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The *hOGG1*Ser326Cys Polymorphism and Increased Lung Cancer Susceptibility in Caucasians: An Updated Meta-Analysis

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***hOGG1* encodes a DNA repair enzyme responsible for the excision of reactive oxygen species (ROS) in damaged DNA. Previous studies have obtained inconsistent results. To validate the association between the *hOGG1*Ser326Cys polymorphism and lung cancer risk, we performed an updated meta-analysis of 20 studies (8739 cases and 10385 controls) using STATA version 11.1. With this approach, we tested the overall and subgroup association between the SNP and lung cancer susceptibility stratified by ethnicity, control sources, cell histotypes, and smoking status. We demonstrated a novel, significant correlation between the *hOGG1* Ser326Cys polymorphism and increased lung cancer susceptibility in Caucasians. Our findings indicate a need for larger-scale studies to verify the association of this SNP with lung cancer risk in Caucasians.**

Human 8-oxoguanine DNA glycosylase -1 (*hOGG1*) is located at chromosome 3p26.2. It encodes an enzyme responsible for removing the most common product of oxidative damage in DNA, namely 8-hydroxyguanine (8-OH-G)[1]. 8-OH-G can induce G→T or A→C base mismatches during DNA replication, thereby possibly triggering the onset of carcinogenesis[2,3].

Codon 326 at position 1245 in exon 7 of *hOGG1* holds a single nucleotide polymorphism (SNP) with a C→G variation, thereby the amino acid translation of codon 326 can be changed from serine (Ser) to cysteine (Cys)[4,5]. Experiments have illustrated that the DNA glycosylase encoded by the Cys326 variant exhibits remarkably lower 8-OH-G excision activity than the wild-type Ser326 allele, because the Cys326 variant enzyme has a lower affinity to lesions of damaged DNA than Ser326 enzyme[6]. Thus, *hOGG1* Ser326Cys polymorphism is speculated to associate with multiple types of cancer due to the compromised cleavage of 8-OH-G[7].

Lung cancer is the most commonly diagnosed cancer (1.61million diagnoses, 12.7% of the total cancer diagnoses), and is estimated to be the leading cause of cancer death (1.38 million deaths, 18.2% of the total cancer deaths) worldwide[8]. Numerous investigations have studied the association between the *hOGG1* Ser326Cys polymorphism and this malignancy[9]. However, the results of these studies have been inconsistent, partly due to genetic or other sources of heterogeneity, including differences in eligibility criteria and analysis approaches, small sample sizes, publication biases, and exogenous confounders[10]. For this reason, meta-analyses with robust statistical power have been frequently performed to validate the association between the *hOGG1* Ser326Cys polymorphism and the risk of lung cancer. Li *et al*[11] found no association between the *hOGG1* Ser326Cys polymorphism and increased risk of lung cancer susceptibility except in Asians, while Kiyohara *et al* [12] found a significant association between the *hOGG1* Ser326Cys polymorphism and the risk of lung cancer in the overall population and in an Asian subgroup. In another study, Guan *et al*[13] uncovered a potential trend of significant linkage between *hOGG1* Ser326Cys polymorphism and lung cancer risk in Caucasians. Since these publications, more studies of the *hOGG1* Ser326Cys polymorphism in relation to lung cancer susceptibility have been completed. Thus, we conducted an updated meta-analysis by adding the latest data and avoiding sample overlapping with the aim of gaining a more reliable evaluation of the association between *hOGG1* Ser326Cys polymorphism and lung cancer susceptibility.

Results

Study characteristics. Twenty-eight articles were identified to meet the inclusion criteria. We thoroughly reviewed these articles to detect overlapping samples. Studies by Vogel *et al*[14], Sorensen *et al*[15], Hatt *et al*[16], and Loft *et al*[17,18] were found to share a common sample sources from a Danish prospective follow-up study. Therefore, only the study by Sorensen *et al*, which had the largest sample size, was used in our meta-analysis. The studies by Sunaga *et al*[19] and Kohno *et al*[20]consisted of the same lung adenocarcinoma cases; we included only the study by Kohno *et al* because it had a larger sample size. The studies by Liang *et al*[21], Zienolddiny *et al*[22], and Liu *et al*[23] were excluded because the genotype distribution among the controls was deviated significantly from HWE ($P<0.05$). Finally, 20 articles, including 8739 lung cancer cases and 10385 controls were ascertained for use in our meta-analysis[15,20,24–41].We treated each ethnic population within each paper as a separate study to perform an ethnicity-based subgroup analysis. In a multi-ethnic study by Le *et al*[27], the data were extracted into Asian, Caucasian, and Hawaiian subgroups. In the article by Chang *et al*[34], data were separated into Latino and African-American subgroups. Considering the comparability with previous published meta-analyses[12,13], we defined data by Karahalil *et al*[33] as Turkish ethnicity in a concordant manner. Eight studies contained population-based controls, while twelve utilised hospital-based controls. Essential characteristics about each original study, HWE values, odd ratio (OR), 95% confidence interval (95%CI), and approaches used to confirm genotyping results are shown in Table 1.

Heterogeneity and model. All heterogeneity statistic I^2 values except that in smoking subgroup ($I^2=53.4\%$) were observed less than 50% in the present study, which indicated that the appropriate pooling model should be fixed effects (Inverse Variance). For the smoking subgroup, a random effects model was used. Furthermore, using a suitable underlying genetic model in genetic association studies is crucial for combining data biologically rather than just statistically. According to the methodology for genetic model selection developed by Thakkinstian *et al*[42], we decided to use the recessive genetic model. After a sensitivity analysis, no individual study was found to affect the overall result robustly, which implied the magnitude of the summary evaluation.

Gene effect. The overall frequency of the Cys allele in the case group was significantly higher than that in the control group (39.7% versus 35.1%, $P<0.01$). Among the Asian subgroup, the Cys variant frequency was 54.0% in the cases and 51.7% in the controls ($P<0.01$). More or less, the higher frequency of the Cys allele in cases suggested a potential association of the variant with risk of lung cancer.

The overall results of the genetic analysis indicated a significant association between the *hOGG1* Ser326Cys polymorphism and lung cancer risk (OR=1.20, 95%CI: 1.10–1.30) (Table 2). In the subgroups by ethnicity, a significant association was observed in Caucasians (OR=1.32, 95%CI: 1.05–1.67), and in Asians (OR=1.18, 95% CI: 1.07–1.29) respectively (Figure 1). In the stratified analysis based on control sources, our study also showed a significant linkage of the *hOGG1* Ser326Cys polymorphism with lung cancer risk in both population-based (OR=1.18, 95%CI: 1.04–1.34) and hospital-based controls (OR=1.21, 95%CI: 1.08–1.35) (Figure 2).

For the study stratified by smoking status, only eight studies were available[20,26,29,30,33,36–38]. No correlation was found between *hOGG1* Ser326Cys polymorphism and lung cancer among non-smoking (OR=1.09, 95%CI: 0.92–1.29) or smoking subgroups (OR=1.24, 95%CI: 0.95–1.61). Another stratified study referring to histological subtypes, due to a lack of well-documented pathological data in most original studies, only ten studies were useful for stratification by the following histological subtypes: small cell carcinoma, squamous cell

Table 1 | Characteristics of studies included in this meta-analysis

Study (ref)	Year	Ethnicity	Source of control	No. of cases CC/CG/GG	No. of controls CC/CG/GG	OR (95%CI) [a]	Confirming method[b]	*P* value HWE
Sugimura *et al* [24]	1999	Asian	Hospital	85/115/41	63/107/27	1.29 (0.76–2.19)	Sequencing	0.082
Wikman *et al* [25]	2000	Caucasian	Hospital	68/32/5	60/43/2	2.58 (0.49–13.58)	Sequencing	0.067
Ito *et al* [26]	2002	Asian	Hospital	40/71/27	68/118/54	0.84 (0.50–1.41)	None	0.837
Le *et al* [27]	2002	Caucasian	Population	78/39/9	98/53/8	1.45 (0.54–3.88)	Sequencing	0.810
Le *et al* [27]	2002	Asian	Population	30/40/27	50/74/26	1.84 (1.00–3.40)	Sequencing	0.878
Le *et al* [27]	2002	Hawaiian	Population	15/31/29	29/48/19	2.56 (1.29, 5.06)	Sequencing	0.914
Lan *et al* [28]	2004	Asian	Population	37/61/20	51/43/15	1.28 (0.62–2.65)	None	0.232
Park *et al* [29]	2004	Caucasian	Hospital	101/65/13	255/87/8	3.35 (1.36–8.24)	Sequencing	0.857
Hung *et al* [30]	2005	Caucasian	Hospital	1401/661/93	1368/716/79	1.19 (0.88–1.62)	Replication	0.215
Liang *et al* [21][c]	2005	Asian	Hospital	27/132/68	28/123/76	0.85 (0.57–1.26)	Sequencing	0.043
Zienolddiny *et al* [22][c]	2006	Caucasian	Population	182/100/44	194/117/75	0.65 (0.43–0.97)	Replication	0.001
Sorensen *et al* [15]	2006	Caucasian	Population	254/155/22	479/284/33	1.24 (0.72–2.16)	Replication	0.258
Kohno *et al* [20]	2006	Asian	Hospital	285/544/268	123/190/81	1.25 (0.94–1.65)	None	0.628
Matullo *et al* [31]	2006	Caucasian	Population	66/46/4	673/371/50	0.75 (0.26–2.10)	Replication	0.901
De Ruyck *et al* [32]	2007	Caucasian	Hospital	74/33/3	60/46/4	0.74 (0.16–3.40)	None	0.176
Karahalil *et al* [33]	2008	Turkish	Hospital	86/65/14	115/106/29	0.71 (0.36–1.38)	None	0.546
Chang *et al* [34]	2009	Latino	Population	53/47/12	135/132/29	1.10 (0.54–2.25)	Replication	0.691
Chang *et al* [34]	2009	African-American	Population	170/78/6	202/70/8	0.82 (0.28–2.40)	Replication	0.521
Okasaka *et al* [35]	2009	Asian	Population	117/257/141	250/544/236	1.27 (1.00–1.62)	None	0.070
Chang *et al* [36]	2009	Asian	Hospital	142/518/436	154/482/361	1.16 (0.98–1.39)	Replication	0.741
Miyaishi *et al* [37]	2009	Asian	Hospital	27/55/26	39/54/28	1.05 (0.57–1.94)	None	0.271
Liu *et al* [23][c]	2010	Asian	Hospital	68/158/132	110/294/312	0.76 (0.58–0.98)	None	0.004
Li *et al* [38]	2011	Asian	Population	83/208/164	60/219/164	0.96 (0.73–1.26)	Sequencing	0.329
Kohno *et al* [39]	2011	Asian	Hospital	115/162/100	98/164/63	1.50 (1.05–2.15)	None	0.704
Janik *et al* [40]	2011	Caucasian	Hospital	48/24/16	57/21/1	17.33(2.24–134.04)	Sequencing	0.542
Qian *et al* [41]	2011	Asian	Population	100/288/193	125/291/185	1.12 (0.88–1.43)	Replication	0.592

[a]Odds ratio (OR) and 95% confidence interval (CI) of the individual study based on a recessive genetic model.
[b]Approaches for quality control of genotyping results.
[c]Excluded from meta-analysis for deviation from Hardy–Weinberg equilibrium (HWE) ($p<0.05$).

Table 2 | OR and 95% CI for the association between *hOGG1* Ser326Cys and lung cancer risk

Variables	Cys allele frequency Cases/Controls (%) [b]	Cys/Cys versus Ser/Ser + Ser/Cys OR (95%CI)	I^2 (%)
Summary	39.7 / 35.1	1.20 (1.10–1.30)	27.0
Ethnicity[a]			
Asian	54.0 / 51.7	1.18 (1.07–1.29)	0.0
Caucasian	20.9 / 20.5	1.32 (1.05–1.67)	46.4
Source of Control			
Population	43.5 /.36.4	1.18 (1.04–1.34)	10.4
Hospital	37.8 / 33.8	1.21 (1.08–1.35)	41.8

[a]Only Asian and Caucasian ethnicities are shown. Multiethnic data were extracted for the subgroup analysis based on ethnicity as a separate independent study.
[b]$P_{caucasian} = 0.514$ by Chi-Square analysis. All others were $P < 0.05$.

carcinoma, and adenocarcinoma[20,24,25,29,30,33,36–39]. Significant association between *hOGG1* Ser326Cys polymorphism and an increased risk of lung cancer was found only in lung adenocarcinoma subgroup (OR= 1.31, 95% CI: 1.14–1.51) (Table 3).

The current study also examined the association between the *hOGG1* Ser326Cys polymorphism and lung cancer risk, adjusting for both study design and ethnicity. Interestingly, we observed a significant relationship between this SNP and lung cancer suscept-

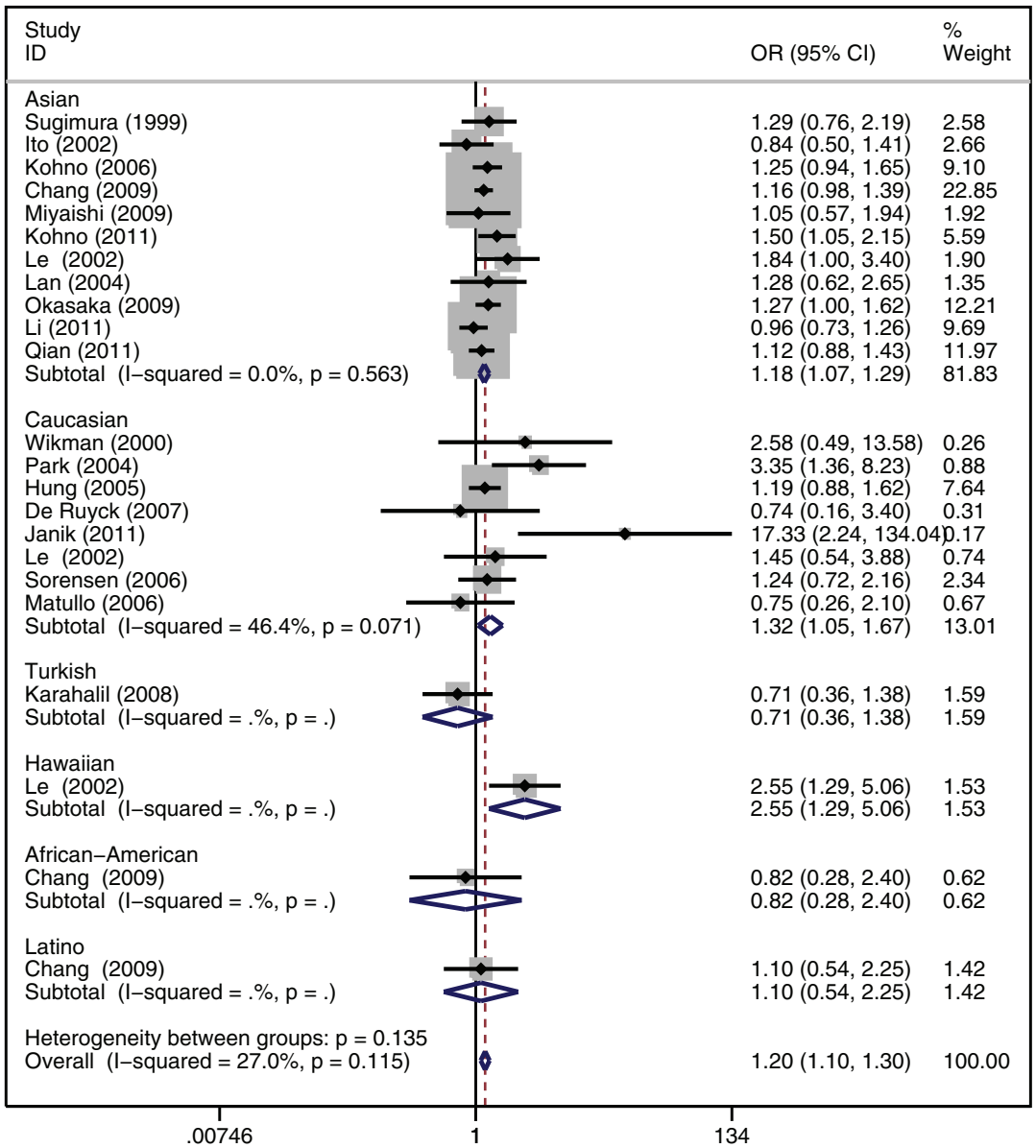

Figure 1 | Stratified analysis based on ethnicity for the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk using a recessive genetic model.

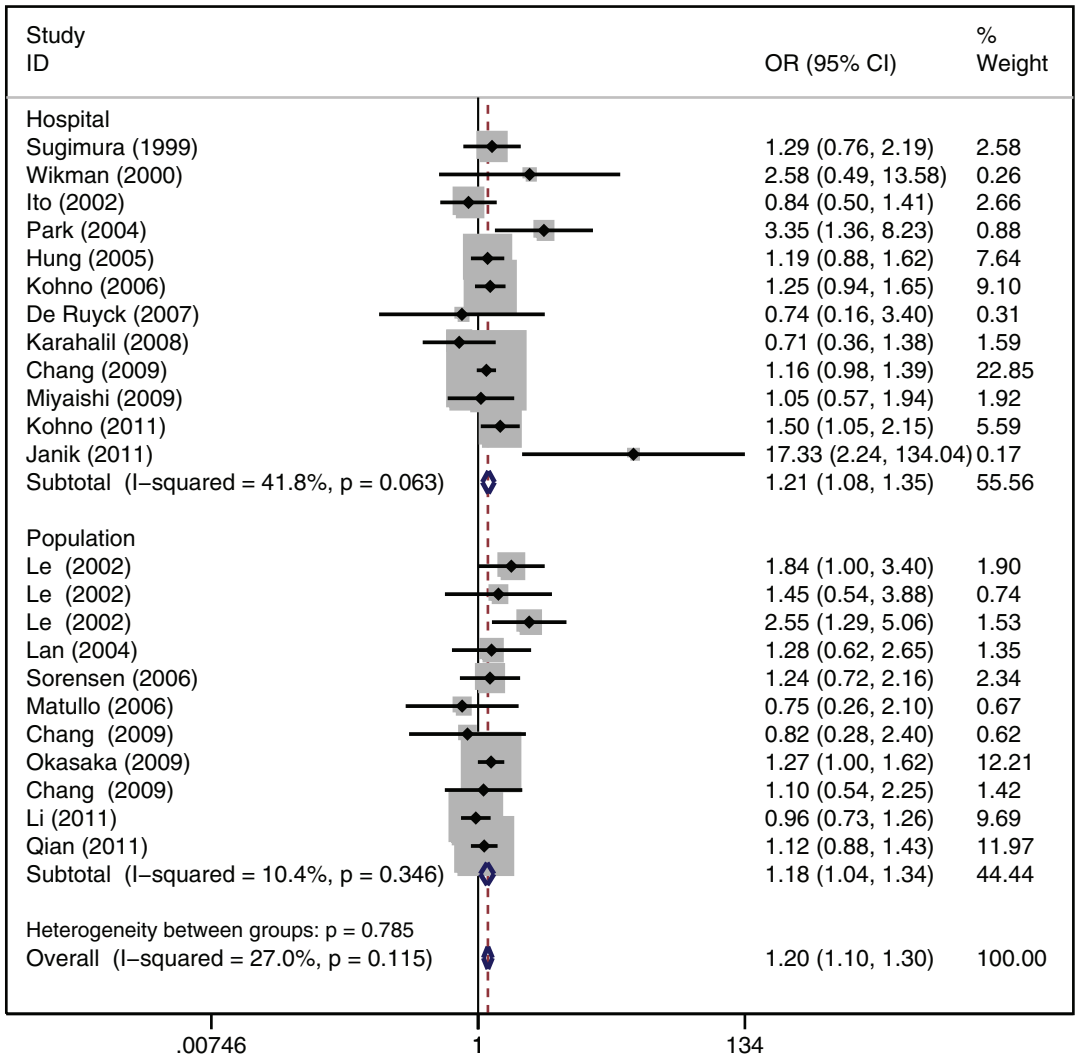

Figure 2 | **Stratified analysis based on the source of controls for the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk using a recessive genetic model.**

ibility among smokers in the Asian population (OR=1.25, 95%CI: 1.04–1.51), but an assessment of Caucasians was not possible due to the limited data available. Similar to the results of the combined analysis, the *hOGG1* Ser326Cys polymorphism showed a significant association with lung cancer susceptibility only in the adenocarcinoma cell type subgroups in the Asian and Caucasian populations respectively (Table 4).

The weight of each study contributing to the overall result was calculated. Of the statistical power, 81.83% was from the Asians, while 13.01% was from the Caucasians. The weight of each individual study varied widely, from 22.85% to 0.17%. The hospital-based controls contributed more power than the population-based controls (55.56% versus 44.44%), with the heterogeneity statistic I^2 being remarkably higher in the hospital-based control group than that in the population-based controls (41.8% versus 10.4%).

Publication bias. The publication bias was accessed using Begg's (P = 0.303) and Egg's (P =0.185) tests. The funnel plot displayed a symmetric shape (Figure 3), indicating the absence of a publication bias for both positive and negative or non-significant findings from published studies.

Table 3 | Stratified analysis of *hOGG1* Ser326Cys association by histotype and smoking status

Variables	No. of cases / controls	Cys/Cys versus Ser/Ser + Ser/Cys OR(95%CI)	I^2 (%)
Histotype			
Small cell	165 / 1444	0.95 (0.64–1.41)	0.0
Squamous cell	1767 / 4258	1.15 (0.96–1.39)	37.4
Adenocarcinoma	2606 / 4770	1.31 (1.14–1.51)	0.0
Smoking status			
Smoking	3939 / 2741	1.24 (0.95–1.61)	53.4[a]
Non-smoking	1416 / 2062	1.09(0.92–1.29)	0.0

[a]Random effects model was used.

Table 4 | Analysis of *hOGG1* Ser326Cys association adjusted for study design and ethnicity

Ethnicity	Status/histotypes	Cys/Cys versus Ser/Ser + Ser/Cys OR (95%CI)	I^2 (%)
Asian	Smoking	1.25 (1.04–1.51)	23
	Non-smoking	1.05 (0.88–1.26)	0
Caucasian	Smoking	NA	NA
	Non-smoking	NA	NA
Asian	Small cell	0.99 (0.66–1.50)	0
	Squamous cell	1.17 (0.95–1.44)	45.7
	Adenocarcinoma	1.26 (1.09–1.46)	0
Caucasian	Small cell	NA	NA
	Squamous cell	1.10 (0.74–1.63)	41.9
	Adenocarcinoma	1.82 (1.22–2.71)	43.1

NA: data of the group were not available from the original study.

Discussion

Genetic epidemiological studies have proposed that there is a relationship between SNPs and diseases. However, large and well-designed genotype-phenotype investigations with robust statistical power are required to detect these mild to moderate associations. Additionally, there has been increased focus on the modified effects of certain exogenous factors. A predominant DNA glycosylase, encoded by *hOGG1*, has the ability to recognise and remove an oxidative DNA damage product, namely 8-OH-G. This substance is generally treated as a mutagen because of its ability to induce mutation. Studies have revealed that the Cys-mutant enzyme is less effective at repairing DNA than Ser wild type enzyme[6–8].

In a published pooled analysis, Li *et al* reported that there is no relationship between *hOGG1* Ser/Cys polymorphism and lung cancer risk[11]. However, Kiyohara *et al* found a significant association between this genetic polymorphism and lung cancer by adding several additional case-control studies[12]. With more studies about *hOGG1* and lung cancer were available recently, our updated meta-analysis, which has the largest sample size thus reported, yielded a positive relationship between *hOGG1* Ser/Cys polymorphism and lung cancer risk in Caucasians (OR=1.32, 95%CI: 1.05–1.67). In addition, a recent meta-analysis by Guan *et al* has predicted a potential connection between the variant and lung cancer in Caucasians[13]. Our novel finding may be due to an increase in sample sizes and the avoidance of sample overlapping. Another reason may be that we objectively and precisely stratified the population based on ethnicity subgroups. Because the detection for mild to modest risk genetic risk effects requires sufficient statistical power, we proposed that large case-control studies may help to further validate the true association between the genetic variant and lung cancer among Caucasians.

Based on source of controls, we were able to observe that the heterogeneity statistic I^2 in the hospital-based subgroup was higher than that in the population-based subgroup (41.8%versus10.4%). To some extent, hospital-based controls were recruited as lung cancer-free individuals regardless of their status concerning other diseases, which might be a potential source of heterogeneity because of a mixture of other diseases, particularly if the disease had effect upon genotyped results[11].We suggested that the use of population-based controls should be more representative.

In another analysis, stratified according to smoking status, no significant association was observed between the *hOGG1* Ser326Cys polymorphism and lung cancer susceptibility. Contrary to this finding, Cys allele has been reported to be associated with lung cancer risk among heavy smokers[39]. Another study by Li *et al* identified a marginally increased risk of *hOGG1* Ser326Cys polymorphism in non-smoking subjects harbouring the Cys allele[11]. To the best of our best knowledge, multiple tobacco-related chemicals are capable of inducing DNA mutations and initiating carcinogenesis, especially

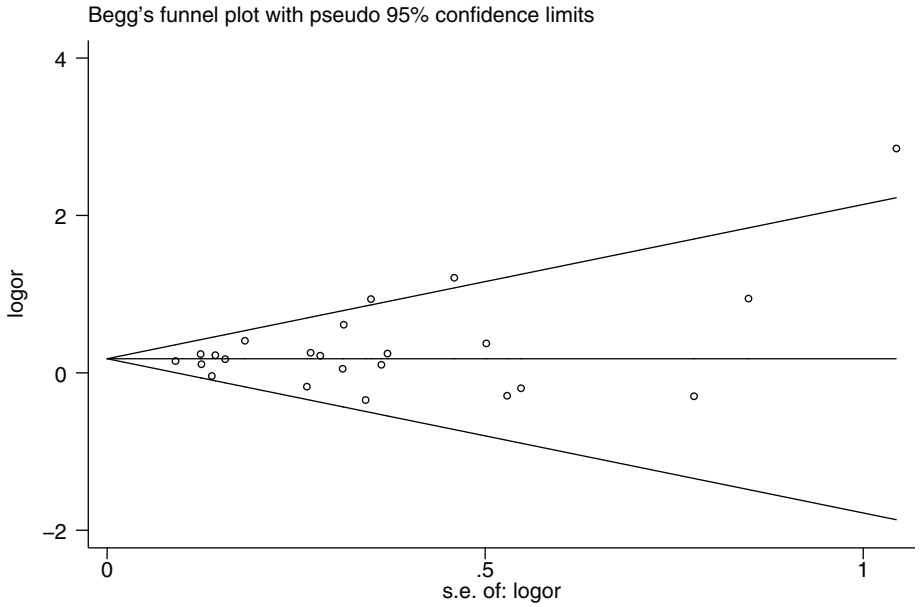

Figure 3 | **Begg's funnel plot displaying a symmetric shape.**

in lung cancer[43]. Thus, the complexities of exogenous modification to gene and gene-environment interactions remain a field to be explored. We attributed the inconsistency of different studies to a lack of universal standards when delineating subgroups, including different category criteria such as smoking duration and intensity. Otherwise, the data were primarily obtained from self-reported data from questionnaires of participants, so inaccurate confounders should be taken into account. In addition, the current study employed analyses adjusted for study design and ethnicity and yielded a positive association between the *hOGG1*condon326 polymorphism and increased lung cancer risk in smoking group among Asians. We assumed that modification of the study design and ethnicity could lower the heterogeneity and reduce the potential of confounders. It also implied the important role of the modified analyses in pooled studies.

Given the diversity of histopathologic categories in lung cancer, stratified evaluation was conducted for small cell carcinoma, squamous cell carcinoma, and adenocarcinoma. We found a significant association between the *hOGG1* Ser/Cys polymorphism and lung adenocacinoma. Our result was consistent with one former meta-analysis focused on histological types of lung cancer[35]. Future independent studies are proposed to collect well-documented characteristics of participants incorporating smoking details and histological details by well-trained investigators. The control populations, matched for age, gender, and alcohol use, should be twice the size of the case populations in future study.

Our meta-analysis had some limitations. First, a great proportion of statistical power was contributed by the Asian ethnicity, although the subgroup analysis was able to significantly reduce the between-ethnicity heterogeneity. Indeed, more relevant studies of Caucasians are essential. Second, due to the limitation of eligible data, the subgroups based on smoking status were crudely classified into smoking and non-smoking subgroups, regardless of the smoking duration and consumption. Thus, potential sources of heterogeneity were included when the data were combined. Although the interaction between smoking status and *hOGG1* condon326 is of great interest, the limited data available for use in the current meta-analysis were not sufficient to identify an association between the genotype and cigarette smoking. Third, the small sample size of lung cancer cell subtypes might have restricted the power of our meta-analysis to reveal a potential connection.

Methods

Eligiblity of relevant studies. All original articles published in English that examined the association of the *hOGG1* Ser326Cys polymorphism with lung cancer (published before November 2011) were considered for our meta-analysis. The PubMed, Embase, HuGENet, and Ovid databases were searched to identify appropriate studies. The following combinations of terms were used in our database searches: ("Lung cancer" or "Lung Neoplasms" or "Pulmonary Cancer" or "Pulmonary Neoplasms") and ("polymorphism" or "SNP" or "allele" or "variant") and ("*OGG1*" or "*hOGG1*" or "*OGG1* enzyme" or "*hOGG1*: Human 8-oxoguanine DNA glycosylase-1"). Furthermore, the searches were supplemented by references cited in other papers. Inclusion criteria were: (1) studies assessed linkage of *hOGG1* Ser326Cys polymorphism with lung cancer risk; (2) lung cancer cases should be diagnosed explicitly; (3) controls should be unrelated cancer-free individuals. When multiple reports had overlapping sample populations, only the study with largest sample size was retained.

Data extraction. For each available study, the following information was extracted: the first author, year of publication, ethnicity of participants, source of controls, number of genotyped cases/controls, method for quality control of genotyping result, smoking status, and histological sub-type. The data were primarily extracted from tables and supplemented by significant information presented in texts and/or figures. Two investigators (Y-L H and D-N Z) handled the data simultaneously and separately.

Statistical analysis. Hardy-Weinberg equilibrium (HWE) was assessed for each study using the chi-square test. Studies were considered to deviate from HWE at $P<0.05$[44]. The inconsistency index, I^2, was calculated to evaluate the variation among studies owing to heterogeneity (0%–25% was considered to have no heterogeneity; 25%–50% was considered to have moderate heterogeneity; 50%–75% was considered to have large heterogeneity; 75%–100% was considered to have extreme heterogeneity)[45]. The data were combined using logistic regression with the fixed-effects pooling model if there was no or moderate heterogeneity ($I^2<50\%$). Alternatively, the random effects model was used ($I^2>50\%$). Sensitivity analysis was performed by excluding one study at a time to determine the corresponding magnitude of the weight of each study to the summary results. The most biologically fit genetic model was selected according to the comprehensive effect of the gene using logistic regression[42,46]. To extensively explore the genetic heterogeneity, stratified analyses were conducted by ethnicity, source of controls, smoking status, and histological sub-types. The association between *hOGG1* Ser326Cys polymorphism and lung cancer risk was evaluated using the odds ratio (OR) and the 95% confidence interval (CI). Funnel plots, used to observe the publication bias, were complemented with Egger's regression[47]and Begg's rank correlation test ($P > 0.10$)[48]. The statistical analyses were performed using STATA version 11.1 (Stata Corporation, USA). All p values were two-sided.

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Author contributions

HYL and ZDN have contributed to the conception and design of the study, the analysis and interpretation of data, and the revision of the article. ZDN and WJZ searched and selected the studies, carried out the statistical analysis, and drafted and revised the article. LGJ and LJX participated in the statistical analysis and helped to search the trials.

Additional information

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