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ORIGINAL RESEARCH

Cytochrome P450 1A1 exon 7 polymorphism and susceptibility to lung cancer in the Chinese population: an updated meta-analysis and review

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Background: Although many epidemiologic studies have investigated the cytochrome P450 1A1 (CYP1A1) exon 7 gene polymorphism and its association with lung cancer (LC), definitive conclusions cannot be drawn.

Objective: To clarify the effects of CYP1A1 exon 7 polymorphism on the risk of LC, an updated meta-analysis was performed in the Chinese population.

Methods: Related studies were identified from PubMed, Springer Link, Ovid, the Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and the Chinese Biology Medicine (CBM) databases until October 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the associations.

Results: A total of 25 articles including 3,540 LC cases and 5,284 controls were included in this meta-analysis. Overall, significant association was found between CYP1A1 exon 7 polymorphism and LC risk when all studies in the Chinese population were pooled into this meta-analysis (GG versus AA: OR =1.71, 95% CI: 1.46–2.01; GG versus AG: OR =1.41, 95% CI: 1.21–1.64; GG + AG versus AA: OR =1.37, 95% CI: 1.16–1.62; GG versus AA + AG: OR =1.52, 95% CI: 1.32–1.76). In subgroup analyses stratified by ethnicity, source of controls, and geographical locations, significantly increased risk was found in Chinese Han people, in population-based studies, in hospital-based studies, in South China, and in North China.

Conclusion: This meta-analysis provides the evidence that CYP1A1 exon 7 polymorphism may contribute to LC development in the Chinese population, and studies with a larger sample size and wider population spectrum are warranted to verify this finding.

Keywords: epidemiology, gene, lung neoplasm, CYP1A1

Introduction

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally, with 1.6 million newly confirmed cases and 1.4 million deaths from lung cancer annually.[1] In the last decade, the incidence and mortality rates of lung cancer in the People's Republic of China have increased significantly and constantly.[1] It was estimated that 605,946 lung cancer cases were diagnosed in 2010 in the People's Republic of China, with a crude incidence rate of 46.08/100,000, and 486,555 patients died from lung cancer, with a crude mortality rate of 37.00/100,000.[2] Although risk of lung cancer has been conclusively associated with tobacco smoking,[3] fewer than 20% of smokers develop the disease, indicating that genetic variations and other environmental factors may play important roles in the development of lung cancer.[4,5] In recent years, the impact of inherited polymorphisms in the cytochrome P450 1A1 (CYP1A1) gene on susceptibility to lung cancer has received particular interest since this enzyme plays an essential role in the metabolic activation of major classes of tobacco procarcinogen

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such as aromatic amines and polycyclic aromatic hydrocarbons. The CYP1A1 exon 7 polymorphism, resulting in the substitution of isoleucine with valine (Ile462Val) (National Center for Biotechnology Information single-nucleotide polymorphism identifier rs1048943; adenine [A] to guanine [G] substitution at nucleotide 2455 [A2455G]), is one of the most extensively studied genes in lung cancer susceptibility. An association between CYP1A1 exon 7 polymorphism and lung cancer was first reported by Nakachi et al in 1993 among the Japanese population,[6] after which many studies analyzed the influence of CYP1A1 exon 7 polymorphism on lung cancer risk; no clear consensus, however, was reached. Meta-analyses of studies on the gene in other ethnic groups have been reported elsewhere and produced conflicting results.[7–12] In order to lessen the impact of different genetic backgrounds, we performed this updated meta-analysis to assess the relationship of CYP1A1 exon 7 polymorphism with risk of lung cancer in the Chinese population.

Materials and methods
Search strategy and selection criteria
We systematically searched the PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) databases for studies published before October 10, 2014, using the following MeSH terms: ("Lung Neoplasms" [MeSH] or "lung cancer" or "lung tumor" or "lung carcinoma" or "carcinoma of lung") and ("cytochrome P450 1A1" or "CYP1A1") and ("China" or "Chinese" or "Taiwan"). The search was performed without any restrictions on language and focused on studies conducted in humans. Additional studies were identified by handsearching references in original research articles and review articles. Studies were selected according to the following criteria: 1) case–control study or cohort study studying on association between the CYP1A1 exon 7 polymorphism and lung cancer susceptibility; 2) all patients with the diagnosis of lung cancer confirmed by pathological or histological examination; 3) sufficient published data about sample size, odds ratio (OR), and their 95% confidence interval (CI); 4) all participants were Chinese; and 5) in the case of duplication with multiple articles publishing data on the same population, the most complete dataset was included. Review papers, letters, case reports, or editorial articles were excluded.

Data extraction
Information was carefully extracted from all eligible publications independently by the two authors according to the inclusion criteria. Disagreements were resolved through a discussion between the two authors. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data were collected from each study: first author's surname, year of publication, geographical location, ethnicity of subjects, source of controls, total numbers of cases and controls, genotype frequencies, and Hardy–Weinberg equilibrium test. Ethnicities were categorized as Han and other ethnic Chinese. We did not define any minimum number of patients to include a study in our meta-analysis. For articles including different ethnicities or areas, data were extracted separately.

Statistical analysis
The ORs with 95% CIs were used to determine the strength of association between the CYP1A1 exon 7 polymorphisms and lung cancer risk. The pooled ORs were performed for allele model (G versus A), dominant model (GG + AG versus AA), recessive model (GG versus AG + AA), heterozygous model (GG versus AG), and homozygous model (GG versus AA), respectively. The distributions of genotypes in controls were tested by Hardy–Weinberg equilibrium using the χ^2 test. Heterogeneity assumptions were assessed by χ^2-based Q-test. A P-value greater than 0.10 for the Q-test indicated a lack of heterogeneity among the studies. Thus, the pooled OR estimate of each study was calculated using either the fixed-effects model (the Mantel–Haenszel method) or the random-effects model (the DerSimonian and Laird method). The significance of the pooled OR was determined by the z-test. Sensitivity analysis was conducted to verify stability of the meta-analysis using both models (the fixed-effects and random-effects). Potential publication biases were estimated by funnel plot, in which the standard error of log OR of each study was plotted against its log OR. An asymmetrical plot suggests a publication bias. Funnel plot asymmetry was assessed by Egger's linear regression test, a linear regression approach that measures the funnel plot asymmetry on a natural logarithm scale of the OR. The significance of the intercept was determined by t-test, as suggested by Egger[13] ($P<0.05$ was considered a statistically significant publication bias). In addition, subgroup analysis stratified by ethnicity, source of controls, and geographical locations was also performed. All the statistical analyses were performed using the STATA statistical package (version 10; StataCorp LP, College Station, TX, USA).

Results

Eligible studies

According to the inclusion criteria, 25 case–control studies[14–38] were included and 163 articles were excluded. The publication year of included studies ranged from 1998 to 2014. A flowchart of the study selection process is shown in Figure 1. In total, 3,540 lung cancer cases and 5,284 controls were involved in this meta-analysis, which evaluated the relationship between CYP1A1 exon 7 polymorphism and lung cancer risk. The source of controls was mainly based on a healthy population. Fifteen of these studies were written in Chinese, and ten studies were in English. The characteristics of the included studies are summarized in Table 1.

Quantitative synthesis

Table 2 lists the primary results. Overall, a significantly elevated risk of lung cancer was associated with all variants of CYP1A1 exon 7 (G versus A: OR =1.30, 95% CI: 1.17–1.45; GG versus AA: OR =1.71, 95% CI: 1.46–2.01; GG versus AG: OR =1.41, 95% CI: 1.21–1.64; GG + AG versus AA: OR =1.37, 95% CI: 1.16–1.62; GG versus AA + AG: OR =1.52, 95% CI: 1.32–1.76) (Figure 2). However, there was significant heterogeneity between some models. Hence, we then performed subgroup analysis by geographical locations, ethnicity, and source of controls. In the stratified analysis by geographical locations, significantly increased risk was found both in North China (G versus A: OR =1.28, 95% CI: 1.13–1.46; GG versus AA: OR =1.60, 95% CI: 1.33–1.91; GG versus AG: OR =1.31, 95% CI: 1.10–1.55; GG + AG versus AA: OR =1.41, 95% CI: 1.15–1.73; GG versus AA + AG: OR =1.41, 95% CI: 1.20–1.65) and South China (G versus A: OR =1.39, 95% CI: 1.10–1.76; GG versus AA: OR =2.13, 95% CI: 1.51–3.01; GG versus AG: OR =1.80, 95% CI: 1.26–2.58; GG versus AA + AG: OR =2.01, 95% CI: 1.44–2.81). In the stratified analysis by source of controls, significantly increased risk was found both in the population-based studies (G versus A: OR =1.32, 95% CI: 1.15–1.50; GG versus AA: OR =1.77, 95% CI: 1.36–2.31; GG versus AG: OR =1.38, 95% CI: 1.15–1.66; GG + AG versus AA: OR =1.40, 95% CI: 1.15–1.71; GG versus 1G: OR =1.49, 95% CI: 1.25–1.77) and hospital-based studies (G versus A: OR =1.29, 95% CI: 1.13–1.47; GG versus AA: OR =2.05, 95% CI: 1.50–2.79; GG versus AG: OR =1.44, 95% CI: 1.10–1.88; GG + AG versus AA: OR =1.39, 95% CI: 1.13–1.72; GG versus AA + AG: OR =1.59, 95% CI: 1.23–2.06). In the subgroup analysis by ethnicity, significantly increased association was found in Chinese Han people (GG versus AA: OR =1.59, 95% CI: 1.11–2.30; GG versus AG: OR =1.38, 95% CI: 1.12–1.68; GG versus AA + AG: OR =1.40, 95% CI: 1.16–1.70).

Sensitivity analysis and bias diagnosis

In order to compare the difference and evaluate the sensitivity of the meta-analysis, we used both models (fixed-effects and random-effects) to evaluate the stability of the meta-analysis.
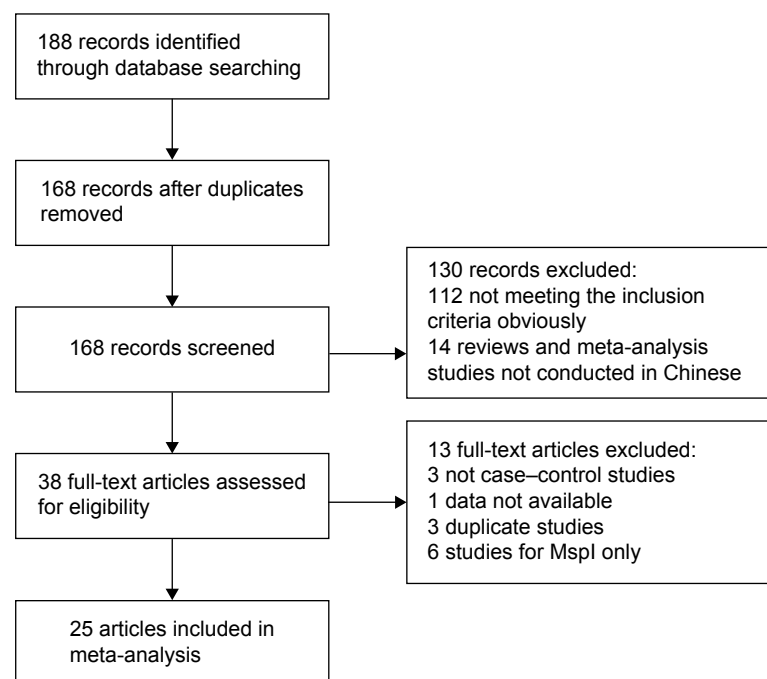

Figure 1 Flow diagram of the literature search.

Table 1 Characteristics of studies included in the meta-analysis

Study	Source of controls	Area	Ethnicity	Number of cases	Number of controls	Case AA	Case AG	Case GG	Control AA	Control AG	Control GG	HWE χ^2	HWE P-value
Hu and Zhang[14]	PB + HB	Guangdong	Han	59	132	19	33	7	21	102	9	41.12	0.000
Qu et al[15]	PB	Shanghai	Not stated	100	95	56	36	8	56	35	4	0.26	0.612
Qu et al[15]	PB	Heilongjiang	Not stated	80	87	42	36	2	52	32	3	0.52	0.470
Chen et al[16]	PB	Jiangsu	Not stated	68	105	35	21	12	66	30	9	3.78	0.052
Persson et al[17]	PB	Beijing	Not stated	76	119	50	20	6	77	37	5	0.04	0.835
Song et al[18]	PB	Beijing	Not stated	150	391	53	90	7	200	178	13	12.74	0.000
London et al[19]	PB	Shanghai	Not stated	214	669	167	39	8	512	130	27	21.86	0.000
Song et al[20]	PB	Beijing	Not stated	217	404	78	130	9	210	181	13	12.45	0.000
Zhang et al[21]	HB	Jiangsu	Not stated	40	30	17	13	10	18	10	2	0.14	0.708
Chen et al[22]	PB	Jiangsu	Not stated	106	106	58	38	10	70	33	3	0.14	0.704
Zhou et al[23]	HB	Hubei	Not stated	92	98	15	66	11	27	65	6	14.93	0.000
Zhang et al[24]	HB	Jiangsu	Not stated	65	60	24	29	12	32	23	5	0.09	0.765
Dong et al[25]	HB	Sichuan	Not stated	82	91	28	36	18	49	32	10	1.74	0.187
Yang et al[26]	PB	Liaoning	Not stated	197	144	90	96	11	98	39	7	0.82	0.239
Ng et al[27]	HB	Singapore	Not stated	126	161	74	39	13	91	63	7	0.91	0.339
Liu et al[28]	PB	Shandong	Han	110	125	18	80	12	35	83	7	19.820	0.000
Song et al[29]	PB	Shandong	Han	125	125	20	90	15	36	80	9	14.68	0.000
Zhou et al[30]	PB	Henan	Not stated	209	208	39	135	35	55	128	25	13.73	0.000
Wang et al[31]	PB	Liaoning	Han	72	90	37	9	26	54	25	11	7.06	0.008
Bai et al[32]	HB	Inner Mongolia	Han	106	250	25	66	15	54	172	24	39.22	0.000
Wang et al[33]	PB	Henan	Han	209	256	95	66	48	148	70	38	27.76	0.000
Lv et al[34]	HB	Inner Mongolia	Han	116	216	17	75	24	44	133	39	11.64	0.001
Liu et al[35]	HB	Inner Mongolia	Han	174	324	26	112	36	66	200	58	17.94	0.000
He et al[36]	PB	Hebei	Han	275	406	141	103	31	165	183	58	0.40	0.529
Jiang et al[37]	PB	Inner Mongolia	Mongolian	142	190	18	101	23	28	136	26	35.42	0.000
Jiang et al[37]	PB	Inner Mongolia	Han	180	266	42	112	26	57	183	26	41.48	0.000
Yang et al[38]	PB	Hebei	Not stated	150	136	52	75	23	61	65	10	1.72	0.190

Abbreviations: HB, hospital-based; HWE, Hardy–Weinberg equilibrium; PB, population-based.

None of the results were materially altered (Table 2). Hence, the results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. Begg's funnel plot and Egger's test were performed to assess publication bias. The shape of the funnel plots did not reveal obvious asymmetry (Figure 3A). Subsequently, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there was no obvious publication bias under the allele model in overall analysis (Figure 3B) (t=2.09, P=0.058).

Discussion

Cytochrome P450 genes are large families of endoplasmic and cytosolic enzymes that catalyze the activation and detoxification, respectively, of reactive electrophilic compounds, including many environmental carcinogens (eg, benzo[a]pyrene). CYP1A1 is a phase I enzyme that regulates the metabolic activation of major classes of tobacco procarcinogens, such as aromatic amines and polycyclic aromatic hydrocarbons.[39] Thus, CYP1A1 may affect the metabolism of environmental carcinogens and alter the

susceptibility to lung cancer. Although many studies have analyzed the CYP1A1 exon 7 polymorphism and its association with lung cancer, definitive conclusions cannot be drawn. Therefore, we performed the current meta-analysis to estimate the relationship between CYP1A1 exon 7 polymorphism and susceptibility to lung cancer among the Chinese population only, in order to lessen the impact of different genetic backgrounds. The meta-analysis involved 25 articles including 3,540 lung cancer cases and 5,284 controls. The results showed that the variant genotypes of the CYP1A1 exon 7 polymorphism were significantly associated with lung cancer risk in the Chinese population. Our results were consistent with a previously published meta-analysis in Chinese populations,[40] which found that, compared with the wild-type homozygous genotype (AA), lung cancer risk for the combined variant genotypes (GG and AG) was 1.61-fold (95% CI: 1.24–2.08) (Z=3.62, P<0.001). However, this previously published meta-analysis did not search some other databases in the People's Republic of China (Wanfang Data Knowledge Service Platform and CBM), and included a smaller number of studies than ours did.

Table 2 Main results in the total and subgroup analysis

Analysis model	Study groups	n	Random-effects model OR (95% CI)	Fixed-effects model OR (95% CI)	Heterogeneity χ^2	P-value
G versus A	Total analysis	27	1.30 (1.17–1.45)	1.26 (1.18–1.35)	61.48	0.000
	PB	18	1.32 (1.15–1.50)	1.27 (1.17–1.37)	46.80	0.000
	HB	8	1.32 (1.12–1.56)	1.29 (1.13–1.47)	10.36	0.169
	Chinese Han	10	1.18 (0.98–1.42)	1.13 (1.03–1.25)	31.77	0.000
	South China	9	1.39 (1.10–1.76)	1.32 (1.14–1.53)	18.47	0.018
	North China	17	1.28 (1.13–1.46)	1.25 (1.16–1.35)	42.07	0.000
GG versus AA	Total analysis	27	1.81 (1.48–2.22)	1.71 (1.46–2.01)	37.36	0.069
	PB	18	1.77 (1.36–2.31)	1.63 (1.35–1.97)	29.23	0.032
	HB	8	2.02 (1.48–2.77)	2.05 (1.50–2.79)	5.54	0.595
	Chinese Han	10	1.59 (1.11–2.30)	1.46 (1.17–1.81)	22.29	0.008
	South China	9	2.18 (1.43–3.33)	2.13 (1.51–3.01)	10.47	0.233
	North China	17	1.69 (1.33–2.15)	1.60 (1.33–1.91)	24.78	0.074
GG versus AG	Total analysis	27	1.40 (1.20–1.64)	1.41 (1.21–1.64)	26.21	0.452
	PB	18	1.38 (1.13–1.70)	1.38 (1.15–1.66)	19.24	0.315
	HB	8	1.43 (1.09–1.87)	1.44 (1.10–1.88)	5.90	0.552
	Chinese Han	10	1.45 (1.11–1.89)	1.38 (1.12–1.68)	14.14	0.118
	South China	9	1.79 (1.24–2.58)	1.80 (1.26–2.58)	3.43	0.905
	North China	17	1.31 (1.09–1.58)	1.31 (1.10–1.55)	18.08	0.319
GG + AG versus AA	Total analysis	27	1.37 (1.16–1.62)	1.33 (1.21–1.47)	73.01	0.000
	PB	18	1.40 (1.15–1.71)	1.35 (1.22–1.51)	51.52	0.000
	HB	8	1.43 (1.10–1.87)	1.39 (1.13–1.72)	10.40	0.167
	Chinese Han	10	1.16 (0.84–1.59)	1.10 (0.94–1.27)	35.24	0.000
	South China	9	1.35 (0.97–1.89)	1.28 (1.05–1.55)	21.40	0.006
	North China	17	1.41 (1.15–1.73)	1.38 (1.24–1.55)	48.58	0.000
GG versus AA + AG	Total analysis	27	1.54 (1.32–1.80)	1.52 (1.32–1.76)	28.79	0.321
	PB	18	1.53 (1.24–1.88)	1.49 (1.25–1.77)	21.82	0.192
	HB	8	1.57 (1.20–2.03)	1.59 (1.23–2.06)	6.73	0.458
	Chinese Han	10	1.49 (1.13–1.95)	1.40 (1.16–1.70)	16.29	0.061
	South China	9	1.99 (1.41–2.80)	2.01 (1.44–2.81)	5.72	0.678
	North China	17	1.42 (1.19–1.71)	1.41 (1.20–1.65)	18.74	0.283

Notes: South China including Guangdong, Shanghai, Jiangsu, Hubei, and Sichuan; North China including Heilongjiang, Beijing, Liaoning, Inner Mongolia, Hebei, Shandong, and Henan.
Abbreviations: CI, confidence interval; HB, hospital-based; OR, odds ratio; PB, population-based.

The effects of genetic polymorphisms on cancer risk seem to be affected by ethnic background. Several studies have shown that the CYP1A1 exon 7 polymorphism is associated with an increased lung cancer risk in the Asian population.[7–9] However, previous research, including some pooled analyses, suggest that there is not an established association between this polymorphism and increased lung cancer risk in Caucasian populations.[10,41] Therefore, we performed the subgroup analyses by ethnicity, source of controls, and geographical locations. The results revealed that significant association with susceptibility to the development of lung cancer was found in Chinese Han people, in population-based studies, in hospital-based studies, in South China, and in North China. The ethnic differences might be ascribed to genetic backgrounds and the gene–environment interactions in the etiology. In addition, the CYP1A1 exon 7 variant genotype has a high prevalence among Asians compared with Caucasians and African–Americans.

The pathways of carcinogen metabolism are complex, mediated by the activity of multiple enzymes. The effect of any single gene might have a more limited impact than has so far been anticipated. Lung cancer has some known major environmental determinants other than tobacco smoke, and large studies with detailed exposure information are needed to evaluate reliably any moderate genetic effects. Otherwise, some limitations should be acknowledged. First, we did not perform subgroup analysis on smoking status, because of the lack of sufficient data. Second, our results were based on unadjusted estimates. More precise analyses can be conducted if individual data were available, which would allow for the adjustment by other covariates including age, sex, location, race, and other factors. Final, heterogeneity is a potential problem when interpreting the results of meta-analysis. As significant between-study heterogeneity existed in a few comparisons, the results from meta-analysis should
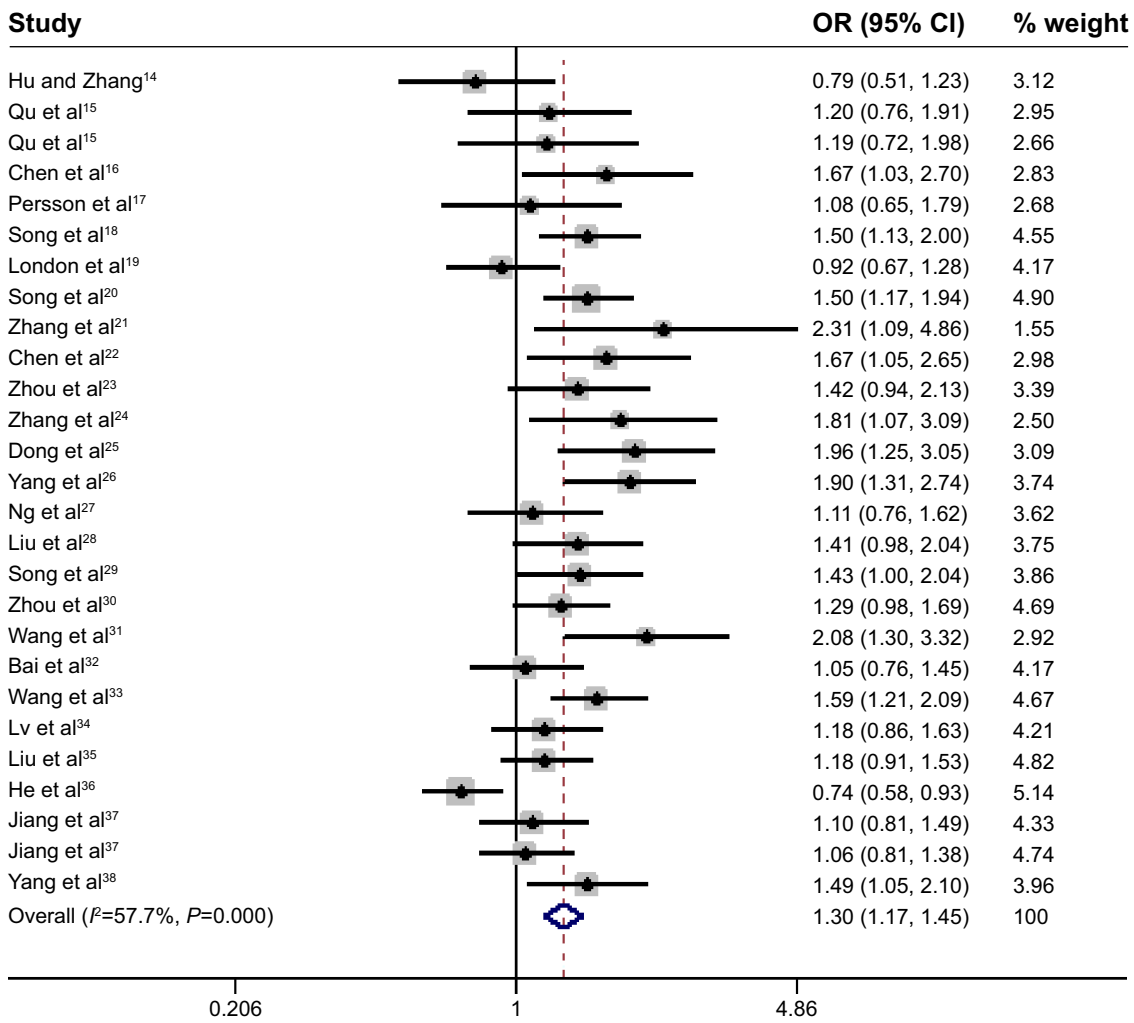
Study		OR (95% CI)	% weight
Hu and Zhang[14]		0.79 (0.51, 1.23)	3.12
Qu et al[15]		1.20 (0.76, 1.91)	2.95
Qu et al[15]		1.19 (0.72, 1.98)	2.66
Chen et al[16]		1.67 (1.03, 2.70)	2.83
Persson et al[17]		1.08 (0.65, 1.79)	2.68
Song et al[18]		1.50 (1.13, 2.00)	4.55
London et al[19]		0.92 (0.67, 1.28)	4.17
Song et al[20]		1.50 (1.17, 1.94)	4.90
Zhang et al[21]		2.31 (1.09, 4.86)	1.55
Chen et al[22]		1.67 (1.05, 2.65)	2.98
Zhou et al[23]		1.42 (0.94, 2.13)	3.39
Zhang et al[24]		1.81 (1.07, 3.09)	2.50
Dong et al[25]		1.96 (1.25, 3.05)	3.09
Yang et al[26]		1.90 (1.31, 2.74)	3.74
Ng et al[27]		1.11 (0.76, 1.62)	3.62
Liu et al[28]		1.41 (0.98, 2.04)	3.75
Song et al[29]		1.43 (1.00, 2.04)	3.86
Zhou et al[30]		1.29 (0.98, 1.69)	4.69
Wang et al[31]		2.08 (1.30, 3.32)	2.92
Bai et al[32]		1.05 (0.76, 1.45)	4.17
Wang et al[33]		1.59 (1.21, 2.09)	4.67
Lv et al[34]		1.18 (0.86, 1.63)	4.21
Liu et al[35]		1.18 (0.91, 1.53)	4.82
He et al[36]		0.74 (0.58, 0.93)	5.14
Jiang et al[37]		1.10 (0.81, 1.49)	4.33
Jiang et al[37]		1.06 (0.81, 1.38)	4.74
Yang et al[38]		1.49 (1.05, 2.10)	3.96
Overall (I^2=57.7%, P=0.000)		1.30 (1.17, 1.45)	100

0.206　　　　1　　　　4.86

Figure 2 Forest plot (random-effects model) of lung cancer risk associated with CYP1A1 MspI polymorphism using the allele genetic model.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio.

A Funnel plot with pseudo 95% confidence limits

B Egger's publication bias plot
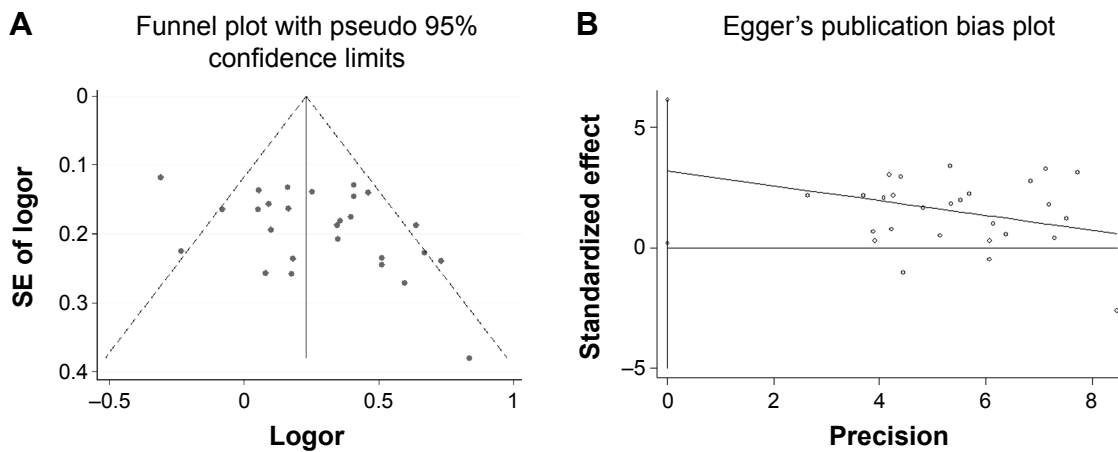
Figure 3 Publication bias assessment of CYP1A1 MspI polymorphism and lung cancer risk under the allele genetic model.
Notes: (**A**) Begg's funnel plot. (**B**) Egger's test.
Abbreviation: SE, standard error.

be interpreted with an appropriate degree of caution. In spite of these limitations, our meta-analysis still had some advantages. Most of all, we obeyed the inclusion and exclusion criteria strictly to reduce selection bias. Besides, our inclusion of non-English-language reports was important in minimizing a major potential threat to the validity of any meta-analysis publication bias and the related threat of a language bias. Last but not least, there was no evidence of publication bias in this meta-analysis and the sensitivity analysis confirmed the reliability and stability of the results. Therefore, the 25 studies would appear to be comparable in all respects relevant to our meta-analysis.

Conclusion

Our meta-analysis supports that CYP1A1 exon 7 polymorphism might contribute to individual susceptibility to lung cancer in Chinese. Concerning lung cancer with multifactorial etiology, to further evaluate gene–gene and gene–environment interactions on CYP1A1 exon 7 and lung cancer, larger studies in selected populations with different environmental backgrounds or other risk factors are required. Such studies may eventually lead to a better, comprehensive understanding of the association between the CYP1A1 exon 7 and lung cancer risk.

Disclosure

The authors report no conflicts of interest in this work.

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