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ORIGINAL RESEARCH

The association of *GSTT1* deletion polymorphism with lung cancer risk among Chinese population: evidence based on a cumulative meta-analysis

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Objective: Previous studies investigating the relationship between glutathione S-transferase T1 (*GSTT1*) gene deletion polymorphism and lung cancer risk among Chinese population produced inconsistent results. To obtain a precise conclusion, we performed this meta-analysis to evaluate the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population.

Methods: The databases of Medline/PubMed, Embase, Web of Science, Wanfang Med Online, and Chinese National Knowledge Infrastructure were searched. The strength of the association was assessed by odds ratio (OR) with 95% confidence intervals (95% CI).

Results: Overall, we found an increased lung cancer risk among subjects carrying *GSTT1* null genotype compared with those carrying present genotype (OR =1.31, 95% CI: 1.12–1.52) on the basis of 20 studies with 3,351 cases and 4,683 controls. We also observed an increased risk of lung cancer among subjects carrying *GSTT1* null genotype compared with those carrying present genotype in stratified analyses (OR =1.31, 95% CI: 1.11–1.55 for healthy subjects-based control; OR =2.29, 95% CI: 1.84–2.85 for squamous cell carcinoma and OR =1.47, 95% CI: 1.22–1.77 for adenocarcinoma, respectively).

Conclusion: This meta-analysis suggested that *GSTT1* deletion polymorphism might contribute to lung cancer risk among Chinese population.

Keywords: lung cancer, risk, *GSTT1*, polymorphism, meta-analysis, Chinese

Introduction

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally, and it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death among females in 2008.[1] In the United States, there were about 228,190 estimated new lung cancer cases and 159,480 estimated deaths in 2013.[2] In the People's Republic of China, lung cancer increased 465% during the past 30 years and became the leading cause of cancer death in the current decade. It is estimated that over one million Chinese will be diagnosed with lung cancer by the year 2025.[3]

Lung cancer has been considered as a disease determined solely by environmental exposure, such as exposure to cigarette smoke and asbestos.[4,5] However, only a small proportion of persons who are exposed to such risk factors will develop lung cancer, which suggests that an individual's susceptibility might contribute to lung cancer risk. Recently, more and more results have supported the hypothesis that common genetic variations of drug-metabolizing enzyme genes may be of importance in determining an individual's sensitivity to develop lung cancer.[6]

Glutathione S-transferase theta-1 (GSTT1), a member of glutathione S-transferases (GSTs), is a kind of phase II detoxification enzyme that is involved in detoxifying

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several kinds of carcinogens such as benzo(a)pyrene present in tobacco smoke.[7,8] *GSTT1* deletion polymorphism is known to abolish enzyme activities and modulate lung cancer risk.[9] Lan et al,[10] for the first time, explored the association of *GSTT1* deletion polymorphism with lung cancer risk in the Chinese population in 1999. After that, a series of epidemiological studies investigated this association in the Chinese population,[11–30] successively. However, the conclusions by previous studies remained controversial rather than conclusive. This urged us to perform this meta-analysis using the updated data, which aims at deriving a precise estimate of *GSTT1* deletion polymorphism associated with lung cancer risk among Chinese population.

Materials and methods

Literature source and analytical methods

Systematic searches were conducted through the databases of Medline/PubMed, Embase, Web of Science, Wanfang Med Online, and Chinese National Knowledge Infrastructure, with the following keywords: "lung cancer" or "lung neoplasm" or "lung carcinoma" and "*GSTT1*" or "glutathione S-transferase T1" and "polymorphism" and "Chinese" or "China." The starting date for searched publications was January 1, 1990 and the ending date of searched publications was January 31, 2015. We also searched the reference list of relevant publications to identify additional studies manually.

Criteria for inclusion: 1) the subjects of study must be Chinese; 2) papers should include *GSTT1* deletion polymorphism and lung cancer risk; 3) case–control study and cohort study; and 4) complete data on genotype of *GSTT1* deletion polymorphism for calculating odds ratio (OR) with 95% confidence intervals (95% CI). Accordingly, reviews and repeated or overlapping literatures were excluded. If studies contained overlapping cases and/or controls, the latest publication including more information was preferred. We only included journal articles, and not dissertations.

In total, 38 published studies were identified which studied the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population. We reviewed all papers in accordance with the aforementioned criteria defined and excluded 5 dissertations, 4 reviews,[31–34] and 9 overlapping articles.[10,35–42] Therefore, 20 studies were selected for our study.

Data extraction

Data were extracted and tabulated first, and then inputted into an electronic database. The following information was extracted from each study: authors' names, year of publication, area, source of control, number of cases and controls, genotype frequency, and stratified factors. Characteristics of individual studies are summarized in Table 1.

Quantitative data synthesis

A meta-analysis was conducted to evaluate the relationship between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population. The heterogeneity was assessed

Table 1 General information of selected studies in this meta-analysis

Study	Area	Source of control	Number of cases	Number of controls	Stratified factors
Cao et al[11]	Hunan	Healthy subjects	104	205	Histological type
Chan-Yeung et al[12]	Hong Kong	Healthy subjects	229	197	
Fowke et al[13]	Shanghai	Healthy subjects	208	784	
He and Chan[14]	Yunnan	Healthy subjects	61	46	
Jiang et al[15]	Inner Mongalia	Healthy subjects	322	456	Smoke
Lan et al[16]	Yunnan	Healthy subjects	122	122	
Liang et al[17]	Jiangsu	Hospitalized patients	152	152	Histological type
Liang et al[18]	Guangxi	Hospitalized patients	68	70	
Liu et al[19]	Jilin	Healthy subjects	100	135	Smoke
London et al[20]	Shanghai	Healthy subjects	232	710	
Ma et al[21]	Sichuan	Healthy subjects	125	125	Sex
Pan et al[22]	Jiangxi	Hospitalized patients	523	523	Smoke, histological type and sex
Qi et al[23]	Gansu	Hospitalized patients	53	72	Smoke, histological type and age
Wang et al[24]	Beijing	Hospitalized patients	112	119	Smoke
Wang et al[25]	Henan	Healthy subjects	77	107	Histological type
Wang et al[26]	Henan	Healthy subjects	209	256	
Yuan et al[27]	Sichuan	Healthy subjects	150	152	Smoke and histological type
Zhang et al[28]	Yunnan	Healthy subjects	110	100	
Zhang et al[29]	Guangdong	Healthy subjects	161	165	Smoke, histological type and sex
Zhao et al[30]	Singapore	Hospitalized patients	233	187	

by Cochrane *Q* statistics test.[43] Data were combined using either a fixed-effects model or a random-effects model depending on the results of heterogeneity test. A fixed-effects model is used when there is no heterogeneity, while a random-effects model is used when heterogeneity exists.[43] Cumulative meta-analysis was performed to investigate the tendency of results by accumulating single study year by year.[44] Funnel plot was drawn to evaluate the publication bias. Egger's test (an adjusted rank correlation test is proposed as a technique for identifying publication bias)[45] and Begg's test (a linear regression approach is used to measure funnel plot asymmetry on the natural logarithm scale of the OR)[46] were applied to assess the symmetry of funnel plot. Sensitivity analysis was performed by deleting one study each time.[44]

All of the statistical analyses were performed using Review Manager (Version 5.0.24, The Cochrane Collaboration) and STATA 10.0 software package (Stata Corporation, College Station, TX, USA). All the tests were two-sided; a *P*-value of 0.05 for any test or model was considered to be statistically significant.

Results

Meta-analysis databases

A database was created according to the extracted information from selected articles. Some essential information is listed in Table 1. It indicates the study (first author et al), year of publication, area, source of control, number of cases and controls, and stratified factors. There were a total of 20 studies, with 3,351 cases and 4,683 controls concerning the association of *GSTT1* deletion polymorphism with lung cancer risk among Chinese population. The frequency of *GSTT1* null genotype was 53.4% and 48.0% in cases and controls, respectively.

Test of heterogeneity

Table 2 shows the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population. Our results showed that there was no heterogeneity for *GSTT1* null genotype versus present genotype in the subgroup analyses of squamous cell carcinoma and adenocarcinoma. Therefore, we calculated the summary ORs for them with a fixed-effects model. Random-effects model was used to calculate the summary ORs for the rest.

Quantitative data synthesis

Table 2 listed the summary ORs of the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population on the basis of 3,351 cases and 4,683 controls. Overall, there was a statistically significant correlation of *GSTT1* null genotype with an increased lung cancer risk among Chinese population, and the summary OR was 1.31 (95% CI: 1.12–1.52; Figure 1). The cumulative meta-analysis accumulated the studies according to the year of publications, which may determine whether new studies are needed or not. Our results showed that there was still a significant association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population; the cumulative OR was 1.31 with 95% CI: 1.12–1.52 (Figure 2).

In subgroup analysis for source of control, we observed an increased risk of lung cancer among subjects carrying *GSTT1* null genotype compared with those carrying present genotype in healthy subjects-based controls (OR =1.31, 95% CI: 1.11–1.55), but not in hospitalized patient-based controls (OR =1.28, 95% CI: 0.89–1.83). We observed an increased risk of lung squamous cell carcinoma and lung adenocarcinoma among subjects carrying *GSTT1* null genotype compared with those carrying present genotype in stratified analysis by histological subtype (OR =2.29,

Table 2 Combined ORs on the relation of the *GSTT1* deletion polymorphism to lung cancer risk among Chinese population

Null versus present	Cases/controls	Heterogeneity test		Combined OR (95% CI)	Hypothesis test		*df*	Begg's test		Egger's test	
		Q	*P*-value		*Z*	*P*-value		*Z*	*P*-value	*t*	*P*-value
Total	3,351/4,683	46.23	0.0005	1.31 (1.12–1.52)	3.44	0.0006	19	0.23	0.820	0.56	0.586
Stratified by source of control											
Healthy subjects	2,210/3,560	27.75	0.01	1.31 (1.11–1.55)	3.14	0.02	13	1.09	0.274	1.51	0.156
Hospitalized patients	1,141/1,123	18.13	0.003	1.28 (0.89–1.83)	1.34	0.18	5	0.38	0.707	0.44	0.683
Stratified by smoking status											
Smokers	680/673	18.09	0.003	1.54 (0.97–2.43)	1.84	0.07	5	0.00	1.000	0.45	0.674
Nonsmokers	636/884	15.45	0.02	1.03 (0.70–1.51)	0.14	0.89	6	0.75	0.452	1.10	0.334
Stratified by histological subtype											
Squamous cell carcinoma	520/1,113	8.66	0.12	2.29 (1.84–2.85)	7.45	<0.00001	5	2.25	0.024	2.59	0.061
Adenocarcinoma	691/1,350	4.36	0.63	1.47 (1.22–1.77)	4.03	0.0001	6	1.20	0.230	1.46	0.205

Abbreviations: OR, odds ratio; *GSTT1*, glutathione S-transferase T1; CI, confidence interval.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M–H, random, 95% CI
Cao et al[11]	69	104	87	205	4.7%	2.67 (1.63, 4.37)
Chan-Yeung et al[12]	143	229	102	197	5.8%	1.55 (1.05, 2.28)
Fowke et al[13]	108	208	381	784	6.7%	1.14 (0.84, 1.55)
He and Chan[14]	33	61	29	46	2.7%	0.69 (0.32, 1.51)
Jiang et al[15]	147	322	203	456	6.9%	1.05 (0.79, 1.39)
Lan et al[16]	73	122	64	122	4.6%	1.35 (0.81, 2.24)
Liang et al[17]	85	152	58	152	5.0%	2.06 (1.30, 3.25)
Liang et al[18]	45	68	34	70	3.2%	2.07 (1.04, 4.12)
Liu et al[19]	57	100	56	135	4.4%	1.87 (1.11, 3.16)
London et al[20]	134	232	426	710	6.8%	0.91 (0.67, 1.23)
Ma et al[21]	57	125	56	125	4.6%	1.03 (0.63, 1.70)
Pan et al[22]	270	523	212	523	7.4%	1.57 (1.23, 2.00)
Qi et al[23]	17	53	27	72	2.9%	0.79 (0.37, 1.66)
Wang et al[24]	53	112	54	119	4.5%	1.08 (0.64, 1.81)
Wang et al[25]	44	77	54	107	3.9%	1.31 (0.73, 2.36)
Wang et al[26]	90	209	100	256	5.9%	1.18 (0.81, 1.71)
Yuan et al[27]	82	150	58	152	5.0%	1.95 (1.24, 3.09)
Zhang et al[28]	75	110	53	100	4.1%	1.90 (1.08, 3.33)
Zhang et al[29]	74	161	72	165	5.2%	1.10 (0.71, 1.70)
Zhao et al[30]	132	233	120	187	5.7%	0.73 (0.49, 1.08)
Total (95% CI)		**3,351**		**4,683**	**100%**	**1.31 (1.12, 1.52)**
Total events	1,788		2,246			

Heterogeneity: τ^2=0.07; χ^2=46.23, df=19 (P=0.0005); I^2=59%
Test for overall effect: Z=3.44 (P=0.0006)

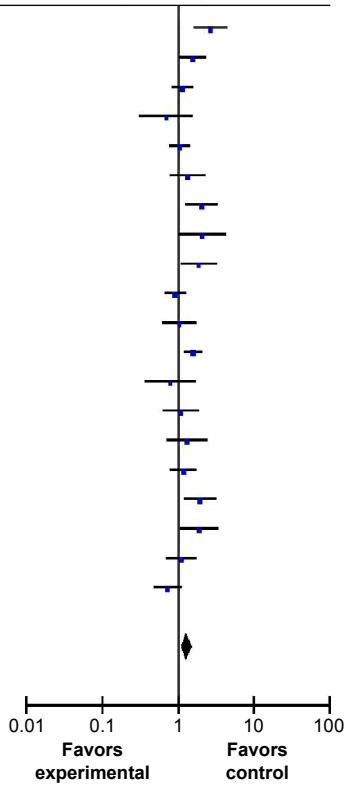

Figure 1 Forest plot of OR for *GSTT1* deletion polymorphism associated with lung cancer risk among Chinese population.
Abbreviations: *GSTT1*, glutathione S-transferase T1; OR, odds ratio; CI, confidence interval; M–H, Mantel–Haenszel test.

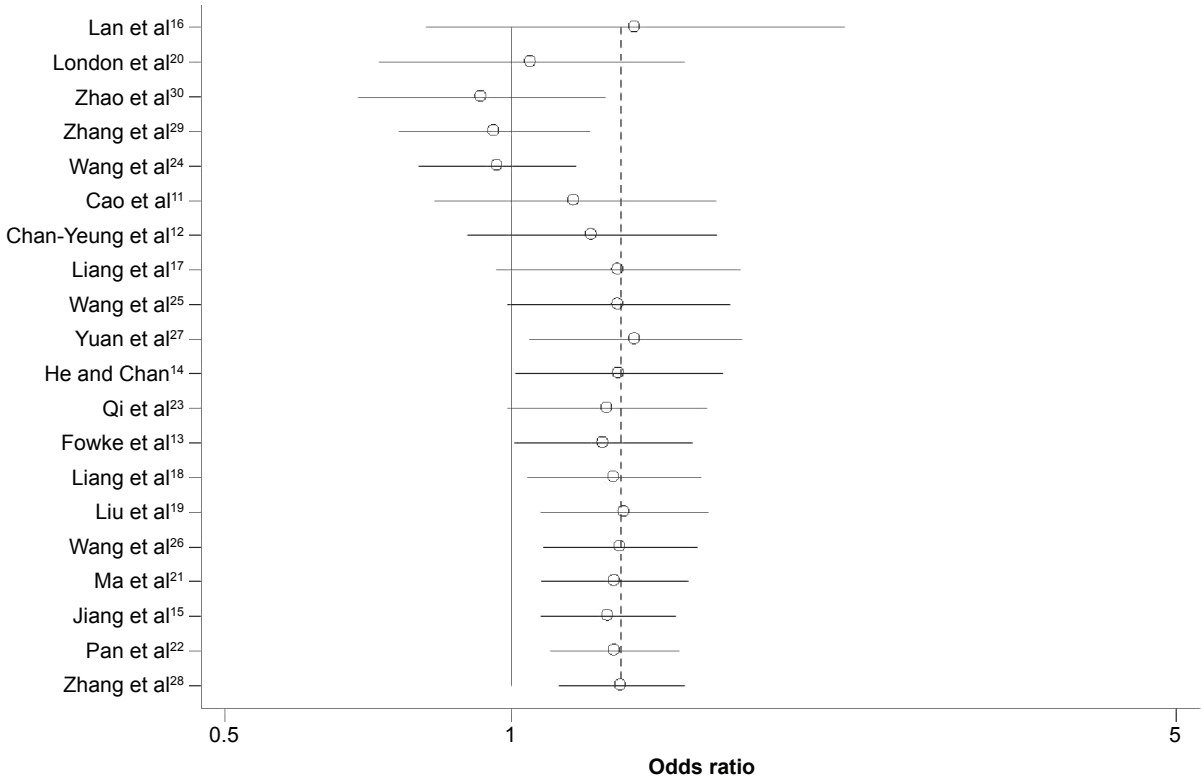

Figure 2 Forest plot for cumulative meta-analysis of OR for *GSTT1* deletion polymorphism associated with lung cancer risk among Chinese population.
Abbreviations: *GSTT1*, glutathione S-transferase T1; OR, odds ratio.

95% CI: 1.84–2.85 and OR =1.47, 95% CI: 1.22–1.77, respectively). We did not observe any association between *GSTT1* null genotype and lung cancer risk stratified by smoking status (OR =1.54, 95% CI: 0.97–2.43 for smokers and OR=1.03, 95% CI: 0.70–1.51 for nonsmokers, respectively; Table 2).

Bias diagnosis

Publication bias was examined by using funnel plot analysis. The shape of the funnel plot seemed to be approximately symmetrical (Figure 3). Both Egger's test and Begg's test suggested that publication bias might have few effects on the summary estimates, except for the subgroup analysis of squamous cell carcinoma, owing to *P*-value being equal to 0.024 in Begg's test.

Sensitivity analysis

We performed a sensitivity analysis to determine the influence of individual dataset on the summary OR by consecutively deleting individual studies. The combined OR was not significantly altered by deleting each selected study sequentially, which indicated that our results were stable and robust (Figure 4).

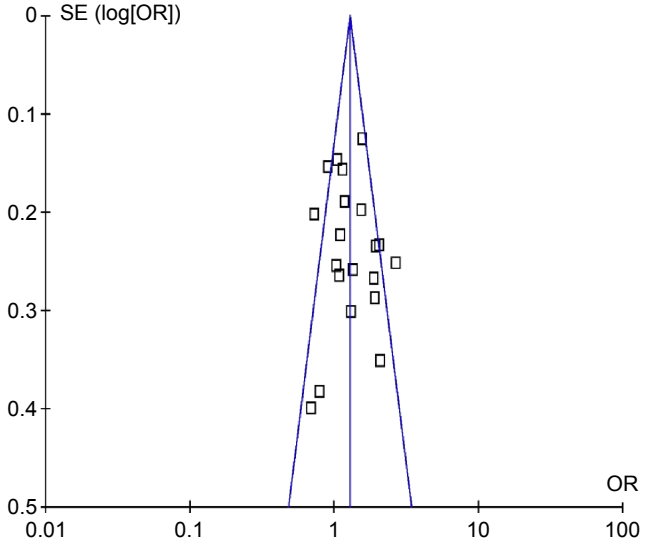

Figure 3 Funnel plot analysis to detect publication bias for *GSTT1* deletion polymorphism associated with lung cancer risk among Chinese population.
Abbreviations: GSTT1, glutathione S-transferase T1; OR, odds ratio; SE, standard error of mean.

Discussion

GSTT1 gene is mapped on chromosome 22q11.23. It is 8,146 bp in length, consisting of five exons and four introns, which encodes a cytoplasmic protein of 240 amino acid residues with a molecular weight of 28-kDa. *GSTT1* gene has a functional and nonfunctional allele. Homozygosity for the nonfunctional allele of *GSTT1* (null genotype) gene causes an absence of GSTT1 enzyme activity.[47] Individuals who carry homozygous deletions in this gene are thought to be at increased risks for malignancies.[8] Studies have shown that the

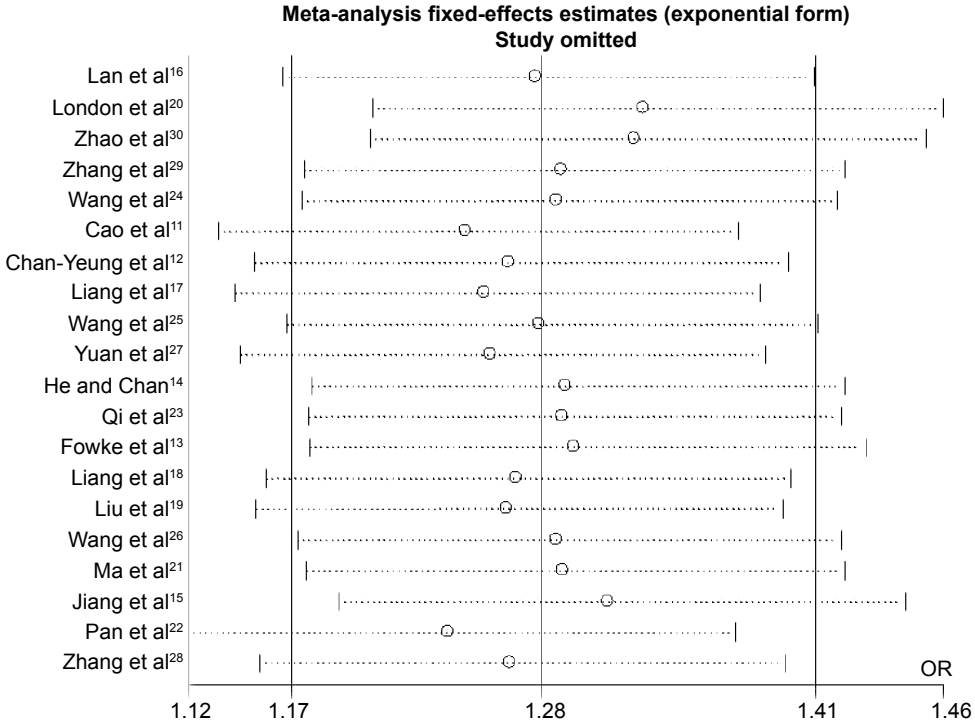

Figure 4 Sensitivity analysis on the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population.
Abbreviation: *GSTT1*, glutathione S-transferase T1.

GSTT1 gene deletion have effects on survival and clinical outcomes of lung cancer patients. Ruano-Ravina et al[48] reported that lung cancer patients with deleted *GSTT1* genotype had a significantly shorter survival than those with present *GSTT1* genotype. Sreeja et al[49] reported that the *GSTT1* –/– genotype along with stage was significantly associated with overall survival and was found to be an independent prognostic factor for shorter lung cancer survival. Gonlugur et al's[50] study showed that none of the patients with *GSTT1* null genotype, but 30% of the patients with *GSTT1*-positive genotype had liver metastasis among 81 lung cancer patients.[50]

Several meta-analyses explored the association of *GSTT1* null genotype with the development of several kinds of cancers among Chinese population.[51–57] In this paper, we performed a systematic literature review to comprehensively evaluate the association of *GSTT1* deletion polymorphism with lung cancer risk among Chinese population. We also evaluated the possible effect modifications by source of control, smoking status, and histological subtype. In summary, we observed an increased lung cancer risk among Chinese population with *GSTT1* null genotype compared with those carrying present genotype. To our knowledge, four published papers have addressed the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population. However, the conclusions are mixed, for example, three previous meta-analyses observed a positive association between *GSTT1* null genotype and an increased lung cancer risk among Chinese population,[31,33,34] but one not.[32] Furthermore, there are several key limitations in all four previous meta-analyses. Namely, one eligible paper[14] published before 2010 was not included in Wang et al's paper;[34] two eligible papers[13,25] published before 2013 were not included in Liu et al's paper[32] and Gui et al's paper.[31] Moreover, the number of cases and controls reported by Gui et al[31] for Chan-Yeung et al's study[12] did not seem in line with the data in Chan-Yeung et al's original publication;[12] for Liu et al's paper,[33] two overlapping papers[10,37] were not excluded and two eligible papers[13,40] published before 2013 were not included. Therefore, the conclusions from them are not entirely reliable. Our cumulative meta-analysis included 20 selected studies, with 3,351 cases and 4,683 controls on the basis of the updated data. We believed that this current meta-analysis presented a precise estimate of the association between *GSTT1* deletion polymorphism and lung cancer risk among Chinese population.

Cigarette smoke is an evident risk factor for lung cancer, and *GSTT1* gene is involved in metabolizing various carcinogens present in cigarette smoke. To address the effect of cigarette smoke on the correlation of *GSTT1* deletion polymorphism with lung cancer risk, subgroup analysis was conducted in the light of smoking status. We did not observe any association of *GSTT1* null genotype with increased risk of lung cancer among smokers or nonsmokers, which might be owing to the relatively small sample size (680 cases in smokers and 636 cases in nonsmokers).

To our knowledge, lung cancer consists of at least three major histological subtypes: squamous cell carcinoma, adenocarcinoma, and small-cell carcinoma. Studies have shown that the development of squamous cell carcinoma and small-cell carcinoma is more often attributed to cigarette smoking, whereas adenocarcinoma is more weakly associated with cigarette smoking than those two subtypes, indicating there is a difference in carcinogenic processes among different histological subtypes of lung cancer.[58] Therefore, a subgroup analysis was performed according to histological subtype. We observed a statistically significant association of *GSTT1* deletion polymorphism with an increased risk of squamous cell carcinoma and adenocarcinoma. We did not perform subgroup analysis in additional histological subtypes, since the sample size for those was relatively small.

There are some potential limitations inherent in this meta-analysis. First, only published articles were included in this study, which may cause publication bias. To address this issue, both Egger's test and Begg's test were applied in this study. Our results demonstrated that the likelihood of key publication bias was negligible in this current meta-analysis. Second, although some confounders were matched perfectly between cases and controls for each study at the beginning of study design, different study might have different eligibility criteria for subjects and different source of controls, which should be considered when expounding the combined effects. When the subgroup analysis was conducted by source of control, the association with *GSTT1* null genotype was much stronger in the conducted analysis of studies including healthy subjects as controls (OR =1.31, 95% CI: 1.11–1.55) than that of studies including hospitalized patients controls (OR =1.28, 95% CI: 0.89–1.83), indicating that the distribution frequency of *GSTT1* null genotype in the hospitalized patients-based control groups might not be representative of the general population. Third, this meta-analysis is based on an unadjusted estimate; thus, a more precise analysis depending on adjusted factors should be conducted in the future study.

In summary, this meta-analysis found that *GSTT1* null genotype was associated with an increased risk of lung cancer among Chinese population. Studies with larger sample size

are required to evaluate gene–gene and gene–environment interactions on *GSTT1* deletion polymorphism and lung cancer risk among Chinese population further.

Disclosure

The authors report no conflicts of interests in this work.

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