RESEARCH ARTICLE

Lack of Association of Glutathione S-transferase M3 Gene Polymorphism with the Susceptibility of Lung Cancer

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Abstract

Objective: The conclusions of published reports on the relationship between the glutathione S-transferase M3 (GSTM3) A/B gene polymorphism and the risk of lung cancer are still debated. This meta-analysis was performed to evaluate the association between GSTM3 and the risk of lung cancer. Methods: Association investigations were identified from PubMed, Embase, and Cochrane Library, and eligible studies were included and synthesized using a meta-analysis method. Results: Eight reports were included into this meta-analysis for the association of GSTM3 A/B gene polymorphism and lung cancer susceptibility, covering 1,854 patients with lung cancer and 1,926 controls. No association between the GSTM3 A/B gene polymorphism and lung cancer was found in this meta-analysis (B allele: OR = 1.25, 95% CI: 0.89-1.76, P = 0.20; BB genotype: OR = 1.53, 95% CI: 0.71-3.32, P = 0.28; AA genotype: OR = 0.85, 95% CI: 0.59-1.23, P = 0.39). Conclusions: The GSTM3 A/B gene polymorphism is not associated with lung cancer susceptibility. However, more studies on the relationship between GSTM3 A/B gene polymorphism and the risk of lung cancer should be performed in the future.

Keywords: Lung cancer - glutathione S-transferase M3 - A/B gene polymorphism - meta-analysis

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Introduction

Lung cancer is one of the most common cancer types that lead to death in cancer patients across the world (Tian et al., 2011). It is very often a deadly disease with 5-year survival rates of about 14% (Lou et al., 2011). There lacks a well-document therapeutic regimen to treat the patients with lung cancer. Furthermore, there are also few markers to predict the risk of lung cancer at present. Current evidences indicate that there is a link between gene polymorphism and the risk of lung cancer susceptibility (Dai et al., 2012).

Glutathione S-transferases (GSTs), important detoxification enzymes, take part in the pathogenesis of cancers. Glutathione S-transferase M3 (GSTM3) is an important GSTs variant and the present evidences show that GSTM3 gene polymorphism is associated with the risk of cancer susceptibility (Singh et al., 2008; Kesarwani et al., 2009). There were lots of investigations reporting that GSTM3 were associated with lung cancer susceptibility.

The factor of gene polymorphism has been reported to be associated with the risk of lung cancer. In the past decades, most of the epidemiologic studies investigating the association of GSTM3 gene polymorphism with lung cancer risk were conducted. However, the available evidences are weak at present, due to sparseness of data or disagreements among the reported investigations. The evidence from meta-analysis may be powerful compared with the individual study. This meta-analysis was performed to investigate whether the GSTM3 A/B gene polymorphism was associated with the onset of lung cancer, by widely collect the reported investigations.

Materials and Methods

Search strategy for the relationship between GSTM3 gene polymorphism and the risk of lung cancer

The relevant studies were searched from the electronic databases of PubMed, Embase, and Cochrane Library on May 1, 2012. The retrieval strategy of (glutathione S-transferase M3 OR GSTM3) and (lung cancer OR lung carcinoma OR pulmonary carcinoma) was entered into these databases. The additional reports were identified through references cited in recruited articles.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) The outcome had to be lung cancer; (2) There had to be at least two comparison groups (lung cancer group vs control group); (3) Investigation should provide the data of GSTM3 genotype distribution. Exclusion criteria: (1) Review articles and editorials;

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Table 1. Characteristics of the Studies Evaluating the Effects of GSTM3 A/B Gene Polymorphism on Lung Cancer Risk

First author, year	Ethnicity	Control Source	Case				Control				B allele (%)		P (HWE)
			BB	AB	AA	Total	BB	AB	AA	Total			
Saarikoski 1998	Caucasian	Population	3	52	146	201	7	61	226	294	14.42	12.76	0.245
Jourenkova-Mironova 1998	Caucasian	Hospital	8	36	106	150	5	42	125	172	17.33	15.12	0.525
Risch 2001	Caucasian	Hospital	12	93	284	389	11	83	256	350	15.04	15	0.19
Tsai 2003	Caucasian	Hospital	0	68	167	235	0	24	70	94	14.47	12.77	0.156
Sørensen 2004	Caucasian	Population	33	104	117	254	8	59	197	264	33.46	14.2	0.177
Loft 2007	Caucasian	Population	3	65	178	246	8	56	192	256	14.43	14.06	0.129
Reszka 2007	Caucasian	Hospital	-	-	88	119			94	138	-	-	-
Zienolddiny 2008	Caucasian	Population	19	43	198	260	8	102	248	358	15.58	16.48	0.508

Table 2. Meta-analysis of the Association of GSTM3 A/B Gene Polymorphism with Risk of Lung Cancer

Genetic contrasts	Studies number	Q test P value	Model seclected	OR (95%CI)	P
B vs A	7	<0.00001	Random	1.25 (0.89, 1.76)	0.2
BB vs (AB+AA)	7	0.003	Random	1.53 (0.71, 3.32)	0.28
AA vs (AB+BB)	8	<0.00001	Random	0.85 (0.59, 1.23)	0.39
Sensitivity analysis					
HWE					
B vs A	7	<0.00001	Random	1.25 (0.89, 1.76)	0.2
BB vs (AB+AA)	7	0.003	Random	1.53 (0.71, 3.32)	0.28
AA vs (AB+BB)	8	<0.00001	Random	0.85 (0.59, 1.23)	0.39
Population					
B vs A	4	<0.00001	Random	1.36 (0.77, 2.40)	0.29
BB vs (AB+AA)	4	0.002	Random	1.58 (0.50, 4.97)	0.43
AA vs (AB+BB)	4	<0.00001	Random	0.73(0.37,1.44)	0.37
Hospital					
B vs A	3	0.78	Fixed	1.07(0.87,1.33)	0.52
BB vs (AB+AA)	3	0.37	Fixed	1.24(0.63,2.41)	0.53
AA vs (AB+BB)	4	0.66	Fixed	0.99(0.80, 1.24)	0.96

(2) Case reports; (3) Preliminary result not on GSTM3 gene polymorphism or outcome; (4) Investigating the role GSTM3 gene expression to disease; (5) If multiple publications for the same data from the same study group occurred, we only recruited the later paper into our final analysis.

Data extraction

The following information from each eligible study was extracted independently by two investigators: first author's surname, year of publication, ethnicity, control source of the control group and the number of cases and controls for GSTM3 genotypes. Frequencies of null genotype of GSTM3 were calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreement was resolved by discussion.

Statistical Analysis

Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each investigation. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the P value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. $P < 0.05$ was required for the pooled OR to be statistically significant. I^2 was used to test the heterogeneity among the included studies. A chi-square test using a web-based program was applied to determine if genotype distribution of the control population reported for GSTM3 conformed to Hardy-Weinberg equilibrium (HWE; $P < 0.05$ was considered significant). Sensitivity analysis was performed if HWE disequilibrium existed. Sensitivity analysis was also performed by sequential omission of individual studies (Wang et al., 2011), and according to the source of the controls (population vs hospital). Stata 11.0 was used to test the publication bias. The Begg adjusted rank correlation test (Begg & Mazumdar, 1994) and the Egger regression asymmetry test (Egger et al., 1997) were used for exploring publication bias ($P<0.1$ was considered significant), when the number of the included studies was more than eight.

Results

Study characteristics

Eight studies (Jourenkova-Mironova et al., 1998; Saarikoski et al., 1998; Risch et al., 2001; Tsai et al., 2003; Sorensen et al., 2004; Loft et al., 2007; Reszka et al., 2007; Zienolddiny et al., 2008) reporting the relationship between GSTM3 A/B gene polymorphism and lung cancer susceptibility were recruited into this meta-analysis. Interestingly, all the included studies were performed in Caucasians. The control source of the control group in four investigations (Saarikoski et al., 1998; Sorensen et al., 2004; Loft et al., 2007; Zienolddiny et al., 2008) was from Population and that in others was from Hospital

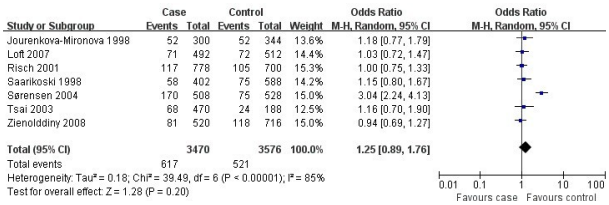

Figure 1. Association Between GSTM3 B Allele and Lung Cancer Susceptibility

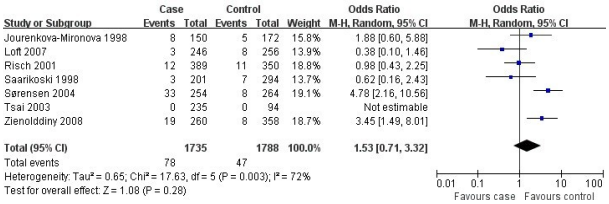

Figure 2. Association Between GSTM3 BB Genotype and Lung Cancer Susceptibility

(Table 1). The data of our interest were extracted, and the frequencies of null genotype of GSTM3 for case group and control group were calculated (Table 1). Those 8 investigations contained 1854 patients with lung cancer and 1926 controls. The average distribution frequency of GSTM3 B allele in case group was 17.82% and the average frequency in control group was 14.34%. The average distribution frequency of GSTM3 B allele in case group was increased when compared with that in control group (Case/Control = 1.24).

Association of GSTM3 A/B gene polymorphism with lung cancer risk

In this meta-analysis, we found that GSTM3 A/B gene polymorphism was associated with lung cancer risk (B allele: OR = 1.25, 95% CI: 0.89-1.76, P = 0.20; BB genotype: OR = 1.53, 95% CI: 0.71-3.32, P = 0.28; AA genotype: OR = 0.85, 95% CI: 0.59-1.23, P = 0.39; Figure 1 for B allele, and Figure 2 for BB genotype; Table 2).

Sensitivity analysis

Sensitivity analysis was performed according to the HWE test. All the genotype distribution of the control population reported for GSTM3 in the included studies was in HWE. So, the results of sensitivity analysis were the same as those of non-sensitivity analysis (Table 2).

Sensitivity analysis also performed by sequential omission of individual studies, and we found that the results were similar with those of non-sensitivity analysis (data not shown).

Sensitivity analysis was also performed according to the source of the controls (population vs hospital). The results from this sensitivity analysis were similar with those from non-sensitivity analysis (Table 2).

Evaluation of publication bias

No significant publication bias was showed for the association of GSTM3 A/B gene polymorphism with lung cancer susceptibility (Begg P=0.711; Egger P=0.845).

Discussion

The factor of genetic origin of lung cancer had been a focus of research in the past years, and some studies found that the genetic alteration was associated with the risk of lung cancer (Liu et al., 2010; Guan et al., 2011; Dai et al., 2012). GSTs are implicated in the inactivation of pro-carcinogens that contribute to cancer progression (Gong et al., 2012). There were numerous significant evidences showing that the GSTM3 had taken part in the risk of lung cancer, and some studies found that some mutant sites of the GSTM3 gene might play the multifunctional physiological processes in lung cancer. However, findings on the association of GSTM3 A/B gene polymorphism with the susceptibility of lung cancer have been controversial since the first investigation was reported. In this study, we investigated whether the GSTM3 A/B gene polymorphism could become a valuable indicator to predict the risk of lung cancer, and tried to draw a more robust conclusion using meta-analysis method.

In our meta-analysis, we found that GSTM3 B allele/BB genotype was not a risk factor for the onset of lung cancer, and the AA genotype seemed not to play a protective role against the risk of lung cancer. However, there was significant heterogeneity among the included studies. When we took the fixed effects model to pool the OR for B allele, BB genotype and AA genotype, we found that GSTM3 A/B gene polymorphism was associated with the risk of lung cancer (B allele: OR = 1.28, 95% CI: 1.13-1.46, P = 0.0001; BB genotype: OR = 1.90, 95% CI: 1.31-2.75, P = 0.0006; AA genotype: OR = 0.83, 95% CI: 0.72-0.96, P = 0.01). We speculated that this disagreement was caused by that the number of included studies was small (only eight reports were included). The conclusion in our meta-analysis should be confirmed in the future, although there was no publication bias.

Sensitivity analysis was also performed according to the HWE test, by equential omission of individual studies, and according to source of the controls (population vs hospital), and the results for GSTM3 from the sensitivity analysis were consistent with the non-sensitivity analysis. The results from our meta-analysis might be robust to some extent. However, more rigorous studies should be conducted to explore the relationship between GSTM3 A/B gene polymorphism and lung cancer risk in the future.

In the pasts, there was one meta-analysis to investigate the association of GSTM3 A/B gene polymorphism and lung cancer risk. Ye et al. (2006) performed a meta-analysis and included five eligible studies to study the relationship between GSTM3 A/B genetic variants and found that there was no statistical difference in the genotype distribution of GSTM3 between the lung cancer group and control group, and they did not performed the sensitivity analysis. The number of included studies in our meta-analysis was larger than the previous meta-analysis, and our results were similar with Ye et al. (2006). More original studies should be conducted in further.

There were some investigations reported that GSTM3 A/B gene polymorphism was associated with the onset of cancers in the past decades. Malik et al. (2010) reported that GSTM3 A/B genotype was associated with the lower risk of both esophageal squamous cell carcinoma and esophageal adenocarcinoma in patients with esophageal cancer. Kesarwani et al. (2009) reported that GSTM3 (AB

+ BB) genotype to be significantly associated with prostate cancer risk. Singh et al. (2008) reported that GSTM3*AB genotypes might confer higher susceptibility to cervical cancer and cancer risk in a North Indian population. However, Ladero et al. (2007) showed that the studied polymorphisms affecting GSTM3 genes was probably not related to the risk of developing hepatocellular carcinoma in 184 white Spanish patients diagnosed with hepatocellular carcinoma. In our meta-analysis, we found that the GSTM3 A/B gene polymorphism was not associated with the onset of lung cancer. However, more studies should be performed in the future.

Our results indicated that an association between GSTM3 A/B gene polymorphism and lung cancer risk was not observed. However, those findings should be regarded cautiously because many other ingredients, such as language bias, small sample size of the included report, limited statistical power, heterogeneity of enrolled cases, variable study designs and different interventions, were closely related to affect the results.

In conclusion, the results in our meta-analysis support that GSTM3 A/B gene polymorphism is not associated with the risk of lung cancer. However, more association investigations are required to further clarify the role of the GSTM3 A/B gene polymorphism in the pathogenesis of lung cancer.

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The author(s) declare that they have no competing interests.

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