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GST genotypes and lung cancer susceptibility in Asian populations with indoor air pollution exposures: a meta-analysis

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Abstract

About half of the world's population is exposed to smoke from heating or cooking with coal, wood, or biomass. These exposures, and fumes from cooking oil use, have been associated with increased lung cancer risk. Glutathione S-transferases play an important role in the detoxification of a wide range of human carcinogens in these exposures. Functional polymorphisms have been identified in the *GSTM1*, *GSTT1*, and *GSTP1* genes, which may alter the risk of lung cancer among individuals exposed to coal, wood and biomass smoke and cooking oil fumes. We performed a meta-analysis of six published studies (912 cases; 1063 controls) from regions in Asia where indoor air pollution makes a substantial contribution to lung cancer risk, and evaluated the association between the *GSTM1* null, *GSTT1* null, and *GSTP1 105Val* polymorphisms and lung cancer risk. Using a random effects model, we found that carriers of the *GSTM1* null genotype had a borderline significant increased lung cancer risk (odds ratio (OR), 1.31; 95% confidence interval (CI), 0.95–1.79; $p=0.100$), which was particularly evident in the summary risk estimate for the four studies carried out in regions of Asia that use coal for heating and cooking (OR, 1.64; 95% CI, 1.25–2.14; $p=0.0003$). The *GSTT1* null genotype was also associated with an increased lung cancer risk (OR, 1.49; 95% CI, 1.17–1.89; $p=0.001$), but no association was observed for the *GSTP1 105Val* allele. Previous meta- and pooled-analyses suggest at most a small association between the *GSTM1* null genotype and lung cancer risk carried out in populations where the vast majority of lung cancer is attributed to tobacco, and where indoor air pollution from domestic heating and cooking is much less than in developing Asian countries. Our results suggest that the *GSTM1* null genotype may be associated with a more substantial risk of lung cancer in populations with coal exposure.

Keywords

coal; heating and cooking; nonsmoking lung cancer; *GSTM1*; *GSTT1*; *GSTP1*

1. Introduction

About half of the world's population or 3 billion people, almost all living in developing countries such as China and India, use coal, wood, and biomass for heating and cooking [1]. The annual global health burden of indoor air pollution from solid fuel use is estimated to be 1.6 million deaths and over 38.5 million disability-adjusted life years [2]. This equates to 3%

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of the total global disease burden. Coal, wood, and biomass smoke, and cooking oil fumes have been associated with a variety of health outcomes [3–13], the most notable being lung cancer [14–16]. Recently, an IARC Working Group met to assess the potential carcinogenicity of household use of solid fuels (coal and biomass) and of high-temperature frying. This comprehensive review concluded that indoor emissions from household combustion of coal are carcinogenic to humans (Group 1), while indoor emissions from household combustion of biomass fuel (primarily wood) and emissions from high-temperature frying are probably carcinogenic to humans (Group 2A) [17].

The associations observed between indoor air pollution and lung cancer risk are not surprising since fuel combustion products are known to contain carcinogens. In-home smoky coal combustion increases levels of sulfur dioxide, carbon monoxide, fluorine, and known carcinogens such as polycyclic aromatic hydrocarbons (PAHs), benzene, arsenic, and formaldehyde [18;19]. The corresponding concentrations of benzo(a)pyrene, an indicator of PAHs, from indoor exposures to coal smoke due to cooking and heating can be comparable in some instances to coke oven occupational exposure levels [20]. Cooking oils are commonly heated to high temperatures in woks in Asian cultures and frequently contain numerous mutagens and carcinogens [21]. Peanut oil for example, releases 12 mutagenic compounds when heated [22]. Soybean oil, sunflower oil, rapeseed oil, and lard induce oxidative stress and have been found to have genotoxic properties [23;24].

Genetic variation in enzymes responsible for activating and detoxifying PAHs or other carcinogens present in these environments may alter susceptibility in individuals exposed to coal, wood, and biomass smoke, as well as to cooking oil fumes. This variation could result in significant inter-individual differences in risk at the same level of exposure. Glutathione S-transferases (GSTs) are involved in the metabolic detoxification of reactive electrophilic compounds, such as PAHs, that are formed during incomplete combustion of carbon-based fuels such as coal and wood [18;25]. There are five known classes of GST enzymes in humans that are important in the metabolism of xenobiotics: GSTA (α), GSTM (μ), GSTP (π), GSTS (σ), and GSTT (θ) [26]. Genetic variants in three of these genes (*GSTM1*, *GSTT1*, and *GSTP1*) have been extensively studied in relation to risk of lung cancer [27]. The *GSTM1* and *GSTT1* enzymes have been shown to inhibit cellular damage from cytotoxic substances in *in vitro* studies [28]. The most common functional polymorphism in both the *GSTM1* and *GSTT1* genes is a deletion, which leads to a lack of function and decreased ability to detoxify electrophilic carcinogens efficiently [29]. Similarly, subjects carrying the *GSTP1* Ile105Val Val/Val genotype have a lower ability to detoxify electrophilic compounds than subjects carrying the wildtype genotype, Ile/Ile [29]. Variants in these genes may reduce an individual's ability to detoxify PAHs and could increase risk for various cancers, including lung cancer [30;31].

The association between lung cancer and the *GSTM1* deletion, *GSTT1* deletion, and *GSTP1* Ile105Val polymorphisms have been studied and reviewed in meta-analyses and a pooled analysis, with most work focusing on the *GSTM1* null genotype [32–35]. After consideration of potential publication bias, there is little evidence that the *GSTM1* null genotype is associated with risk of lung cancer, either among ever-smokers or never-smokers [32;33].

To summarize findings on genetic susceptibility to cancer in populations exposed to coal, wood, and biomass smoke and cooking oil fumes, a systematic review of studies evaluating *GSTM1*, *GSTT1*, and *GSTP1* genotypes and risk of lung cancer in Asian populations, where exposure to indoor air pollution is ubiquitous and in some instances present at relatively high levels, was carried out.

Methods

Studies examining the association between *GSTM1*, *GSTT1*, and *GSTP1* genotypes and susceptibility to lung cancer with indoor air pollution exposures were identified by searching the PubMed and Science Citation Index databases. Studies in English published between January 1966 and July 2006, were identified through searches that used keywords associated with relevant genes (e.g., *GSTM1*, *GSTT1*, *GSTP1*) in combination with words related to indoor air pollution (e.g., indoor air pollution, coal, wood, biomass, cook fume, cook oil) and words related to lung cancer (lung cancer, lung neoplasm). For this analysis, only studies in populations carried out in Asian populations with exposure to coal, wood, and biomass smoke, and cooking oil fumes were considered. Studies were then selected using a three tiered exclusion/inclusion approach. First, studies in which tobacco smoke was the primary cause of lung cancer in the study population were excluded. This included studies that were comprised of only smokers or those in which the lung cancer risk was attributed to smoking in the conclusion of the article. Of the remaining studies, those with either a quantitative or qualitative exposure assessment of coal, wood, or biomass smoke, or cooking oil fumes were included. Finally, for studies that did not carry out an assessment of these exposures, those that had potential indoor air pollution exposures were included if one of the following criteria were met: (1) the article explicitly stated that the subjects' lung cancer was attributed to exposure from coal, wood, or biomass smoke, or cooking oil fumes or (2) exposure to coal, wood, or biomass smoke, or cooking oil fumes was previously shown to play an important role in the etiology of lung cancer in the same study subjects in previously published reports referenced by the article. For the latter, the respective previous studies were reviewed and the primary exposure was determined to be either smoke from coal, wood, or biomass smoke, or cooking oil fumes.

Studies were identified by a search using “*GSTM1*” and “lung cancer” in combination with “coal”, “wood”, “biomass”, or “cooking”. The papers were then reviewed to identify case-control studies in Asian populations. A total of 11 case-control studies [36–46] were found. Five studies [36–40] were excluded because there was no exposure assessment and no evidence provided in the study that indoor air pollution from any source made an important contribution to lung cancer. The remaining 6 studies [41–46] satisfied all inclusion criteria, and data related to study design, geographic location, population setting, case selection, control selection, genotyping method, Hardy-Weinberg equilibrium, type of exposure, exposure assessment, smoking, and number of genotyped cases and controls were extracted.

Overall, one study utilized a quantitative exposure assessment [41], one a qualitative exposure assessment [42], and the presence of indoor air pollution was determined for four studies [43–46]. Lan *et al.*'s [41] study was in Xuan Wei, where more than 95% of the population was exposed to coal and a substantial portion of lung cancer has been attributed to indoor coal use [14;47]. Similarly more than 95% of the population in the Shenyang study reported by Yang *et al.* [45] was also exposed to coal [45;48], and epidemiologic studies have shown that coal exposure is associated with increased risk of lung cancer in Shenyang [49–51]. Approximately 80% of the population in Changsha City in the Hunan study for nonsmoking lung cancer cases and controls by Chen *et al.* [43] were exposed to coal up until 1997 (Han-chun Chen, personal communication), and about 80% of the population in the Beijing study by Wang *et al.* [46] used coal in their homes (Jingwen Wang, personal communication). Although formal risk estimates have not been published for coal use and lung cancer in these two studies, it is highly likely that this exposure is associated with risk of lung cancer [17]. Furthermore, the primary source of fuel for household use in Thailand up to 1- year before Pisani *et al.*'s [42] study began was wood and charcoal [52]. Finally, the primary fuel sources in Hong Kong up until recently were kerosene and liquid petroleum gas [53]. Since combustion from these fuel sources is not known to be associated with lung cancer, while an excess of lung cancer risk has been attributed to cooking oil fume exposure in Chan-Yeung *et al.*'s [44] and other study populations in Hong

Kong [54;55], the primary exposure for Chan-Yeung *et al*'s [44] Hong Kong study population was classified as cooking oil fumes. In conclusion, the four studies [41;43;45;46] carried out in mainland China were classified as having primarily coal exposure, the study in Thailand [42] was classified as wood and charcoal exposure, and the study in Hong Kong [44] was classified as cooking oil fume exposure.

All statistical analyses were performed using STATA version 9 (College Station, Texas). Heterogeneity among studies was determined using a χ^2 -based Q-statistic [56]. For the only two possible genotypes for *GSTM1* and *GSTT1* status, the unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) from each study were used to estimate summary odds ratios. For *GSTP1*, the unadjusted odds ratio for the dominant genetic model (*Val/Val* + *Val/Ile* vs. *Ile/Ile*) for each study was calculated and used to estimate summary odds ratios. Since there was some evidence of heterogeneity in preliminary analyses, summary odds ratios were determined using a random effects model in which the contribution of each study was weighted by the inverse of the sum of the inter- and intra-study variance. Summary odds ratios were also calculated after stratification by control selection methodology (population-based only) and type of exposure (coal smoke only). Finally, publication bias was assessed via funnel plots and the Begg's test [57].

3. Results

Six studies evaluating *GSTM1*, *GSTT1*, and *GSTP1* genotypes and their association with risk of lung cancer met the inclusion criteria for the meta-analysis [41–46]. Table 1 provides a summary of each gene's name and chromosomal location. All studies were case-control by design and five studies used population-based controls [41;43–46], while one used a combination of population- and hospital-based controls [42] (Table 2). One study was in a rural setting [41], three in an urban setting [44–46], and two in a mixed setting, consisting of both rural and urban [42;43]. In four studies, coal was the primary fuel exposure [41;43;45;46], in one study cooking oil fumes was the exposure [44], and in the final study, exposure to both charcoal and wood was present [42].

All six studies evaluated the association of the *GSTM1* null genotype and risk of lung cancer for a total of 912 cases and 1063 controls [41–46]. The average sample size was 152 cases and 177 controls and the studies were found to be statistically heterogeneous ($p = 0.01$). Heterogeneity in the summary risk estimate was decreased somewhat by removing the only study that utilized hospital- and population-based controls, which also had not been carried out in China ($p = 0.04$). There was no evidence of heterogeneity ($p = 0.31$) in the summary risk estimate based on the four studies with coal exposure. Four of the studies found the *GSTM1* null genotype to be associated with an increased risk of lung cancer, which was statistically significant in two studies [41;43]. No association was observed by the other two studies. In our meta-analysis, carriers of the *GSTM1* null genotype were found to have a borderline significant increased risk of lung cancer compared to those with at least one allele present (OR, 1.31; 95% CI, 0.95–1.79; $p = 0.100$) (Figure 1a). The *GSTM1* null genotype was significantly associated with an increased risk of lung cancer among the five studies that used population-based controls (OR, 1.44; 95% CI, 1.03–2.00; $p = 0.033$) and among the four studies that identified coal exposure as an important contributor to lung cancer (OR, 1.64; 95% CI, 1.25–2.14; $p = 0.0003$) (Table 3).

Of the six studies, four evaluated the *GSTT1* null genotype and lung cancer risk for a total of 560 cases and 635 controls [41;43;44;46]. The average sample size was 140 cases and 159 controls and there was not evidence of heterogeneity ($p = 0.36$). All four of these studies used population-based controls and found an elevated risk of lung cancer associated with the *GSTT1* null genotype, which was statistically significant in two studies [43;44]. The increased

risk of lung cancer observed among carriers of the *GSTT1* null genotype compared to those with at least one allele present was statistically significant for this meta-analysis (OR, 1.49; 95% CI, 1.17–1.89; $p = 0.0001$) (Figure 1b). The *GSTT1* null genotype was associated with a significant increased risk of lung cancer among the three studies that reported coal exposure (OR, 1.45; 95% CI, 1.00 – 2.09; $p = 0.048$) (Table 3).

Only three studies evaluated the *GSTP1 Ile105Val* (rs947894) polymorphism and lung cancer risk for a total of 438 cases and 513 controls, with an average sample size of 146 cases and 171 controls per study [43;44;46]. There was no evidence of heterogeneity ($p = 0.77$). Due to the reporting limitations in the original studies, only the dominant genetic model (*Ile/Val* + *Val/Val* vs *Ile/Ile*) could be evaluated. All three of the studies found a non-significant increased risk of lung cancer associated with the *GSTP1 105Val* allele. In this meta-analysis, carriers of the *Val* allele were found to have a non-significant increased risk of lung cancer (OR, 1.24; 95% CI, 0.94–1.64; $p = 0.136$) (Figure 1c). Due to the low number of studies and one study that did not report if the genotype frequencies in the control subjects were in Hardy-Weinberg equilibrium [43], meaningful conclusions could not be drawn from the stratifications of study characteristics for the *GSTP1 105Val* allele. Of note, the odds ratio for *GSTP1 Val* variant was elevated among the two studies with coal exposure (OR, 1.41; 95% CI, 0.96–2.06; $p = 0.076$) compared to the summary odds ratio for all studies (Table 3).

Finally, there was no evidence of publication bias for the *GSTM1* ($p = 0.85$), *GSTT1* ($p = 0.50$), and *GSTP1* ($p = 0.60$) studies (Figure 2), or for the four studies that evaluated *GSTM1* genotype and coal exposure ($p = 0.73$).

4. Discussion

We carried out what is, to the best of our knowledge, the first systematic review of the growing literature on genetic susceptibility of lung cancer in Asian populations with exposure to coal, wood, and biomass smoke, and cooking oil fumes. This meta-analysis found that the *GSTM1* null genotype may be associated with an increased risk of lung cancer in populations exposed to these sources of indoor air pollution from cooking and heating, with no evidence of publication bias. Further, the association between the *GSTM1* null genotype and lung cancer was particularly evident in studies carried out in populations that used coal for home heating and cooking (OR, 1.64; 95% CI, 1.25 – 2.14; $p = 0.0003$).

In the most recent meta-analysis of 119 studies, almost all of which were carried out in populations where tobacco use is likely to be the primary cause of lung cancer, the *GSTM1* null genotype was associated with a significantly increased lung cancer risk (OR, 1.18; 95% CI, 1.14–1.23) [32]. However, there was strong evidence of publication bias from positive findings in smaller studies (Begg's test $p < 0.0001$). Restriction to the five studies with greater than 500 cases yielded no association with the *GSTM1* null genotype (OR = 1.04; 95% CI, 0.95–1.14). A pooled analysis of 21 studies found similar risks for ever-smokers (OR, 1.1; 95% CI, 1.0 – 1.2) and never-smokers (OR, 1.1; 95% CI, 0.8 – 1.4) [33]. In sub-analyses for studies carried out in Asia, there was a non-significant increase in risk for ever-smokers (OR, 1.2; 95% CI, 0.9 – 1.7) and a non-significant decrease in risk for never-smokers (OR, 0.7; 95% CI, 0.4 – 1.4). However, these estimates were based on a relatively small number of study subjects [33]. Overall, the weight of evidence suggests that the *GSTM1* null genotype is associated with at most a small risk of lung cancer. The results of our meta-analysis suggest that this genetic variant may play a more substantial role in lung cancer among populations that use coal for home heating and cooking in certain parts of Asia.

There is further evidence supporting the unique characteristics of lung cancer attributed to coal exposure, with evidence that risk may be driven in great part by PAHs, which are substrates

for detoxification by *GSTM1* [30;31]. The *GST* family members' ability to catalyze the detoxification of PAHs varies for *GSTM1*, *GSTT1*, and *GSTP1* [58–60]. Both *in vivo* and *in vitro* studies have concluded that the *GSTM1* null and *GSTP1* 105Val genotypes decrease the body's PAH detoxification efficiency [58;59], while the *GSTT1* null genotype seems to not play an important role in PAH metabolism [31]. Since *GSTM* enzymes have a 20-fold higher reaction velocity than the *GSTP* enzymes, it is conceivable that the *GSTM1* gene may have greater importance for detoxifying PAHs [61]. DeMarini *et al.*, reported that 76% of the *p53* mutations in a series of 24 tumor samples from nonsmoking women in Xuan Wei, China, where exposure to combustion products of smoky coal accounts for the vast majority of lung cancer, were G to T transversions, consistent with the mutational spectrum of PAHs. In lung cancer tumors from the IARC *TP53* mutation database (version DataR4, April 2000), this transversion was present in only 29% of tumors from smokers ($p = 0.09$ versus smoky coal users) and 11% of tumors from non-smokers ($p = 0.0003$ versus smoky coal users) [62]. This mutational spectrum suggests that PAHs may play a more important role in the pathogenesis of lung cancer in Xuan Wei, China, than their role in the etiology of lung cancer among smokers and nonsmokers in populations without smoky coal exposure. Exposure to smoky coal has also been associated with increased PAH–DNA adducts levels in Xuan Wei, China [63]. Similarly, 58% of the placentas and 77.8% of peripheral and cord white blood cells of women from Xuan Wei burning smoky coal in homes without chimneys were positive for PAH–DNA adducts compared to only 5% and 33.3% of controls, respectively [64]. In addition, the *GSTM1* null genotype has been associated with the presence of PAH–DNA adducts in lung tissue (OR, 8.6; 95% CI, 1.03–100) [65]. Further, one study included in our meta-analysis [41] found that the risk of lung cancer increased 1.2 fold (95% CI, 0.8 – 1.9) for *GSTM1* positive subjects per 100 tons of lifetime smoky coal use and increased 2.4 fold per 100 tons for those with the *GSTM1* null genotype (95% CI, 1.6 – 3.9) (p for interaction = 0.05). Although the *GSTT1* null genotype was associated with increased risk of lung cancer in our meta-analysis, there was some evidence of an effect among coal users, which is a bit unexpected given that this enzyme may not play an important role in PAH metabolism [31].

Our meta-analysis has several limitations. Although no evidence of publication bias was observed, our assessment was based on relatively few studies and publication bias can not be definitively ruled out. Secondly, the crude odds ratios from each study were used to estimate summary odds ratios and it is possible that some uncontrolled confounding was present. However, with the exception of age and race, confounding is unlikely to be a major source of bias in genetic studies. To support this assertion, a meta-analysis of the limited number of studies that reported adjusted odds ratios in this study was conducted and found similar results.

In conclusion, we found evidence that the *GSTM1* null genotype was associated with a statistically significant increased risk of lung cancer in Asian populations exposed to coal smoke, based on a meta-analysis of four studies. Although consistent with the biology of PAH metabolism and the known function of the *GSTM1* null genotype, this finding should be considered hypothesis generating and requires replication in additional and larger studies. It is also important that future studies include a detailed assessment for exposure to fuels from all possible sources and by all potential routes, and for amount as well as frequency and other characteristics of use. Such studies will also provide an opportunity to identify other genetic factors that may modify the effect of exposure to combustion products of coal and other indoor fuel sources and fumes, as well as other important co-factors.

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Figure 1. Odds ratio and 95% confidence intervals for the association between lung cancer and (a) *GSTM1* null, (b) *GSTT1* null, and (c) *GSTP1* Ile105Val (*Ile/Val* + *Val/Val* vs *Ile/Ile*) genotypes, using random effects.

(a)

(b)

(c)

Figure 2.

Begg's funnel plot with pseudo 95% confidence limits for studies evaluating the association between lung cancer and (a) *GSTM1* null, (b) *GSTT1* null, and (c) *GSTP1* Ile105Val (*Ile/Val* + *Val/Val* vs *Ile/Ile*) genotypes, using random effects.

Table 1

Description of glutathione S-transferase polymorphisms.

Gene	Name	Chromosomal Location	SNP rs number	Nucleotide change	Amino Acid Change	Studies
<i>GSTM1</i>	glutathione S-transferase M1	1p13.3		gene deletion		[41–46]
<i>GSTP1</i>	glutathione S-transferase pi	11q13	rs947894	Ex5-24A>G	Ile105Val	[43;44;46]
<i>GSTT1</i>	glutathione S-transferase theta 1	22q11.23		gene deletion		[41;43;44;46]

Table 2

Characteristics of case-control studies included in the meta-analysis.

Study	Region	Population Setting	Controls		Number Genotyped		HWE?	Exposure	Smokers		
			Source	Matching Factors	Cases	Controls			Cases (%)	Controls (%)	
<i>GSTM1</i> null (gene deletion)											
Lan, 2000	Yunnan	Rural	Population-based	gender, age, village, type fuel	122	122	N/A	Coal	70 (57%)	69 (57%)	
Wang, 2003	Beijing	Urban	Population-based	gender, age	112	119	N/A	Coal	48 (43%)	48 (40%)	
Chan-Yeung, 2004	Hong Kong	Urban	Population-based	none	229	197	N/A	Cooking Oil	130 (57%)	79 (40%)	
Yang, 2004	Shenyang	Urban	Population-based	age	186	139	N/A	Coal	111 (55.5%)	54 (37.5%)	
Chen, 2006	Hunan	Mixed	Population-based	gender, age	97	197	N/A	Coal	0 (0%)	0 (0%)	
Pisani, 2006	Thailand	Mixed	Population- and hospital-based	gender, age	166	289	N/A	Charcoal/Wood	93 (44%)	145 (36%)	
				TOTAL	912	1063					
<i>GSTT1</i> null (gene deletion)											
Lan, 2000	Yunnan	Rural	Population-based	gender, age, village, type fuel	122	122	N/A	Coal	70 (57%)	69 (57%)	
Wang, 2003	Beijing	Urban	Population-based	gender, age	112	119	N/A	Coal	48 (43%)	48 (40%)	
Chan-Yeung, 2004	Hong Kong	Urban	Population-based	none	229	197	N/A	Cooking Oil	130 (57%)	79 (40%)	
Chen, 2006	Hunan	Mixed	Population-based	gender, age	97	197	N/A	Coal	0 (0%)	0 (0%)	
				TOTAL	560	635					
<i>GSTP1</i> Ile105Val (rs947894)											
Wang, 2003	Beijing	Urban	Population-based	gender, age	112	119	Yes	Coal	48 (43%)	48 (40%)	
Chan-Yeung, 2004	Hong Kong	Urban	Population-based	none	229	197	Yes	Cooking Oil	130 (57%)	79 (40%)	
Chen, 2006	Hunan	Mixed	Population-based	gender, age	97	197	*	Coal	0 (0%)	0 (0%)	
				TOTAL	438	513					

* Not reported

Table 3

Summary odds ratios (OR) and 95% confidence intervals (CI) for *GSTM1*, *GSTT1*, and *GSTP1* genotypes and lung cancer risk stratified by study characteristics, using the random effects model.

	All studies	Population-based Controls	Coal Smoke Exposure
<i>GSTM1</i> null	1.31 (0.95–1.79)	1.44 (1.03–2.00)	1.64 (1.25–2.14)
# of studies	6	5	4
Cases/Controls (n)	912/1063	746/774	517/577
<i>GSTT1</i> null	1.49 (1.17–1.89)	1.49 (1.17–1.89)	1.45 (1.00–2.09)
# of studies	4	4	3
Cases/Controls (n)	560/635	560/635	331/438
<i>GSTP1</i> Ile105Val*	1.24 (0.94–1.64)	1.24 (0.94–1.64)	1.41 (0.96–2.06)
# of studies	3	3	2
Cases/Controls (n)	438/513	438/513	209/316

* *GSTP1* Ile105Val and Val105Val versus *GSTP1* Ile105Ile