RESEARCH ARTICLE

GSTM1 Polymorphisms and Lung Cancer Risk in the Chinese Population: a Meta-Analysis Based on 47 Studies

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Abstract

Although a number of studies have been conducted on the association between GSTM1 polymorphisms and lung cancer in China, this association remains elusive and controversial. To clarify the effects of GSTM1 polymorphisms on the risk of lung cancer, a meta-analysis was performed in the Chinese population. Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 5th April 2014. A total of 45 articles (47 studies) including 6,623 cases and 7,865 controls were involved in this meta-analysis. Overall, a significant association (OR = 1.45, 95%CI: 1.32-1.60) was found between the null GSTM1 and lung cancer risk when all studies in Chinese population pooled into the meta-analysis. In subgroup analyses stratified by quality score, geographic area and source of controls, the same results were observed under all the models. This meta-analysis showed that the null GSTM1 may be a potential biomarker for lung cancer risk in Chinese, but further studies with gene-gene and gene-environment interactions are required for definite conclusions.

Keywords: Meta-analysis - GSTM1 - polymorphism - lung cancer - Chinese population

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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 (Jemal et al., 2011). Human cancers can be initiated by DNA damage caused by environmental chemical agents, such as polycyclic aromatic hydrocarbons (PAHs), and some adverse habits including tobacco smoking and alcohol use (Neumann et al., 2005).

Studies have shown that exposures to environmental and occupational PAHs are risk factors for lung cancer (Kriek et al., 1993; Li et al., 2004; Vineis & Husgafvel-Pursiainen, 2005). However, not all of those who have been exposed to the risk factors will develop lung cancer, suggesting that there is individual variation in cancer susceptibility in the general population (Neumann et al., 2005). To understand the contribution of genetic variations in lung cancer, genetic association approach has been widely used and has been fruitful. For example, studies have consistently associated the development of lung cancer with the genetic factors such as glutathione S-transferase M1 (GSTM1).

The association between GSTM1 gene and lung cancer has been investigated in numerous epidemiologic studies since glutathione S-transferase was first suggested as a potential marker for susceptibility to lung cancer in 1986 (Seidegard et al., 1986). Glutathione S-transferases consist five distinct families, namely alpha (GSTA), sigma (GSTS), mu (GSTM), pi (GSTP), and theta (GSTT) (Kiyohara et al., 2002). Located on the chromosome 1p13.3, the GSTM1 plays an important role in the xenobiotics' detoxification. The most common genotype of GSTM1 gene is homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity, increased vulnerability to cytogenetic damage and resulted in the increased susceptibility to cancer (Hayes et al., 2005; McIlwain et al., 2006).

Recently, the role of GSTM1 polymorphism in the etiology of different types of cancer has drawn more and more attention, including lung cancer. A number of studies in China have been conducted to explore whether GSTM1 polymorphism is associated with lung cancer susceptibility, but provided controversial or inconclusive results. Therefore, we conducted a meta-analysis to more precisely define the effect of GSTM1 polymorphism on risk for lung cancer in Chinese populations.

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Materials and Methods

Search strategy

We searched databases containing PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 5th April 2014, using combination of the following terms: (1) GSTM1 or GST M1; (2) lung cancer or lung neoplasm or lung tumor; (3) polymorphism or variant or variation; and (4) Chinese or China. We limited the languages to English and Chinese. Besides, the references from retrieved articles were also searched.

Eligibility criteria

Studies were included in this meta-analysis if they met the following criteria: (1) case-control study or cohort study studying on associations between GSTM1 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) published in English or Chinese language; (5) all participants were Chinese. Studies were excluded when they were: (1) not case-control study or cohort study; (2) duplicate of previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, case reports, or editorial articles.

Data extraction

Data were independently extracted by two reviewers (Xin-ping Chen and Wei-hua Xu) using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by the all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were then scrutinized if the title and abstract were ambiguous. The following data were extracted from the identified studies: the first author, publication year, source of controls, geographic area, sample size, and the number of subjects with two GSTM1 genotypes. In this meta-analysis, the quality assessment of individual study was conducted according to the nine-star Newcastle-Ottawa Scale (Wells et al., 2009). For articles including different source of controls, data were extracted separately (Table 1).

Statistical analysis

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the association of GSTM1 genetic polymorphism with lung cancer risk in Chinese population. Given that there was distribution of null/present heterozygote in only one study selected, the Hardy-Weinberg equilibrium (HWE) test could not be conducted. Cochrane's Q test was performed to test the between-study heterogeneity. If there was heterogeneity, then the random-effects model was chosen to pool the ORs with 95 % CIs, otherwise the fixed-effects model was used. Publication bias was investigated with the funnel plot, in which the Standard Error (SE) of log OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of Egger's linear regression test (Egger et al., 1997). All the P values were two sided. P value less than 0.05 was considered statistically significant. All statistical analysis was conducted by using Stata version 10.0 (Stata Corp, College Station, Texas, USA).

Results

Study selection

We identified 114 articles that examined the association between GSTM1 polymorphism and risk of Lung cancer in Chinese. However, after screening of the titles and abstracts of all 114 articles, 50 were excluded. Of the 64 potentially relevant articles identified for further assessment, one article (Wu et al., 2003) was excluded because it did not provide sufficient data about the distribution of GSTM1 genotype, 18 (Gao et al., 1998; Gao & Zhang, 1998; Hu et al., 1998; Chen et al., 1999; Xue et al., 2001; Zhang et al., 2002; Wang et al., 2003; Gu et al., 2004; Luo et al., 2004; Ye et al., 2005; Zeng et al., 2005; Chang et al., 2006; Wang et al., 2006; Wang et al., 2007; Chang et al., 2009; Li et al., 2011; Li et al., 2012; Ma et al., 2013) were excluded because they concerned duplicate subjects. Finally, a total of 45 articles (47 studies) (Ge et al., 1996; Gao & Zhang, 1999; Lan et al., 2000; London et al., 2000; Chen et al., 2001; Zhao et al., 2001; Chan et al., 2002; Lu et al., 2002; Zhang et al., 2002; Zhang et al., 2002a; Chen et al., 2003; Wang et al., 2003; Xian et al., 2003; Chan-Yeung et al., 2004; Li et al., 2004; Liang et al., 2004; Yang et al., 2004; Chan et al., 2005; Li et al., 2005; Li et al., 2005a; Qiao et al., 2005; Wang et al., 2005; Chen et al., 2006; Qian et al., 2006; Wang et al., 2006; Yao et al., 2006; Gu et al., 2007; Lei et al., 2007; Liu et al., 2008; Xia et al., 2008; Wang et al., 2009; Fan et al., 2010; Jin et al., 2010; Song et al., 2010; Zheng et al., 2010; Zhu, 2010; Du et al., 2011; Zhang et al., 2011; Chen et al., 2012; Han et al., 2012; Liang et al., 2012; Liu et al., 2012; Wang et al., 2012; Yao et al., 2012; Lu, 2013) containing 6,623 cases and 7,865 controls were included in this meta-analysis, and the characteristics of these studies are shown in Table 1. Among 45 included articles, 22 articles provided ethnic information, with 18 being Han, the others being Mongolian, Zhuang and Man, respectively. Unfortunately, the ethnic information of the rest 23 articles was unknown.

Overall analysis

There was evidence of between-study heterogeneity in all included studies (χ^2=88.54, p<0.001). Therefore, the random-effects model was used in overall analysis. The results showed that the pooled OR with 95% CI for lung cancer in Chinese with null GSTM1 was 1.45 (1.32-1.60) (Figure 1)

Subgroup analysis

In the subgroup analysis based on source of control, the results showed that the GSTM1 polymorphism was significantly related to lung cancer risk among population-based population (OR = 1.55, 95%CI: 1.39-1.73), as well

Table 1. Characteristics of Studies Included in the Meta-analysis

Refence	Source of controls	Area	Case/Control	Case		Control		Quality score
				Null genotype	Non-null	Null genotype	Non-null	
Ge 1996	NR	Hong Kong	89/25	59	30	16	9	6
Gao 1999	PB	Guangdong	59/73	34	25	36	37	7
Gao 1999	HB	Guangdong	59/59	34	25	29	30	7
London 2000	NR	Shanghai	232/710	122	110	427	283	8
Lan 2000	PB	Yunnan	122/122	82	40	60	62	6
Chen 2001	PB	Jiangsu	106/106	56	50	39	67	8
Zhao 2001	HB	Singapore	233/187	146	87	119	68	7
Chan 2002	PB	Yunnan	56/99	43	13	65	34	6
Lu 2002	PB	Beijing	314/320	158	156	158	162	8
Zhang 2002	PB	Guangdong	161/165	94	67	92	73	7
Zhang2002a	HB	Jiangsu	65/60	41	24	27	33	7
Chen 2003	PB	Anhui	38/99	24	14	57	42	8
Wang 2003	PB	Beijing+Tianjin	164/181	97	67	90	91	7
Xian 2003	HB+PB	Guangdong	91/138	56	35	73	65	8
Chan-Yeung 2004	PB	Hong Kong	229/197	130	99	117	80	8
Li 2004	HB	Beijing	217/200	127	90	95	105	8
Liang 2004	HB	Jiangsu	152/152	82	70	79	73	6
Yang 2004	PB	Liaoning	186/139	108	78	75	64	8
Wang 2005	PB	Henan	77/107	45	32	45	62	7
Li 2005	HB	Sichuan	99/66	57	42	27	39	6
Qiao 2005	HB	Guangdong	213/64	130	83	31	33	8
Qiao 2005	PB	Guangdong	213/135	130	83	64	71	8
Chan 2005	HB	Hong Kong	75/162	31	44	91	71	6
Li 2005a	PB	Henan	103/138	63	40	61	77	7
Qian 2006	PB	Tianjin	108/108	69	39	53	55	8
Wang 2006	PB	Hubei	56/42	40	16	19	23	6
Chen 2006	PB	Hunan	97/197	60	37	89	108	8
Yao 2006	PB	Henan	77/107	45	32	45	62	7
Lei 2007	PB	Sichuan	42/103	24	18	57	46	6
Gu 2007	HB+PB	Beijing	279/684	164	115	325	359	8
Liu 2008	PB	Shandong	110/125	66	44	57	68	7
Xia 2008	HB	Gansu	58/131	34	24	76	55	6
Wang 2009	PB	Inner Mongolia	304/310	143	161	119	197	8
Fan 2010	PB	Guangxi	58/60	40	18	33	27	6
Jin 2010	HB	Anhui	150/150	95	55	79	71	7
Song 2010	PB	Shandong	125/125	74	51	55	70	7
Zhu 2010	HB+PB	Hunan	160/160	93	67	72	88	7
Zheng 2010	PB	Tianjin	265/307	150	115	175	132	7
Du 2011	HB	Sichuan	125/125	73	52	71	54	7
Zhang 2011	PB	Yunnan	50/50	34	16	22	28	7
Han 2012	PB	Inner Mongolia	128/214	79	49	89	125	6
Yao 2012	PB	Beijing	150/150	96	54	68	82	7
Wang 2012	PB	Henan	209/256	122	87	113	143	7
Liu 2012	PB	Heilongjiang	360/360	145	215	107	253	8
Chen 2012	PB	Zhejiang	200/189	123	77	110	79	7
Liang 2012	HB	Guangxi	68/70	47	21	39	31	6
Lu 2013	PB	Guangdong	91/138	61	30	70	68	7

NR, not reported; HB, hospital-based; PB, population-based

Table 2. Main Results in the Total and Subgroup Analysis

Subgroups		Random-effect model OR(95%CI)	Fixed-effect model OR(95%CI)	Heterogeneity χ^2	*P*
Total analysis	1.45 (1.32-1.60)	1.40(1.31-1.50)	88.54	<0.001	
Source of control	Population-based	1.55(1.39-1.73)	1.51(1.39-1.64)	44.75	0.031
	Hospital-based	1.27(1.04-1.57)	1.26(1.08-1.46)	19.38	0.055
Quality score	8	1.37(1.17-1.61)	1.33(1.20-1.47)	33.22	0.003
	7	1.51(1.32-1.72)	1.47(1.32-1.64)	27.08	0.103
	6	1.47(1.11-1.94)	1.46(1.22-1.73)	26.08	0.006
Area	South China	1.40(1.19-1.66)	1.30(1.17-1.44)	54.57	<0.001
	North China	1.53(1.38-1.70)	1.52(1.39-1.66)	25.38	0.187

as among hospital-based studies (OR = 1.26, 95%CI: 1.08-1.46) (Table 2). In addition, we also performed stratified analysis based on the quality score and geographic area, it revealed the similar results with all the studies (Table 2).

Sensitive analysis

To evaluate the stability of the results, we performed a sensitivity analysis by different model. All the results were not materially altered (Table 2). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible.

Bias diagnosis

The Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. As showed in Figure 2, the shape of the funnel plots did

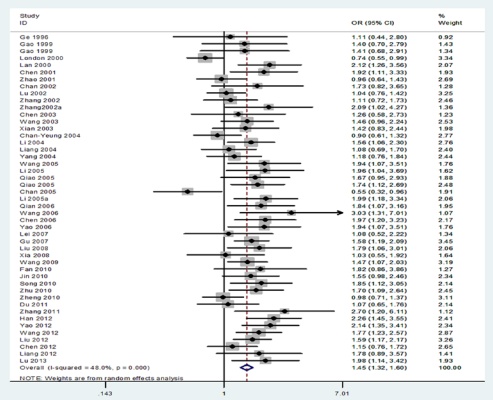

Figure 1. The Forest Plot of All Selected Studies on the Association between GSTM1 Polymorphism and Lung Cancer Risk in Chinese

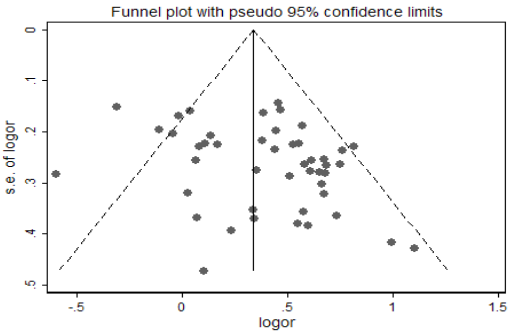

Figure 2. The Funnel plot of all Selected Studies on the Association between GSTM1 Polymorphism and Lung Cancer Risk in Chinese

reveal obvious asymmetry. Similarly, the Egger's test indicated some publication bias in the 47 reviewed studies (t=-2.51, p=0.016).

Discussion

Till date, a series of studies in China have focused on the relation between GSTM1 polymorphism and lung cancer risk. Nevertheless, the results were inconclusive and inconsistent. Some papers have reported that a statistically significant correlation was found between null GSTM1 and lung cancer risk. Conversely, the results from other studies suggested that the null GSTM1 was not associated with lung cancer risk. Therefore, we conducted this update meta-analysis by critically reviewing 47 individual studies on GSTM1 gene polymorphism with lung cancer risk in Chinese population. In the meta-analysis, we found that the GSTM1 null variant was significantly associated with lung cancer risk. However, our results showed a stronger association with lung cancer risk than those reported by the Carlste's study (Carlsten et al., 2008) on the GSTM1 polymorphism that included 19,638 cases and 25,266 controls of the world's overall populations (OR = 1.22, 95% CI = 1.14-1.30). Furthermore, our results are almost the same as those of Shi's results (Shi et al., 2008) (OR = 1.54, 95% CI = 1.31-1.80). His report only included 2235 cases and 2315 controls of Chinese population. To our knowledge, our study represented the first meta-analysis with a large sample size on the interaction of GSTM1 variant with lung cancer in Chinese population.

When we performed stratified analyses by quality score, geographic area and source of controls, significant association with susceptibility for the development of lung cancer was found in all the subgroups. With regard to heterogeneity, some of the factors extracted in this study were the main source of heterogeneity. But it might also make attributions for other unknown factors, such as dietary habits, dinking status, other environmental exposures (passive smoking and cooking oil fume), family history of cancer, other genetic-related respiratory diseases as well as other related genetic polymorphisms.

The pathways of carcinogen metabolism are complex, mediated by the activities of multiple genes. The effect of any single gene might have a limited impact on lung cancer risk than have so far been anticipated. Many controversial data are present in literature. Positive associations were found in certain populations and not confirmed in others. In addition to an expected interethnic variability in allele frequencies, variability has also been found within an ethnic group, resulting in heterogeneity in association studies. Gene-environment interactions could be a confounding factor in these studies, with controversial findings on cancer risk. Studies taking these factors into account may eventually lead to have a better, comprehensive understanding of the association between the GSTM1 polymorphism and lung cancer risk.

This study has some limitations. First, we didn't perform subgroup analysis on smoking status and other exposure history. Second, our results were based on unadjusted estimates. Therefore, the confounding factors might influence the estimates. Third, some publication bias was detected. Because the papers included in our meta-analysis were limited to those published in either English or Chinese only in the periods between 1989 and 2014, it is possible that some relevant published studies and unpublished studies that are likely to have null results were not included, which may have biased the results.

In summary, although studies investigating the association between GSTM1 polymorphism and the risk of lung cancer arrived at different conclusions (Piao et al., 2013; Shukla et al., 2013), this meta-analysis suggested that there was a significant association between null GSTM1 variant and lung cancer risk in the Chinese. Several recommendations on the future association studies of GSTM1-lung cancer can be made from this meta-analysis. First, a well thought-out study design is crucial for an association study. Second, it is important to make an effort to control risk factors, preferably in the design stage. Third, larger research articles in other populations with different environmental background are required. Lastly, care should be exercised in genotyping and in checking for abnormality, such as the deviation from HWP.

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