The hOGG1 Ser326Cys Polymorphism and Lung Cancer Risk: A Meta-analysis

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Abstract

The potentially functional polymorphism Ser326Cys in the human 8-oxoguanine DNA glycosylase (hOGG1) gene has been implicated in lung cancer risk, but published studies have mixed findings. To summarize published data, we did a comprehensive meta-analysis. Two investigators extracted data independently from 17 case control studies published in the PubMed using the search phrases "hOGG1/OGG1/OGG" and polymorphism/genetic variation and lung cancer." The meta-analysis included 6,375 cancer cases and 6,406 control subjects. The results showed that individuals carrying the hOGG1 Cys/Cys genotype did not have significantly increased risk of lung cancer [odds ratios (OR), 1.15; 95% confidence interval (CI), 0.94-1.41] compared with those with the Ser/Ser genotype; similarly, no significant association with lung cancer risk was found either in the recessive (OR, 1.09; 95% CI, 0.90-1.32 for Cys/Cys versus Ser/Ser plus Ser/Ser) or dominant model of the Ser326 allele (OR, 1.06; 95% CI, 0.93-1.21 for Cys/Cys + Ser/Cys versus Ser/Ser). However, significantly increased risks were found among Asian subjects (OR, 1.18; 95% CI, 1.01-1.38 for Cys/Cys + Ser/Cys versus Ser/Ser) in a dominant model. In stratified analyses by control source, compared with the Ser/Ser genotype, lung cancer risk associated with the hOGG1 Cys/Cys genotype was significantly increased in population-based studies (OR, 1.32; 95% CI, 1.04-1.67) but not in hospital-based studies (OR, 1.18; 95% CI, 0.98-1.42); in stratified analyses by the smoking status, however, the increased risk was observed only among nonsmokers in a dominant model (OR, 1.32; 95% CI, 1.04-1.67). The meta-analysis suggested that a careful matching should be considered in future larger genetic association studies including multiple ethnic groups.

Introduction

DNA is continuously exposed to the assaults by various endogenous and exogenous mutagens or carcinogens. Among them, the oxidants, as one of the most common threats to genomic stability, are thought to cause oxidative damage to DNA and mutations, leading to activation of oncogenes, inactivation of tumor suppressor genes, or carcinogenesis (1, 2). However, multiple DNA repair enzymes protect DNA against such oxidative damage. For instance, one of the most common forms of oxidative damage is DNA 8-hydroxydeoxyguanine caused by oxidative stress. 8-hydroxydeoxyguanine is mutagenic or carcinogenic, resulting in G:C to T:A transversions. The 8-hydroxydeoxyguanine lesions are subject to the base-excision repair, especially by hOGG1 (3), encoded by the hOGG1 gene on chromosome 3p26, catalyzes the cleavage of the glycosyl bond between the modified base and the sugar moiety, leaving an abasic apurinic/apyrimidinic site in DNA; the resulting apurinic/apyrimidinic site is then incised, and the repair is completed by successive actions of a phosphodiesterase, a DNA polymerase, and a DNA ligase (5, 6).

Previous studies have revealed the presence of several polymorphisms at the hOGG1 locus. A study on small cell lung cancer found 2 homozygous mutations at codons 85 and 131 (7). Later, two single nucleotide polymorphisms, codon 46 Arg/Gln and codon 154 Arg/His, were described in another study, in which the hOGG1-Gln46 allele was shown to have a reduced activity for excision of 8-OH-G, whereas the hOGG1-His154 allele was less effective in the repair than the hOGG1-Ser326 allele (8). Furthermore, the codon 229 Arg/Gln in exon 4 has been reported in a recent study (9), in which it was shown that human KG-1 leukemia cells had a homozygous Arg229Gln amino acid substitution in hOGG1 that was thought to alter the function of hOGG1, resulting in elevated levels of genomic 8-oxoG and hypersensitivity to 8-hydroxydeoxyguanosine nucleoside and ionizing radiation observed in these cells. In addition, two other hOGG1 single nucleotide polymorphisms, 7143A/G and 11657A/G, located further downstream in a noncoding region, were found to be associated with prostate cancer risk (10, 11). However, among these polymorphisms of hOGG1, more studies focused on the common single nucleotide polymorphism Ser326Cys. The C/G polymorphism at bp 1245 (C1245G) in the 1a-specific exon 7 of the hOGG1 gene results in an amino acid substitution of serine (Ser) with cysteine.
Table 1. Study characteristics and genotype prevalence from published studies on the relation of the Human hOGG1 Ser326Cys polymorphism to lung cancer risk

<table>
<thead>
<tr>
<th>Ref no.</th>
<th>First author</th>
<th>Year</th>
<th>Location</th>
<th>Ethnicity</th>
<th>No. of cases</th>
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<td>Japan</td>
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<td>45</td>
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<td>Sugimura</td>
<td>1999</td>
<td>Japan</td>
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<td>241</td>
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<td>(29)</td>
<td>Wikman</td>
<td>2000</td>
<td>Germany</td>
<td>Caucasian</td>
<td>105</td>
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<tr>
<td>(18)</td>
<td>Ito</td>
<td>2002</td>
<td>Japan</td>
<td>Asian</td>
<td>138</td>
</tr>
<tr>
<td>(16)</td>
<td>Le</td>
<td>2002</td>
<td>America</td>
<td>Mixed</td>
<td>298</td>
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<tr>
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<td>Sunaga</td>
<td>2002</td>
<td>Japan</td>
<td>Asian</td>
<td>198</td>
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<td>(32)</td>
<td>Lan</td>
<td>2004</td>
<td>China</td>
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<td>118</td>
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<tr>
<td>(17)</td>
<td>Park</td>
<td>2004</td>
<td>America</td>
<td>Caucasian</td>
<td>179</td>
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<tr>
<td>(20)</td>
<td>Vogel</td>
<td>2004</td>
<td>Denmark</td>
<td>Caucasian</td>
<td>256</td>
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<tr>
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<td>Hung</td>
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<td>(24)</td>
<td>Liang</td>
<td>2005</td>
<td>China</td>
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<td>227</td>
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<td>2006</td>
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<td>Asian</td>
<td>200</td>
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<td>Loft</td>
<td>2006</td>
<td>Denmark</td>
<td>Caucasian</td>
<td>251</td>
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<td>(19)</td>
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<td>Denmark</td>
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<td>431</td>
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<tr>
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<td>2006</td>
<td>Norway</td>
<td>Caucasian</td>
<td>326</td>
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<tr>
<td>(34)</td>
<td>De Ruyck</td>
<td>2007</td>
<td>Belgium</td>
<td>Caucasian</td>
<td>110</td>
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</table>

*p < 0.05.

(Cys) at codon 326 (Ser326Cys; rs1052133; ref. 12). The hOGG1 protein encoded by the wild-type Ser326 allele exhibited substantially higher DNA repair activity than the Cys326 allele because the Cys allele more likely caused a low activity of the enzyme, and the change of hOGG1 Ser to Cys was speculated to alter human cancer susceptibility (13, 14). Subsequently, many studies have investigated the association of genetic variation in hOGG1 and cancer susceptibility as well as gene environment interactions, most of which focused on the single nucleotide polymorphism Ser326Cys (13–17). Several studies have suggested that Cys326 allele is associated with increased lung cancer risk (13, 15–17), particularly among individuals homozygous for the Cys326 allele, although the findings of these association studies have been inconsistent (18–21). To comprehensively evaluate the role of the hOGG1 Ser326Cys polymorphism in the risk of lung cancer, we did a meta-analysis based on searchable published association studies.

Materials and Methods

Identification and Eligibility of Relevant Studies. Relevant studies were identified in the PubMed database4 using combinations of the search phrases "hOGG1/OGG1/OGG and polymorphism/genetic variation and lung cancer" (the last search update on November 15, 2007). In a total of 38 retrieved relevant references, 17 publications were identified to be eligible for the inclusion in the meta-analysis because these 17 studies had a case control study design that assessed the association between the hOGG1 Ser326Cys polymorphism and risk of lung cancer using human genomic DNA samples. Of all screened studies, one (22) was written in Korean, which nevertheless provided relevant data about hOGG1 Ser326Cys polymorphism (only for a dominant model) in English. So it was still included in the meta-analysis. The 17 studies included in the final analysis had a total of 6,375 cancer cases and 6,406 controls that had the genotyping data for the hOGG1 Ser326Cys polymorphism.

Data Extraction. Two authors (Haixin Li and Kexin Chen) extracted data and reached a consensus on all of the eligibility items, including author, journal and year of publication, location of study, selection and characteristics of cancer cases and controls, control source, demographics, ethnicity, smoking status, and genotyping information. For those studies that included subjects of different ethnic groups, data were extracted separately for each of ethnic groups categorized as Caucasians, Asians, or Mixed that included more than one ethnic group, such as both Caucasians and Asians, but no Africans were identified in these studies.

Meta-analysis. The risks (odds ratios, OR) of lung cancer associated with the hOGG1 Ser326Cys polymorphism were estimated for each study independently. We estimated the risk first for the variant homozygous Cys/Cys genotype, compared with the wild-type homozygous Ser/Ser genotype and then for the Cys/Cys versus (Ser/Cys+Ser/Ser) or (Cys/Cys+Ser/Cys) versus Ser/Ser, assuming recessive and dominant effect models, respectively. Besides comparisons using all subjects, subgroup analyses were done according to the ethnicity (Caucasian, Asian, and mixed), control sources (hospital- and population-based), and smoking status (never smoker and ever smoker).

Statistical Analysis. We calculated OR and 95% confidence intervals (CI) to estimate lung cancer risk associated with the hOGG1 Ser326Cys polymorphism for each study. Inevitably, studies included in the meta-analysis differed in the variables of interest, and thus, any kind of variability among studies may be termed heterogeneity. In the meta-analysis, the heterogeneity can be assessed by ORs for different stratum of each variable included in the analysis. We also did the Q test to assess the heterogeneity between individual studies, and the heterogeneity was considered...
significant, if the \( P \) value is <0.05, which was used to estimate summary ORs and 95% CIs by weighing the results of each study by a factor of within- and between-study variance according to a random effect model, and if the \( P \) value is >0.05 in heterogeneity evaluation, a fixed effect model was then used to estimate summary ORs and 95% CIs. Publication bias was assessed by a funnel plot and Egger’s test (23). All analyses were done using Statistical Analysis System software (v.8.1; SAS Institute) and Review Manage (v.5.0). All the \( P \) values were two-sided.

Results

Meta-analysis Database. The basic information including cancer type, ethnicity of the study populations, and the numbers of cases and controls of each study are listed in Table 1. There were a total of 17 case control studies, and the distribution of genotypes for the \( hOGG1 \) polymorphism in the controls of all studies was consistent with that expected from the Hardy-Weinberg equilibrium, except for two studies (21, 24).

Quantitative Synthesis. We included 6,375 cancer patients and 6,406 control subjects in the final analysis. Individuals carrying the \( hOGG1 \) Cys/Cys genotype did not have significantly increased lung cancer risk compared with those carrying the Ser/Ser genotype (OR, 1.15; 95% CI, 0.94-1.41; \( P = 0.02 \) for heterogeneity; data not shown). Similarly, no significant association with lung cancer risk was found in either a recessive model (OR, 1.09; 95% CI, 0.90-1.32 for Cys/Cys versus Ser/Cys+Ser/Ser; \( P = 0.02 \) for heterogeneity; data not shown) or a dominant model (OR, 1.06; 95% CI, 0.93-1.21 for Cys/Cys+Ser/Cys versus Ser/Ser; \( P = 0.003 \) for heterogeneity; Fig. 1).

In the stratified analysis by ethnicity, significantly increased risk were found among Asian subjects (OR, 1.18; 95% CI, 1.01-1.38 for Cys/Cys versus Ser/Cys+Ser/Ser; \( P = 0.02 \) for heterogeneity; data not shown) or a dominant model (OR, 1.06; 95% CI, 0.93-1.21 for Cys/Cys+Ser/Cys versus Ser/Ser; \( P = 0.003 \) for heterogeneity; Fig. 2) in a dominant model. However, among Caucasian subjects,

![Figure 1. ORs of lung cancer associated with the \( hOGG1 \) Cys/Cys+Ser/Cys genotypes compared with the Ser/Ser genotype. For each study, the estimates of OR and its 95% CI are plotted with a box and a horizontal line. ♠, pooled OR and its 95% CI.](image-url)
no significant association with lung cancer risk was found in either a dominant model (OR, 0.99; 95% CI, 0.83-1.19 for Cys/Cys+Ser/Cys versus Ser/Ser; P = 0.003 for heterogeneity; data not shown) or a recessive model (OR, 1.08; 95% CI, 0.78-1.49 Cys/Cys versus Ser/Cys+Ser/Ser; P = 0.04 for heterogeneity; data not shown).After excluding two studies whose controls had inconsistent genotype distribution with that of the Hardy-Weinberg equilibrium, there were significant differences in terms of the variant Cys326 allele frequency in control subjects among three ethnic groups (Caucasian, 21.7%; Asian, 42.2%; Mixed, 37.8%; P < 0.0001; Fig. 3). In further sensitivity analysis, we found that the ORs in the Park’s study, whose controls were selected from cancer screening center, were significantly apart away from those of other studies with either hospital- or population-based controls. When the Park’s study was excluded, there was no evidence of heterogeneity in the quantitative analysis among Caucasians (P = 0.23 for heterogeneity).

Further stratified analysis by control source was done for the remaining studies after the two studies were excluded because the distributions of the genotyping data of their controls deviated from that of the Hardy-Weinberg equilibrium. Compared with the Ser/Ser genotype, the OR for the hOGG1 Cys/Cys genotype was 1.32 (95% CI, 1.01-1.71; Fig. 4) for population-based studies and 1.18 (95% CI, 0.98-1.42; Fig. 5) for hospital-based studies. By comparing the genotype distribution in controls between population- and hospital-based studies, we found that the proportion of the Cys/Cys genotype among controls in hospital-based studies was a nonsignificantly higher than those in population-based studies (13.6% versus 12%; P > 0.05; Table 2). These data imply that in those studies whose controls were selected from hospitals, the estimate for lung cancer risk may be underestimated.

In the stratified analysis by smoking status, because of different smoking status grouped into one reference group in each study, we had to use smoking information from those studies with data on ever smokers versus never smokers. As a result, only four studies were included in the stratified analysis. The hOGG1 polymorphism was found to be associated with a significantly increased risk among nonsmokers (OR, 1.32; 95% CI, 1.04-1.67 for Cys/Cys+Ser/Cys versus Ser/Ser; P = 0.82 for heterogeneity; data not shown) but with a nonsignificantly decreased risk (OR, 0.94; 95% CI, 0.83-1.06 for Cys/Cys+Ser/Cys versus Ser/Ser; P = 0.44 for heterogeneity) among smokers in dominant model (data not shown).

Bias Diagnostics. In the bias diagnosis, we found that the summary ORs were changing around 1 in early studies. In a random effect model, the summary OR for Cys/Cys versus Ser/Ser was 1.01 for studies published before 2002, 1.29 during 2004 to 2005, and 0.98 during 2006 to 2007. In the funnel plot analysis of publication bias (in the contrast of homozygous genotype plotted against the precision), the shape of the funnel plot seemed symmetrical, suggesting that the main estimate of the association belonged to the larger study (Fig. 6). Furthermore, the Egger’s test provided statistical evidence of the funnel plot symmetry (23). In the linear regression analysis, the intercept value provided admeasure of asymmetry—the larger its deviation from zero, the more pronounced the asymmetry. We observed an intercept value of 0.44, which did not deviate from zero (t = 0.57; P = 0.575).

Discussion

We conducted a meta-analysis of published studies to evaluate the association between the hOGG1 Ser326Cys polymorphism and lung cancer risk because no such meta-analysis has been published to date. We found no statistical evidence of an overall effect of the Ser326Cys polymorphism on lung cancer risk in either recessive or

<table>
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<th>Study or Subgroup</th>
<th>Case</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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<td>Total</td>
<td>Weight</td>
<td>M.H. Fixed, 95% CI</td>
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<td>136</td>
<td>172</td>
<td>240</td>
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<tr>
<td>lung menacing 1998</td>
<td>29</td>
<td>46</td>
<td>27</td>
<td>42</td>
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<td>812</td>
<td>1097</td>
<td>271</td>
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<td>91</td>
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<td>lung Le et al. 2002</td>
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<td>97</td>
<td>100</td>
<td>150</td>
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<td>160</td>
<td>200</td>
<td>169</td>
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<td>200</td>
<td>277</td>
<td>195</td>
<td>227</td>
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<tr>
<td>lung Sunaga et al. 2002</td>
<td>144</td>
<td>198</td>
<td>102</td>
<td>152</td>
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<tr>
<td>Total (95% CI)</td>
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<td>1514</td>
<td>100.0%</td>
<td>1.18 [1.01, 1.38]</td>
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<tr>
<td>Total events</td>
<td>1591</td>
<td>1098</td>
<td></td>
<td></td>
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Figure 2. ORs of lung cancer associated with the hOGG1 Cys/Cys+Ser/Cy genotype compared with the Ser/Ser genotype among Asian subjects. For each study, the estimates of OR and its 95% CI are plotted with a box and a horizontal line. In the funnel plot analysis of publication bias (in the contrast of homozygous genotype plotted against the precision), the shape of the funnel plot seemed symmetrical, suggesting that the main estimate of the association belonged to the larger study (Fig. 6). Furthermore, the Egger’s test provided statistical evidence of the funnel plot symmetry (23). In the linear regression analysis, the intercept value provided admeasure of asymmetry—the larger its deviation from zero, the more pronounced the asymmetry. We observed an intercept value of 0.44, which did not deviate from zero (t = 0.57; P = 0.575).

Figure 3. Variant Cys326 allele frequency among control subjects between the three major ethnicities.
dominant effect models. Compared with the homozygous Ser/Ser genotype, the variant Cys/Cys homozygous genotype was not significantly associated with overall lung cancer risk in all subjects from 17 eligible studies included in the analysis.

Generally, oxidative damage to DNA is continuously produced as a result of endogenous oxidative stress and exposure to chemical carcinogens. If hOGG1 is dysfunctional, the damage could be left unrepaired, leading to mutations or carcinogenesis. Some studies have suggested that the amino acid change in hOGG1 may affect the catalytic properties of the enzyme (25, 26). One explanation for the functional relevance of the polymorphism is that the variant allele may be tightly linked to other possibly functional polymorphisms in hOGG1 or other genes involved in repair of oxidative damage to DNA. Another possible explanation is that the Cys326Cys genotype may be deficient in repair of oxidative damage to DNA only under conditions of excessive cellular oxidative stress (25). However, these hypotheses need to be tested in future studies.

In the stratified analysis by ethnicity, a fixed 18% increased lung cancer risk associated with the Ser326Cys polymorphism in a dominant effect model (i.e., Ser/Cys+Cys/Cys versus Ser/Ser) was found in Asian, but not in Caucasian, subjects. The frequency of variant Cys326 allele among Asian subjects was much higher than that of Caucasians (42.2% versus 21.7%), suggesting that this allele may be differently distributed among ethnic groups (16–18, 27–29). This ethnic difference might reflect the fact that different ethnic and environmental exposures may have modified the associations. It seems that Asians may have a much higher susceptibility to lung cancer due to having a higher frequency of the variant Cys326 allele.

In the case-control studies included in the analysis, some controls were selected from populations living in the same community and others from hospitalized patients admitted for diseases other than lung cancer. Compared among different control populations, hospital inpatients were relatively easier, more convenient, and economical to be recruited as the needed controls. However, they may just represent a sample of ill-defined reference population, and selection bias sometimes cannot be avoided, particularly if genotyping data were associated with the disease conditions the controls had. Indeed, we found that the proportion of the Cys/Cys genotype among controls in hospital-based studies was a slightly higher than that in population-based controls (13.6% versus 12%), which may explain why the OR (for the hOGG1 Cys/Cys versus Ser/Ser) in population-based studies were higher than that in hospital-based studies (1.32 versus 1.18); in particular, one study used controls selected from cancer screening center (17), who had an ever lower proportion of the Cys/Cys genotype, and generated a much greater OR (4.1 for Cys/Cys

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**Figure 4.** ORs of lung cancer associated with the hOGG1 Cys/Cys genotype compared with the Ser/Ser genotype in population-based studies excluding one study that deviated from the Hardy-Weinberg equilibrium. For each study, the estimates of OR and its 95% CI are plotted with a box and a horizontal line. ◆, pooled OR and its 95% CI.

**Figure 5.** ORs of lung cancer associated with the hOGG1 Cys/Cys genotype compared with the Ser/Ser genotype in hospital-based studies excluding one study that deviated from the Hardy-Weinberg equilibrium. For each study, the estimates of OR and its 95% CI are plotted with a box and a horizontal line. ◆, pooled OR and its 95% CI.
versus Ser/Ser) than that observed in other studies included in this meta-analysis. Therefore, the use of a proper, representative control population is important in reducing biases in reported case-control studies.

It is believed that tobacco carcinogens that induce 8-hydroxydeoxyguanine are a major cause for development of lung cancers, and that the risk for developing lung cancer could be modulated by the \textit{hOGG1} polymorphism. In this meta-analysis, we found it difficult to assemble the data that had different grouping methods for reporting tobacco use. As a result, from 4 of the 17 studies (15, 24, 27, 30), we could extract the \textit{hOGG1} polymorphism data for smokers and nonsmokers only. Although the \textit{hOGG1} polymorphism was not associated with lung cancer risk in smokers, significant associations were found in nonsmokers. The nonsmokers with \textit{hOGG1} Cys/Cys+Cys/Ser genotypes had an increase lung cancer risk by 32% compared with those with the \textit{hOGG1} Ser/Ser genotype. It is possible that individuals with the variant \textit{hOGG1} 326Cys allele were more susceptible to smoking-related cancer even being exposed to low levels of tobacco smoke, and it is also likely that these nonsmokers may have been exposed to passive smoking. These hypotheses also need to be tested in future studies.

There are some limitations inherent in this meta-analysis. First, selection bias could have played a role because the genotype distribution of this polymorphism among control subjects deviated from the Hardy-Weinberg equilibrium at least in two studies (21, 24). Second, lack of the original data limited our further evaluation of potential gene-gene and gene-environment interactions. Third, lack of information on disease status, genotypes, and well-documented smoking status may also influence the results. Fourth, most of the studies except for two (15, 27) had a relatively small sample sizes (<500 cases and 500 controls) and included only one ethnic group. Finally, the studies included in the analysis may have used different genotyping methods that had different quality control issues.

In summary, large studies including different ethnic groups with a careful matching between cases and controls should be considered in future association studies to confirm results from this meta-analysis and to further evaluate the effect of gene-gene and gene-environment interactions on the \textit{hOGG1} polymorphism–associated lung cancer risk. Another area of interest is functional studies of the two \textit{hOGG1} polymorphic protein forms in DNA repair ability and their potential use as biomarkers for lung cancer risk in Asian populations.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

**Acknowledgments**
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### Table 2. The distribution of Cys/Cys and Ser/Ser genotype among control groups from hospital-, population-, and cancer screening–based studies

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<tr>
<th>Control source</th>
<th>Genotype distribution of control group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>Hospital based</td>
<td>Cys/Cys 83 (13.6%) Ser/Ser 1,792 (86.4%)</td>
<td>2,075</td>
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<tr>
<td>Population based</td>
<td>Cys/Cys 139 (12%) Ser/Ser 1,020 (88%)</td>
<td>1,159</td>
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<tr>
<td>Cancer Screening</td>
<td>Cys/Cys 8 (3%) Ser/Ser 255 (97%)</td>
<td>263</td>
</tr>
<tr>
<td>Total</td>
<td>Cys/Cys 589 (14.3%) Ser/Ser 3,544 (85.7%)</td>
<td>4,133</td>
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**NOTE:** $\chi^2 = 24.452, P < 0.0001$ for overall comparison between 1, 2, and 3; $\chi ^2 = 1.775, P > 0.05$ for comparison between 1 and 2.
References


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