Tumor Biol. (2014) 35:1609–1618
DOI 10.1007/s13277-013-1222-0

RESEARCH ARTICLE

Smoking and *hOGG1* Ser326Cys polymorphism contribute to lung cancer risk: evidence from a meta-analysis

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Received: 20 August 2013 / Accepted: 16 September 2013 / Published online: 2 October 2013

Abstract The human 8-oxoguanine DNA glycosylase (*hOGG1*) gene plays an important role in the repair of oxidatively damaged DNA base lesions and its functional single nucleotide polymorphisms (SNPs) may alter DNA repair capacity and thus contributes to cancer susceptibility. Numerous studies have investigated the association between *hOGG1* Ser326Cys polymorphism and lung cancer susceptibility; however, the conclusions are still inconclusive. We searched eligible publications from MEDLINE, EMBASE, and CBM and performed a meta-analysis to assess the associations between *hOGG1* Ser326Cys polymorphism and lung cancer risk. Pooled odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated to estimate risk associations, and false-positive report probability (FPRP) analysis was also carried out to evaluate significant findings. A total of 31 investigations with 10,220 cases and 12,284 controls were identified. When all studies were pooled, a significantly increased overall lung cancer risk was found (Cys/Cys vs. Ser/Ser: OR=1.24, 95 % CI=1.05–1.47, P=0.013; recessive model: OR=1.22, 95 % CI=1.05–1.41, P=0.008, and Cys vs. Ser: OR=1.11, 95 % CI=1.02–1.21, P=0.022), and further stratification analysis showed that the association was stronger in Asians, never smokers, and more-cigarette takers. These results were confirmed by FPRP analysis. Despite some limitations, this meta-analysis provides solid evidence that *hOGG1* Ser326Cys polymorphism may contribute to lung cancer risk, particularly for Asian populations, never smokers, and more-cigarette takers. Nevertheless, these findings warrant further validation in single large investigations.

Keywords *hOGG1* · Polymorphism · Lung cancer · Susceptibility · Meta-analysis

Abbreviations

BER	Base excision repair
hOGG1	Human 8-oxoguanine DNA glycosylase1
SNP	Single nucleotide polymorphism
CBM	Chinese Biomedical
OR	Odds ratio
CI	Confidence interval
FPRP	False-positive report probability
HWE	Hardy–Weinberg equilibrium

Introduction

Lung cancer is the most frequently diagnosed cancer worldwide, accounting for 13 % (1.6 million) of all cancer cases and

Electronic supplementary material The online version of this article (doi:10.1007/s13277-013-1222-0) contains supplementary material, which is available to authorized users.

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18 % (1.4 million) of all cancer deaths in 2008 [1]. It is recognized as the leading cause of cancer death in males and the second one in females [1]. Cigarette smoking is the main necessary etiologic factor for lung cancer, accounting for 80 % of the worldwide lung cancer burden in males and at least 50 % of the burden in females [2, 3]. Tobacco smoke contains free radicals as well as 55 carcinogens that can generate reactive oxygen species and lead to mutations [4]. Among them, 20 compounds have been found convincingly to induce lung tumors in at least one animal species [5]. The carcinogens can react with human DNA and cause DNA damages, and if left unrepaired, such DNA damages can induce mutations and initiate tumorigenesis [6]. Nevertheless, only a small fraction of smokers eventually develop lung cancer, suggesting a wide inter-individual variability in susceptibility [7]. Polymorphisms of DNA repair genes may modulate DNA repair capacity, thus lead to genomic instability and contribute to inter-individual diversity in cancer susceptibility, including lung cancer [8, 9].

Over 130 DNA repair genes have been identified in the four major DNA repair pathways, including base excision repair (BER) pathway [10]. The BER pathway plays an important role in repairing small base lesions in DNA resulting from oxidation and alkylation damage by the specific DNA glycosylase [11]. Mammalian cells contains a series of DNA glycosylases including human 8-oxoguanine DNA glycosylase1 (*hOGG1*), which encodes the hOGG1 enzyme responsible for the excision of 8-oxoguanine, a mutagenic base byproduct resulting from exposure to reactive oxygen [12].

The *hOGG1* gene is located at chromosome 3p26.2 and expressed as twelve alternatively spliced isoforms, among which only the 1α form contains a nuclear translocation signal [13]. A few coding region single nucleotide polymorphisms (SNPs) have been identified in the *hOGG1* gene, including the most commonly investigated Ser326Cys polymorphism, which has been reported to be associated with a reduced enzyme activity in a bacterial complementation assay system [14]. Numerous studies have explored the association between *hOGG1* Ser326Cys polymorphism and lung cancer susceptibility [14–50]; however, the results were inconsistent and conflicting. To overcome the deficiency of small sample size included in each study and limited statistical power, we performed this meta-analysis from all eligible studies to derive a more precise estimation of the association under different genetic models, especially for the smoking status and smoking intensity.

Material and methods

Search strategy and selection criteria

We performed a comprehensive literature search from MEDLINE and EMBASE databases using the following key words: "*hOGG1* or *OGG1*," "polymorphism or variant or variation," and "lung" (last search was updated on May 13, 2013). Additional studies and review articles were hands-on searched from references of related original studies or review articles. If more than one article was published using the same patient population or overlapping data from the same institutions, only the latest or the largest study would be included in the final meta-analysis. We also searched related investigations from Chinese Biomedical (CBM) database (http://cbmwww.imicams.ae.cn/cbmbin) with the combinations of "*hOGG1*" and "lung cancer" in Chinese to maximize the coverage and minimize the selection bias.

Studies included in the final meta-analysis had to meet the following inclusion criteria: a case–control design, an evaluation of the association between *hOGG1* Ser326Cys and lung cancer risk, sufficient information to estimate odds ratios (ORs) and their 95 % confidence intervals (CIs), and independence from other studies.

Data extraction

Two authors (Zong-Bao Yin and Rui-Xi Hua) independently assessed the articles and extracted data for compliance with the inclusion criteria. Disagreements were resolved by discussions between the two authors until consensus on all of the eligibility items was reached. Disputes were resolved by an additional author, and the final decision was made by the majority of the votes.

The following data were extracted from each publication: the first author's surname, year of publication, country of origin, ethnicity, match, source of controls, smoking status, cigarette takes, genotyping methods, total number of cases and controls, and numbers of cases and controls with the Ser/Ser, Ser/Cys, and Cys/Cys genotypes. The stratification analysis was conducted by ethnicity (categorized as Asians, Caucasians, Africans, Latinos, or Hawaiian), control source (hospital-based and population-based), smoking status (never smokers and ever smokers), and smoking intensity.

Statistical methods

We evaluated the strength of association between *hOGG1* Ser326Cys polymorphism and lung cancer susceptibility by crude ORs together with their corresponding 95 % CIs. We also calculated the pooled ORs and 95 % CIs for Ser326Cys by homozygous model (Cys/Cys vs. Ser/Ser), recessive model (Cys/Cys vs. (Ser/Cys+Ser/Ser)), and dominant model ((Ser/Cys+Cys/Cys) vs. Ser/Ser) as well as allele comparison (Cys vs. Ser). Chi square-based Q test was performed to assess the between-study heterogeneity. Additionally, the heterogeneity was also quantified using the I^2 values, and I^2 lies between 0 and 100 % with higher values indicating a greater degree of heterogeneity [51]. We used the fixed effects model (Mantel–Haenszel method) when the P value of the heterogeneity test

was ≥0.10 [52]; otherwise, we used the random effects model (DerSimonian and Laird method) which tends to provide wider 95 % CIs because the constituent studies differ among themselves [53]. The potential publication bias was verified by standard error of log (OR) for each study plotted against its log (OR). Funnel plot asymmetry was assessed by Egger's linear regression test [54]. Sensitivity analyses were performed by excluding a single study individually each time and recalculating the ORs and the 95 % CIs.

We performed the false-positive report probability (FPRP) [55, 56] analysis for all the significant findings, and set 0.2 as FPRP threshold and assigned a prior probability of 0.1 to detect an OR of 1.50 (for risk effects) for associations with genotypes under investigation. Only the results with FPRP values less than 0.2 were considered as significant findings.

We performed all the analyses using the STATA software (version 11.0; Stata Corporation, College Station, TX, USA) and SAS software (version 9.1; SAS Institute, Cary, NC, USA). All *P* values were two sided, and *P* values less than 0.05 were considered statistically significant.

Results

Characteristics of the study

A total of 86 publications that examined the association between *hOGG1* Ser326Cys and lung cancer risk were identified from MEDLINE and EMBASE, and additional 14 publications were identified from CBM using the search terms described previously (Fig. 1). Only 37 case–control studies which met the crude inclusion criteria were chosen for further analysis [14–50]. Among them, four studies [43, 45, 47, 48] were excluded for data overlapping with another one [24] which covered the largest sample size, one [42] was covered by a later investigation [23], and another one [46] was covered by a former investigation with larger sample size [21]; three studies [44, 49, 50] were also excluded in the final analysis because they used the same samples as others [19, 22, 40]. The distribution of genotypes for the *hOGG1* Ser326Cys polymorphism in the controls of all studies was in agreement with Hardy–Weinberg equilibrium (HWE), except for three studies [22, 27, 35]. Thus, the other polymorphisms in the controls were in agreement with HWE [22, 27], so these two were not excluded to enlarge the sample size; no further evidence from other polymorphisms was presented in the study of Liu et al. [35], so we performed the analysis with and without this one and found no substantial difference between the two analyses (data not shown), so this study was also included in the final analysis. The studies carried out by Le et al. [18] and Chang et al. [33] were extracted separately according to the ethnic groups. Overall, 28 publications with 31 investigations were included in the final meta-analysis (Table 1), consisting of 10,220 cases and 12,284 controls for the *hOGG1* Ser326Cys polymorphism. Of the 31 investigations, sample sizes of cases ranged from 45 to 2,155 and from 42 to 2,163 for controls. There were 18 studies on Asians, 10 studies on Caucasians, and 1 study on African–Americans, Latinos, and Hawaiian, respectively. Of all the studies, 11 were population-based, 19 were hospital-based, and one was not available. As to the smoking status, we observed that there were 15 studies which provided the genotype frequency information for ever smokers and 12 for never smokers. Controls were mainly matched for sex and age. Almost all of the cases were histologically or cytologically confirmed. The detailed genotype frequency data for all the studies was shown in Supplemental Table 1; for the smoking status, in Supplemental Table 2; and for the smoking intensity, in Supplemental Table 3.

Meta-analysis results

When all the eligible studies for the Ser326Cys polymorphism and lung cancer risk were pooled together, we found that the *hOGG1* Cys carriers were significantly associated with the overall lung cancer risk (homozygous model: OR=1.24, 95 % CI=1.05–1.47, *P*=0.013; recessive model: OR=1.22, 95 % CI=1.05–1.41, *P*=0.008; and allele comparing: OR=1.11, 95 % CI=1.02–1.21, *P*=0.022), as shown in Table 2 and Fig. 2. In the stratified analysis by ethnicity, the comparisons showed that a statistically significant association was found for Asians (homozygous model: OR=1.25, 95 % CI=1.03–1.52, *P*=0.022; recessive model: OR=1.22, 95 % CI=1.04–1.43, *P*=0.017; and allele comparing: OR=1.12, 95 % CI=1.01–1.25, *P*=0.035) and hospital-based studies (homozygous model: OR=1.24, 95 % CI=1.00–1.52, *P*=0.047 and recessive model: OR=1.20, 95 % CI=1.01–1.42, *P*=0.034). As to the smoking status and intensity, a statistically significant association was found for never smokers (homozygous model: OR=1.27, 95 % CI=1.02–1.58, *P*=0.031; dominant model: OR=1.18, 95 % CI=1.01–1.39, *P*=0.042; and allele comparing: OR=1.13, 95 % CI=1.02–1.25, *P*=0.022), and more-cigarette takers (homozygous model: OR=6.97, 95 % CI=1.51–32.17, *P*=0.013; recessive model: OR=5.66, 95 % CI=1.24–25.83, *P*=0.025; dominant model: OR=2.22, 95 % CI=1.31–3.76, *P*=0.003; and allele comparing: OR=2.20, 95 % CI=1.40–3.46, *P*=0.001 for more than 34 pack-years, and homozygous model: OR=2.70, 95 % CI=1.40–5.23, *P*=0.003 and recessive model: OR=1.74, 95 % CI=1.25–2.41, *P*=0.001 for more than 40 pack-years).

The FPRP values for significant findings from the Ser326Cys polymorphism and lung cancer risk at different prior probability levels are shown in Table 3. For a prior probability of 0.1, with a statistical power of 1.000, the FPRP values were 0.103, 0.065, and 0.168 for the homozygous model, recessive model, and allele comparing,

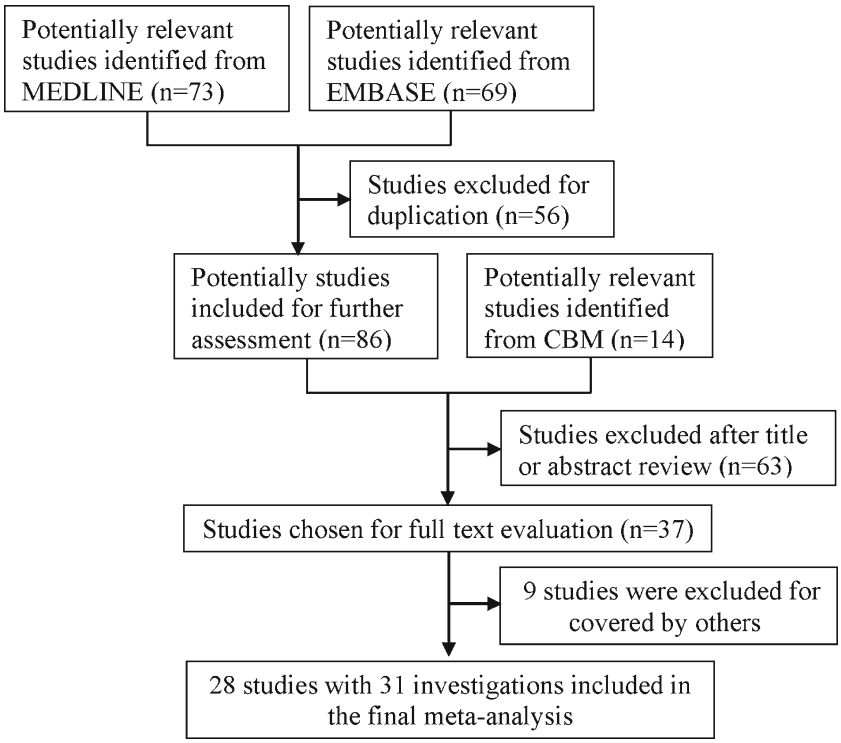

Fig. 1 Flow chart for the process of selecting the final 31 investigations

respectively, with an increased risk of lung cancer for all individuals. Positive associations with the Cys/Cys genotype were observed in the subgroups of Asians at homozygous and recessive models, ≥40 pack-years at recessive and allele comparing, and never smokers at allele comparing were also considered as noteworthy findings, for their probability to be a false-positive finding was less than 20 %. In contrast, greater FPRP values were observed for other noteworthy findings between *hOGG1* variants, and lung cancer risk may be ascribed to the reduced sample size in some subgroups, which need further validation in larger investigations.

Heterogeneity and sensitivity analyses

We used the random effects model to generated wider CIs for all genetics models, for substantial heterogeneities were observed among all the studies for *hOGG1* Ser326Cys polymorphism and overall lung cancer risk (homozygous model: $P<0.001$, $I^2=60.4$ %; recessive model: $P<0.001$, $I^2=62.2$ %; dominant model: $P=0.004$, $I^2=58.1$ %; and allele comparing: $P<0.001$, $I^2=72.6$ %). Therefore, we found that no single study can alter the pooled ORs qualitatively by leave-one-out sensitivity analysis (data not shown).

Publication bias

The shapes of the funnel plots seemed symmetrical, indicating that there was no obvious publication bias for the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk (Fig. 3). The Egger's test further provided statistical evidence that no publication bias existed in this meta-analysis (homozygous model: $P=0.175$; recessive model: $P=0.114$; dominant model: $P=0.168$; and allele comparing: $P=0.145$).

Discussion

In this updated meta-analysis including 10,220 lung cancer cases and 12,284 controls from a total of 31 investigations for the *hOGG1* Ser326Cys polymorphism, we found that the Ser326Cys polymorphism was significantly associated with the overall lung cancer risk in the homozygous model, recessive model, as well as allele comparing. Furthermore, the stratification analysis showed that the risk was more prominent in studies of Asian subjects, hospital-based controls, never smokers, and more-cigarette takers. We also performed FPRP analysis and calculated the statistical power for all the significant findings. To our knowledge, there is no quite similar meta-analysis that has comprehensively evaluated the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk especially for smoking status and smoking intensity as we did here.

There were several meta-analyses which investigated the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk. In a previous meta-analysis by Li et al. [57] including 6,375 cases and 6,406 controls from 17 studies, no significant increased lung cancer risk was found for the

Table 1 Characteristics of studies included in the meta-analysis

Surname	Year	Country	Ethnicity	Cases	Controls	SC	Matching	MAF	HWE
Kohno [14]	1998	Japan	Asian	45	42	PB	Sex, region	0.40	0.939
Sugimura [15]	1999	Japan	Asian	241	197	HB	Sex, region	0.41	0.082
Wikman [16]	2000	Germany	Caucasian	105	105	HB	Sex, age, smoking	0.22	0.067
Ito [17]	2002	Japan	Asian	138	240	HB	Sex, age, smoking	0.47	0.837
Le [18]	2002	USA	Caucasian	126	159	PB	Sex, age, ethnicity	0.22	0.810
Le [18]	2002	USA	Asian	97	150	PB	Sex, age, ethnicity	0.42	0.877
Le [18]	2002	USA	Hawaiian	75	96	PB	Sex, age, ethnicity	0.45	0.914
Lan [19]	2004	China	Asian	118	109	PB	Sex, age	0.33	0.232
Park [20]	2004	USA	Caucasian	179	350	Screening	Sex, age, race	0.15	0.857
Hung [21]	2005	European	Caucasian	2,155	2,163	HB	Sex, age, region	0.20	0.215
Liang [22]	2005	China	Asian	227	227	HB	Sex, age, ethnicity	0.61	0.043
Kohno [23]	2006	Japan	Asian	1,097	394	HB	Sex, smoking status	0.45	0.627
Sorensen [24]	2006	Denmark	Caucasian	431	796	PB	Sex, age, smoking	0.22	0.258
Lee [25]	2006	Korea	Asian	200	200	NA	Sex, age	NA	NA
Matullo [26]	2006	European	Caucasian	116	1,094	PB	Sex, age, smoking	0.22	0.901
Zienolddiny [27]	2006	Norway	Caucasian	326	386	PB	Sex, age, smoking	0.35	0.000
De Ruyck [28]	2007	Belgium	Caucasian	110	110	HB	Sex, age	0.25	0.176
Karahalil [29]	2008	Turkey	Caucasian	165	250	HB	Sex, age	0.33	0.546
Chang [30]	2009	Taiwan	Asian	1,096	997	HB	Sex, age, ethnicity	0.60	0.741
Miyaishi [31]	2009	Japan	Asian	108	121	HB	Sex, age, smoking	0.45	0.271
Okasaka [32]	2009	Japan	Asian	515	1,030	HB	Sex, age	0.49	0.070
Chang [33]	2009	USA	Latinos	112	296	PB	Sex, age, ethnicity	0.32	0.691
Chang [33]	2009	USA	African	254	280	PB	Sex, age, ethnicity	0.15	0.521
Klinchid [34]	2009	Thailand	Asian	76	75	HB	Sex, age	NA	NA
Liu [35]	2010	Taiwan	Asian	358	716	HB	Sex, age	0.64	0.004
Janik [36]	2011	Poland	Caucasian	88	79	HB	Sex, age, smoking	0.15	0.542
Kohno [37]	2011	Japan	Asian	377	325	HB	NA	0.45	0.704
Li [38]	2011	China	Asian	455	443	HB	Sex, age, region	0.62	0.329
Qian [39]	2011	China	Asian	581	601	HB	Sex, age	0.55	0.592
Cheng [40]	2012	China	Asian	124	128	PB	Sex, age	0.38	0.059
Du [41]	2012	China	Asian	125	125	HB	Sex, age	0.47	0.097

SC source of control, *HB* hospital-based, *PB* population-based, *MAF* minor allele frequency, *HWE* Hardy–Weinberg equilibrium, *NA* not available

hOGG1 Ser326Cys polymorphism in homozygous and recessive models; however, significant increased risk was found for Asians in a dominant model and for the population-based studies as well as never smokers. In another meta-analysis, Guan et al. [58] included a total of 7,592 patients and 8,129 controls from 18 studies and found that the *hOGG1* Ser326Cys polymorphism was associated with the risk of lung cancer. In the subgroup analyses, this risk was more prone in Asians, squamous carcinoma and adenocarcinoma patients, and heavy smokers. In the third meta-analysis written in Chinese including 8,575 cases and 9,484 controls, 326Cys genotype can significantly increase the lung cancer risk especially for Asians and hospital-based studies [59]. In the fourth meta-analysis, Duan et al. [60] did not find any association between *hOGG1* Ser326Cys polymorphism and the overall lung cancer risk; however, significant increased risk was found for adenocarcinoma. In the meta-analysis by Wei et al. [61], including 9,203 cases and 10,994 controls from 25 studies, significant risk was observed in homozygous and recessive models, and in the stratified analysis, significant increased risk was found for the population-based studies and non-smokers. Zhong et al. [62] performed an updated meta-analysis including 8,739 cases and 10,385 controls from 20 studies and found a significant increased risk for the Caucasians. Some of the findings were not repeated in the current meta-analysis, such as the Caucasians had a significant increased risk [62]; with two more additional studies, this risk disappeared. We noticed that some of the previous meta-analyses found significant increased risk for the population-based studies [57, 61], hospital-based studies [39], both

Table 2 Meta-analysis of the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk

Variables	No. of studies	Cases/controls	Homozygous			Recessive			Dominant			Allele		
			Cys/Cys vs. Ser/Ser			Cys/Cys vs. (Ser/Cys+Ser/Ser)			(Ser/Cys+Cys/Cys) vs. Ser/Ser			Cys vs. Ser		
			OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)	OR (95 % CI)	P^{het}	I^2 (%)
All	31	10,220/12,284	1.24 (1.05–1.47)	<0.001	60.4	1.22 (1.05–1.41)	<0.001	62.2	1.08 (0.97–1.20)	<0.001	58.1	1.11 (1.02–1.21)	<0.001	72.6
Ethnicity														
Asian	18	5,978/6,120	1.25 (1.03–1.52)	0.001	60.4	1.22 (1.04–1.43)	<0.001	66.2	1.09 (0.95–1.26)	0.007	50.6	1.12 (1.01–1.25)	<0.001	69.4
Caucasian	10	3,801/5,492	1.21 (0.80–1.83)	0.002	66.1	1.20 (0.82–1.77)	0.005	62.0	1.02 (0.84–1.25)	<0.001	70.7	1.06 (0.87–1.28)	<0.001	79.0
Source of control														
PB	11	1,824/3,536	1.26 (0.93–1.71)	0.069	42.0	1.27 (0.94–1.73)	0.035	48.6	1.08 (0.93–1.25)	0.237	21.7	1.12 (0.97–1.28)	0.045	46.4
HB	19	8,196/8,548	1.24 (1.00–1.52)	<0.001	68.1	1.20 (1.01–1.42)	<0.001	68.9	1.09 (0.94–1.26)	<0.001	68.4	1.11 (0.99–1.24)	<0.001	79.6
Bias			0.175			0.114			0.168			0.145		
Smoking status														
Ever	15	5,628/5,218	1.16 (0.87–1.54)	0.002	61.0	1.18 (0.96–1.46)	0.002	59.9	0.99 (0.85–1.16)	0.016	50.3	1.04 (0.91–1.19)	<0.001	69.2
Never	12	1,667/2,917	1.27 (1.02–1.58)	0.908	0.0	1.13 (0.96–1.33)	0.757	0.0	1.18 (1.01–1.39)	0.605	0.0	1.13 (1.02–1.25)	0.826	0.0
Smoking intensity														
≤20 cd	2	335/461	1.03 (0.40–2.70)	0.153	51.1	0.98 (0.37–2.57)	0.140	54.1	1.13 (0.85–1.50)	0.598	0.0	1.08 (0.83–1.42)	0.279	14.7
>20 cd	2	210/166	0.50 (0.21–1.21)	0.332	0.0	0.61 (0.26–1.42)	0.554	0.0	0.62 (0.27–1.45)	0.101	62.8	0.68 (0.35–1.29)	0.092	64.7
≤14.0 py	1	312/1,088	1.61 (0.94–2.76)	–	–	1.60 (0.94–2.72)	–	–	1.09 (0.84–1.40)	–	–	1.14 (0.92–1.40)	–	–
14.1–38.26 py	1	963/704	1.18 (0.69–2.03)	–	–	1.20 (0.70–2.07)	–	–	0.96 (0.78–1.18)	–	–	0.99 (0.83–1.18)	–	–
>38.26 py	1	874/363	1.40 (0.68–2.86)	–	–	1.47 (0.72–3.01)	–	–	0.89 (0.69–1.15)	–	–	0.96 (0.77–1.19)	–	–
<34 py	1	24/112	0.98 (0.05–21.28)	–	–	0.90 (0.04–19.39)	–	–	1.25 (0.49–3.21)	–	–	1.12 (0.48–2.60)	–	–
≥34 py	1	135/118	6.97 (1.51–32.17)	–	–	5.66 (1.24–25.83)	–	–	2.22 (1.31–3.76)	–	–	2.20 (1.40–3.46)	–	–
<40 py	3	1,045/1,776	1.18 (0.88–1.58)	0.833	0.0	1.13 (0.96–1.34)	0.812	0.0	1.08 (0.83–1.41)	0.332	0.0	1.07 (0.94–1.23)	0.693	0.0
≥40 py	3	757/389	2.70 (1.40–5.23)	0.329	0.0	1.74 (1.25–2.41)	0.519	0.0	1.29 (0.43–3.87)	0.019	81.7	1.39 (0.78–2.46)	0.053	73.3

het heterogeneity, *HB* hospital-based, *PB* population-based, *cd* cigarette per day, *py* pack-year

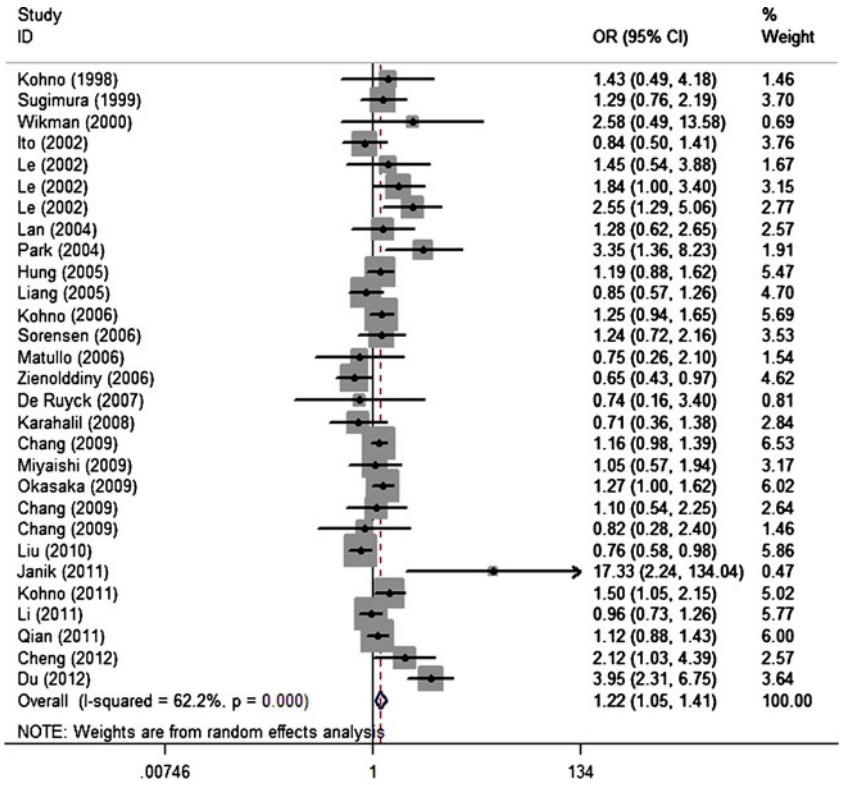

Fig. 2 Forest plot of overall lung cancer associated with the *hOGG1* Ser326Cys polymorphism in a recessive model (Cys/Cys vs. Ser/Cys+Ser/Ser) by the random effects for each of the 31 investigations. For each study, the estimates of OR and its 95 % CI are plotted with a *box* and a *horizontal line*. *Diamond* indicates pooled ORs and its 95 % CIs.

hospital-based and population-based studies [58, 62], as well as no associations [60]. In the current one, we found significant increased risk for the hospital-based studies; thus, after we performed the FPRP analysis, this risk disappeared. Some of the discoveries may be false-positive findings due to the limited sample size in each stratum, so it is important to perform FPRP analysis to avoid them, especially when the sample size is not large enough. Though some of the previous meta-analysis paid attention to the smoking status [58, 61, 62], nearly none of them paid attention to smoking intensity, allele comparing as well as the statistical power and the opportunity to be false-positive findings.

BER pathway is initiated by the recognition and excision of small lesions such as oxidized or reduced bases, fragmented or nonbulky adducts, or byproducts of methylating agents [63]. The role of BER in carcinogenesis has been evaluated extensively, and polymorphisms of BER genes may be associated with cancer risk especially for those caused by tobacco use [33]. The *hOGG1* gene is one of the major genes involved in the BER pathway [11], and polymorphisms of the *hOGG1* gene may lead to the defective repair of 8-hydroxyguanine [14]. One of the most commonly investigated polymorphisms is Ser326Cys; thus, the conclusions from numerous studies were still inconsistent, for example, the frequency of the *hOGG1* 326Cys/Cys genotype was found to be significantly higher in the lung cancer patients when compared with controls [18, 20, 36, 37, 41] and significantly lower in some studies [27, 35]; however, no association was found by other studies. Overall, we found that the *hOGG1* Cys carriers had significantly increased lung cancer risk when compared with the Ser carriers, which was also confirmed in the subgroup analysis for Asians, never smokers, and more-cigarette takers. There are several possible reasons for our findings. The Asians who carry the *hOGG1* 326Cys allele had an obviously higher risk than Caucasians which may be ascribed to the ethnicity difference. The never smokers with the *hOGG1* 326Cys were more prone to get lung cancer which may be ascribed to their genetic susceptibility even being exposed to a low level of tobacco smoke, as well as more susceptible to second-hand smoke. More-cigarette takers with the 326Cys had obviously higher risk than the fewer takers which may be due to the fact that tobacco smoke contains lots of carcinogens that can induce various kinds of DNA damage and may accumulate when more cigarettes are consumed.

Of note, several limitations in the current meta-analysis need to be addressed. Firstly, some studies provided insufficient genotype as well as different studies provided different definitions of smoking status and smoking intensity. Secondly, we found that most studies included in this meta-analysis had relatively small sample size for cases (<500) except for five studies [21, 23, 30, 32, 39], which were insufficient for genetic association study and may attenuate the statistical power. Thirdly, lacking detailed information, this meta-analysis was based on unadjusted estimates of ORs, while a more precise association should be performed if individual's age, sex, and occupation exposure data were

Table 3 False-positive report probability values for associations between lung cancer risk and the frequency of genotypes of *hOGG1* gene

Variables	Crude OR (95 % CI)	*P* value[a]	Statistical power[b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
Homozygous (Cys/Cys vs. Ser/Ser)								
All	1.24 (1.05–1.47)	0.013	1.000	0.037	0.103	0.559	0.927	0.992
Asian	1.25 (1.03–1.52)	0.022	1.000	0.061	0.164	0.683	0.956	0.995
HB	1.24 (1.00–1.52)	0.047	1.000	0.124	0.299	0.824	0.979	0.998
Never smoker	1.27 (1.02–1.58)	0.031	0.993	0.087	0.223	0.759	0.970	0.997
≥34 py	6.97 (1.51–32.17)	0.013	0.020	0.654	0.850	0.984	0.998	1.000
≥40 py	2.70 (1.40–5.23)	0.003	0.042	0.185	0.405	0.882	0.987	0.999
Recessive (Cys/Cys vs. (Ser/Cys+Ser/Ser))								
All	1.22 (1.05–1.41)	0.008	1.000	0.023	0.065	0.433	0.885	0.987
Asian	1.22 (1.04–1.43)	0.017	1.000	0.047	0.129	0.619	0.942	0.994
HB	1.20 (1.01–1.42)	0.034	1.000	0.094	0.237	0.774	0.972	0.997
≥34 py	5.66 (1.24–25.83)	0.025	0.035	0.682	0.866	0.986	0.999	1.000
≥40 py	1.74 (1.25–2.41)	0.001	0.236	0.013	0.037	0.295	0.809	0.977
Dominant ((Ser/Cys+Cys/Cys) vs. Ser/Ser)								
Never smoker	1.18 (1.01–1.39)	0.042	0.999	0.113	0.276	0.807	0.977	0.998
≥34 py	2.22 (1.31–3.76)	0.003	0.070	0.121	0.293	0.820	0.979	0.998
Allele (Cys vs. Ser)								
All	1.11 (1.02–1.21)	0.022	1.000	0.063	0.168	0.689	0.957	0.996
Asian	1.12 (1.01–1.25)	0.035	1.000	0.096	0.243	0.779	0.973	0.997
Never smoker	1.13 (1.02–1.25)	0.022	1.000	0.061	0.163	0.681	0.956	0.995
≥34 py	2.20 (1.40–3.46)	0.001	0.040	0.043	0.119	0.599	0.938	0.993

CI confidence interval, *OR* odds ratio, *HB* hospital-based, *py* pack-year

[a] Chi-square test was used to calculate the genotype frequency distributions

[b] Statistical power was calculated using the number of observations in the subgroup and the OR and *P* values in this table

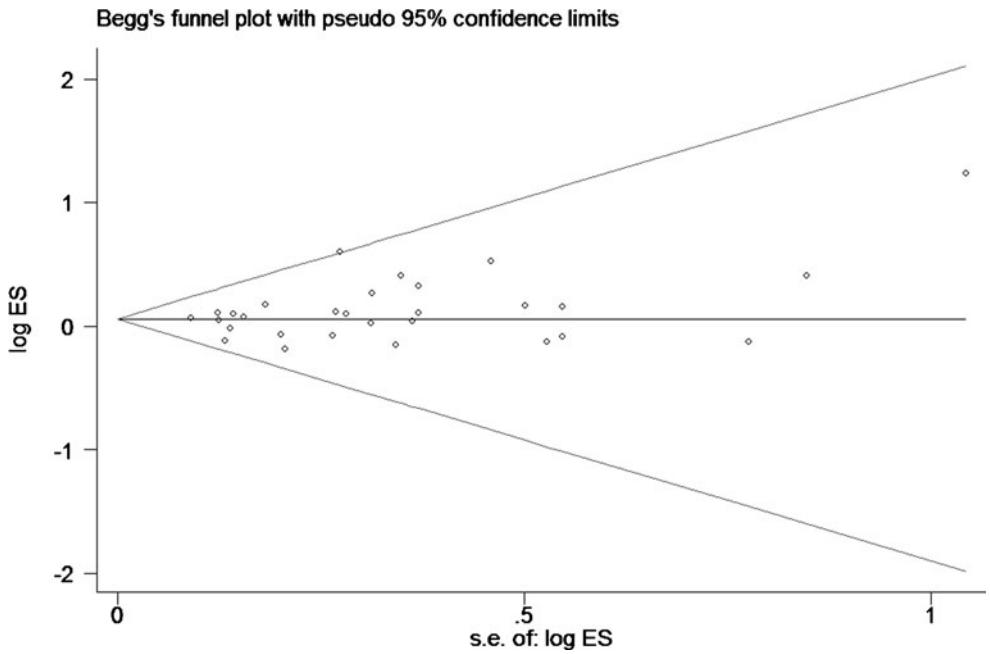

Fig. 3 Begg's funnel plot to detect publication bias in a recessive model. Each point represents an individual study for the indicated association

available. Finally, some of the findings in stratification analysis may have been overestimated for there was only one trail available.

Despite these limitations, our meta-analysis strongly suggests that *hOGG1* Ser326Cys polymorphism may be associated with lung cancer, especially for Asians, never smokers, and more-cigarette takers. However, well-designed prospective studies with larger sample sizes, more information for smoking status, as well as smoking intensity are required to validate our findings.

Acknowledgments We thank Ruoxin Zhang for providing help in the revision and modification of this paper. This work was supported by the Scientific Research Project of Hainan Provincial Department of Health (no. 2011-SWK-06-132/QIONGWEI 2011–61).

Conflicts of interest None

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