RESEARCH ARTICLE

Functional *RsaI/PstI* Polymorphism in Cytochrome P450 2E1 Contributes to Bladder Cancer Susceptibility: Evidence from a Meta-analysis

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Abstract

Background: Cytochrome P450 2E1 (CYP2E1) might be involved in the development of bladder cancer. However, previous studies of any association between CYP2E1 *RsaI/PstI* polymorphism and bladder cancer risk have yielded conflicting results. In this study, we performed a more precise estimation of the relationship by a meta-analysis based on the currently available evidence from the literature. Method: To assess the effect of CYP2E1 *RsaI/PstI* polymorphism on bladder cancer susceptibility, a meta-analysis of 6 available studies with 1,510 cases and 1,560 controls were performed through Feb 2014. Summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to estimate the strength of association for CYP2E1 *RsaI/PstI* polymorphism under different genetic models. Results: When available studies were pooled into the meta-analysis, we found that the C1C2 and C2C2 genotypes of CYP2E1 *RsaI/PstI* polymorphism significantly decreased bladder cancer risk under different genetic models (heterozygote: OR=0.766, 95%CI=0.613-0.957, P_{OR}=0.019; homozygote: OR=0.51, 95%CI=0.303- 0.858, P_{OR}=0.011; dominant: OR=0.733, 95%CI=0.593-0.905, P_{OR}=0.004; recessive: OR=0.565, 95%CI=0.337-0.947, P_{OR}=0.030). Subgroup analysis indicated that C2C2 genotype was significantly associated with decreased bladder cancer risk under the homozygote genetic model in Caucasians. There was no evidence of heterogeneity or publication bias. Conclusions: The current meta-analysis suggested that the CYP2E1 *RsaI/PstI* polymorphism might be associated with bladder cancer susceptibility, especially in Caucasians. Further studies are needed to validate the above conclusion.

Keywords: Cytochrome P450 2E1 - SNP - genetic susceptibility - bladder cancer - meta-analysis

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Introduction

Bladder cancer was the ninth most common malignancy and the thirteenth most common cancer-related cause of mortality in the world, which was a complex disorder with both environmental and genetic influences (Parkin, 2008). The major environmental factors included tobacco smoking and occupational exposures (Clapp et al., 2008; Strope and Montie, 2008), which could cause DNA damage, such as cross-links, bulky adducts and single or double strand breaks resulting in unregulated cell growth and even cancer (Johansson et al., 1990; Hoeijmakers, 2001; Yue et al., 2009). Nevertheless, only a small proportion of the individuals exposed to these environmental factors eventually developed bladder cancer, indicating that host genetic factors may play an important role in bladder carcinogenesis (Taioli and Raimondi, 2005). A few gene polymorphisms associated with bladder cancer risk have been identified. Metabolizing enzymes were involved in the bioactivation and detoxification of xenobiotics, particularly the cytochrome P450 2E1 (CYP2E1), and its polymorphisms might be associated with bladder cancer risk (Gonzalez, 2005).

The CYP2E1 gene, located on chromosome 10q26.3, is a member of the CYP450 superfamily, is constitutively expressed in various organs and tissues including urothelial cells (Sheweita et al., 2001). It is a key ethanol-inducible enzyme in the metabolic activation of many low-molecular-weight carcinogens, such as vinyl chloride, benzene, and tobacco-specific nitrosamines (Guengerich et al., 1991; Yamazaki et al., 1992). Of the many known CYP2E1 genetic polymorphisms, *RsaI/PstI* polymorphism in the 5'-flanking region were in close linkage disequilibrium and affected the transcriptional activation of the gene (Hayashi et al., 1991). The wild allele (C1) and/or the less mutant allele (C2) of CYP2E1 *RsaI/PstI* polymorphism have been reported as conferring higher risk for developing liver, esophageal and lung cancer by meta-analysis (Wang et al., 2009; Leng et al., 2012; Tian et al., 2012). Therefore, the CYP2E1 *RsaI/PstI*

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Table 1. Characteristics of Eligible Studies

Author (Year)	Ethnicity (Country)	Case/controls	Genotype of cases/controls (n)			HWE	Genotyping	Matching criteria	
		(n)	C1C1	C1C2	C2C2			Age	Gender
Shao J (2008)	Asia (China)	202/272	131/170	62/91	9/11	Yes	PCR-RFLP	Yes	Yes
Basma HA (2013)	Caucasian (Lebanon)	45/85[a]	36/46	2/12	7/27	No	PCR-RFLP	Yes	Yes
Mittal RD (2005)	Asia (India)	50/50	50/50	0/0	0/0	No	PCR-RFLP	NA	Yes
Choi JY (2003)	Asia (Korea)	214/194[a]	124/93	86/89	4/12	Yes	PCR-RFLP	Yes	No
Cantor KP (2010)	Caucasian (Spain)	627/611[a]	590/569	37/42	0/0	Yes	GoldenGate assay	Yes	Yes
Brockmoller J (1996)	Caucasian (Germany)	372/348	358/328[a]	14/20[a]	0/0	Yes	PCR-RFLP	Yes	Yes

[a]Data were counted by our ourselves due to unavailable data directly

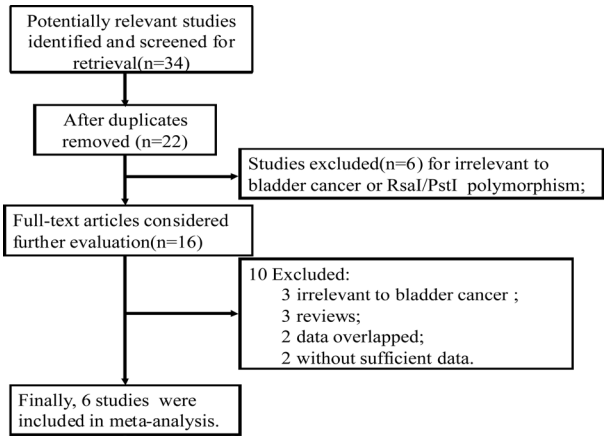

Figure 1. Flow Diagram of Included/Excluded Studies

polymorphism was believed to be risk factors for bladder cancer.

The associations of the CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer susceptibility have been extensively studied (Brockmoller et al., 1996; Choi et al., 2003; Mittal et al., 2005; Shao et al., 2008; Cantor et al., 2010; Basma et al., 2013). However, these studies yielded contradictory results, some studies showing significant association (Choi et al., 2003; Cantor et al., 2010; Basma et al., 2013), while others did not show such association, even in the same population (Brockmoller et al., 1996; Mittal et al., 2005; Shao et al., 2008). The inconsistency results might be resulted from a single study and the relatively small sample size, which had lower statistical power to detect the overall effects. Therefore, a quantitative synthesis of the combined data from different studies was necessary to estimate the association between CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer risk. In our study, we performed a systematic review and meta-analysis of the currently available literatures of the literature to clarify the accurate relationship between CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer risk.

Materials and Methods

Identification and eligibility of relevant studies

We conducted a comprehensive search in the PubMed, Medline, Embase, and Web of Science databases for all literatures about the association between CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer (updated on Feb, 2014). Search term combinations were as follows: (Cytochrome P4502E1 or CYP2E1), (polymorphisms or SNPs or mutation or variant or variation) and (bladder cancer or bladder neoplasm or bladder tumor). All reference lists from the main literatures and relevant reviews were hand searched for additional eligible studies. Only those studies assessing the association between the CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer risk were included in this meta-analysis: (1) Case-control studies (retrospective or nested case-control); (2) Only English language articles reporting human studies were considered; (3) Studies with available data for estimating odds ratios (ORs) and the 95% confidence interval (CI); (4) For duplicated publications, only the study with the largest sample numbers was included; (5) We did not define a minimum number of cases or controls in the meta-analysis.

Data extraction

Information was independently extracted from all eligible publications by two investigators (Deng XD and Qin Gao) according to the inclusion criteria. The original extraction data were checked by Ma Y, and in case of disagreement, an agreement was reached after a discussion. For each of the eligible case-control studies, the following data were recorded: first author's last name, year of publication, ethnicity, country, number of cases and controls, number of different genotypes in cases and controls, Hardy-Weinberg equilibrium (HWE), genotyping methods, matching criteria. The main data of eligible studies are presented in Table 1. Different ethnicity descents were categorized as Asian, Caucasian, and African.

Statistical analysis

The HWE was assessed by Fisher's exact test and *P* value less than 0.05 was considered significant. Summary ORs with corresponding 95%CIs were used to evaluate the strength of association between CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer risk under different genetic models, including heterozygote (C1C2 vs C1C1), homozygote (C2C2 vs C1C1), dominant (C2C2/C1C2 vs C1C1), and recessive (C2C2 vs C1C1/C1C2) genetic model. The Q test and I^2 statistics were evaluated to test statistical heterogeneity among studies (Higgins and Thompson, 2002). Pooled ORs estimation of each study was calculated by the fixed effects model (Mantel and Haenszel, 1959) or the random effects model (DerSimonian and Laird, 1986) according to the heterogeneity. The fixed-effects model was adopted when the studies were found to be homogeneous (P_Q>0.1 and I^2<50%). Otherwise, the random-effects model was applied. Subgroup analysis was conducted by ethnicity.

Table 2. Main Analysis of the CYP2E1 RsaI/PstI Polymorphism and Bladder Cancer Risk

	Studies	Heterozygote (C1C2 vs C1C1)		Homozygote (C2C2 vs C1C1)		Dominant (C2C2/C1C2 vs C1C1)		Recessive (C2C2 vs C1C1/C1C2)	
	(cases/controls)	ORs (95%CI)[a] ; P_{OR}	P_Q, I^2 (%)[b]	ORs (95%CI)[a]; P_{OR}	P_Q, I^2 (%)[b]	ORs (95%CI)[a]; P_{OR}	P_Q, I^2 (%)[b]	ORs (95%CI)[a]; P_{OR}	P_Q, I^2 (%)[b]
Total	6 (1510/1560)	0.766 (0.613-0.957)	0.601	0.510 (0.303-0.858)	0.375	0.733 (0.593-0.905)	0.264	0.565 (0.337-0.947)	0.486
		0.019	0	0.011	6.5	0.004	22.6	0.03	0
Orig									
Caucasian	3 (1044/1044)	0.706 (0.490-1.019)	0.226	0.398 (0.173-0.915)	0.643	0.598 (0.338-1.058)c	0.094	0.460 (0.201-1.051)	0.728
		0.063	32.7	0.03	0	0.077	57.6	0.065	0
Asian	3 (466/516)	0.803 (0.607-1.063)	0.777	0.603 (0.309-1.178)	0.149	0.784 (0.599-1.027)	0.54	0.649 (0.334-1.261)	0.188
		0.125	0	0.139	47.5	0.077	0	0.202	40.3

[a]95% confidence intervals, [b]P_Q value of Q-test for heterogeneity test, and associated $I^2$are shown, [c]Random-effects model was used when I^2>50% and/or P_Q<0.1;otherwise, Fixed-effects model was used

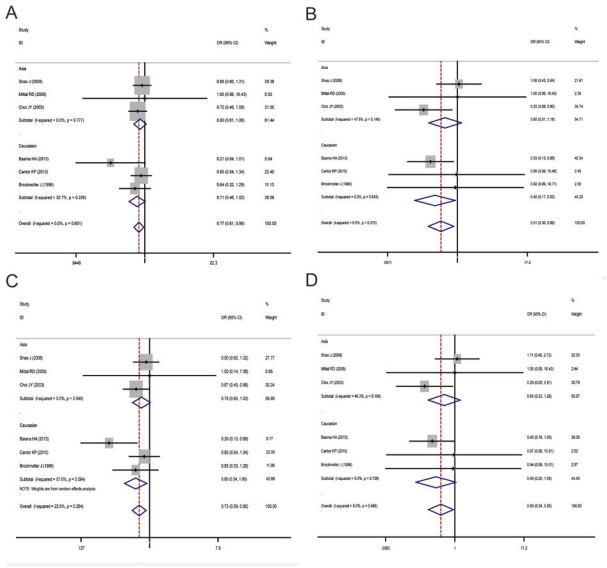

Figure 2. Forest Plots of Bladder Cancer Risk Significantly Associated with the CYP2E1 RsaI/PstI Polymorphism under under Different Genetic Models. (A) Heterozygote model. (B) Homozygote model. (C) Dominant model. (D) Recessive model

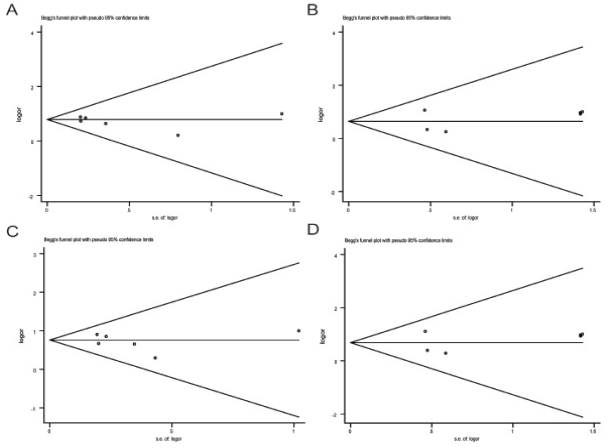

Figure 3. Begg's Funnel Plots of CYP2E1 RsaI/PstI Polymorphism and Bladder Cancer Risk for Publication Bias Test under Different Genetic Models. (A) Heterozygote model. (B) Homozygote model. (C) Dominant model. (D) Recessive model

Sensitivity analysis was carried out to assess the stability of the results. Publication bias among the literatures was assessed by Begg's funnel plot and Egger's regression asymmetry test. All statistical tests were performed by Stata software, version 11.0 (STATA Corp, College Station, TX).

Results

Study characteristics

Figure1 show that relevant studies were retrieved and preliminarily screened. In total, 6 publications including 1, 510 cases and 1, 560 controls met the inclusion criteria (Brockmoller et al., 1996; Choi et al., 2003; Mittal et al., 2005; Shao et al., 2008; Cantor et al., 2010; Basma et al., 2013). The characteristics of the studies included in this meta-analysis are summarized in Table1. Among the 6 studies, there were 3 studies of Asians (Choi et al., 2003; Mittal et al., 2005; Shao et al., 2008), and 3 studies of Caucasians (Brockmoller et al., 1996; Cantor et al., 2010; Basma et al., 2013). The sample size varied considerably among the studies, ranging from 100 (Mittal et al., 2005) to 1238 (Cantor et al., 2010). The genotyping methods among all studies were consistent with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) except Cantor's study by GoldenGate assay (Cantor et al., 2010). Controls were mainly matched by age and sex. The genotype distributions of the controls in 2 studies were not consistent with HWE (Mittal et al., 2005; Basma et al., 2013).

Main results of meta-analysis

The main results of the meta-analysis and heterogeneity test are listed in Table 2. Currently meta-analysis suggested a significant association of the CYP2E1 *RsaI/PstI* polymorphism with bladder cancer risk under all genetic model (heterozygote: OR=0.766, 95%CI=0.613-0.957, P_{OR}=0.019; homozygote: OR=0.51, 95%CI=0.303- 0.858, P_{OR}=0.011; dominant: OR=0.733, 95%CI=0.593-0.905, P_{OR}=0.004; recessive: OR=0.565, 95%CI=0.337-0.947, P_{OR}=0.030). Subgroup analysis by ethnicity showed that CYP2E1 *RsaI/PstI* polymorphism C2C2/C1C2 significantly decreased risk of bladder cancer among the Caucasians under homozygote genetic model (homozygote: OR=0.398, 95%CI=0.173-0.915, P_{OR}=0.030) (Figure 2), but not in Asians.

All I^2 values of heterogeneity were less than 50% and P_Q values were greater than 0.10 in overall, unfortunately, significant heterogeneity with subgroup analysis were found in Caucasians under dominant genetic models (dominant: I^2=57.6%, P_Q=0.094, P_{OR}=0.077, OR=0.598, 95%CI=0.338-1.058) (Table 2). Due to only 3 studies in Caucasians, we failed to explore the sources of heterogeneity.

Sensitivity analysis and Publication bias

Sensitivity analysis was carried out by sequential omission of individual studies. The significance of

summary ORs was not influenced excessively by omitting any single study under different genetic models, indicating that currently meta-analysis results were statistically reliable.

The shape of funnel plots did not show any evidence of obvious asymmetry under all genetic model (Figure 3), and the result s of Egger's test did not reveal any evidence of publication bias (P>0.361).

Discussion

Bladder cancer is increasing common cancer which is likely to be caused by multi-factors, including environmental, genetic and their interactions factors (Parkin, 2008). Only environmental factor cannot explain the phenomenon completely, and then genetic factors may play an important role. In recent years, genetic susceptibility was used to evaluate the risk of bladder cancer, but the results were inconsistent. In our study, we conducted a systematic review and meta-analysis to confirm the accurate relationship between the CYP2E1 *RsaI*/*PstI* polymorphism and bladder cancer risk.

In current meta-analysis, we found that the CYP2E1 *RsaI*/*PstI* polymorphism were significantly associated with bladder cancer susceptibility including 6 case-control studies, especially in Caucasians (Table 2). It was indicated that the C2 carrier genotypes of CYP2E1 *RsaI*/*PstI* polymorphism might be a protective factor which decreased the risk of bladder cancer. The bladder was prone to expose under carcinogens which were known to induce DNA strand breaks in the bladder epithelium cell due to being the urine collecting area (Johansson et al., 1990; Hoeijmakers, 2001; Yue et al., 2009). The CYP2E1 played an important role in the metabolic activation of low molecular weight compounds and pro-carcinogens such as benzene, N-nitrosamines, and halogenated hydrocarbons, which might be involved in bladder cancer development (Guengerich et al., 1991; Yamazaki et al., 1992). The population and molecular biological studies indicated that the C2 allele or the C2 carrier genotypes of the CYP2E1 *RsaI*/*PstI* polymorphism had a lower ethanol- induced enzyme activity and basal CYP2E1 activity because the CYP2E1 PstI and RsaI restriction sites located in the transcription-regulation region might affect transcriptional activity, and decrease/lose the inducibility to pro-carcinogen (Uematsu et al., 1991; Lucas et al., 1995; Carriere et al., 1996; Kim et al., 1996). Although studies showed that the C2/C2 genotype produced higher enzyme activity than the Cl/Cl genotype in vitro (Hayashi et al., 1991; Ladero et al., 1996). However, this finding could not be verified in several in vivo and in vitro phenotyping studies (Kim and O'Shea, 1995; Lucas et al., 1995; Carriere et al., 1996; Kim et al., 1996). Additionally, a number of studies have suggested that individuals with C2 allele have lower risk in developing cancers of the lung, liver, and esophagus (Persson et al., 1993; Yu et al., 1995; Le Marchand et al., 1998; Lin et al., 1998). Thus, in view of the role of CYP2E1 in the metabolic activation of pro-carcinogen and our results suggesting a protective effect of the C2/C2 genotype against bladder cancer, we consider that this genotype may result in poor CYP2E1 activity/inducibility toward bladder epithelial cells pro-carcinogens than the corresponding Cl/Cl genotype. Unfortunately, due to power limitations, ethnic difference and the fact that other contributors of CYP2E1 variability were not adjusted, other studies have not found such a relation (Hirvonen et al., 1993; London et al., 1996). Although the explanation for the discordancy is unknown, power limitations, ethnic difference and other contributors of sex, dietary, age and smoking, for example, may be provide a mechanistic explanation (Zgheib et al., 2010).

Subgroup analysis based on the ethnic showed that Caucasians with carried the C2 genotypes had a decreased risk of bladder cancer, but not in Asians. It was indicated that the genetic diversity and variants among different ethnicities or populations might contribute to cancer risk (Shahriary et al., 2012; Lakkakula et al., 2013). Although the underlying mechanisms were not clear, ethnic diversity might affect bladder cancer risk. The study showed that the C2 allele frequencies of Asians (~25-50%) were significantly higher than those of Caucasians (~5-10%) (Stephens et al., 1994). Of course, it might also exist in weak effect or some selection bias due to small sample size. Further investigations are needed to confirm the possible effects of CYP2E1 *RsaI*/*PstI* polymorphism on bladder cancer risk, such as gene-gene and gene-environment interaction from different genetic background and lifestyles, in which it may play a role.

Although this meta-analysis has been recognized as a more precise and systematic method to evaluate the effect of selected genetic polymorphisms on the risk of disease than single case-control study and cohort study (Munafo and Flint, 2004), some limitations should be acknowledged in this meta-analysis. Firstly, bladder cancer was considered to be a multi-factorial disease, interacted by environmental factors and many genetic factors. A major route of metabolism from the body for most drugs and chemical carcinogens is mainly constituted by drug-metabolizing enzymes (DMEs) with phase I oxidation enzymes and phase II enzymes system. Cytochrome P450 (CYP) is the most important phase I enzymes system, which is usually involved in the activation of carcinogens; and phase II enzymes, particularly N-acetyltransferase (NAT) and glutathione s-transferase (GSTs), which mostly detoxify the products to be excreted in the urine and possibly played an important role in cancer etiology (Steck and Hebert, 2009; Zgheib et al., 2010). Although studies suggested that CYP2E1 genetic polymorphisms have an impact on the incidence of cancer (Danko and Chaschin, 2005), epidemiological studies suggest that the NAT1, NAT2, GSTM1 and GSTP1 polymorphisms modify the risk of developing cancers of the urinary bladder (Zhang et al., 2012; Pandith et al., 2013; Zabost et al., 2013). Therefore, not only is CYP2E1 suspected to be involved with the development of bladder cancer, but also other DMEs genetic factors may be associated with bladder cancer. However, lacking the original data of gene-environment and gene-gene interactions limited a more precise analysis. Secondly, in the current meta-analysis, only six studies were collected, statistical power was limited to assess the effects well. Thus, the results should be interpreted with caution.

In summary, the present meta-analysis suggested that CYP2E1 *RsaI/PstI* polymorphism might be associated with bladder cancer risk in Caucasians. However, further studies with larger sample sizes and well-designed randomized studies in various ethnicities are needed to verify this association comprehensively.

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