RESEARCH ARTICLE

Lack of Assocation of Glutathione S-transferase T1 Gene Null and Susceptibility to Lung Cancer in China: a Meta-analysis

Hong-Zhou Liu[1], Jie Peng[2] , Fang Zheng[1]*, Chun-Hong Wang[3], Ming-Jun Han[1]

Abstract

Background: Variation in metabolic genes is regarded as an important factor in processes leading to cancer. However, the effect of GSTT1 null genotype is divergent in the form of lung cancer. Methods: Studies were conducted at different research databases from 1990 to 2013 and the total odds ratio (OR) and 95% confidence interval (CI) were calculated for lung cancer. Review Manager 5.2 and STATE 12 are employed. Results: Total OR value is calculated from 17 articles with 2,118 cases and 2,915 controls. We discovered no significant increase in lung cancer risk among subjects carrying GSTT1 null genotype [OR = 1.15; 95% CI 0.97-1.36] in this meta-analysis. Conclusion: The GSTT1 deletion polymorphism does not have a significant effect on the susceptibility to lung cancer overall in China.

Keywords: Glutathione S-transferase T1 gene (GSTT1) - genetic polymorphism - lung cancer

Asian Pac J Cancer Prev, **14 (12)**, 7215-7219

Introduction

According to World Health Organization (WHO), lung cancer is one of the most important cancers because of its high morbidity and mortality. Lung cancer increases roughly 400% during the past 30 years in China (Zhao et al., 2010). The WHO forecasts that over a million Chinese will be diagnosed in each year by the year 2025 (Zhao et al., 2010). Researchers think that there are many factors that can lead to lung cancer in our surroundings. Cigarettes are regarded as the most important environmental factor. However, not all of those who smoked get lung cancer. This phenomenon indicates that other factors also can contribute to the etiology of lung cancer, such as genetic variation. Variation of metabolic genes which involve in carcinogens metabolism is known as an important cause in the formation of cancer. As we all known that there are many metabolic genes can metabolize carcinogens. These genes include cytochrome P450 (CYP450), microsomal epoxide hydrolase, glutathione S-transferase and N-acetyltransferase. Glutathione S-transferase (GST) consists of GSTM1, GSTP1 and GSTT1. GSTT1 gene is situated at 22q11.23. It has eight thousand base pairs and consists of 5 exons and 4 introns. It encodes a protein that consists of 240 amino acids. GSTT1 has similar function to GSTM1, but it has lower binding activity. Although some researchers think that GSTT1 is involved in some carcinogens metabolism, there is no clear evidence that GSTT1 takes part in detoxifying nicotine. Besides, GSTT1 has two alleles. It consists of functional and non-functional genotypes. The distribution of GSTT1 null genotype is in great differences among different ethnic groups. Some researchers consider that the susceptibility of lung cancer is different because the distribution of GSTT1 null genotype varies in different populations. However, GSTM1 and CYP450 maybe have a more important role in detoxification of carcinogens, and GSTM1 and CYP450 can compensate the function of GSTT1. We doubt that GSTT1 null genotype is the etiology of lung cancer.

A number of studies have investigated the association between GSTT1 null genotype and lung cancer, but the results are divergent. Dongxu He et al. found that the distribution of GSTT1 null genotype was not significantly higher in lung cancer group than that in control group (OR=0.69 and 95% CI [0.32, 1.51]) (He et al., 2006). Tianzhu Yuan et al. found that the distribution frequency of GSTT1 null genotype was significantly higher in group with lung cancer than that in control group (OR=1.95 and 95% CI [1.24, 3.09]) (Yuan et al., 2005) without consideration of smoking. When it took cigarettes into account, OR value became 0.47 and 95% CI became [0.22, 1.00] in the non-smokers. This outcome makes us doubt that GSTT1 is the etiology of lung cancer. Furthermore, smoking is a major factor that can not be ignored. In the meta-analysis published in 2010, it caught a conclusion that there was a significant association between GSTT1 null genotype and the susceptibility of lung cancer (Wang et al., 2010). However, there are a small number of articles and a fewer cases and controls in that study. Especially, it does not rule out the impact of smoking. We enlarge the number of cases and controls to rule out publish bias, and eliminate the influence of cigarettes by using the subgroup of non-smokers.

[1]*Center for Gene Diagnosis, Zhongnan Hospital of Wuhan University,* [2]*Department of Stomatology, Zhongnan Hospital of Wuhan University,* [3]*Department of Public Health, Wuhan University, Wuhan, China *For correspondence: zhengfang@whu.edu.cn*

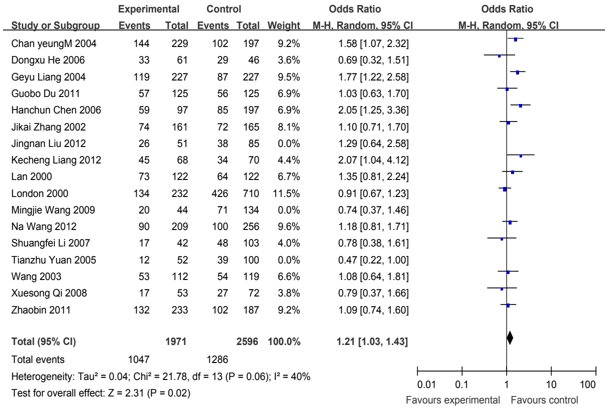

Figure 1. Forest Plot of Without Consideration of Smoking. The papers included in this forest plot did not consider the effect of smoking. It was analyzed by Review Manager 5.2. There are 14 papers in this figure. The weight of Jingnan Liu 2012, Mingjie Wang 2009 and Tianzhu Yuan 2005 is 0.0%, because they are the subgroup of non-smoking. They were just inputted in the same figure. Heterogeneity test was also be done in the figure, and the result is important for choosing the model of meta-analysis

Materials and Methods

Literature inclusion criteria

(1) The subjects of literature must be Chinese; (2) The papers should include the risk of lung cancer and GSTT1 null genotype; (3) Only case-control and cohort studies are considered; (4) The papers must provide the sample size, the OR values and 95% confidence interval or provide the related information such as genotype frequency that can be used to calculate OR and 95% CI; (5) When the same study population was used in more than one paper, we included a recent literature; (6) If there were non-smokers subgroups in articles, we used this data.

Literature exclusion criteria

(1) There is no controls; (2) No row data; (3) The articles are reviews; (4) Controls are with other malignancies.

Search strategy

PubMed, Wanfang Med Online, VIP database and Chinese national knowledge infrastructure (CNKI) were searched by using key words: ''lung cancer'';''GSTT1''; ''glutathione S-transferase T1''; ''polymorphism''. The date of the search interval was from 1990 to 2013 and the scope of the search was all papers consisting of journals and dissertations.

Study selection and data extraction

According to pre-established criteria of inclusion and exclusion, a double-check procedure was carried out to make sure the accuracy of the data entry. The following information was extracted from the studies: first author, published year, the data of total and exposure number in case and control groups, odds ratio and 95% CI. A standardized procedure was performed to estimate Odds Ratio of cases and controls. Characteristics of studies were summarized.

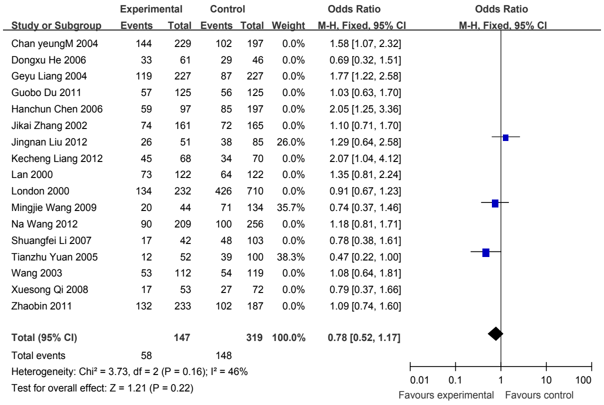

Figure 2. Forest Plot of Non-smoking. This figure consists of three papers of Jingnan Liu 2012, Mingjie Wang 2009 and Tianzhu Yuan 2005, because they are the subgroup of non-smoking

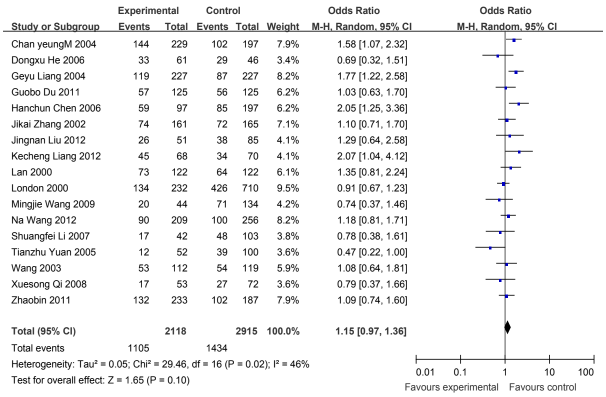

Figure 3. Forest Plot of All 17 Papers. This figure consists of all 17 papers, and it indicates that the mixture of two groups is interesting, because the total OR and total 95% CI decline. The result of the mixture shows that if we eliminate the effect of smoking in all 17 papers, there is no significant relationship between GSTT1 and lung cancer

Statistical analysis methods

Statistical analysis was done by using Review Manager5.2 and STATA 12. Adjusted OR value and 95% CI were calculated for each study, and crude OR value should be calculated if adjusted OR value was not available. The meta-analysis was carried out on adjusted odds ratios, because the adjusted odds ratios were comparable. The Cochrane Q statistics test was performed for heterogeneity in this meta-analysis. A fixed effects model was used when P>0.10 and I^2<50%, simultaneously, while a random effects model was selected when P<0.10 or I^2>50%. The funnel plot was drawn to evaluate publication bias. Egger's test and Begg's test were also done to check the publication bias. All the tests were two-sided, a P value of 0.05 for any test or model was considered to be statistically significant.

Results

Overview of included studies

According to the search strategy, 34 papers were selected. We had read all the papers and 25 papers were included because they had complete data. However, 8 papers were excluded owing to duplicate data. Therefore, 14 papers were included in Figure 1, and this group took

Table 1. Literature Inclusion and Exclusion

First author	Year	cases	controls	OR(95%CI)	Remark
Tianzhu Yuan	2005	150(52)	152(100)	1.95 [1.24,3.09]	inclusion (non-smoking subgroup)
Geyu Liang	2005	227	227	1.77 [1.22,2.58]	inclusion
Geyu Liang	2004	152	152	2.06 [1.30,3.25]	exclusion (duplication of data)
Yanfei Cao	2004	104	205	2.67 [1.63,4.37]	exclusion (duplication of data)
Chan Yeung	2004	229	197	1.58 [1.07,2.32]	inclusion
Lan	2000	122	122	1.35 [0.81,2.24]	inclusion
London	2000	232	710	0.91 [0.67,1.23]	inclusion
Zhaobin	2001	233	187	1.09 [0.74,1.60]	inclusion
Jikai Zhang	2002	161	165	1.10 [0.71,1.70]	inclusion
Wang J	2003	112	119	1.08 [0.64,1.81]	inclusion
Na Wang	2006	77	107	1.31 [0.73,2.36]	exclusion (duplication of data)
Wu Yao	2006	77	107	1.31 [0.73,2.36]	exclusion (duplication of data)
Xuesong Qi	2008	53	72	0.79 [0.37,1.66]	inclusion
Juan Fan	2010	58	60	2.03 [0.97,4.26]	exclusion (duplication of data)
Daiyuan Ma	2011		100		exclusion (no control)
Mingjie Wang	2009	106(44)	250(134)	0.74 [0.37,1.46]	inclusion (non-smoking subgroup)
Shuangfei Li	2007	42	103	0.78 [0.38,1.61]	inclusion
Jikai Zhang	2002	42	55	0.51 [0.23,1,15]	exclusion (duplication of data)
Dongxu He	2006	61	46	0.69 [0.32,1.51]	inclusion
Qing Lan	1991	86	86	1.00 [0.54,1.84]	exclusion (duplication of data)
Jingnan Liu	2012	100(51)	135(85)	1.29 [0.64,2.58]	inclusion (non-smoking subgroup)
Na wang	2012	209	256	1.18 [0.81,1.71]	inclusion
Hanchun Chen	2006	97	197	2.05 [1.25,3.36]	inclusion
Guobo Du	2011	125	125	1.03 [0.63,1.70]	inclusion
Xingzhou He	2001	122	122	1.35 [0.81,2.24]	exclusion (duplication of data)
Kecheng Liang	2012	68	70	2.07 [1.04,4.12]	inclusion

This table shows all usefull details,and the following information is extracted from the studies in this table. Inclusion and exclusion are determined by the information

Table 2. Egger's Test and Begg's Test

Egger's test					
Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]
slope	0.63741	0.3908243	1.63	0.124	-.1956123 1.470432
bias	-2.625242	1.58884	-1.65	0.119	-6.011774 .7612903
Begg's test					
adj. Kendall's Score (P-Q)	Std.Dev.of Score	Number of studies	z	Pr> |z|	
-34	24.28	17	-1.4	0.161	
			1.36	0.174	(continuity corrected)

Two tests were done by STATE12 to test publication bias. The result of Egger's test is P=0.119>0.05 and Begg's test is P=0.174>0.05. It indicates there is no publication bias

no consideration of smoking. Three articles had non-smoking subgroup, so the data of non-smoking subgroup was selected in Figure 2. All of 17 papers were analysis in Figure 3.

Details of the literature

Tianzhu Yuan et al., Minjie Wang et al. and Jingnan Liu et al. had non-smoking subgroups of GSTT1 and lung cancer susceptibility. Therefore, the data of non-smoking subgroup was used to exclude the influence of smoking factors. Geyu Liang et al.; Jikai Zhang et al.; Yanfei Cao et al. and Hanchun Chen et al.; Qing Lan et al., Lan et al. and Xingzhou He et al.; Na Wang et al. and Wu Yao et al.; Kecheng Liang et al.and Juan Fan et al. had the duplicate data and data of later articles was selected in Table 1.

Test of heterogeneity

The relationship between GSTT1 null genotype and lung cancer susceptibility was shown in Figure 3. The total heterogeneity was analyzed for 17 case–control studies and the results was P=0.02 and I^2=46%. P value was less than 0.10, so we analyzed the summary odds ratios with random effects model. There are many causes may lead to heterogeneity. The distribution of GSTT1 null genotype is different in various regions; the selection of control group is different among articles; the mean reason that generates heterogeneity is the factor of smoking and subtypes of lung cancer.

Data analysis

The result was 1.21 and 95% CI was [1.03-1.41] in Figure 1 and the group of non-smoking was 0.78 and 95% CI was [0.52-1.17] in Figure 2. Total OR value was calculated from 2118 cases and 2915 controls in Figure 3 and the result was 1.15 and 95% CI was [0.97-1.36]. When we combined Figure 1 and Figure 2, the OR declined and turned to be insignificant. If the factor of smoking was excluded in all papers, the conclusion that there was

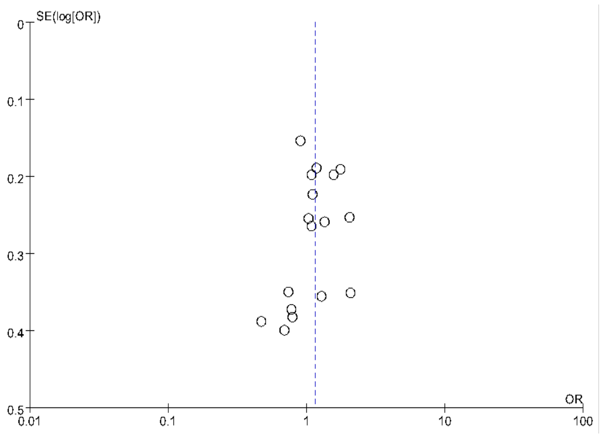

Figure 4. The Funnel Plot. This figure is necessary for test of publication bias. The distribution of data is uniform through the funnel plot, and shape of the funnel plot is symmetrical, we can consider that there is no publication bias

no significant correlation between GSTT1 null genotype and lung cancer might be more convincible. We caught a conclusion that single GSTT1 null type and lung cancer risk did not have a significant correlation. However, it was significant in Figure 1. It indicated that GSTT1 null genotype and smoking might have a joint action, or might be the effect of smoking.

Sources of bias and evaluation

The distribution of data was uniform through the funnel plot, and shape of the funnel plot was symmetrical, we could consider that there was no publication bias in Figure 4. In addition, the Egger's test and Begg's test were selected to test publication bias in Table 2. We used the inverse of the standard error as the independent variable and the standardized estimate of the size effect as the dependent variable in this analysis. The result of egger's test was P=0.119>0.05, and begg's test was P=0.174>0.05. It indicated that there was no publication bias.

Discussion

The article published by Qing Lan et al. (Lan et al., 1991) is the fist paper about the relationship between GSTT1 null genotype and the susceptibility of lung cancer among Chinese in 1991. More than one hundred papers about GSTT1 have been published during the past twenty years. Several articles discussed the relationships between lung cancer and GSTT1 null genotypes, but the results were instable and controversial. The meta-analysis published by Wang et al. (2010) in 2010 found that GSTT1 null genotype and risk of lung cancer had a significant association. However, a few studies were included and the factor of smoking was not excluded in his study. In addition, it would be better to chose a random effects model because of P=0.02<0.10 in this meta-analysis. Therefore, we re-did a meta-analysis to analyze the relationship between GSTT1 null genotype and lung cancer risk. We discovered that there was no significant association between GSTT1 null genotype and lung cancer risk.

It indicates that the there is no link between GSTT1 and susceptibility of lung cancer in this meta-analysis. Many reasons can lead to this result. Firstly, GSTT1 may be not take part in detoxification of nicotine and formation of lung cancer. Secondly, GSTT1 genotype has weak effect on detoxification of nicotine, and GSTT1 null genotype is less important than GSTM1 and CYP450 in the etiology of lung cancer. Thirdly, the function of GSTT1 can be compensated by GSTM1 and CYP450, so the GSTT1 null genotype does not cause any effect alone.

There were some limitations in this meta-analysis. First, only published papers were included in this meta-analysis, and it will cause publication bias. However, funnel plot, Egger's test and begg's test indicated that publication bias was negligible. Second, there were a few cases and controls in non-smoking subgroup in this meta-analysis and this suggests that further analysis needs to gather complete data which includes gender, age, smoking and type of lung cancer.

In a word, we found that there was no significant association between GSTT1 null genotype and the susceptibility of lung cancer.

Acknowledgements

This work was supported by the National Basic Research Program of China (973 Program, 2012CB720600). We declare that we have no conflict of interest.

References

Chan-Yeung M, Tan-Un KC, Ip MS, et al (2004). Lung cancer susceptibility and polymorphisms of glutathione-S-transferase genes in Hong Kong. *Lung Cancer*, **45**, 155-60.

Cao YF, Chen HC, Liu XF, et al (2004). Study on the relationship between the genetic polymorphisms of GSTM1 and GSTT1 genes and lung cancer susceptibility in the population of Hunan Province of China. *Life Sci Res*, **8**, 126-32.

Chen HC, Cao YF, Hu WX, et al (2006). Genetic polymorphisms of phase II metabolic enzymes and lung cancer susceptibility in a population of Central South China. *Disease Markers,* **22**, 141-52.

Du GB (2011). A study on relationship between genetic polymorphism of GSTM1 and GSTT1 gene and susceptibility to lung cancer in the population of northern Sichuan of China[D]. CHINA: *North Sichuan Medical College*, 12-4

Fan J, Gan LG, Liang KC, et al (2010). Study on the relationship between the genetic polymorphisms of GSTM1 and GSTT1 genes and lung cancer susceptibility among the Zhuang population in Guangxi Province of China. *Journal of Oncology,* **16**, 922-5.

He XZ (2001). Indoor Coal Combustion Emissions, Lung Cancer and Susceptibility. Journal of Practical Oncology, 16, 369-70.

He DX, Tan Y (2006). The Relationship of GSTTl Polymorphism and Chromosome 15 Aberration in Lung Cancer Patients. *Cancer Prev Res*, **33**, 308-10.

Lan Q, He XZ, Costa DJ, et al (1991). Glutathione S-transferase GSTM1 and GSTT1 genotypes and susceptibility to lung cancer. *Journal of Hygiene Research*, **28**, 9-11.

London SJ, Yuan JM, Chung FL, et al (2000). Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. *Lancet*, **356**, 724-9.

Lan Q, Xingzhou He XZ, Costa DJ, et al (2000). Indoor coal combustion emissions, GSTM1 and GSTT1 genotypes, and lung cancer risk: a case–control study in Xuan Wei, China. *Cancer Epidemiol Biomarkers Prev*, **9**, 605-8.

Liang GY, Pu YP, Yin LH (2004). Studies of the genes related to lung cancer susceptibility in Nanjing Han population, China. *Hereditas (Beijing)*, **26**, 584-8.

Liang GY (2005). Studies on susceptibility genes of lung cancer in Chinese han population and rapid detection techniques of single nucleotide polymorphisms [D]. *CHINA: Southeast University*, 17-9.

Li SF (2007). A case-control study on the associations between polymorphism of GSTM1, GSTT1 and susceptibility to breast cancer and lung cancer[D]. *CHINA: Sichuan University*, 26-42.

Liu JN, Zhou CC, Piao HM, et al (2012). Relationship between GSTT1 genetic polymorphism, smoking and lung cancer susceptibility. *Basic & Clinical Medicine*, **32**, 1194-7.

Liang KC, Gan LK, Ruan L, et al (2012). Correlational research of the relationship between the genetic polymorphism of GSTM1 and GSTT1 in the Zhuang population and lung cancer. *Acta Medicinae Sinica*, **25**, 813-7.

Ma DY, Du GB, Tan BX, et al (2011). Genetic polymorphism of GSTT1 to lung cancer patients in north Sichuan. *Chin J Cancer Prev Trea*t, **18**, 989-91.

Qi XS, Lv HM, Xia Y, et al (2008). A primary case–control study on the relationship between genetic polymorphisms of GSTT1 and lung cancer susceptibility to the people living in high radon-exposed area. Chin Occup Med, **35**, 361-7.

Wang J, Deng Y, Cheng J, et al (2003). GST genetic polymorphisms and lung adenocarcinoma susceptibility in a Chinese population. *Cancer Lett*, **201**, 185-93.

Wang N, Wu Y, Wu YJ, et al (2004). Research on relationship between deletion of GSTM1, GSTTI genes and susceptibility to lung cancer. *J Hyg Res*, **33**, 586-8.

Wang MJ (2009). The Study on the Polymorphisms of CYPlA1 and GSTT1 Genes Associated With Susceptibility to Lung Cancer [D]. *CHINA: Inner Mongolia Medical College*, 15-7.

Wang YD, Yang HY, Li L, et al (2010). Glutathione S-transferase T1 gene deletion polymorphism and lung cancer risk in Chinese population: A meta-analysis. *Cancer Epidemiol*, **34**, 593-7.

Wang N, Zhou F, Wu YJ, et al (2012). The relationship between genetic polymorphism of four metabolizing enzymes and susceptibility to lung cancer. *Zhongguo Fei Ai Za Zhi*., **39**, 4545-7. [Article in Chinese]

Yuan TZ, Zhou QH, Zhu W, et al (2005). Relationship between genetic polymorphism of GSTTI gene and inherent susceptibility to lung cancer in Han population in Sichuan, China. *Chin J Lung Cancer*, **8**, 107-11.

Yao W, Wang N, Wu YJ, et al (2006). Relationship between deletion of GSTM1, GSTT1 genes and susceptibility to lung cancer. *Chin J Public Health,* **22**, 1070-2.

Zhao B, Seow A, Lee EJ, et al (2001). Dietary isothiocyanates, glutathione S-transferase-M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. *Cancer Epidemiol Biomarkers Prev,* **10**, 1063-7.

Zhang JK, Hu YL, Hu CF, et al (2002). Relationship between genetic polymorphisms of GSTM1 as well as GSTT1 and lung cancer. *Chin J Pathophysiol,* **18**, 352-5.

Zhang JK, Hu YL, Hu CF, et al (2002). Study on Genetic Polymorphisms of GSTM1 and GSTT1 Related with Inherent Susceptibility to Lung Cancer in Woman. *China Public Health*, **18**, 273-5

Zhao P, Dai M, Chen W, et al (2010). Cancer trends in China. *Jpn J Clin Oncol,* **40**, 281-5.