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The Polymorphism of CYP2E1 Rsa I/Pst I Gene and Susceptibility to Respiratory System Cancer

A Systematic Review and Meta-Analysis of 34 Studies

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Abstract: The purpose of this articles is to determine whether the cytochrome P450 2E1 (CYP2E1) Rsa I/Pst I gene polymorphism is correlated with respiratory system cancers.

Respiratory system cancers included lung cancer, laryngeal cancer, nasopharyngeal cancer, and cancers of other respiratory organs, which are the most common malignant tumors worldwide; the significant relationship between CYP2E1 Rsa I/Pst I gene polymorphism and some respiratory system cancer have been reported, but results of some other studies are controversial. The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the association.

PubMed, EMBASE, Cochrane Library Databases, China National Knowledge Infrastructure, and Wanfang Database (up to July 20, 2014) were searched for all case–control studies those mainly studied the relationship between CYP2E1 Rsa I/Pst I gene polymorphism and the susceptibility of respiratory system cancer.

A total of 332 articles were collected, among which 34 studies that involved 7028 cases and 9822 controls fulfilled the inclusion criteria after being assessed by 2 reviewers. When stratified by cancer site, the C2/C2 polymorphism could increase the risk of nasopharyngeal cancer under the homozygote model (C2C2 vs C1C1: OR = 1.85, 95% CI = 1.20–2.85, $P = 0.005$) and recessive model (C2C2 vs C1C2/C1C1: OR = 1.89, 95% CI = 1.23–2.89, $P = 0.003$). Protection effect was found in lung cancer in heterozygote model (C1C2 vs C1C1: OR = 0.82, 95% CI = 0.74–0.91, $P < 0.001$), dominant model (C1C2/C2C2 vs C1C1: OR = 0.83, 95% CI = 0.76–0.90, $P < 0.001$), and allele contrast model (C2 vs C1: OR = 0.85, 95% CI = 0.73–1.00, $P = 0.045$). With regard to ethnicity subgroup analysis, there was significant association in Asian population in heterozygote model (C1C2 vs C1C1: OR = 0.85, 95% CI = 0.78–0.94, $P = 0.001$), dominant model (C1C2/C2C2 vs C1C1: OR = 0.88, 95% CI = 0.81–0.95, $P = 0.001$), and recessive model (C2C2 vs C1C2/C1C1: OR = 1.25, 95% CI = 1.01–1.53, $P = 0.036$).

CYP2E1 Rsa I/Pst I gene polymorphism may reduce the risk of respiratory system cancer. Furthermore, significant association was also found in Asian populations.

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Abbreviations: CNKI = China National Knowledge Infrastructure, HWE = Hardy–Weinberg equilibrium, NPC = nasopharyngeal carcinoma.

INTRODUCTION

Respiratory system cancer, including lung cancer, laryngeal cancer, nasopharyngeal cancer, bronchus cancer, and cancers of other respiratory organs, is the most common malignant tumors that threaten the health of human worldwide.[1,2] Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males and was the leading cancer types for the estimated deaths in 2014.[1,3] Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers in Southern Asia and Northern Africa; the incidence reaches 25 per 100,000 people that is only 0.5–2 per 100,000 people in Europe and America.[4] With regard to laryngeal cancer, among the most common forms of cancers are the cancers of the upper respiratory tract.[3,5] Despite recent advances in the therapy, the survival rate of laryngeal cancer remains low.[6] More and more researches have generally indicated that respiratory system carcinogenesis is a multifactorial, complex, and multistep event, in which several risk factors, such as the environmental factors, life habits, genes, and gene polymorphisms may play an important role in the development and progression of respiratory system cancers.[7–12] However, the exact mechanism of cancer developments remains uncertain. Recently, many researches have been performed focusing on the relationship between gene polymorphism and susceptibility to respiratory system cancers.[9,10,13–15]

Many research dedicated that cytochrome P450 (CYP) superfamily catalyzed enzymes for carcinogens. CYP enzymes were involved in the initiation of various cancers by activating several environmental pollutants to form DNA adducts.[16,17] CYP 2E1, ethanol-inducible enzyme, a member of the CYP superfamily, is involved in the metabolic activation of many low-molecular-weight compounds, such as N-nitrosamines, aniline, vinyl chloride, and urethane.[18,19] Molecular biological evidence showed that CYP2E1 Rsa I/Pst I polymorphism [−1239G>C (rs3813867) and −999C>T (rs2031920)] in the promoter of CYP2E1 enhanced the transcriptional activity of gene by altering its binding to transcription factor, that is, hepatocyte nuclear factor-1,[20] and influenced the susceptibility to N-nitrosamine-linked carcinogenesis,[21] indicating that genetic polymorphism of the Rsa I/Pst I gene might be associated with increased risk for cancers; therefore, many researches

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were performed to determine whether the Rsa I/Pst I polymorphism is associated with respiratory system cancers. Recently, in several studies, significant association has been found between CYP2E1 Rsa I/Pst I polymorphism and respiratory system cancer. For instance, the study by Su et al[22] suggested that CYP2E1 Rsa I/Pst I polymorphism reduced the risk of lung cancer; however, Hildesheim et al[23] thought that the presence of the high-producer C2 allele of CYP2E1 Rsa I/Pst I was correlated with an increased risk of NPC in the Taiwan population. The study by Tai et al[24] showed no statistically significant increased risk of laryngeal cancer among individuals that carried the C2 allele of CYP2E1 Rsa I/Pst I gene. Furthermore, no consolidated report has been conducted to investigate the association between CYP2E1 Rsa I/Pst I polymorphism and respiratory system cancers. Therefore, we performed the meta-analysis to make contribution to obtain a more exact evaluation of the association between CYP2E1Rsa I/Pst I polymorphism and respiratory system cancer risk.

MATERIALS AND METHODS

Search Strategy

We performed a literature research for all relevant articles studying association between the CYP2E1Rsa I/Pst I polymorphism and respiratory system cancers on PubMed, EMBASE, Cochrane Library Databases, China National Knowledge Infrastructure, and Wanfang Database (up to July 20, 2014), using the following searching terms: ''cytochrome p450 2E1 OR cytochrome p450 IIE1 OR CYP2E1 OR CYP2E1'' AND ''SNP OR polymorphism OR allele OR variation'' AND '''cancer OR carcinoma OR adenocarcinoma OR tumour OR tumor.'' There was no restriction on language; later, these articles were selected by reviewers to find out studies focusing on respiratory system cancers. The combined phrases and a hand search of references of original studies are also quoted on this topic.

Inclusion and Exclusion Criteria

Any study that was included was to meet the following criteria: evaluating the association between CYP2E1Rsa I/Pst I polymorphism and respiratory cancer risk; case–control studies; and sufficient data (allele and gene types frequency). Excluded criteria were: not case–control studies, such as reviews, comments, or case reports; and no sufficient data.

Data Extraction

Data extraction was carried out independently by 2 reviewers according to the predetermined criteria. Every discrepancy was settled through discussions till consensus was reached. Information extracted from each eligible study was extracted as follows: first author's name, year of publication, ethnicity of the study population, characteristics of cancer cases, source of controls, number of cases and controls, and number of different genotypes in cases and controls.

Data Synthesis and Statistical Analysis

Odds ratio (OR) with 95% confidence interval (CI) were calculated to assess the strength of the association between the CYP2E1Rsa I/Pst I polymorphism and the

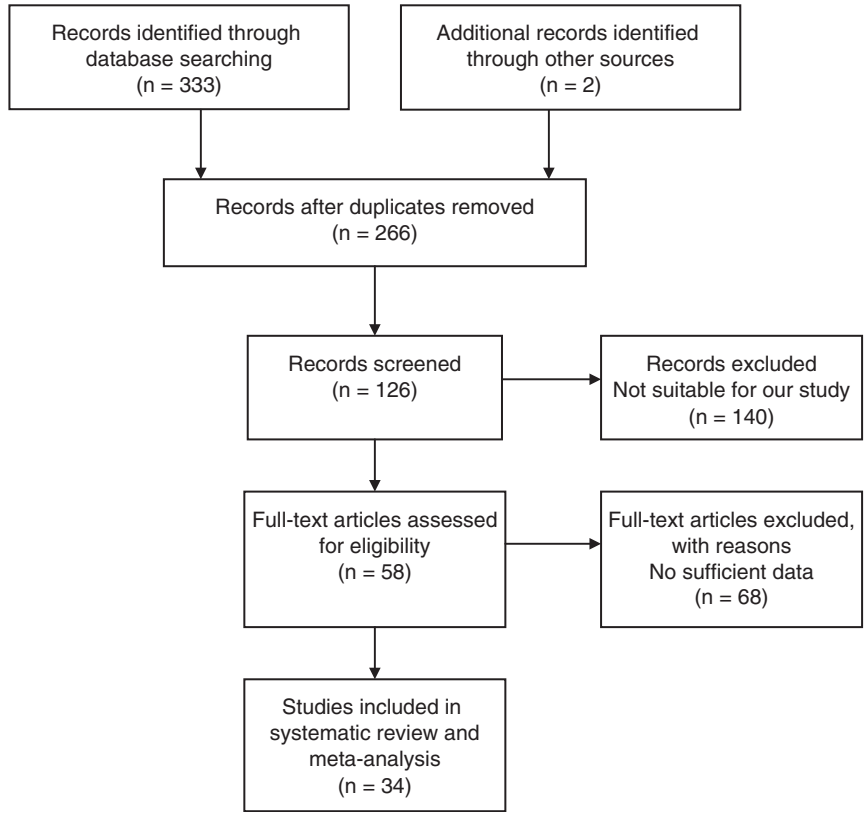

FIGURE 1. The study selection and inclusion process.

TABLE 1. General Characteristics of Studies Included in the Meta-Analysis

Author	Year	Cancer Type	Ethnicity	Sample Size		Case		Control		HWE *P* Value
				Case	Control	C2/C1	C2C2/C1C2/C1C1	C2/C1	C2C2/C1C2/C1C1	
Wang DQet al	2006	Lung cancer	Asian	91	91	37/145	7/23/61	40/142	2/36/53	0.14
Lee et al	2006	Lung cancer	Asian	169	191	113/225	8/97/64	113/269	12/89/90	0.11
Li W et al	2012	Lung cancer	Asian	217	198	126/308	25/76/116	95/301	11/73/114	0.89
Li WYet al	2004	Lung cancer	Asian	99	66	39/159	3/33/63	36/96	4/28/34	0.57
Cao et al	2014	Lung cancer	Asian	526	526	152/900	12/128/386	204/848	18/168/340	0.62
Wang SLet al	1999	Lung cancer	Asian	119	446	43/195	1/41/77	296/596	81/134/231	<0.001
Marchand et al	1998	Lung cancer	Caucasian	337	454	70/604	2/66/269	130/778	14/102/338	0.07
Li Z et al	2000	Lung cancer	Asian	92	137	28/156	3/22/67	67/207	5/57/75	0.14
Oyama et al	2002	Lung cancer	Asian	126	612	46/206	7/32/87	246/978	25/196/391	0.94
Persson et al	1993	Lung cancer	Caucasian	184	148	8/360	0/8/176	16/280	1/14/133	0.36
Sugimura et al	1995	Lung cancer	Caucasian	113	108	11/215	0/11/102	12/204	0/12/96	0.54
London et al	1996	Lung cancer	Mixed	341	706	13/669	0/13/328	41/1371	0/41/665	0.43
Su et al	2011	Lung cancer	Asian	64	64	14/114	2/10/52	24/104	1/22/41	0.31
Zienolddiny et al	2009	Lung Cancer	Caucasian	311	343	77/545	14/49/248	57/629	8/41/294	0.10
Quinones et al	2001	Lung cancer	Mixed	59	148	14/104	0/14/45	46/250	3/40/105	0.72
Minegishi et al	2007	Lung cancer	Asian	505	256	235/775	30/175/300	112/400	3/106/147	0.08
Ye et al	2006	Lung cancer	Asian	58	62	27/89	5/17/36	30/94	3/24/35	0.66
Huang et al	2000	Lung cancer	Asian	54	267	32/76	3/26/25	122/412	7/108/152	0.02
Wu et al	1997	Lung cancer	Mixed	92	115	10/174	0/10/82	17/213	1/15/99	0.61
Wang BGet al	2004	Lung cancer	Asian	91	91	37/145	7/23/61	40/142	2/36/53	0.14
Watanabe et al	1995	Lung cancer	Asian	316	503	122/510	13/96/207	192/814	16/160/327	0.50
Liang et al	2004	Lung Cancer	Asian	152	152		71/81*		77/75*	
Gu et al	2007	Lung cancer	Asian	279	684		110/169*		277/407*	
Eom et al	2009	Lung cancer	Asian	387	387		133/254*		145/242*	
Li D et al	2008	Lung cancer	Asian	150	152		56/94*		69/83*	
Wang J et al	2003		Asian	164	181		51/113*		84/97*	
Hildesheim et al	1997	Nasopharyngeal cancer	Asian	364	320	161/565	27/107/229	131/509	9/113/198	0.13
Guo et al	2010	Nasopharyngeal cancer	Asian	356	624	148/564	20/108/228	238/1010	26/186/412	0.39
Kongruttanachok et al	2001	Nasopharyngeal cancer	Asian	217	297	87/347	8/71/138	113/481	5/103/189	0.08
Yang et al	2005	Nasopharyngeal cancer	Asian	103	553		46/57*		222/331*	
Morita et al	1999	Laryngeal cancer	Asian	69	164	31/107	6/19/44	66/262	7/52/105	0.86
Tai et al	2010	Laryngeal cancer	Asian	278	278	107/449	13/81/184	108/448	12/84/182	0.56
Gajecka et al	2005	Laryngeal cancer	Caucasian	288	323	9/567	0/9/279	18/628	0/18/305	0.61
Matthias et al	1998	Laryngeal cancer	Caucasian	257	175	18/496	1/16/240	10/340	0/10/165	0.70

* C2C2+C1C2/C1C1.

respiratory system cancers under 5 genetic models: the allele contrast (C2 vs C1), dominant (C1C2 + C2C2 vs C1C1), recessive (C2C2 vs C1C2 + C1C1), homozygous (C2C2 vs C1C1), and heterozygous (C1C2 vs C1C1) models. Meanwhile, stratified analyses were performed by ethnicity and the type of tumor. The statistical heterogeneity assumption was assessed by

TABLE 2. Results of Allele Contrast, Heterozygote, and Homozygote Models for CYP2E1 RsaI/PstI Polymorphism and Respiratory System Cancers

Group	N	C2 vs C1			C2C2 vs C1C1			C1C2 vs C1C1		
		OR (95% CI)	*P*	Model	OR (95% CI)	*P*	Model	OR (95% CI)	*P*	Model
Overall	34	0.90 (0.80, 1.02)	0.105	R*	1.15 (0.94, 1.40)	0.163	F†	0.85 (0.78, 0.93)	<0.001	F†
Cancer type										
Lung cancer	26	0.85 (0.73, 1.00)	0.045	R*	0.97 (0.77, 1.24)	0.823	F†	0.82 (0.74, 0.91)	<0.001	F†
Nasopharyngeal cancer	4	1.10 (0.95, 1.28)	0.213	R*	1.85 (1.20, 2.85)	0.005	F†	0.94 (0.78, 1.14)	0.530	F†
Laryngeal cancer	4	1.00 (0.79, 1.25)	0.966	R*	1.34 (0.70, 2.57)	0.370	F†	0.89 (0.68, 1.17)	0.410	F†
Ethnicity										
Asian	25	0.93 (0.82, 1.06)	0.299	R*	1.21 (0.98, 1.49)	0.078	F†	0.85 (0.78, 0.94)	0.001	F†
Caucasian	6	0.84 (0.54, 1.30)	0.422	R*	0.86 (0.46, 1.61)	0.636	F†	0.90 (0.71, 1.13)	0.349	F†
Mixed	3	0.70 (0.47, 1.03)	0.071	R*	0.36 (0.04, 3.20)	0.359	F†	0.73 (0.49, 1.11)	0.140	F†

* Random effect model.
† Fixed effect model.

the I^2 statistics to quantify inconsistency, which represents the proportion of interstudy variability that can be due to heterogeneity other than to chance. An I^2 value of >50% was considered as a significant heterogeneity among studies; so the pooled OR estimate of each study was calculated by the random effect model, otherwise, the fixed effect model was used. Sensitivity analysis and publication bias were also evaluated in our study. All statistical analyses were carried out using STATA version 12.0 (STATA Corp, College Station, TX). $P < 0.05$ was considered statistically significant. This is a systemic review about literatures, therefore ethical approval was not necessary for our research.

RESULTS

Study Characteristics

A total of 332 articles were preliminarily reviewed, among which 34 studies[22–55] with 7028 cases and 9822 controls eventually met the eligibility criteria (Figure 1). Among these studies, 25 studies[22–27,29–33,35,36,40–43,46–52,55] were performed in Asian patients, 6 studies[28,37,39,45,53,54] in Caucasian patients, and 3 studies[34,38,44] in mixed populations. Three cancer types were addressed: 26 studies were performed in lung cancer,[22,25–49] 4 studies[23,50–52] focused on nasopharyngeal cancer, and 4 studies[24,53–55] reported laryngeal cancer. For lung cancer,

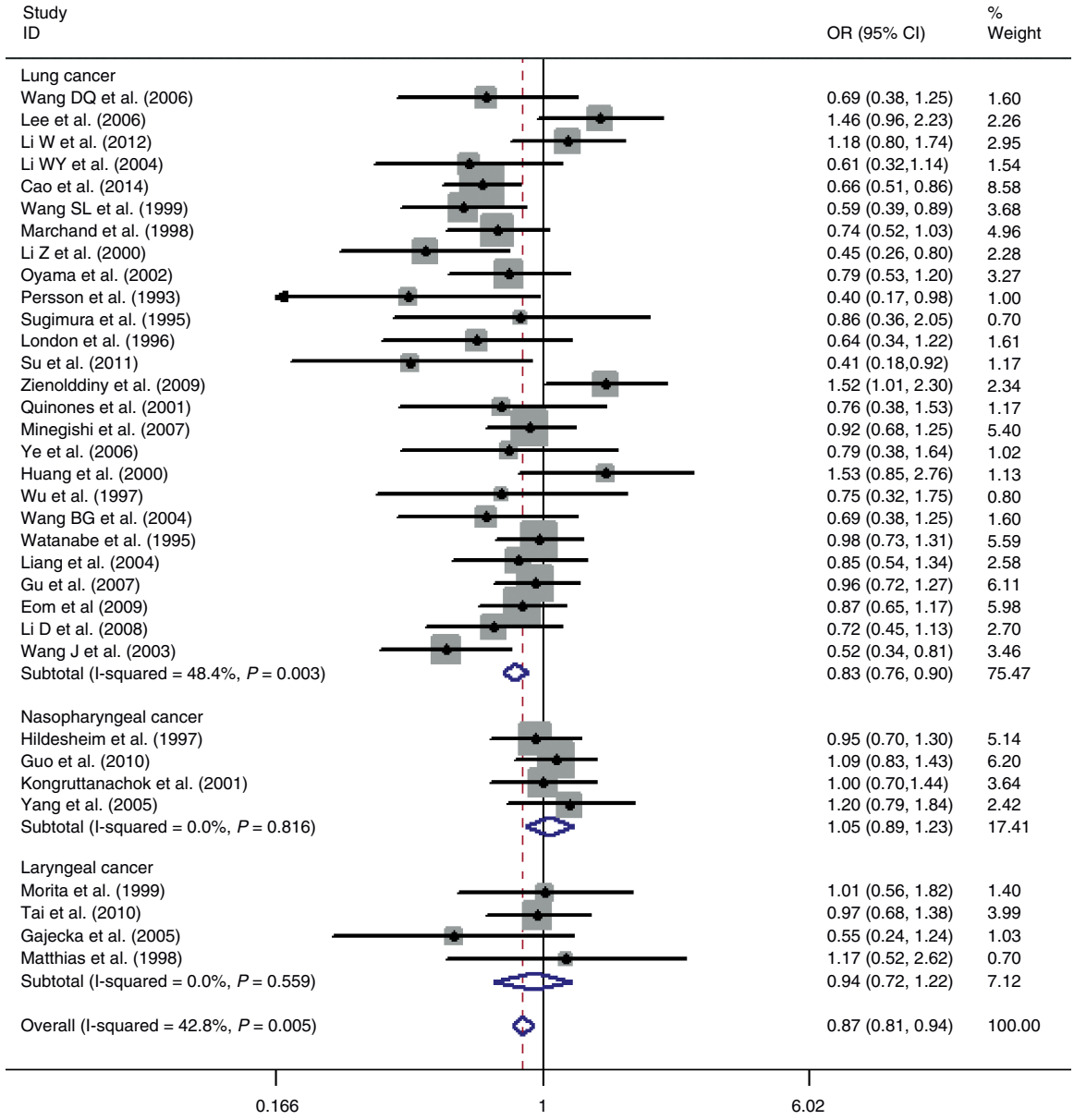

FIGURE 2. Forest plot describing the meta-analysis under dominant model for the association between CYP2E1 Rsa I/Pst I polymorphism and the risk of digestive system cancer. (A) Stratified by cancer types. (B) Stratified by ethnicity.

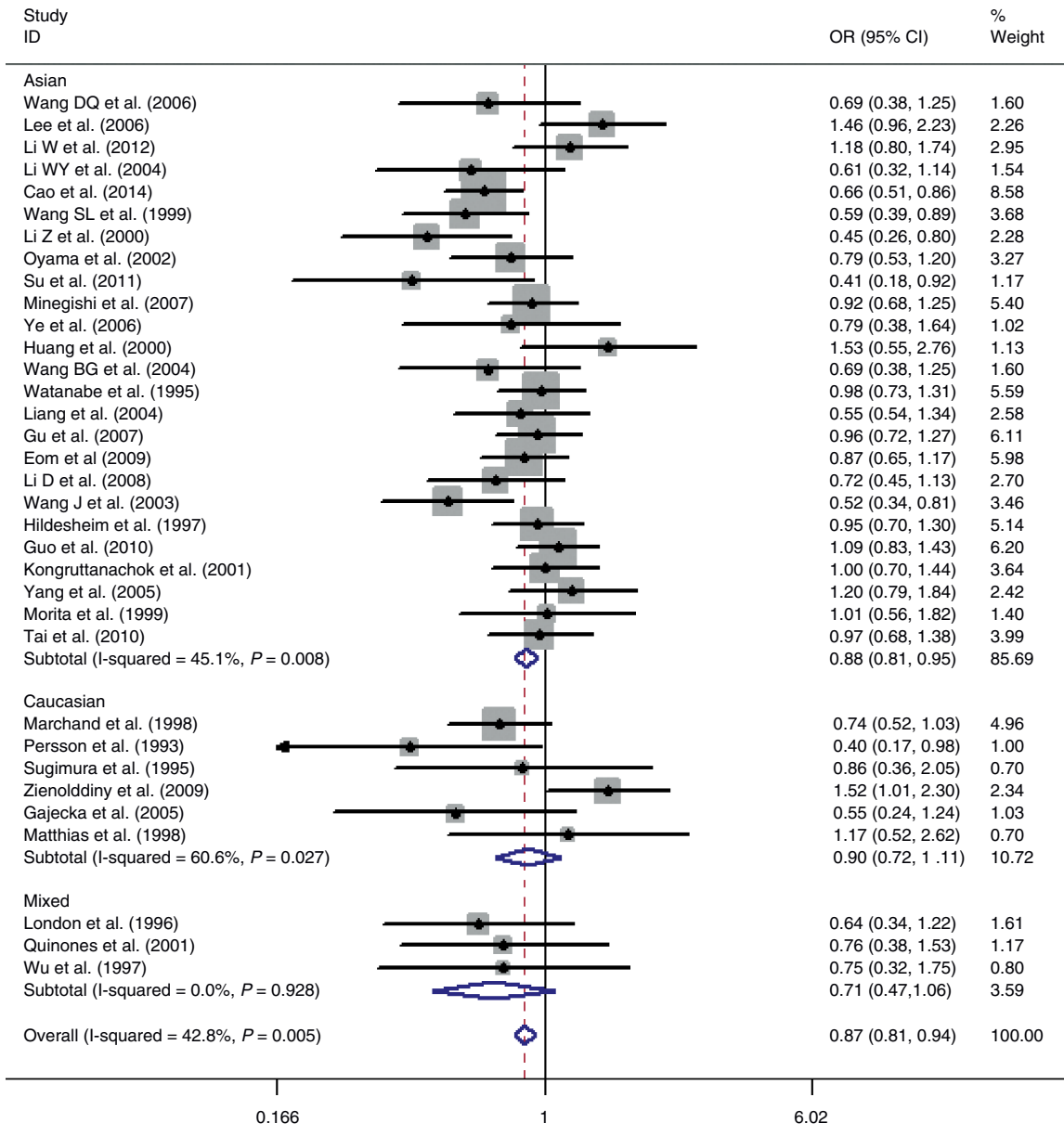

FIGURE 2. (*Continued*).

21 studies[22,25,28–32,34–40,42–46,48,49] reported both of alleles and genotypes of CYP2E1Rsa I/Pst I polymorphism and 5 studies[26,27,33,41,47] only reported the genotype of C1C1 and C1C2/C2C2. As to nasopharyngeal cancer, 3 studies[23,50,51] reported both of alleles and genotypes and just 1 study[52] reported the genotype of C1C1 and C1C2/C2C2. For laryngeal cancer, all of the 4 studies[24,53–55] reported both of alleles and genotypes. The general demographic characteristic of studies included in this meta-analysis is summarized in Table 1. The genotype distributions in the controls of 8 studies were not consistent with Hardy–Weinberg equilibrium (HWE).

Meta-Analysis Results

Overall, there was significant association between CYP2E1Rsa I/Pst I polymorphism and respiratory system cancers risk (C1C2 vs C1C1: OR = 0.85, 95% CI = 0.78–0.93, $P < 0.001$; C1C2/C2C2 vs C1C1: OR = 0.87, 95% CI = 0.81–0.94, $P < 0.001$; Table 2, Figures 2 and 3). When stratified by the cancer type, significant associations were found in nasopharyngeal cancer (C2C2 vs C1C1: OR = 1.85, 95% CI = 1.20–2.85, $P = 0.005$; C2C2 vs C1C2/C1C1: OR = 1.89, 95% CI = 1.23–2.89, $P = 0.003$), lung cancer (C1C2 vs C1C1: OR = 0.82, 95% CI = 0.74–0.91, $P < 0.001$; C1C2/C2C2 vs C1C1: OR = 0.83, 95% CI = 0.76–0.90, $P < 0.001$; C2 vs C1: OR = 0.85, 95% CI = 0.73–1.00, $P = 0.045$), but not in laryngeal cancer (Table 2, Figures 2 and 3). In the subgroup analysis of ethnicity, there was significant association in Asian population (C1C2 vs C1C1: OR = 0.85, 95% CI = 0.78–0.94, $P = 0.001$; C1C2/C2C2 vs C1C1: OR = 0.88, 95% CI = 0.81–0.95, $P = 0.001$; C2C2 vs C1C2/C1C1: OR = 1.25, 95% CI = 1.01–

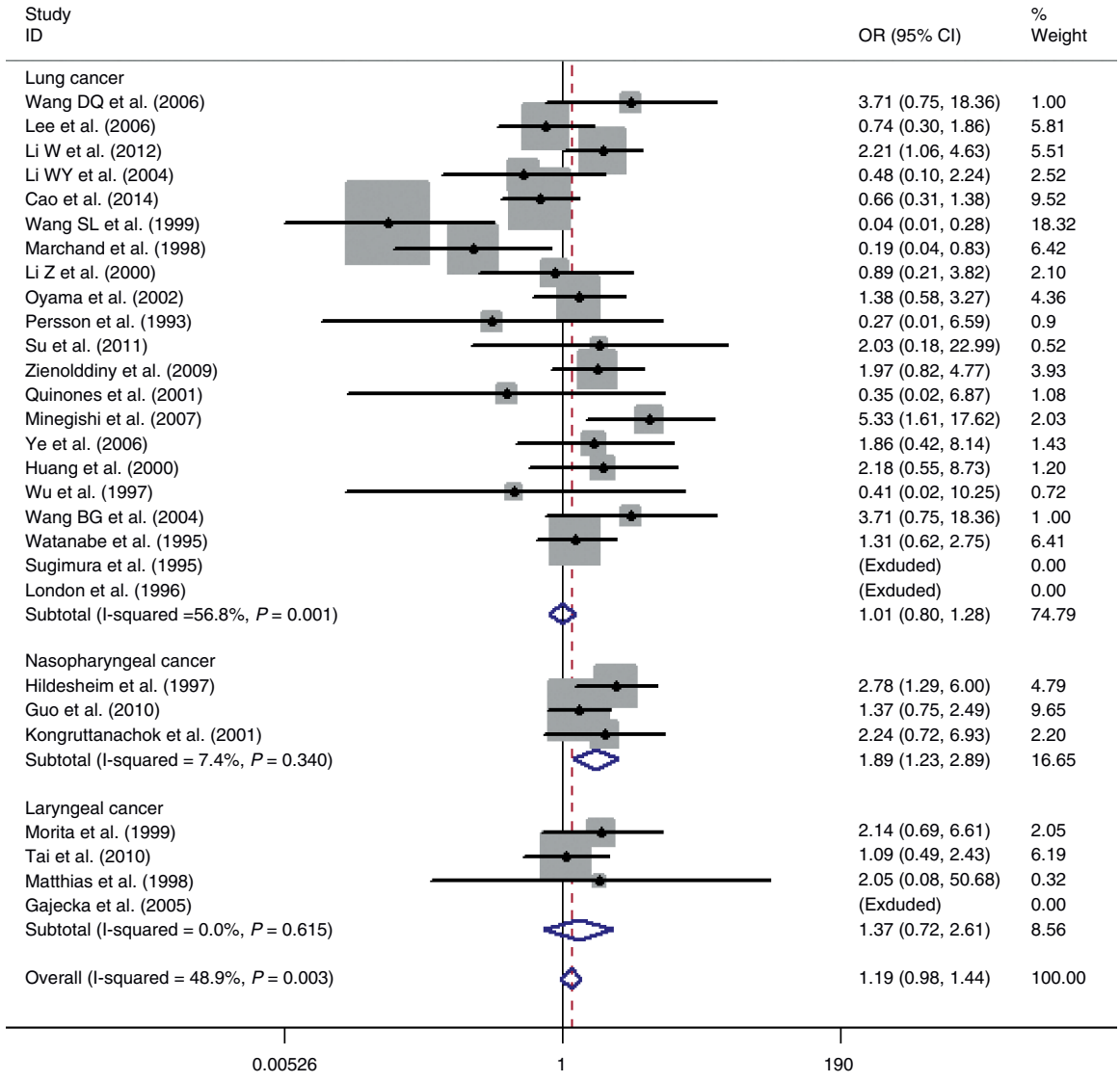

FIGURE 3. Forest plot describing the meta-analysis under recessive model for the association between CYP2E1Rsa I/Pst I polymorphism and the risk of digestive system cancer. (A) Stratified by cancer types. (B) Stratified by ethnicity.

1.53, $P = 0.036$), whereas no significant associations were found in Caucasian and mixed population (Table 2, Figures 2 and 3).

Sensitive Analysis and Publication Bias

We performed a leave-one-out sensitivity analysis to estimate the sensitivity of our study. Any single study was omitted, while the overall statistical significance does not change, indicating that the results are stable. Therefore, we can conclude that our meta-analysis data is relatively stable and credible.

Funnel plot and Begg test were performed to estimate the publication bias of studies. The shapes of funnel plot seemed symmetrical, suggesting without publication bias (Figure 4). These results were further supported by analysis via Begg and Egger tests ($P = 0.262$).

DISCUSSION

The etiology of respiratory system cancers was so complicated that several risk factors were involved in the progression of respiratory cancers. In recent years, more researches focus on the relationship between genetic susceptibility and respiratory system cancers, such as ERCC1, XRCC1, Nt590 P21, Cylin D1, and BSF2.[13,15,56–58] CYP2E1 Rsa I/Pst I polymorphism was assessed in different types of respiratory system cancers. For lung cancer, the research by Su et al,[22] which included 64 patients with lung cancer and 64 healthy controls of the same ethnic origin, proved that the carrier state of 1 copy of the C2 CYP2E1 gene decreased the risk of lung cancer, which corresponded to some other studies.[25,28,32,37,41,44,47] But Lee et al[29] enrolled 169 male patients with lung cancer and 191 age and sex-matched healthy Korean

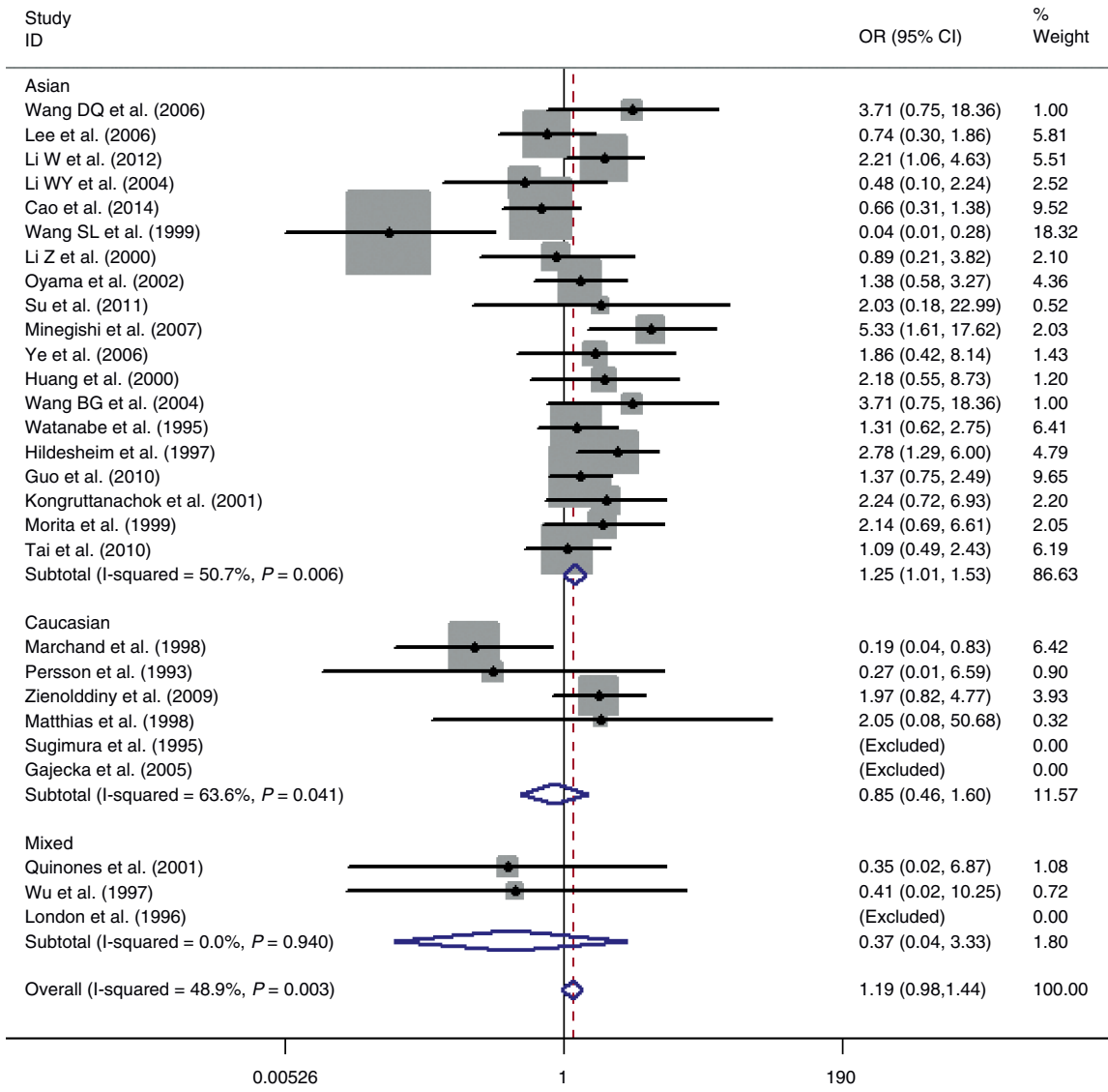

FIGURE 3. (*Continued*).

subjects with no evidence of respiratory disease or cancer in any organ, with a conclusion that genetic polymorphisms of CYP2E1 was not associated with the overall risk of lung cancer, which was consistent with others.[26,31,33–35,38–40,42,43,46,48,49] With regard to nasopharyngeal and laryngeal cancer, the results of the studies[23,24,50–55] were also controversial. The case–control study by Tai et al[24] indicated that an increased risk was associated with the CYP1A1 462Val/Val genotype, but not with the CYP2E1 Rsa I/Pst I genotype in a Han Chinese population. The study by Hildesheim et al[23] suggested that the CYP2E1 gene detected by Rsa I digestion (C2 allele) was found to have an increased risk of NPC. Therefore, it was necessary to integrate all these studies to make a comprehensive assessment. Furthermore, to our knowledge, no comprehensive study has previously been conducted to address this issue. Because of these conflicting results, we conducted this meta-analysis to provide a comprehensive assessment of the associations between CYP2E1 Rsa I/Pst I polymorphism and respiratory cancer risk.

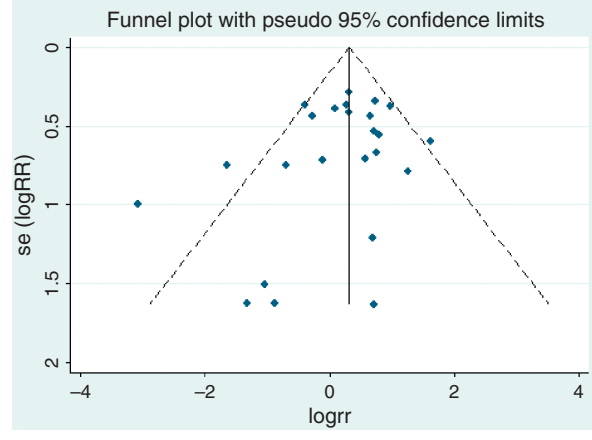

FIGURE 4. Funnel plot of CYP2E1Rsa I/Pst I polymorphism and digestive system cancer risk.

In our meta-analysis, significant association was found between CYP2E1 Rsa I/Pst I polymorphism and respiratory cancer risk, indicating that the carriers of C2 allele might be a genetic protective factor for the susceptibility to respiratory cancer. When stratified by cancer type, our study indicated that CYP2E1 Rsa I/Pst I polymorphism led to an decreased incidence of lung cancer risk under the heterozygote model (OR = 0.82, 95% CI = 0.74–0.91, $P < 0.001$), dominant model (OR = 0.83, 95% CI = 0.76–0.90, $P < 0.001$), and allele contrast (OR = 0.85, 95% CI = 0.73–1.00, $P = 0.045$), which was consistent with several studies we included,[25,28,32,37,41,44,47] but not with some other studies.[26,27,29–31,33–36,38–40,42,43,45,46,48,49] Previous meta-analyses[25,59] also drew the same conclusion. Furthermore, the genotypes of CYP2E1 Rsa I/Pst I polymorphism among the patients with lung cancer in the study by Wang et al[42] and Huang et al[46] did not follow HWE, which might make contribution to the reason for these significant differences. In addition, our study also suggested that CYP2E1Rsa I/Pst I C2/C2 polymorphism led to an increased incidence of NPC risk in homozygote model (OR = 1.85, 95% CI = 1.20–2.85, $P = 0.005$) and recessive model (OR = 1.89, 95% CI = 1.23–2.89, $P = 0.003$), which was consistent with the findings of Hildesheim et al.[23] Small sample size of the study by Kongruttanachok et a[51] and insufficient statistical power in the study by Guo et al[50] might explain the difference from our result. However, with regard to laryngeal cancer, no significant association with CYP2E1 Rsa I/Pst I polymorphism was found in our meta-analysis, and all of the studies[24,53–55] we included showed the same results.

In the subgroup of ethnicity, significant association was found in Asian populations, while there was no significant association in Caucasian and mixed populations, indicating that ethnicity might be an important risk factor in the development and progression of respiratory cancer. Several factors may lead to this difference, including living environment, racial background, and life habits. Besides, the unclear interaction of identified and unidentified genes may also contribute to carcinogenesis in respiratory system.

However, similar to most researches, our meta-analysis has limitations that may affect the veracity of result. First, respiratory system cancers included several cancers, while the association between CYP2E1Rsa I/Pst I polymorphism and other respiratory system cancers, such as bronchus cancer, were not performed by researchers, and was not involved in our meta-analysis, which might lead to some biases in the final conclusion. Second, the studies we included and these raw data did not provide sufficient information about the interaction between CYP2E1Rsa I/Pst I polymorphism and other risk factors, such as other gene polymorphism, living habits, and other exposures. Without these considerations, we could not draw an exact conclusion. Last, some of our studies[42,46] we included were not abided by HWE, which might also lead to some biases.

In summary, our meta-analysis indicated that CYP2E1Rsa I/Pst I polymorphism may be a protective factor for respiratory system cancer. Furthermore, significant association was also found in Asian populations. Considering the limitations listed above, larger well-designed studies are needed to further evaluate the associations of CYP2E1 Rsa I/Pst I polymorphism with the risk of respiratory system cancers.

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