Published in final edited form as:

Pharmacogenet Genomics. 2010 October ; 20(10): 586–597. doi:10.1097/FPC.0b013e32833c3892.

Assessment of cumulative evidence for the association between glutathione S-transferase polymorphisms and lung cancer: application of the Venice interim guidelines

Scott M. Langevin¹, John P.A. Ioannidis², Paolo Vineis³, Emanuela Taioli⁴, and GSEC^{*}

¹Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

²Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina, Greece; Center for Genetic Epidemiology and Modeling, Tufts Medical Center and Tufts University School of Medicine, Boston, MA

³Imperial College London, London, UK

⁴SUNY Downstate Medical Center, Brooklyn, NY

Abstract

There is an overwhelming abundance of genetic association studies available in the literature, which often can be collectively difficult to interpret. To address this issue, the Venice interim guidelines were established for determining the credibility of the cumulative evidence. The objective of this report is to evaluate the literature on the association of common GST variants (*GSTM1* null, *GSTT1* null and *GSTP1* Ile105Val polymorphism) and lung cancer, and to assess the credibility of the associations using the newly proposed cumulative evidence guidelines. Information from the literature was enriched with an updated meta-analysis and a pooled analysis using data from the Genetic Susceptibility to Environmental Carcinogens (GSEC) database. There was a significant association between *GSTM1* null and lung cancer for the meta- (meta OR = 1.17, 95% CI: 1.10–1.25) and pooled analysis (adjusted OR = 1.10, 95% CI: 1.04–1.16), although substantial heterogeneity was present. No overall association between lung cancer and *GSTT1* null or *GSTP1* Ile105Val was found. When the Venice criteria was applied, cumulative evidence for all associations were considered “weak”, with the exception of East Asian carriers of the G allele of *GSTP1* Ile105Val, which was graded as “moderate” evidence. In spite of large amounts of studies, and several statistically significant summary estimates produced by meta-analyses, the application of the Venice criteria suggests extensive heterogeneity and susceptibility to bias for the studies on association of common genetic polymorphisms, such as with GST variants and lung cancer.

^{*}Genetic Susceptibility to Environmental Carcinogens group; collaborators to the present analysis: José A.G. Agundez, Anna-Karin Alexandrie, Ravindran Ankathil, Herman Autrup, Judith L.C. Autrup, Juan M. Barros-Dios, Simone Benhamou, Paolo Boffetta, Katja Breskvar, Jurgen Brockmoller, Dorota Butkiewicz, Ingolf Cascorbi, Margie L. Clapper, Michele L. Cote, Ioanna A. Dialyna, Vita Dolzan, Tommaso Dragani, K.M. Fong, Martha P. Gallegos-Arreola, Seymour Garte, Andrea Gsur, Curtis C. Harris, Aage Haugen, Evgeny N. Imyanitov, Magnus Ingelman-Sundberg, Ivan Kalina, Daehae Kang, Masahiro Kihara, Chikako Kiyohara, Pierre Kremers, Qing Lan, H. Lee, Loïc Le Marchand, Stephanie J. London, D. Lucas, Maria Li Lung, Valle Nazar-Stewart, Kazumasa Noda, Hatice Pinarbasi, Paola Pisani, Andrew C. Povey, Yuepu Pu, Agneta Rannug, Angela Risch, Liliane Roelandt, Marjorie Romkes, David Ryberg, Joachim Schneider, Bernadette Schoket, Janeric Seidegard, Adeline Seow, Peter G. Shields, Ranbir C. Sobti, Margaret R. Spitz, Richard C. Strange, Isabel Stücker, Haruhiko Sugimura, Jordi To-Figueras, Jingwen Wang, John Wiencke, Ping Yang, Jun Yokota, Lair Zambon

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

meta-analysis; pooled analysis; GSTM1; GSTT1; GSTP1; lung cancer; evidence

INTRODUCTION

The literature is awash with a plethora of genetic association studies on low penetrance genes, often with conflicting results, making it difficult to discern the true nature of the risk associated with variants in these genes. There have been many attempts at summarizing overall effects through systematic literature reviews and meta-analyses. According to the Human Genome Epidemiology Literature Finder, 1,167 meta-analyses on associations of various genes and diseases had been published as of October 30, 2009 [1]. Unpublished data and potential for bias among the published literature threatens the validity and credibility of summary estimates produced by meta-analyses; as bias increases, the chances of findings being true decreases [2]. Thus particular caution must be exercised when assessing the true effect of genes with borderline significant results [3], which is often the case with low penetrance variants. To address these issues, the Human Genome Epidemiology Network Working Group on the Assessment of Cumulative Evidence was established. In November 2006, the group convened and developed interim guidelines for assessment of the credibility of the cumulative epidemiologic evidence surrounding genetic association studies that were published one year later [4].

Lung cancer is the leader in cancer incidence and mortality in the United States, accounting for an estimated 215,020 cases and 161,840 deaths in 2008 [5]. Although smoking is still the main risk factor responsible for lung cancer, individual susceptibility to the harmful effects of tobacco exists [6]. This has elicited a strong interest in and a multitude of studies on polymorphisms involved in tobacco carcinogen metabolism and DNA repair to determine how genetic factors might modulate tobacco-related lung cancer risk.

Among the metabolic gene products, glutathione S-transferases (GSTs; EC 2.5.1.18) are a large family of cytosolic phase II xenobiotic metabolizing enzymes, whose function is to catalyze the detoxification of electrophilic metabolites, including benzo[α]pyrene and other polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke, forming soluble, nontoxic peptide derivatives to be excreted or compartmentalized by phase III enzymes [7]. The most commonly studied GST variants include *GSTM1* deletion, *GSTT1* deletion, and *GSTP1* Ile105Val (rs1695) polymorphism. The *GSTM1* and *GSTT1* deletions (null) are recessive variants for which homozygous deletions result in null activity of their respective enzymes. *GSTP1* Ile105Val is a non-synonymous A>G SNP that leads to a substitution of isoleucine by valine resulting in alterations in the substrate binding site and enzyme activity [8].

The glutathione S-transferase gene family is the most extensively studied genetic susceptibility factor in relation to lung cancer, thus offering the opportunity to conduct the exercise of assessing and quantifying the credibility of the association, using the aforementioned Venice guidelines. The objective of this report is to summarize the evidence of the association of *GSTM1* deletion, *GSTT1* deletion and *GSTP1* Ile105Val with lung cancer as it is currently reported in the literature and to apply the published interim cumulative evidence guidelines (4) to assess the credibility of the associations. The published information was enriched with a newly performed updated meta-analysis and a pooled (individual-level data) analysis.

METHODS

Updated meta-analysis of published data

All genotype-based case-control studies reporting on *GSTM1* deletion, *GSTT1* deletion or *GSTP1* Ile105Val and susceptibility to lung cancer, published in English language from January 1991 (the first study examining the association of lung cancer and GST genotype [9]) through May 2009 were identified, along with all genome-wide association studies of lung cancer. The results of the search were further validated by reviewing the references included in recent published meta-analyses to ensure that all appropriate studies were captured. When a publication reported data in an ancestry-specific manner, each ancestral subset was considered as a discreet study. Overlap of study subjects between publications was evaluated by comparing sources of data described in the methods and through cross-referencing using dataset identifiers available through the Genetic Susceptibility to Environmental Carcinogens (GSEC) database (www.gsec.net) [10]; in the case of overlap, the more inclusive publication was selected for inclusion in the meta-analysis.

Data were combined across studies utilizing inverse-variance weighting to calculate fixed effects and random effects estimates (DerSimonian and Laird method) with corresponding 95% confidence intervals [11]. In the absence of between-study heterogeneity (Q-statistic $P > 0.05$), fixed and random effects estimates are identical and therefore fixed effects were reported to conserve statistical power; otherwise random effects were reported. Heterogeneity was assessed using the Q-statistic and I^2 metric, and susceptibility to bias was assessed using the Harbord [12] and significance chasing bias [13] tests. Details on these tests are provided in the *Application of Venice Criteria* section below.

Subset analyses were also conducted by ancestry (Whites, East Asian, African descent) and type of controls (hospital and community based) as potential sources of heterogeneity.

Gene-wide association studies (GWAS)

None of the six genome-wide association studies on lung cancer [14–19] reported results on *GSTM1*, *GSTT1* or *GSTP1* polymorphisms. Two of the GWAS studies employed platforms containing probes for copy-number variants [15,17], whereas the other platforms require special protocols for *GSTM1* or *GSTT1* deletion [20]. *GSTP1* Ile105Val can be discerned by any of the platforms used in these studies. The authors were contacted, requesting results on the association between *GSTM1*, *GSTT1*, *GSTP1* and lung cancer but they were unable to provide this information.

Analysis of individual participant data from the GSEC database

The Genetic Susceptibility to Environmental Carcinogens (GSEC) database [10], which compiles published and unpublished case-control data from participating investigators on genetic metabolic polymorphisms and various types of cancer was used to obtain data sets on lung cancer and *GSTM1* deletion, *GSTT1* deletion and *GSTP1* Ile105Val for performing analyses on individual participant data. Analyses of pooled data were conducted for each GST variant using unconditional logistic regression models to produce estimates for the association with lung cancer, adjusted for age, gender, smoking status (*ever/never*), ancestry (*White*, *East Asian*, *African descent* and *Other*) and study. Heterogeneity and susceptibility to bias were tested using the same techniques as described for the meta-analysis; study-specific adjusted odds ratios were used for these analyses.

Application of the Venice criteria

The cumulative evidence for the association of *GSTM1* deletion, *GSTT1* deletion and *GSTP1* Ile105Val polymorphism with lung cancer was assessed according to the Venice interim

guidelines [4] that use 3 major criteria: 1) amount of evidence; 2) replication of results; and 3) protection from bias. In the present paper for each gene-disease association, the cumulative evidence was derived for the current updated meta-analysis and from re-analyzing individual-level data from the GSEC database. The criteria were applied as previously described [4,21]. In brief:

Assessment of amount of evidence—For each genetic polymorphism, the size of the smallest genetic group (n_{minor}) was calculated by adding the total number of cases and controls with the least frequent genotype. The frequency of the minor genetic group (f_{minor}) was estimated using the frequency of the minor genotype among the control subjects. When considering dominant models, the frequency of the less common genetic group was used. Grade A requires $n_{\text{minor}} > 1000$, grade B is given for $100 \leq n_{\text{minor}} \leq 1000$ and grade C for $n_{\text{minor}} < 100$.

Assessment of consistency of replication of results—When a non-significant association ($P > 0.05$) was observed, the association was considered as unreplicated (grade C). In addition, heterogeneity was assessed with the Q-statistic [22] and the I^2 metric, given by $(Q\text{-df})/Q$ [23] and 95% confidence intervals. I^2 is a measure of how much heterogeneity is beyond chance, with values ranging from 0–100%. Values of $I^2 < 25\%$ were classified as low heterogeneity, 25–50% as moderate heterogeneity, and $>50\%$ as large heterogeneity (grades A, B, and C, respectively) [4]. However, qualitative aspects should also be considered when assessing consistency of replication.

Assessment of protection from bias—Lack of protection from bias was claimed when any of the following criteria applied:

1. The summary OR deviated less than 1.15-fold from the null (range 0.87–1.15) in a retrospective meta-analysis of published data.
2. Statistical significance was lost when the first published study was excluded.
3. Statistical significance was lost when studies or datasets with significant violation of Hardy-Weinberg equilibrium ($P < 0.05$ by exact test) were excluded. *GSTM1* and *GSTT1* were not tested for Hardy-Weinberg equilibrium since most publications reported genotypes as *null* versus *present*, where *present* combined homozygous wild type and heterozygotes.
4. There is evidence for small-study effects based on a modified regression test (Harbord test), considered significant at $P < 0.10$ [12]. This analysis tests the hypothesis that small published studies yield larger estimates than larger studies.
5. Significant chasing bias is present (considered significant at $P < 0.10$ [13]). This test addresses the possibility that there are more studies/datasets with significant results than would be expected even if the summary effect were true

Previous meta-analyses

A Medline search was conducted to identify all previous meta-analyses published to date on *GSTM1* deletion, *GSTT1* deletion, or *GSTP1* Ile105Val polymorphisms and lung cancer. The I^2 metric and corresponding 95% confidence intervals were calculated for the meta-analysis whenever possible based on available information if not specifically reported. Results were contrasted with the results of the updated meta-analyses and each previous meta-analysis was graded whenever possible according to the same Venice criteria in an attempt to assess temporal changes in cumulative evidence.

Software

All statistical analyses were performed using the Stata 10 software package (Stata Corporation, College Station, TX).

RESULTS

Amount of evidence

GSTM1—There were 82 publications on distinct datasets reporting on *GSTM1* deletion and lung cancer [9,24–104], 3 of which reported ancestry-specific subset analyses [36,55,68], for a total of 85 studies, consisting of 18,777 cases and 24,050 controls (Table 1).

Individual-level data for 48 of the 85 studies (56.5%) was available through the GSEC study, plus 8 unpublished datasets, for a total of 11,392 cases and 16,165 controls. The GSEC datasets corresponding to the published studies that were used in the meta-analysis contained 10,320 cases and 14,394 controls. The 8 unpublished datasets accounted for 1,072 cases (9.4%) and 1,771 controls (11.0%).

For published studies included in the meta-analysis, n_{minor} was 21,042 and f_{minor} in the control subjects was 0.493 (Table 1).

GSTT1—There were 43 publications on distinct datasets reporting on *GSTT1* deletion and lung cancer [25,27,28,33,^{34,36,38,40,50,53,55,59,63,65,67,69,71,74,82,86,88,92,94,97,100,101,103,105–110}], 2 of which reported ancestry-specific subset analyses [36,55], for a total of 45 studies with 12,569 cases and 15,545 controls (Table 1).

Individual-level data for 34 of 45 studies (75.6%) included in the meta-analysis was available through the GSEC study, plus 5 unpublished data sets, totaling 8,556 cases and 12,287 controls. The GSEC datasets corresponding to the published studies included in the meta-analysis contained 8,308 cases and 11,729 controls. The 5 unpublished datasets accounted for 248 cases (2.9%) and 558 controls (4.5%).

For published studies used in the meta-analysis, $n_{\text{minor}} = 6,585$ and $f_{\text{minor}} = 0.232$ (Table 1).

GSTP1—There were 34 publications on distinct datasets reporting on *GSTP1* Ile105Val and lung cancer that analyzed the combined *AG* and *GG* genotypes (**G*) [30,32–34,36,^{47,50,57,59,60,63,66,74,77,82,83,85,86,88,89,92,96,100,101,110–119}], consisting of 10,125 cases and 10,867 controls, 30 of which (9,427 cases and 9,887 controls) also reported the association for the *GG* genotype separately from the *AG* genotype [30,32,36,47,^{50,57,59,60,63,66,74,83,85,86,88,89,92,96,100,101,110–113,115–120}] (Table 1). One of 34 publications reported subset data by ancestry [36], resulting in 35 and 31 datasets, respectively.

Individual-level data from 19 of 35 studies (52.9%) was available through the GSEC study, plus an additional 2 unpublished data sets, for a total of 5,506 cases and 6,206 controls. The GSEC datasets corresponding to published studies that were used in the meta-analysis contained 5,149 cases and 5,810 controls. The 2 unpublished datasets accounted for 357 cases (6.5%) and 396 controls (6.4%).

The n_{minor} for *GSTP1* Ile105Val publications used in the meta-analysis was 1,870 for the *GG* genotype, with $f_{\text{minor}} = 0.161$ (Table 1). For the meta-analysis combining *AG* and *GG* genotypes, the *AA* genotype was the minor genetic group, where $n_{\text{minor}} = 10,458$ and $f_{\text{minor}} = 0.497$.

Replication of results

GSTM1—The current updated meta-analysis (Table 1) showed an overall significant association between *GSTM1* null and lung cancer (meta OR = 1.17, 95% CI: 1.10–1.25). These findings were consistent with the adjusted estimates from the pooled analysis (OR = 1.10, 95% CI: 1.04–1.16). After conducting subset analyses by ancestry, a significant association among East Asian populations was observed in both the meta-analysis (meta OR = 1.21, 95% CI: 1.05–1.39) and pooled analysis (OR = 1.25, 95% CI: 1.07–1.45); there was a significant association among White populations in the meta-analysis (meta OR = 1.15, 95% CI: 1.06–1.26), which remained robust after excluding the first published study [9], while the adjusted estimate from the pooled analysis was not significant (OR = 1.05, 95% CI: 0.98–1.12); and there was no significant association in the meta-analysis for populations of African descent (meta OR = 1.25, 95% CI: 0.95–1.64), while the adjusted estimate from the pooled analysis was significant (OR = 1.32, 95% CI: 1.00–1.74).

The updated meta-analysis shows significant heterogeneity among studies ($P < 0.001$; $I^2 = 55\%$, 95% CI: 44%–63%). When stratified by ancestry (Table 1), heterogeneity was still present between studies conducted on East Asian and White populations, but not between the 4 studies on populations of African descent. Studies using community-based controls still showed a higher degree of heterogeneity ($P < 0.001$; $I^2 = 60\%$, 95% CI: 49%–69%), than those using hospital-based controls ($P = 0.034$; $I^2 = 34\%$, 95% CI: 5%–55%).

Previous meta-analyses: There are 6 previous meta-analyses for *GSTM1* deletion and lung cancer [121–126], with summary point estimates ranging from 1.14 to 1.34, all statistically significant (Table 1), and similar to the results of the current updated meta- and pooled analyses.

The ORs in the meta-analyses restricted to East Asian populations [121–125,127,128] ranged from 1.38 to 1.60, all statistically significant and similar, although slightly higher in magnitude, to those of the current meta- and pooled analyses.

The summary estimates for the White population meta-analyses [121–125,127] ranged from 1.04–1.32, with three meta-analyses showing statistically significant results. The current updated meta- and pooled analyses produced results that are in the middle of the continuum of the previously published meta-analyses.

The only previous meta-analysis on populations of African descent [121] reported a summary OR = 1.19 (95% CI: 0.88–1.62), similar to the findings of the current updated meta-analysis, although differing from the pooled analysis for which the adjusted estimate was significant.

Results on heterogeneity were not reported by the oldest overall meta-analysis [125]; all but one [124] of the most recent five meta-analyses reported significant heterogeneity (Table 1). When tested, heterogeneity was present in meta-analyses on East Asian studies [121,122,128], while no significant heterogeneity was reported by 2 of the 3 meta-analyses on Whites that tested for heterogeneity [121–123].

GSTT1—The current updated meta-analysis (Table 1) found no significant association of *GSTT1* null and lung cancer (meta OR = 1.07, 95% CI: 0.97–1.17), with similar results from the pooled analysis (OR = 1.05, 95% CI: 0.97–1.14). A borderline association was observed among East Asians in the meta-analysis (meta OR = 1.19, 95% CI: 0.99–1.45), with a stronger association observed in the adjusted estimate from the pooled analysis (OR = 1.25, 95% CI: 1.07–1.45); no association was observed in White populations in the meta- (meta OR = 1.01, 95% CI: 0.91–1.14) or pooled analysis (OR = 1.04, 95% CI: 0.94–1.14).

Significant heterogeneity was observed in the current meta-analysis (Table 1), and was still observed in the subset analysis according to type of controls (community-based: $P = 0.026$ and $I^2 = 38\%$, 95% CI: 43%–76%; hospital-based: $P < 0.001$ and $I^2 = 63\%$, 95% CI: 8%–56%). The amount of heterogeneity was reduced in the subset analysis by ancestry.

Previous meta-analyses: There have been 2 published meta-analyses on *GSTT1* deletion and lung cancer (Table 1) yielding comparable results (Raimondi [129]: meta OR = 1.07, 95% CI: 0.96–1.19; Ye [126]: meta OR = 1.09, 95% CI: 1.02–1.16) to those of the current updated meta- and pooled analyses.

There was 1 published meta-analysis that conducted subset analysis by ancestry for *GSTT1* polymorphism [129] (Table 1), reporting a significant association among East Asians (meta OR = 1.28, 95% CI: 1.10–1.49), with borderline heterogeneity ($P = 0.09$); null findings were observed in White populations (meta OR = 0.99, 95% CI: 0.87–1.12) with significant heterogeneity ($P = 0.02$), consistent with the updated estimates.

GSTP1—The current updated meta-analysis (Table 1) shows no association of lung cancer with combined *AG* and *GG* genotypes (meta OR = 1.03, 95% CI: 0.97–1.09) or for *GG* genotype alone (meta OR = 1.05, 95% CI: 0.95–1.16). The results from the pooled analysis are consistent with these findings (OR = 0.98, 95% CI: 0.86–1.13 and 1.06, 95% CI: 0.97–1.15 respectively).

There was a significant association between *G* allele carriers and lung cancer in East Asian populations in the current meta-analysis (OR = 1.16, 95% CI: 1.01–1.32); and for the *AG* genotype in the pooled analysis (OR = 1.31, 95% CI: 1.03–1.67). There was no significant association with the *GSTP1* Ile105Val polymorphism and lung cancer among White populations.

There was no significant between-study heterogeneity overall or in any of the subset analyses other than in East Asian populations (Table 1).

Previous meta-analyses: Two recent meta-analyses on *GSTP1* Ile105Val and lung cancer reported borderline associations of the *G* allele and lung cancer (Ye [126]: meta OR = 1.04, 95% CI: 0.99–1.09; Cote [130]: meta OR = 1.04, 95% CI: 0.97–1.10), with no heterogeneity, consistent with the current updated meta-analysis (Table 1).

Protection from bias

GSTM1—The recently run meta-analysis of *GSTM1* deletion and lung cancer suggests the presence of small-study effect (Table 2) overall (Harbord test: $P = 0.011$) and in the community-based control subset ($P = 0.010$) but not in the ancestry-specific analyses.

In the overall analysis, the significant findings among the published studies were not statistically significantly more than expected (Table 2). However, the test was statistically significant in the East Asian subset ($P = 0.002$) and in studies involving hospital-based controls ($P = 0.010$).

GSTT1—There was no evidence of small-study effect in the overall meta-analysis of *GSTT1* deletion and lung cancer (Table 2). In the subset analyses, there was evidence of small-study effect only in studies involving community-based controls ($P = 0.079$).

The significant findings were more than expected among the published studies (Table 2) overall (significance chasing bias: $P < 0.001$), in the subset analyses according to control source ($P = 0.001$ for both hospital- and community-based) and in the subset of studies conducted in Whites ($P < 0.001$).

GSTP1—There was evidence of small-study effect (Table 2) among publications on the association between *GSTP1* Ile105Val *G* allele carriers and lung cancer (Harbord test: $P = 0.014$), but not for studies evaluating the association of *GG* genotype and lung cancer. In the subset analyses, only the community-based control group had significant evidence for small study effect ($P = 0.024$).

There were not more than expected significant findings for the overall associations of *GSTP1* Ile105Val *G* allele carriers or *GG* genotype (Table 2). In the subset analyses, there were more than expected significant findings among studies on the *GG* genotype in White populations ($P = 0.002$) and in hospital control studies ($P = 0.067$).

Five publications did not report the genotype distribution of the controls [33,34,77,82,114] and therefore Hardy-Weinberg equilibrium (HWE) could not be calculated. Controls for 5 (16.1%) of the remaining 31 studies were not in HWE (Supplemental Table S1). When the meta-analysis was run excluding those 5 studies not in HWE, the results did not significantly change (data not shown).

Cumulative evidence

GSTM1—Based on the previously proposed guidelines [4], the *amount of evidence* was categorized as A since its n_{minor} is above 1,000 ($n_{\text{minor}} = 20,941$); *replication* was assigned to category B because, despite the amount of between-study heterogeneity ($I^2 = 55\%$), the vast majority of the point estimates from the individual studies are positive ($OR > 1.0$); even after performing subset analyses by ancestry, the meta and pooled analyses consistently showed a significant association with lung cancer, with the exception of the meta-analysis for people of African descent; and *protection from bias* was graded as category C due to considerable potential for bias, as evidenced by the Harbord test for small study effect. The HWE could not be evaluated due to lack of publication of necessary genotyping data (homozygous *present* genotype was always reported combined with heterozygotes). The overall assessment of the association between *GSTM1* deletion and lung cancer would be: *weak* cumulative evidence (Table 3). A similar overall assessment is reached for the ancestry-specific subset analyses.

GSTT1—The *amount of evidence* was scored as A since n_{minor} exceeds 1,000 ($n_{\text{minor}} = 6,585$); *replication* was classified as C as a result of large-scale between-study heterogeneity ($I^2 = 51\%$) and lack of statistically significant findings; and *protection from bias* was placed into category C since there were more than expected significant results (significance chasing bias). The overall classification of the association between *GSTT1* deletion and lung cancer is: *weak* evidence (Table 3). A similar assessment is reached for the ancestry-specific subset analyses.

GSTP1—For the association between *GSTP1* Ile105Val *GG* genotype and lung cancer, the *amount of evidence* was classified as A since it exceeds the n_{minor} threshold of 1,000 ($n_{\text{minor}} = 1,870$); *replication* was considered in category C because there was no overall significant association; and *protection from bias* was considered as category B because the Harbord and excess-significance tests were non-significant, but the ORs consistently deviated less than 1.15-fold from the null, thus potential for bias cannot be entirely ruled out. The overall classification of the association between *GSTP1* Ile105Val *GG* genotype and lung cancer is: *weak* evidence (Table 3). A similar assessment is reached for the ancestry-specific subset analyses.

For the association of the *G* allele (*AG* and *GG* genotypes combined) and lung cancer, the *amount of evidence* was categorized as A since n_{minor} greatly exceeds 1,000 ($n_{\text{minor}} = 10,458$); *replication* was classified as C due to lack of overall significant findings; and *protection from bias* was categorized as C due to significant potential for bias as evidenced by significance of the Harbord test. The overall classification of the association between *GSTP1* Ile105Val *AG*

and *GG* genotype and lung cancer is: *weak* evidence (Table 3). A similar assessment is reached for the White subset, although for East Asian populations there was *moderate* evidence.

Grading of previous meta-analyses: Among the meta-analyses providing sufficient information for grading, all would be assessed as having *weak* cumulative evidence based on the Venice criteria (Table 4). The criteria used to score the existing meta-analyses are presented in the Supplemental Table S2. For most of the meta-analyses, incomplete information was given for fully assessing heterogeneity and publication bias.

DISCUSSION

Glutathione S-transferase polymorphisms have been widely studied in the literature, and thus there have been many attempts over time to synthesize the effect of genetic variants through meta-analyses. Compared to previous attempts of meta-analyzing data, we have used more rigorous and standardized criteria, as defined through the Venice initiative [4]. These have been specifically developed for genetic data, and include an evaluation of the amount of evidence available, the degree of consistency/replication of findings, and of bias. With such strict criteria we have found that overall there is not strong evidence of an involvement of commonly studied GST polymorphisms in lung cancer.

Application of the Venice criteria indicates *weak* evidence in support of an association with *GSTM1* null, *GSTT1* null, and *GSTP1* Ile105Val polymorphisms and lung cancer, both overall and after analysis of ancestral subsets. The only exception is for the *GSTP1* Ile105Val *G* allele in East Asian populations, where the evidence for association with lung cancer is *moderate*. This result may be attributable to differences in genotype frequencies in East Asian populations, more carefully designed studies, or local differences in exposure to relevant carcinogens, although bias cannot be fully excluded [131].

The available *a priori* evidence on a role of GSTs in lung cancer is rather strong, i.e. a criterion of biological plausibility can be easily met. This is why, in fact, they have been studied extensively. Glutathione S-transferases catalyze the detoxification of electrophilic metabolites, including benzo[α]pyrene and other polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke, which are likely to play a key role in lung carcinogenesis. The *GSTM1* and *GSTT1* deletions result in null activity of their respective enzymes, and so a strong functional impact would be expected. However, the loss of function associated with these gene variants is likely compensated by the existence of alternative metabolic pathways, which may help to explain why the effect, if any, is weak.

Despite the fact that GST variants are considered to be among the most extensively studied genetic markers of susceptibility, and that *GSTM1* deletion in particular exhibited statistically significant associations with lung cancer in previous meta-analyses, the application of the Venice criteria shows that when this standardized method for evaluating the cumulative evidence of association is applied, the previous meta-analyses would fall into the category of “weak evidence”. While the estimates of effect size changed over time for some associations, inconsistencies dominate and the evaluation of “weak” is mainly related to heterogeneity and/or lack of protection from bias.

In spite of the systematic approach outlined by the Venice interim criteria, the present exercise shows that there may be room for improvement in the standardization and performance of the Venice criteria [56]. One issue that emerged from this analysis is the possibility that different weights should be assigned to the different criteria included in the Venice method. For example, the assessment of *protection from bias* should probably have less weight than the consistent replication across studies and meta-analyses of a very strong association, with a large effect

estimate (e.g. an odds ratio of 2.0). However, when small effects are observed, as in the case of the associations of GST variants and lung cancer, the presence of a modest bias could easily contribute to producing a spurious, small association of the magnitude reported in this re-analysis. In the area of genetic susceptibility, where small associations are expected, hints for bias cannot be discarded even though tests for bias are not perfect [132,133].

One aspect emerging from our exercise is the good correspondence of the results obtained with the meta- and respective pooled (individual-level) analyses. These two approaches have different principles, strengths, and limitations and may not always agree in their results [134]. For some analyses, such as those restricted to populations of African descent, the pooled analysis offered the appropriate data that were missing in the meta-analysis, thus allowing the drawing of a more complete picture. Another potential strength is that in several instances the *replication* of the meta-analysis was classified with a grade of C due to large amounts of heterogeneity, while the pooled analysis constantly produces less heterogeneity. This could be attributable to the ability of pooled analyses to deliver adjusted estimates but also may reflect the smaller sample size relative to the meta-analyses. It should also be acknowledged that heterogeneity estimates have substantial uncertainty, as evidenced by the large 95% confidence intervals of heterogeneity metrics, even when a large number of studies are available [22].

As expected from the role that metabolic genes have in carcinogenesis, the associations derived from individual studies and from summary estimates in meta- and pooled analysis confirm the definition of “low penetrance” genes, with increases in lung cancer risk ranging from 15%–21% at the most, but with many studies showing no significant associations. The original Venice criteria applied here weight the credibility that an association is present, but do not score the certainty that the association is absent. Very small effects (e.g. odds ratios of 1.05) cannot be excluded with certainty.

The effort to date regarding elucidation of the true effects of *GSTM1* deletion, *GSTT1* deletion, and *GSTP1* Ile105Val polymorphism has been a resource-consuming, laborious task with a lot of uncertainties surrounding the evidence collected so far. In spite of the biologic plausibility due to involvement in xenobiotic detoxification, GST polymorphisms have not fulfilled their early promise as biomarkers of lung cancer susceptibility. Rather, the large body of literature either displays wide variability between studies, yields no overall significant summary effect, or both. This seems to be a common feature of studies on metabolic gene variants and cancer. Metabolic gene variants are known to produce very small odds ratios in both directions, either for a positive or negative association, and the significant heterogeneity and susceptibility to bias shown in most of the analyses conducted so far may have contributed to dilute the real effect, if any exist. It is certainly possible that poor replication – leading to a high degree of heterogeneity - is related to local differences in exposures affecting the populations from which samples are drawn, (for example differences in environmental pollution, smoking habits or dietary factors) which are difficult to incorporate in the score proposed by the Venice guidelines. It is possible that restricting the assessment to studies including a formal test for gene-environment interaction would yield more positive evaluations of the overall associations. One should also consider the degree of misclassification that is much higher for environmental or lifestyle exposures than for gene variants [135].

A further aspect highlighted by this exercise is that certain ethnic groups, such as populations of African descent, are still highly understudied. No conclusion about a possible association between susceptibility genes and cancer can be drawn at present.

In light of the limitations and determination of weak cumulative evidence shown by this exercise that evaluated the credibility of the association between commonly studied GST polymorphisms and lung cancer, future studies may try to evaluate interaction of GST variants

with other genes in adequately powered datasets, as well as include the assessment of gene-environment interaction. This may allow for identification of gene-disease associations and interactions where the cumulative evidence for association is strong, while evidence for main effects is conclusively uniformly weak. Application of criteria for assessment of the strength of cumulative evidence, such as the Venice criteria, to meta-analyses will help to clarify the validity of summary estimates for gene-disease associations, making it easier for researchers and clinicians to comprehend the true nature of the risk involved, if any.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Barbara Stadterman for her assistance in preparation of the GSEC data.

Funding sources: the Environmental Cancer Risk, Nutrition and Individual Susceptibility European Union Network of Excellence (ECNIS, Contract No. FOOD-CT-2005-513943); Clinical and Translational Science Institute and the Institute for Clinical Research Education at the University of Pittsburgh (grant 5TL1RR024155-03 to SM Langevin)

REFERENCES

1. Yu, W., et al. HuGE Literature Finder. HuGE Navigator. 2009. [cited 2009 October 30]; www.hugenavigator.net/HuGENavigator/startPagePubLit.do. Available from: www.hugenavigator.net/HuGENavigator/startPagePubLit.do
2. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005;2(8):e124. [PubMed: 16060722]
3. Ioannidis JP. Effect of formal statistical significance on the credibility of observational associations. *Am J Epidemiol* 2008;168(4):374–383. discussion 384-90. [PubMed: 18611956]
4. Ioannidis JP, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. *Int J Epidemiol* 2008;37(1):120–132. [PubMed: 17898028]
5. Jemal A, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58(2):71–96. [PubMed: 18287387]
6. Tobacco smoke and involuntary smoking, in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon, France: IARC; 2004. p. 59-80.
7. Frova C. Glutathione transferases in the genomics era: new insights and perspectives. *Biomol Eng* 2006;23(4):149–169. [PubMed: 16839810]
8. Ali-Osman F, et al. Molecular cloning, characterization, and expression in *Escherichia coli* of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. *J Biol Chem* 1997;272(15):10004–10012. [PubMed: 9092542]
9. Zhong S, et al. Glutathione S-transferase mu locus: use of genotyping and phenotyping assays to assess association with lung cancer susceptibility. *Carcinogenesis* 1991;12(9):1533–1537. [PubMed: 1680031]
10. Taioli E. International collaborative study on genetic susceptibility to environmental carcinogens. *Cancer Epidemiol Biomarkers Prev* 1999;8(8):727–728. [PubMed: 10744134]
11. Sterne, JAC.; Bradburn, MJ.; Egger, M. Meta-analysis in Stata, in *Systematic Reviews in Health Care: Meta-Analysis in Context*. Egger, M.; Davey Smith, G.; Altman, DG., editors. London: BMJ; 2001. p. 347-369.
12. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25(20):3443–3457. [PubMed: 16345038]
13. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials* 2007;4(3):245–253. [PubMed: 17715249]
14. Amos CI, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet* 2008;40(5):616–622. [PubMed: 18385676]

15. Liu P, et al. Familial aggregation of common sequence variants on 15q24–25.1 in lung cancer. *J Natl Cancer Inst* 2008;100(18):1326–1330. [PubMed: 18780872]
16. McKay JD, et al. Lung cancer susceptibility locus at 5p15.33. *Nat Genet* 2008;40(12):1404–1406. [PubMed: 18978790]
17. Rafnar T, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. *Nat Genet* 2009;41(2):221–227. [PubMed: 19151717]
18. Spinola M, et al. Genome-wide single nucleotide polymorphism analysis of lung cancer risk detects the KLF6 gene. *Cancer Lett* 2007;251(2):311–316. [PubMed: 17223258]
19. Wang Y, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nat Genet* 2008;40(12):1407–1409. [PubMed: 18978787]
20. Carter NP. Methods and strategies for analyzing copy number variation using DNA microarrays. *Nat Genet* 2007;39((7 Suppl)):S16–S21. [PubMed: 17597776]
21. Khoury MJ, et al. Genome-wide association studies, field synopses, and the development of the knowledge base on genetic variation and human diseases. *Am J Epidemiol* 2009;170(3):269–279. [PubMed: 19498075]
22. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;8:101–129.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539–1558. [PubMed: 12111919]
24. Adonis M, et al. Smoking habit and genetic factors associated with lung cancer in a population highly exposed to arsenic. *Toxicol Lett* 2005;159(1):32–37. [PubMed: 16099114]
25. Alexandrie AK, et al. Influence of CYP1A1, GSTM1, GSTT1, and NQO1 genotypes and cumulative smoking dose on lung cancer risk in a Swedish population. *Cancer Epidemiol Biomarkers Prev* 2004;13(6):908–914. [PubMed: 15184245]
26. Baranov VS, et al. Proportion of the GSTM1 0/0 genotype in some Slavic populations and its correlation with cystic fibrosis and some multifactorial diseases. *Hum Genet* 1996;97(4):516–520. [PubMed: 8834254]
27. Belogubova EV, et al. A novel approach for assessment of cancer predisposing roles of GSTM1 and GSTT1 genes: use of putatively cancer resistant elderly tumor-free smokers as the referents. *Lung Cancer* 2004;43(3):259–266. [PubMed: 15165083]
28. Brennan P, et al. Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomisation approach. *Lancet* 2005;366(9496):1558–1560. [PubMed: 16257343]
29. Brockmoller J, et al. Genotype and phenotype of glutathione S-transferase class mu isoenzymes mu and psi in lung cancer patients and controls. *Cancer Res* 1993;53(5):1004–1011. [PubMed: 8439946]
30. Butkiewicz D, et al. GSTM1, GSTP1, CYP1A1 and CYP2D6 polymorphisms in lung cancer patients from an environmentally polluted region of Poland: correlation with lung DNA adduct levels. *Eur J Cancer Prev* 1999;8(4):315–323. [PubMed: 10493307]
31. Cajas-Salazar N, et al. Combined effect of MPO, GSTM1 and GSTT1 polymorphisms on chromosome aberrations and lung cancer risk. *Int J Hyg Environ Health* 2003;206(6):473–483. [PubMed: 14626895]
32. Chan EC, et al. Polymorphisms of the GSTM1, GSTP1, MPO, XRCC1, and NQO1 genes in Chinese patients with non-small cell lung cancers: relationship with aberrant promoter methylation of the CDKN2A and RARB genes. *Cancer Genet Cytogenet* 2005;162(1):10–20. [PubMed: 16157195]
33. Chan-Yeung M, et al. Lung cancer susceptibility and polymorphisms of glutathione-S-transferase genes in Hong Kong. *Lung Cancer* 2004;45(2):155–160. [PubMed: 15246186]
34. Chen HC, et al. Genetic polymorphisms of phase II metabolic enzymes and lung cancer susceptibility in a population of Central South China. *Dis Markers* 2006;22(3):141–152. [PubMed: 16788248]
35. Chen S, et al. Polymorphisms of the CYP1A1 and GSTM1 genes in relation to individual susceptibility to lung carcinoma in Chinese population. *Mutat Res* 2001;458(1–2):41–47. [PubMed: 11406420]
36. Cote ML, et al. Tobacco and estrogen metabolic polymorphisms and risk of non-small cell lung cancer in women. *Carcinogenesis* 2009b;30(4):626–635. [PubMed: 19174490]
37. Crosbie PA, et al. GSTM1 copy number and lung cancer risk. *Mutat Res* 2009;664(1–2):1–5. [PubMed: 19428374]

38. Deakin M, et al. Glutathione S-transferase GSTT1 genotypes and susceptibility to cancer: studies of interactions with GSTM1 in lung, oral, gastric and colorectal cancers. *Carcinogenesis* 1996;17(4): 881–884. [PubMed: 8625505]
39. Demir A, et al. The role of GSTM1 gene polymorphisms in lung cancer development in Turkish population. *J Carcinog* 2007;6:13. [PubMed: 17897446]
40. Dialyna IA, et al. Genetic polymorphisms of CYP1A1, GSTM1 and GSTT1 genes and lung cancer risk. *Oncol Rep* 2003;10(6):1829–1835. [PubMed: 14534704]
41. Dresler CM, et al. Gender differences in genetic susceptibility for lung cancer. *Lung Cancer* 2000;30(3):153–160. [PubMed: 11137199]
42. Ford JG, et al. Glutathione S-transferase M1 polymorphism and lung cancer risk in African-Americans. *Carcinogenesis* 2000;21(11):1971–1975. [PubMed: 11062156]
43. Gao Y, Zhang Q. Polymorphisms of the GSTM1 and CYP2D6 genes associated with susceptibility to lung cancer in Chinese. *Mutat Res* 1999;444(2):441–449. [PubMed: 10521684]
44. Ge H, et al. Analysis of L-myc and GSTM1 genotypes in Chinese non-small cell lung carcinoma patients. *Lung Cancer* 1996;15(3):355–366. [PubMed: 8959680]
45. Gsur A, et al. Genetic polymorphisms of CYP1A1 and GSTM1 and lung cancer risk. *Anticancer Res* 2001;21(3C):2237–2242. [PubMed: 11501853]
46. Habalova V, et al. Combined analysis of polymorphisms in glutathione S-transferase M1 and microsomal epoxide hydrolase in lung cancer patients. *Neoplasma* 2004;51(5):352–357. [PubMed: 15640939]
47. Harris MJ, et al. Polymorphism of the Pi class glutathione S-transferase in normal populations and cancer patients. *Pharmacogenetics* 1998;8(1):27–31. [PubMed: 9511178]
48. Harrison DJ, et al. Frequency of glutathione S-transferase M1 deletion in smokers with emphysema and lung cancer. *Hum Exp Toxicol* 1997;16(7):356–360. [PubMed: 9257159]
49. Hong YS, et al. Polymorphism of the CYP1A1 and glutathione-S-transferase gene in Korean lung cancer patients. *Exp Mol Med* 1998;30(4):192–198. [PubMed: 9894148]
50. Honma HN, et al. Influence of p53 codon 72 exon 4, GSTM1, GSTT1 and GSTP1*B polymorphisms in lung cancer risk in a Brazilian population. *Lung Cancer* 2008;61(2):152–162. [PubMed: 18280004]
51. Hou SM, et al. Differential interactions between GSTM1 and NAT2 genotypes on aromatic DNA adduct level and HPRT mutant frequency in lung cancer patients and population controls. *Cancer Epidemiol Biomarkers Prev* 2001a;10(2):133–140. [PubMed: 11219770]
52. Hou SM, et al. GSTM1 and NAT2 polymorphisms in operable and non-operable lung cancer patients. *Carcinogenesis* 2000;21(1):49–54. [PubMed: 10607733]
53. Jourenkova N, et al. Effects of glutathione S-transferases GSTM1 and GSTT1 genotypes on lung cancer risk in smokers. *Pharmacogenetics* 1997;7(6):515–518. [PubMed: 9429237]
54. Kawajiri K, et al. Genetic polymorphisms of drug-metabolizing enzymes and lung cancer susceptibility. *Pharmacogenetics* 1995;5:S70–S73. Spec No. [PubMed: 7581493]
55. Kelsey KT, et al. Polymorphisms in the glutathione S-transferase class mu and theta genes interact and increase susceptibility to lung cancer in minority populations (Texas, United States). *Cancer Causes Control* 1997;8(4):554–559. [PubMed: 9242470]
56. Kihara M, Noda K. Distribution of GSTM1 null genotype in relation to gender, age and smoking status in Japanese lung cancer patients. *Pharmacogenetics* 1995;5:S74–S79. Spec No. [PubMed: 7581494]
57. Kihara M, Noda K. Lung cancer risk of the GSTM1 null genotype is enhanced in the presence of the GSTP1 mutated genotype in male Japanese smokers. *Cancer Lett* 1999;137(1):53–60. [PubMed: 10376794]
58. Kiyohara C, et al. Risk modification by CYP1A1 and GSTM1 polymorphisms in the association of environmental tobacco smoke and lung cancer: a case-control study in Japanese nonsmoking women. *Int J Cancer* 2003;107(1):139–144. [PubMed: 12925969]
59. Kiyohara C, et al. Polymorphism in GSTM1, GSTT1, and GSTP1 and Susceptibility to Lung Cancer in a Japanese Population. *Asian Pac J Cancer Prev* 2000;1(4):293–298. [PubMed: 12716303]
60. Kumar M, Agarwal SK, Goel SK. Lung cancer risk in north Indian population: role of genetic polymorphisms and smoking. *Mol Cell Biochem* 2009;322(1–2):73–79. [PubMed: 19009239]

61. Lam TK, et al. Copy Number Variants of GSTM1 and GSTT1 in Relation to Lung Cancer Risk in a Prospective Cohort Study. *Ann Epidemiol*. 2009
62. Lan Q, et al. Indoor coal combustion emissions, GSTM1 and GSTT1 genotypes, and lung cancer risk: a case-control study in Xuan Wei, China. *Cancer Epidemiol Biomarkers Prev* 2000;9(6):605–608. [PubMed: 10868696]
63. Larsen JE, et al. CYP1A1 Ile462Val and MPO G-463A interact to increase risk of adenocarcinoma but not squamous cell carcinoma of the lung. *Carcinogenesis* 2006;27(3):525–532. [PubMed: 16195240]
64. Le Marchand L, et al. Associations of CYP1A1, GSTM1, and CYP2E1 polymorphisms with lung cancer suggest cell type specificities to tobacco carcinogens. *Cancer Res* 1998;58(21):4858–4863. [PubMed: 9809991]
65. Lee KM, et al. Interactive effect of genetic polymorphism of glutathione S-transferase M1 and smoking on squamous cell lung cancer risk in Korea. *Oncol Rep* 2006;16(5):1035–1039. [PubMed: 17016589]
66. Lewis SJ, et al. GSTM1, GSTT1 and GSTP1 polymorphisms and lung cancer risk. *Cancer Lett* 2002;180(2):165–171. [PubMed: 12175548]
67. Liu G, et al. Differential association of the codon 72 p53 and GSTM1 polymorphisms on histological subtype of non-small cell lung carcinoma. *Cancer Res* 2001;61(24):8718–8722. [PubMed: 11751390]
68. London SJ, Smart J, Daly AK. Lung cancer risk in relation to genetic polymorphisms of microsomal epoxide hydrolase among African-Americans and Caucasians in Los Angeles County. *Lung Cancer* 2000a;28(2):147–155. [PubMed: 10717332]
69. London SJ, et al. Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. *Lancet* 2000b;356(9231):9724–9729.
70. Lu W, et al. Genetic polymorphism in myeloperoxidase but not GSTM1 is associated with risk of lung squamous cell carcinoma in a Chinese population. *Int J Cancer* 2002;102(3):275–279. [PubMed: 12397651]
71. Malats N, et al. Lung cancer risk in nonsmokers and GSTM1 and GSTT1 genetic polymorphism. *Cancer Epidemiol Biomarkers Prev* 2000;9(8):827–833. [PubMed: 10952100]
72. Moreira A, et al. Glutathione S-transferase mu polymorphism and susceptibility to lung cancer in the Portuguese population. *Teratog Carcinog Mutagen* 1996;16(5):269–274. [PubMed: 9122892]
73. Nazar-Stewart V, et al. The glutathione S-transferase mu polymorphism as a marker for susceptibility to lung carcinoma. *Cancer Res* 1993;53(10 Suppl):2313–2318. [PubMed: 8485718]
74. Nazar-Stewart V, et al. A population-based study of glutathione S-transferase M1, T1 and P1 genotypes and risk for lung cancer. *Lung Cancer* 2003;40(3):247–258. [PubMed: 12781423]
75. Osawa Y, et al. NAT2 and CYP1A2 polymorphisms and lung cancer risk in relation to smoking status. *Asian Pac J Cancer Prev* 2007;8(1):103–108. [PubMed: 17477782]
76. Ozturk O, et al. GST M1 and CYP1A1 gene polymorphism and daily fruit consumption in Turkish patients with non-small cell lung carcinomas. *In Vivo* 2003;17(6):625–632. [PubMed: 14758730]
77. Perera FP, et al. Associations between carcinogen-DNA damage, glutathione S-transferase genotypes, and risk of lung cancer in the prospective Physicians' Health Cohort Study. *Carcinogenesis* 2002;23(10):1641–1646. [PubMed: 12376472]
78. Persson I, et al. Genetic polymorphism of xenobiotic metabolizing enzymes among Chinese lung cancer patients. *Int J Cancer* 1999;81(3):325–329. [PubMed: 10209943]
79. Pinarbasi H, et al. Strong association between the GSTM1-null genotype and lung cancer in a Turkish population. *Cancer Genet Cytogenet* 2003;146(2):125–129. [PubMed: 14553946]
80. Pisani P, et al. GSTM1 and CYP1A1 polymorphisms, tobacco, air pollution, and lung cancer: a study in rural Thailand. *Cancer Epidemiol Biomarkers Prev* 2006;15(4):667–674. [PubMed: 16614107]
81. Quinones L, et al. CYP1A1, CYP2E1 and GSTM1 genetic polymorphisms. The effect of single and combined genotypes on lung cancer susceptibility in Chilean people. *Cancer Lett* 2001;174(1):35–44. [PubMed: 11675150]
82. Reszka E, et al. Evaluation of selenium, zinc and copper levels related to GST genetic polymorphism in lung cancer patients. *Trace Elements and Electrolytes* 2004;21:1–10.

83. Risch A, et al. Glutathione-S-transferase M1, M3, T1 and P1 polymorphisms and susceptibility to non-small-cell lung cancer subtypes and hamartomas. *Pharmacogenetics* 2001;11(9):757–764. [PubMed: 11740339]
84. Ruano-Ravina A, et al. GSTM1 and GSTT1 polymorphisms, tobacco and risk of lung cancer: a case-control study from Galicia, Spain. *Anticancer Res* 2003;23(5b):4333–4337. [PubMed: 14666648]
85. Saarikoski ST, et al. Combined effect of polymorphic GST genes on individual susceptibility to lung cancer. *Int J Cancer* 1998;77(4):516–521. [PubMed: 9679751]
86. Schneider J, et al. GSTM1, GSTT1, and GSTP1 polymorphism and lung cancer risk in relation to tobacco smoking. *Cancer Lett* 2004;208(1):65–74. [PubMed: 15105047]
87. Shah PP, et al. Interaction of cytochrome P4501A1 genotypes with other risk factors and susceptibility to lung cancer. *Mutat Res* 2008;639(1–2):1–10. [PubMed: 18082227]
88. Sobti RC, et al. Combined effect of GSTM1, GSTT1 and GSTP1 polymorphisms on histological subtypes of lung cancer. *Biomarkers* 2008;13(3):282–295. [PubMed: 18415801]
89. Sorensen M, et al. Interactions between GSTM1, GSTT1 and GSTP1 polymorphisms and smoking and intake of fruit and vegetables in relation to lung cancer. *Lung Cancer* 2007;55(2):137–144. [PubMed: 17123660]
90. Spitz MR, et al. Dietary intake of isothiocyanates: evidence of a joint effect with glutathione S-transferase polymorphisms in lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2000;9(10):1017–1020. [PubMed: 11045782]
91. Sreeja L, et al. Possible risk modification by CYP1A1, GSTM1 and GSTT1 gene polymorphisms in lung cancer susceptibility in a South Indian population. *J Hum Genet* 2005;50(12):618–627. [PubMed: 16228113]
92. Stucker I, et al. Genetic polymorphisms of glutathione S-transferases as modulators of lung cancer susceptibility. *Carcinogenesis* 2002;23(9):1475–1481. [PubMed: 12189190]
93. Sun GF, et al. Gene deficiency of glutathione S-transferase mu isoform associated with susceptibility to lung cancer in a Chinese population. *Cancer Lett* 1997;113(1–2):169–172. [PubMed: 9065818]
94. Sunaga N, et al. Contribution of the NQO1 and GSTT1 polymorphisms to lung adenocarcinoma susceptibility. *Cancer Epidemiol Biomarkers Prev* 2002;11(8):730–738. [PubMed: 12163326]
95. Tang DL, et al. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. *Carcinogenesis* 1998;19(11):1949–1953. [PubMed: 9855008]
96. To-Figueras J, et al. Lung cancer susceptibility in relation to combined polymorphisms of microsomal epoxide hydrolase and glutathione S-transferase P1. *Cancer Lett* 2001;173(2):155–162. [PubMed: 11597790]
97. Tsai YY, et al. Genetic susceptibility and dietary patterns in lung cancer. *Lung Cancer* 2003;41(3):269–281. [PubMed: 12928118]
98. Wang J, et al. Association of GSTM1, CYP1A1 and CYP2E1 genetic polymorphisms with susceptibility to lung adenocarcinoma: a case-control study in Chinese population. *Cancer Sci* 2003a;94(5):448–452. [PubMed: 12824892]
99. Woodson K, et al. Effect of vitamin intervention on the relationship between GSTM1, smoking, and lung cancer risk among male smokers. *Cancer Epidemiol Biomarkers Prev* 1999;8(11):965–970. [PubMed: 10566550]
100. Yang M, et al. Combined effects of genetic polymorphisms in six selected genes on lung cancer susceptibility. *Lung Cancer* 2007;57(2):135–142. [PubMed: 17428572]
101. Yang P, et al. Glutathione pathway genes and lung cancer risk in young and old populations. *Carcinogenesis* 2004;25(10):1935–1944. [PubMed: 15192016]
102. Yang XR, et al. CYP1A1 and GSTM1 polymorphisms in relation to lung cancer risk in Chinese women. *Cancer Lett* 2004;214(2):197–204. [PubMed: 15363546]
103. Zhao B, et al. Dietary isothiocyanates, glutathione S-transferase -M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. *Cancer Epidemiol Biomarkers Prev* 2001;10(10):1063–1067. [PubMed: 11588132]
104. Zupa A, et al. GSTM1 and NAT2 Polymorphisms and Colon, Lung and Bladder Cancer Risk: A Case-control Study. *Anticancer Res* 2009;29(5):1709–1714. [PubMed: 19443391]

105. Gallegos-Arreola MP, et al. GSTT1 gene deletion is associated with lung cancer in Mexican patients. *Dis Markers* 2003;19(6):259–261. [PubMed: 15258326]
106. Harms C, et al. Polymorphisms in DNA repair genes, chromosome aberrations, and lung cancer. *Environ Mol Mutagen* 2004;44(1):74–82. [PubMed: 15199549]
107. Hou SM, Falt S, Nyberg F. Glutathione S-transferase T1-null genotype interacts synergistically with heavy smoking on lung cancer risk. *Environ Mol Mutagen* 2001b;38(1):83–86. [PubMed: 11473392]
108. Salagovic J, et al. Genetic polymorphism of glutathione S-transferases M1 and T1 as a risk factor in lung and bladder cancers. *Neoplasma* 1998;45(5):312–317. [PubMed: 9921921]
109. To-Figueras J, et al. Genetic polymorphism of glutathione S-transferase P1 gene and lung cancer risk. *Cancer Causes Control* 1999;10(1):65–70. [PubMed: 10334644]
110. Wang J, et al. GST genetic polymorphisms and lung adenocarcinoma susceptibility in a Chinese population. *Cancer Lett* 2003b;201(2):185–193. [PubMed: 14607333]
111. Jourenkova-Mironova N, et al. Role of glutathione S-transferase GSTM1, GSTM3, GSTP1 and GSTT1 genotypes in modulating susceptibility to smoking-related lung cancer. *Pharmacogenetics* 1998;8(6):495–502. [PubMed: 9918133]
112. Katoh T, et al. Human glutathione S-transferase P1 polymorphism and susceptibility to smoking related epithelial cancer; oral, lung, gastric, colorectal and urothelial cancer. *Pharmacogenetics* 1999;9(2):165–169. [PubMed: 10376763]
113. Liang G, Pu Y, Yin L. Rapid detection of single nucleotide polymorphisms related with lung cancer susceptibility of Chinese population. *Cancer Lett* 2005;223(2):265–274. [PubMed: 15896461]
114. Lin P, et al. Analysis of NQO1, GSTP1, and MnSOD genetic polymorphisms on lung cancer risk in Taiwan. *Lung Cancer* 2003;40(2):123–129. [PubMed: 12711112]
115. Miller DP, et al. An association between glutathione S-transferase P1 gene polymorphism and younger age at onset of lung carcinoma. *Cancer* 2006;107(7):1570–1577. [PubMed: 16933328]
116. Sreeja L, et al. Glutathione S-transferase M1, T1 and P1 polymorphisms: susceptibility and outcome in lung cancer patients. *J Exp Ther Oncol* 2008;7(1):73–85. [PubMed: 18472644]
117. Wang Y, et al. Association between glutathione S-transferase p1 polymorphisms and lung cancer risk in Caucasians: a case-control study. *Lung Cancer* 2003;40(1):25–32. [PubMed: 12660004]
118. Yoon KA, et al. CYP1B1, CYP1A1, MPO, and GSTP1 polymorphisms and lung cancer risk in never-smoking Korean women. *Lung Cancer* 2008;60(1):40–46. [PubMed: 17980933]
119. Zienolddiny S, et al. A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of non-small cell lung cancer in smokers. *Carcinogenesis* 2008;29(6):1164–1169. [PubMed: 18258609]
120. Reszka E, et al. Glutathione S-transferase M1 and P1 metabolic polymorphism and lung cancer predisposition. *Neoplasma* 2003;50(5):357–362. [PubMed: 14628089]
121. Benhamou S, et al. Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. *Carcinogenesis* 2002;23(8):1343–1350. [PubMed: 12151353]
122. Carlsten C, et al. Glutathione S-transferase M1 (GSTM1) polymorphisms and lung cancer: a literature-based systematic HuGE review and meta-analysis. *Am J Epidemiol* 2008;167(7):759–774. [PubMed: 18270371]
123. d'Errico A, et al. Review of studies of selected metabolic polymorphisms and cancer. *IARC Sci Publ* 1999;(148):323–393. [PubMed: 10493265]
124. Houlston RS. Glutathione S-transferase M1 status and lung cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 1999;8(8):675–682. [PubMed: 10744127]
125. McWilliams JE, et al. Glutathione S-transferase M1 (GSTM1) deficiency and lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 1995;4(6):589–594. [PubMed: 8547824]
126. Ye Z, et al. Five glutathione s-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. *PLoS Med* 2006;3(4):e91. [PubMed: 16509765]
127. d'Errico A, et al. Genetic metabolic polymorphisms and the risk of cancer: a review of the literature. *Biomarkers* 1996;1:149–173.

128. Shi X, et al. CYP1A1 and GSTM1 polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. *Lung Cancer* 2008;59(2):155–163. [PubMed: 17900751]
129. Raimondi S, et al. Meta- and pooled analysis of GSTT1 and lung cancer: a HuGE-GSEC review. *Am J Epidemiol* 2006;164(11):1027–1042. [PubMed: 17000715]
130. Cote ML, et al. Meta- and pooled analysis of GSTP1 polymorphism and lung cancer: a HuGE-GSEC review. *Am J Epidemiol* 2009a;169(7):802–814. [PubMed: 19240225]
131. Pan Z, et al. Local literature bias in genetic epidemiology: an empirical evaluation of the Chinese literature. *PLoS Med* 2005;2(12):e334. [PubMed: 16285839]
132. Lau J, et al. The case of the misleading funnel plot. *BMJ* 2006;333(7568):597–600. [PubMed: 16974018]
133. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007;176(8):1091–1096. [PubMed: 17420491]
134. Janssens AC, et al. An empirical comparison of meta-analyses of published gene-disease associations versus consortium analyses. *Genet Med* 2009;11(3):153–162. [PubMed: 19367188]
135. Vineis P. A self-fulfilling prophecy: are we underestimating the role of the environment in gene-environment interaction research? *Int J Epidemiol* 2004;33(5):945–946. [PubMed: 15319401]

Table 1

Description of current and published meta-analyses for select *glutathione S-transferase (GST)* polymorphisms and lung cancer.

	Number of Studies	Cases	Controls	n(minor)	f(minor)	OR (95% CI)	Heterogeneity		
							Q-Statistic P-Value	I ² (95% CI)	Publication Bias Test P-Value
Overall									
GSTM1 (deletion)									
McWilliams, 1995 [125]	8	1254	1780	1496 ^c	n/a	1.34 (1.16–1.55)	n/a	n/a	n/a
Houlston, 1999 [124]	19	3305	5740	4459 ^c	n/a	1.14 (1.03–1.25)	0.275	15% (0%–46%)	n/a
d'Errico, 1999 [123]	21	n/a	n/a	n/a	n/a	1.34 (1.21–1.48)	Present ^g	n/a	n/a
Benhamou, 2002 [121]	43	7463	10789	8998 ^c	n/a	1.17 (1.07–1.27)	0.007	n/a	0.4 ^d
Ye, 2006 [126]	119	19729	25931	22510 ^c	n/a	1.18 (1.14–1.23)	< 0.001	44% (30%–55%)	< 0.0001 ^e
Carlsten, 2008 [122]	98	19638	25266	22138 ^c	n/a	1.22 (1.14–1.30)	< 0.001	58% (46%–66%)	0.003 ^e
Present meta-analysis	85	18777	24050	21042	0.493	1.17 (1.10–1.25)	< 0.001	55% (44%–63%)	0.011 ^f
Present pooled analysis ^h	56	11392	16165	13555	0.492	1.10 (1.04–1.16)	< 0.001	48% (31%–60%)	0.003 ^f
GSTT1 (deletion)									
Raimondi, 2006 [129]	34	7629	10087	4240	0.239	1.07 (0.96–1.19)	< 0.001	n/a	0.02 ^e
Ye, 2006 [126]	44	9636	12322	5094 ^c	n/a	1.09 (1.02–1.16)	< 0.001	57% (40%–70%)	0.14 ^d
Present meta-analysis	45	12569	15545	6585	0.232	1.07 (0.97–1.17)	< 0.001	51% (34%–63%)	0.200 ^f
Present pooled analysis ^h	38	8556	12287	4960	0.238	1.05 (0.97–1.14)	0.004	42% (19%–58%)	0.463 ^f
GSTP1 (Ile105Val)									
Ye, 2006 [126] (per G allele)	25	6221	7602	6870 ^c	n/a	1.04 (0.99–1.09)	0.66	0% (0%–44%)	n/a
Cote, 2009 [130] (*G)	27	8322	5870	7053 ^c	n/a	1.04 (0.97–1.10)	0.27	14% (0%–42%)	0.02 ^e
Present meta-analysis (*G)	35	10125	10867	10458	0.497	1.03 (0.97–1.09)	0.376	5.5% (0%–31%)	0.014 ^f
Present meta-analysis (GG)	31	9427	9887	1870	0.161	1.05 (0.95–1.16)	0.506	0% (0%–34%)	0.400 ^f
Present Pooled analysis (AG) ^h	20	4948	5561	5029	0.479	1.06 (0.97–1.15)	0.629	0% (0%–33%)	0.388 ^f
Present Pooled analysis (GG) ^h	20	3096	3587	1203	0.180	0.98 (0.86–1.13)	0.372	7% (0%–37%)	0.404 ^f
African Descent									

	Number of Studies	Cases	Controls	n(minor)	f(minor)	OR (95% CI)	Heterogeneity		
							Q-Statistic P-Value	I ² (95% CI)	Publication Bias Test P-Value
<i>GSTM1 (deletion)</i>									
Benhamou, 2002 [121]	3	383	503	231 ^c	n/a	1.19 (0.88–1.62)	n/a	n/a	n/a
Present meta-analysis	4	494	615	289	0.242	1.25 (0.95–1.64)	0.292	20% (0%–61%)	0.509 ^f
Present pooled analysis ⁱ	6	487	694	362	0.307	1.32 (1.00–1.74)	0.376	7% (0%–40%)	0.421 ^f
East Asian									
<i>GSTM1 (deletion)</i>									
McWilliams, 1995 [125]	3	475	729	565 ^c	n/a	1.60 (1.25–2.13)	n/a	n/a	n/a
d'Errico, 1996 [127]	3	475	729	565 ^c	n/a	1.60 (1.26–2.04)	n/a	n/a	n/a
Houlston, 1999 [124]	2	659	827	697 ^c	n/a	1.38 (1.12–1.69)	n/a	n/a	n/a
d'Errico, 1999 [123]	6	n/a	n/a	n/a	n/a	1.45 (1.23–1.70)	n/a	n/a	n/a
Benhamou, 2002 [121]	12	1841	2787	2171 ^c	n/a	1.33 (1.06–1.67)	0.001	n/a	0.7 ^e
Shi, 2008 [128] (Chinese)	20	2235	2315	2104	0.462	1.49 (1.32–1.68)	0.030	40% (6%–62%)	0.058 ^e
Carlsten, 2008 [122]	42	6088	7222	6242 ^c	n/a	1.38 (1.24–1.55)	< 0.001	56% (34%–68%)	n/a
Present meta-analysis	25	4301	5278	4333	0.452	1.21 (1.05–1.39)	< 0.001	60% (42%–72%)	0.568 ^f
Present pooled analysis ⁱ	11	1536	1816	1434	0.428	1.25 (1.07–1.45)	0.222	22% (0%–55%)	0.661 ^f
<i>GSTT1 (deletion)</i>									
Raimondi, 2006 [129]	8	1364	1727	1575	0.510	1.28 (1.10–1.49)	0.09	n/a	0.16 ^e
Present meta-analysis	9	1596	2161	1723	0.470	1.19 (0.99–1.45)	0.052	48% (1%–73%)	0.279 ^f
Present pooled analysis ⁱ	8	1366	1749	1507	0.484	1.06 (0.88–1.27)	0.308	15% (0%–52%)	0.359 ^f
<i>GSTP1 (Ile105Val)</i>									
Cote, 2009 [130] (*G)	8	1332	1504	944 ^c	n/a	1.09 (0.93–1.28)	0.51	0% (0%–61%)	n/a
Present meta-analysis (*G)	11	1959	2267	1472	0.333	1.16 (1.01–1.32)	0.641	0% (0%–42%)	0.434 ^f
Present meta-analysis (GG)	8	1459	1541	105	0.043	1.39 (0.92–2.10)	0.635	0% (0%–9%)	0.809 ^f
Present Pooled analysis (AG) ^j	4	604	744	457	0.339	1.31 (1.03–1.67)	0.697	0% (0%–52%)	0.620 ^f
Present Pooled analysis (GG) ^j	4	399	533	41	0.044	1.36 (0.69–2.65)	0.77	0% (0%–42%)	0.771 ^f

	Number of Studies	Cases	Controls	n(minor)	f(minor)	OR (95% CI)	Heterogeneity			Publication Bias Test P-Value
							Q-Statistic P-Value	I ² (95% CI)		
White										
GSTM1 (deletion)										
McWilliams, 1995 ^a [125]	6	958	1249	1077 ^c	n/a	1.17 (0.98–1.40)	n/a	n/a	n/a	n/a
d'Errico, 1996 ^b [127]	8	1032	1139	1059 ^c	n/a	1.32 (1.12–1.57)	n/a	n/a	n/a	n/a
Houlston, 1999 [124]	12	1850	3924	2818 ^c	n/a	1.08 (0.97–1.22)	n/a	n/a	n/a	n/a
d'Errico, 1999 [123]	13	n/a	n/a	n/a	n/a	1.21 (1.06–1.39)	Present ^g	n/a	n/a	n/a
Benhamou, 2002 [121]	20	4039	6000	4899 ^c	n/a	1.10 (1.01–1.19)	0.5	n/a	n/a	0.8 ^e
Carlsten, 2008 [122]	36	9071	12237	10398 ^c	n/a	1.04 (0.97–1.11)	0.117	22% (0%–48%)	n/a	n/a
Present meta-analysis	42	11793	14868	13229	0.488	1.15 (1.06–1.26)	< 0.001	61% (48%–70%)	0.116 ^f	0.116 ^f
Present pooled analysis ⁱ	40	9006	13080	10760	0.487	1.05 (0.98–1.12)	0.001	46% (26%–61%)	0.133 ^f	0.133 ^f
GSTT1 (deletion)										
Raimondi, 2006 [129]	23	5585	7300	2380	0.185	0.99 (0.87–1.12)	0.02	n/a	0.42 ^e	0.42 ^e
Present meta-analysis	26	9454	11176	3837	0.184	1.01 (0.91–1.14)	0.003	49% (25%–65%)	0.965 ^f	0.965 ^f
Present pooled analysis ⁱ	28	6747	9809	3135	0.189	1.04 (0.94–1.14)	0.034	36% (5%–56%)	0.516 ^f	0.516 ^f
GSTP1 (Ile105Val)										
Cote, 2009 [130] (*G)	14	5959	5870	5560 ^c	n/a	1.00 (0.93–1.07)	0.23	21% (0%–53%)	n/a	n/a
Present meta-analysis (*G)	19	7186	7297	6795	0.470	1.00 (0.94–1.07)	0.221	19% (0%–49%)	0.120 ^f	0.120 ^f
Present meta-analysis (GG)	18	6988	7043	1460	0.178	1.02 (0.91–1.15)	0.151	26% (0%–54%)	0.799 ^f	0.799 ^f
Present Pooled analysis (AG) ^j	16	4180	4622	4336	0.493	1.02 (0.93–1.11)	0.758	0% (0%–26%)	0.722 ^f	0.722 ^f
Present Pooled analysis (GG) ^j	16	2627	2946	1107	0.199	0.96 (0.83–1.11)	0.322	12% (0%–53%)	0.430 ^f	0.430 ^f

Notes: n/a = information not available

^a includes 1 phenotype-based study

^b includes 3 phenotype-based studies

^c estimated using the *f_{minor}* from the corresponding present meta-analysis

^d Begg's test

^e Egger's test

^f Harbord test

^g Authors state that heterogeneity was present but do not report test results

^h Adjusted for age, gender, ancestry, smoking status and study

ⁱ Adjusted for age, gender, smoking status and study

Table 2

Tests for vulnerability to bias for the current meta-analyses of common *glutathione S-transferase (GST)* polymorphisms and lung cancer

	n	P-value			Observed Significant
		Harbord Test	Significance Chasing Bias	Expected Significant	
GSTM1 (deletion)					
Overall	85	0.011	0.132	9.6	14
African Descent	4	0.509	0.513	0.4	0
East Asian	25	0.568	0.002	3.0	8
White	42	0.116	0.920	4.8	5
Hospital Controls	31	0.497	0.010	1.2	3
Community Controls	50	0.010	0.566	9.4	11
GSTT1 (deletion)					
Overall	45	0.200	<0.001	1.8	8
East Asian	9	0.279	0.272	1.0	2
White	26	0.965	<0.001	0.8	4
Hospital Controls	17	0.812	0.001	0.5	3
Community Controls	26	0.079	0.001	1.4	5
GSTP1 (Ile105Val) GG					
Overall	31	0.400	0.125	1.3	3
East Asian	8	0.809	0.438	0.6	0
White	18	0.799	0.002	0.6	3
Hospital Controls	16	0.551	0.067	0.6	2
Community Controls	15	0.637	0.693	0.7	1
GSTP1 (Ile105Val) *G					
Overall	35	0.014	0.966	1.0	1
East Asian	11	0.434	0.871	0.9	1
White	19	0.120	0.438	0.6	0
Hospital Controls	17	0.358	0.766	0.7	1

P-value				
n	Harbord Test	Significance Chasing Bias	Expected Significant	Observed Significant
Community Controls	18	0.024	0.452	0.5
				0

Table 3

Assessment of cumulative evidence for the association of select *glutathione S-transferase (GST)* polymorphisms and lung cancer

	Amount	Replication	Protection From Bias	Cumulative Evidence
<i>GSTM1 (deletion)</i>				
Overall	A	B	C	Weak
African Descent	B	C	B	Weak
East Asian	A	C	C	Weak
White	A	C	C	Weak
<i>GSTT1 (deletion)</i>				
Overall	A	C	C	Weak
East Asian	A	C	B	Weak
White	A	C	C	Weak
<i>GSTP1 (Ile105Val) GG</i>				
Overall	A	C	B	Weak
East Asian	B	C	B	Weak
White	A	C	C	Weak
<i>GSTP1 (Ile105Val) *G</i>				
Overall	A	C	C	Weak
East Asian	A	A	B	Moderate
White	A	C	B	Weak

Table 4

Assessment of cumulative evidence from previous meta-analyses of commonly studied *glutathione S-transferase* (*GST*) polymorphisms and lung cancer

	Amount	Replication	Protection From Bias	Cumulative Evidence
Overall				
<i>GSTM1</i> (deletion)				
McWilliams, 1995 [125]	A	n/a	B	n/a
Houlston, 1999 [124]	A	A	C	Weak
d'Errico, 1999 [123]	n/a	C	B	Weak
Benhamou, 2002 [121]	A	C	B	Weak
Ye, 2006 [126]	A	B	C	Weak
Carlsten, 2008 [122]	A	C	C	Weak
<i>GSTT1</i> (deletion)				
Raimondi, 2006 [129]	A	C	C	Weak
Ye, 2006 [126]	A	C	C	Weak
<i>GSTP1</i> (I105V)				
Ye, 2006 [126]	A	C	C	Weak
Cote, 2009 [130] (*G)	A	C	C	Weak
African Descent				
<i>GSTM1</i> (deletion)				
Benhamou, 2002 [121]	B	C	B	Weak
East Asian				
<i>GSTM1</i> (deletion)				
McWilliams, 1995 [125]	B	n/a	B	n/a
d'Errico, 1996 [127]	B	n/a	B	n/a
Houlston, 1999 [124]	B	n/a	B	n/a
d'Errico, 1999 [123]	n/a	n/a	B	n/a
Benhamou, 2002 [121]	A	C	B	Weak
Shi, 2008 (Chinese) [128]	A	B	C	Weak
Carlsten, 2008 [122]	A	C	B	Weak
<i>GSTT1</i> (deletion)				
Raimondi, 2006 [129]	A	C	B	Weak
<i>GSTP1</i> (I105V)				
Cote, 2009 [130] (*G)	B	C	B	Weak
White				
<i>GSTM1</i> (deletion)				
McWilliams, 1995 ^a [125]	A	C	B	Weak
d'Errico, 1996 ^b [127]	A	n/a	B	n/a

	Amount	Replication	Protection From Bias	Cumulative Evidence
Houlston, 1999 [124]	A	C	B	Weak
d'Errico, 1999 [123]	n/a	C	B	Weak
Benhamou, 2002 [121]	A	A	C	Weak
Carlsten, 2008 [122]	A	C	B	Weak
<i>GSTT1 (deletion)</i>				
Raimondi, 2006 [129]	A	C	B	Weak
<i>GSTP1 (I105V)</i>				
Cote, 2009 [130] (*G)	A	C	B	Weak

^a includes 1 phenotype-based study

^b includes 3 phenotype-based studies

Note: n/a = insufficient information provided for grading