

RESEARCH COMMUNICATION

Association of the hOGG1 Ser326Cys Polymorphism with Increased Lung Cancer Susceptibility in Asians: a Meta-analysis of 18 Studies Including 7592 Cases and 8129 Controls

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Abstract

Objective: To understand the influence of the hOGG1 Ser326Cys polymorphism on lung cancer susceptibility, an updated meta-analysis was performed. **Methods:** A total of 7,592 patients and 8,129 controls from 18 studies, identified by searching ISI Web of Knowledge, PubMed, EMBase and CNKI database up to January 2011, were included. Unconditional multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** Overall, the hOGG1 Ser326Cys polymorphisms were associated with the risk of lung cancer. In the subgroup analyses by ethnicity, histological type, smoking status, significant association with lung cancer risk in Asians was found either in the dominant (crude OR, 1.19; 95% CI, 1.07-1.33 for Cys/Cys+Ser/Cys versus Ser/Ser) or recessive (crude OR, 1.21; 95% CI, 1.08-1.35 for Cys/Cys versus Ser/Cys+Ser/Ser) model. An increased risk with statistical significance was found in recessive model for squamous carcinoma (adjusted OR, 1.91; 95% CI, 1.30-2.80) and adenocarcinoma (adjusted OR, 1.52; 95% CI, 1.23-1.87). Significant association with lung cancer risk among heavy smokers was found in the recessive model (crude OR, 1.67; 95% CI, 1.26-2.21). **Conclusions:** The results indicated that the hOGG1 Ser326Cys polymorphism might contribute to the risk of non-small cell lung cancer in the Asian population.

Keywords: hOGG1 polymorphism - lung cancer - meta-analysis - Asian populations

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Introduction

As a complex disease and the leading cause of cancer-related death in many countries (Parkin et al., 2005; Jemal et al., 2011), lung cancer has environmental and genetic risk factors. DNA repair mechanisms have been reported to play an important role in the pathogenesis and development of lung cancer, more studies about DNA repair gene polymorphisms are available recently (Gackowski et al., 2003; Osawa et al., 2010; Shiraishi et al., 2010; Pramanik et al., 2011). One environmental well-known risk factor of lung cancer is tobacco smoking, tobacco smoke can lead to the formation of oxidative DNA damage. 8-Hydroxyguanine, produced by reactive oxygen species in tobacco smoke, is a major form of DNA damage and attracted more attention in the past years (Asami et al., 1996). Thus, human 8-oxoguanine DNA glycosylase 1 (hOGG1), encoded by the hOGG1 gene on chromosome 3p26 has been investigated as the key enzyme that involved in the repair of 8oxoG DNA adducts. It has been reported that activity in the repair of 8-Hydroxyguanine is greater with the hOGG1-Ser326 protein than the hOGG1-Cys326 protein, and a number of studies have examined the role of hOGG1 common

single nucleotide polymorphism (SNP) Ser326Cys in lung cancer susceptibility (Hung et al., 2005). The study by Lee et al. revealed that Cys326Cys genotype may be deficient in repair of oxidative damage to DNA only under conditions of excessive cellular oxidative stress (Lee et al., 2005), these results or conclusions need to be tested in future studies.

Negative association findings were reported by a previous meta-analysis (Li et al., 2008), this study indicated that individuals carrying the hOGG1 Cys/Cys genotype did not have significantly increased risk of overall lung cancer compared with those with the Ser/Ser genotype, and in stratified analyses by smoking status, the increased risk was observed only among nonsmokers in a dominant model. Another meta-analysis of lung cancer risk and genetic polymorphisms in DNA repair pathways indicated that hOGG1 Ser326Cys was associated with lung cancer risk with the OR of 1.22 (Kiyohara et al., 2010b). We found that in both of these two meta-analyses only crude pooled odds ratios (OR) were analyzed, limited attention was paid to the adjusted pooled ORs by other confounding factors. And some clarification is also needed for the included studies in the analyses, three included single studies (Vogel et al., 2004; Loft et al.,

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2005; Sørensen et al., 2006) shared the same data source, a Danish prospective follow-up study called Diet, Cancer and Health (DCH), also, another two studies (Sunaga et al., 2002; Kohno et al., 2006) were found to be with the overlapped population. These data duplication may have some possible effect on the final result.

To investigate the question in greater detail, the aims of our study were thus to update the meta-analysis with new searchable data and to evaluate the relationship between hOGG1 Ser326Cys polymorphism and lung cancer susceptibility.

Materials and Methods

Identification of eligible studies

Candidate studies were identified by searching the ISI Web of Knowledge database, PubMed, EMBase and the database of China National Knowledge Infrastructure (CNKI) for relevant articles without language restriction or publication year with the keywords “hOGG1/OGG1/OGG” and “polymorphism/genetic variation /single nucleotide polymorphisms/SNPs” and “lung cancer” (up to 10 January 2011). The references cited in the retrieved publications or graduation theses were also screened to trace further relevant studies. When studies from the same research group with overlapped population were found, only the one with larger population was included to avoid data duplication. Included studies had to meet the following criteria: (1) based on an unrelated lung cancer case-control design (only histologically confirmed diagnoses were included in the study); (2) reporting of genotyping data for the hOGG1 Ser326Cys polymorphism.

Data extraction

Two investigators (Guan P and Huang DS) independently extracted the data with the standard protocol and all the discordances were submitted to and decided by a third investigator (Zhou BS). The following

key eligibility items were collected and recorded for each study: last name of the first author, publication source (journal, graduation thesis, conference proceeding and etc.), year of publication, location of study, selection process and characteristics of cancer cases and controls, control source, demographics, ethnicity, gender, smoking status, variables used for adjustment or matching and genotyping information. Source of control included that controls came from population or hospital, histological type of lung cancer was divided into 3 subgroups, lung adenocarcinoma, lung squamous carcinoma and small cell lung carcinoma, ethnicity was sub-grouped into Caucasians, Asians and mixed, smoking status included never smoker, light smoker and heavy smoker.

Statistical analysis

Hardy-Weinberg equilibrium was first adopted to test the deviation of genotype distribution in the control group for each selected study. The heterogeneity between the studies was assessed by the Chi square-based Q-statistic and the heterogeneity was considered significant when $P < 0.05$.

Dependent on the results of heterogeneity test among individual studies, the fixed effect model or random effect model was selected to summarize the pooled OR. Pooled ORs and their corresponding 95% CIs were used to assess the strength of the associations between lung cancer and hOGG1 Ser326Cys polymorphism.

The pooled ORs were first estimated for the variant homozygous Cys/Cys and heterozygous Cys/Ser 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 dominant and recessive effect models, respectively. Furthermore, to investigate the origin of heterogeneity, the studies were categorized into subgroup analyses according ethnicity, gender, source of controls, histotype and smoking status.

Publication bias was assessed by a funnel plot and

Table 1. Characteristics of the Studies of hOGG1 Ser326Cys Polymorphism and Lung Cancer Risk

Author year	Location		No. of Cases/Controls			Matching	Source of controls	P value for Hardy-Weinberg
	Ethnicity	Total	Ser/Ser	Ser/Cys	Cys/Cys			
Kohno et al., 1998	Japan, A	45/42	16/15	19/20	10/7	No clear	Hospital	0.94
Sugimura et al., 1999	Japan, M	241/197	85/63	115/107	41/27	No clear	Hospital	0.08
Wikman et al., 2000	Germany, C	105/105	68/60	32/43	5/2	A/G/S	Hospital	0.07
Ito et al., 2002	Japan, A	138/241	40/68	71/119	27/54	No clear	Hospital	0.84
Le et al., 2002	USA, M	298/405	123/177	110/175	65/53	A/G/E	Population	0.35
Lan et al., 2004	China, A	118/109	37/51	61/43	20/15	A/G/R	Population	0.23
Park et al., 2004	USA, C	179/350	101/255	65/87	13/8	A/G/E	Screening	0.86
Hung et al., 2005	East Europe, C	2155/2163	1401/1368	661/716	93/79	A/G/C/R	Hospital	0.22
Wang et al., 2005	China, A	124/128	49/45	51/70	24/13	A/G/S	Hospital	0.06
Kohno et al., 2006	Japan, A	1097/394	285/123	544/190	268/81	No clear	Hospital	0.63
Sørensen et al., 2006	Denmark, C	431/796	254/479	155/284	22/33	G/S	Population	0.25
De Ruyck et al., 2007	Belgium, C	110/110	74/60	33/46	3/4	Gender	Hospital	0.18
Karahalil et al., 2008	Turkey, C	165/250	86/115	65/106	14/29	A/G/S/BMI	Hospital	0.55
Chang et al., 2009	Taiwan, A	1096/997	142/154	518/482	436/361	A/G/E/Ed	Population	0.74
Gao et al., 2009	China, A	86/90	27/30	35/49	24/11	No	Hospital	0.19
Miyaishi et al., 2009	Japan, A	108/121	27/39	55/54	26/28	A/G/S	Hospital	0.27
Okasaka et al., 2009	Japan, A	515/1030	117/250	257/544	141/236	Age	Hospital	0.07
Qian et al., 2010	China, A	581/601	100/125	288/291	193/185	A/G	Hospital	0.59

A, Asian; M, mixed; C, Caucasian; A/G/S/E/C/R/Ed, Age, gender, smoking, ethnicity, centre, region, education

Egger’s test (Egger et al., 1997). All analyses were done using NCSS (Number Cruncher Statistical Systems, Version 2.4; Kaysville, Utah) and Review Manager (Version 5.0). All the P values were two-sided.

Results

Characteristics of the studies and quality assessment

A total of 27 studies examining the association of the hOGG1 Ser326Cys polymorphism met our inclusion criteria, 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 three studies (Lee et al., 2005; Liang et al., 2005; Zienolddiny et al., 2006). There was one study that the results of Hardy-Weinberg equilibrium test could not be obtained, these 4 studies were subsequently excluded. And, the overlapped data was found in several studies, Vogel et al (2004), Loft et al (2006) and Sørensen et al (2006) adopted the same database, the study by Sørensen et al had the largest population; Kohno et al (2006) and Sunaga et al (2002) shared the same data source, Sunaga analyzed the part of lung adenocarcinoma. Finally, 18 studies including 7592 lung cancer cases and 8129 controls entered the final meta-analysis. Among them, 17 studies

were published in journals and one study was from an unpublished Master degree thesis. The characteristics of the included studies were summarized in Table 1.

Diverse genotyping methods were adopted in the collected studies, including TaqMan, PCR-RFLP (PCR-restriction fragment length polymorphism), PCR-SSCP (PCR-single strand conformation polymorphism), PCR-CTPP (PCR-polymerase chain reaction with confronting two-pair primers) and real-time PCR. Only half (9/18) of the studies mentioned quality control of the genotyping, such as random repeat or validation using a different genotyping method.

Quantitative synthesis

The frequency of hOGG1 326Cys allele varied across different ethnicities, the mean frequency was 54.2% (39.9%-63.4%) in the Asian lung cancer patient subjects and 20.8% (17.7%-28.2%) in Caucasian patient subjects.

Individuals carrying the hOGG1 Cys/Cys genotype had a modest but significantly increased lung cancer risk compared with those carrying the Ser/Ser genotype (adjusted OR, 1.35; 95% confidence interval (CI), 1.17-1.56; Q=17.85, P=0.16 for heterogeneity test, Table 2). Significant association with lung cancer risk was found in the recessive model (crude OR, 1.24; 95% CI, 1.13-1.36

Table 2. Summary of Pooled ORs of Overall and Subgroup Analysis of the Association of the hOGG1 Ser326Cys Polymorphism with Lung Cancer Risk

Strata/Subgroup		Cys/Cys : Ser/Ser		Cys/Cys+Ser/Cys : Ser/Ser ¹		Cys/Cys : Ser/Cys+Ser/Ser ²	
		Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Source of Controls							
Hospital	N OR	13 1.24 (1.08-1.42)	10 1.27 (1.08-1.49)	13 0.99(0.91-1.07)	-	13 1.20 (1.07-1.35)	2 1.42 (1.12-1.80)
	Q (P value)	9.79 (0.63)	9.72 (0.37)	17.3 (0.14)	-	13.1 (0.36)	3.80 (0.05)
Population	N OR	4 1.50 (1.19-1.89)	3 1.67 (1.13-2.46)	5 1.34 (1.05-1.72)	1	5 1.29 (1.11-1.50)	-
	Q (P value)	1.53 (0.68)	2.29 (0.32)	13.97(0.02)	-	8.80(0.07)	-
Ethnicity							
Asian	N OR	12 1.35 (1.18-1.55)	8 1.36 (1.14-1.63)	12 1.19 (1.07-1.33)	-	11 1.21 (1.08-1.35)	-
	Q (P value)	5.88 (0.88)	4.80(0.68)	7.47 (0.76)	-	11.3 (0.33)	-
Caucasian	N OR	7 1.20(0.95-1.51)	7 1.25(0.96-1.62)	7 0.97(0.88-1.07)	1	7 1.22 (0.98-1.54)	-
	Q (P value)	11.8 (0.07)	11.0 (0.09)	21.6 (0.00)	-	8.72 (0.19)	-
Histotype							
SCC	N OR	6 1.23(0.90-1.67)	5 1.45 (1.01-2.10)	6 1.01(0.88-1.16)	-	9 1.95 (1.14-3.35)	4 1.91 (1.30-2.80)
	Q (P value)	5.99 (0.31)	6.31(0.18)	10.8 (0.06)	-	35.8 (0.00)	7.50 (0.06)
AC	N OR	9 1.43 (1.20-1.70)	8 1.45 (1.18-1.78)	8 1.18(0.95-1.47)	-	11 1.33 (1.17-1.50)	5 1.52 (1.23-1.87)
	Q (P value)	7.14 (0.52)	6.46 (0.49)	16.8 (0.02)	-	10.4 (0.40)	3.91 (0.42)
Small	N OR	4 0.85(0.51-1.42)	3 0.96(0.48-1.93)	4 0.73(0.51-1.05)	-	6 1.33(0.98-1.80)	2 2.63 (1.47-4.70)
	Q (P value)	2.22 (0.53)	2.09 (0.35)	3.20 (0.36)	-	9.26 (0.10)	0.27 (0.60)
Gender							
Male	N OR	2 0.82(0.46-1.47)	2 0.80(0.43-1.51)	3 0.84(0.61-1.15)	-	2 1.04(0.60-1.81)	-
	Q (P value)	0.38 (0.54)	0.64 (0.42)	3.93 (0.14)	-	1.47 (0.23)	-
Female	N OR	2 2.45(0.62-9.66)	2 2.42(0.60-9.83)	3 1.96 (1.08-3.53)	-	2 2.28(0.61-8.45)	-
	Q (P value)	4.81 (0.03)	4.89 (0.03)	5.07 (0.08)	-	4.41 (0.04)	-
Smoking status							
Never	N OR	8 1.22(0.95-1.57)	7 1.21(0.88-1.66)	6 1.22(0.99-1.51)	-	6 1.02(0.84-1.23)	-
	Q (P value)	6.52 (0.48)	3.93 (0.69)	3.34 (0.65)	-	7.23 (0.20)	-
Light	N OR	5 1.10(0.72-1.66)	4 0.90(0.52-1.56)	6 0.96(0.75-1.22)	-	6 1.18(0.92-1.52)	-
	Q (P value)	3.31 (0.51)	0.75 (0.86)	1.23 (0.94)	-	4.23 (0.52)	-
Heavy	N OR	6 2.05(0.97-4.35)	5 1.84(0.68-4.96)	6 1.04(0.86-1.27)	-	7 1.67 (1.26-2.21)	-
	Q (P value)	12.1 (0.03)	10.5 (0.03)	20.5 (0.00)	-	10.5 (0.10)	-
Total							
N OR	N OR	18 1.33 (1.18-1.49)	14 1.35 (1.17-1.56)	18 1.09(0.96-1.23)	1	18 1.24 (1.13-1.36)	2 1.42 (1.12-1.80)
	Q (P value)	19.7 (0.29)	17.9 (0.16)	38.3 (0.00)	-	22.4 (0.17)	3.80 (0.05)

¹Dominant model; ²Recessive model; OR, OR (95%CI); Bold indicates significant ORs at the level of 0.05; SCC, squamous cell carcinoma; AC, adenocarcinoma; Small, small cell cancer; N, number of studies

for Cys/Cys versus Ser/Cys+Ser/Ser; $Q=22.44$, $P=0.17$ for heterogeneity test, Table 2).

In the subgroup analysis on the source of control, significantly increased risks were associated with Cys/Cys genotypes in the studies both with population-based controls and with hospital-based controls (Cys/Cys versus Ser/Ser, studies with population-based controls: adjusted OR, 1.67; studies with hospital-based controls: adjusted OR, 1.27). For the studies with population-based controls, significant associations were found in both dominant model and recessive model (dominant model: crude OR, 1.34; recessive model: crude OR, 1.29, Table 2). For the studies with hospital-based controls, significant associations were only found in recessive model (crude OR, 1.20).

Further stratified analysis on ethnicity found that among Asian subjects, significantly elevated risks were associated with SNP326 variant genotypes in all models tested (Cys/Cys versus Ser/Ser: adjusted OR, 1.36; dominant model: crude OR, 1.19; recessive model: crude OR, 1.21;). However, we did not find significant associations for Caucasian subjects in these three models (Table 2).

In the stratified analysis by histological type, the adjusted OR for the hOGG1 Cys/Cys genotype versus Ser/Ser genotype was 1.45 for squamous carcinoma and adenocarcinoma, both with statistical significance. The significant associations were also found for both squamous carcinoma and adenocarcinoma in recessive model (squamous carcinoma: adjusted OR, 1.91; adenocarcinoma: adjusted OR, 1.52). While, the ORs for the associations for small cell lung cancer were not significant in all the available comparisons except the adjusted OR in the recessive model, however only two studies could be included on that occasion. No significant associations were found in the dominant model for adenocarcinoma and squamous carcinoma (Table 2).

Further stratified analysis by gender, significant association with lung cancer risk was only found in the dominant model among female subjects (crude OR=1.96). However, for this stratified analysis, only 3 studies had detailed genotypes distribution information among male and female subjects. We then evaluated the effects of hOGG1 SNP326 according to smoking status, and found the increased risks with statistical significance among heavy smokers in the recessive model (crude OR=1.67). No associations were found among never smokers and light smokers (Table 2).

Evaluation of Publication Bias

Moving forward, funnel plot and Egger's test were performed to evaluate the publication bias. The shapes of funnel plots seemed symmetrical in the crude ORs and adjusted ORs of homozygote comparisons. Egger's test was adopted to examine the symmetry of funnel plots, the larger of the intercept deviated from zero in the linear analysis indicated more evident asymmetry. We obtained the intercept value of 0.35 (95% CI: -0.96-1.65, $P=0.58$) and -0.03 (95% CI: -1.96-1.90, $P=0.97$) for crude ORs and adjusted ORs of homozygote comparisons. At the significant level of 0.05, no significant asymmetry was

found which suggested no significant publication bias.

Discussion

After the inclusion of 18 case-control studies focused on hOGG1 SNP326 and lung cancer risk, our meta-analysis provided evidence that overall, hOGG1 Ser326Cys polymorphism was associated with a slight but significantly increased risk of lung cancer. And additionally, a clear association between hOGG1 Ser326Cys polymorphism and lung cancer risk was found in Asian subjects but not in Caucasians. Subgroup analysis on the histotype and smoking status indicated significant association with non-small cell lung cancer and among heavy smokers in the recessive model.

The results do not replicate the association reported by the previous meta-analysis (Li et al., 2008), which did not find an overall effect of the Ser326Cys polymorphism on lung cancer risk. The differences may be attributed to the duplicate data in that meta-analysis, we excluded two studies in the Caucasian subjects and one study in Asian subjects because of the overlapped data. Another possible reason is that the majority of the gain of eligible studies for this update meta-analysis was from Asian population, the differences between ethnicity proportions could affect the result. We also noticed that although no statistical association was found in the previous meta-analysis, the lower limits of confidence intervals of ORs were near zero and the ORs might varied if new studies were included.

Our results from stratified analysis by control source were consistent with the result of the previous meta-analysis, which reported that the ORs (for the hOGG1 Cys/Cys versus Ser/Ser) in population-based studies were higher than that in hospital-based studies. If the controls were randomly selected and the controls from hospitalized patients other than cancer or pulmonary diseases, theoretically there should be no significant difference of the frequency of genotypes between population-based controls and hospital-based controls. There should be special concern over selecting controls for the case-control studies if the genotyping data were associated with the diseases the controls suffered from.

There is a consensus that tobacco smoking is the major cause of lung cancer and tobacco smoke contains some carcinogens that induce 8-hydroxydeoxyguanine may contribute to the development of lung cancer. Several studies have studied the interaction or joint effect of hOGG1 polymorphism and smoking status on lung cancer (Radak et al., 2005; Liu et al., 2010). In the present meta-analysis, we found that the heavy smokers with hOGG1 Cys/Cys genotypes had an increased lung cancer risk by 66.9% compared with those with the hOGG1 Cys/Ser+Ser/Ser genotype. It is possible that individuals with the variant hOGG1 326Cys allele were more susceptible to smoking-related lung cancer when being exposed to higher level of tobacco smoke. It has been concluded that women may be more susceptible to tobacco smoke and potentially more vulnerable to lung cancer development (Kiyohara et al., 2010a). While in the present meta-analysis, it is not possible to investigate the joint effect of tobacco smoke, gender and genotype, due to limited available data.

The authors recognize that there are some limitations inherent in this meta-analysis. First, although under the premise of the inclusion criteria, the variations of the quality of the included studies remained a potential source of bias which might affect the result. It is not possible to get the individual-level genotyping data and to evaluate the quality of SNP detection assays for each study. Second, different studies provided different definitions of heavy smokers, thus the data absence of well-documented smoking exposure sent a challenge of grouping smoking status data. In the present study, we had to use the highest level of smoking exposure as the heavy smoker subgroup for the stratified analysis. Third, we tried to adopt adjusted ORs to evaluate the combined OR, while no adequate studies provided adjusted ORs as we expected. So we considered adjusted OR, crude OR for the Cys/Cys of hOGG1 SNP326 and also for the dominant and recessive model comprehensively. Theoretically, there was no great difference between the adjusted OR and crude OR, if these two were of concordance, we could draw the conclusion. Finally, potential gene-gene and gene-environment interactions may hinder the evaluation of the association between this SNP and lung cancer risk.

In conclusion, the results of the present meta-analysis suggested that hOGG1 Ser326Cys polymorphism may confer an increased risk for lung cancer. In addition, the results of stratified analysis indicated the significant positive association among Asian subjects and heavy smokers. Further studies on race-specific populations and smoking status are needed in larger sets of well-designed case-control studies so as to clarify the effect of hOGG1 Ser326Cys polymorphism on lung cancer.

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