Genetics and Molecular Research

The 341C/T polymorphism in the GSTP1 gene and lung cancer risk: a meta-analysis

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Genet. Mol. Res. 15 (3): gmr.15038172
Received December 22, 2015
Accepted February 11, 2016
Published July 29, 2016
DOI http://dx.doi.org/10.4238/gmr.15038172

ABSTRACT. Numerous studies have evaluated the association between the 341C/T polymorphism in glutathione S-transferase P1 (*GSTP1*) and lung cancer risk. However, there are conflicting results from previous studies. To derive a more precise estimation of the association, we conducted this meta-analysis. A comprehensive search was conducted to identify the eligible studies examining the *GSTP1* 341C/T polymorphism and lung cancer risk. We used odds ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of the association. The meta-analysis results showed that the *GSTP1* 341C/T polymorphism was significantly associated with lung cancer risk (TT *vs* CC: OR = 3.33, 95%CI = 1.49-7.44; CT *vs* CC: OR = 1.35, 95%CI = 1.10-1.65; dominant model: OR = 1.43, 95%CI = 1.05-1.96; recessive model: OR = 0.31, 95%CI = 0.14-0.70). The results indicate that the

GSTP1 341C/T polymorphism may contribute to lung cancer risk. Conclusive evidence on the effects of this variant in lung cancer should be addressed in further studies.

Key words: GSTP1; Gene polymorphism; Lung cancer; Meta-analysis

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 annually (Jemal et al., 2011). The mechanism of lung carcinogenesis is still not fully understood. Epidemiological studies have demonstrated that tobacco smoking as well as exposure to environmental tobacco smoke in healthy non-tobacco users is the major risk factor for lung cancer (Hecht, 2002). However, 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 (Hecht, 2002).

Cells have highly effective pathways for repairing DNA damage and maintaining their genomic integrity. Glutathione S-transferases (GSTs) are a family of eukaryotic and prokaryotic phase II metabolic isozymes. They feature significantly in the protection of cells against xenobiotics and oxidative stress by catalyzing the conjugation of electrophilic compounds to glutathione in the detoxification process (Dusinska et al., 2012). GSTP1 is a member of the GST superfamily and plays an important role in the inactivation of toxic and carcinogenic electrophiles (Mannervik et al., 1992). Previous studies showed that GSTP1 is the major GST expressed in extra-hepatic tissues, such as the lungs and the esophagus, with very little expression in the liver (Sherratt et al., 1997; de Bruin et al., 2000).

The *GSTP1* gene encodes the pi class of enzymes. The gene is located on chromosome 11q13 and it has nine exons (Okcu et al., 2004). There is a C to T transition at nucleotide 341 (codon 114) in exon 6, which results in an amino acid change from alanine (Ala) to valine (Val), that is named 341C/T (rs1138272, Ala114Val). In the past few decades, there has been increasing interest in the study of the association between the *GSTP1* 341C/T polymorphism and the risk of lung cancer. However, these studies show conflicting results, possibly owing to relatively small sample sizes, ethnic differences, or differences in the clinical status of patients. Therefore, in the present study, we further evaluated the association of the *GSTP1* 341C/T polymorphism with lung cancer susceptibility using a meta-analysis.

MATERIAL AND METHODS

This meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement, including the search strategy, selection criteria, data extraction, and data analysis (Moher et al., 2009).

Literature search

PubMed and Web of Science electronic databases were reviewed to search potential articles that tested the association of the *GSTP1* 341C/T polymorphism with lung cancer susceptibility up to October 30, 2015. The search terms used were as follows: “glutathione

S-transferases" or "GSTP1" in combination with "polymorphism", "polymorphisms", and "mutation" or "variant in combination with lung cancer". Only articles published in the English language were considered in this study. In order to avoid possibly missing hits, the reference lists of major original articles and reviews were checked manually.

Eligibility of relevant studies

In this meta-analysis, the following inclusion criteria were applied to select eligible studies: a) a case-control design; b) sufficient related genotype frequency data in case and control groups; and c) studies focused on the *GSTP1* 341C/T polymorphism and lung cancer risk in humans. Review articles, case reports, editorials, conference abstracts, letters, and family-based studies were excluded. Article selection process was independently completed by two authors and there was no disagreement.

Data extraction

Two reviewers independently assessed publications for inclusion in the review. If the two investigators could not reach an agreement, discrepancies were then resolved through discussion by the review team. Data extracted from eligible studies included the baseline characteristics, such as the first author's name, year of publication, area, number of patients and controls, distributions of genotypes and alleles, and evidence of Hardy-Weinberg equilibrium (HWE).

Statistical analysis

The strength of the association between the *GSTP1* 341C/T polymorphism and lung cancer risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs) for homozygote comparison (TT *vs* CC), heterozygote comparison (CT *vs* CC), dominant model (TT/CT *vs* CC), and recessive model (TT *vs* CT/CC). The heterogeneity among these studies was checked by the I^2 test. When $I^2 > 50\%$ indicated heterogeneity across studies, the random-effect model was used for meta-analysis, otherwise the fixed-effect model was used. HWE among controls for each study was examined by the Pearson's goodness of fit chi-square test. Sensitivity analysis was performed by comparing the random-effect model values with the fixed-effect model values. To assess the potential publication bias, visual inspection of Begger's funnel plot and the Egger test were performed. All statistical tests for this meta-analysis were performed with STATA (version 11.0; Stata Corporation, College Station, TX, USA).

RESULTS

Characteristics of included studies

Our initial search identified 361 studies according to the search terms. Through screening the title and reading the abstract/article, 5 eligible articles were selected for this meta-analysis (Harris et al., 1998; Wang et al., 2003; Yang et al., 2004; Zienolddiny et al., 2008; Vural et al., 2012). The detailed screening process is shown in Figure 1. The included studies took place in Australia, USA, Norway, and Turkey. The HWE test was performed on

genotype distribution of the controls and all were in agreement. The main characteristics of eligible studies are summarized in Table 1.

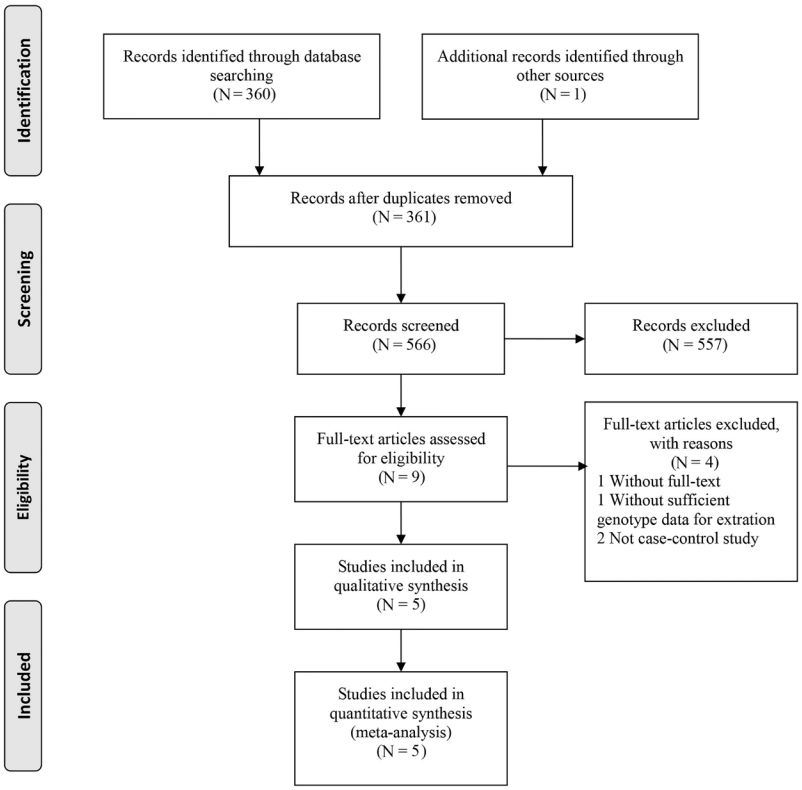

Figure 1. Flow chart showing study selection procedure.

Table 1. Characteristics of the included studies for meta-analysis.

Study included	Year	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
					CC	CT	TT	CC	CT	TT	
Harris et al.	1998	Australia	Caucasians	184/199	154	28	2	170	29	0	0.27
Wang et al.	2003	USA	Caucasians	579/598	468	108	3	511	84	3	0.82
Yang et al.	2004	USA	Caucasians	229/229	192	32	5	189	38	2	0.95
Zienolddiny et al.	2008	Norway	Caucasians	319/381	250	60	9	333	46	2	0.76
Vural et al.	2012	Turkey	Caucasians	108/89	86	18	4	82	7	0	0.70

HWE, Hardy-Weinberg equilibrium.

Meta-analysis

The results of the meta-analysis on the *GSTP1* 341C/T polymorphism and lung cancer risk are shown in Figure 2 and Table 2. Overall, significant association was found between the *GSTP1* 341C/T polymorphism and lung cancer risk under any genetic model when all the eligible studies were pooled into the meta-analysis (TT *vs* CC: OR = 3.33, 95%CI = 1.49-

7.44; CT *vs* CC: OR = 1.35, 95%CI = 1.10-1.65; dominant model: OR = 1.43, 95%CI = 1.05-1.96; recessive model: OR = 0.31, 95%CI = 0.14-0.70). Sensitivity analysis was performed by altering the statistical models and the result was not altered, indicating that the result of the meta-analysis was statistically significant.

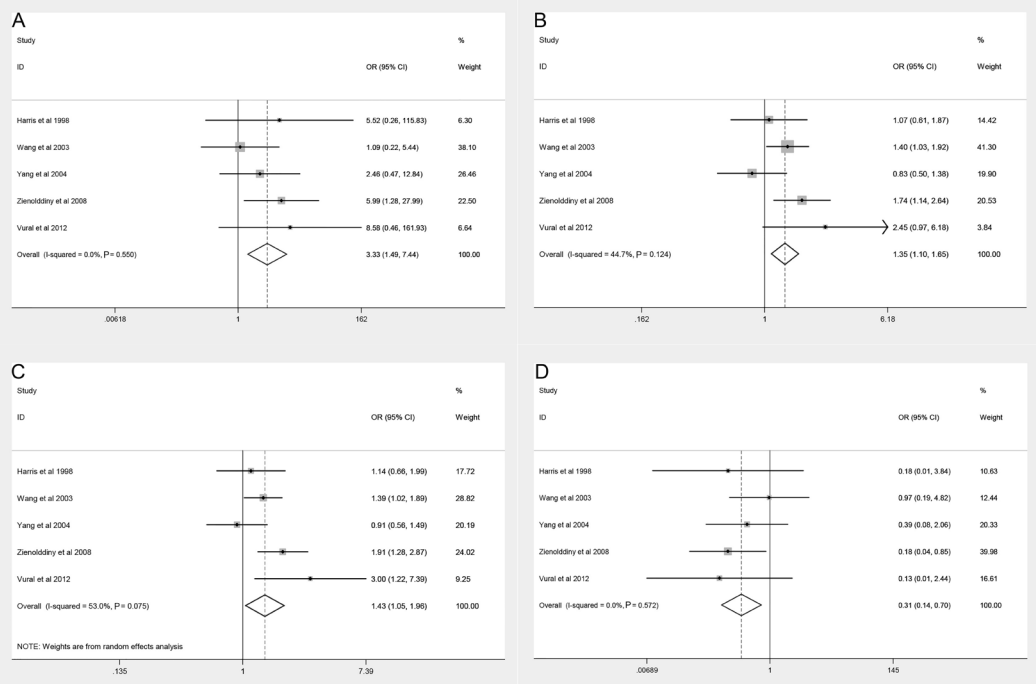

Figure 2. Forest plot of lung cancer risk associated with *GSTP1* 341C/T polymorphism using (A) TT *vs* CC, (B) CT *vs* CC, (C) dominant model, and (D) recessive model.

Table 2. Summary ORs and 95%CI of the *GSTP1* 341C/T polymorphism and lung cancer risk.

Genetic model	Type of model	Test of heterogeneity		Test of association
		I^2	P	OR (95%CI)
TT *vs* CC	Fixed	0.0%	0.55	3.33 (1.49-7.44)
CT *vs* CC	Fixed	44.7%	0.12	1.35 (1.10-1.65)
Dominant model	Random	53.0%	0..08	1.43 (1.05-1.96)
Recessive model	Fixed	0.0%	0.57	0.31 (0.14-0.70)

OR, odds ratio; CI, confidence interval.

Publication bias

Begg's funnel plot and the Egger test were performed to assess publication bias of the selected literature. No evidence of publication bias in our study was observed (Figures 3 and 4).

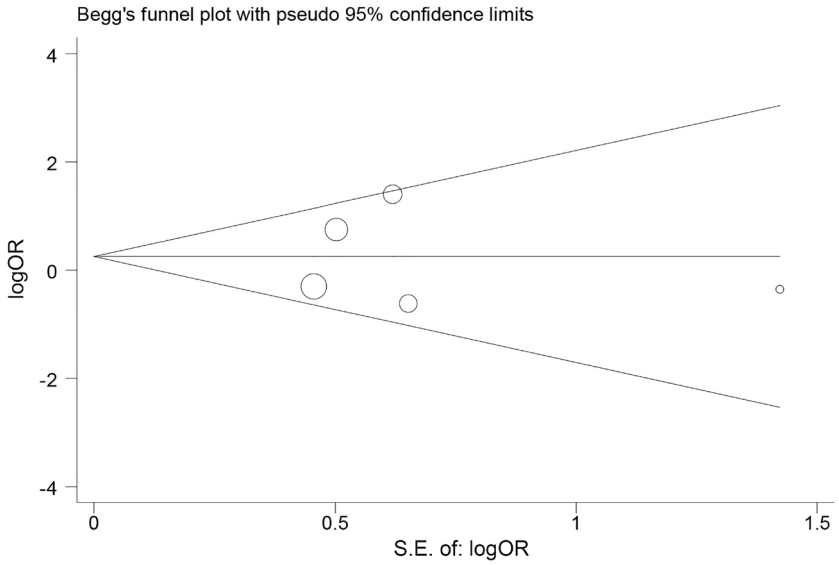

Figure 3. Begg's funnel plot of lung cancer risk associated with the *GSTP1* 341C/T polymorphism.

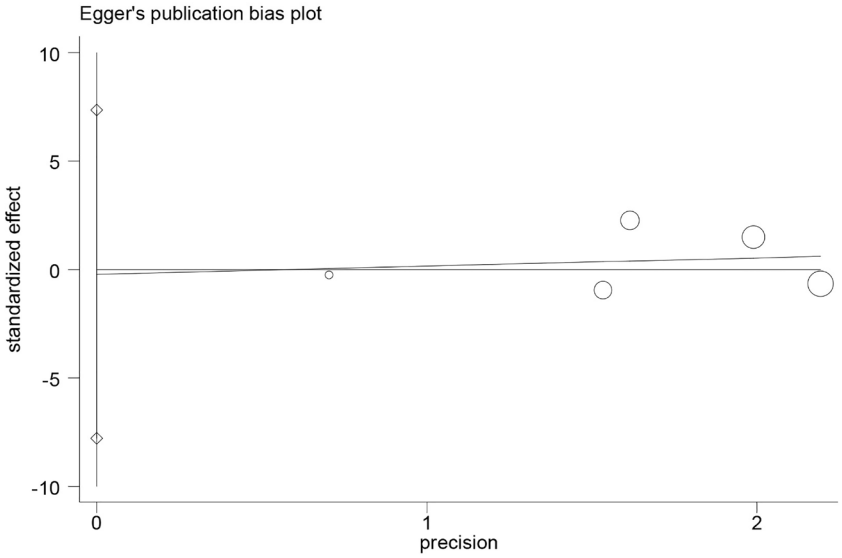

Figure 4. Egger test of lung cancer risk associated with the *GSTP1* 341C/T polymorphism.

DISCUSSION

GSTP1 is widely expressed in different human epithelial tissues and is the most abundant GST isoform in the lung (Anttila et al., 1993). The *GSTP1* gene is located on chromosome 11q13.2, and the *GSTP1* 341C/T polymorphism was identified. Moreover, the single nucleotide polymorphism at the *GSTP1* loci results in an amino acid substitution that

leads to reduced activity, which may alter susceptibility to cancer. Since Harris et al. (1998) first examined the association between the *GSTP1* 341C/T polymorphism and the risk of lung cancer, a number of other studies have been conducted to evaluate the role of the 341C/T polymorphism in the *GSTP1* gene on lung cancer risk (Wang et al., 2003; Yang et al., 2004; Zienolddiny et al., 2008; Vural et al., 2012). However, the results remain conflicting rather than conclusive. To help resolve these conflicting results using as large a sample as possible, we conducted a meta-analysis of case-control studies analyzing potential associations between the *GSTP1* 341C/T polymorphism and risk of lung cancer.

The present meta-analysis, including 1419 cases and 1496 controls from 5 case-control studies, explored the association between the 341C/T polymorphism of the *GSTP1* gene and lung cancer risk. In doing this, a larger sample size and increased statistical power could be obtained. The results indicated that the *GSTP1* 341C/T polymorphism might be associated with increased lung cancer risk. The mechanism of how the 341C/T polymorphism of the *GSTP1* gene relates to lung cancer risk is still unclear. GSTP1 is a major GST, which detoxifies potentially mutagenic and cytotoxic DNA-reactive metabolites produced by phase I reactions (Mannervik, 1985). As a result, the DNA or other important biomolecules are protected against damage. The 341C/T polymorphism results in an amino acid substitution that leads to reduced GSTP1 enzyme activity (Watson et al., 1998), which may increase the risk of lung cancer. In addition, the potential function of this polymorphism might be affected via gene-environment interactions, which should be taken into consideration in future analysis.

However, there are still some limitations in this meta-analysis. Firstly, this meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs or when they did, the ORs were not adjusted by the same potential confounding factor such as age, gender, ethnicity, and exposures. Lacking information for this data analysis may cause confounding bias. Secondly, the sample size is relatively small and might not provide sufficient statistical power to estimate the association of the 341C/T polymorphism with lung cancer. Finally, we did not test for gene-environment interactions because of the issue of multiple testing and the lack of sufficient studies. It is possible for specific environmental and lifestyle factors (such as smoking) to alter the associations between gene polymorphisms and cancer risk.

In conclusion, our results suggest that the 341C/T polymorphism of the *GSTP1* gene is involved in susceptibility to lung cancer. Considering the limitations of the present meta-analysis, it is necessary to conduct further research with standardized unbiased methods, larger sample studies, and well-matched controls.

Conflicts of interest

The authors declare no conflict of interest.

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