



Human Genome Epidemiology (HuGE) Review

Meta- and Pooled Analysis of *GSTP1* Polymorphism and Lung Cancer: A HuGE-GSEC Review

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Lung cancer is the most common cancer worldwide. Polymorphisms in genes associated with carcinogen metabolism may modulate risk of disease. Glutathione *S*-transferase pi (*GSTP1*) detoxifies polycyclic aromatic hydrocarbons found in cigarette smoke and is the most highly expressed glutathione *S*-transferase in lung tissue. A polymorphism in the *GSTP1* gene, an A-to-G transition in exon 5 (Ile105Val, 313A → 313G), results in lower activity among individuals who carry the valine allele. The authors present a meta- and a pooled analysis of case-control studies that examined the association between this polymorphism in *GSTP1* and lung cancer risk (27 studies, 8,322 cases and 8,844 controls and 15 studies, 4,282 cases and 5,032 controls, respectively). Overall, the meta-analysis found no significant association between lung cancer risk and the *GSTP1* exon 5 polymorphism. In the pooled analysis, there was an overall association (odds ratio = 1.11, 95% confidence interval: 1.03, 1.21) between lung cancer and carriage of the *GSTP1* Val/Val or Ile/Val genotype compared with those carrying the Ile/Ile genotype. Increased risk varied by histologic type in Asians. There appears to be evidence for interaction between amount of smoking, the *GSTP1* exon 5 polymorphism, and risk of lung cancer in whites.

Asian continental ancestry group; epidemiology; glutathione *S*-transferase pi; *GSTP1*; lung neoplasms; smoking

Abbreviations: CI, confidence interval; GSEC, Genetic Susceptibility to Environmental Carcinogens; *GSTP1*, glutathione *S*-transferase pi; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon.

Editor's note: This paper is also available on the website of the Human Genome Epidemiology Network (<http://www.cdc.gov/genomics/hugenet/>).

GENE AND GENE VARIANTS

Glutathione *S*-transferases are a supergene family of phase II enzymes present in many tissues, including lung (1). These enzymes catalyze the detoxification (through conjugation of glutathione) of a variety of reactive electrophilic compounds,

including many environmental carcinogens such as benzo [*a*]-pyrene and polycyclic aromatic hydrocarbons (PAHs) (2). The soluble glutathione *S*-transferases comprise 4 main gene classes, alpha (α), mu (μ), pi (π), and theta (θ) (3). Polymorphisms in the glutathione *S*-transferase pi gene, *GSTP1*, located on chromosome 11q13 in humans, have been associated with a reduction in enzymatic activity toward several substrates, including both chemotherapy agents (such as cisplatin, a common agent used in lung cancer treatment) and carcinogens found in tobacco smoke (4–9). Of the several thousand chemicals found in tobacco smoke, at least 50 are known to be carcinogenic, including PAHs, aromatic amines, and nitroso compounds (10).

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GSTP1 detoxifies PAHs and is the most abundant glutathione *S*-transferase isoform in the lungs (1). Two single nucleotide polymorphisms in *GSTP1* that result in a change in amino acids have been identified. A single nucleotide polymorphism in exon 5 (Ile105Val, 313A → 313G), the A-to-G transition that results in an amino acid change from isoleucine to valine, results in significantly lower conjugating activity among individuals who carry one or more copies of the *G* (guanine) allele (Ile/Val or Val/Val) compared with those who have the *A/A* (adenine/adenine; Ile/Ile) genotype (11–13). Having at least one copy of the *G* allele at this locus is also associated with increased levels of hydrophobic adducts in the lung and higher levels of PAH-DNA adducts in human lymphocytes (14). A second single nucleotide polymorphism in exon 6 (Ala114Val, 341C → 341T) results in an amino acid change from alanine to valine, which also appears to confer lower activity (11). Additionally, 3 functional haplotypes have been identified: GSTP1*A (105Ile;114Ala), GSTP1*B (105Val;114Ala), and GSTP1*C (105Val;114Val) (11). A meta-analysis published in 2006 of 5 polymorphisms in glutathione *S*-transferases found no association with *GSTP1* polymorphisms and lung cancer risk in 25 studies published prior to August 2005 (15). The present report includes additional studies published since that time and a pooled analysis examining the association between the *GSTP1* Ile105Val polymorphism and risk of lung cancer.

DISEASE

Lung cancer is the most common cancer worldwide and is responsible for 17.2% of all cancer-related deaths (16). In the United States, overall 5-year survival is about 16% for all stages combined (17). Data from the Surveillance, Epidemiology, and End Results Program indicate that if lung cancer is diagnosed in local stages, survival is significantly better, with overall 5-year survival rates of 49.1%, although fewer than 20% of lung cancers are diagnosed at this stage (17). Along with stage at diagnosis, prognosis also depends on histology type. Because of recent advances in technology that allow a more accurate diagnosis, it is difficult to analyze historic trends in histology types; however, adenocarcinomas of the lung have been increasing in proportion over the last 2–3 decades, especially among women (18). Overall, lung cancer survival rates have not significantly improved with advances in surgical, radiation, or chemotherapy treatments (17).

SMOKING

Cigarette smoking is the greatest risk factor associated with lung cancer development. In the United States and the United Kingdom, approximately 90% of all cases of lung cancer are attributable to current or former cigarette smoking, while the population attributable risks appear to be lower in Japanese populations, especially among women (population attributable risk for men = 67.0%, population attributable risk for women = 14.6%) (19, 20). Other Asian populations report similar risk of lung cancer due to smok-

ing (21, 22). Worldwide, smoking rates have been declining for the past several decades in developed countries and increasing significantly in developing countries. If these trends in smoking rates continue, by 2030, developing countries will account for an estimated 80% of the annual 8 million tobacco-related deaths, many of which will be due to lung cancers (23). Since the induction period for lung cancer appears to be decades, lung cancer will continue to be a major public health issue for generations to come. In addition, the negative health effects of cigarette smoking are not limited to current smokers. In a cohort of former smokers in the United States, 10 years after smoking cessation, the risk of lung cancer is 30%–50% lower than the risk for those who continue to smoke, but lifelong risk remains elevated compared with that for never smokers (24). Furthermore, while cigarette smoking remains the most significant modifiable risk factor, exposure to radon and other occupational and environmental risk factors is associated with development of lung cancer (25, 26).

MATERIALS AND METHODS

Associations and interactions

The association between the exon 5 (Ile105Val, 313A → 313G) polymorphism in *GSTP1* and lung cancer was examined through a meta-analysis of all published papers and a pooled analysis of selected published studies. A MEDLINE search was performed from January 1988 (when the structure of *GSTP1* was first described (27)) until March 31, 2007, using different combinations of “glutathione *S*-transferase pi,” “*GSTP1*,” “lung,” and “lung cancer,” restricting the analysis to “human” with no restriction on language. This search was supplemented by examining the reference sections of all selected papers, plus 2 reviews (28, 29) and a pooled analysis of polymorphisms in candidate genes associated with early-onset (<60 years of age at diagnosis) lung cancer (30).

After reviewing all abstracts ascertained from these searches, 34 articles containing information on *GSTP1* polymorphisms and lung cancer were identified. Eligible studies included the frequency of *GSTP1* genotypes or the crude odds ratio for the *GSTP1* exon 5 polymorphism and lung cancer. Both hospital- and population-based case-control studies were included in the analysis. Additionally, 1 study was a nested case-control study from a large cohort of physicians (31). Of the 34 articles selected, 4 were excluded because they were case-only analyses (32–35), 2 because of subject overlap with more recently published studies (36, 37), and 1 because it did not report the genotypes or unadjusted odds ratios (38). Two studies were included in the meta-analysis even though they contained a small number of overlapping subjects (39, 40). Two studies were found in both non-English and, later, English journals; therefore, the data from the English journals were used (41, 42). Only 4 studies reported on the exon 6 (Ala114Val, 341C → 341T) polymorphism, so we restricted the analysis to the exon 5 polymorphism in *GSTP1*. The final number of studies in the meta-analysis was 27, including 8,322 cases and 8,844 controls (31, 39–64) (Table 1).

Table 1. Description of the Studies Included in the Meta-analysis by Ethnicity and Year of Publication

First Author (Reference No.)	Year	No. of Cases	No. of Controls	Country	Mean Age of Cases, Years	Male Cases, %	Histology	Source of Controls	Matching Criteria
Asian studies									
Katoh (47)	1999	47	122	Japan	64.6 (SD, 10.3)	85	SqCC = 51.1%, AC = 25.5%, SCC = 19.1%, LCC = 4.3%	Hospital	None
Kihara (48)	1999	358	257	Japan	62.7 (range, 58–67)	100	SqCC = 33.3%, SCC = 20.4%, AC = 46.3%	Hospital	None
Kiyohara (41)	2000	86	88	Japan	63.8 (range, 35–86)	100	AC = 45.5%, SqCC = 7.9%, SCC = 13.9%, LCC = 4.7%, others = 7.0%	Hospital	None
Lin (51)	2003	198	332	Taiwan	64 (SD, 9)	72.2	AC = 53.0%, SCC = 42.0%, others = 5.0%	Hospital	None
Wang (60)	2003	112	119	China	56.5 (range, 37–75; SD, 8.1)	64.3	AC = 100%	Healthy	Age and gender (frequency matching)
Chan-Yeung (44)	2004	229	197	China	53.8 (SD, 14.3)	67.2	AC = 55.5%, SqCC = 16.6%, NSCLC = 19.2%, others = 8.7%	Healthy	Ethnicity
Chan (43)	2005	75	162	China	63 (no range or SD)	82	AC = 58.7%, SqCC = 41.3%	Hospital	Sex and age
Liang (42)	2005	227	227	China	62.5 (range, 31–86)	74	SqCC = 41.4%, AC = 58.6%	Hospital	Age, gender, and ethnicity (frequency matching)
White studies									
Ryberg (64)	1997	138	297	Norway	62.3 (SD, 10.3)	100	NSCLC = 100%	Healthy	Age, smoking, and ethnicity
Harris (45)	1998	178	199	Australia	66 (range, 38–91; SD, 9.1)	69	SqCC = 43.5%, AC = 18.2%, LCC = 7.7%, SCC = 7.1%, NSCLC = 1.9%, others = 21.6%	Healthy	None
Jourenkova-Mironova (46)	1998	150	172	France	58.4 (no range or SD)	93	SqCC = 65.3%, SCC = 34.7%	Hospital	Age and gender (frequency matching)
Saarikoski (55)	1998	206	293	Finland	62 (SD, 9)	79.8	SqCC = 45.2%, AC = 39.4%, others = 15.4%	Healthy	None
To-Figueras (59)	1999	164	200	Spain	59 (range, 32–87)	88.4	SCC = 34.8%, SqCC = 31.7, AC = 25.6%, LCC = 7.9%	Healthy	Gender
Risch (63)	2001	388	353	Germany	60.9 (range, 28–87)	75.8	SqCC = 44.0%, AC = 39.0%, LCC = 4.9%, SCC = 2.8%, others = 10.8%	Hospital	Ethnicity
Lewis (50)	2002	93	151	United Kingdom	67.4 (SD, 10.4)	63.8	SCC = 16.1%, SqCC = 34.4%, AC = 10.9, others and nonclassified = 38.7%	Hospital	None
Stucker (58)	2002	251	264	France	59.3 (SD, 9.6)	100	SqCC = 46.0%, SCC = 19%, AC = 24.0%, others = 11.0%	Hospital	Age, ethnicity, and gender (frequency matching)
Reszka (54)	2003	138	165	Poland	59.7 (no range or SD)	76.8	SqCC = 44.2%, SCC = 25.4%, NSCLC = 17.4%, AC = 8.7%, others = 4.3%	Hospital	Age and gender (frequency matching)
Wang (61)	2003	362	419	United States	60.9 (SD, 10.1)	52.4		Hospital	Age, gender, ethnicity, and smoking (frequency matching)
Schneider (56)	2004	446	622	Germany	64.4 (SD, 8.7)	90.6	SCC = 15.0%, LCC = 3.6%, AC = 25.1%, SqCC = 41.1%, others = 15.2%	Hospital	None

Larsen (49)	2006	1,095	626	Australia	63.4 (SD, 9.4)	71.9	AC = 45.2%, SqCC = 45.1%, others = 9.7%	Hospital	Age and smoking
Miller (52)	2006	1,921	1,343	United States	66 (no range or SD)	49.7	AC = 43.7%, SqCC = 21.4%, LCC = 7.3%, SCC = 9.2%, others = 18.4%	Healthy	None
Sorensen (57)	2007	429	766	Denmark	No mean age (range, 50–64)	53	SCC = 19%, AC = 32%, SqCC = 23%, others = 26%	Healthy	None
Other studies									
Perera (31)	2002	85	163	United States	61.8 (SD, 7.7)	100	AC = 36.0%, SCC = 16.9%, SqCC = 21.3%, LCC = 9.0%, others = 16.8%	Healthy	Smoking, age, and duration of follow-up
Nazar-Stewart (53)	2003	253	487	United States	No mean age (range, 18–74)	100	SqCC = 29.6%, SCC = 19.0%, NSCLC = 12.0%, LCC = 3.3%, AC = 35.0%, others = 1.1%	Healthy	Age and gender (frequency matching)
Yang (62)	2004	235	233	United States			SqCC = 13.5%, SCC = 7.6%, NSCLC = 13.1%, AC = 52.3%, LCC = 3.8%, others = 9.7%	Hospital	None
Cote (39)	2005	317	407	United States	42.1 (no range or SD)	50	SqCC = 11.7%, SCC = 13.2%, AC = 47.7%, LCC = 9.4%, NSCLC = 3.7%, others = 14.3%	Healthy	Race, sex, 5-year age group, and county of residence
Wenzlaff (40)	2005	141	180	United States	62.4 (range, 40–84; SD, 13.9)	57.8	SqCC = 15.7%, SCC = 6.6%, AC = 54.2%, LCC = 7.2%, others = 16.3%	Healthy	Race, sex, county of residence, and age (frequency matching)

Abbreviations: AC, adenocarcinoma; LCC, large-cell carcinoma; NSCLC, non-small cell lung cancer; SCC, small-cell carcinoma; SD, standard deviation; SqCC, squamous-cell carcinoma.

The pooled analysis was performed by using information collected from researchers who submitted information to the Genetic Susceptibility to Environmental Carcinogens (GSEC) database (www.gsec.net). The design of this study is explained in greater detail elsewhere (65). The primary goal of the GSEC project is to examine the associations between various cancers and genetic polymorphisms by using published and unpublished data solicited from collaborating investigators. These data are then cleaned and entered into a main database that is available to interested investigators for analyses related to the overall goals of the study. Each participating center provided information on the study design, source of controls, laboratory methods used for genotyping, source of DNA for genotyping, and response rates for cases and controls.

From the GSEC database, we selected all studies that included information on *GSTP1* and lung cancer. Only 3 studies (46, 55, 62) provided information on the exon 6 (Ala114Val, 341C → 341T) polymorphism; thus, as in the meta-analysis, all analyses reported on in this paper focus on the polymorphism in exon 5 only. Investigators who had not initially participated in the GSEC project were contacted and asked to provide their data for the pooled analysis. We were able to obtain data from 14 of the 27 studies (51.9%) included in the meta-analysis (Wenzlaff et al. (40) and Cote et al. (39), 2 studies from the same principal investigator, combined their data into a single data set, referred to as Cote et al. in the pooled analyses). An additional study not included in the meta-analysis was used in the pooled analysis (32). The number of subjects included in the published reports may differ somewhat from the numbers in this pooled analysis because the GSEC data set includes some unpublished data. The total number of subjects included in the pooled analysis was 4,282 cases and 5,032 controls.

Statistical analysis

For the meta-analysis, study-specific crude odds ratios and 95% confidence intervals were calculated to estimate the association between the exon 5 (Ile105Val, 313A → 313G) polymorphism in *GSTP1* and lung cancer based on the reported frequencies of *Ile/Ile*, *Ile/Val*, and *Val/Val* genotypes in cases and controls. Odds ratios and 95% confidence intervals were calculated for individuals carrying 1 (*Ile/Val*) or 2 (*Val/Val*) valine alleles compared with individuals carrying 2 isoleucine (*Ile/Ile*) alleles. Homogeneity among studies was tested by using the Breslow-Day test for homogeneity, and, when not statistically significant (based on $P > 0.05$), a fixed-effects model was used for the meta-analysis (66). Heterogeneity was also quantified by using the *I*-squared statistic (67). To test for publication bias, both the Begg and Mazumdar adjusted rank correlation test (68) and the Egger et al. regression asymmetry test (69) were performed. Funnel plots were also created to graphically display evidence of publication bias, and sensitivity analyses to examine the influence of each study on the overall estimate were also performed.

Because the frequency of the polymorphism differs by ethnicity, studies were stratified by the reported ethnicity

of the subject population, with 14 studies in whites, 8 studies in Asians, and 5 studies in populations comprising a mix of other ethnic groups, including whites, African Americans, and Mexican Americans. Crude odds ratios and 95% confidence intervals were also estimated by source of controls (healthy or hospital) and then by both ethnicity and control source.

Summary odds ratios and 95% confidence intervals were calculated for all studies combined, as well as for each ethnic group (white, Asian, other), control source (healthy or hospital), and then by both ethnicity and control source. All analyses were performed by examining risk associated with carrying at least 1 valine allele compared with *Ile/Ile* genotypes at *GSTP1* exon 5 (Ile105Val, 313A → 313G). All meta-analyses were performed with the STATA software package (Stata Corporation, College Station, Texas).

To reduce the potential for confounding associated with ethnicity, the pooled analyses were performed separately for the 2 ethnic groups with the greatest number of studies and participants (whites and Asians). Chi-squared tests were conducted to test for Hardy-Weinberg equilibrium in the reported genotype frequencies among the controls in the pooled analysis, after stratification by ethnicity. Study-specific crude odds ratios and 95% confidence intervals for lung cancer and *GSTP1* genotype were estimated by using unconditional logistic regression models. As with the meta-analysis, odds ratios and 95% confidence intervals were calculated for individuals carrying 1 or 2 *105Val* alleles compared with individuals carrying 2 *Ile* alleles. Heterogeneity between studies was tested by using the Breslow-Day test for homogeneity. Crude and adjusted odds ratios were calculated for each ethnic group, as well as stratified by control source (healthy and hospital), smoking status (nonsmoker/ever smoker), and histologic type (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). Regarding studies that provided information on pack-years of smoking, this paper presents adjusted odds ratios and 95% confidence intervals for nonsmokers and by tertile of numbers of pack-years of smoking. Regression lines were fitted to test for linear trend between the odds ratios and amount smoked. To formally test for interactions between amount smoked and genotype, cross-product terms were created and tested in the logistic model. The cutpoints for the tertiles of amount smoked were calculated from the controls who smoked. All pooled analyses were performed by using SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The genotype frequencies for the *GSTP1* exon 5 polymorphism varied according to ethnicity. When ethnicity-specific individual data from the controls were used in the pooled analysis, 46.9% of whites carried the *Ile/Ile* genotype, 41.8% carried the *Ile/Val* genotype, and 11.3% carried the *Val/Val* genotype (data not shown). In Asians, the respective percentages were 66.8%, 30.2%, and 3.0%. These frequencies are similar to those for the *GSTP1* exon 5 polymorphism found in other control populations for differ-

ent cancer sites (70, 71). Among all controls in the pooled analysis, the genotype frequencies were in Hardy-Weinberg equilibrium for both Asians ($P = 0.38$) and whites ($P = 0.17$).

Meta-analysis

For all 27 studies combined, the meta-odds ratio was 1.04 (95% confidence interval (CI): 0.97, 1.10), with no apparent heterogeneity between the studies (P for Q test = 0.27) (data not shown). Thus, a fixed-effects model versus a random-effects model was used. Sensitivity analysis was conducted to examine the influence of each study. Exclusion of the study by Miller et al. (52) resulted in a summary odds ratio of 1.08 (95% CI: 1.00, 1.15) (data not shown).

Two tests were performed to detect publication bias. Publication bias was not identified when Begg's test was performed ($P = 0.10$), but the Egger et al. (69) regression asymmetry test, which tends to suggest the presence of publication bias more frequently than Begg's test, did suggest that publication bias was present ($P = 0.02$). To adjust for this bias, a trim and fill method developed by Duval and Tweedie (72) was implemented. Trimming was based on the fixed-effects model, and the adjusted estimate obtained by using a random-effects model was an odds ratio of 0.99 (95% CI: 0.91, 1.07). Thus, the overall conclusion that there is no association between lung cancer and carrying at least 1 valine allele remained unchanged.

Because of the ethnicity-specific differences in genotype frequency, study-specific crude odds ratios and 95% confidence intervals, stratified by ethnicity, are presented in Figure 1 for individuals carrying at least 1 *105Val* (*Ile/Val* and *Val/Val* vs. *Ile/Ile*) allele. Among studies of whites, only 1 study (64) reported a statistically significant association (odds ratio (OR) = 1.70, 95% CI: 1.13, 2.57). The remaining 13 studies were clustered around the null effect (6 below 1.0 and 7 above 1.0) and were not statistically significant. None reported a negative association. The overall odds ratio for studies in whites was 1.00 (95% CI: 0.93, 1.07). No heterogeneity was identified between the 14 studies included ($P = 0.23$, data not shown). Among the 8 studies in Asian populations, none were statistically significant, with 4 slightly below the null and 4 slightly above the null. The overall odds ratio in Asian studies was 1.09 (95% CI: 0.93, 1.28). No heterogeneity was identified between the 8 studies included ($P = 0.51$, data not shown). In the studies that reported other ethnicities, 4 of the 5 had odds ratio estimates above the null, and 1 was slightly below the null. The overall risk associated with lung cancer and carrying at least 1 valine allele was statistically significant in studies not limited to a single ethnicity, with an odds ratio of 1.19 (95% CI: 1.01, 1.40). No heterogeneity was identified between the 5 studies included ($P = 0.49$, data not shown).

No statistically significant differences were identified when studies were stratified by control source (healthy or hospital, data not shown). Stratifying by both ethnicity and control source resulted in sparse strata for "Asian and healthy" (2 studies) and "other and hospital" (1 study). For other strata, no statistically significant associations between genotype and lung cancer were identified, nor were

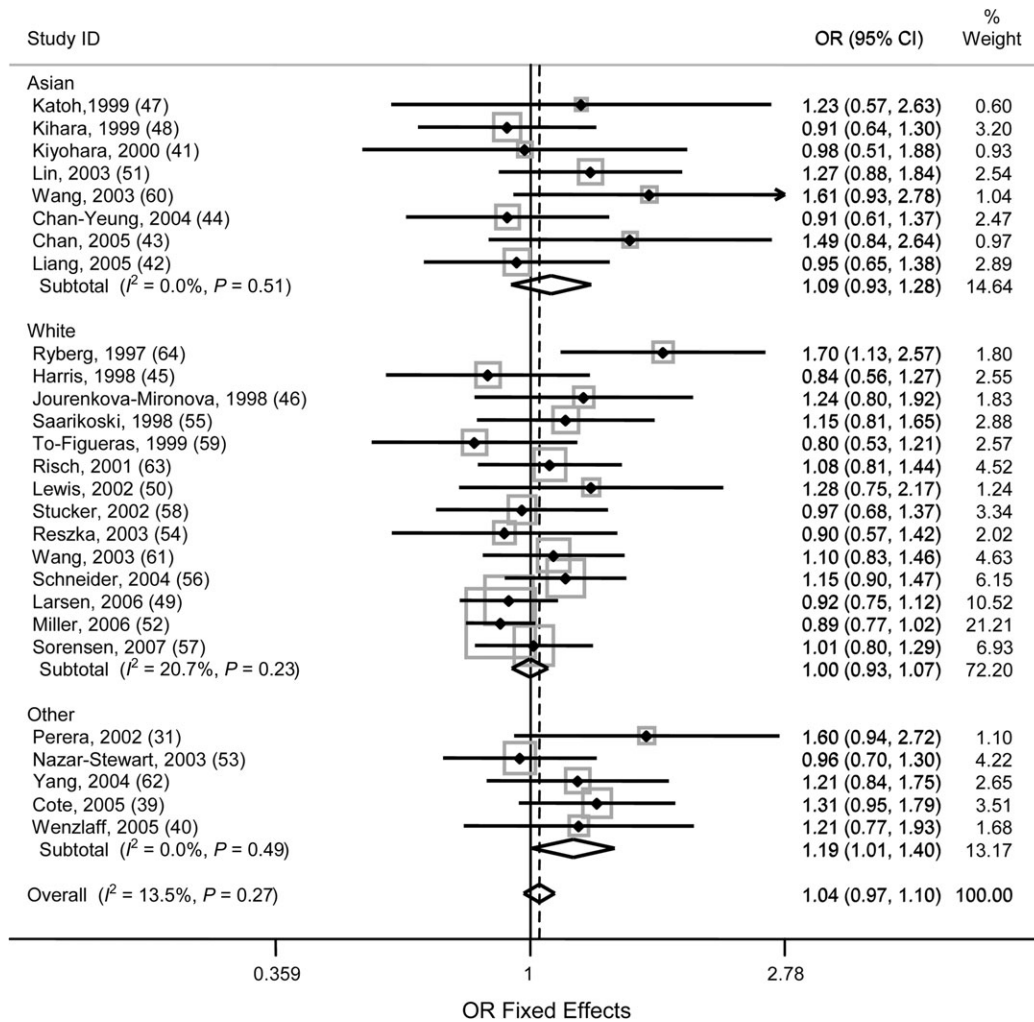


Figure 1. Study-specific (first author, year of publication (reference no.)) and meta-log odds ratios (ORs) with 95% confidence intervals (CIs) for a glutathione S-transferase pi gene (*GSTP1*) exon 5 (Ile105Val, 313A → 313G) polymorphism for individuals carrying at least 1 valine allele (*Ile/Val* and *Val/Val* vs. *Ile/Ile*), by ethnicity. The shading around the point estimate reflects the weight of the study in the meta-analysis. The dashed line indicates the overall OR. ID, an assigned study identifier for each study population; Ile, isoleucine.

there any significant differences between strata (data not shown).

Pooled analysis

Table 2 describes the 15 studies included in the pooled analysis. Crude odds ratios and 95% confidence intervals for the association between carrying at least 1 *I05Val* allele at *GSTP1* exon 5 are presented. The overall pooled odds ratio associated with carrying at least 1 valine allele is 1.11 (95% CI: 1.03, 1.21) (Table 2).

Table 3 presents ethnicity-specific crude and adjusted odds ratios and 95% confidence intervals for the association between carrying at least 1 *I05Val* allele at *GSTP1* exon 5 and lung cancer. In the crude analysis or after adjusting for study ID (an assigned study identifier for each study population), age, sex, or smoking status (ever/never), no in-

creased risk of lung cancer was seen for whites carrying at least 1 valine allele compared with those with the *Ile/Ile* genotype. We found no differences in estimates based on whether the control source was healthy or hospital based. There were also no statistically significant differences in risk when subjects were stratified by ever smoker or nonsmoker status; after adjusting for study ID, age, and sex among nonsmokers; and after adjusting for study ID, age, sex, and number of pack-years of smoking among participants who had ever smoked (Table 3).

Regarding Asian study subjects, those who carried at least 1 *GSTP1 I05Val* allele compared with those with the *Ile/Ile* genotype were shown to be at increased risk of lung cancer in both crude analysis (OR = 1.34, 95% CI: 1.07, 1.67) and after adjustment for study ID, age, sex, and smoking status (OR = 1.35, 95% CI: 1.07, 1.70) (Table 3). With the exception of 4 cases and 10 controls, these findings were all based

Table 2. Description of Studies Included in the Pooled Analysis: Study-Specific and Overall Crude Odds Ratios and 95% Confidence Intervals for the Association Between *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphisms and Lung Cancer, by Continent, Country, and Year of Publication

First Author, Year (Reference No.)	No. of Cases	No. of Controls	Country of Study Origin	Source of Controls	Val/Val and Ile/Val vs. Ile/Ile	
					Crude OR	95% CI
Asia						
Wang, 2003 (60)	112	119	China	Hospital	1.61	0.93, 2.78
Liang, 2005 (42)	227	227	China	Hospital	1.22	0.84, 1.78
Kiyohara, 2000 (41)	62	80	Japan	Hospital	1.18	0.58, 2.42
Lin, 2003 (51)	198	332	Taiwan	Hospital	1.27	0.88, 1.84
Australia						
Larsen, 2006 (49)	1,095	626	Australia	Hospital	0.92	0.75, 1.12
Europe						
Sorensen, 2007 (57)	429	765	Denmark	Healthy	1.01	0.80, 1.28
Saarikoski, 1998 (55)	199	293	Finland	Healthy	1.49	1.03, 2.16
Jourenkova-Mironova, 1998 (46)	150	172	France	Hospital	1.24	0.80, 1.92
Schneider, 2004 (56)	480	630	Germany	Hospital	1.09	0.86, 1.39
Butkiewicz, 1999 (32)	165	326	Poland	Healthy	0.94	0.65, 1.37
Reszka, 2003 (54)	217	251	Poland	Hospital	0.93	0.64, 1.33
To-Figueras, 1999 (59)	173	202	Spain	Healthy	1.01	0.67, 1.51
Lewis, 2002 (50)	93	151	United Kingdom	Hospital	1.28	0.75, 2.17
North America						
Yang, 2004 (62)	235	234	United States	Healthy	1.22	0.85, 1.76
Cote, 2005 (39)	447	624	United States	Healthy	1.31	1.02, 1.69
Total	4,282	5,032			1.11	1.03, 1.21

Abbreviations: CI, confidence interval; *GSTP1*, glutathione *S*-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

on studies with hospital-recruited controls; thus, in this paper, these data are not presented for healthy controls. After we stratified by ever/never smoking status, the association between genotype and lung cancer was significant among only Asian nonsmokers (OR = 1.52, 95% CI: 1.09, 2.13) after we adjusted for study ID, age, and sex (Table 3).

Risk of lung cancer and *GSTP1* exon 5 polymorphism by amount smoked. The large sample of whites for whom we had individual pack-year information (92.3% of the cases and 79.7% of the controls) allowed us to perform an analysis stratified by number of pack-years of cigarette smoking. Table 4 shows the relation among amount smoked, genotype, and lung cancer risk. For nonsmokers, no statistically significant association was seen between carrying at least 1 *105Val* allele and lung cancer risk after we adjusted for study ID, sex, and age (OR = 1.17, 95% CI: 0.92, 1.50). For participants who smoked for 1–28 pack-years, the odds of having lung cancer were 1.23-fold higher among those carrying at least 1 valine allele compared with those with the *Ile/Ile* genotype (95% CI: 1.00, 1.52) after we adjusted for study ID, sex, and age. Among moderate smokers who smoked for 28.01–48 pack-years, risk was not increased

(OR = 1.01, 95% CI: 0.82, 1.24), and, among those with the heaviest reported pack-years of smoking (≥ 48.01), carrying at least 1 *105Val* allele was associated with a decreased risk of lung cancer compared with that for those with *Ile/Ile* genotypes after adjustment for study ID, age, and sex (OR = 0.83, 95% CI: 0.67, 1.03). We found no statistically significant linear trend between risk of lung cancer due to genotype and amount smoked ($P = 0.16$) when nonsmokers were included. There was a statistically significant trend between amount smoked and risk of lung cancer due to genotype ($P = 0.05$) when only ever smokers were examined. The overall effect of interactions between amount of smoking and genotype on lung cancer risk was marginally significant ($P = 0.08$, data not shown). When we used nonsmoking and *Ile/Ile* as the reference group, the group of heavy smokers with *Ile/Val* or *Val/Val* had a significantly increased risk ($P = 0.03$, Table 4).

Risk of lung cancer and *GSTP1* exon 5 polymorphism by histologic type and ethnicity. Crude and adjusted odds ratios and 95% confidence intervals for the association between carrying at least 1 valine allele and lung cancer risk are presented stratified by histologic type and ethnicity in Table 5. Among whites, there were no statistically

Table 3. Odds Ratios and 95% Confidence Intervals for the Association Between a *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphism (Ile/Val and Val/Val vs. Ile/Ile) and Lung Cancer in the Pooled Analysis, Stratified by Smoking Status and Ethnicity

Ethnic Group	No. of Cases	No. of Controls	OR	95% CI
Asian				
All studies: unadjusted	603	768	1.34	1.07, 1.67
All studies: adjusted ^a	603	768	1.35	1.07, 1.70
Hospital controls: unadjusted	599	758	1.32	1.06, 1.65
Hospital controls: adjusted ^a	599	758	1.32	1.05, 1.68
Smoker: unadjusted	287	298	1.23	0.88, 1.72
Smoker: adjusted ^b	287	298	1.17	0.83, 1.66
Smoker: adjusted ^c	48	49	1.06	0.41, 2.75
Nonsmoker: unadjusted	254	390	1.49	1.08, 2.07
Nonsmoker: adjusted ^b	254	390	1.52	1.09, 2.13
White				
All studies: unadjusted	3,538	4,098	1.07	0.98, 1.17
All studies: adjusted ^a	3,490	4,077	1.05	0.95, 1.16
Healthy controls: unadjusted	1,503	2,268	1.12	0.98, 1.27
Healthy controls: adjusted ^a	1,497	2,254	1.15	0.99, 1.33
Hospital controls: unadjusted	2,035	1,830	1.02	0.90, 1.16
Hospital controls: adjusted ^a	1,993	1,823	1.00	0.87, 1.14
Smoker: unadjusted	3,044	2,737	1.02	0.93, 1.14
Smoker: adjusted ^b	3,035	2,729	1.05	0.95, 1.17
Smoker: adjusted ^c	2,809	2,181	1.00	0.89, 1.13
Nonsmoker: unadjusted	465	1,352	1.18	0.95, 1.45
Nonsmoker: adjusted ^b	455	1,348	1.17	0.92, 1.49

Abbreviations: CI, confidence interval; *GSTP1*, glutathione S-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

^a Adjusted for study ID (an assigned study identifier for each study population), age, sex, and smoking status (ever/never).

^b Adjusted for study ID, age, and sex.

^c Adjusted for study ID, age, sex, and pack-years of smoking.

significant differences in risk associated with the *GSTP1* gene polymorphism and adenocarcinoma, squamous cell carcinoma, or small cell carcinoma. In Asian populations, individuals carrying at least 1 valine allele were at increased risk of adenocarcinoma (OR = 1.33, 95% CI: 1.02, 1.74) after adjustment for study ID, age, sex, and smoking status. Risk of squamous cell lung cancer was increased for Asians carrying at least 1 valine allele (OR = 1.44, 95% CI: 1.05, 1.98), but the odds ratio was no longer statistically significant after adjusting for study ID, age, sex, and smoking status (OR = 1.36, 95% CI: 0.95, 1.94).

DISCUSSION

The meta-analysis found no association (OR = 1.04, 95% CI: 0.97, 1.10) between lung cancer risk and carrying 1 or

more *GSTP1* 105Val alleles. This finding is similar to that of another meta-analysis of 25 studies with a combined 6,221 cases and 7,602 controls, which reported an unadjusted odds ratio of 1.04 (95% CI: 0.99, 1.09) for the association between lung cancer and carrying the *GSTP1* exon 5 Ile105Val variant (15). After stratifying by the ethnicity of study subjects, studies that included subjects of various ethnic backgrounds (i.e., the study had both African-American and white participants) reported an increase in risk associated with carrying at least 1 105Val allele compared with those with Ile/Ile genotypes.

The pooled analysis did identify an overall statistically significant increase in lung cancer risk associated with carrying at least 1 valine allele, with an odds ratio of 1.11 (95% CI: 1.03, 1.21). When the studies were stratified by subject ethnicity, this association was seen among Asian subjects but not among white subjects. A pooled analysis of whites diagnosed with early-onset lung cancer (under age 60 years) also reported no association between lung cancer risk and the *GSTP1* exon 5 genotype (30). Unlike the white control populations, who were recruited through either population-based methods or hospitals, almost all Asian controls were recruited by using hospital-based methods. Among Asians, this association between the Ile/Val and Val/Val genotypes and lung cancer risk was strongest among nonsmokers and those with adenocarcinoma. The higher prevalence of adenocarcinoma of the lung in Asians, particularly among women nonsmokers, was identified decades ago (73) and has received more attention recently with the success of using epidermal growth factor receptor tyrosine kinase inhibitors in these populations (74).

The results from the meta-analyses suggest no association between lung cancer risk and the *GSTP1* exon 5 polymorphism, either overall or stratified by race/ethnicity, whereas the results from the pooled analysis suggest risk of carrying at least 1 105Val allele is associated with increased risk of lung cancer overall and also in Asians. Examination of the 95% confidence intervals associated with the risk estimates suggests that these apparently discrepant results are not statistically significant. In addition, the pooled analysis did not contain subjects from all studies included in the meta-analysis, and vice versa, and the pooled analysis allowed for individual adjustment by age, sex, and smoking status. It has been suggested that results from individual subject data that allow for adjustment of confounders, such as the pooled analysis presented here, may best summarize results of multiple studies (75).

We found an interaction between *GSTP1* exon 5 genotype and personal smoking history. Among whites, those classified as "light" smokers (1–28.00 pack-years) were at increased risk of lung cancer if they carried the Ile/Val or Val/Val genotype compared with those with the Ile/Ile genotype. Conversely, heavy-smoking (≥48.01 pack-years) whites carrying the Ile/Val or Val/Val genotypes were at decreased risk compared with those with the Ile/Ile genotype. This interaction may explain some of the variability seen between populations with different recruitment criteria (i.e. early-onset cases who likely do not have as extensive smoking histories) and highlights the need to investigate the gene-environment interactions between genotype and amount smoked (i.e., pack-years).

Table 4. Odds Ratios and 95% Confidence Intervals for the Association Between a *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphism (Ile/Val and Val/Val vs. Ile/Ile) and Lung Cancer in Whites in the Pooled Analysis, Stratified by Pack-years of Smoking

Smoking Status	No. of Cases		No. of Controls		OR ^a	95% CI	P Trend	P Value ^b
	Ile/Ile	Ile/Val or Val/Val	Ile/Ile	Ile/Val or Val/Val				
Nonsmoker	204	251	656	692	1.17	0.92, 1.50	0.16 ^c	Reference
1–28 pack-years	279	386	459	539	1.23	1.00, 1.52		0.09
28.01–48 pack-years	490	557	292	334	1.01	0.82, 1.24		0.57
≥48.01 pack-years	505	592	228	329	0.83	0.67, 1.03	0.05 ^d	0.03

Abbreviations: CI, confidence interval; *GSTP1*, glutathione S-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

^a Adjusted for study ID (an assigned study identifier for each study population), age, and sex.

^b P value for nonsmokers and with Ile/Ile as the reference group, adjusted for study ID, age, and sex.

^c P-value test for trend among all 4 categories.

^d P-value test for trend among smokers only.

Laboratory evidence suggests that carrying a *105Val* allele results in reduced *GSTP1* enzymatic activity in the cell (11–13). These characterizations, while important for developing a hypothesis about the biologic mechanisms through which carcinogenesis evolves, do not necessarily represent what is occurring in the environment of the human lung. The seemingly protective effect of the *Val/Val* or *Ile/Val* genotype in heavy smokers identified in this pooled analysis does not directly support reduced activity associated with carrying the *Val* allele because it would be expected that those with reduced *GSTP1* activity would be at increased risk of malignant transformation after exposure to

carcinogens. The continuous assault from heavy smoking may change cellular activity in ways we are currently unable to assess in the human lung. A recent murine model, using *GSTP*-null mice, found a significantly higher number of adenomas in null mice compared with wild-type mice after exposure to 3 PAHs (76). When adducts in these mice were examined, there were significant differences in the number of adducts formed depending on the PAH they were exposed to, with 1 PAH resulting in no increase in adducts, suggesting that an alternative protective pathway in response to this specific exposure exists. While this study in mice is the first known in vivo model showing the importance of *GSTP1* in

Table 5. Odds Ratios and 95% Confidence Intervals for the Association Between a *GSTP1* Exon 5 (Ile105Val, 313A → 313G) Polymorphism (Ile/Val and Val/Val vs. Ile/Ile) and Lung Cancer in the Pooled Analysis, Stratified by Histologic Type and Ethnicity

Ethnic Group	Unadjusted				Adjusted ^a			
	No. of Cases	No. of Controls	OR	95% CI	No. of Cases	No. of Controls	OR	95% CI
White								
Adenocarcinoma	1,048	4,098	1.08	0.95, 1.24	1,043	4,077	1.041	0.90, 1.21
Squamous cell carcinoma	1,394	4,098	1.00	0.86, 1.09	1,377	4,077	0.994	0.87, 1.14
Small cell carcinoma	399	4,098	1.11	0.90, 1.36	393	4,077	1.103	0.91, 1.41
Asian								
Adenocarcinoma	384	768	1.32	1.02, 1.70	384	768	1.33	1.02, 1.74
Squamous cell carcinoma	206	768	1.44	1.05, 1.98	206	768	1.36	0.95, 1.94
Small cell carcinoma	5	768	0.50	0.06, 4.52	5	768	0.44	0.04, 4.56
Total								
Adenocarcinoma	1,496	5,032	1.05	0.94, 1.18	1,491	5,009	1.11	0.98, 1.26
Squamous cell carcinoma	1,617	5,032	1.02	0.91, 1.14	1,600	5,009	1.03	0.91, 1.16
Small cell carcinoma	412	5,032	1.22	1.00, 1.49	406	5,009	1.12	0.90, 1.39

Abbreviations: CI, confidence interval; *GSTP1*, glutathione S-transferase pi gene; Ile, isoleucine; OR, odds ratio; Val, valine.

^a Adjusted for study ID (an assigned study identifier for each study population), sex, smoking (ever/never), and age.

lung carcinogenesis, it is also apparent that the role of glutathione *S*-transferase has yet to be fully elucidated. In this study, we were not able to explore the other major roles that GSTP1 is thought to have in the cell, including resistance to chemotherapy (77), because we did not have information on chemotherapy or other exposures that might help clarify this gene-environment interaction.

The variation in risk associated with lung cancer and GSTP1 exon 5 genotypes between Asians and whites is likely due to a number of factors, including different exposures in the populations. For example, studies in Asian women nonsmokers suggest that exposure to the carcinogens found in cooking oils increases risk of lung cancer (78, 79). Further studies of gene-environment interactions in lung cancer should also include occupational risk factors such as ionizing radiation (through radon exposure), asbestos, chromium, and arsenic (25, 80). The ability to examine only a small number of potential confounding variables is a limitation to both pooled and meta-analysis studies. It is also possible that publication bias accounts for some of the difference in risk seen between the Asian and white populations. It has been shown that a large proportion of Chinese literature does not reach PubMed and that studies that do are more likely than non-Chinese studies to be statistically significant and report larger measures of effect (i.e., odds ratios) (81). Thus, our findings may be a result of this publication bias, and the inability to include the entire collection of literature is a limitation of this analysis.

Other potential limitations include the presence of heterogeneity between studies. We tested for heterogeneity and performed a sensitivity analysis to determine whether a particular study or studies were a source of heterogeneity. Various amounts of data regarding smoking behaviors were collected, so we were unable to examine number of years of smoking or number of cigarettes smoked per day; therefore, our analyses were restricted to use of the 2 most commonly collected variables: pack-years of use or dichotomous classification as never or ever smokers. Additionally, pack-years of smoking was missing for approximately 20% of individuals identified as ever smokers. There were also differences in how the subjects were identified (hospital based or population), the histologic types of lung cancers included in the studies, the types of tissues used to extract DNA, and genotyping methods. When possible, we stratified by source of controls and histologic type of cancer. It was not feasible to control for the variation in pathologic reports of histology type that may occur by region or country.

LABORATORY TESTS

The methods used for determining GSTP1 exon 5 genotypes are described in each article. The majority of the studies included in the analyses used genomic DNA extracted from blood, although 3 studies included DNA extracted from blood or lung tissue (32, 43, 49); 2 studies included DNA extracted from blood, lung tissue, or buccal samples (39, 40); and 1 study used blood and bronchial lavage (50). Polymerase chain reaction–based restriction fragment length polymorphism methods were the most

frequently cited technique to determine GSTP1 exon 5 genotypes.

POPULATION TESTING

The evidence to date regarding the polymorphism in GSTP1 exon 5 and lung cancer risk is insufficient to suggest testing at the population level.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

Overall, the meta-analysis found no significant association between lung cancer and the GSTP1 exon 5 (Ile105Val) polymorphism for individuals carrying at least 1 105Val allele. No association was seen when we stratified by ethnicity in white or Asian populations. In the 5 studies that included more than 1 ethnic group, the meta-analysis suggested that an association between lung cancer and carrying at least 1 valine allele (Ile/Val and Val/Val vs. Ile/Ile) was statistically significant, with an odds ratio of 1.19 (95% CI: 1.01, 1.40), although this finding may be the result of population stratification.

In the pooled analysis, there was a statistically significant, mild overall association (OR = 1.11, 95% CI: 1.03, 1.21) between lung cancer and the GSTP1 exon 5 (Ile105Val) polymorphism for individuals carrying a Val/Val or Ile/Val genotype compared with those carrying the Ile/Ile genotype. After stratification by ethnicity and adjustment for study ID, age, sex, and smoking status, increased risk associated with the Val/Val or Ile/Val genotypes and lung cancer was seen in Asian populations only. Among Asians, this risk was highest for nonsmokers and those with adenocarcinoma of the lung.

There is evidence for interaction among amount of smoking (i.e., pack-years), the GSTP1 exon 5 (Ile105Val) polymorphism, and risk of lung cancer in whites. The odds of lung cancer associated with carrying at least 1 valine allele appear to decrease as the amount of pack-years of smoking increases, with heavy smokers who carry a Ile/Val or Val/Val genotype at decreased risk of lung cancer compared with their heavy-smoking counterparts with the Ile/Ile genotype. This finding highlights the importance of context when studying gene-environment interactions and clearly shows the need to collect detailed exposure information on all study participants, because gene expression, and risk of lung cancer, may differ by the environmental exposure.

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