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Association between *CYP2E1* genetic polymorphisms and lung cancer risk: A meta-analysis

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ABSTRACT

Genetic variations in metabolic genes are thought to modify the metabolic process of carcinogens and are suggested to be related to cancer risk. However, epidemiological results are not always consistent. In this meta-analysis, we assessed reported studies of associations between polymorphisms of *CYP2E1 RsaI/PstI* and *DraI*, and the risk of lung cancer. We found decreased lung cancer risk among subjects carrying *CYP2E1 RsaI/PstI* c1/c2 and c1/c2 + c2/c2 genotype [odds ratio (OR) = 0.80, 95% confidence interval (CI): 0.72–0.89 and OR = 0.82, 95% CI: 0.72–0.93, respectively], using 4436 cases and 6385 controls from 26 studies. We also observed a decreased lung cancer risk among subjects carrying c1/c2 and c1/c2 + c2/c2 genotypes in the Asian population and on the basis of population control in stratified analysis. We found a protective effect of the *CYP2E1 DraI* CC and CD + CC polymorphisms for lung cancer (OR = 0.58, 95% CI: 0.41–0.81 and OR = 0.84, 95% CI: 0.73–0.96, respectively). The meta-analysis suggests that *CYP2E1 RsaI/PstI* and *DraI* polymorphisms may affect the susceptibility of lung cancer, and a study with a larger sample size is needed to further evaluate gene–environment interaction on *CYP2E1* polymorphisms and lung cancer risk.

1. Introduction

Lung cancer is nowadays the most widespread cancer worldwide and is the most important and frequent type of lung tumour, representing over 90% of all cases of primary malignant and benign lung tumours.[1] There were 219,440 new cases expected in the United States in 2009, representing 14.8% of total cancer incidence. It was also the main cause of death of all cancers, killing more people every year than cancers of the breast, prostate and colon combined. The estimated new deaths were up to 159,390 and represented 28.5% of the total deaths from cancer in the United States in 2009.[2]

Lung cancer has been considered a disease determined solely by environmental exposures such as cigarette smoking and asbestos. However, not all of those who have been exposed to the risk factors will develop lung cancer, suggesting that other causes, including genetic susceptibility, might contribute to the variation in individual lung cancer risk.[3–5] This genetic susceptibility may result from inherited polymorphisms in the genes involved in carcinogen metabolism.[6,7] To our knowledge, many studies have reported that the variations of several drug-metabolising enzymes, such as Cytochrome P450, NAD(P)H quinone reductase 1, myeloperoxidase, Glutathione S-transferase, and arylamine N-acetyltransferases, are associated with the sensitivity of lung cancer.[8–12]

Cytochrome P450 2E1 (CYP2E1), a member of the cytochrome P450 superfamily, is a natural ethanol-inducible enzyme that is involved in the metabolic oxidation of low

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molecular weight carcinogens such as N-nitrosoamines, benzene and vinyl chloride. *CYP2E1* gene is located on 10q24.3-qter. It is 18,754 bp long consisting of nine exons and eight introns, which encodes a 493 amino acid protein. *CYP2E1* gene contains six restriction fragment length polymorphisms, of which the *RsaI/PstI* polymorphism in its 5′-flanking region has been shown to affect its transcription level. The variant type of this polymorphic site can enhance the transcription and increase the level of CYP2E1 enzymatic activity *in vitro*.[13,14]

Many studies have investigated associations between *CYP2E1* gene variation and lung cancer risk. The most extensively studied single nucleotide polymorphisms of *CYP2E1* are *RsaI/PstI* site in the 5′-flanking region and the *DraI* site in intron 6. However, the results from epidemiological studies have been inconsistent and controversial. Wu et al. found that the c1/c1 genotype was associated with a 14-fold increased risk of lung cancer in Mexican Americans, a 9.9-fold increased risk of lung cancer in Mexican American former smokers, a 15-fold increased risk of lung cancer in Mexican American males, and that patients with the susceptible genotype appeared to have developed cancer at an earlier age and with lower cigarette pack-year of exposure than patients with the c1/c2 or c2/c2 genotypes. Oyama's study showed that incidence of *CYP2E1 RsaI/PstI* c2/c2 polymorphism in patients with squamous cell carcinoma (9.4%) was significantly higher than that in healthy controls (4.1%).[15] Uematsu et al. reported that host susceptibility to lung cancer is associated with the *DraI* polymorphism of the *CYP2E1* gene.[16] Additional studies did not find an association between polymorphisms of *CYP2E1 RsaI/PstI* and *DraI*, and lung cancer risk.[17–19] Therefore, we collected published data to evaluate the association between *CYP2E1 RsaI/PstI* and *DraI*, and lung cancer risk using meta-analysis.

In this report, we summarised reported case-control studies on the two most studied polymorphisms in all ethnic populations. Because a single study may have been underpowered in detecting the effect of low penetrance genes, particularly in assessing dose-response relationships, a quantitative synthesis of accumulated data from published studies may enhance statistical power to explore the correlation between genetic polymorphisms and the risk of lung cancer.

2. Materials and methods

2.1. Literature and methods

We carried out a comprehensive search using the databases Medline, Elsevier, SpringerLink and Chinese national knowledge infrastructure (CNKI), and papers published before the end of May 2009 were identified with a combination of the following terms: 'lung cancer', 'lung neoplasm' or 'lung carcinoma' and '*CYP2E1/CYPIIE1*'or 'cytochrome P4502E1/IIE1'. A cited reference search of the retrieved papers was conducted, and further publications were also identified by retrieving the bibliographies of the retrieved papers. The search and evaluation were carried out from June to September 2009.

Data from studies were included in this meta-analysis only if the study met the following criteria: (1) The papers should include lung cancer risk and polymorphisms of *CYP2E1 RsaI/PstI* or *DraI*; (2) Only the case-control studies and cohort studies were considered; (3) The paper must offer the size of the sample, odds ratios (ORs) and their 95% confidence intervals (CI) or the information that can help infer the results; (4) Those publications that presented data allowing such outcomes to be derived were also included; (5) When more than one article was identified for the same study population, we included the most recent population or publication including more information.

Accordingly, papers that could not offer the source of cases and controls or other essential information were excluded; reviews and repeated literatures were also excluded.

In total, 53 published studies were identified with the association between *CYP2E1* polymorphism and lung cancer risk. We reviewed all papers in accordance with the criteria defined above and excluded four reviews, 13 repeated articles, and four papers that did not offer full information. Therefore, 32 studies were ultimately entered into our study. Among them, 26 studies focused on the *CYP2E1 RsaI/PstI* and 13 studies focused on the *CYP2E1 DraI*. Apparently, there were seven articles that had reported two kinds of polymorphism.

2.2. Data extraction

Two data managers tabulated the data first, and then inputted them from these studies to an electric database, independently. A double-check procedure was performed to ensure the accuracy of the data entrance. The following information was subtracted from the study: first author, publishing year, journal, source of controls, ethnicity of subjects, the extract data of total and exposure number in case and control groups, and ORs and their 95% CIs.

A standardised procedure was carried out to estimate the OR from the exact data of subject numbers of cases and controls offered in several of the papers. We computed the OR if the study provided stratum information; the data coming from similar stratum were added up to make full use of the data. Characteristics of individual studies are summarised in Tables 1 and 2.

2.3. Quantitative data synthesis

To estimate the association between the polymorphisms of *CYP2E1 RsaI/PstI* and *DraI*, and the risk of lung cancer, we conducted a meta-analysis of identified studies. Data were combined using either a fixed effects (the inverse variance-weighted method) or random effects (DerSimonian and Laird method) model.[49] The Cochrane Q statistics test was used for the assessment of heterogeneity. The fixed effects model is used when the effects are assumed to be homogenous, while the random effects model is used when they are heterogeneous. We calculated the crude OR and 95% CI for each study whenever possible. The meta-analysis was performed on crude ORs, since the adjusted ORs were not comparable because of different covariates being included in the multivariate regression models. Using persons with the homozygous common allele as the reference group, we calculated ORs for persons with the heterozygous and homozygous variants separately.

Publication bias is always of concern in a meta-analysis. The presence of publication bias indicates that non-significant

Table 1 – Studies on the association between the genetic polymorphism of the *CYP2E1 RsaI/PstI* site and the risk of lung cancer included in the meta-analysis.

First author	Year	No. of cases	No. of controls	Source of controls	Ethnicity of subjects	OR(95% CI)		
						c1/c2	c2/c2	c1/c2 + c2/c2
Kato[20]	1992	67	41	Hospital	Japanese, Caucasian and African–American	0.91(0.15–5.72)	Not estimable	0.91(0.15–5.72)
Wu[21]	1997	137	206	Population	African–American and Mexican–American	0.51(0.27–0.96)	0.68(0.06–7.56)	0.52(0.28–0.96)
Le Marchand[22]	1998	337	454	Population	Caucasian, Japanese and Hawaiians	0.81(0.57–1.15)	0.18(0.04–0.80)	0.74(0.52–1.03)
Minegishi[23]	2007	505	256	Hospital	Japanese	0.81(0.59–1.10)	4.90(1.47–16.32)	0.92(0.68–1.25)
Lee[24]	2006	169	191	Hospital	Korea	1.53(1.00–2.36)	0.94(0.36–2.42)	1.46(0.96–2.23)
Hamada[25]	1995	113	108	Hospital	Mullatoes, Black and White	0.86(0.36–2.05)	Not estimable	0.86(0.36–2.05)
Shi[26]	2002	120	120	Hospital	Chinese	0.51(0.29–0.91)	0.42(0.19–0.96)	0.49(0.29–0.82)
Ye[27]	2006	58	62	Hospital	Chinese	0.69(0.32–1.50)	1.62(0.36–7.30)	0.79(0.38–1.64)
Zou[28]	2004	41	61	Hospital	Chinese	1.22(0.48–3.14)	2.29(0.84–6.25)	1.61(0.72–3.61)
Chen[29]	2002	91	138	Hospital	Chinese	0.58(0.32–1.05)	3.14(0.78–12.62)	0.72(0.41–1.25)
Li[30]	2008	150	152	Hospital health	Chinese	0.73(0.45–1.17)	0.59(0.16–2.16)	0.72(0.45–1.13)
Huang[31]	2000	54	260	Hospital	Chinese	1.57(0.86–2.86)	2.61(0.63–10.75)	1.63(0.91–2.94)
Li[32]	2000	92	137	Population	Chinese	0.43(0.24–0.78)	0.67(0.15–2.92)	0.45(0.26–0.80)
Qu[33]	1998	182	184	Hospital	Chinese	0.77(0.50–1.17)	2.16(0.54–8.58)	0.82(0.54–1.23)
Li[34]	2004	217	200	Hospital	Chinese	1.00(0.66–1.50)	2.23(1.05–4.75)	1.15(0.78–1.70)
Quinones[35]	2001	59	148	Hospital	Chilean	0.82(0.40–1.65)	0.33(0.02–6.54)	0.76(0.38–1.53)
Wang[36]	1999	119	231	Hospital	Taiwanese	0.88(0.55–1.41)	0.11(0.01–0.84)	0.75(0.48–1.19)
Watanable[18]	1995	316	503	Population	Japanese	0.95(0.70–1.29)	1.28(0.60–2.72)	0.98(0.73–1.31)
Wang[37]	2003	164	181	Hospital	Chinese	0.58(0.37–0.91)	0.05(0.00–0.79)	0.52(0.34–0.81)
Oyama[38]	2003	126	612	Population	Japanese	0.73(0.47–1.14)	1.26(0.53–3.00)	0.79(0.53–1.20)
Persson[39]	1993	184	202	Population	Swedish	0.44(0.19–1.02)	0.34(0.01–8.52)	0.41(0.18–0.96)
Persson[40]	1999	76	113	Population	Chinese	0.78(0.42–1.43)	0.44(0.08–2.26)	0.74(0.41–1.33)
El-Zein[41]	1997	52	48	Volunteer	Galveston–Houston area	Unknown	Unknown	3.58(0.70–18.16)
Gu[42]	2007	279	684	Hospital and Volunteer	Chinese	Unknown	Unknown	0.96(0.72–1.27)
London[19]	1996	341	706	Population	African–American and Caucasian	0.64(0.34–1.22)	Unknown	0.64(0.34–1.22)
Eom[43]	2009	387	387	Hospital health	Korea	Unknown	Unknown	0.87(0.65–1.17)

or negative findings remain unpublished. The funnel plot was drawn to evaluate publication bias and Egger's test was applied to test for the funnel plot symmetry, in which a regression model was set up, using the inverse of the standard error as an independent variable and the standardised estimate of size effect as a dependent variable.[49–51]

All of the statistical analyses were performed with Review Manager (Version 4.2.10, The Cochrane Collaboration) and Statistical Package for Social Science Version 12.0 (SPSS, Chicago, IL). All the tests were two-sided and a *P* value of 0.05 for any test or model was thought to be statistically significant.

3. Results

3.1. *Meta-analysis databases*

We established a database according to the extracted information from each article. All essential information is listed in Tables 1 and 2. Table 1 shows first author, publishing year, the numbers of cases and controls, source of control, ethnicity of subjects, ORs and 95% CIs for *CYP2E1 RsaI/PstI*. There were a total of 26 studies with 4436 cases and 6385 controls concerning the *CYP2E1 RsaI/PstI* polymorphism (Table 1), 13 studies with 1666 cases and 2093 controls concerning the *CYP2E1 DraI* (Table 2).

3.2. *Test of heterogeneity*

Table 3 shows the association between the *CYP2E1 RsaI/PstI* polymorphism and the risk of lung cancer. The heterogeneity of *CYP2E1 RsaI/PstI* c1/c2 versus c1/c1, c2/c2 versus c1/c1, and c1/c2 + c2/c2 versus c1/c1 was analysed for 26 case-control studies. The results showed that *CYP2E1 RsaI/PstI* c2/c2 versus c1/c1 and c1/c2 + c2/c2 versus c1/c1 for the total population, c2/c2 versus c1/c1 and c1/c2 + c2/c2 versus c1/c1 for the population based on hospital control and all three genotypes for the Asian population had heterogeneity with a *P* value less than 0.05. Therefore, we analysed the summary ORs for these

Table 2 – Studies on the association between the genetic polymorphism of the *CYP2E1 DraI* site and the risk of lung cancer included in the meta-analysis.

First author	Year	No. of cases	No. of controls	Source of controls	Ethnicity of subjects	OR(95% CI)		
						CD	CC	CD + CC
Kato[44]	1994	58	38	Hospital	Japanese, Caucasian and African–American	1.72(0.55–5.36)	Not estimable	1.72(0.55–5.36)
Le Marchand[45]	1998	338	452	Population	Caucasian, Japanese and Hawaiians	0.98(0.71–1.35)	0.26(0.10–0.68)	0.86(0.63–1.16)
Wu[46]	1998	126	193	Population	African–American and Mexican–American	0.47(0.25–0.88)	0.33(0.04–3.00)	0.46(0.25–0.84)
Uematsu[47]	1992	74	73	Hospital	Japanese	1.79(0.89–3.60)	0.22(0.05–1.07)	1.28(0.67–2.46)
Liang[48]	2004	152	152	Hospital	Chinese	0.84(0.53–1.35)	0.93(0.36–2.35)	0.85(0.54–1.34)
Qu[33]	1998	174	178	Hospital	Chinese	0.85(0.55–1.32)	1.18(0.47–2.99)	0.89(0.58–1.35)
Quinones[35]	2001	58	129	Hospital	Chilean	1.33(0.69–2.56)	0.69(0.14–3.49)	1.23(0.65–2.32)
Wang[36]	1999	119	231	Hospital	Taiwanese	0.73(0.45–1.18)	0.59(0.24–1.45)	0.70(0.45–1.11)
Uematsu[16]	1991	47	56	Unknown	Japanese	1.71(0.75–3.87)	0.10(0.01–1.88)	1.26(0.58–2.76)
Persson[39]	1993	193	206	Population	Swedish	0.90(0.54–1.51)	0.21(0.01–4.36)	0.86(0.51–1.42)
Hirvonen[17]	1993	101	121	Population	Finnish	0.66(0.32–1.35)	2.26(0.20–25.36)	0.72(0.36–1.44)
Persson[40]	1999	76	112	Population	Chinese	0.64(0.34–1.20)	1.05(0.30–3.64)	0.69(0.38–1.24)
Li[30]	2008	150	152	Hospital health	Chinese	0.78(0.48–1.26)	0.67(0.27–1.68)	0.76(0.48–1.20)

Table 3 – Summary ORs – relationship of the *CYP2E1 RsaI/PstI* site polymorphism to lung cancer risk.

Genotype	Heterogeneity test		Summary OR(95% CI)	Hypothesis test		Egger's test	
	Q	P		Z	P	t	P
c1/c2	31.06	0.09	0.80(0.72–0.89)	4.24	<0.0001	–0.584	0.565
c2/c2	41.47	0.002	1.01(0.65–1.55)	0.04	0.97	2.043	0.056
c1/c2 + c2/c2	42.96	0.01	0.82(0.72–0.93)	3.03	0.002	–1.431	0.165
Stratification by source of control							
Population							
c1/c2	8.98	0.25	0.73(0.62–0.87)	3.64	0.0003	1.533	0.176
c2/c2	7.38	0.29	0.78(0.49–1.22)	1.11	0.27	0.759	0.482
c1/c2 + c2/c2	13.31	0.1	0.75(0.64–0.88)	3.56	0.0004	–1.929	0.095
Hospital							
c1/c2	20.54	0.11	0.85(0.74–0.97)	2.49	0.01	–0.609	0.553
c2/c2	32.33	0.001	1.19(0.66–2.14)	0.58	0.56	1.836	0.093
c1/c2 + c2/c2	26.47	0.03	0.87(0.74–1.03)	1.62	0.11	–0.680	0.507
Stratification by ethnicity							
Asian							
c1/c2	26.33	0.03	0.81(0.69–0.96)	1.51	0.01	–0.230	0.821
c2/c2	33.7	0.004	1.17(0.75–1.82)	0.69	0.49	2.148	0.050
c1/c2 + c2/c2	32.97	0.01	0.86(0.74–0.99)	2.14	0.03	–0.422	0.679

with a random-effect model. Fixed-effect models were used to analyse the summary ORs for the rest.

Table 4 indicates the relationship between the *CYP2E1 DraI* polymorphism and the risk of lung cancer. We analysed the heterogeneity for all 13 case-control studies. The results showed that there was no heterogeneity for *CYP2E1 DraI* CD versus DD, CC versus DD and CD + CC versus DD. Therefore, we analysed the summary ORs for these with a fixed-effect model.

3.3. *Quantitative data synthesis*

Table 3 shows the summary ORs of *CYP2E1 RsaI/PstI* on the basis of 4436 cases and 6385 controls. We observed a difference in c1/c2 versus c1/c1 and c1/c2 + c2/c2 versus c1/c1 in the total population and the summary ORs were 0.80 (95% CI: 0.72–0.89) and 0.82 (95% CI: 0.72–0.93), respectively. However, we did not observe a relationship between c2/c2 versus c1/c1 and the risk of lung cancer. Given the ethnic differences in the allelic frequency of this sequence variant, we evaluated the effect of *CYP2E1 RsaI/PstI* in the Asian population. We found a difference in c1/c2 versus c1/c1 and c1/c2 + c2/c2 versus c1/c1 with the summary ORs being equal to 0.81 (95% CI: 0.69–0.96) and 0.86 (95% CI: 0.74–0.99), respectively. Summary ORs for *CYP2E1 RsaI/PstI* stratified by source of controls were evaluated, and we observed a difference in c1/c2 versus c1/c1 on the basis of population control and hospital control; the summary ORs were 0.73 (95% CI:

Table 4 – Summary ORs – relationship of the *CYP2E1 DraI* site polymorphism to lung cancer risk.

Genotype	Heterogeneity test		Summary OR (95% CI)	Hypothesis test		Egger's test	
	Q	P		Z	P	t	P
CD	16.15	0.18	0.89(0.76–1.02)	1.64	0.1	1.738	0.110
CC	11.72	0.38	0.58(0.41–0.81)	3.17	0.002	0.089	0.931
CD + CC	10.93	0.53	0.84(0.73–0.96)	2.46	0.01	–2.295	0.042

0.62–0.87) and 0.85 (95% CI: 0.74–0.97), respectively. However, we only observed a difference in c1/c2 + c2/c2 versus c1/c1 on the basis of population control – the summary OR was 0.75 (95% CI: 0.64–0.88); we did not observe an association on the basis of hospital control – the summary OR was 0.87 (95% CI: 0.74–1.03).

Table 4 shows the summary ORs of *CYP2E1 DraI* on the basis of 1666 cases and 2093 controls. We observed an association between the *CYP2E1* CC versus DD and CD + CC versus DD, and the risk of lung cancer; the summary ORs were 0.58 (95% CI: 0.41–0.81) and 0.84 (95% CI: 0.73–0.96), respectively. However, there was no association between *CYP2E1 DraI CD* versus DD and the risk of lung cancer.

3.4. *Bias diagnosis*

Publication bias was examined by using funnel plot analysis (the contrast of homozygous genotype plotted against the precision): the shape of the funnel plot seemed to be approximately symmetrical, but there was some uncertainty because the symmetrical degrees were not content. Therefore, the Egger's test based on linear regression of the standard normal deviate against its precision was applied to test the funnel plot symmetry. In this analysis, we used the inverse of the standard error as the independent variable and the standardised estimate of the size effect (ln OR upon its standard error) as the dependant variable. The estimate of the effect is considered biased when the intercept is significantly different from zero. The test results are listed in Tables 3 and 4. The Egger's test suggested that publication biases might not have a significant effect on the results of *CYP2E1 RsaI/PstI* and *DraI*, except for *CYP2E1 DraI* CD + CC versus DD because there was some uncertainty with the *P* value being equal to 0.042.

4. Discussion

Watanable et al. found *PstI* and *RsaI* polymorphisms, being in complete linkage disequilibrium, in the 5′-flanking region of the human *P4502E1* gene in 202 unrelated healthy Japanese.[52] Hayashi's study showed that genetic polymorphisms in *RsaI/PstI* changed transcriptional regulation of the human cytochrome *P4502E1* gene.[14] A series of epidemiological studies investigated the association between *CYP2E1 RsaI/PstI* polymorphism and lung cancer risk (data shown in Table 1), but the findings were inconsistent. This urged us to undertake the present meta-analysis, which aims to derive an estimate of the lung cancer risk associated with *CYP2E1 RsaI/PstI* genotype. The main findings of this meta-analysis were that subjects carrying the *CYP2E1 RsaI/PstI* c1/c2 and c1/c2 + c2/c2 genotype had a decreased risk of lung cancer, compared to c1/c1 carriers. However, it has been reported that the transcriptional activity of *CYP2E1* c2/c2 genotype in HepG2 cells is 10 times greater than that in c1/c1 cells.[14] This suggests that the transcriptional activity of the c2 allele is greater than the activity of the c1 allele. This finding *in vitro* was inconsistent with our results.

Three reports on the relationship between *CYP2E1* genotypes and phenotypes in humans supported our conclusions. For example, Tan et al. investigated the relationship between the *RsaI* genotype and the expression of CYP2E1 in human liver. The results showed that the mean content of CYP2E1 protein was significantly higher among individuals with the c1/c1 genotype than that among those having c1/c2 or c2/c2 genotype, and the mean activity of CYP2E1 towards p-nitrophenol for the c1/c1 genotype was also higher than that for the variant genotypes.[53] Marchand et al. found that the oral clearance of chlorzoxazone decreased with the number of variant c2 alleles after adjustment for age and sex, and its mean in the c2/c2 genotype was statistically lower than that for either the homozygous wild-type or the heterozygote genotypes.[22] A substantially reduced chlorzoxazone 6-hydroxylation was observed in the single c2/c2 individual. Additionally, patients with the mutated genotype appeared to have less induction of CYP2E1 than wild-type individuals after ethanol administration.[54]

In this meta-analysis we found that individuals with *CYP2E1* CC or CD + CC genotype had a decreased risk of lung cancer. The polymorphism caused by the presence or absence of a *DraI* site in *CYP2E1* intron 6 may not affect gene expression. The reason that *CYP2E1 DraI* polymorphism is related to lung cancer risk is not known. On the one hand, it may be linked to another mutation in the same gene involved in the structure or regulation of the gene products, or it may cosegregate with another tumour suppressor gene or susceptibility gene;[46] On the other hand, the function of *CYP2E1 DraI* variation might be similar to *ATM* gene IVS10-6T→G mutation, which leads to incorrect splicing of exon 11 and to exon skipping, and results in a frameshift and subsequent truncation of the protein at amino acid residue 419.[55]

There are some limitations inherent in this meta-analysis. First, only published articles were included in this study. Therefore, publication bias may have occurred; of note, four studies did not offer their full information in the present meta-analysis. To evaluate the problem, Egger's test based on linear regression of the standard normal deviate against its precision was used. The results showed that the likelihood of key publication bias in the present analysis was negligible, expect for *CYP2E1 DraI* CD + CC versus DD. Second, this meta-analysis is based on unadjusted estimates, while a

more precise analysis might be conducted if individual data were available, which could allow for an adjustment estimate by sex, age, smoking or drinking. Therefore, it is required for authors of all of the published papers to share their data. Third, each study had different eligibility criteria for subjects and a different source of controls, which should be taken into account when interpreting the summary estimates. When studies were stratified by control source, the lung cancer ORs for the *CYP2E1 RsaI* c1/c2 and c1/c2 + c2/c2 genotype were 0.73 (0.62–0.87) and 0.75 (0.64–0.88) using data from population-based studies, and 0.85 (0.74–0.97) and 0.87 (0.74–1.03) using data from hospital-based studies which indicated that the allele distribution of the *CYP2E1 RsaI/PstI* polymorphism in the hospital control groups might not have been representative of the general population.

Ethnicity is an important biological factor which may influence CYP2E1 functions through gene–gene interactions. The allelic frequencies were markedly different among ethnicities. The c2 allele of *CYP2E1 RsaI/PstI* polymorphism is more common in Orientals than in the Western population.[20] Therefore, we conducted further meta-analysis on the association of *CYP2E1 RsaI/PstI* polymorphisms with lung cancer risk stratified by ethnicity. We observed a decreased lung cancer risk among subjects with *CYP2E1 RsaI/PstI* c1/c2 or c1/c2 + c2/c2 genotype in Asian populations. We did not perform a meta-analysis in additional ethnicities, since the number of reports for these was small.

In summary, this systematic review found that *CYP2E1 RsaI/PstI* c2 carriers and *DraI* C carriers had a decreased risk of lung cancer. Large studies with the pooling of individual data should be considered in future association studies to verify results from this meta-analysis and to further evaluate the effect of gene–gene and gene–environment interactions on the *CYP2E1 RsaI/PstI* and *DraI* polymorphisms-associated lung cancer risk.

Conflict of interest statement

None declared.

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