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ORIGINAL PAPER

Association between the CYP2E1 polymorphisms and lung cancer risk: a meta-analysis

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Abstract The previous, published data on the association between CYP2E1 RsaI (rs2031920), DraI (rs6413432) polymorphisms and lung cancer risk remained controversial. Hence, we performed a meta-analysis to investigate the association between lung cancer and CYP2E1 RsaI (5,074 cases and 6,828 controls from 34 studies), and CYP2E1 DraI (2,093 cases and 2,508 controls from 16 studies) in different inheritance models. Overall, significantly decreased lung cancer risk was observed (dominant model: odds ratio (OR) 0.80, 95 % confidence interval (95 % CI) 0.71–0.90; heterozygote model: OR 0.80, 95 % CI 0.70–0.90; additive model: OR 0.82, 95 % CI 0.72–0.94) when all the eligible studies were pooled into the meta-analysis of CYP2E1 RsaI polymorphism. In further stratified and sensitivity analyses, significantly decreased lung cancer risk was found among Asians (dominant model: OR 0.81, 95 % CI 0.71–0.93; heterozygous model: OR 0.81, 95 % CI 0.69–0.95), population-based studies (dominant model: OR 0.69, 95 % CI 0.54–0.88; recessive model: OR 0.39, 95 % CI 0.16–0.91; additive model: OR 0.67, 95 % CI 0.53–0.84; homozygous model: OR 0.34, 95 % CI 0.14–0.80; heterozygous model: OR 0.70, 95 % CI 0.54–0.91), hospital-based studies (dominant model: OR 0.80, 95 % CI 0.69–0.93; additive model: OR 0.84, 95 % CI 0.70–1.00; heterozygous model: OR 0.80, 95 % CI 0.68–0.95), lung AC (heterozygous model: OR 0.84, 95 % CI 0.71–1.00), smokers (dominant model: OR 0.72, 95 % CI 0.55–0.94), and non-smokers (dominant model: OR 0.74, 95 % CI 0.61–0.91). There was no significant association between CYP2E1 DraI polymorphism and the risk of lung cancer when all the eligible studies were pooled into the meta-analysis. However, in further stratified and sensitivity analyses, significant association was observed among smokers (dominant model: OR 0.49, 95 % CI 0.35–0.69). In summary, this meta-analysis indicates that CYP2E1 RsaI polymorphism is associated with lung cancer risk among Asians, CYP2E1 RsaI polymorphism may be associated with lung adenocarcinoma risk, and CYP2E1 RsaI and DraI polymorphisms may be associated with decreased lung cancer risk in smokers.

Keywords CYP2E1 · Polymorphism · Lung cancer · Susceptibility · Meta-analysis

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Introduction

Lung cancer is the leading cause of cancer-related death in the worldwide (lberg and Samet 2003; Kuper et al. 2002). Human lung cancer is associated with exposure to

carcinogens such as polycyclic aromatic hydrocarbons (PAH) and asbestos; these mainly come from tobacco smoke, diet, and occupational exposure (Peto et al. 1996; Beckett 1993; Cote et al. 2009). 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 (Schabath et al. 2002; Hayashi et al. 1991a, b; Agarwal 2001; Kiyohara et al. 2004). The exact mechanism of lung cancer is still under investigation. This genetic susceptibility may result from inherited polymorphisms in the genes involved in carcinogen metabolism. 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*-acetyltransferses, are associated with the sensitivity of lung cancer (Agundez 2008; Carlsten et al. 2008; Raimondi et al. 2006; Kiyohara et al. 2005; Le Marchand et al. 2003; Uematsu et al. 1991). 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-molecular weight carcinogens such as *N*-nitrosoamines, benzene and vinyl chloride and aniline. *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. The variant type of this polymorphic site can enhance the transcription and increase the level of CYP2E1 enzymatic activity in vitro (Liu et al. 2009; Hayashi et al. 1991a). Genetic mutations in the CYP2E1 gene are considered to be associated with increased CYP2E1 activity and may be linked to the carcinogenic process. CYP2E1 is an ethanol-inducible enzyme that metabolically activates various carcinogens, such as benzene, vinyl chloride and *N*-dimethylnitrosamines (Yamazaki et al. 1992; Bellec et al. 1996). *N*-nitrosamines are present in tobacco smoke, and activation of nitrosamines has been linked to the development of various cancers (Hoffmann and Hecht 1985; Hecht and Hoffmann 1988). Several CYP2E1 polymorphisms had been identified by restriction fragment length polymorphism analysis (Hayashi et al. 1991a; Uematsu et al. 1991). The most extensively studied single nucleotide polymorphisms of CYP2E1 are RsaI polymorphism in the 50-flanking region and the DraI polymorphism in intron 6.

However, many epidemiologic studies have reported to evaluate the association between CYP2E1 RsaI (rs2031920), DraI (rs6413432) polymorphisms and lung cancer risk in diverse populations (Li et al. 2000, 2004, 2005, 2008, 2012; Klinchid et al. 2009; Eom et al. 2009; Chen et al. 2002; Zienolddiny et al. 2008; Minegishi et al. 2007; Lee et al. 2006; Oyama et al. 2003; Liu et al. 2010; Liang et al. 2004; Gu et al. 2004; Su et al. 2011; Qu et al. 1998; Quiñones et al. 2001; Wang et al. 1999, 2003, 2006; Persson et al. 1999; Le Marchand et al. 1998; Wu et al. 1997, 1998; El-Zein et al. 1997a, b; Oyama et al. 1997; London et al. 1996; Watanabe et al. 1995; Sugimura et al. 1995; Hamada et al. 1995; Kato et al. 1994; Huang et al. 2000; Persson et al. 1993; Kato et al. 1992; Hirvonen et al. 1992, 1993; Uematsu et al. 1991; Shi et al. 2002; Ye et al. 2006; Zou et al. 2004). The results were inconsistent or even contradictory. The reason for this disagreement may be related to gene–gene, gene–environment interactions in lung cancer carcinogenesis. Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between CYP2E1 RsaI (rs2031920), DraI (rs6413432) polymorphisms and the risk of lung cancer that have been investigated.

Materials and methods

Identification and eligibility of relevant studies

A bibliographical search was performed in PubMed, CNKI, and EMBASE database to identify studies that evaluated CYP2E1 polymorphisms and lung cancer up to May 10, 2014. The search terms used were: (polymorphism or mutation or variant) and (CYP2E1 or "cytochrome P-450 2E1" or "cytochrome P450 2E1") and lung. The search was not limited to language. Additional studies were identified by hand searching references in original articles and review articles. Authors were contacted directly regarding crucial data not reported in original articles. In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. We included all the case–control studies and cohort studies that investigated the association between CYP2E1 RsaI and DraI polymorphisms and lung cancer risk with genotyping data. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications.

Inclusion criteria

The included studies needed to have met the following criteria: (1) only the case–control studies or cohort studies were considered, (2) evaluated the CYP2E1 RsaI and DraI polymorphisms and lung cancer risk, and (3) the genotype distributions of the polymorphisms in cases and controls were described in detail and the results were expressed as odds ratio (OR) and corresponding 95 % confidence interval (95 % CI). Major reasons for exclusion of studies were as follows: (1) not for lung cancer research, (2) only case population, and (3) duplicate of previous publication (when the same patient population was used in several

publications, only the most recent, largest or complete study was included following careful examination).

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators according to the inclusion criteria listed above. The following data were collected from each study: first author's name, year of publication, country of origin, ethnicity, source of controls, genotyping method, and numbers of cases and controls in the CYP2E1 RsaI and DraI genotypes whenever possible. Ethnicity was categorized as ''Caucasian,'' ''African,'' (including African Americans) and ''Asian.'' When one study did not state as to which ethnic groups were included or if it was impossible to separate participants according to phenotype, the sample was termed as ''mixed population.'' We did not define any minimum number of patients to include in this meta-analysis. For articles that reported different ethnic groups and different countries or locations, we considered them as different study samples for each category cited above.

Statistical analysis

Crude ORs together with their corresponding 95 % CIs were used to assess the strength of association between the CYP2E1 RsaI and DraI polymorphisms and lung cancer risk. The pooled ORs were performed for dominant model (RsaI: C2/C2 + C1/C2 vs. C1/C1 and DraI: CD + DD vs. CC); recessive model (RsaI: C2/C2 vs. C1/C2 + C1/C1 and DraI: DD vs. CD + CC); homozygous model (RsaI: C2/C2 vs. C1/C1 and DraI: DD vs. CC), heterozygous model (RsaI: C1/C2 vs. C1/C1 and DraI: CD vs. CC), and additive model (RsaI: C2 vs. C1 and DraI: D vs. C), respectively. Heterogeneity assumption was checked by a Chi square-based Q test (heterogeneity was considered statistically significant if $P < 0.10$) (Davey and Egger 1997) and quantified using the I^2 value, a value that describes the percentage of variation across studies that are due to heterogeneity rather than chance, where I^2 0 % indicates no observed heterogeneity, with 25 % regarded as low, 50 % as moderate, and 75 % as high (Higgins et al. 2003). If results were not heterogeneous, the pooled ORs were calculated by the fixed-effect model (we used the Q-statistic, which represents the magnitude of heterogeneity between-studies) (Mantel and Haenszel 1959). Otherwise, a random-effect model was used (when the heterogeneity between-studies were significant) (DerSimonian and Laird 1986). In addition to the comparison among all subjects, we also performed stratification analyses by ethnicity, source of controls, smoking status, and histological type. Moreover, the extent to which the combined risk estimate might be affected by individual studies was assessed by consecutively omitting every study from the meta-analysis (leave-one-out sensitivity analysis). This approach would also capture the effect of the oldest or first positive study (first study effect). In addition, we also ranked studies according to sample size, and then repeated this meta-analysis. Sample size was classified according to a minimum of 200 participants and those with fewer than 200 participants. The cite criteria were previously described (Klug et al. 2009). Last, sensitivity analysis was also performed, excluding studies whose allele frequencies in controls exhibited significant deviation from the Hardy–Weinberg equilibrium (HWE), given that the deviation may denote bias. Deviation of HWE may reflect methodological problems such as genotyping errors, population stratification or selection bias. HWE was calculated by using the goodness-of-fit test, and deviation was considered when $P < 0.05$. Begg's funnel plots (Begg and Mazumdar 1994) and Egger's linear regression test (Egger et al. 1997) were used to assess publication bias. A meta-regression analysis was carried out to identify the major sources of between-studies variation in the results, using the log of the ORs from each study as dependent variables, and ethnicity, sample size, HWE, and source of controls as the possible sources of heterogeneity. All of the calculations were performed using STATA version 10.0 (STATA Corporation, College Station, TX, USA).

Results

Literature search and meta-analysis databases

Relevant publications were retrieved and preliminarily screened. As shown in Fig. 1, 318 publications were identified, among which 132 irrelevant papers were excluded. Thus, 186 publications were eligible. Among these publications, 144 articles were excluded because they were review articles, case reports, and other polymorphisms of CYP2E1. In addition, of these published articles, four articles (El-Zein et al. 1997a; Hirvonen et al. 1992; Sugimura et al. 1995; Oyama et al. 2003) were excluded because of their populations overlapped with another included five articles (El-Zein et al. 1997b, Hirvonen et al. 1993; Hamada et al. 1995; Oyama et al. 1997). As summarized in Table 1, 38 publications with 50 case–control studies publications were selected in the final meta-analysis, including 5,074 cases and 6,828 controls for CYP2E1 RsaI (from 34 studies) and 2,093 cases and 2,508 controls for DraI (from 16 studies). Table 1 lists all essential information such as the publication year, first author, Country, ethnicity, source of controls, and Genotyping method for CYP2E1 RsaI and DraI, respectively. Genotype frequencies for lung cancer cases and controls are listed in Tables 2 and 3. And six

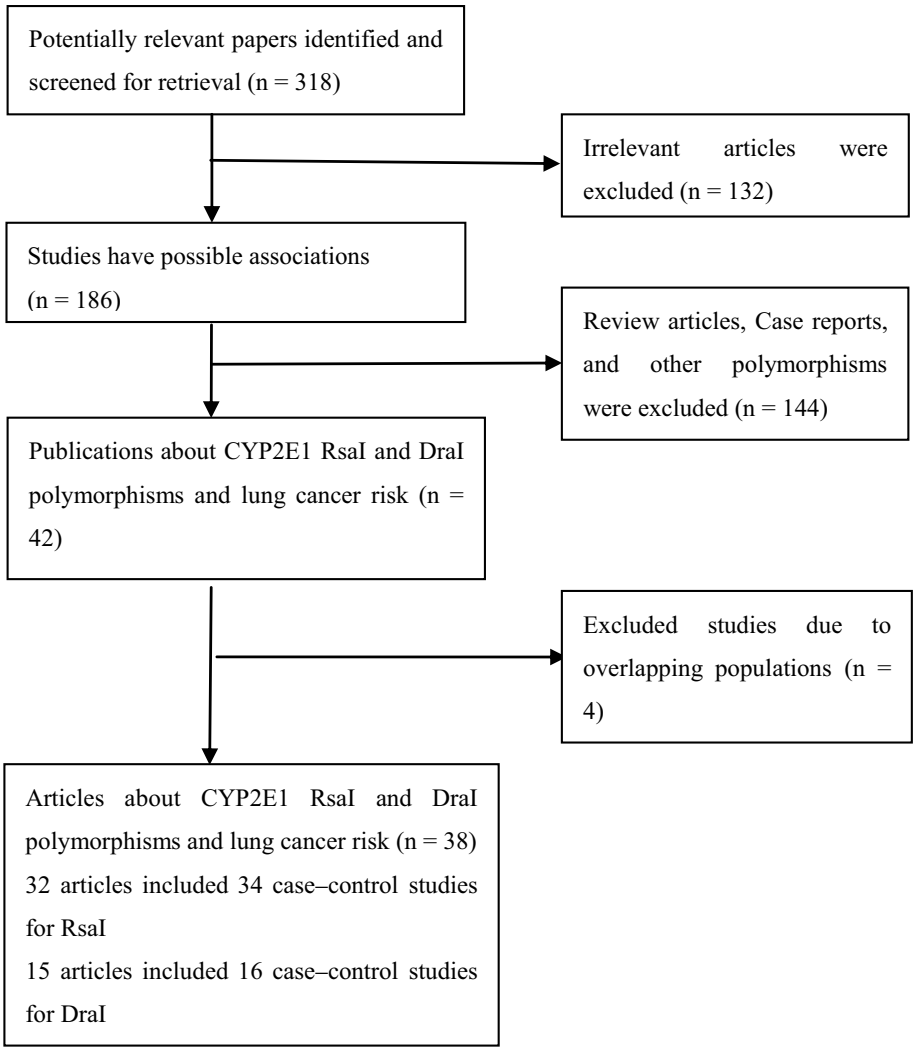

Fig. 1 Study flow chart explaining the selection of the 38 eligible case–control studies included in the meta-analysis

studies (Klinchid et al. 2009; Li et al. 2008; El-Zein et al. 1997b; Zienolddiny et al. 2008; Eom et al. 2009; Gu et al. 2004) were analyzed only in dominant model because their provided the limited genotyping information for CYP2E1 RsaI and DraI polymorphisms. All of the cases were pathologically confirmed.

Quantitative synthesis

Table 4 lists the main results of the meta-analysis of CYP2E1 RsaI polymorphism and lung cancer risk. Significantly decreased lung cancer risk was observed (dominant model: OR 0.80, 95 % CI 0.71–0.90, *P* value of heterogeneity test [P_h] = 0.015, I^2 = 37.8 %; heterozygous model: OR 0.80, 95 % CI 0.70–0.90, P_h = 0.050, I^2 = 32.3 %; additive model: OR 0.82, 95 % CI 0.72–0.94, P_h < 0.001, I^2 = 58.9 %) when all the eligible studies were pooled into the meta-analysis. However, we did not observe an association between lung cancer risk and the risk of lung cancer among recessive and homozygous models. In the subgroup analysis by ethnicity, significantly decreased lung cancer risk was observed among Asians (dominant model: OR 0.81; 95 % CI 0.71–0.93; P_h = 0.003, I^2 = 50.3 %, Fig. 2; heterozygous model: OR 0.81, 95 % CI 0.69–0.95, P_h = 0.012, I^2 = 46.7 %) and Caucasians (heterozygous model: OR 0.56, 95 % CI 0.32–0.98, P_h = 0.441, I^2 = 0.0 %; additive model: OR 0.55, 95 % CI 0.32–0.94, P_h = 0.347, I^2 = 0.0 %). There were only two studies of Africans and no significant association was found among any genetic model (Table 4). In the subgroup analysis by pathological type, significant association was found among lung adenocarcinoma (AC) (heterozygous model: OR 0.84, 95 % CI 0.71–1.00, P_h = 0.129, I^2 = 36.1 %). However, no significant association was found in lung squamous cell carcinomas (SC) or non-small cell lung cancer (NSCLC). In the subgroup analysis by source of controls, significant association was observed among the population-based studies (dominant model: OR 0.69, 95 % CI 0.54–0.88, P_h = 0.304, I^2 = 17.4 %; recessive model: OR 0.39, 95 % CI 0.16–0.91, P_h = 0.327, I^2 = 10.6 %; additive model: OR 0.67, 95 % CI 0.53–0.84, P_h = 0.677, I^2 = 0.0 %; homozygous model:

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

References	Country	Ethnicity	SC	SNP	CC	MBT
Li et al. (2012)	China	Asian	HB	RsaI (rs2031920)	217–198	PCR–RFLP
Su et al. (2011)	China	Asian	HB	RsaI (rs2031920)	64–64	PCR–RFLP
Su et al. (2011)	China	Asian	HB	DraI (rs6413432)	64–64	PCR–RFLP
Liu et al. (2010)	China	Asian	PB	RsaI (rs2031920)	108–108	PCR–RFLP
Klinchid et al. (2009)	Thailand	Asian	HB	DraI (rs6413432)	82–81	PCR–RFLP
Eom et al. (2009)	Korea	Asian	HB	RsaI (rs2031920)	387–387	PCR–RFLP
Zienolddiny et al. (2008)	Norway	Caucasian	PB	DraI (rs6413432)	311–343	PCR–RFLP
Zienolddiny et al. (2008)	Norway	Caucasian	PB	RsaI (rs2031920)	136–179	PCR–RFLP
Minegishi et al. (2007)	Japan	Asian	HB	RsaI (rs2031920)	505–256	PCR–RFLP
Wang et al. (2006)	China	Asian	HB	RsaI (rs2031920)	91–91	PCR–RFLP
Lee et al. (2006)	Korea	Asian	HB	RsaI (rs2031920)	169–191	PCR–RFLP
Li et al. (2004)	China	Asian	HB	RsaI (rs2031920)	217–200	PCR–RFLP
Li et al. (2005)	China	Asian	HB	RsaI (rs2031920)	99–66	PCR–RFLP
Liang et al. (2004)	China	Asian	HB	DraI (rs6413432)	152–152	PCR–RFLP
Gu et al. (2004)	China	Asian	HB	RsaI (rs2031920)	180–224	PCR–RFLP
Wang et al. (2003)	China	Asian	HB	RsaI (rs2031920)	164–181	PCR–RFLP
Li et al. (2000)	China	Asian	PB	RsaI (rs2031920)	92–137	PCR–RFLP
Quiñones et al. (2001)	Chile	Mixed	NR	RsaI (rs2031920)	59–148	PCR–RFLP
Quiñones et al. (2001)	Chile	Mixed	NR	DraI (rs6413432)	58–129	PCR–RFLP
Wang et al. (1999)	China	Asian	HB	RsaI (rs2031920)	119–446	PCR
Wang et al. (1999)	China	Asian	HB	DraI (rs6413432)	119–231	PCR
Persson et al. (1999)	China	Asian	NR	RsaI (rs2031920)	76–113	PCR
Persson et al. (1999)	China	Asian	NR	DraI (rs6413432)	76–112	PCR
Le Marchand et al. (1998)	USA	Mixed	PB	RsaI (rs2031920)	337–454	PCR
Le Marchand et al. (1998)	USA	Mixed	PB	DraI (rs6413432)	338–432	PCR
Wu et al.(1998)	USA	African	HB	DraI (rs6413432)	85–104	PCR
Wu et al. (1998)	USA	Mixed	HB	DraI (rs6413432)	41–89	PCR
Wu et al. (1997)	USA	African	HB	RsaI (rs2031920)	92–114	PCR
Wu et al. (1997)	USA	Mixed	HB	RsaI (rs2031920)	45–92	PCR
El-Zein et al. (1997a, b)	USA	Mixed	NR	RsaI (rs2031920)	54–50	PCR–RFLP
Oyama et al. (1997)	Japan	Asian	NR	RsaI (rs2031920)	126–612	PCR–RFLP
London et al. (1996)	USA	Caucasian	HB	RsaI (rs2031920)	184–459	PCR
London et al. (1996)	USA	African	HB	RsaI (rs2031920)	157–247	PCR
Watanabe et al. (1995)	Japan	Asian	NR	RsaI (rs2031920)	316–503	PCR–RFLP
Hamada et al. (1995)	Braze	Mixed	HB	RsaI (rs2031920)	113–108	PCR
Kato et al. (1994)	USA	Mixed	HB	DraI (rs6413432)	58–38	PCR–RFLP
Persson et al. (1993)	Sweden	Caucasian	HB	DraI (rs6413432)	193–206	PCR–RFLP
Persson et al. (1993)	Sweden	Caucasian	HB	RsaI (rs2031920)	184–202	PCR–RFLP
Hirvonen et al. (1993)	Finland	Caucasian	HB	DraI (rs6413432)	101–121	PCR–RFLP
Kato et al. (1992)	USA	Mixed	HB	RsaI (rs2031920)	67–41	PCR–RFLP
Uematsu et al. (1991)	Japan	Asian	NR	DraI (rs6413432)	91–76	PCR–RFLP
Shi et al. (2002)	China	Asian	HB	RsaI (rs2031920)	120–120	PCR–RFLP
Ye et al. (2006)	China	Asian	HB	RsaI (rs2031920)	58–62	PCR
Zou et al. (2004)	China	Asian	HB	RsaI (rs2031920)	61–41	PCR–RFLP
Chen et al. (2002)	China	Asian	HB	RsaI (rs2031920)	91–138	PCR
Li et al. (2008)	China	Asian	HB	RsaI (rs2031920)	150–152	PCR–RFLP
Li et al. (2008)	China	Asian	HB	DraI (rs6413432)	150–152	PCR–RFLP
Huang et al. (2000)	China	Asian	HB	RsaI (rs2031920)	54–260	PCR–RFLP
Qu et al. (1998)	China	Asian	HB	DraI (rs6413432)	174–178	PCR
Qu et al. (1998)	China	Asian	HB	RsaI (rs2031920)	182–184	PCR

MBT molecular biology techniques, *HB* hospital-based studies, *PB* population-based studies, *NR* not reported

Table 2 Genotype distribution of CYP2E1 RsaI polymorphism used in the meta-analysis

References	Case			Control			HWE	MAF
	C1/C1	C1/C2	C2/C2	C1/C1	C1/C2	C2/C2		
Li et al. (2012)	116	76	25	114	73	11	0.995	0.24
Su et al. (2011)	52	10	2	41	22	1	0.572	0.19
Liu et al. (2010)	70	36	2	61	43	4	0.551	0.24
Eom et al. (2009)	254	133		242	145		NA	NA
Zienolddiny et al. (2008)	127	9		169	10		NA	NA
Minegishi et al. (2007)	300	175	30	147	106	3	0.004	0.22
Wang et al. (2006)	61	23	7	53	36	2	0.338	0.22
Lee et al. (2006)	64	97	8	90	89	12	0.243	0.30
Li et al. (2004)	116	76	25	114	75	11	0.942	0.24
Li et al. (2005)	33	63	3	28	34	4	0.314	0.32
Gu et al. (2004)	114	66		120	104		NA	NA
Wang et al. (2003)	113	51	0	97	75	9	0.512	0.26
Li et al. (2000)	67	22	3	75	57	5	0.336	0.24
Quiñones et al. (2001)	45	14	0	105	40	3	0.925	0.16
Wang et al. (1999)	77	41	1	231	134	81	<0.001	0.33
Persson et al. (1999)	48	26	2	63	44	6	0.898	0.25
Le Marchand et al. (1998)	269	66	2	338	102	14	0.198	0.14
Wu et al. (1997)	82	10	0	99	14	1	0.964	0.07
Wu et al. (1997)	39	5	1	65	26	1	0.665	0.15
El-Zein et al. (1997a, b)	47	7		47	3		NA	NA
Oyama et al. (1997)	87	32	7	391	196	25	0.999	0.20
London et al. (1996)	174	10	0	423	36	0	0.901	0.04
London et al. (1996)	154	3	0	242	5	0	0.982	0.01
Watanabe et al. (1995)	207	96	13	327	160	16	0.829	0.19
Hamada et al. (1995)	102	11	0	96	12	0	0.910	0.06
Persson et al. (1993)	176	8	0	182	19	1	0.915	0.05
Kato et al. (1992)	64	3	0	39	2	0	1.000	0.02
Shi et al. (2002)	78	31	11	57	44	19	0.128	0.34
Ye et al. (2006)	36	17	5	35	24	3	0.913	0.24
Zou et al. (2004)	31	19	11	16	12	13	0.031	0.46
Chen et al. (2002)	61	23	7	82	53	3	0.247	0.21
Li et al. (2008)	94	56		83	69		NA	NA
Huang et al. (2000)	25	26	3	152	101	7	0.109	0.22
Qu et al. (1998)	108	67	7	100	81	3	0.014	0.24

HWE Hardy–Weinberg equilibrium, *MAF* minor allele frequency, *C1* the major allele, *C2* the minor allele, *NA* not available

OR 0.34, 95 % CI 0.14–0.80, $P_h = 0.445$, $I^2 = 0.0$ %; heterozygous model: OR 0.70, 95 % CI 0.54–0.91, $P_h = 0.194$, $I^2 = 39.1$ %) and hospital-based studies (dominant model: OR 0.80, 95 % CI 0.69–0.93, $P_h = 0.008$, $I^2 = 45.2$ %; additive model: OR 0.84, 95 % CI 0.70–1.00, $P_h < 0.001$, $I^2 = 64.9$ %; heterozygous model: OR 0.80, 95 % CI 0.68–0.95, $P_h = 0.025$, $I^2 = 40.9$ %). In the subgroup analysis by smoking status, there was significant association among smokers (dominant model: OR 0.72, 95 % CI 0.55–0.94, $P_h = 0.374$, $I^2 = 7.2$ %) and non-smokers (dominant model: OR 0.74, 95 % CI 0.61–0.91, $P_h = 0.311$, $I^2 = 14.7$ %).

Table 5 shows the summary ORs of CYP2E1 DraI on the basis of 2,093 cases and 2,508 controls. Overall, there was no significant association between CYP2E1 DraI polymorphism and the risk of lung cancer when all the eligible studies were pooled into the meta-analysis. In the subgroup analysis by ethnicity, significantly decreased lung cancer risk was found among Asians (dominant model: OR 0.79, 95 % CI 0.66–0.95, $P_h = 0.319$, $I^2 = 14.2$ %; additive model: OR 0.82, 95 % CI 0.69–0.97, $P_h = 0.579$, $I^2 = 0.0$ %). In the subgroup analyses by source of controls and histological type, no significant association was observed among population-based studies, hospital-based studies, lung NSCLC, lung AC, and lung SC. In the subgroup analysis by smoking status, significant association was observed among

Table 3 Genotype distribution of CYP2E1 DraI (rs6413432) polymorphism used in the meta-analysis

References	Case			Control			HWE	MAF
	CC	CD	DD	CC	CD	DD		
Su et al. (2011)	40	21	3	24	37	3	0.061	0.34
Qu et al. (1998)	96	67	11	93	76	9	0.463	0.26
Li et al. (2008)	88	62		79	73		NA	NA
Uematsu et al. (1991)	47	42	2	43	22	11	0.037	0.29
Klinchid et al. (2009)	49	33		49	32		NA	NA
Hirvonen et al. (1993)	85	14	2	96	24	1	0.968	0.11
Kato et al. (1994)	46	12	0	33	5	0	0.949	0.07
Persson et al. (1993)	160	33	0	166	38	2	0.997	0.10
Le Marchand et al. (1998)	240	93	5	306	121	5	0.184	0.15
Wu et al. (1998)	77	8	0	82	21	1	0.959	0.11
Wu et al. (1998)	32	8	1	62	24	3	0.955	0.17
Persson et al. (1999)	47	24	5	59	47	6	0.685	0.26
Wang et al. (1999)	74	38	7	124	87	20	0.651	0.27
Quiñones et al. (2001)	34	22	2	82	40	7	0.783	0.21
Liang et al. (2004)	81	61	10	75	67	10	0.672	0.29
Zienolddiny et al. (2008)	248	55	8	294	47	2	0.997	0.07

HWE Hardy–Weinberg equilibrium, *MAF* minor allele frequency, *C* the major allele, *D* the minor allele, *NA* not available

smokers (dominant model: OR 0.49, 95 % CI 0.35–0.69, $P_h = 0.149$, $I^2 = 43.8$ %).

Test of heterogeneity and sensitivity

There was significant heterogeneity among these studies for dominant model (RsaI: $P_h = 0.015$), recessive model (RsaI: $P_h = 0.041$ and DraI: $P_h = 0.075$), homozygote model (RsaI: $P_h < 0.001$), heterozygote model (RsaI: $P_h = 0.050$ and DraI: $P_h = 0.033$), and additive model (RsaI: $P_h < 0.001$ and DraI: $P_h = 0.079$). Then, we assessed the source of heterogeneity by ethnicity and source of controls. The results of meta-regression indicated that ethnicity (dominant model: $P = 0.713$ for RsaI and $P = 0.094$ for DraI; recessive model: $P = 0.161$ for RsaI and $P = 0.140$ for DraI; additive model: $P = 0.314$ for RsaI and $P = 0.062$ for DraI; homozygote model: $P = 0.161$ for RsaI; heterozygote model: $P = 0.637$ for RsaI) and source of controls (dominant model: $P = 0.752$ for RsaI and $P = 0.248$ for DraI; recessive model: $P = 0.691$ for RsaI and and $P = 0.115$ for DraI; additive model: $P = 0.982$ for RsaI and $P = 0.578$ for DraI; homozygote model: $P = 0.637$ for RsaI; heterozygote model: $P = 0.989$ for RsaI) did not contribute to substantial heterogeneity among the meta-analysis. Although there were five studies (Zou et al. 2004; Minegishi et al. 2007; Qu et al. 1998; Wang et al. 1999; Uematsu et al. 1991) deviated from HWE for this meta-analysis, the corresponding pooled ORs were not materially altered by excluding these studies in overall and subgroup analyses. The sample size for cases and controls in all eligible studies ranged from 96 to 819, the corresponding pooled ORs were not qualitatively altered with or without the study of small sample in the overall analysis and all subgroup analyses. However, when the study of Su et al. (2011) was excluded, the results were changed in Asians for DraI (dominant model: OR 0.84, 95 % CI 0.70–1.01; additive model: OR 0.85, 95 % CI 0.72–1.02). In addition, when the study of Persson et al. (1993) was excluded, the results were changed in Caucasians for RsaI (additive model: OR 0.68, 95 % CI 0.34–1.39; dominant model: OR 0.68, 95 % CI 0.33–1.39).

Publication bias

Both Begg's funnel plot and Egger's test were performed to access the publication bias of this meta-analysis. Begg's funnel plots did not reveal any evidence of obvious asymmetry in any genetic model in the overall meta-analysis (Fig. 3). The Egger's test results also suggested no evidence of publication bias in the meta-analysis of RsaI ($P = 0.325$ for dominant model, $P = 0.147$ for recessive model, $P = 0.065$ for additive model, $P = 0.101$ for homozygote model, and $P = 0.119$ for heterozygote model) and DraI ($P = 0.247$ for dominant model, $P = 0.607$ for recessive model, $P = 0.237$ for additive model, $P = 0.605$ for homozygote model, and $P = 0.353$ for heterozygote model), respectively.

Discussion

A number of epidemiologic studies have reported the association of CYP2E1 with lung cancer risk. However, the results remained controversial. Some original studies

Table 4 Results of meta-analysis for CYP2E1 RsaI (rs2031920) polymorphism and the risk of lung cancer

Generic model		Recessive model			Dominant model			Homozygous model			Heterozygous model			Additive model		
RsaI	*n*	C2/C2 vs. C1/C2 + C1/C1			C1/C2 + C2/C2 vs. C1/C1			C2/C2 vs. C1/C1			C1/C2 + vs. C1/C1			C2 vs. C1		
		OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)
Overall	34 (5,074/6,828)	1.02 (0.67–1.53)*	<0.001	57.7	**0.80 (0.71–0.90)**	0.015	37.8	0.96 (0.63–1.46)	<0.001	57.6	**0.80 (0.70–0.90)**	0.050	32.3	**0.82 (0.72–0.94)**	<0.001	58.9
Ethnicity																
Caucasian	3 (504/840)	0.36 (0.01–8.99)	–	–	0.66 (0.42–1.06)	0.252	27.3	0.34 (0.01–8.52)	–	–	**0.56 (0.32–0.98)**	0.441	0.0	**0.55 (0.32–0.94)**	0.347	0.0
Asian	23 (3,646/4,734)	1.13 (0.74–1.04)*	<0.001	61.2	**0.81 (0.71–0.93)**	0.003	50.3	1.07 (0.69–1.66)	<0.001	61.1	**0.81 (0.69–0.95)**	0.012	46.7	0.86 (0.74–1.01)	<0.001	67.9
African	2 (249/361)	0.41 (0.02–10.16)	–	–	0.84 (0.40–1.75)	0.853	0.0	0.40 (0.02–10.00)	–	–	0.88 (0.42–1.85)	0.917	0.0	0.80 (0.39–1.63)	0.800	0.0
Source of control																
PB	4 (673/878)	**0.39 (0.16–0.91)**	0.327	10.6	**0.69 (0.54–0.88)**	0.304	17.4	**0.34 (0.14–0.80)**	0.445	0.0	**0.70 (0.54–0.91)**	0.194	39.1	**0.67 (0.53–0.84)**	0.677	0.0
HB	25 (3,770/4,524)	1.16 (0.68–1.98)*	<0.001	64.5	**0.80 (0.69–0.93)**	0.008	45.2	1.11 (0.64–1.91)	<0.001	63.9	**0.80 (0.68–0.95)**	0.025	40.9	**0.84 (0.70–1.00)**	<0.001	64.9
Histological type																
NSCLC	12 (2,048/3,700)	1.24 (0.70–2.18)*	0.031	52.8	0.86 (0.68–1.07)	0.001	63.8	1.20 (0.67–2.17)	0.023	54.9	0.87 (0.71–1.06)	0.033	50.6	0.92 (0.76–1.12)	0.003	64.6
AC	11 (1,183/3,502)	0.92 (0.38–2.22)*	0.033	54.2	0.89 (0.69–1.15)	0.021	52.4	0.91 (0.37–2.22)	0.033	54.1	**0.84 (0.71–1.00)**	0.129	36.1	0.86 (0.69–1.09)	0.022	55.3
SCC	9 (624/3,271)	1.25 (0.75–2.09)	0.359	9.1	0.85 (0.63–1.15)	0.027	53.9	1.19 (0.70–2.00)	0.393	4.4	0.89 (0.64–1.25)	0.025	56.2	0.95 (0.79–1.12)	0.173	31.9
Smoking status																
Non-smokers	9 (469/1,055)	0.12 (0.01–2.10)	–	–	**0.72 (0.55–0.94)**	0.374	7.2	0.11 (0.01–1.98)	–	–	0.64 (0.36–1.13)	0.473	0.0	0.60 (0.33–1.11)	0.890	0.0
Smokers	10 (1,293/1,227)	0.26 (0.03–2.23)	–	–	**0.74 (0.61–0.91)**	0.311	14.7	0.25 (0.03–2.23)	–	–	0.78 (0.52–1.17)	0.532	0.0	0.74 (0.51–1.07)	0.692	0.0

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models. The bold values indicate that the results are statistically significant

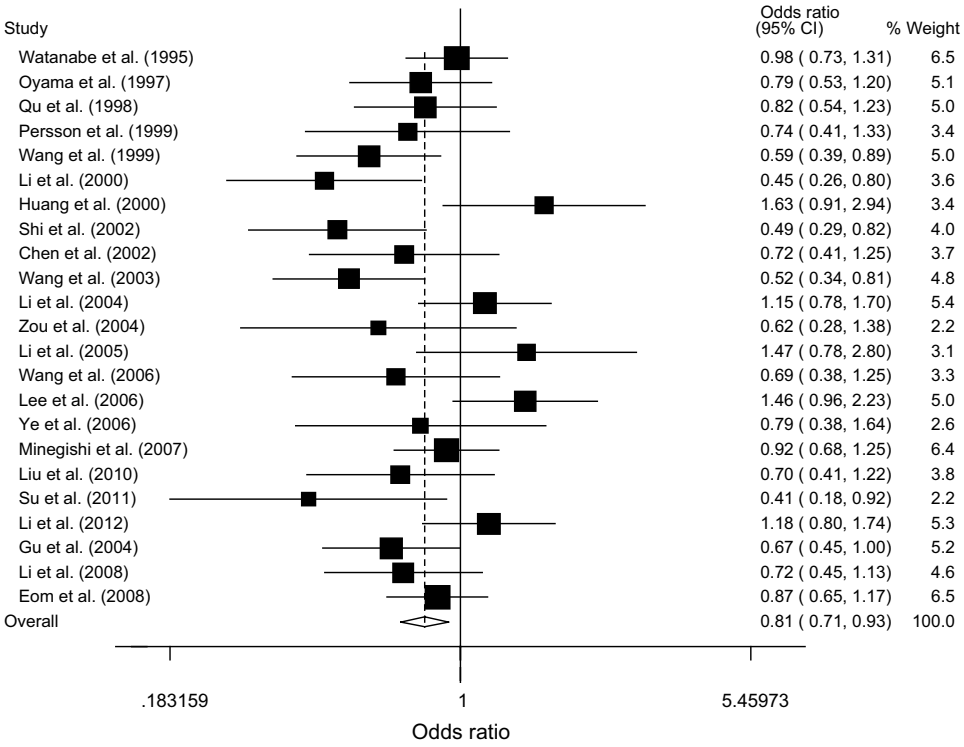

Fig. 2 Forest plot of CYP2E1 RsaI polymorphism and lung cancer risk among Asians (dominant model)

thought that CYP2E1 RsaI (rs2031920), DraI (rs6413432) polymorphisms were associated with lung cancer risk, but others had different opinions. Available data on the effect of CYP2E1 polymorphisms in lung cancer are scarce, especially in comparison with the bulk of studies on other genes involved in carcinogen activation/detoxification. In order to resolve this conflict, a meta-analysis was conducted to explore the association between CYP2E1 RsaI (rs2031920), DraI (rs6413432) polymorphisms and lung cancer risk.

When all the eligible studies were pooled into the meta-analysis of polymorphism, there was no significant association between CYP2E1 DraI polymorphism and the risk of lung cancer. In further stratified and sensitivity analyses, no significant association was observed in any subgroup analysis, but not smoking status. Persson et al. (1999) and Zienolddiny et al. (2008) found that CYP2E1 DraI polymorphism was not associated with lung cancer risk in Caucasians. Persson et al. (1999), Wang et al. (1999), Qu et al. (1998), Liang et al. (2004), Li et al. (2008), and Klinchid et al. (2009) found that CYP2E1 DraI polymorphism was not associated with lung cancer risk in Asians. The results of our meta-analysis supported the negative association between CYP2E1 DraI polymorphism and lung cancer risk. In the subgroup analysis by smoking status, significant association was observed among smokers (dominant model: OR 0.49, 95 % CI 0.35–0.69). However, at any case, the association between CYP2E1 DraI polymorphism and lung cancer risk among smokers essentially remains an open field, as the number of studies ($n = 4$) is considerably smaller than that needed for the achievement of robust conclusions (Higgins and Green 2008).

When all the eligible studies were pooled into the meta-analysis of CYP2E1 RsaI polymorphism, significantly decreased lung cancer risk in the total population (dominant model: OR 0.80, 95 %CI 0.71–0.90; heterozygote model: OR 0.80, 95 % CI 0.70–0.90; additive model: OR 0.82, 95 % CI 0.72–0.94). In further stratified and sensitivity analyses by ethnicity, significantly decreased lung cancer risk was only observed among Asians. Wang et al. (1999), Li et al. (2000), Shi et al. (2002), Wang et al. (2003), Sunaga et al. (2002), and Gu et al. (2004) found that CYP2E1 RsaI polymorphism contributed to the development of lung cancer in Asians. The results of our meta-analysis supported the positive association between CYP2E1 RsaI polymorphism and lung cancer risk. We did not observe significantly decreased lung cancer risk among Caucasians and Africans, the reason may be because only two small studies are included among Africans and three small studies are included among Caucasians in the meta-analysis. Hence, at any case, the association between CYP2E1 RsaI polymorphism and lung cancer risk among Caucasians and Africans essentially remains an open field, as the number of studies ($n = 2$ for Africans and $n = 3$ for Caucasians) is considerably smaller than that needed for the achievement of robust conclusions (Higgins and Green 2008). In the subgroup analysis by source of controls, significant association was observed among the population-based studies

Table 5 Results of meta-analysis for CYP2E1 DraI (rs6413432) polymorphism and the risk of lung cancer

Generic model		Recessive model			Dominant model			Homozygous model			Heterozygous model			Additive model		
DraI	*n*	DD vs. CD + CC			CD + DD vs. CC			DD vs. CC			CD vs. CC			D vs. C		
		OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)	OR (95 % CI)	P_h	I^2 (%)
Overall	16 (2,093/2,508)	0.89 (0.63–1.27)	0.320	12.5	0.87 (0.73–1.03)	0.075	36.0	0.85 (0.60–1.22)	0.402	4.4	0.87 (0.71–1.07)	0.033	45.5	0.89 (0.76–1.05)	0.079	37.2
Ethnicity																
Caucasian	3 (605/670)	2.14 (0.76–6.01)	0.211	35.7	1.03 (0.65–1.65)*	0.092	58.1	2.16 (0.77–6.05)	0.196	38.6	1.05 (0.78–1.42)	0.165	44.4	1.06 (0.65–1.73)	0.049	66.8
Asian	8 (908/1046)	0.77 (0.51–1.18)	0.201	31.2	**0.79 (0.66–0.95)**	0.319	14.2	0.71 (0.46–1.10)	0.372	7.0	0.78 (0.56–1.09)	0.046	55.6	**0.82 (0.69–0.97)**	0.579	0.0-
Source of control																
PB	2 (649/775)	2.25 (0.89–5.70)	0.214	35.1	1.16 (0.91–1.49)	0.102	62.5	2.29 (0.91–5.81)	0.195	40.5	1.11 (0.86–1.43)	0.199	39.3	1.25 (0.79–1.97)	0.052	73.6
HB	11 (1,219/1,416)	0.90 (0.57–1.41)	0.896	0.0	0.76 (0.64–0.91)	0.384	6.3	0.80 (0.50–1.26)	0.876	0.0	0.74 (0.61–0.90)	0.288	17.4	0.80 (0.68–0.94)	0.394	5.0
Histological type																
NSCLC	8 (903/1,174)	0.84 (0.47–1.51)	0.157	39.7	0.89 (0.73–1.08)	0.391	5.1	0.86 (0.47–1.57)	0.284	20.5	0.89 (0.61–1.29)	0.068	51.4	0.92 (0.76–1.11)	0.580	0.0
AC	7 (438/1,093)	0.74 (0.35–1.55)	0.498	0.0	0.85 (0.66–1.08)	0.174	33.3	0.77 (0.36–1.64)	0.691	0.0	0.89 (0.53–1.49)	0.053	54.1	0.90 (0.71–1.13)	0.548	0.0
SCC	7 (373/1,093)	1.11 (0.54–2.29)	0.248	26.0	0.97 (0.74–1.26)	0.676	0.0	1.24 (0.59–2.61)	0.321	14.6	1.00 (0.73–1.37)	0.494	0.0	1.02 (0.79–1.32)	0.533	0.0
Smoking status																
Non-smokers	4 (120/333)	0.54 (0.11–2.52)	–	–	0.74 (0.47–1.16)	0.987	0.0	0.48 (0.10–2.33)	–	–	0.75 (0.35–1.61)	–	–	0.71 (0.39–1.29)	–	–
Smokers	4 (339/307)	0.72 (0.23–2.23)	–	–	**0.49 (0.35–0.69)**	0.149	43.8	0.61 (0.19–1.97)	–	–	0.67 (0.36–1.27)	–	–	0.72 (0.45–1.17)	–	–

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models. The bold values indicate that the results are statistically significant

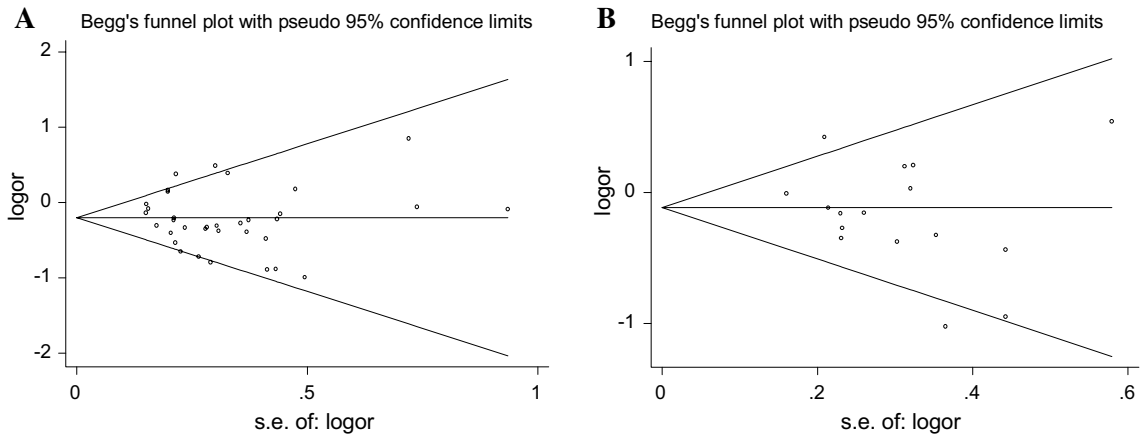

Fig. 3 Begg's funnel plot of publication bias between the CYP2E1 polymorphisms and lung cancer risk in dominant model (**a** DraI, **b** RsaI)

and hospital-based studies. The hospital-based studies have some biases because such controls may be a sample of ill-defined reference population, particularly when the genotypes under investigation were associated with the disease conditions. Hence, using a proper and representative population-based study was much important in the studies. In the subgroup analysis by smoking status, there was significant association among smokers and non-smokers. The results indicated that there could be an interaction between cigarette smoking and CYP2E1 RsaI polymorphism. It is possible that some non-smokers with the variant CYP2E1 RsaI polymorphism were susceptible to be exposed to low levels of tobacco smoke, and it is also likely that these nonsmokers may have been exposed to passive smoking. These hypotheses also need to be tested in future studies. However, only small number of studies examined the association between the CYP2E1 RsaI polymorphism and lung cancer risk in smokers or nonsmokers, hence, our meta-analysis should be interpreted with caution. It is well known that the development of squamous and small cell carcinoma is strongly associated with smoking, whereas that of adenocarcinoma is less associated compared with those two subtypes, indicating that carcinogenic processes are different among the histological subtypes of lung cancer (Sato et al. 1994). Therefore, stratified analyses were performed by histological type. In the subgroup analysis by pathological type, significantly decreased lung AC risk was observed for CYP2E1 RsaI polymorphism.

Lung cancer is a multi-factorial disease that results from complex interactions between many genetic and environmental factors. This means that there will not be single gene or single environmental factor that has large effects on lung cancer susceptibility. For lung cancer, although different results in published meta-analyses were partly explained by the different ethnic populations included in the analyses, large studies with detailed genetic and environmental exposure information are needed to evaluate reliably any moderate genetic effects. In order to control these environmental factors, some statistical methods, such as the logistic regression models, multilevel models and artificial neural networks (ANNs) could be applied in future analyses.

We noticed that two meta-analysis had been reported on the lung cancer risk with CYP2E1 polymorphisms. Wang et al. (2010) included 26 case–control studies (4,436 cases and 6,385 controls) for CYP2E1 RraI and 13 case–control studies (1,666 cases and 2,093 controls) for CYP2E1 DraI. Their meta-analysis had observed a decreased lung cancer risk among subjects carrying c1/c2 and c1/c2 + c2/c2 genotypes in the Asians and on the basis of population control in stratified analysis. Their meta-analysis also 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). Zhan et al. (2010) included 21 case–control studies (3,984 cases and 5,496 controls) for CYP2E1 RraI. Their meta-analysis suggests that CYP2E1 RraI polymorphism was a decreased risk factor for the developing lung cancer among Asians and lung SC. However, the results of the present meta-analysis are not in accordance with those reported the previous two meta-analyses (Wang et al. 2010; Zhan et al. 2010). Our meta-analysis included more studies than previous two meta-analyses, there are 5,074 cases and 6,828 controls for CYP2E1 RsaI (from 34 studies) and 2,093 cases and 2,508 controls for DraI (from 16 studies). Our meta-analysis indicates that CYP2E1 RsaI polymorphism is associated with lung cancer risk among Asians, CYP2E1 RsaI polymorphism may be associated with lung adenocarcinoma risk, and CYP2E1 RsaI and DraI polymorphisms may be associated with decreased lung cancer risk in smokers.

There are several limitations in this meta-analysis. First, the controls were not uniformly defined. Although all the

controls were healthy populations, most of them were common populations, some controls were population-based; other controls were hospital-based. Hence, non-differential misclassification bias is possible. Second, in the subgroup analysis may have had insufficient statistical power to check an association. Third, we were also unable to examine the interactions among gene–environment, lacking of the original data of the included studies limited our further evaluation of potential interactions, which may be an important component of the association between *CYP2E1* RsaI (rs2031920) and DraI (rs6413432) polymorphisms and environment and lung cancer risk. Fourth, it was much difficult to get the all articles published in various languages. We only included the studies published in English and Chinese. Last, our results were based on unadjusted published estimates. Because of data limitations, we were unable to adjust them such as age, smoking, alcohol consumption, etc.

In summary, this meta-analysis indicates that CYP2E1 RsaI polymorphism is associated with lung cancer risk among Asians, CYP2E1 RsaI polymorphism may be associated with lung adenocarcinoma risk, and CYP2E1 RsaI and DraI polymorphisms may be associated with decreased lung cancer risk in smokers. However, and a study with a larger sample size is needed to further evaluate gene–environment interaction on CYP2E1 polymorphisms and lung cancer risk.

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