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ORIGINAL ARTICLE

hOGG1 Ser326Cys polymorphism and risk of lung cancer by histological type

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Human 8-oxoguanine DNA glycosylase 1 (*hOGG1*) has a major role in the repair of 8-hydroxyguanine, a major promutagenic DNA lesion. The genetic polymorphism rs1052133, which leads to substitution of the amino acid at codon 326 from Ser to Cys, shows functional differences, namely a decrease in enzyme activity in *hOGG1*-Cys326. Although several studies have investigated the association between rs1052133 and lung cancer susceptibility, the effect of this locus on lung cancer according to histology remains unclear. We therefore conducted a case–control study with 515 incident lung cancer cases and 1030 age- and sex-matched controls without cancer, and further conducted a meta-analysis. In overall analysis, the homozygous Cys/Cys genotype showed a significant association with lung cancer compared to Ser allele carrier status (odds ratio (OR)=1.31, 95% confidence interval (CI)=1.02–1.69). By histology-based analysis, the Cys/Cys genotype showed a significantly positive association with small-cell carcinoma (OR=2.40, 95% CI=1.32–4.49) and marginally significant association with adenocarcinoma (OR=1.32, 95% CI=0.98–1.77). A meta-analysis of previous and our present study revealed that this polymorphism is positively associated with adenocarcinoma, although suggestive associations were also found for squamous- and small-cell lung cancers. These results indicate that rs1052133 contributes to the risk of adenocarcinoma of lung.
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Keywords: *hOGG1*; lung cancer; polymorphism

INTRODUCTION

Cancer is linked to environmental exposure to various carcinogens, of which tobacco smoke is a well-known example. Exposure leads to various types of DNA damage, such as oxidative damage. Genetic variations in DNA repair genes are associated with DNA repair capacity, suggesting a consequent association with cancer risk.[1]

8-Hydroxyguanine, produced by reactive oxygen species in tobacco smoke, is a major form of DNA damage.[2] This alteration to the DNA structure causes G:C to T:A transversions, and may thus be responsible for mutations that lead to carcinogenesis.[3] Human 8-oxoguanine DNA glycosylase 1 (*hOGG1*) has been extensively studied as the main enzyme involved in the repair of 8-oxoG DNA adducts. Although it has a major role in the repair of 8-hydroxyguanine, however, its role in carcinogenesis has not been well elucidated.[4] Genetic polymorphisms of *hOGG1* have been documented, and the polymorphism Ser326Cys (rs1052133) is associated with complementation activity for *Escherichia coli* mutants that are defective in the repair of 8-hydroxyguanine. Activity in the repair of 8-hydroxyguanine is greater with the *hOGG1*-Ser326 protein than the *hOGG1*-Cys326 protein,[5] and the possible contribution of this locus to the risk of a variety of human cancers has been reported.[6]

A number of studies[7–14] and systematic approaches[15–17] have examined the role of the Ser326Cys polymorphism in lung cancer susceptibility. One meta-analysis showed that the overall odds ratio (OR) of homozygotes for the *hOGG1*-326Cys allele against those for the *hOGG1*-326Ser allele was 1.24 (95% confidence interval (CI)=1.01–1.53), suggesting that the locus is involved in susceptibility to overall lung cancer.[17] In contrast, another meta-analysis reported no significant association.[15] A recent pooled analysis from the International Lung Cancer Consortium involving a substantial number of cases and controls showed a suggestive association for this polymorphism in Caucasians.[16] One question that remains unanswered is whether the impact of rs1052133 differs according to histological subtype of lung cancer.

Here, we evaluated the role of the *hOGG1* Ser326Cys polymorphism in lung cancer susceptibility among a Japanese population in

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consideration of histology. We also conducted a meta-analysis of the literature to evaluate the impact of this polymorphism by histology.

MATERIALS AND METHODS

Subjects

The case subjects were 515 patients who were newly and histologically diagnosed with lung cancer and who had no history of cancer. Controls were randomly selected from among the 2395 cancer-free individuals and matched by age (± 3 years) and sex to cases in a 1:2 case/control ratio. All subjects were recruited within the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), as described elsewhere,[18,19] and were exactly the same cohort we reported on in a previous paper.[20] In brief, information on lifestyle factors was collected using a self-administered questionnaire from all first-visit outpatients at Aichi Cancer Center Central Hospital aged 18–79 who were enrolled in the HERPACC between January 2001 and November 2005. Response was checked by a trained interviewer. Outpatients were also asked to provide blood samples. Each patient was asked about their lifestyle when healthy or before the current symptoms developed. Approximately 95% of eligible subjects completed the questionnaire and 60% provide blood samples. The data were loaded into the HERPACC database and routinely linked with the hospital-based cancer registry system to update the data on cancer incidence. All participants gave written informed consent and the study was approved by institutional ethical committee of Aichi Cancer Center.

Genotyping of *hOGG1*

DNA from each sample was extracted from the buffy coat fraction using a BioRobot EZ1 with an EZ1 DNA Blood 350 µl kit or QIAamp DNA Blood mini kit (Qiagen KK, Tokyo, Japan). Polymorphisms of *hOGG1* Ser326Cys were examined based on TaqMan assays by Applied Biosystems (Foster City, CA, USA). The principle of the TaqMan real-time polymerase chain reaction (PCR) assay system using fluorogenic probes and 5′ nuclease has been described by Livak.[21] All of the assays were carried out in 96-well PCR plates using a 7500 Fast Real-Time PCR System (Applied Biosystems) coupled with the 7500 Fast System SDS software. Amplification reactions (5 µl) were carried out in duplicate with 30 ng of template DNA, 2× TaqMan Universal Master Mix buffer (Applied Biosystems) and 20× primer and probe mix (Applied Biosystems). Thermal cycling was initiated with a first denaturation step of 20 s at 95 °C, and then by 40 cycles of 3 s at 95 °C and 30 s at 62 °C. Genotyping quality was statistically assessed using the Hardy–Weinberg test in our laboratory; when allelic distributions for controls departed from the Hardy–Weinberg frequency, genotyping was assessed using another method.

Consumption of tobacco, alcohol, fruits and vegetables

Cumulative smoking dose was evaluated as pack-years (PY), the product of the number of packs consumed per day and the number of years of smoking. Smoking habit was entered in the four categories of never, former, and current smokers of <40 and ≧40 PY. Former smokers were defined as those who quit smoking at least 1 year before the survey. Drinking habit was categorized in the three categories of never, former and current drinkers. Former drinkers were defined as those who quit drinking at least 1 year before the survey. Consumption of fruits and vegetables was determined using a semiquantitative food frequency questionnaire (SQFFQ), described in detail elsewhere.[22] Briefly, the SQFFQ consisted of 47 single food items with frequencies in eight frequency categories. We estimated average daily intake by multiplying the frequency of intake by the serving size of food (in grams). Energy-adjusted intake of fruits and vegetables was calculated by the residual method.[23] The SQFFQ was validated using a 3-day weighed dietary record as standard, which showed that reproducibility and validity were acceptable.[24]

Statistical analysis

To assess the strength of associations between *hOGG1* polymorphism and risk of lung cancer, we estimated ORs with 95% CIs, using conditional logistic models adjusted for potential confounders. For stratified analyses exploring interactions, we applied unconditional logistic regression models because matching was not retained after stratification by smoking and drinking habit and carotene intake in conditional models. Fruit and vegetable intake was categorized into three levels by applying thresholds of tertiles among controls. Potential confounders considered in the multivariate analyses were age, sex, smoking habit (never smokers, former smokers, current smokers of less than 40 or 40 or more PY), drinking habit (never, former and current drinkers), total energy intake (as a continuous variable), and dietary fruit and vegetable intake (g per day, tertiles). Missing values for each covariate were treated as dummy variables and were included in the model. Trend for genotype was assessed by application of a score test value for each genotype (0, homozygous for reference allele or combined reference genotypes; 1, heterozygote or one reference genotype and 2, homozygous nonreference allele or nonreference genotype). Differences in categorized demographic variables between cases and controls were tested by the χ^2-test. Mean values for age and total energy intake were compared for cases and controls by Wilcoxon's signed-rank test. Accordance with the Hardy–Weinberg equilibrium was checked for controls using the χ^2-test and the exact *P*-value was used to assess any discrepancies between

Table 1 Characteristics of case and control subjects

	Cases (n=*515*) n *(%)*	*Controls* (n=*1030*) n *(%)*	P-*value*
Age			
<50	53 (10.3)	108 (10.5)	
50–59	142 (27.6)	283 (27.5)	
60–69	193 (37.5)	389 (37.8)	
70–79	127 (24.7)	250 (24.3)	1.00
Mean age (range)	61.9 (23–79)	61.8 (26–79)	0.87
Sex			
Male	381 (74.0)	762 (74.0)	
Female	134 (26.0)	268 (26.0)	1.00
Smoking (Pack-years)			
<5	136 (26.4)	424 (41.2)	
5–19.9	31 (6.0)	118 (11.5)	
20–39.9	88 (17.1)	208 (20.2)	
>40	258 (50.1)	275 (26.7)	<0.001
Unknown	2 (0.4)	5 (0.5)	
Drinking status			
Never	196 (38.1)	378 (36.7)	
Former[a]	15 (2.9)	56 (5.4)	
Current	304 (59.0)	596 (57.9)	0.08
Fruit/vegetable consumption (g per day)			
Tertile 1 (<118.4)	199 (38.8)	342 (33.2)	
Tertile 2 (118.4–211.3)	140 (27.3)	341(33.1)	
Tertile 3 (>211.4)	166 (32.4)	341(33.1)	0.03
Unknown	8(1.6)	6 (0.6)	
Total energy intake (kcal, s.d.)[b]	1670 (371)	1676 (352)	1.00
Histology			
AD	316 (61.4)		
SQ	91 (17.7)		
SM	55 (10.7)		
LA	40 (7.8)		
Others	13 (2.5)		

Abbreviations: AD, adenocarcinoma; LA, large-cell carcinoma; SM, small-cell carcinoma; SQ, squamous-cell carcinoma.
[a]Former drinkers were defined as subjects who had quit drinking at least 1 year previously.
[b]Energy-adjusted.

genotypes and allele frequencies, with a *P*-value of less than 0.05 considered statistically significant. All analyses were performed using STATA version 10.1 (Stata, College Station, TX, USA).

Meta-analysis

We conducted a meta-analysis of relevant articles reporting associations between the *hOGG1* polymorphism and lung cancer in consideration of the histological subtypes adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. Medline was searched for papers published between January 1995 and March 2009 and indexed with the terms (lung neoplasms AND (hOGG1 OR OGG1)). Inclusion criteria were (1) reporting of ORs or risk ratios calculated by comparing the Ser/Ser to the Cys/Cys or Cys allele carrier according to histological subtype; (2) a cohort, nested case–control, population-based case–control or hospital-based case–control study design and (3) use of cancer-free controls. All potentially relevant papers were independently reviewed by at least two investigators (TO and KM) and any disagreements were resolved by consensus. The reference lists of studies identified through the search process were also checked. Among the 65 papers identified through this process, 7 were considered eligible.[5,7–11,17] Two investigators (TO and KM) abstracted the data independently. We used OR from a random-effect model as a summary statistic for association.[25] Heterogeneity among the studies was examined based on the *Q* and I^2 statistics. The latter indicates the proportion of variation in summary estimates attributable to heterogeneity.[26] We determined which model to use to calculate summary OR and its 95% CI, a random- or fixed-effect model, based on significance in the *Q* statistics. The meta-analysis was conducted using the 'metan' command[27] in STATA version 10.1.

RESULTS

Characteristics of the 515 cases and 1030 controls are shown in Table 1. Age and sex were appropriately matched. Smoking habits differed remarkably between cases and controls, with the proportion of current smokers of 40 PY or more significantly higher in cases. Former drinkers tended to be more common among cases, albeit without statistical significance. Consumption of fruits and vegetables was significantly lower among cases. The distribution of histological type among cases was as follows: adenocarcinoma, 61.4% (n=316); squamous-cell carcinoma, 17.7% (n=91); small-cell carcinoma, 10.7% (n=55); large cell carcinoma, 7.8% (n=40) and others, 2.5% (n=13).

Table 2 presents the frequency distribution of *hOGG1* genotypes and ORs with 95% CI for lung cancer cases compared with controls. No significant dissociation from the Hardy–Weinberg equilibrium was observed among controls. In overall analysis, Cys/Cys showed a significantly positive association with lung cancer. The confounder-adjusted OR for Cys/Cys relative to Ser/Ser+Ser/Cys was 1.31 (1.02–1.69, P=0.036). In histology-based analysis, those with the Cys/Cys genotype were at significantly increased risk of small-cell carcinoma and marginally significantly increased risk of adenocarcinoma, compared to those with the Ser/Cys and Ser/Ser genotypes combined. No significant associations were observed for squamous-cell carcinoma.

Table 3 shows associations between *hOGG1* Ser326Cys polymorphism combined with smoking and lung cancer risk. In overall analysis, the effect of cumulative smoking dose was stronger in those with Cys/Cys. In analyses by histology, a similar trend was observed for adenocarcinoma and small-cell carcinoma but not for squamous-cell carcinoma. This trend was more prominent for small-cell carcinoma. Adjusted ORs for heavy smoking (PY≧40) were 26.3 (5.34–129.6) for the Ser allele carrier and 72.3 (14.6–358.2) for those with the Cys/Cys.

To further examine the impact of *hOGG1* Ser326Cys polymorphism according to histology, we conducted a meta-analysis. Table 4 shows a summary of studies that have investigated the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk, including the present study. As shown in Figure 1, *hOGG1* Ser326Cys polymorphism summary ORs showed a significant association with adenocarcinoma (OR=1.44, 95% CI=1.18–1.77) with no significant heterogeneity. Although squamous-cell carcinoma showed a similarly increased risk (OR=1.81, 95% CI=1.06–3.07), the significant heterogeneity across studies (I^2=58.5) was a limitation. Although without significance and from a limited number of studies, the pooled estimate was 2.05 (0.91–4.63), suggesting an increased risk for small-cell carcinoma.

Table 2 *hOGG1* genotype distribution and ORs for lung cancer

	Cases	*Controls*				
Genotype	n=*515*	n=*1030*	*OR1 (95% CI)*[a]	P-*value*	*OR2 (95% CI)*[b]	P-*value*
Overall						
Ser/Ser	117	250	1.00 (reference)		1.00 (reference)	
Ser/Cys	257	544	1.01 (0.77–1.32)		0.96 (0.72–1.26)	
Cys/Cys	141	236	1.28 (0.94–1.73)	0.054	1.27 (0.93–1.75)	0.047
Ser/Ser+Ser/Cys	374	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	141	236	1.27 (1.00–1.62)	0.05	1.31 (1.02–1.69)	0.036
Adenocarcinoma						
Ser/Ser+Ser/Cys	227	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	89	236	1.29 (0.97–1.72)	0.085	1.32 (0.98–1.77)	0.066
Squamous-cell carcinoma						
Ser/Ser+Ser/Cys	72	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	19	236	0.99 (0.58–1.70)	0.98	1.10 (0.63–1.94)	0.73
Small-cell carcinoma						
Ser/Ser+Ser/Cys	34	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	21	236	2.22 (1.26–3.92)	0.006	2.40 (1.22–4.12)	0.009

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, smoking habit, drinking habit, total energy intake and energy-adjusted fruit/vegetable intake.

Table 3 Associations between *hOGG1* Ser326Cys polymorphisms and smoking by PY on lung cancer risk

	Ser (+)		*Cys/Cys*	
Histology	*Case/Control*	*OR (95% CI)*[b]	*Case/Control*	*OR (95% CI)*[b]
Overall[a]				
Smoking (pack-years)		Ser (+)		Cys/Cys
<5	95/317	1.0 (reference)	41/107	1.35 (0.88–2.09)
5–19.9	22/89	1.26 (0.72–2.21)	9/29	1.29 (0.55–3.03)
20–39.9	66/160	2.38 (1.53–3.68)	22/48	2.54 (1.39–4.63)
>40	191/223	5.26 (3.54–7.78)	67/52	7.44 (4.53–12.2)
Adenocarcinoma				
Smoking		Ser (+)		Cys/Cys
<5	89/317	1.0 (reference)	39/107	1.36 (0.87–2.13)
5–19.9	15/89	0.95 (0.50–1.79)	5/29	0.70 (0.23–2.13)
20–39.9	39/160	1.62 (0.98–2.66)	13/48	1.75 (0.86–3.54)
>40	84/223	2.75 (1.77–4.28)	30/52	3.99 (2.25–7.08)
Squamous-cell carcinoma				
Smoking		Ser (+)		Cys/Cys
5–19.9	3/406	1.0 (reference)	3/136	3.22 (0.64–16.3)
20–39.9	13/160	6.99 (1.93–25.4)	5/48	8.99 (2.04–39.5)
>40	56/223	19.5 (5.87–64.3)	11/52	16.6 (4.37–63.0)
Small-cell carcinoma				
Smoking		Ser (+)		Cys/Cys
5–19.9	2/406	1.0 (reference)	1/136	1.50 (0.13–16.7)
20–39.9	8/160	12.6 (2.39–66.2)	4/48	18.8 (3.09–114.3)
>40	24/223	26.3 (5.34–129.6)	16/52	72.3 (14.6–358.2)

Abbreviations: CI, confidence intervals; OR, odds ratios.
[a]Five controls and two cases are excluded from analysis because of smoking information unknown.
[b]ORs were adjusted for age, sex, smoking habit, drinking habit, total energy intake and energy-adjusted fruit/vegetable intake.

Table 4 Summary of published studies examining association between *OGG1* polymorphism and lung cancer risk according to histology

		Subjects in each study						*Odds ratio (95% CI) for Cys/Cys relative to Ser/Ser*		
		Case								
Author	*Year*	*Total*	*Adeno*	*Squamous*	*Small*	*Control*	*Ethnicities*	*Adeno*	*Squamous*	*Small*
Sugimura *et al.*[7]	1999	241	1974	78	118	197	Japanese	1.34 (0.53–3.39)	2.27 (0.92–5.60)	0.51 (0.09–2.87)
Wikman *et al.*[8]	2000	105	50	50	NA	105	Caucasian	1.84 (0.41–14.41)	1.76 (0.24–13.1)	NE
Ito *et al.*[9]	2002	138	138	0	0	241	Japanese	0.81 (0.44–1.52)	NE	NE
Le Marchand *et al.*[10]	2002	298	141	66	43	405	Caucasian, Japanese and Hawaiian	2.1[a] (1.1–3.9)	3.7[a] (1.7–8.3)	3.4[a] (1.1–10.4)
Park *et al.*[11]	2004	179	63	56	32	358	Caucasian	4.20 (1.10–15.8)	4.8 (1.1–21.0)	NE
Hung *et al.*[17]	2005	2188	499	902	0	2198	Caucasian	1.66 (1.04–2.66)	1.02 (0.63–1.64)	NE
Kohno *et al.*[12]	2006	1097	1097	0	0	394	Japanese	1.47 (1.02–2.13)	NE	NE
Our study	2009	515	316	91	55	1030	Japanese	1.32 (0.98–1.77)	1.10 (0.63–1.94)	2.40 (1.22–4.12)

Abbreviations: CI, confidence intervals; NE, not estimated; OR, odd ratios.
[a]ORs are calculated as that of the homozygous Cys/Cys genotype compared to those with the Ser/Ser and Ser/Cys genotype combined.

DISCUSSION

In this case–control study, we found that the *hOGG1* 326Cys/Cys genotype, which results in weaker activity, was associated with a significantly increased risk of lung cancer overall. By subtype we found a significant association of the Cys/Cys genotype with small-cell carcinoma and a marginally significant association with adenocarcinoma. Moreover, in our subsequent meta-analysis of epidemiological studies based on histology, we observed that this genotype was associated with an increased risk of adenocarcinoma. Although results for squamous- and small-cell carcinoma were not conclusive,

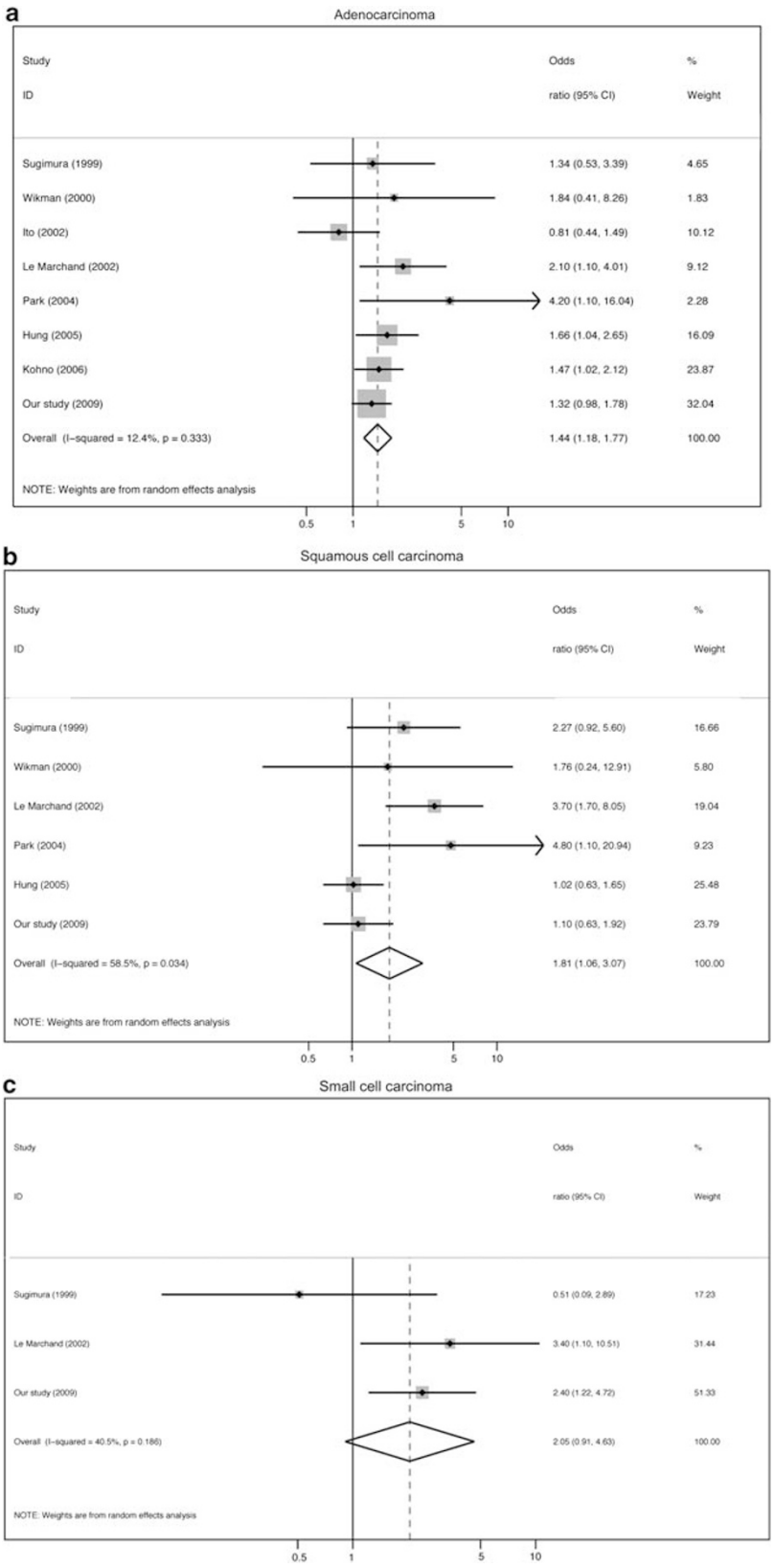

Figure 1 Meta-analysis for human 8-oxoguanine DNA glycosylase 1 (hOGG1) polymorphism according to histological subtype. A meta-analysis was conducted of the studies listed in Table 4. We extracted the ORs and 95% CIs for the Cys/Cys homozygotes of *hOGG1* relative to the Ser/Ser according to histological subtype from each study. We applied a random-effect model. An OR >1.0 indicates a higher risk with the Cys/Cys genotype than with Ser/Ser homozygotes. I^2 indicates the proportion of variation in summary estimates attributable to heterogeneity. All analyses were performed using the 'metan' command in STATA (version 10.1).

we also identified a potentially increased risk for these types of lung cancer.

Results of a number of studies examining the role of the *hOGG1* Ser326Cys polymorphism in lung cancer susceptibility conducted to date have been inconsistent.[7–12,17] Our case–control study showed a significant association between *hOGG1* Ser326Cys polymorphism and lung cancer overall, supporting the potential effect of this polymorphism on lung cancer susceptibility. Because the question of whether the effect of this polymorphism differed by histology remained unanswered, we also conducted a meta-analysis with consideration to histology. To the best of our knowledge, this is the first report to summarize the association between *hOGG1* polymorphism and susceptibility by histological type. Results of our meta-analysis indicated that the effect is consistent for adenocarcinoma, but not for squamous- or small-cell carcinoma. This inconsistency might be due to the heterogeneity of populations and distribution of subtypes across studies. The subjects included in the analyses were mainly Japanese and Caucasian. The most common subtype was adenocarcinoma in Japanese but squamous-cell carcinoma in Caucasians. Given that the magnitude of effect of smoking on risk differs by histological subtype,[28] the magnitude of effect of the *hOGG1* polymorphism might also differ across subtypes and populations. Even within the same histological subtype, the effect of smoking differs with the presence of certain gene mutations in cancer.[29] A comprehensive understanding of the *hOGG1* polymorphism will thus require further study, with particular focus on squamous- and small-cell carcinomas.

Our case–control study had several potential limitations. One methodological issue was the selection of hospital-based patients without cancer as controls. However, because cases and controls were selected from the same hospital and almost all patients lived in the Tokai area of central Japan, the internal validity of this case–control study is likely acceptable. External validity (generalizability of the results) has been confirmed in our previous study.[30] In addition, to dilute any bias that might have resulted from the inclusion of a specific diagnostic group that is related to the exposure, we did not set eligibility criteria for control diseases. As for allele frequencies in the subjects, given that our frequencies were comparable to those previously reported in public databases such as HapMap JPT,[31] bias in the distribution of selected polymorphisms was negligible. Second, the self-reported values for lifestyle factors considered as potential confounders may be inaccurate. If present, however, any such misclassification would likely be nondifferential, and would likely underestimate the causal association. The meta-analysis was based on published data, and the potential for publication selection bias could not be ruled out even if heterogeneity across the studies was limited for adenocarcinoma.

In conclusion, we found a positive association between lung cancer and Cys/Cys individuals in a Japanese population. The association was clear for small-cell carcinoma and adenocarcinoma of the lung in this population. Further systematic evaluation revealed that associations with the locus were conclusive for adenocarcinoma. Further studies are needed to clarify the effect of genotype on squamous-cell carcinoma and small-cell carcinoma.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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