Human Genome Epidemiology (HuGE) Review

Meta- and Pooled Analysis of GSTT1 and Lung Cancer: A HuGE-GSEC Review


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Lung cancer is the most common malignancy in the Western world, and the main risk factor is tobacco smoking. Polymorphisms in metabolic genes may modulate the risk associated with environmental factors. The glutathione S-transferase theta 1 gene (GSTT1) is a particularly attractive candidate for lung cancer susceptibility because of its involvement in the metabolism of polycyclic aromatic hydrocarbons found in tobacco smoke and of other chemicals, pesticides, and industrial solvents. The frequency of the GSTT1 null genotype is lower among Caucasians (10–20%) than among Asians (50–60%). The authors present a meta- and a pooled analysis of case-control, genotype-based studies that examined the association between GSTT1 and lung cancer (34 studies, 7,629 cases and 10,087 controls for the meta-analysis; 34 studies, 7,044 cases and 10,000 controls for the pooled analysis). No association was observed between GSTT1 deletion and lung cancer for Caucasians (odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.87, 1.12); for Asians, a positive association was found (OR = 1.28, 95% CI: 1.10, 1.49). In the pooled analysis, the odds ratios were not significant for either Asians (OR = 0.97, 95% CI: 0.83, 1.13) or Caucasians (OR = 1.09, 95% CI: 0.99, 1.21). No significant interaction was observed between GSTT1 and smoking on lung cancer, whereas GSTT1 appeared to modulate occupational-related lung cancer.

disease susceptibility; epidemiology; genes; genetic predisposition to disease; GSTT1; lung neoplasms; meta-analysis

Abbreviations: CI, confidence interval; GSEC, Genetic Susceptibility to Environmental Carcinogens; GST, glutathione S-transferase; GSTT1, glutathione S-transferase theta 1 gene; OR, odds ratio.

**GENE**

The glutathione S-transferase (GST) supergene family consists of phase II detoxifying enzymes catalyzing several reduced glutathione-dependent reactions with compounds containing an electrophilic center (1). The GST family comprises at least eight classes of GST isoenzymes: alpha, mu, pi, sigma, theta, kappa, omega, and zeta (2). Genetic polymorphisms have been described in all these classes (3). The soluble GSTs exist as dimeric proteins of approximately 25 kDa; they are highly expressed, constituting up to 4 percent of the total soluble proteins (4).

Two theta-class GSTs, GSTT1 and GSTT2, have been identified in the human liver, and the corresponding genes are localized in the same region on human chromosome 22, specifically in the subband 22q11.2 (5, 6). GSTT1 enzymes show important differences in their catalytic activity compared with other GSTs: they have lower glutathione binding activity, with increased catalytic efficiency (7, 8). Theta is considered the most ancient of the GSTs, and theta-like GSTs are found in almost all organisms investigated (2). The encoded GSTT1 human subunit is about 25,300 Da (9); the gene is 8.1 kb long (10).

Among the GST substrates, there are several environmental carcinogens found in food, air, or medications, such as polycyclic aromatic hydrocarbons, found in combustion products, diet, and tobacco smoke (11). Polycyclic aromatic hydrocarbons are activated by members of the phase I cytochrome P-450 supergene family to epoxide-containing metabolites (e.g., benzo[a]pyrene-7,8-diol-9,10-oxide), which are substrates for the mu, alpha, and pi GST classes. GSTT1 is an interesting candidate gene for lung cancer susceptibility because of its involvement in the metabolism of chemicals such as methylating agents, pesticides, and industrial solvents (2). In vitro studies suggest that both GSTT1 and GSTM1 enzymes protect cells from the toxic products of phase I detoxification reactions (12, 13).

However, GSTT1-catalyzed reactions can also increase the toxicity of some compounds, such as dichloromethane (2). GSTs also conjugate isothiocyanates, which are potent inducers of enzymes that detoxify environmental mutagens (14). The conjugation process diverts the isothiocyanates from the enzyme induction pathway into excretion (15), leading to elimination of these anticarcinogenic substances (16) and thus decreasing their potential chemopreventive effect (17).

**GENE VARIANTS**

The most common polymorphism in GSTT1 consists of a deletion of the whole gene, resulting in the lack of active enzyme (18). Complete deletion at the GSTT1 locus (19) was hypothesized by observing the phenotypic variation in glutathione-related detoxification of halomethanes by human erythrocytes, resulting in “conjugator” and “nonconjugator” phenotypes (20). Recently, another less common polymorphism (Thr104Pro) in the GSTT1 gene was described that also results in a nonconjugator phenotype (21).

The frequency of the GSTT1 deletion varies among different populations (22). In particular, the prevalence of the GSTT1 null genotype is lower among Caucasians (10–20 percent) compared with Asians (50–60 percent) (23). The frequency of the GSTT1 null polymorphism in the controls included in the present meta- and pooled analyses is similar to what was previously published (22): 18.7 percent (meta-analysis) and 19.0 percent (pooled analysis) in Caucasians; 53.8 percent and 53.6 percent, respectively, in Asians; and
19.4 percent (meta-analysis only) for other ethnic groups (Latinos, African Americans, and mixed). The frequency of the GSTT1 deletion is graphically presented in figure 1 for each study included in the meta-analysis and is stratified according to ethnicity. Among Caucasians, the frequency of the deletion is significantly lower in northern European countries (Sweden, Denmark, and Finland) than elsewhere in Europe, as previously reported (22, 24). The frequency of the GSTT1 deletion according to geographic area is 52.2 percent (meta-analysis) and 51.2 percent (pooled analysis) in Asians, 17.3 percent (meta-analysis) and 18.0 percent (pooled analysis) in Europeans, and 21.7 percent (meta-analysis) and 27.0 percent (pooled analysis) in North Americans.

Gene function

The main function of the GST enzymes is detoxification of electrophiles by conjugation to glutathione. A wide variety of both endogenous electrophilic substrates, such as by-products of reactive oxygen species activity, and exogenous electrophilic substrates, have been identified (2, 25). GSTT1 also catalyzes the detoxification of oxidized lipids and DNA (2, 8, 26). Halogenated organic compounds, for example, the ethylene dibromide, p-nitrobenzyl chloride (27), p-nitrophenethyl bromide (28), methyl chloride, and methyl iodide (29, 30), are known substrates for GSTT1. The GSTT1+ phenotype catalyzes conjugation of dichloromethane to glutathione, a metabolic pathway that has been shown to be more mutagenic than GSTT1 null in Salmonella typhimurium mutagenicity tester strains (31) and was suggested to be responsible for the carcinogenicity of dichloromethane in the mouse (32). The consequence of the null genotype is reduced or null conjugation activity and, in most cases, an inability to efficiently eliminate electrophilic carcinogens (19, 33).

DISEASE

Lung cancer is the most common malignancy in the Western world. Although incidence has apparently now peaked in the United States and most of Europe, increasing incidence and mortality is observed in several developing countries. More than a million new cases were diagnosed in 2000, accounting for 12.3 percent of all new cases of cancer, and more than a million subjects died of lung cancer in the same period, accounting for 17.8 percent of all cancer deaths (34). The case fatality (ratio of mortality to incidence), which is an indicator of prognosis, is 0.89, the third worst after that for the pancreas and liver (35).

The main histologic types of lung cancer are squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma. The first three are also referred to as non–small cell lung carcinomas. Squamous cell carcinoma, large cell carcinoma, and small cell carcinoma are more strongly associated with smoking than other histologic types. The histologic characteristics of lung cancer have changed in recent decades: the frequency of adenocarcinoma has risen, while that of squamous cell carcinoma has declined (36–39).

Smoking

The main risk factor for lung cancer is tobacco smoking. Worldwide, the population attributable fraction of lung cancer mortality due to smoking is 79 percent for men and
<table>
<thead>
<tr>
<th>Authors (reference no.), year</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Country</th>
<th>Mean age in years (range/SD*)</th>
<th>Male (%)</th>
<th>Histology</th>
<th>Source of controls</th>
<th>Matching criteria</th>
<th>Crude OR*, †</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reszka et al. (59), 2005‡</td>
<td>119</td>
<td>138</td>
<td>Poland</td>
<td>58.9 (range, 30–78)§</td>
<td>74.6§</td>
<td>SqCC – 36.6%, SCC – 25.0%, NSCC – 18.6%, AC – 8.9%, others – 8.9%</td>
<td>Hospital</td>
<td>Age and gender</td>
<td>0.51</td>
<td>0.28, 0.94</td>
</tr>
<tr>
<td>Alexandrie et al. (60), 2004‡</td>
<td>524</td>
<td>530</td>
<td>Sweden</td>
<td>54.9 (range, 19–88)</td>
<td>71.8</td>
<td>SqCC – 31.6%, SCC – 19.5%, AC – 27.5%, LCC – 3.1%, others – 8.8%, nonclassified – 9.5%</td>
<td>Healthy</td>
<td>None</td>
<td>0.92</td>
<td>0.65, 1.31</td>
</tr>
<tr>
<td>Belogubova et al. (61), 2004</td>
<td>167</td>
<td>663</td>
<td>Russia</td>
<td>57.6 (range, 18–95; SD, 7.9)</td>
<td>54.3</td>
<td>SqCC – 52.7%, SCC – 12.6%, NSCC – 11.4%, AC – 23.3%</td>
<td>Healthy</td>
<td>None</td>
<td>0.94</td>
<td>0.61, 1.46</td>
</tr>
<tr>
<td>Hamrs et al. (62), 2004</td>
<td>110</td>
<td>119</td>
<td>United States</td>
<td>58.5 (SD, 10.3)</td>
<td>52.4</td>
<td>No information</td>
<td>Healthy</td>
<td>Age, ethnicity, and gender (frequency matching)</td>
<td>1.55</td>
<td>0.84, 2.96</td>
</tr>
<tr>
<td>Schneider et al. (63), 2004‡</td>
<td>446</td>
<td>622</td>
<td>Germany</td>
<td>63.9 (range, 20–96; SD, 10.1)</td>
<td>94.0</td>
<td>SqCC – 41.1%, SCC – 15.0%, AC – 25.1%, LCC – 3.6%, others – 12.2%</td>
<td>Hospital</td>
<td>None</td>
<td>0.89</td>
<td>0.65, 1.23</td>
</tr>
<tr>
<td>Sobti et al. (64), 2004‡</td>
<td>100</td>
<td>76</td>
<td>India</td>
<td>53.5 (range, 27–80; SD, 9.9)</td>
<td>95.5</td>
<td>SqCC – 71.0%, SCC – 24.0%, AC – 4.0%, LCC – 1.0%</td>
<td>Healthy</td>
<td>Ethnicity</td>
<td>1.30</td>
<td>0.57, 2.94</td>
</tr>
<tr>
<td>Sørensen et al. (65), 2004‡</td>
<td>254</td>
<td>265</td>
<td>Denmark</td>
<td>No information</td>
<td>No information</td>
<td>SqCC – 22.0%, SCC – 20.0%, AC – 33.0%, LCC – 6.0%, others – 19.0%</td>
<td>Healthy</td>
<td>Age, gender, and smoking (frequency matching)</td>
<td>2.65</td>
<td>1.44, 4.90</td>
</tr>
<tr>
<td>Dialyna et al. (66), 2003‡</td>
<td>122</td>
<td>178</td>
<td>Greece</td>
<td>61.2 (no range or SD)</td>
<td>84.3</td>
<td>SqCC – 18.0%, SCC – 17.2%, NSCC – 38.5%, AC – 24.6%, others – 1.7%</td>
<td>Healthy</td>
<td>None</td>
<td>1.64</td>
<td>0.85, 3.18</td>
</tr>
<tr>
<td>Ruano-Ravina et al. (67), 2003‡</td>
<td>125</td>
<td>187</td>
<td>Spain</td>
<td>63.2 (SD, 10.3)</td>
<td>90.4</td>
<td>No information</td>
<td>Hospital</td>
<td>None</td>
<td>0.84</td>
<td>0.49, 1.45</td>
</tr>
<tr>
<td>Lewis et al. (68), 2002‡</td>
<td>87</td>
<td>143</td>
<td>United States</td>
<td>62.4 (SD, 12.8)§</td>
<td>59.6</td>
<td>SqCC – 33.3%, SCC – 17.2%, NSCC – 10.3%, AC – 11.5%, nonclassified – 27.6%</td>
<td>Hospital</td>
<td>None</td>
<td>1.15</td>
<td>0.60, 2.21</td>
</tr>
<tr>
<td>Stucker et al. (69), 2002‡</td>
<td>251</td>
<td>268</td>
<td>France</td>
<td>59.4 (SD, 9.8)</td>
<td>100</td>
<td>SqCC – 46.0%, SCC – 19.0%, AC – 24.0%, others – 11.0%</td>
<td>Hospital</td>
<td>Age, ethnicity, and gender</td>
<td>0.74</td>
<td>0.47, 1.17</td>
</tr>
<tr>
<td>Hou et al. (70), 2001</td>
<td>184</td>
<td>162</td>
<td>Sweden</td>
<td>68.1 (range, 30–92)</td>
<td>&lt;30</td>
<td>SqCC – 22.0%, AC – 51.0%, others – 27.0%</td>
<td>Healthy</td>
<td>Age, gender, and smoking (frequency matching)</td>
<td>1.06</td>
<td>0.60, 1.85</td>
</tr>
<tr>
<td>Liu et al. (71), 2001</td>
<td>1,024</td>
<td>1,176</td>
<td>United States</td>
<td>61.4 (SD, 11.5)§</td>
<td>49.7§</td>
<td>SqCC – 25.0%, SCC – 8.3%, AC – 51.0%, LCC – 7.6%, others – 6.3%, not classified – 1.4%§</td>
<td>Healthy</td>
<td>None</td>
<td>0.89</td>
<td>0.72, 1.09</td>
</tr>
<tr>
<td>Risch et al. (72), 2001‡</td>
<td>383</td>
<td>346</td>
<td>Germany</td>
<td>58.2 (range, 17–92)§</td>
<td>68.6§</td>
<td>SqCC – 44.0%, SCC – 2.8%, AC – 39.0%, LCC – 4.9%, others – 10.0%§</td>
<td>Hospital</td>
<td>Ethnicity</td>
<td>0.63</td>
<td>0.42, 0.95</td>
</tr>
<tr>
<td>Malats et al. (73), 2000‡</td>
<td>122</td>
<td>121</td>
<td>Sweden, Germany, France, Italy, Russia, Rumania, Poland, and Brazil</td>
<td>61.5 (no range or SD)</td>
<td>21.0</td>
<td>SqCC and SCC – 20.7%, AC – 53.7%, others – 25.6%</td>
<td>Hospital</td>
<td>Ethnicity</td>
<td>0.62</td>
<td>0.36, 1.08</td>
</tr>
<tr>
<td>Spitz et al. (74), 2000‡</td>
<td>484</td>
<td>458</td>
<td>United States</td>
<td>61.6 (SD, 9.7)§</td>
<td>53.3§</td>
<td>No information</td>
<td>Healthy</td>
<td>Age, ethnicity, gender, and smoking</td>
<td>1.28</td>
<td>0.95, 1.72</td>
</tr>
<tr>
<td>To-Figueras et al. (75), 1999‡</td>
<td>164</td>
<td>200</td>
<td>Spain</td>
<td>46.0 (range, 26–87)</td>
<td>88.4</td>
<td>(only cases, no information for controls)</td>
<td>Healthy</td>
<td>Gender (frequency matching)</td>
<td>1.38</td>
<td>0.84, 2.26</td>
</tr>
</tbody>
</table>

*The table includes studies with information on case and control groups, along with the crude odds ratio (OR) and 95% confidence interval (CI) for the association between the specific histological type and the exposure of interest. The studies are categorized by country and include information on matching criteria and other relevant characteristics. The table is structured to facilitate the comparison of findings across different studies.**
<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Controls</th>
<th>Age/sex</th>
<th>Stage</th>
<th>Country</th>
<th>GSTT1 genotypes</th>
<th>Hospital/controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saarikoski et al. (76), 1998</td>
<td>204</td>
<td>294</td>
<td>Finland</td>
<td>Healthy None</td>
<td>49.7 (SD, 10.2)</td>
<td>SqCC = 45.2%, AC = 39.4%, others = 15.4%</td>
<td>0.96 (0.56, 1.63)</td>
<td></td>
</tr>
<tr>
<td>Salagic et al. (77), 1998</td>
<td>117</td>
<td>248</td>
<td>Slovakia</td>
<td>Healthy None</td>
<td>No information</td>
<td>No information</td>
<td>0.78 (0.42, 1.45)</td>
<td></td>
</tr>
<tr>
<td>Jourenkova et al. (78), 1997</td>
<td>150</td>
<td>172</td>
<td>France</td>
<td>Hospital Age and gender (frequency matching)</td>
<td>56.6 (no range or SD)</td>
<td>SqCC = 65.3%, SCC = 34.7%</td>
<td>1.18 (0.66, 2.12)</td>
<td></td>
</tr>
<tr>
<td>Deakin et al. (79), 1996</td>
<td>108</td>
<td>509</td>
<td>United Kingdom</td>
<td>Hospital None</td>
<td>69.7 (no range or SD)</td>
<td>No information</td>
<td>0.82 (0.47, 1.45)</td>
<td></td>
</tr>
<tr>
<td>Chan-Yeung et al. (80), 2004</td>
<td>229</td>
<td>197</td>
<td>China</td>
<td>Healthy None</td>
<td>51.7 (SD, 14.9)</td>
<td>SqCC = 16.6%, NSCC = 19.2%, AC = 55.5%, others = 8.7%</td>
<td>Healthy None</td>
<td>1.55 (1.05, 2.28)</td>
</tr>
<tr>
<td>Liang et al. (81), 2004</td>
<td>152</td>
<td>152</td>
<td>China</td>
<td>Hospital No information (Chinese language)</td>
<td>No information (Chinese language)</td>
<td>No information (Chinese language)</td>
<td>2.06 (1.30, 3.24)</td>
<td></td>
</tr>
<tr>
<td>Wang et al. (82), 2003</td>
<td>112</td>
<td>119</td>
<td>Japan</td>
<td>Healthy Age and gender</td>
<td>55.5 (range, 35–75; SD, 8.2)</td>
<td>AC = 100%</td>
<td>1.08 (0.64, 1.81)</td>
<td></td>
</tr>
<tr>
<td>Sunaga et al. (83), 2002</td>
<td>198</td>
<td>152</td>
<td>Japan</td>
<td>Hospital None</td>
<td>63.9 (SD, 11.3)</td>
<td>AC = 100%</td>
<td>1.58 (1.03, 2.42)</td>
<td></td>
</tr>
<tr>
<td>Zhao et al. (84), 2001</td>
<td>233</td>
<td>187</td>
<td>Singapore</td>
<td>Hospital Age (frequency matching)</td>
<td>64.7 (SD, 12.4)</td>
<td>No information</td>
<td>1.51 (0.83, 2.75)</td>
<td></td>
</tr>
<tr>
<td>Kyochera et al. (85), 2000</td>
<td>86</td>
<td>88</td>
<td>Japan</td>
<td>Healthy Age and gender (individual matching)</td>
<td>61.4 (range, 20–86)</td>
<td>100</td>
<td>1.35 (0.81, 2.24)</td>
<td></td>
</tr>
<tr>
<td>Lan et al. (86), 2000</td>
<td>122</td>
<td>122</td>
<td>China</td>
<td>Healthy Age (individual matching)</td>
<td>55 (SD, 11.5)</td>
<td>64.8</td>
<td>0.91 (0.67, 1.23)</td>
<td></td>
</tr>
<tr>
<td>London et al. (17), 2000</td>
<td>232</td>
<td>710</td>
<td>China</td>
<td>Healthy Age, ethnicity, and gender (frequency matching)</td>
<td>58.8 (range, 45–64; SD, 4.8)</td>
<td>100</td>
<td>0.91 (0.67, 1.23)</td>
<td></td>
</tr>
<tr>
<td>Cote et al. (58), 2005</td>
<td>304</td>
<td>398</td>
<td>United States</td>
<td>Healthy Age, ethnicity, and gender (frequency matching)</td>
<td>41.6 (no range or SD)§</td>
<td>44.7§</td>
<td>1.09 (0.76, 1.58)</td>
<td></td>
</tr>
<tr>
<td>Wenzlaff et al. (57), 2005§</td>
<td>153</td>
<td>175</td>
<td>United States</td>
<td>Healthy Age, ethnicity, and gender (frequency matching)</td>
<td>58.5 (SD, 13.6)§</td>
<td>45.6§</td>
<td>0.84 (0.48, 1.44)</td>
<td></td>
</tr>
<tr>
<td>Yang et al. (87), 2004‡</td>
<td>237</td>
<td>234</td>
<td>United States</td>
<td>Healthy Age, ethnicity, and gender (frequency matching)</td>
<td>54.3 (SD, 4.6) (only cases, no information for controls)§</td>
<td>51.5 (only cases, no information for controls)§</td>
<td>0.88 (0.78, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Nazar-Stewart et al. (88), 2003</td>
<td>274</td>
<td>500</td>
<td>United States</td>
<td>Healthy Age and gender (frequency matching)</td>
<td>No mean age (range, 18–74)</td>
<td>100</td>
<td>1.07 (0.73, 1.56)</td>
<td></td>
</tr>
<tr>
<td>Gallegos-Areola et al. (89), 2003–2004</td>
<td>52</td>
<td>178</td>
<td>Mexico</td>
<td>Healthy None</td>
<td>No information</td>
<td>No information</td>
<td>5.04 (1.79, 14.31)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7,629</td>
<td>10,087</td>
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</table>

* SD, standard deviation; OR, odds ratio; CI, confidence interval; SqCC, squamous cell carcinoma; SCC, small cell carcinoma; NSCC, non–small cell carcinoma; AC, adenocarcinoma; LCC, large cell carcinoma. † Crude ORs were calculated by using the reported frequencies of the GSTT1 null genotype in cases and controls. For this reason, they could be slightly different from the adjusted ORs reported in each paper. ‡ Studies included in the pooled analysis. § The information concerns all subjects included in the original study and not the subset of subjects with data on GSTT1. ¶ Part of the subjects included in this study were also included in the study by Cote et al. (58) (35 cases and 79 controls, personal communication by the authors).
48 percent for women (40). In Western countries, the population attributable fraction due to smoking was estimated to be approximately 90 percent for men and approximately 70 percent for women. Lung cancer risk significantly decreases with smoking cessation; however, the relative risk remains 1.5–2.0 times the risk for never smokers (41). Lung cancer is also associated with environmental tobacco smoke (42). Other risk factors are diet (43), outdoor air pollution, occupational exposures to carcinogens (44), and radon (45).

ASSOCIATIONS AND INTERACTIONS

The association between GSTT1 and lung cancer was assessed through a meta-analysis of all published papers and a pooled analysis of selected published and unpublished studies. A Medline search was performed from January 1995 (the date when the first case-control studies on GSTT1 and lung cancer were published) to March 2005 using different combinations of the keywords “glutathione S-transferase,” “GSTT1,” and “lung” without restriction on language. The computer search was supplemented by consulting the bibliographies from the articles found through the Medline search and by looking at two review papers (2, 46). An initial screening of all the abstracts provided 50 articles containing information on both GSTT1 and lung cancer. Eligible were case-control, genotype-based studies that reported the frequency of GSTT1 or the odds ratio for GSTT1 and lung cancer. Both hospital- and population-based case-control studies were included in the analysis. Of the 50 articles selected, excluded were two because they were a pooled analysis of existing data (47, 48), three because they reported on studies that included either only cases of lung cancer (n = 1) or only controls (n = 2), and three because they did not report the frequency of GSTT1 or the odds ratio of lung cancer for GSTT1 deletion. We also excluded eight studies (49–56) because the subjects were the same as those in other studies. In case of multiple publications on the same population, the most recent publications, with the largest study design, the selection and source of controls, the laboratory methods used for genotyping subjects, the source of DNA for genotype analysis, and the response rates for both cases and controls. Some of this information has been published previously (91).

We selected, from the GSEC database, all studies that had information on GSTT1 and lung cancer. We also contacted all investigators of studies for which data were not available through the GSEC project and asked them to provide their data for this specific pooled analysis. We were able to obtain data from 27 of the 34 studies included in the meta-analysis (79 percent; refer to table 1 for details). The number of subjects included in some data sets is slightly different from the published data because they may also include some unpublished data. The GSEC database contained seven additional studies with completely unpublished data on GSTT1 and lung cancer; therefore, the pooled analysis included 34 studies, for a total of 7,044 cases and 10,000 controls.

Statistical analysis

For the meta-analysis, study-specific crude odds ratios and 95 percent confidence intervals for lung cancer for GSTT1 deletion were estimated on the basis of the reported frequencies of GSTT1 deletion in cases and controls. The Egger test (92) was performed on the overall data sets and after stratification for ethnicity (Caucasians, Asians, other ethnic groups) and source of the control group (healthy or hospitalized controls). Funnel plots were used for a graphic representation of publication bias.

Other ethnic groups were represented by fewer than three studies each and therefore were grouped together as “others” in the analyses on ethnicity. Such ethnic groups included Latinos (one study), African Americans (two studies), and mixed populations (two studies). The hypothesis of homogeneity among studies was tested by the Q statistic, with p values of <0.05 indicating the presence of heterogeneity among studies. The Q statistic was performed on all of the studies and according to ethnicity and type of controls. When the test for heterogeneity was not statistically significant, a fixed-effects model was performed; a random-effects model was used when heterogeneity across studies was statistically observed (93).

Because the frequency of GSTT1 null differs according to ethnicity, summary odds ratios were calculated for all studies combined as well as for subgroups of studies performed with different ethnic groups (Caucasians, Asians, others). Further stratification was performed within each of the three ethnic groups according to type of controls (hospital or healthy controls). Use of hospital-based controls can bias the risk estimates if the diseases of the controls are related to the genetic variant under study.

Pooled analysis was performed separately for the two major ethnic groups (Caucasians and Asians) to avoid the confounding effect of ethnicity already observed in the meta-analysis. Study-specific crude odds ratios and 95 percent confidence intervals for lung cancer and GSTT1 deletion were estimated, and their homogeneity was tested by using both Q and Breslow-Day’s tests. Crude and adjusted odds ratios were calculated for each ethnic group and for the total set of the available studies. Separate analyses were
conducted on the studies included in both the meta- and pooled analyses and on the studies present in the pooled analysis only, which had not been previously published. When heterogeneity between studies was observed, a sensitivity analysis was performed by restricting the analysis to the studies for which evidence for heterogeneity of effects was not found. Stratified analyses were conducted according to the type of control population, smoking habits, and histologic type (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). For smoking habits, subjects were divided into four classes by using the information on packs of cigarettes smoked times years of smoking. The baseline class included never smokers; the other three classes were created according to tertiles of the variable pack-years. A further analysis on histologic type was performed to assess whether the \( \text{GSTT1} \) null polymorphism was more frequent in adenocarcinoma than in squamous cell carcinoma cases (the two histologic types present most often in the data set). For this purpose, crude and adjusted odds ratios and 95 percent confidence intervals were calculated.

For studies including Caucasian subjects, the large sample size enabled us to stratify the data according to occupational exposure. Adjusted odds ratios were calculated by using multiple logistic regression models including study number, age (continuous variable), sex, and smoking status (ever/never) as covariates. In the same ethnic group, interactions between \( \text{GSTT1} \) deletion and smoking habits and occupational exposure were formally assessed by adding a product term, respectively, to a model containing the main effect of \( \text{GSTT1} \), the categories of occupational exposure (exposed/nonexposed), and the other possible confounding variables (study, age, sex, and smoking habits). Models with or without an interaction term were compared by using the likelihood ratio test. The three studies (65, 74, Dragani (unpublished data)) for which the controls were frequency matched to the cases on smoking were excluded from the analysis of an interaction between \( \text{GSTT1} \) and smoking.

The meta-analysis was performed by using the STATA software package (Stata Corporation, College Station, Texas). The pooled analysis was conducted by using SAS, version 8e software (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

**Meta-analysis**

The study-specific odds ratios and the meta-odds ratios for studies including Asian and Caucasian subjects are presented in figure 2. Two studies (57, 58) reported separate analyses for two different ethnic groups (Caucasians and African Americans); therefore, they were included in the analysis of both Caucasians (by calculating the odds ratio for Caucasians only) and the other ethnic groups (by calculating the odds ratio for African Americans only). In the 23 studies on Caucasians, 20 odds ratios were spread around the null effect (nine above the unit and 11 under the unit); only one study (65) reported a significant positive association between lung cancer and \( \text{GSTT1} \) null (odds ratio (OR) = 2.65, 95 percent confidence interval (CI): 1.44, 4.90), whereas two studies (59, 72) reported a significant negative association (OR = 0.63, 95 percent CI: 0.42, 0.95 and...
The meta-odds ratios in table 2 refer to the analyses conducted on all studies and on stratified data. The meta-odds ratio for all studies combined was 1.07 (95 percent CI: 0.96, 1.19), with a large heterogeneity (Q-test p = 0.09). The heterogeneity was no longer present among the studies under the significance level (Egger’s test p = 0.09), and no evidence of publication bias was observed (Egger’s test p = 0.16).

For all the other studies on different ethnic groups, the meta-odds-ratio was 1.08 (95 percent CI: 0.72, 1.59), with heterogeneity (Q-test p = 0.02) but no evidence of publication bias (Egger’s test p = 0.28). The heterogeneity was probably due to the different ethnicities included in these studies. Table 2 presents the meta-odds ratios stratified according to type of controls and according to ethnicity. For Caucasians, the association with GSTT1 null deletion and lung cancer was observed only when the analysis was restricted to studies including hospital controls (OR = 1.47, 95 percent CI: 1.15, 1.87), whereas such an association was less evident for studies including healthy controls (OR = 1.18, 95 percent CI: 0.97, 1.42). No heterogeneity or publication bias was found in these stratified analyses (results not shown).

### Pooled analysis

Crude study-specific odds ratios and 95 percent confidence intervals are reported in table 3 for Asians and table 4 for Caucasians. No heterogeneity between studies including Asian subjects was observed; for Caucasians, the test for heterogeneity was statistically significant. However, exclusion of one case-cohort study (65) made the sample statistically homogenous (p for Q and Breslow-Day’s tests = 0.09).

The summary odds ratios of lung cancer for GSTT1 null and lung cancer are presented in table 5 for Asians and table 6 for Caucasians. The adjusted summary odds ratios for all studies combined were not significant for Asians.
(OR = 0.97, 95 percent CI: 0.83, 1.13) or for Caucasians (OR = 1.09, 95 percent CI: 0.99, 1.21). Among Caucasians, when the analysis was restricted to the studies for which the test for heterogeneity was not statistically significant, lower odds ratios were observed. If the analysis was restricted to studies included in both the meta- and pooled analyses, the odds ratios became similar to the summary odds ratios obtained from the meta-analysis. The analysis restricted to studies included in the pooled analysis only, which include unpublished data on GSTT1 and lung cancer, showed lower odds ratios for both Asian and Caucasian subjects. For both Asians and Caucasians, higher adjusted summary odds ratios were observed. If the analysis was restricted to the studies for which the likelihood ratio test for homogeneity was nonsignificant (p = 0.39), lower odds ratios were observed for subjects occupationally exposed to asbestos. Because the agents reported in the data set were extremely heterogeneous (chemicals, polycyclic aromatic hydrocarbons, asbestos, metals, radiation, etc.), we restricted the analysis to asbestos exposure and found the same protective effect (table 8).

There was no statistical evidence of multiplicative interaction between GSTT1 and smoking for Caucasians (p for the likelihood ratio test = 0.90). A significant antagonist effect of occupational exposure and GSTT1 deletion was observed, with an odds ratio for interaction of 0.69 (95 percent CI: 0.51, 0.94, p for the likelihood ratio test = 0.02; table 9). However, when we restricted the analysis to asbestos exposure, the interaction with GSTT1 was nonsignificant (p for the likelihood ratio test = 0.08; table 9), although subjects carrying the GSTT1 deletion and exposed to asbestos had a lower risk of developing cancer in comparison with not occupationally exposed subjects in whom GSTT1 was present (OR = 0.59, 95 percent CI: 0.41, 0.86).

### DISCUSSION

The meta-analysis highlighted a higher risk of developing lung cancer for Asian subjects carrying the GSTT1 null genotype (OR = 1.28, 95 percent CI: 1.10, 1.49), but the pooled analysis did not confirm this result (adjusted OR = 0.97, 95 percent CI: 0.83, 1.13). The lower odds ratio observed in the pooled analysis was mainly due to two unpublished studies (Sugimura, Kang), which reported a nonsignificant negative association between GSTT1 and lung cancer. No significant association between lung cancer and GSTT1 deletion was present in Caucasian subjects in either the meta-analysis or the pooled analysis. Our results were consistent with a previously published pooled analysis on a subset of subjects included in this study that showed no
A statistically significant effect of \textit{GSTT1} null on lung cancer for Caucasians at younger ages (47). The deletion in the \textit{GSTT1} gene was not associated with lung cancer in two previous reviews (2, 46), even though both authors underlined that \textit{GSTT1} deletion could play a role in lung carcinogenesis when \textit{GSTM1} is concurrently lacking.

Because both smoking and occupational exposure are independent risk factors for lung cancer, we studied their interaction with \textit{GSTT1} by using the pooled data set of individual data. We found no significant interaction between \textit{GSTT1} and lifetime tobacco consumption on lung cancer; however, a negative trend of the odds ratios with increasing amount of lifetime smoking was observed for both Caucasians and Asians. This finding could be explained by the relevant role of genetic factors at low-dose-carcinogen exposures (94–97). The lack of interaction between \textit{GSTT1} and smoking is consistent with the hypothesis that polycyclic aromatic hydrocarbons, carcinogenic compounds found in tobacco smoke, are minor substrates for \textit{GSTT1} (2).

A significant negative interaction was observed between being occupationally exposed and \textit{GSTT1}: exposed subjects for whom \textit{GSTT1} was present were at higher risk of lung cancer than exposed subjects carrying the \textit{GSTT1} null genotype. It has to be kept in mind that the information on occupational exposure available through the GSEC database is very limited. For example, the data set contains information on only broad categories of agents to which subjects were occupationally exposed; no information on amount or length of exposure is available. Therefore, a more in-depth analysis of this interesting result was not possible. A possible hypothesis is that some compounds present in occupational settings—such as dichloromethane

\begin{table}
\centering
\caption{Description of Caucasian studies included in the pooled analysis: study-specific crude odds ratios and 95\% confidence intervals}
\begin{tabular}{llllll}
\hline
Author(s) (reference no.), year & No. of cases & No. of controls & Source of controls & Crude OR*, † & 95\% CI* \\
\hline
Saarikoski et al. (76), 1998‡ & 237 & 347 & Healthy & 1.15 & 0.71, 1.87 \\
Dolzan (unpublished data) & 201 & 102 & Healthy & 0.73 & 0.41, 1.28 \\
Kremers (unpublished data) & 48 & 71 & Healthy & 0.64 & 0.31, 1.33 \\
Alexandrie et al. (60), 2004‡ & 596 & 1,627 & Healthy & 0.88 & 0.67, 1.16 \\
Risch et al. (72), 2001‡ & 399 & 358 & Hospital & 0.73 & 0.49, 1.09 \\
Romkes (unpublished data) & 30 & 43 & Healthy & 0.38 & 0.13, 1.13 \\
Deakin et al. (79), 1996‡ & 163 & 603 & Hospital & 0.89 & 0.56, 1.40 \\
Stucker et al. (69), 2002‡ & 251 & 268 & Hospital & 0.74 & 0.47, 1.17 \\
Spitz et al. (74), 2000‡ & 484 & 458 & Healthy & 1.28 & 0.95, 1.72 \\
To-Figueras et al. (75), 1999‡ & 164 & 324 & Healthy and hospital & 1.23 & 0.79, 1.92 \\
Malats et al. (73), 2000‡ & 242 & 157 & Hospital & 1.05 & 0.68, 1.60 \\
Jourenkova et al. (78), 1997‡ & 150 & 172 & Hospital & 1.18 & 0.66, 2.12 \\
Salagovic et al. (77), 1998‡ & 354 & 394 & Healthy & 1.06 & 0.74, 1.54 \\
Lewis et al. (68), 2002‡ & 87 & 143 & Hospital & 1.15 & 0.60, 2.21 \\
Ruano-Ravina et al. (67), 2003‡ & 125 & 187 & Hospital & 0.84 & 0.49, 1.45 \\
Dragani T/Neri (unpublished data) & 104 & 97 & Healthy & 1.70 & 0.92, 3.16 \\
Dialyna et al. (66), 2003‡ & 122 & 178 & Healthy & 1.64 & 0.85, 3.18 \\
Reszka et al. (59), 2005‡ & 119 & 138 & Hospital & 0.51 & 0.28, 0.94 \\
Schneider et al. (63), 2004‡ & 499 & 644 & Healthy and hospital & 0.87 & 0.64, 1.19 \\
Yang et al. (87), 2004 & 216 & 219 & Healthy & 0.63 & 0.41, 0.98 \\
Belogubova et al. (61), 2004‡ & 167 & 663 & Healthy & 0.94 & 0.61, 1.46 \\
Sobti et al. (64), 2004‡ & 110 & 110 & Healthy & 1.07 & 0.52, 2.21 \\
Cote et al. (58), 2005 and Wenzlaff et al. (57), 2005§ & 342 & 461 & Healthy & 1.30 & 0.93, 1.81 \\
Shields (unpublished data) & 30 & 30 & Hospital & 1.00 & 0.32, 3.14 \\
Sørensen et al. (65), 2004‡ & 254 & 250 & Healthy & 2.67 & 1.43, 5.00 \\
\hline
\end{tabular}
\footnotesize{\textsuperscript{*} OR, odds ratio; CI, confidence interval.}  \\
\textsuperscript{†} \textit{p} value for Breslow-Day’s test for homogeneity = 0.01; excluding the Sørensen et al. study = 0.09. \textit{p} value for \textit{Q} test for homogeneity = 0.01; excluding the Sørensen et al. study = 0.09.  \\
\textsuperscript{‡} Studies included in the meta-analysis on Caucasian subjects.  \\
\textsuperscript{§} The original data set from the two studies did not include overlapping subjects.}
\end{table}
and other halogenated compounds, known substrates of \textit{GSTT1}—are transformed by \textit{GSTT1} into mutagenic intermediates; thus, \textit{GSTT1}-positive subjects might be more prone than \textit{GSTT1}-null subjects to the genotoxic action of halogenated compounds via the \textit{GSTT1} pathway (2).

Some translational studies on intermediate biomarkers of exposure and effect suggest that subjects carrying the \textit{GSTT1} deletion may have lower levels of the biomarkers than subjects with the functional \textit{GSTT1}, pointing at a different role of \textit{GSTT1} on cancer causation (98–104).

To our knowledge, this is the first comprehensive meta- and pooled analysis assessing the role of \textit{GSTT1} deletion on lung cancer, and the only one on Asians. The large number of cancer cases included in this analysis ($N = 6,633$) provided 100 percent statistical power to find an odds ratio of 1.5 for both Asians and Caucasians. Because

### Table 5. Odds ratios and 95% confidence intervals for the association between \textit{GSTT1}* and lung cancer: pooled analysis on Asian subjects

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>No. of \textit{GSTT1} null cases</th>
<th>No. of \textit{GSTT1} controls</th>
<th>OR*</th>
<th>95% CI*</th>
<th>OR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>10</td>
<td>1,373</td>
<td>1,756</td>
<td>695</td>
<td>919</td>
<td>0.93</td>
<td>0.81</td>
<td>1.08</td>
<td>0.97</td>
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<td>Studies included in</td>
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<tr>
<td>the meta-analysis on</td>
<td>6</td>
<td>985</td>
<td>1,384</td>
<td>538</td>
<td>749</td>
<td>1.02</td>
<td>0.87</td>
<td>1.20</td>
<td>1.03</td>
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<td>Asian subjects</td>
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<tr>
<td>Studies not included</td>
<td>4</td>
<td>388</td>
<td>372</td>
<td>157</td>
<td>170</td>
<td>0.81</td>
<td>0.61</td>
<td>1.08</td>
<td>0.78</td>
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<tr>
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<tr>
<td>on Asian subjects</td>
<td>6</td>
<td>558</td>
<td>1,055</td>
<td>309</td>
<td>592</td>
<td>0.97</td>
<td>0.79</td>
<td>1.19</td>
<td>1.01</td>
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<td></td>
</tr>
<tr>
<td>healthy controls</td>
<td>6</td>
<td>815</td>
<td>701</td>
<td>386</td>
<td>327</td>
<td>1.03</td>
<td>0.84</td>
<td>1.26</td>
<td>0.97‡</td>
</tr>
<tr>
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<tr>
<td>hospitalized controls</td>
<td>4</td>
<td>512</td>
<td>396</td>
<td>972</td>
<td>1,075</td>
<td>0.97</td>
<td>0.81</td>
<td>1.13</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* \textit{GSTT1}, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for sex, smoking (ever/never), and age (continuous variable).
‡ ORs calculated by excluding the Sørensen et al. study (65)—crude: 1.04, 95% CI: 0.95, 1.14; adjusted: 1.06, 95% CI: 0.96, 1.17.
§ ORs calculated by excluding the Sørensen et al. study—crude: 1.04, 95% CI: 0.94, 1.15; adjusted: 1.01, 95% CI: 0.90, 1.14.
¶ Two studies (To-Figuera et al. (75), Schneider et al. (63)) contained both healthy and hospital controls. Because it was possible to separate healthy controls from hospital controls, each type of control was included in the correspondent analysis.
# ORs calculated by excluding the Sørensen et al. study—crude: 1.09, 95% CI: 0.98, 1.22; adjusted: 1.07, 95% CI: 0.94, 1.22.
** ORs calculated by excluding controls with other types of cancer or pulmonary diseases—crude: 0.84, 95% CI: 0.72, 0.99; adjusted: 0.88, 95% CI: 0.73, 1.05.

### Table 6. Odds ratios and 95% confidence intervals for the association between \textit{GSTT1}* and lung cancer: pooled analysis on Caucasian subjects

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>No. of \textit{GSTT1} null cases</th>
<th>No. of \textit{GSTT1} controls</th>
<th>OR*</th>
<th>95% CI*</th>
<th>OR†</th>
<th>95% CI†</th>
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<tr>
<td>All studies</td>
<td>25</td>
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<td>8,044</td>
<td>1,086</td>
<td>1,525</td>
<td>1.05</td>
<td>0.97</td>
<td>1.15</td>
<td>1.09‡</td>
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<tr>
<td>the meta-analysis on</td>
<td>18</td>
<td>4,523</td>
<td>7,021</td>
<td>837</td>
<td>1,244</td>
<td>1.05§</td>
<td>0.96</td>
<td>1.16</td>
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<tr>
<td>Studies not included</td>
<td>7</td>
<td>971</td>
<td>1,023</td>
<td>249</td>
<td>281</td>
<td>0.91</td>
<td>0.75</td>
<td>1.11</td>
<td>0.96</td>
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<tr>
<td>on Caucasian subjects</td>
<td>6</td>
<td>3,928</td>
<td>5,518</td>
<td>784</td>
<td>1,012</td>
<td>1.11#</td>
<td>1.00</td>
<td>1.23</td>
<td>1.15#</td>
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<tr>
<td>healthy controls</td>
<td>16¶</td>
<td>2,229</td>
<td>2,526</td>
<td>427</td>
<td>513</td>
<td>0.93**</td>
<td>0.81</td>
<td>1.07</td>
<td>0.99**</td>
</tr>
<tr>
<td>Studies based on</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalized controls</td>
<td>11¶</td>
<td>2,229</td>
<td>2,526</td>
<td>427</td>
<td>513</td>
<td>0.93**</td>
<td>0.81</td>
<td>1.07</td>
<td>0.99**</td>
</tr>
</tbody>
</table>

* \textit{GSTT1}, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ ORs calculated by excluding controls with other pulmonary diseases—crude: 0.94, 95% CI: 0.76, 1.17; adjusted: 0.78, 95% CI: 0.61, 0.99.
§ ORs calculated by excluding the Sørensen et al. study—crude: 1.04, 95% CI: 0.95, 1.14; adjusted: 1.06, 95% CI: 0.96, 1.17.

Meta- and Pooled Analysis of \textit{GSTT1} and Lung Cancer

\textit{Am J Epidemiol} 2006;164:1027–1042
the data set includes information on sex and age, it was possible to adjust the odds ratios for the confounding effect of these variables, and we could perform stratified analyses for both smoking status and occupational exposure in Caucasians. The availability of information on potential confounding variables makes the pooled analyses preferable to the meta-analysis (105). Furthermore, meta-analyses are restricted to published reports and may lead to biased results if publication bias is present; pooled analysis avoids this problem by also including unpublished studies. In our meta-analysis, no evidence of publication bias was found after stratifying for ethnicity. However, for Asian studies, we observed a lower and no longer statistically significant odds ratio when the pooled analysis including unpublished studies was performed.

A limitation of both meta- and pooled analysis could be the presence of heterogeneity between studies. We verified the hypothesis of homogeneity, and we performed Figure 3. Adjusted odds ratios (ORs) for the glutathione S-transferase gene (GSTT1) deletion and lung cancer according to smoking habits (tertiles of pack-years): pooled analysis for Asians and Caucasians. ORs were adjusted for study, sex, and age (continuous variable). Asian never smokers: OR = 1.01, 95% confidence interval (CI): 0.77, 1.32; light smokers (0–22 pack-years): OR = 0.97, 95% CI: 0.64, 1.48; medium smokers (23–42 pack-years): OR = 0.98, 95% CI: 0.68, 1.42; heavy smokers (≥43 pack-years): OR = 0.84, 95% CI: 0.59, 1.21. Caucasian never smokers: OR = 1.20, 95% CI: 0.97, 1.46; light smokers (0–22 pack-years): OR = 1.21, 95% CI: 0.97, 1.51; medium smokers (23–43 pack-years): OR = 1.16, 95% CI: 0.93, 1.44; heavy smokers (≥44 pack-years): OR = 0.97, 95% CI: 0.78, 1.20. p for Breslow-Day’s test for homogeneity = 0.96 for Asians and 0.37 for Caucasians.

**TABLE 7.** Odds ratios and 95% confidence intervals for the association between GSTT1* deletion and lung cancer, stratified according to histologic type: pooled analysis on Asians and Caucasians

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>No. of GSTT1 null cases</th>
<th>No. of GSTT1 null controls</th>
<th>OR*</th>
<th>95% CI*</th>
<th>OR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asians</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>582</td>
<td>913</td>
<td>282</td>
<td>423</td>
<td>1.09</td>
<td>0.88, 1.34</td>
<td>1.06</td>
<td>0.84, 1.34</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>250</td>
<td>649</td>
<td>108</td>
<td>313</td>
<td>0.82</td>
<td>0.61, 1.10</td>
<td>0.81</td>
<td>0.55, 1.17</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>71</td>
<td>549</td>
<td>46</td>
<td>268</td>
<td>1.93</td>
<td>1.15, 3.23</td>
<td>1.45</td>
<td>0.76, 2.77</td>
</tr>
<tr>
<td><strong>Caucasians</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1,106</td>
<td>6,573</td>
<td>209</td>
<td>1,218</td>
<td>1.02</td>
<td>0.87, 1.21</td>
<td>1.12</td>
<td>0.94, 1.34</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1,507</td>
<td>6,777</td>
<td>277</td>
<td>1,267</td>
<td>0.98</td>
<td>0.85, 1.13</td>
<td>1.00</td>
<td>0.84, 1.18</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>593</td>
<td>6,559</td>
<td>103</td>
<td>1,226</td>
<td>0.91</td>
<td>0.73, 1.14</td>
<td>0.98</td>
<td>0.77, 1.26</td>
</tr>
</tbody>
</table>

* GSTT1, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
sensitivity analyses by excluding studies that were a source of heterogeneity. Another possible limitation could be the different method of recruiting controls in the various studies. We considered this possible source of bias by performing a stratified analysis according to the source of controls, in both the meta- and the pooled analysis. Data on hospital controls should provide lower risk estimates if the diseases of the controls were associated with the gene variant under study. We confirmed this hypothesis in the pooled analysis only.

**LABORATORY TESTS**

The detailed methods used for determining the GSTT1 genotype are described in each article. Most of the studies included in the present analyses used genomic DNA extracted from blood. One study also used bronchial lavage (68), one study used paraffin-embedded tissues and buccal swabs (58) in addition to blood, and one study used only buccal cells (86). All of the articles reported the use of polymerase chain reaction, with different polymerase chain reaction conditions and different control samples.

**POPULATION TESTING**

To date, there is insufficient evidence on the role of GSTT1 in the etiology of lung cancer to make population testing an issue.

**CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH**

No significant association was found between lung cancer and GSTT1 deletion either overall or in Caucasians. Among Asians, a positive association was found (OR = 1.28, 95 percent CI: 1.10, 1.49) in the meta-analysis, whereas the association was not confirmed in the pooled analysis (OR = 0.97, 95 percent CI: 0.83, 1.13). GSTT1 appeared to modulate occupational-related lung cancer, at least for asbestos exposure. Further research on GSTT1 in occupationally exposed subjects and in lung cancer patients, including the use of intermediate biomarkers of exposure and effect, will be useful to clarify the role of GSTT1 deletion in the carcinogenic process. Specific studies including subjects exposed to human lung carcinogens could be relevant. Interaction between GSTT1 and other genetic polymorphisms involved in metabolism of environmental carcinogens would be useful to evaluate the possible combined effect of several genetic variants in relation to specific environmental exposures.

**ACKNOWLEDGMENTS**

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**TABLE 8.** Odds ratios and 95% confidence intervals for the association between GSTT1* deletion and lung cancer, stratified according to occupational exposure: pooled analysis on Caucasians

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>No. of controls</th>
<th>No. of GSTT1 null cases</th>
<th>OR*, †</th>
<th>95% CI*</th>
<th>OR†, ‡</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No occupational exposure</td>
<td>1,192</td>
<td>1,040</td>
<td>251</td>
<td>228</td>
<td>0.95</td>
<td>0.78, 1.16</td>
</tr>
<tr>
<td>Occupational exposure (all chemical agents)</td>
<td>1,349</td>
<td>1,138</td>
<td>225</td>
<td>247</td>
<td>0.72</td>
<td>0.59, 0.88</td>
</tr>
<tr>
<td>Only asbestos exposure</td>
<td>272</td>
<td>323</td>
<td>44</td>
<td>68</td>
<td>0.72</td>
<td>0.48, 1.10</td>
</tr>
</tbody>
</table>

* GSTT1, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ p for Breslow-Day’s test for homogeneity = 0.06.

**TABLE 9.** Adjusted odds ratios and 95% confidence intervals for the main effect and interaction of GSTT1*, occupational exposure (all chemicals agents and asbestos only), and lung cancer: pooled analysis on Caucasians

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR*, †, ‡</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All chemical agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTT1 present, no occupational exposure</td>
<td>912</td>
<td>804</td>
<td>1.00</td>
</tr>
<tr>
<td>GSTT1 present, occupational exposure</td>
<td>1,093</td>
<td>888</td>
<td>1.23</td>
</tr>
<tr>
<td>GSTT1 null, no occupational exposure</td>
<td>243</td>
<td>227</td>
<td>1.06</td>
</tr>
<tr>
<td>GSTT1 null, occupational exposure</td>
<td>221</td>
<td>245</td>
<td>0.90</td>
</tr>
<tr>
<td>Asbestos only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTT1 present, no asbestos exposure</td>
<td>912</td>
<td>804</td>
<td>1.00</td>
</tr>
<tr>
<td>GSTT1 present, asbestos exposure</td>
<td>228</td>
<td>255</td>
<td>0.85</td>
</tr>
<tr>
<td>GSTT1 null, no asbestos exposure</td>
<td>243</td>
<td>227</td>
<td>1.07</td>
</tr>
<tr>
<td>GSTT1 null, asbestos exposure</td>
<td>44</td>
<td>68</td>
<td>0.59</td>
</tr>
</tbody>
</table>

* GSTT1, glutathione S-transferase gene; OR, odds ratio; CI, confidence interval.
† OR adjusted for study, sex, smoking (ever/never), and age (continuous variable).
‡ p for interaction (likelihood ratio test) = 0.02 for all chemical agents; 0.08 for asbestos only.
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Meta- and Pooled Analysis of GSTT1 and Lung Cancer 1041


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