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Original Article

Cytochrome P450 2E1 RsaI/PstI polymorphism is associated with urologic cancer risk: evidence from a meta-analysis

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Abstract: Cytochrome P450 2E1 (CYP2E1) is involved in the metabolic activation of various carcinogens. *CYP2E1* RsaI/PstI polymorphism has been identified in urologic cancer patients, while studies of the polymorphism have shown inconclusive trends in the risk of urologic cancers. Therefore, we performed this systematic review to provide a complete picture and conducted a meta-analysis to derive a precise estimation. We searched PubMed, Embase and Web of Science to identify eligible studies up to December 15, 2014. 12 studies with 2712 cases and 2977 controls were included in the meta-analysis.The odds ratio with a 95% confidence interval was used to assess the strength of associations. We observed that the c2 allele of *CYP2E1* RsaI/PstI polymorphism was associated with a decreased risk of urologic cancer under all genetic models (c2 vs. c1: OR = 0.742, 95% CI = 0.659-0.835); c2c2 vs. c1c1: OR = 0.516, 95% CI = 0.357-0.745; c1c2 vs. c1c1: OR = 0.748, 95% CI = 0.748 (0.648-0.863; c2c2 + c1c2 vs. c1c1: OR = 0.722, 95% CI = 0.629-0.829; c2c2 vs. c1c1 + c1c2: OR = 0.578, 95% CI = 0.401-0.832). In the subgroup analysis by cancer type, statistically significant associations were found in urothelial cancer in all genetic models. When stratified by ethnicity, a same trend was also indicated in Asians in all genetic models.To conclude, our results support the conclusion that the *CYP2E1* RsaI/PstI polymorphism may be associated with urologic cancer susceptibility. The c2 allele is a low-penetrance risk factor for urologic cancer development.

Keywords: Cytochrome P450 2E1, polymorphism, urologic cancer, susceptibility, meta-analysis

Introduction

Cancer is a major public health problem and one of the leading causes of death worldwide [1]. Urologic cancer, including prostate cancer, urothelial cancer (bladder cancer and renal pelvis cancer) and renal canceris one of the most common malignancies and major cause of cancer related death worldwide [2]. Tremendous efforts have been made to unravel the underlying mechanism of cancer, with the aim to develop optimal prophylactic and therapeutic strategies. Substantial evidences have shown that genetic susceptibility and environment pollution might play a significant role in an individual's risk of developing cancer [3, 4].

Cytochrome P450 (CYP) is a group of enzymes responsible for oxidation metabolism of endogenous compounds. Cytochrome P450 2E1 (CYP2E1), a member of the CYP450 superfamily, is involved in the metabolic activation of various carcinogens, including N-nitrosamines, aniline, vinylchloride and urethane [5]. *CYP2E1* is mapped to chromosome 10q24.3 and encodes a protein of 493 amino acids. Of several gene polymorphisms in *CYP2E1*, RsaI/PstI polymorphism covers two point mutations (RsaI/C-1055T/rs2031920; PstI/G-1295C/rs3813867) in close linkage disequilibrium in the 5'-flanking promoter region of *CYP2E1* [6]. It occurs as a wild-type homozygous genotype (c1/c1), a heterozygous genotype (c1/c2) and a variant

homozygous rare genotype (c2/c2) [7]. This polymorphism affects the transcriptional activity of the gene and influences the susceptibility to N-nitrosamine-linked carcinogenesis [8].

CYP2E1 RsaI/PstI polymorphism has been interestingly found to be associated with risk of some cancers. Previous meta-analyses showed that the *CYP2E1* RsaI/PstI polymorphism was associated with susceptibility of esophageal cancer [9], lung cancer [10, 11], liver cancer [12], head & neck cancer [13], colorectal cancer [14] and bladder cancer [15]. {Tian, 2012 #1513} However, another two meta-analyses failed to indicate the significant association of *CYP2E1* RsaI/PstI polymorphism with the gastric or oral cancer risk [16, 17]. Some epidemiological studies have investigated the association between the *CYP2E1* RsaI/PstI polymorphism and the risk of urologic cancers. However, these studies seem to result in controversial outcomes. Recently a meta-analysis was conducted for bladder cancer [15], while the conclusions for prostate cancer, urothelial cancer and renal cancer, and overall urologic cancer are still inconclusive. Thus, we performed this meta-analysis to identify all eligible studies and to assess the association between *CYP2E1* RsaI/PstI polymorphism and urologic cancer.

Materials and methods

Publication search

A systematic search through literature databases including PubMed, Embase and Web of Science databases was performed. Combinations of medical subheadings and key words of ("cytochrome P450 2E1" or "CYP2E1" or "cytochrome P450, family 2, subfamily E, polypeptide 1") and ("polymorphism" or "variant") and ("neoplasms" or "cancer" or "carcinoma" or "tumor") were used for database searching. Alternative spellings of these key words were also considered. References of previous meta-analyses were also searched. The latest research was performed on December 15, 2014, and there was no limitation to languages.

Study selection and data extraction

Inclusion criteria were as follows: (1) articles evaluated the *CYP2E1* RsaI/PstI polymorphism and the risk of urologic cancers; (2) the design was case-control study; and (3) genotype distributions in both cases and controls were available for estimating an odds ratio (OR) with 95% confidence interval (CI). The exclusion criteria were as follow: (1) reviews, conference abstracts, case reports, meta-analyses, or systematic reviews; (2) studies based on family or sibling pairs; and (3) publications with insufficient data referring to genotype frequency. In case the overlapped publications existed, the study with the largest sample size or the latest publication date was included. Two reviewers independently checked all potentially relevant studies and reached a consensus on all items. In case of disagreement, it would be resolved by discussion or by the third author. The following data were collected from each study: name of first author, published year, country and ethnicity of the study populations, state of controls, matching criteria, sample source, genotype data, number of cases and controls.

Statistical analysis

Prior to data analysis, the accordance of genotype distribution in controls to Hardy-Weinberg equilibrium (HWE) was examined for each study. The strength of association between RsaI/PstI polymorphism in *CYP2E1* and urologic cancer risk was measured by ORs and 95% CI. The statistical significance of summary OR was determined with *Z*-test. Cochran's *Q* test and I^2 statistic were used to measure heterogeneity across the included studies. If a *P* value for the *Q* test was more than 0.10, the fixed-effects model was used to calculate the summary ORs. Otherwise, the random-effects model was applied. Publication bias was estimated by visually assessing the asymmetry of Begg's funnel plot [18]. Furthermore, Egger's test was performed to provide quantitative evidence for the checking of publication bias [19]. Additionally, sensitivity analysis was performed by sequentially omitting individual study to check the stability of the result. All statistical analyses were performed using STATA12.0 (STATA Corporation, College Station, TX, USA). All *p* values were two-sided and $P < 0.05$ was considered statistically significant.

Results

Eligible studies

In total, 285 relevant publications were identified after initial search. After an initial title and

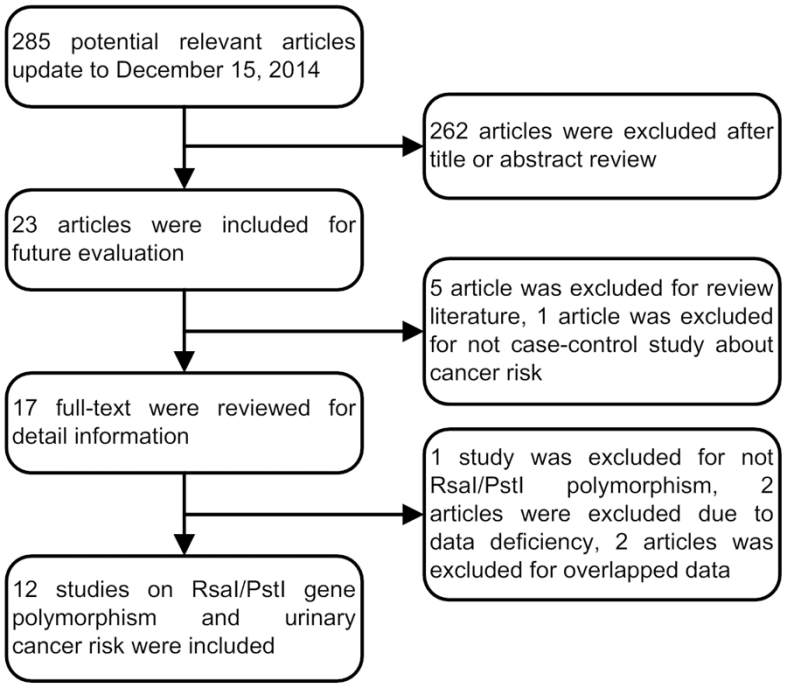

Figure 1. Flow chart of literature search and selection.

abstract screening, 23 potential articles concerning the association between *CYP2E1* polymorphism and urologic cancer were assessed. After the further view, five articles were excluded for review literature, and one additional article [20] was excluded because it was not case-control study about cancer risk. After data extraction of the remaining 17 publications, one study [21] was excluded for not RsaI/PstI polymorphism, two articles [22, 23] were excluded for overlapped data, and two studies [24, 25] was excluded for data deficiency. The process of study selection was summarized in the flow diagram (**Figure 1**). Finally, 12 eligible case-control studies on the relationship between *CYP2E1* RsaI/PstI polymorphism and urologic cancer risk were involved in this meta-analysis, including eight bladder urothelial cancer studies [26-33], three prostate cancer studies [34-36] and one renal cell/urothelial cancer study [37]. It should be noted that Farker et al. studied the RsaI/PstI polymorphism in renal cell carcinoma and urothelial cancer, respectively [37]. Therefore, we treated them as separate data sets during our analysis. As shown in **Table 1**, six studies were conducted in Asians, six studies in Caucasians. As for source of control, there were eight hospital-based(HB) studies and four population-based(PB) studies. Among them, two genotyping methods (PCR-RFLP and GoldenGate assay) were used. All studies except Basma' study [26] indicated that the genotypic distribution of controls was consistent with HWE.

Quantitative data synthesis

Table 2 lists the main results of the meta-analysis for *CYP2E1* RsaI/PstI polymorphism: having the c2 allele is a factor that lowers the overall risk of urologic cancer (c2 vs. c1: OR = 0.742, 95% CI = 0.659-0.835; c2-c2 vs. c1c1: OR = 0.516, 95% CI = 0.357-0.745; c1c2 vs. c1c1: OR = 0.748, 95% CI = 0.648-0.863; c2c2 + c1c2 vs. c1c1: OR = 0.722, 95% CI = 0.629-0.829; c2-c2 vs. c1c1 + c1c2: OR = 0.578, 95% CI = 0.401-0.832) (**Figure 2**). When the study, in which genotype distribution of control population was not consistent with HWE, was excluded, significant results were also obtained (c2c2 vs. c1c1: OR = 0.563, 95% CI = 0.376-0.841; c1c2 vs. c1c1: OR = 0.759, 95% CI = 0.657-0.877; c2c2 + c1c2 vs. c1c1: OR = 0.742, 95% CI = 0.645-0.854; c2c2 vs. c1c1 + c1c2: OR = 0.623, 95% CI = 0.418-0.928). In terms of sources of controls, significantly decreased risk was observed among HB studies for all genetic models, whereasno significant association was found among PB studies.

In the subgroup analysis by cancer type, statistically significant association was found in urothelial cancer (c2 vs. c1: OR = 0.732, 95% CI = 0.638-0.840; c2c2 vs. c1c1: OR = 0.486, 95% CI = 0.319-0.742; c1c2 vs. c1c1: OR = 0.747, 95% CI = 0.632-0.883; c2c2 + c1c2 vs. c1c1: OR = 0.716, 95% CI = 0.609-0.841; c2c2 vs. c1c1 + c1c2: OR = 0.545, 95% CI = 0.359-0.828) and prostate cancer (c2 vs. c1: OR = 0.715, 95% CI = 0.559-0.913 ; c2c2 vs. c1c1: OR = 0.530, 95% CI = 0.238-1.179; c1c2 vs. c1c1: OR = 0.692, 95% CI = 0.516-0.930; c2c2 + c1c2 vs. c1c1: OR = 0.675, 95% CI = 0.506-0.898) (**Figure 2A**). When stratified by ethnicity, a significant association between *CYP2E1*

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

Author	Year	Country	Ethnicity	Type of cancer	Genotyping method	Match	Control source	Case	Control	Case			Control			HWE
										c1c1	c1c2	c2c2	c1c1	c1c2	c2c2	
Basma et al	2013	Lebanon	Caucasian	Bladder urothelial	Pcr-rflp	Region	HB	45	85	36	2	7	46	12	27	0
Cantor et al	2010	Spain	Caucasian	Bladder urothelial	Goldengate assay	Age, gender, region	HB	627	611	590	37	0	569	42	0	0.379
Wang et al	2009	Taiwan	Asian	Bladder urothelial	Pcr-rflp	Age, gender	HB	520	520	335	170	15	292	202	26	0.233
Shao et al	2008	China	Asian	Bladder urothelial	Pcr-rflp	Age, gender	HB	202	272	131	62	9	170	91	11	0.786
Yang et al	2006	China	Asian	Prostate	Pcr-rflp	Age	HB	225	249	156	65	4	147	90	12	0.734
Mittal et al	2005	India	Asian	Bladder urothelial	Pcr-rflp	Age	PB	50	50	50	0	0	50	0	0	1
Choi et al	2003	Korea	Asian	Bladder urothelial	Pcr-rflp	Region	HB	214	194	124	86	4	93	89	12	0.121
Ferreira et al	2003	Portugal	Caucasian	Prostate	Pcr-rflp	Age, gender	PB	95	123	91	4	0	115	8	0	0.709
Murata et al	2001	Japan	Asian	Prostate	Pcr-rflp	Gender	HB	115	200	71	39	5	109	83	8	0.107
Farker et al	1998	Germany	Caucasian	Renal	Pcr-rflp	Region	PB	187	304	174	12	1	289	15	0	0.659
				Urothelial				38	304	37	1	0	289	15	0	0.659
Anwar et al	1996	Egypt	Caucasian	Bladder urothelial	Pcr-rflp	Age, smoking history	PB	22	21	22	0	0	20	1	0	0.911
Brockmoller et al	1996	Germany	Caucasian	Bladder urothelial	Pcr-rflp	Age, gender	HB	372	348	358	14	0	328	20	0	0.581

PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; HB, hospital based; PB, population based; HWE, Hardy-Weinberg equilibrium.

Table 2. Stratified analyses of *CYP2E1* RsaI/PstI polymorphism on urologic cancer risk

Analysis	N	Allele (c2 vs. c1)		Homozygous (c2c2 vs. c1c1)		Heterozygous (c1c2 vs. c1c1)		Dominant (c2c2 + c1c2 vs. c1c1)		Recessive (c2c2 vs. c1c1 + c1c2)	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Total	13	0.742 (0.659-0.835)	0	0.516 (0.357-0.745)	0	0.748 (0.648-0.863)	0	0.722 (0.629-0.829)	0	0.578 (0.401-0.832)	0.003
HWE	12	0.767 (0.679-0.865)	0.054	0.563 (0.376-0.841)	0.005	0.759 (0.657-0.877)	0	0.742 (0.645-0.854)	0	0.623 (0.418-0.928)	0.020
Source of controls											
HB	8	0.731 (0.648-0.825)	0	0.495 (0.341-0.720)	0	0.738 (0.637-0.855)	0	0.709 (0.615-0.817)	0	0.557 (0.385-0.807)	0.002
PB	5	1.038 (0.583-1.846)	0.900	4.977 (0.202-122.849)	0.327	0.929 (0.508-1.700)	0.812	0.982 (0.543-1.778)	0.953	4.898 (0.199-120.861)	0.331
Genotyping methods											
PCR-RFLP	12	0.734 (0.649-0.830)	0	0.516 (0.357-0.745)	0	0.737 (0.634-0.857)	0	0.710 (0.614-0.821)	0	0.578 (0.401-0.832)	0.003
Cancer type											
urothelial	9	0.732 (0.638-0.840)	0	0.486 (0.319-0.742)	0.001	0.747 (0.632-0.883)	0.001	0.716 (0.609-0.841)	0	0.545 (0.359-0.828)	0.004
prostate	3	0.715 (0.559-0.913)	0.007	0.530 (0.238-1.179)	0.120	0.692 (0.516-0.930)	0.015	0.675 (0.506-0.898)	0.007	0.602 (0.272-1.330)	0.209
renal	1	1.537 (0.734-3.222)	0.255	4.977 (0.202-122.849)	0.327	1.329 (0.608-2.905)	0.476	1.439 (0.669-3.097)	0.351	4.898 (0.199-120.861)	0.331
Ethnicity											
Caucasian	7	0.696 (0.527-0.918)	0.010	0.433 (0.184-1.017)	0.055	0.760 (0.556-1.041)	0.128	0.722 (0.536-0.973)	0.032	0.501 (0.215-1.170)	0.110
Asian	6	0.753 (0.660-0.858)	0	0.537 (0.357-0.809)	0.003	0.744 (0.634-0.874)	0	0.722 (0.618-0.844)	0	0.597 (0.401-0.832)	0.013

N, Number of comparisons; OR, odds ratio; CI, confidence interval; *P*, *P* value of *Z*-test for the pooled ORs; HWE: genotype distribution in controls in accordance with Hardy-Weinberg equilibrium; HB, hospital based; PB, population based; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism.

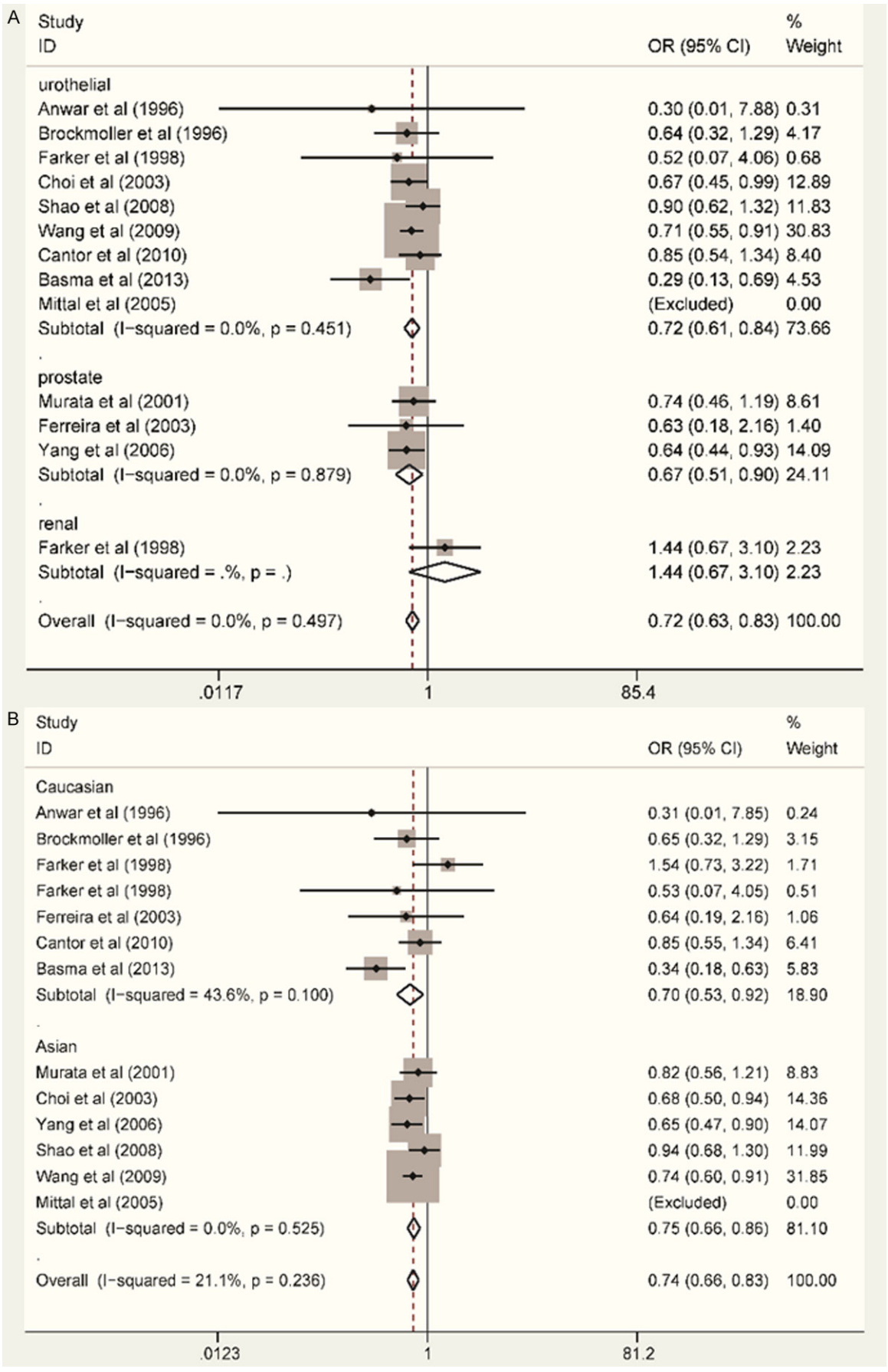
A
Study
ID
OR (95% CI)
%
Weight
urothelial
Anwar et al (1996) 0.30 (0.01, 7.88) 0.31
Brockmoller et al (1996) 0.64 (0.32, 1.29) 4.17
Farker et al (1998) 0.52 (0.07, 4.06) 0.68
Choi et al (2003) 0.67 (0.45, 0.99) 12.89
Shao et al (2008) 0.90 (0.62, 1.32) 11.83
Wang et al (2009) 0.71 (0.55, 0.91) 30.83
Cantor et al (2010) 0.85 (0.54, 1.34) 8.40
Basma et al (2013) 0.29 (0.13, 0.69) 4.53
Mittal et al (2005) (Excluded) 0.00
Subtotal (I-squared = 0.0%, p = 0.451) 0.72 (0.61, 0.84) 73.66
prostate
Murata et al (2001) 0.74 (0.46, 1.19) 8.61
Ferreira et al (2003) 0.63 (0.18, 2.16) 1.40
Yang et al (2006) 0.64 (0.44, 0.93) 14.09
Subtotal (I-squared = 0.0%, p = 0.879) 0.67 (0.51, 0.90) 24.11
renal
Farker et al (1998) 1.44 (0.67, 3.10) 2.23
Subtotal (I-squared = .%, p = .) 1.44 (0.67, 3.10) 2.23
Overall (I-squared = 0.0%, p = 0.497) 0.72 (0.63, 0.83) 100.00
.0117
1
85.4
B
Study
ID
OR (95% CI)
%
Weight
Caucasian
Anwar et al (1996) 0.31 (0.01, 7.85) 0.24
Brockmoller et al (1996) 0.65 (0.32, 1.29) 3.15
Farker et al (1998) 1.54 (0.73, 3.22) 1.71
Farker et al (1998) 0.53 (0.07, 4.05) 0.51
Ferreira et al (2003) 0.64 (0.19, 2.16) 1.06
Cantor et al (2010) 0.85 (0.55, 1.34) 6.41
Basma et al (2013) 0.34 (0.18, 0.63) 5.83
Subtotal (I-squared = 43.6%, p = 0.100) 0.70 (0.53, 0.92) 18.90
Asian
Murata et al (2001) 0.82 (0.56, 1.21) 8.83
Choi et al (2003) 0.68 (0.50, 0.94) 14.36
Yang et al (2006) 0.65 (0.47, 0.90) 14.07
Shao et al (2008) 0.94 (0.68, 1.30) 11.99
Wang et al (2009) 0.74 (0.60, 0.91) 31.85
Mittal et al (2005) (Excluded) 0.00
Subtotal (I-squared = 0.0%, p = 0.525) 0.75 (0.66, 0.86) 81.10
Overall (I-squared = 21.1%, p = 0.236) 0.74 (0.66, 0.83) 100.00
.0123
1
81.2

Figure 2. Forest plot of ORs for association between the *CYP2E1* RsaI/PstI polymorphism and urologic cancer risk. A. Dominant model (c2c2 + c1c2 vs. c1c1) with a fixed effect model. B. Allele model (c2 vs. c1) with a fixed effect model. CI, confidence interval; OR, odds ratio.

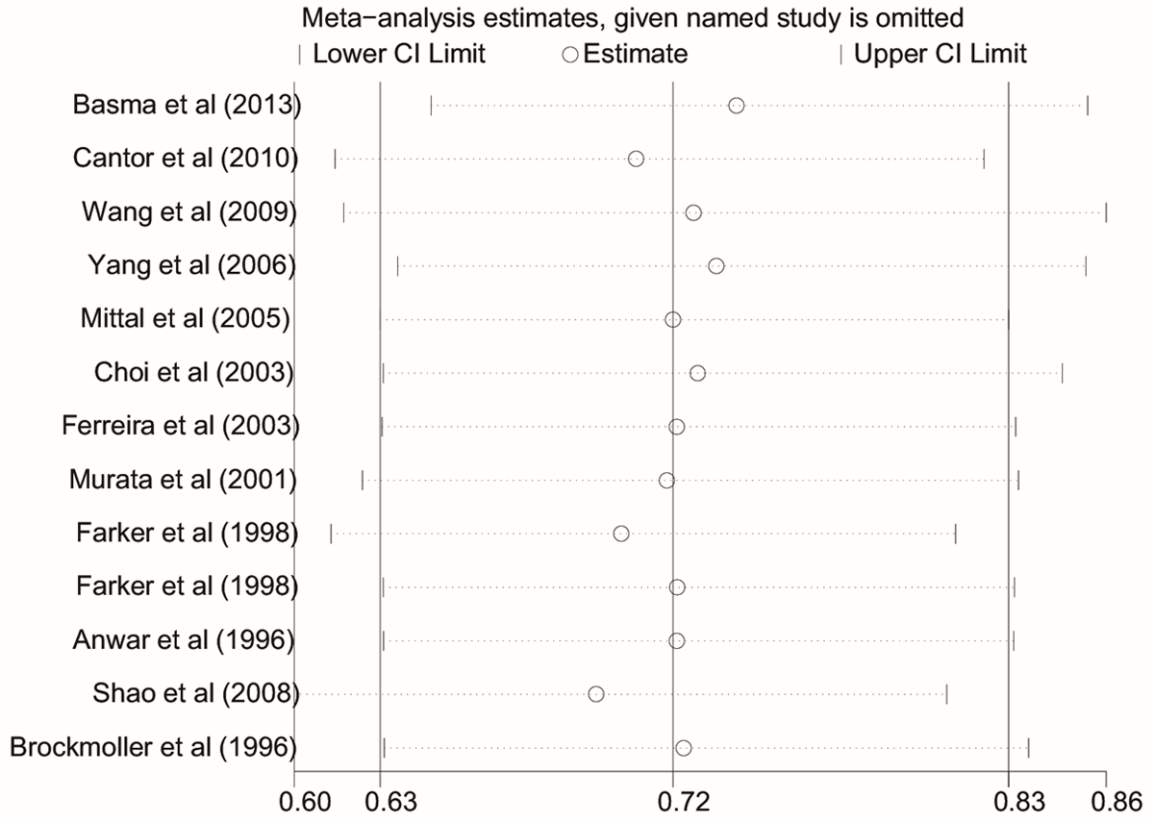

Figure 3. Sensitivity analysis of overall OR coefficients for dominant model (c2c2 + c1c2 vs. c1c1). The horizontal axis shows the omitted study. Every circle indicates the pooled odds ratio when the left study is removed from the meta-analysis. The horizontal axis represents the odds ratio. The two ends of each broken line represent the lower and upper 95% confidence interval.

RsaI/PstI polymorphism and urologic cancer risk was found in Asians (c2 vs. c1: OR = 0.753, 95% CI = 0.660-0.858; c2c2 vs. c1c1: OR = 0.537, 95% CI = 0.357-0.809; c1c2 vs. c1c1: OR = 0.744, 95% CI = 0.634-0.874; c2c2 + c1c2 vs. c1c1: OR = 0.722, 95% CI = 0.618-0.844; c2c2 vs. c1c1 + c1c2: OR = 0.597, 95% CI = 0.401-0.832). However, only two genetic models in Caucasians showed significant result (c2 vs. c1: OR = 0.696, 95% CI = 0.527-0.918; c2c2 + c1c2 vs. c1c1: OR = 0.722, 95% CI = 0.536-0.973) (**Figure 2B**). When stratified by genotyping method, we came up with the same result by analyzing the eleven studies used PCR-RFLP method. A summary of the meta-analysis findings of the association between *CYP2E1* RsaI/PstI gene polymorphism and urothelial cancer risk is provided in **Table 2**.

Sensitivity analysis

In the sensitivity analysis, when each particular study had been removed, meta-analyses were conducted repeatedly. The corresponding pooled ORs were not qualitatively altered with or without this study. As shown in **Figure 3**, the most influencing single study on the overall pooled OR estimates seemed to be the one conducted by Shao et al. However, after removal of the study, the result of the meta-analysis was not influenced significantly (c2c2 + c1c2 vs. c1c1: OR = 0.698, 95% CI: 0.601-0.809), indicating high stability of our results.

Heterogeneity analysis

The *p* values of the *Q* testin all genetic models were more than 0.10 (c2 vs. c1: *P* = 0.236;

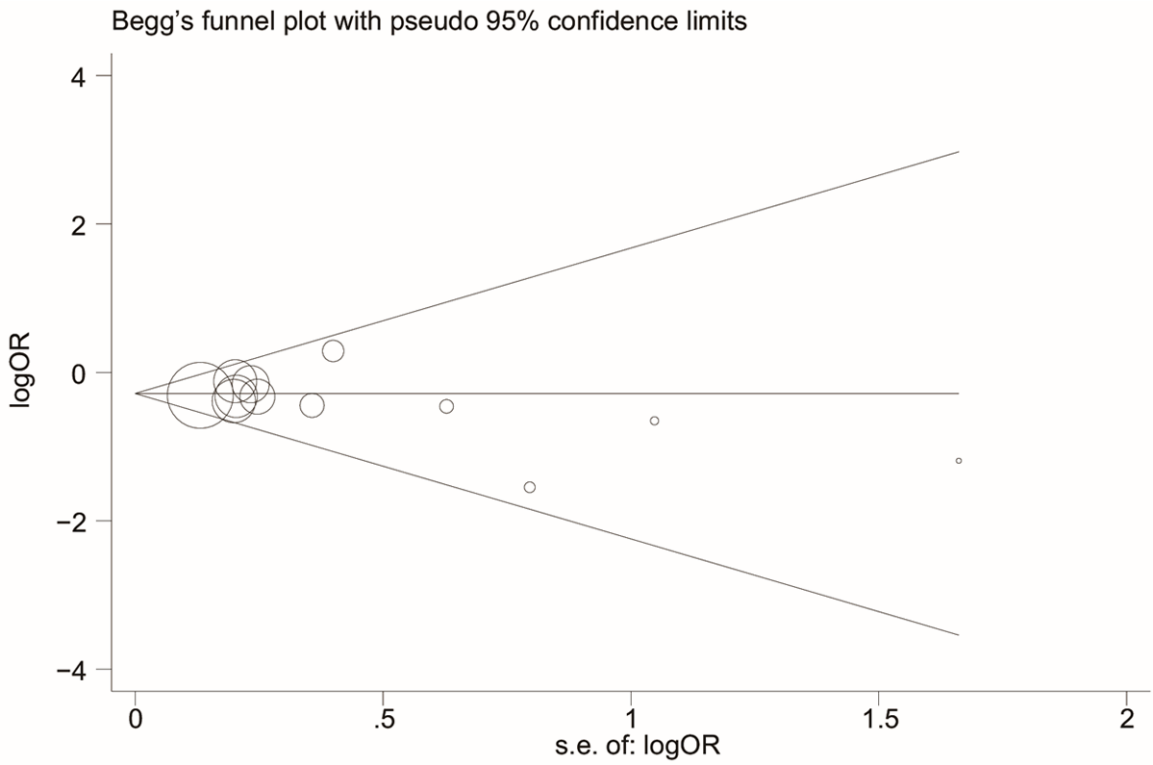

Figure 4. Begg's funnel plot for publication bias test under heterozygous model (c1c2 vs. c1c1). Each point represents a separate study for the indicated association. The circles represent the weight of individual study.

c2c2 vs. c1c1: P = 0.203; c1c2 vs. c1c1: P = 0.837; c2c2 + c1c2 vs. c1c1: P = 0.497; c2c2 vs. c1c1 + c1c2: P = 0.268). The results indicated a lack of heterogeneity, and the fixed-effects model was subsequently used to calculate the summary ORs.

Publication bias

Begg's rank correlation method and Egger's weighted regression method were used to assess publication bias. The results implied slight publication bias in *CYP2E1* RsaI/PstI (Begg's test P = 1, Egger's test P = 0.928, t = -0.09). We also present funnel plot for ORs of c2c2 + c1c2 vs. c1c1 (**Figure 4**).

Discussion

Environmental factors and Genetic predisposition are known as the underlying etiology of urologic cancer [38-42]. The deleterious substance intake through dietary, living environment and occupational exposure influences urologic cancer incidence and mortality [43-45]. Phase I metabolism genes, including Cytochrome P450s, are involved in the metabolism of these carcinogens [46]. Cytochrome P450s are enzymes that catalyze various phase I metabolism actions, such as C-, N- and S-oxidation and dealkylation [47]. CYP2E1 is a member of Cytochrome P450s and a major catalyst for metabolic activation of N-nitrosamines [48, 49]. N-nitrosaminespresent in tobacco and other etiological agents involved in the development of multiple urologic cancers [50-52]. The RsaI/PstI polymorphism in the promoter region of CYP2E1 gene has been reported to influence the transcriptional activity of CYP2E1 [8]. Therefore, functional *CYP2E1* RsaI/PstI polymorphism may have an impact on the metabolism of some carcinogens like N-nitrosamines, and further affect susceptibility of urologic cancer. In recent years, increasing studies have considered *CYP2E1* for genetic predisposition to urologic cancer. Though RsaI/PstI polymorphism in *CYP2E1* has been reported to be associated with the risk of urologic cancer [26-37], the results were controversial. Basma, Wang, Yang and Choi [26, 28, 29, 36] reported that c2 variant allele significantly decreased the risk of urologic cancer, while no

significant association was found in other studies [27, 31-35, 37]. This is the first systematic study of the meta-analysis of relationship between *CYP2E1* RsaI/PstI polymorphism and urologic cancer.

The current meta-analysis-including a total of 2712 cases and 2977 controls from 12 case-control studies [26-31, 34-37] in Caucasians and Asians-revealed the association between the RsaI/PstI polymorphism in *CYP2E1* gene and the risk of urologic cancer. This significant associationindicated that the c2 allele or c2c2 homozygote carriers have a decreased risk of urologic cancer. Although Hardy-Weinberg disequilibrium existed in one study [26], two independent analyses including or excluding this study showed the same results. When stratifying the source of controls, we surprisingly found that the association was significant among studies using the HB but not PB controls. We suppose that this may be due to the little case size of PB subgroup. In the subgroup analysis with different cancer types, decreased cancer risk was indicated to correlate with c2 allele of RsaI/PstI polymorphism in urothelial cancer under all genetic models and prostate cancer under four genetic models. Since there was only one study including renal cancer and the sample size of it was small, the result concerning renal cancer should be treated with caution. As for different ethnicities, *CYP2E1* RsaI/PstI c2c2 genotype and c2 allele were associated with decreased risk of urologic cancer in Asians, while we didn't find this close association in Caucasians. This reflects the role of ethnicity in gene polymorphisms and caner susceptibility [53].

Environmental factors and lifestyles such as smoking status, diet and alcohol consumption can influence urologic cancer development [40, 54, 55]. Choi et al. also discovered that CYP2E1 RsaI/PstI polymorphism modifies the effect of smoking on urologic cancer risk [28]. Because the original data of that of the eligible studies were unavailable, it was difficult for us to evaluate the roles of smoking status in developing urologic cancer. However, it is also reasonable to suppose that urologic cancer susceptibilities would be synergistically decreased in the non-smoking population with c2 allele of *CYP2E1*, for combined effect of genetic and environmental factors.

This meta-analysis is potentially limited in the following ways. First, the number of publication in total and particular subgroup analysis was relatively small. Second, selection bias might exist given the fact that some included studies are hospital-based controls. Hospital-based controls may not be always truly on behalf of the general population, and may thus underestimate the cancer risk. Third, due to limited individual data, the subgroup analysis was unable to be carried out by other categories such as age, gender, or environmental factors.

In summary, in this meta-analysis of 12 eligible studies, we found that the *CYP2E1* RsaI/PstI polymorphism may be associated with the overall risk of urologic cancer, and the C2 allele is a protective factor which decreased the risk of urologic cancer. Similar results were shown in subgroup analyses (urothelial cancer, prostate cancer and Asians). Further high quality studies are warranted to validate these results.

Disclosure of conflict of interest

None.

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