Original Article

The hOGG1 Ser326Cys polymorphism and esophageal cancer risk: a meta-analysis of 1,875 cancer cases and 3,041 controls

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Background: Recently, there have been several studies that have looked at the association between hOGG1 Ser326Cys polymorphism and esophageal cancer (EC) risk. However, the results of previous reports remain controversial and ambiguous. Thus, we performed a meta-analysis to explore more precisely the association between hOGG1 Ser326Cys polymorphism and the risk of EC.

Methods: A meta-analysis was performed to examine the association between hOGG1 Ser326Cys polymorphism and EC risk. Odds ratio (OR) and its 95% confidence interval (CI) were used for statistical analysis.

Results: Our publication search identified a total of 9 studies with 1,875 cases and 3,041 controls. There was no significant associations in all genetic models between hOGG1 Ser326Cys polymorphism and EC observed (OR =1.024, 95% CI: 0.932–1.125 for Cys *vs.* Ser, P=0.624; OR =1.126, 95% CI: 0.901–1.408 for Cys/Cys *vs.* Ser/Ser, P=0.296; OR = 0.961, 95% CI: 0.844–1.093 for Ser/Cys *vs.* Ser/Ser, P =0.540; OR =0.989, 95% CI: 0.874–1.118 for Cys/Cys + Ser/Cys *vs.* Ser/Ser, P=0.855; OR =1.165, 95% CI: 0.945–1.436 for Cys/Cys *vs.* Ser/Cys + Ser/Ser, P=0.153). Also, in the stratified analyses by ethnicity and cancer type, no significant association was observed.

Conclusions: This meta-analysis on hOGG1 Ser326Cys polymorphism and the risk of EC suggests there is no statistically significant association between the two. Additional primary studies may be necessary to provide evidence of any significant association between this specific polymorphism and EC.

Keywords: Polymorphism; esophageal cancer (EC); single nucleotide polymorphism (SNP); hOGG1

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Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, and the sixth most common cause of cancer-related death (1). Generally, EC has two subtypes, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC and EAC arise from different cells of the esophagus. The carcinogenesis of EC is still not clear. It is a complex, multi-factorial, and multistep event, in which many factors are involved, such as poor nutritional status, heavy alcohol drinking, cigarette smoking, high-temperature cooking methods, severe lack of vegetable and fruit intake, and genetic factors (2-4). In recent years, genetic factors, including single nucleotide polymorphisms (SNPs), are increasingly regarded as significant contributors to EC (5).

hOGG1, The human 8-oxoguanine glycosylase 1 gene, encodes 8-hydroxygumine DNA glycosylase 1 (OGG1) that can repair damaged DNA by excising 8-dihydro-

8-oxoguanine (8-OH-G). Many single nucleotide polymorphisms in this gene are thought to influence the expression of the encoding proteins and activity of encoding proteins, thereby being a predisposition to disease (6). A common single nucleotide polymorphism of hOGG1 at codon 326 polymorphism (Ser326Cys, rs1052133) has been described in recent years. Compared to the 326Ser variant enzyme, the enzyme 326Cys of hOGG1 appears to have a reduced capacity to repair oxidized DNA lesions (7).

Conflicting reports show an association of hOGG1 Ser326Cys polymorphism with different tumor types and ethnic groups (8-13). To date, a considerable number of studies have been conducted to investigate the association between hOGG1 gene polymorphism and EC susceptibility in humans. However, the results remain controversial and ambiguous. In 2013, Zhang *et al*. (14) conducted a meta-analysis about the association between the hOGG1 Ser326Cys polymorphism and the risk of ESCC, which did not include EAC. In February 2019, Tian *et al*. (15) collated a comprehensive investigation for cumulative evidence of genetic polymorphisms of EC and its subtype risk. It showed no association between hOGG1 and EC. And the evaluation data were only extracted from previous meta-studies, which may be the main reason for the bias. To derive a more comprehensive and precise estimation of this association, we performed the current meta-analysis.

Methods

Publication search

Computer searches were performed independently by two authors (Chen Zhao and Ji Yang), covering all papers published in PubMed, Embase, Medline, and Google Scholar before November 2018. The keywords were as follows: "EC/oesophageal cancer/ESCC/EAC", and "OGG1/hOGG1/8-Oxoguanine DNA glycosylase 1", and "polymorphism/variant/mutation/SNP". The reference lists of the retrieved articles were hand-searched to obtain other relevant publications. All associated publications were evaluated to identify the most eligible literature. The results were limited to papers published in English. Discrepancies between the two reviewers were resolved by a third reviewer (Liqian Xu).

Inclusion and exclusion criteria

The following criteria were used to select studies for further meta-analysis: (I) the studies were case-controlled; (II) the studies were about hOGG1 Ser326Cys polymorphism and risk of EC; (III) the studies contained at least two comparison groups (cancer group *vs*. control group); (IV) the studies included detailed genotyping data.

Data extraction

The extraction of data from all eligible publications was performed by two investigators (Chen Zhao and Ji Yang) independently, according to the inclusion and exclusion criteria listed above. Moreover, in cases of conflict, a third reviewer (Liqian Xu) was involved in resolving the conflict. For each study, the information that was extracted was the author's last name, year of publication, country of origin, ethnicity, cancer type, sources of control and case groups, specimen of cases, genotyping methods for hOGG1 Ser326Cys, total number of cases and controls as well as number of cases and controls with Ser/Ser, Ser/Cys and Cys/Cys genotypes. All of the cases and control groups were well controlled.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) for the control group of each study was assessed using a goodness-of-fit test (χ^2 of Fisher's exact test). Based on both the fixed-effects and random-effects models, and a pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of association between hOGG1 Ser326Cys polymorphism and EC risk, depending on the heterogeneity of the analysis. In the overall and the subgroup meta-analysis, pooled ORs and 95% CIs for the allele model (Cys *vs*. Ser) and codominant model (Cys/Cys *vs*. Ser/Ser; Ser/Cys *vs*. Ser/Ser); the dominant model (Cys/Cys + Ser/Cys *vs*. Ser/Ser) and the recessive model (Cys/Cys *vs*. Ser/Cys + Ser/Ser) were all calculated. Heterogeneity was assessed using Q-test and I^2 score. If the results of the heterogeneity test were P>0.05, ORs were pooled according to the fixed-effects model (Mantel-Haenszel model). Otherwise, ORs were pooled according to the random-effects model (DerSimonian and Laird model). I^2 was used to qualify variation in OR attributable to heterogeneity.

Publication bias was assessed using the Egger's test and Begg's test. All statistical tests were performed using the software STATA v.12.0 (Stata Corporation, College Station, TX, USA). The results were considered statistically significant if P<0.05.

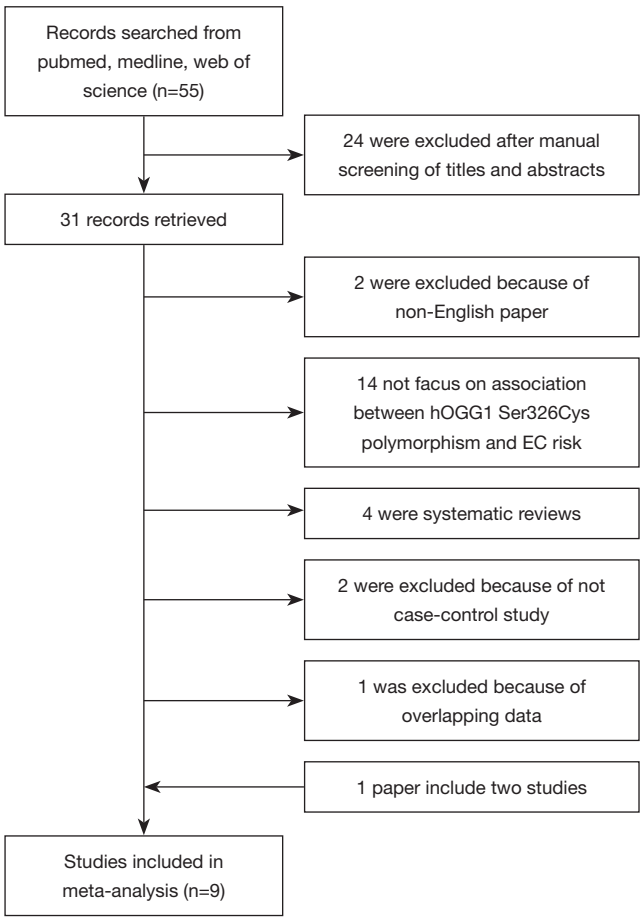


Figure 1 Flow chart of study selection based on the inclusion and exclusion criteria.

Results

Study selection

The study selection process is shown in *Figure 1*. After a preliminary online search, we identified 55 potentially relevant articles for further detailed evaluations. Then, 24 of these were excluded after manual screening of titles and abstracts. Then, a total of 31 records that fulfilled our search criteria were preliminarily identified for further detailed evaluation. Twenty-three studies were excluded because 14 studies were not focused on the association between hOGG1 Ser326Cys polymorphism and EC. Two studies were excluded because they were not written in English. One study was excluded because of overlapping data. Two others were not case-control studies, and the remaining 4 studies were systematic review comments. Finally, 8 records (16-23) on hOGG1 Ser326Cys polymorphism and EC risk were identified, and 1 of them included 2 studies. Finally, a total of 9 case-control studies involving 1,875 cancer cases and 3,041 controls were included in the meta-analysis.

Study characteristics

Characteristics of the papers included in this meta-analysis are presented in *Table 1*. All studies involved in published papers are case-control studies. The studies were carried out in China, UK, France, USA, European, and India. The studies carried out in China and India were used in the Asian subgroup, and the others were used in the Caucasian subgroup. Of the 9 studies, we found that 2 were related to EAC, 4 were related to ESCC, and another 3 studies contained both types of EC (EAC and ESCC) but we could not obtain the specific figures of EAC/ESCC patients even after contacting the authors. The genotype distribution in the controls was consistent with the HWE (P>0.05) in other studies except for two studies (Tse *et al*., P=0.039; Upadhyay *et al*., P=0.019).

Quantitative data synthesis

The results on the associations between hOGG1 Ser326Cys polymorphism and EC risk, and of the heterogeneity test, are shown in *Table 2*. Overall, when all of the eligible studies were pooled into the meta-analysis, no significant associations between hOGG1 Ser326Cys polymorphism and EC susceptibility were found for the allele model: Cys *vs*. Ser (OR =1.024, 95% CI: 0.932–1.125, P=0.624); codominant model: Cys/Cys *vs*. Ser/Ser (OR =1.126, 95% CI: 0.901–1.408, P=0.296), Ser/Cys *vs*. Ser/Ser(OR =0.961, 95% CI: 0.844–1.093, P=0.540); dominant model: Cys/Cys + Ser/Cys *vs*. Ser/Ser (OR =0.989, 95% CI: 0.874–1.118, P=0.855); recessive model: Cys/Cys *vs*. Ser/Cys + Ser/Ser (OR =1.165, 95% CI: 0.945–1.436, P=0.153) (*Figure 2*). In the stratified analysis by ethnicity, no significant results were found for Asian and Caucasian subjects in different statistical models (all P>0.05) (*Table 2*, *Figure 2A*). Similarly, no significant difference was observed in different cancer types (all P>0.05) (*Table 2*, *Figure 2B*).

Tests of heterogeneity

No statistically significant heterogeneity was observed between trials of the following analyses using Q statistic and I^2 score (Cys *vs*. Ser: P=0.108, I^2=39.0%; Cys/Cys *vs*. Ser/Ser: P=0.108, I^2=39.0%; Ser/Cys *vs*. Ser/Ser: P=0.139, I^2=34.9%; Cys/Cys + Ser/Cys *vs*. Ser/Ser: P=0.149,

Table 1 hOGG1 Ser326Cys genotype distribution and allele frequency in cases and controls

Author (year)	Country	Type	Genotype (N)								Allele frequency (N, %)				P for HWE
			Case				Control				Case		Control		
			Total	S/S	S/C	C/C	Total	S/S	S/C	C/C	S	C	S	C	
Lagadu *et al.* (2010)	France	ESCC & EAC & leiomyoma	17	14	3	0	43	22	19	2	31 (91.2%)	3 (8.8%)	63 (73.3%)	23 (26.7%)	0.403
Tse *et al.* (2008)	USA	EAC	310	198	95	17	453	294	133	26	491 (79.2%)	129 (20.8%)	721 (79.6%)	185 (20.4%)	0.039
Ferguson *et al.* (2008)	UK	EAC	209	138	67	4	248	141	96	11	343 (82.1%)	75 (17.9%)	378 (76.2%)	118 (23.8%)	0.288
XING *et al.* (2001)	China	ESCC	196	78	76	42	201	68	106	27	232 (59.2%)	160 (40.8%)	242 (60.2%)	160 (39.8%)	0.154
Li *et al.* (2011)	China	ESCC	225	86	126	13	246	97	123	26	298 (66.2%)	152 (33.8%)	317 (64.4%)	175 (35.6%)	0.154
Upadhyay *et al.* (2010)	India	ESCC & EAC	135	59	66	10	195	94	89	12	184 (68.1%)	86 (31.9%)	277 (71.0%)	113 (29.0%)	0.128
Upadhyay *et al.* (2010)	India	ESCC & EAC	200	84	97	19	207	96	100	11	265 (66.25%)	135 (33.75%)	292 (70.5%)	122 (29.5%)	0.019
Hall *et al.* (2006)	European	ESCC	173	107	56	10	969	622	320	27	270 (78.0%)	76 (22.0%)	1564 (80.7%)	374 (19.3%)	0.061
Hao *et al.* (2004)	China	ESCC	410	153	180	77	479	184	216	79	486 (59.3%)	334 (40.7%)	584 (61.0%)	374 (39.0%)	0.249

HWE, Hardy-Weinberg equilibrium; S/S, Ser/Ser; S/C, Ser/Cys; C/C, Cys/Cys; S, Ser; C, Cys; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

I^2=33.6%. Cys/Cys *vs*. Ser/Cys + Ser/Ser: P=0.054, I^2=47.6%) (*Table 2*), and the fixed-effects model was employed in these studies.

Publication bias

Egger's test and Begg's test were performed to assess publication bias. The Egger weighted regression method did not indicate any evidence for publication bias (Cys *vs*. Ser: P=0.106; Cys/Cys *vs*. Ser/Ser: P=0.452; Ser/Cys *vs*. Ser/Ser: P=0.101; Cys/Cys + Ser/Cys *vs*. Ser/Ser: P=0.086; Cys/Cys *vs*. Ser/Cys + Ser/Ser: P=0.526). This result was confirmed by the Begg rank correlation method (Cys *vs*. Ser: P=0.754; Cys/Cys *vs*. Ser/Ser: P=0.602; Ser/Cys *vs*. Ser/Ser: P=0.754; Cys/Cys + Ser/Cys *vs*. Ser/Ser: P=0.466; Cys/Cys *vs*. Ser/Cys + Ser/Ser: P = 0.602) (*Table 3*).

Discussion

EC is a malignant tumor of the esophagus, and the mechanisms for EC remains unclear. Several studies have found that DNA repair efficiency is lower in cancer patients than in that of normal people, and the variants of the genes involved in DNA repair can increase the cancer risk (24). Among many factors of oxidative DNA damage, 8-hydroy-2-deoxyguanine (8-OHdG) is one of the most abundant oxidative products of highly mutagenic because of its propensity to mispair with adenine during DNA replication (25). Studies have shown that the hOGG1 gene could remove 8-OHdG from DNA by base excision repair (BER) pathway (6,26). Another report also revealed that genetic variations in hOGG1 gene might alter glycosylase activity, increasing the cancer risk (27). There are several polymorphisms in the hOGG1 gene (28), and Ser326Cys polymorphism has attracted widespread attention.

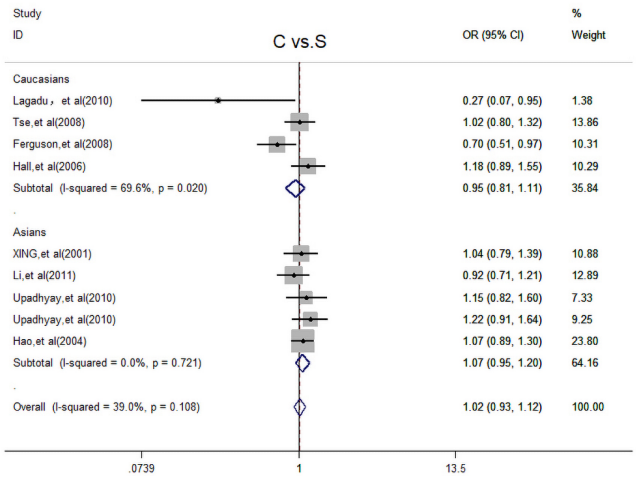
Many epidemiological studies have investigated the association of the Ser326Cys polymorphism in the hOGG1 gene with different types of cancers, but there are conflicting reports. Also, studies on the prevalence of this polymorphism in susceptibility to EC show conflicting

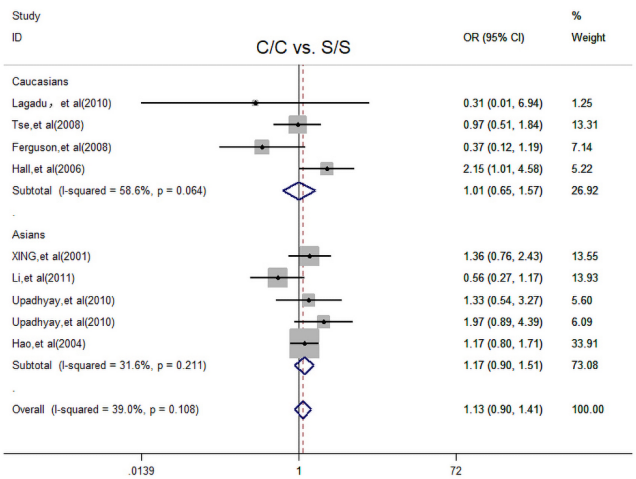
Table 2 Meta-analysis of the association between hoGG1 Ser326 Cys polymorphism and esophageal cancer risk

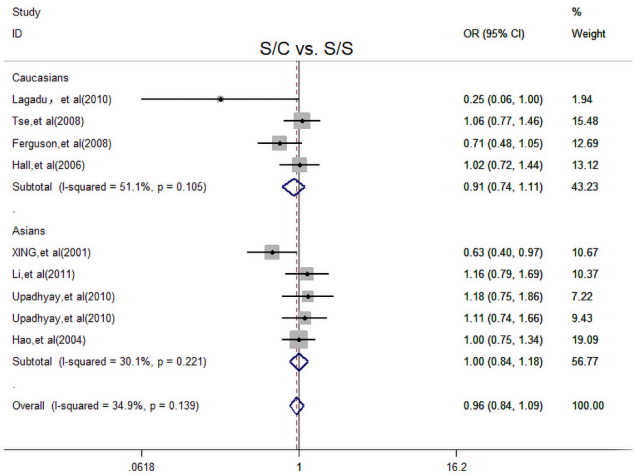
Comparisons	Subgroup analysis	Odds ratio	95% confidence interval	P value	Heterogeneity		Effects model
					I^2 (%)	P value	
C *vs*. S							
	Ethnicity	1.024	0.932–1.125	0.624	39.0	0.108	Fixed
	Asians	1.067	0.950–1.199	0.271	0	0.721	
	Caucasians	0.946	0.805–1.110	0.495	69.6	0.020	
	Cancer type	1.004	0.904–1.114	0.946	27.7	0.227	Fixed
	AC	0.886	0.726–1.081	0.233	69.5	0.070	
	SCC	1.053	0.931–1.190	0.411	0	0.667	
C/C *vs*. S/S							
	Ethnicity	1.126	0.901–1.408	0.296	39.0	0.108	Fixed
	Asians	1.169	0.902–1.515	0.238	31.6	0.211	
	Caucasians	1.010	0.649–1.573	0.964	58.6	0.064	
	Cancer type	1.066	0.836–1.359	0.607	51.9	0.065	Fixed
	AC	0.762	0.438–1.323	0.334	50.2	0.157	
	SCC	1.159	0.884–1.521	0.286	54.9	0.084	
S/C *vs.* S/S							
	Ethnicity	0.961	0.844–1.093	0.540	34.9	0.139	Fixed
	Asians	1.000	0.844–1.184	0.998	30.1	0.221	
	Caucasians	0.909	0.745–1.109	0.348	51.1	0.105	
	Cancer type	0.941	0.815–1.086	0.405	31.5	0.200	Fixed
	AC	0.904	0.706–1.157	0.423	58.0	0.123	
	SCC	0.960	0.805–1.146	0.652	37.0	0.190	
C/C + S/C *vs*. S/S							
	Ethnicity	0.989	0.874–1.118	0.855	33.6	0.149	Fixed
	Asians	1.041	0.886–1.223	0.624	0	0.575	
	Caucasians	0.920	0.761–1.113	0.391	64.0	0.040	
	Cancer type	0.966	0.843–1.107	0.619	15.2	0.316	Fixed
	AC	0.884	0.698–1.120	0.307	67.3	0.080	
	SCC	1.010	0.854–1.194	0.908	0	0.565	
C/C *vs*. S/C + S/S							
	Ethnicity	1.165	0.945–1.436	0.153	47.6	0.054	Fixed
	Asians	1.206	0.950–1.531	0.124	55.2	0.063	
	Caucasians	1.036	0.668–1.607	0.876	52.3	0.098	
	Cancer type	1.074	0.709–1.627	0.738	63.0	0.019	Random
	AC	0.736	0.349–1.552	0.420	32.5	0.223	
	SCC	1.234	0.746–2.043	0.413	69.8	0.019	

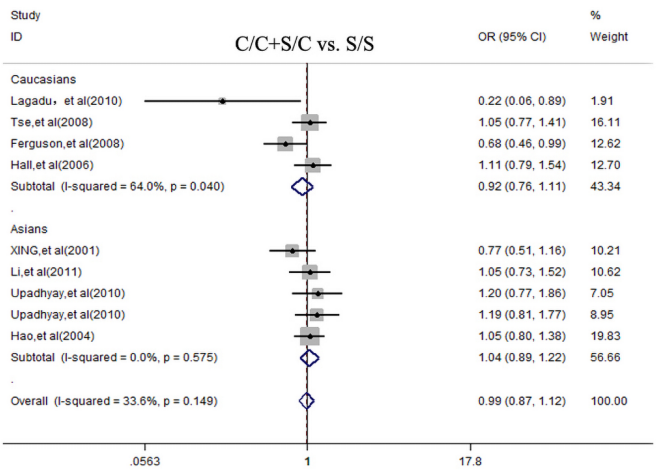
S/S, Ser/Ser; S/C, Ser/Cys; C/C, Cys/Cys; S, Ser; C, Cys.

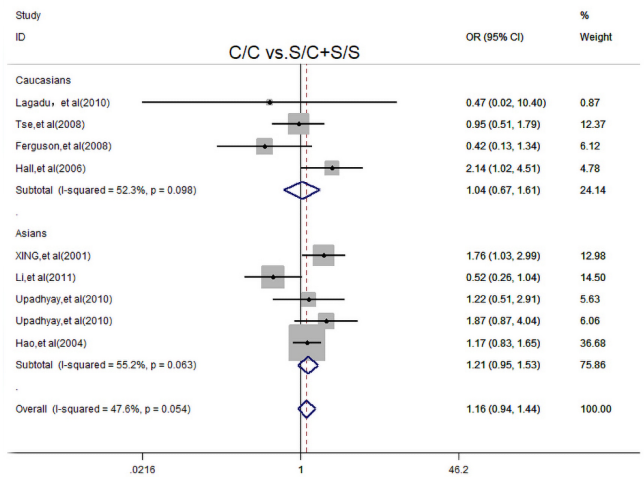
A











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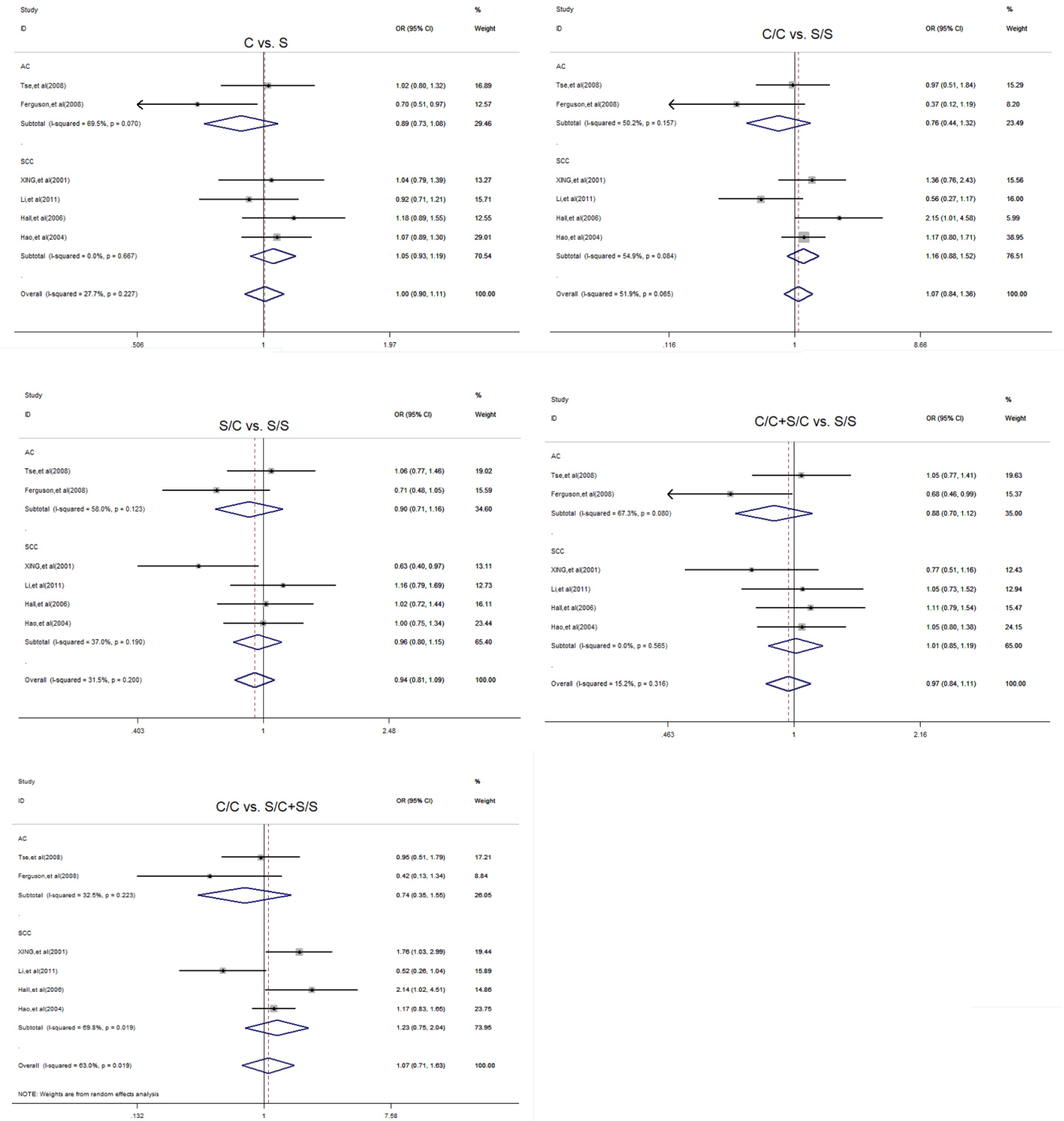

Figure 2 Forest plots of hOGG1 Ser326Cys in esophageal cancer *vs.* normal control *vs.* normal control and subgroup analyses. (A) Subgroup analyses based on ethnicity; (B) subgroup analyses based on cancer types. The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; CI, confidence interval.

Table 3 Publication bias test for hOGG1 Ser326Cys polymorphism

Comparisons	Egger's test			Begg's test
	Coefficient	P value	95% confidence interval	P value
C *vs*. S	–2.216	0.106	–5.040 to 0.608	0.754
C/C *vs*. S/S	–0.861	0.452	–3.420 to 1.700	0.602
S/C *vs*. S/S	–2.418	0.101	–5.450 to 0.609	0.754
C/C + S/C *vs*. S/S	–2.411	0.086	–5.266 to 0.444	0.466
C/C *vs*. S/C + S/S	–0.748	0.526	–3.400 to 1.904	0.602

S/S: Ser/Ser; S/C: Ser/Cys; C/C: Cys/Cys; S: Ser; C: Cys.

results. Xing *et al*. (17) reported that homozygosity for the Cys/Cys genotype significantly increased the risk of developing ESCC in Asians, which indicated that the hOGG1 326Cys allele might play a role in the carcinogenesis of the esophagus whereas Tse *et al*. (18) and Ferguson *et al*. (19) reported no statistical association between hOGG1 gene polymorphism and EAC in Caucasians. Hence, this meta-analysis was needed to provide a quantitative approach for combining the different results. A study conducted in Asians by Upadhyay *et al*. (21) indicated that no significant association was found between hOGG1 Ser326Cys genotypes and EC risk. To derive a more precise estimation of the association, we conducted a meta-analysis. The present meta-analysis, including 1,875 cancer cases and 3,041 controls, explored the relationship between the hOGG1 Ser326Cys polymorphism and the overall EC risk. This meta-analysis on hOGG1 Ser326Cys polymorphism and the risk of EC suggests no statistically significant association between the two. Additional primary studies may be necessary to provide evidence of any significant association between this specific polymorphism and EC. We found that there was no statistically significant difference between hOGG1 Ser326Cys polymorphism and EC risk in any types of the statistical model (all P>0.05). In the subgroup meta-analysis based on ethnicity, no significant results were found for Asian and Caucasian subjects in the different statistical model (all P>0.05). Similarly, no significant results were found for ESCC and EAC in the different statistical model (all P>0.05). These results were inconsistent with those of Zhang *et al*. A meta-analysis conducted by Zhang *et al*. in 2013 (14) suggested that the hOGG1 Ser326Cys polymorphism was associated with ESCC susceptibility. Cys/Cys carriers have more risk on ESCC rather than Ser/Ser and Ser/Cys carriers. The reasons for this difference were as follows: firstly, the literature we selected was limited to English, which limited the scale of the data to the meta-analysis and avoided duplication of studies enrolled; secondly, two studies enrolled by Zhang *et al*. were abandoned when we read the full text of articles because they are mixed cancer types (ESCC and EAC). These results revealed that ethnicity or environment might not be critical factors on the effects of the polymorphic alleles. Further studies are still needed to use standardized unbiased homogenous cancer patients and well-matched controls to investigate the combined effects.

Several limitations of this meta-analysis should be addressed. First, the analysis did not consider gene-gene and gene-environment interactions, and a more precise analysis might be conducted, which could allow for an adjustment estimate by sex, age, and lifestyle such as smoking and alcohol drinking. Second, the controls were not uniformly defined, as although most of the patients in the control groups were selected from healthy populations, some might have benign disease. Third, they were mixed cancer types, and we could not get the numbers of ESCC or EAC patients from studies or authors, which may limit the scale of the data in the meta-analysis.

In conclusion, the current meta-analysis suggests that hOGG1 Ser326Cys polymorphism is the lack of any association with EC risk. Our results should be interpreted with cautions considering the limited studies in both overall and subgroup analyses. Unbiased, well designed, and prospective studies with a larger sample size focusing on diverse ethnicities, sex, age, lifestyle, and pathological cancer types should be conducted to determine further whether there exist any correlations between the hOGG1 Ser326Cys polymorphism and the risk of EC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was a systematic review and meta-analysis of all published literature and institutional review deemed this study exempt from ethical approval.

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