RESEARCH ARTICLE

Updated Meta-analysis of the Association Between *CYP2E1 RsaI/PstI* Polymorphisms and Lung Cancer Risk in Chinese Population

Ya-Dong Wang[1&*], Hai-Yan Yang[2&], Jing Liu[2], Hai-Yu Wang[1]

Abstract

Background: A number of studies have reported relationships of *CYP2E1 RsaI/PstI* polymorphisms with susceptibility to lung cancer in Chinese population. However, the epidemiologic results have been conflictive rather than conclusive. The purpose of this study was to address the associations of *CYP2E1 RsaI/PstI* polymorphisms with lung cancer risk in Chinese population comprehensively. Materials and Methods: Systematic searches were conducted in the PubMed, Science Direct, Elsevier, CNKI and Chinese Biomedical Literature Databases. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of association. Results: Overall, we observed a decreased lung cancer risk among subjects carrying *CYP2E1 RsaI/PstI* c1/c2 and c1/c2+c2/c2 genotypes (OR=0.76, 95%CI: 0.64-0.90 and OR=0.78, 95%CI: 0.66-0.93, respectively), as compared with subjects carrying the c1/c1 genotype. In subgroup analysis, we observed a decreased lung cancer risk among c1/c2 carriers in hospital-based studies (OR=0.81, 95%CI: 0.68-0.98) and among carriers with c1/c2 and c1/c2+c2/c2 genotypes in population-based studies(OR=0.57, 95%CI: 0.42-0.79 and OR=0.58, 95%CI: 0.43-0.79, respectively), as compared with subjects carrying the c1/c1 genotype. Limiting the analysis to studies with controls in Hardy-Weinberg equilibrium (HWE), we similarly observed a decreased lung cancer risk among c1/c2 and c1/c2+c2/c2 carriers (OR=0.73, 95%CI: 0.60-0.88 and OR=0.73, 95%CI: 0.60-0.88, respectively), as compared with c1/c1. Conclusions: Our results suggested that *CYP2E1 RsaI/PstI* c1/c2 and c1/c2+c2/c2 variants might be a protective factor for developing lung cancer in Chinese population. Further well-designed studies with larger sample size are required to verify our findings.

Keywords: CYP2E1 - RsaI/PstI - polymorphism - lung cancer - meta-analysis - Chinese

Asian Pac J Cancer Prev, **15 (13)**, 5411-5416

Introduction

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally, and among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death (Jemal et al., 2011). In the United States, an estimated 228,190 new cases of lung cancer are expected in 2013, accounting for about 14% of cancer diagnoses and an estimated 159,480 deaths, accounting for about 27% of all cancer deaths, are expected to occur in 2013 (Siegel et al., 2013). In China, lung cancer was increased 465% during the past 30 years and became the leading cause of cancer-related death in the current decade as well. The World Health Organization (WHO) estimated that more than a million Chinese will be diagnosed with lung cancer in each year by the year of 2025 (Zhao et al., 2010; Liu et al., 2014).

Lung cancer is associated strongly with environmental exposures (Luqman et al., 2014; Phukan et al., 2014). However, only a minority of those who have been exposed to these risk factors will develop lung cancer, suggesting that other potential factors such as genetic polymorphism, might contribute to the difference in host's susceptibility to lung cancer (Wang et al., 2010b; Zhou et al., 2013). This genetic susceptibility may derive from inherited polymorphisms in genes involved in the metabolism of xenobiotic chemical carcinogens (Shields et al., 2000; Shah et al., 2008). Results from published studies have shown that the variations of drug-metabolizing enzymes including cytochrome P450 (CYP), microsomal epoxide hydrolase 1 (EPHX1), glutathione S-transferase (GST), NAD(P)H quinone oxidoreductase 1 (NQO1), myeloperoxidase (MPO) and arylamine N-acetyltransferases (NATs) were associated with the sensitivity of lung cancer (Kiyohara et al., 2005; Agundez, 2008; Liu et al., 2013; Wang et al., 2013; Zhou et al., 2013).

Cytochrome P450 2E1 (CYP2E1), a member of cytochrome P450 superfamily, plays an important role in the detoxification of xenobiotics and in the activation of

*[1]Department of Toxicology, Henan Center for Disease Control and Prevention, [2]Department of Epidemiology and Health Statistics, School of Public Health, Zhengzhou University, Zhengzhou, China [&]Equal contributors *For correspondence: wangyd76@163.com*

potential carcinogens found in the environment, such as N-nitrosoamines, benzene and benzo(a)pyrene. CYP2E1 gene is mapped to chromosome 10q24.3-qter (Lakkakula et al., 2013). It is 18,754bp long consisting of eight introns and nine exons, which encodes a membrane-bound protein of 493 amino acid residues with a molecular weight of ~57 kDa. CYP2E1 gene contains at least 34 variants to date (http://snp500cancer.nci.nih.gov), of which the RsaI/PstI [-1239G>C (rs3813867) and -999C>T (rs2031920)] polymorphisms in its 5'-flanking region has been shown to affect its transcription level. The variant type of this polymorphic site could enhance the transcription and increase the level of CYP2E1 enzymatic activity in vitro (Hayashi et al., 1991; Liu et al., 2009).

A series of studies have investigated the associations between *CYP2E1 RsaI/PstI* polymorphisms and lung cancer risk in Chinese population (Qu et al., 1998; Persson et al., 1999; Wang et al., 1999; Huang et al., 2000; Li et al., 2000; Chen et al., 2002; Shi et al., 2002; Wang et al., 2003; Zou et al., 2004; Gu et al., 2007; Li et al., 2008; Liu et al., 2010; Su et al., 2011; Guo et al., 2012; Li et al., 2012; Cao et al., 2013). However, the results from epidemiologic studies were inconsistent and controversial. Two meta-analyses have reported that the *CYP2E1 RsaI/PstI* c2 allele is a protective factor for developing lung cancer among Asians and all ethnic population (Wang et al., 2010b; Zhan et al., 2010). However, it is well established that the frequencies of *CYP2E1 RsaI/PstI* polymorphisms differ markedly among different ethnic and racial groups (Soya et al., 2005; Ulusoy et al., 2007; Shahriary et al., 2012; Lakkakula et al., 2013). Therefore, it is necessary to address this issue in different ethnic groups. Recently, two meta-analyses have reported the association of *CYP2E1 RsaI/PstI* polymorphisms with lung cancer risk in Chinese population (Wang et al., 2010a; Cao et al., 2013). Unfortunately, there are several limitations in these two papers. For example, one repeated article (Ye et al., 2006) was not excluded in Wang et al's paper (Wang et al., 2010a). For Cao et al's paper (Cao et al., 2013), some repeated articles were not excluded (Li et al., 2004; Wang et al., 2006; Ye et al., 2006), one paper was mistakenly included (Liang et al., 2004), three papers published before 2013 were missing (Liu et al., 2010; Su et al., 2011; Guo et al., 2012) and the number of case from one paper was not correct (Gu et al., 2007). Therefore, it is required to clarify the association between *CYP2E1 RsaI/PstI* variation and lung cancer risk in Chinese population objectively and comprehensively. In this study, we used the most updated data to address this issue by performing meta-analysis.

Materials and Methods

Literature and methods

We searched for studies in the PubMed, Science Direct, Elsevier, CNKI and Chinese Biomedical Literature Database with a combination of the terms: "CYP2E1/CYPIIE1" or "cytochrome P4502E1/IIE1" and "RsaI/PstI" or "rs3813867/rs2031920" and "lung cancer", "lung neoplasm" or "lung carcinoma" and "China" or "Chinese". The ending date was December 31, 2013.

Selection criteria were as follows: they (1) evaluated lung cancer risk and *CYP2E1 RsaI/PstI* polymorphisms in Chinese population; (2) were case-control studies or cohort studies; (3) included sufficient data to estimate odds ratio (OR) and their 95% confidence intervals (CI). Papers with incomplete information and reviews were excluded. For overlapping studies, the most recent publication with more information was selected.

In total, 31 published studies were identified with the association between *CYP2E1 RsaI/PstI* polymorphisms and lung cancer risk in Chinese population. We reviewed all papers in accordance with the criteria defined above and excluded 3 reviews and 12 repeated articles. Therefore, 16 studies were determined to enter this study.

Data extraction

Firstly, data were carefully extracted and tabulated by two data managers, and then inputted into an electric database, independently. The following data were subtracted from each eligible study: first author's surname, year of publication, source of controls, number of case and control, and OR and their 95%CI. Characteristics of individual study were summarized in Table 1.

Quantitative data synthesis

To estimate the association between *CYP2E1 RsaI/PstI* polymorphisms and lung cancer risk in Chinese population, we conducted a meta-analysis of identified studies. The Cochrane Q statistics test was used for the assessment of heterogeneity. The fixed-effects model and the random-effects model were used to compute the combined OR (DerSimonian et al., 1986). If the effects are assumed to be homogenous, the fixed-effects model is used; otherwise, the random-effects model is used. First, the funnel plot was drawn to evaluate publication bias visually, and then Egger's test and Begg's test were applied to test the publication bias further (Begg et al., 1994; Egger et al., 1997). We tested whether genotype frequencies of controls were in agreement with Hardy-Weinberg equilibrium (HWE) using the x^2 test.

Table 1. Studies on the Association between Genetic Polymorphisms of *CYP2E1 RsaI/PstI* and the Risk of Lung Cancer in Chinese Population Included in this Study

First author	Year	No. of case	No. of control	Source of control	HWE
(Qu et al., 1998)	1998	182	184	Hospital	0.002
(Wang et al., 1999)	1999	119	231	Hospital	0.437
(Persson et al., 1999)	1999	76	113	Population	0.635
(Huang et al., 2000)	2000	54	260	Hospital	0.039
(Li et al., 2000)	2000	92	137	Population	0.139
(Shi et al., 2002)	2002	120	120	Hospital	0.042
(Chen et al., 2002)	2002	91	138	Hospital	0.094
(Wang et al., 2003)	2003	164	181	Hospital	0.251
(Zou et al., 2004)	2004	41	61	Hospital	0.018
(Gu et al., 2007)	2007	279	684	Hospital	Not estimable
(Li et al., 2008)	2008	150	152	Hospital	0.155
(Liu et al., 2010)	2010	108	108	Population	0.28
(Su et al., 2011)	2011	64	64	Population	0.305
(Li et al., 2012)	2012	217	198	Hospital	0.877
(Guo et al., 2012)	2012	684	602	Hospital	0.907
(Cao et al., 2013)	2013	526	526	Hospital	0.619

*HWE, Hardy Weinberg Equilibrium

All of the statistical analyses were performed with Review Manager (Version 5. 0. 24, the Cochrane Collaboration) and STATA10.0 software package (Stata Corporation, College Station, Texas). All the tests were two-side, a P value of less than 0.05 for any test or model was thought to be statistically significant.

Results

Meta-analysis databases

We established a database according to the extracted information from each eligible paper. A total of 16 studies with 2967 cases and 3759 controls were included in this study. All essential information was listed in Table 1. Table 1 showed first author, year of publication, number of cases and controls, source of control and the P value of HWE.

Test of heterogeneity

The heterogeneities of *CYP2E1 RsaI/PstI* c1/c2 *vs* c1/c1, c2/c2 *vs* c1/c1, and c1/c2+c2/c2 *vs* c1/c1 were analyzed for 16 case-control studies. Our results indicated that there were no heterogeneities in the groups of *CYP2E1 RsaI/PstI* c2/c2 *vs* c1/c1, c1/c2 *vs* c1/c1 and c1/c2+c2/c2 *vs* c1/c1 for population-based study (Table 2). Therefore, we calculated the pooled OR for them with a fixed-effects model. The random-effects model was used to calculate the pooled OR for the rest.

Quantitative data synthesis

Table 2 listed the summary OR of *CYP2E1 RsaI/PstI* polymorphisms and lung cancer risk on the basis of 2967 cases and 3759 controls, a decreased lung cancer risk was observed among subjects carrying c1/c2 and c1/c2+c2/c2 genotypes in the total population compared with subjects carrying c1/c1 genotype, and the summary odds ratios were 0.76 (95%CI: 0.64-0.90) (Figure 1B) and 0.78 (95%CI: 0.66-0.93) (Figure 1C), respectively. However, we did not observe a relationship between c2/c2 *vs* c1/c1 and lung cancer risk in total population (Figure 1A). Summary odds ratios for *CYP2E1 RsaI/PstI* polymorphisms and lung cancer risk stratified by source of controls were evaluated, and a decreased lung cancer risk was observed among subjects with c1/c2 and c1/c2+c2/c2 genotypes in population-based control compared with subjects with c1/c1 genotype, the summary odds ratios were 0.57 (95%CI: 0.42-0.79) and 0.58 (95%CI: 0.43-0.79); a decreased lung cancer risk was observed among subjects with c1/c2 genotype in hospital-based control compared with subjects with c1/c1 genotype, the summary odds ratio was 0.81 (95%CI: 0.68-0.98) (Table 2). When stratified by HWE of control, a decreased lung cancer risk was observed among carriers with c1/c2 and c1/c2+c2/c2 genotypes in the controls in agreement with HWE compared with c1/c1 carries, the summary odds ratios were 0.73 (95%CI: 0.60-0.88) and 0.73 (95%CI: 0.60-0.88), respectively (Table 2).

Table 2. Summary Odds Ratios on the Relation of the *CYP2E1 RsaI/PstI* Site Polymorphism to Lung Cancer Risk in Chinese Population

Genotype	Case/Control	Heterogeneity test		Summary	Hypothesis test			Begg's test		Egger's test	
		Q	*P*	OR(95%CI)	Z	*P*	df	Z	*P*	t	*P*
c2/c2	1838/1940	30.07	0.007	0.93(0.59-1.45)	0.34	0.74	14	0.77	0.443	0.07	0.945
c1/c2	2564/2926	27.57	0.02	0.76(0.64-0.90)	3.15	0.002	14	0.99	0.322	1.33	0.205
c1/c2+c2/c2	2967/3759	35.56	0.002	0.78(0.66-0.93)	2.82	0.005	15	0.68	0.499	1.09	0.294
Stratification by source of control											
Population											
c2/c2	247/256	0.73	0.87	0.66(0.29-1.52)	0.97	0.33	3	0.34	1.000	1.59	0.252
c1/c2	330/406	3.53	0.32	0.57(0.42-0.79)	3.44	0.0006	3	0.34	0.734	1.08	0.392
c1/c2+c2/c2	340/422	2.53	0.47	0.58(0.43-0.79)	3.49	0.005	3	0.34	1.000	0.90	0.462
Hospital											
c2/c2	1591/1684	28.51	0.001	0.99(0.57-1.69)	0.05	0.96	10	0.00	1.000	0.25	0.808
c1/c2	2234/2520	19.45	0.03	0.81(0.68-0.98)	2.2	0.03	10	0.00	1.000	0.40	0.698
c1/c2+c2/c2	2627/3337	27.61	0.004	0.84(0.70-1.01)	1.85	0.06	11	0.21	0.837	0.18	0.860
Stratification by HWE											
Yes											
c2/c2	1577/1560	19.94	0.03	0.79(0.47-1.34)	0.86	0.39	10	0.72	0.474	0.73	0.485
c1/c2	2201/2341	16.93	0.03	0.73(0.60-0.88)	3.25	0.001	10	1.71	0.087	2.48	0.035
c1/c2+c2/c2	2291/2450	22	0.02	0.73(0.60-0.88)	3.2	0.001	10	0.93	0.350	1.42	0.188

*HWE, Hardy Weinberg Equilibrium

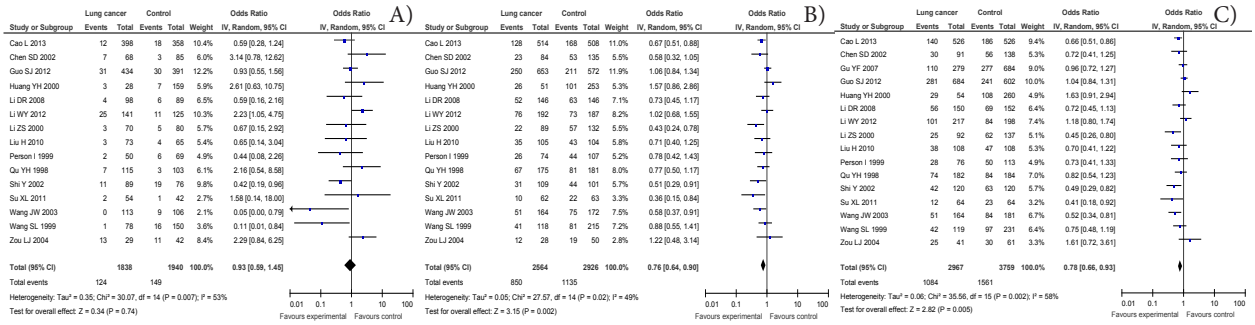

Figure 1. Forest Plots of Odds Ratio for c2/c2 *vs* c1/c1 (A), c1/c2 *vs* c1/c1 (B) and c1/c2+c2/c2 *vs* c1/c1 (C) of *CYP2E1 RsaI/PstI* Variant associated with Lung Cancer Risk in Chinese Population

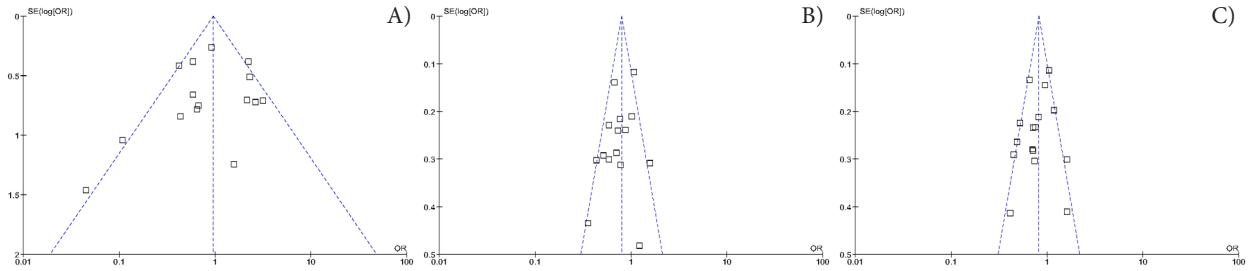

Figure 2. Funnel Plot Analysis to Detect Publication bias for c2/c2 *vs* c1/c1 (A), c1/c2 *vs* c1/c1 (B) and c1/c2+c2/c2 *vs* c1/c1 (C) of *CYP2E1 RsaI/PstI* Variant associated with Lung Cancer Risk in Chinese Population

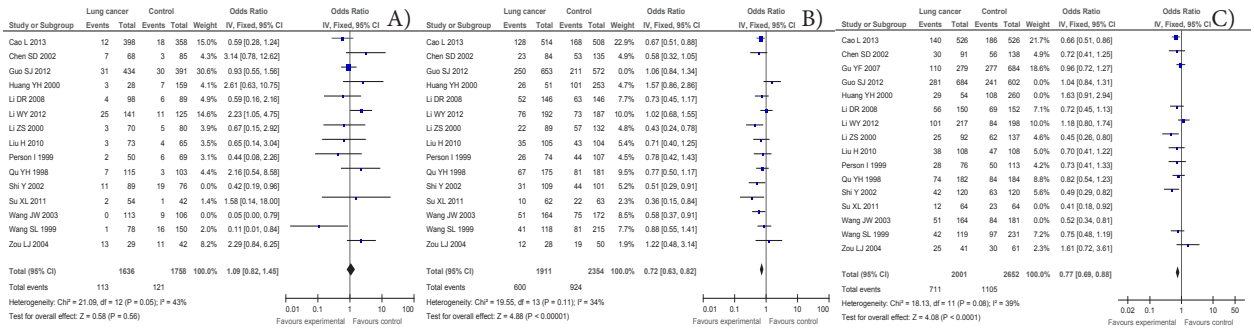

Figure 3. Sensitivity Analysis was Performed in this Study. The study was homogenous for c2/c2 *vs* c1/c1, while excluding Shi (2002, 31: 14-17) and Wang (2003, 94: 448-452). The summary OR was 1.09 (95%CI: 0.82-1.45) (A).The study was homogenous for c1/c2 *vs* c1/c1, while excluding Guo (2012, 7: e39814). The summary OR was 0.72 (95%CI: 0.63-0.82) (B). The study was homogenous for c1/c2+c2/c2 *vs* c1/c1, while excluding Guo (2012, 7: e39814), Huang (2000, 16: 350-352), Su (2011, 23: 107-111) and Wang (2003, 94: 448-452). The summary OR was 0.77 (95%CI: 0.69-0.88) (C)

Bias diagnosis

The shape of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 2A, 2B and 2C), which suggested that no potential publication bias existed. Results from Begg's test and Egger's test suggested that publication biases might not have significant effects on the results, except for *CYP2E1 RsaI/PstI* c1/c2 *vs* c2/c2 in the subgroup analysis of the control in agreement with HWE, because there was some uncertainty with the P value being equal to 0.035 in Egger's test (Table 2).

Sensitivity analyses

Sensitivity analyses were performed to identify the effects of the individual dataset on the pooled odds ratios by sequential omission of each eligible study. The overall effects were not modified when the studies were homogenous for c2/c2 *vs* c1/c1, c1/c2 *vs* c1/c1 and c1/c2+c2/c2 *vs* c1/c1 among total population by removing some eligible studies (Figure 3).

Discussion

Two polymorphic sites (CYP2E1 PstI and RsaI) were found to be in complete linkage disequilibrium in the 5'-flanking region of the human CYP2E1 gene in 202 unrelated healthy Japanese in 1990 (Watanabe et al., 1990). Latter, Hayashi et al found that genetic polymorphisms in RsaI/PstI restriction enzyme digestion sites changed transcriptional regulation of the human CYP2E1 gene (Hayashi et al., 1991). Recently, a number of epidemiologic studies have explored the relationship between *CYP2E1 RsaI/PstI* variations and lung cancer risk in Chinese population (Data listed in Table 1), however these findings were inconsistent, which urged us to perform this current meta-analysis, the aim of this study was to derive a precise estimate of the lung cancer risk associated with *CYP2E1 RsaI/PstI* polymorphisms. The main findings from this meta-analysis were that subjects carrying the *CYP2E1 RsaI/PstI* c1/c2 and c1/c2+c2/c2 genotypes had a decreased risk of lung cancer, compared with c1/c1 genotype carriers. However, it has been reported that the transcriptional activity of CYP2E1 c2/c2 genotype in HepG2 cells is ten times greater than that in HepG2 cells with c1/c1 genotype (Hayashi et al., 1991), suggesting that the transcriptional activity of the c2 allele is greater than that of the c1 allele. This previous experimental finding in vitro was not consistent with our present results.

Three studies focusing on to evaluate the relationship between *CYP2E1 RsaI/PstI* genotypes and phenotypes in population study supported our conclusions, to certain extent. For example, Marchand et al. found that the activity of CYP2E1 decreased with the number of variant c2 allele. The activity of CYP2E1 in c2/c2 genotype is lower than that in c1/c2 genotype, and the activity of CYP2E1 in c1/c2 genotype is lower than that in c1/c1 genotype (Marchand et al., 1999). Lucas et al' results showed that a substantially reduced chlorzoxazone 6-hydroxylation was observed in the single c2/c2 genotype carriers. Additionally, patients with the mutated genotype appeared to have less induction of CYP2E1 than wild-type carriers after ethanol administration (Lucas et al., 1995). Tan et al's results showed that the levels of CYP2E1 protein was significantly higher among subjects carrying the c1/c1 genotype than that among those carrying c1/c2 or c2/c2 genotype, and the mean activity of CYP2E1 towards

p-nitrophenol for the c1/c1 genotype was higher than that for the variant genotypes (Tan et al., 2001).

Some limitations inherent in this meta-analysis should be acknowledged. First, only published papers were included in this study. Therefore, publication bias may have occurred. To address this issue, Egger's test and Begg's test were applied. Our results indicated that the likelihood of key publication bias in the present study was negligible, except for c1/c2 *vs* c1/c1 in subgroup analysis of control in agreement with HWE. Secondly, each study had different eligibility criteria for subjects and different source of controls, which should be taken into account when expounding the pooled estimates. When studies were stratified by source of control, we observed a decreased risk of lung cancer among subjects carrying *CYP2E1 RsaI/PstI* c1/c2 and c1/c2+c2/c2 genotypes in population-based studies and a decreased risk of lung cancer among subjects carrying *CYP2E1 RsaI/PstI* c1/c2 genotype in hospital-based studies, compared with c1/c1 genotype carries. Thirdly, this meta-analysis is based on unadjusted estimate. Although the cases and controls were matched on age, sex and cigarette smoke in all studies, these confounding factors might slightly modify the effective estimates and a more precise analysis is needed to perform by the potentially suspected factors if detailed individual data were available.

It is widely acknowledged that, if the distribution frequency of genotypes in the controls deviated from Hardy-Weinberg equilibrium, the results from genetic association studies might be spurious (Salanti et al., 2005). To address this issue, subgroup analysis was conducted in this study by HWE in controls. When the studies that were not in agreement with HWE were excluded from this study, the results remained persistent and robust, suggesting that this factor might have no significant influences on the overall estimates in this study.

In summary, this updated meta-analysis suggested that *CYP2E1 RsaI/PstI* c1/c2 or c1/c2+c2/c2 polymorphisms might be a protective factor for developing lung cancer in Chinese population. Large studies with the pooling of individual data should be taken into account in the future association studies to verify results from this current meta-analysis and to further evaluate the effects of gene-gene and gene-environment interactions on the *CYP2E1 RsaI/PstI* polymorphisms-associated lung cancer risk in Chinese population.

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