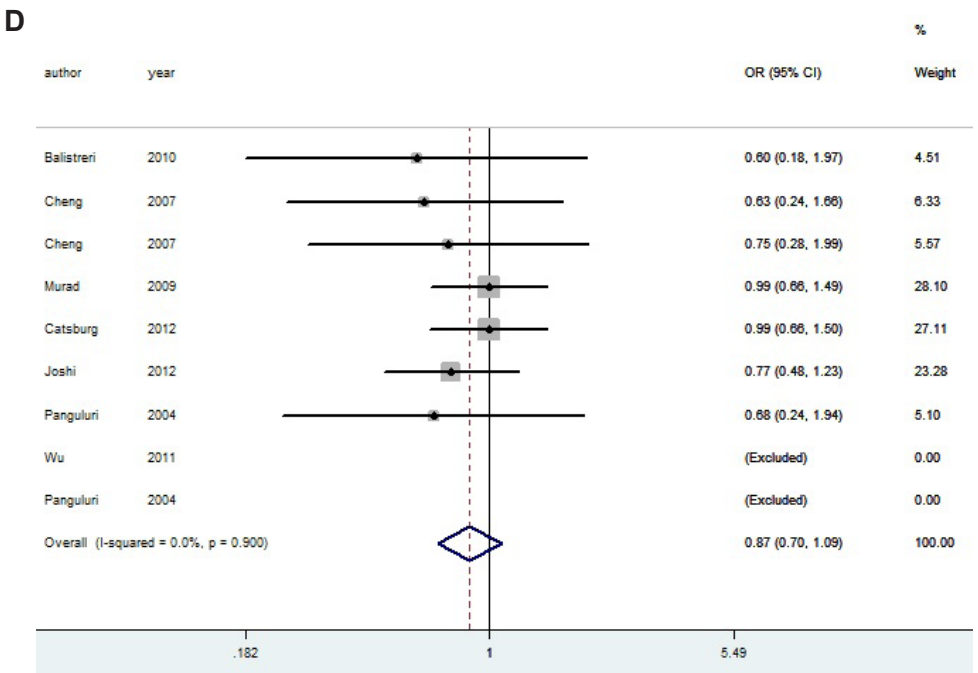

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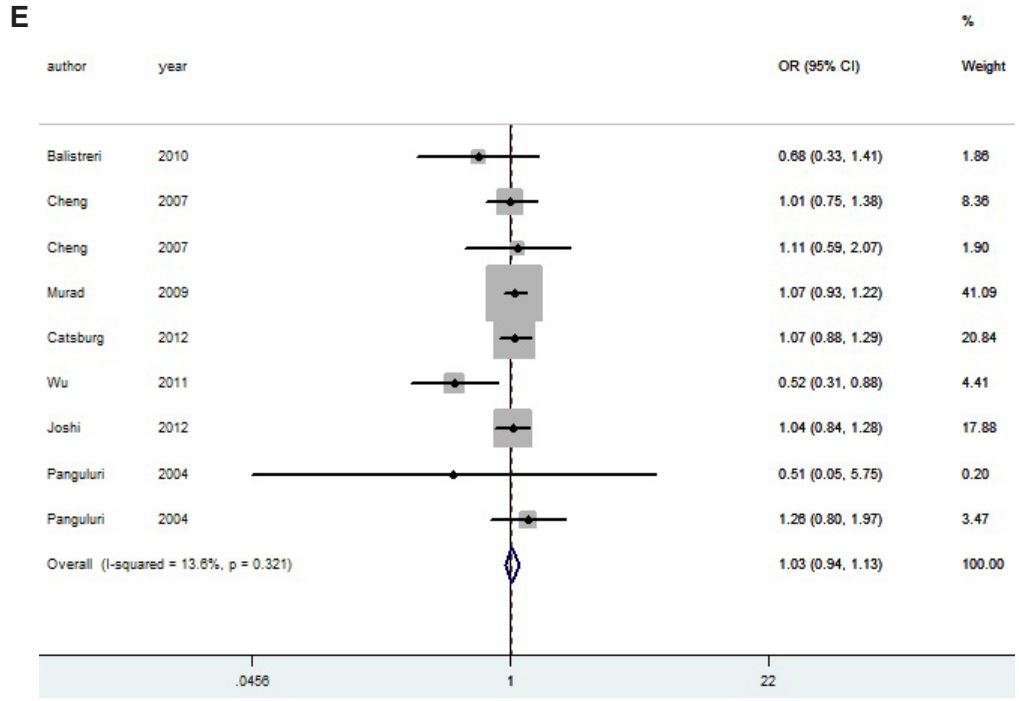

Both Begg's funnel plot and the Egger test were conducted to assess the publication bias of the currently available literature (Table 4). The Egger test results suggested that publication bias was evident in the heterozygote comparison (P = 0.038). Therefore, the Duval and Tweedie non-parametric "trim-and-fill" method was used to adjust for publication bias. Meta-analyses with and without using the "trim-and-fill" method did not draw different conclusions (data not shown). The shapes of the funnel plots were roughly symmetrical in the other comparison models (data not shown). Together, these findings indicated that our results were statistically robust.

Table 4. Statistical analysis of publication bias for *COX2* -765G>C polymorphism association with prostate cancer risk.

Category	CC vs GG	GC + CC *vs* GG	CC *vs* GC + GG	CC *vs* GG	GC *vs* GG
Begg's test	0.404	0.211	0.881	0.300	0.458
Egger's test	0.038	0.121	0.347	0.111	0.379

DISCUSSION

COX2 -765G>C is a functional polymorphism, located at 765 bp upstream (-765 bp) from the transcription start site of the *COX2* gene. The polymorphic variant changes a putative stimulatory protein-binding site in the promoter of *COX2* between -766 and -761 bp (Papafili et al., 2002), and it also creates an E2 promoter factor-binding site, leading to high *COX2* transcription

activity, which may be the mechanism of the *COX2* -765G>C polymorphism increasing cancer risk (Szczeklik et al., 2004).

To explore the exact association between the *COX2* -765G>C polymorphism and cancer risk, a meta-analysis (Murad et al., 2009) had been conducted in 2009; however, only the author's own work and two additional studies were contained in that meta-analysis, and due to the relatively small overall sample size and deficits in data collection, the results were conflicting. Therefore, we conducted the current meta-analysis to derive the potential relationship of the target SNP with cancer susceptibility after integrating data from all eligible studies. This meta-analysis of nine studies containing 5078 patients with PC and 5952 controls systematically evaluated the association between a functional polymorphism within the *COX-2* promoter, -765G>C (rs20417), and PC risk. Overall results from all genetic models tested consistently suggested that *COX2* -765G>C polymorphism did not constitute a conspicuous risk factor in the susceptibility of PC. Subgroup analysis by ethnicity also demonstrated similar results. These internally consistent results suggested that *COX2* -765G>C might have no impact on the pathogenesis of PC. Previous meta-analyses have shown an association between the *COX2* -765G>C polymorphism and cancer risk in gastric (Zhao et al., 2014), esophageal (Liang et al., 2011), and colorectal cancers (Wang et al., 2013). One possible explanation for this discrepancy is that different types of cancer have various mechanisms of carcinogenesis. Although preclinical research has suggested that the *COX2* -765G>C polymorphism might be related to PC risk (Wu et al., 2011; Catsburg et al., 2012; Joshi et al., 2012), the results from our study indicated that *COX2* -765G>C was unlikely to be associated with PC risk. Since Panguluri et al. (2004) first claimed that this SNP played a role in the development of PC, considerable research has been conducted in this field. However, most of the studies failed to obtain a significant result. Furthermore, a stratified analysis by ethnicity was conducted herein, and a null significant association was found, with the exception of the homozygote comparison (CC *vs* GG) and dominant model (GC+CC *vs* GG) analyses of Asian populations, in which *COX2* -765G>C was positively associated with PC risk. However, as this result is, to our knowledge, unique among published studies, we still need further preclinical research to confirm the possibility that the *COX2* -765G>C variant may have an association with PC risk in Asian populations.

The meta-analysis presented here demonstrated several strengths. For *COX2* -765G>C and PC risk, no significant heterogeneity was observed in all the genetic models. In addition, we did not identify any publication bias for our meta-analysis. Furthermore, our sample size was sufficient to provide adequate statistical power for our analyses, which strengthened the reliability of our results. However, potential limitations of this study should also be addressed. First, our results were based on unadjusted estimates, and a more precise evaluation stratified by age, gender, cigarette consumption, family history, and environmental exposures could be performed if individual data are available. Second, only published full-text articles were included in the current meta-analysis, which might cause publication bias even though both Begg's and Egger's tests did not confirm the existence of bias. Finally, the obtained results might potentially be false negatives, as some of the individual studies included in the current meta-analysis reported a significant association of the *COX2* -765G>C polymorphism with PC risk.

Despite these limitations, this meta-analysis has provided reliable results based on ample study power. In summary, our study demonstrated that *COX2* -765G>C (rs20417) is unlikely to be associated with PC risk. However, additional well-designed and unbiased studies, with larger sample size, in diverse ethnic populations, and with the consideration of gene-gene and gene-environment interactions are still required to resolve this issue in the future.

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