

Original Article

Association of *hOGG1* Ser326Cys polymorphism with susceptibility to hepatocellular carcinoma

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Abstract: Background: Since, the relationship between *hOGG1* Ser326Cys polymorphism and HCC was inconsistent in the recent literatures. The present meta-analysis based on previous studies was to obtain precise estimation on the issue. Methods: A computer search was carried out from PubMed, CBM and EMBASE databases. A total of nine case-control publications with 2583 HCC patients and 2271 controls were included in the meta-analysis. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the relationship of Ser326Cys polymorphism and HCC susceptibility. Z test was used to assess the significance of pooled OR. The fixed-effect model or random-effect model was employed according to heterogeneity. Results: Overall, *hOGG1* Ser326Cys polymorphism was in relation with increased risk for HCC under the following genetic models: GG versus CC: OR=2.51, 95% CI=1.67-3.78; GG versus CG + CC: OR=2.27, 95% CI=1.57-3.30; GG + CG versus CC: OR=1.13, 95% CI=1.03-1.24. The subgroup analysis by ethnicity suggested that high risk for HCC was observed in Asians with GG and GG + CG genotype (GG versus CC: OR=2.17, 95% CI=1.49-3.17; GG versus CG + CC: OR=1.96, 95% CI=1.41-2.73; GG + CG versus CC: OR=1.13, 95% CI=1.03-1.25). For subgroup analysis based on source of control, GG genotype of Ser326Cys was significantly associated with HCC risk in hospital-based (HB) controls (GG versus CC: OR=2.31, 95% CI=1.50-3.56; GG versus CG + CC: OR=2.17, 95% CI=1.44-3.28), as well as in population-based (PB) models (GG vs. CC: OR=2.80, 95% CI=1.16-6.77; GG versus CG + CC: OR=2.39, 95% CI=1.08-5.30). Conclusions: According to the results, *hOGG1* Ser326Cys polymorphism was associated with increased risk of HCC.

Keywords: Human 8-oxoguanine glycosylase 1, Ser326Cys, hepatocellular carcinoma, risk

Introduction

Hepatocellular carcinoma (HCC), one of the most common malignancies all over the world, causes over 700,000 new cases and more than a half million deaths each year. Over 80% HCC cases occur in the developing countries and the cases of China accounts for around 55% of the total [1]. Epidemiology studies have demonstrated that some environmental factors, such as chronic hepatitis B virus (HBV) infection, smoking, and excessive drinking may exacerbate HCC [2, 3]. However, like other cancers, genes may be decisive factors in the pathogenesis of HCC. It has been demonstrated that certain genetic mutation involving in the cell proliferation and apoptosis could promote the occurrence of HCC.

The 8-oxoguanine lesion, one of the primary forms of oxidative DNA damage, can be removed from DNA by human 8-oxoguanine DNA N-glycosylase 1 (*hOGG1*) [4-6]. The *hOGG1* gene, located on chromosome 3, encodes a DNA glycosylase/apurinic-apyrimidinic lyase which induces the excision and removal of 8-hydroxy-2-deoxyguanine adducts [7]. It is so polymorphic that at least 231 single nucleotide polymorphisms (SNPs) in the gene have been reported and at least 20 sequence variants have been identified [8-11]. It is reported that *hOGG1* is a possible suppressor of lung carcinogenesis in *OGG1*-knockout mice and the Ser326Cys polymorphism of *hOGG1* in a bacterial complementation assay system is likely to dampen the activity of 8-oxoguanine lesion removal [12, 13]. However, among the reported

HOGG1 Ser326Cys polymorphism and HCC

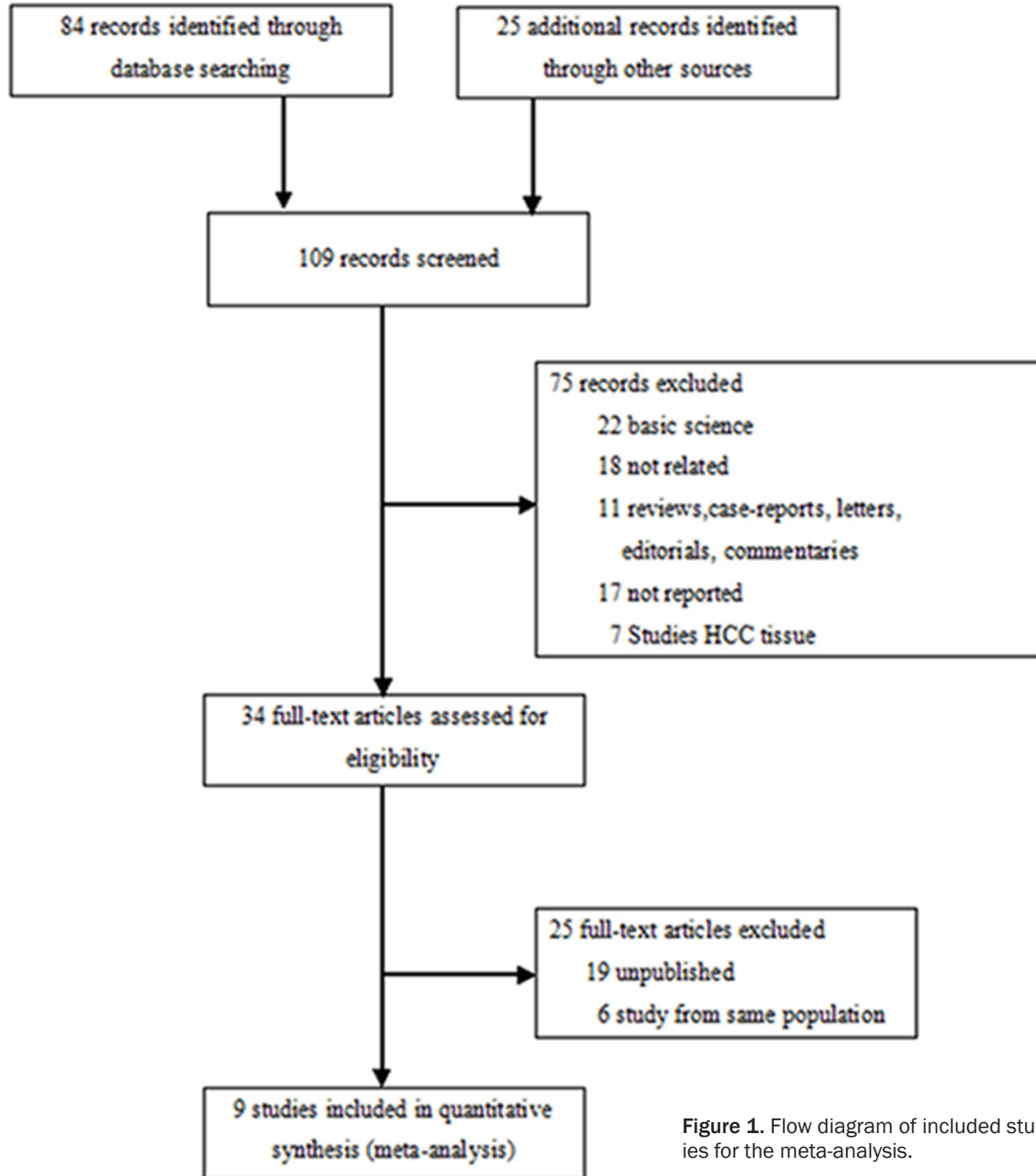


Figure 1. Flow diagram of included studies for the meta-analysis.

SNPs, several ones have been identified to be related with HCC susceptibility [14]. In recent years, *hOGG1* Ser326Cys (rs1052133), resulting in an amino acid substitution of serine (Ser) with cysteine (Cys) at codon 326, has been broadly investigated in the pathogenesis of HCC [15-17]. However, a consensus cannot be reached among these findings. Therefore, we designed a meta-analysis to further explore the association between *hOGG1* Ser326Cys polymorphism and HCC risk.

Materials and methods

Search strategy

We mainly searched PubMed, CBM and EMBASE databases to obtain relevant studies concerning *hOGG1* Ser326Cys polymorphism and HCC with the following keywords: “human 8-oxoguanine glycosylase 1” or “*hOGG1*”, “polymorphism” or “variants”, “HCC” or “hepatocellular carcinoma”. We also retrieved related

HOGG1 Ser326Cys polymorphism and HCC

Table 1. Main characteristics of all studies included in the meta-analysis

First author	Country	Ethnicity	Genotyping method	Case	Control	HWE
Zhu	China	Asian	PCR-RFLP	193	134	0.71
Sakamoto	Japan	Asian	PCR-CTPP	209	275	0.08
Zhang	China	Asian	Sequencing	86	90	0.21
Wang	China	Asian	TaqMan	175	119	0.81
Ji	China	Asian	TaqMan	500	507	<0.001
Tang	China	Asian	PCR-RFLP	150	150	0.88
Jung	Korean	Asian	SNPstream	706	386	0.26
Yuan T	China	Asian	PCR-RFLP	350	400	0.07
Sujoy Bose	India	Caucasian	PCR-RFLP	214	210	0.99

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; PCR-LDR: PCR-ligation detection reaction; TaqMan: TaqManSNP; HWE: Hardy-Weinberg equilibrium.

articles by reviewing the reference from searched articles.

Selection criteria

Studies correlated with *hOGG1* Ser326Cys polymorphism and HCC were required to conform to the following criteria: (1) independent case-control studies; (2) providing efficient genotype data to calculate odds ratio (OR) and 95% confidence interval (CI); (3) concerning human studies. Exclusion criteria included: (1) without control population; (2) without eligible genotype frequencies; (3) duplicated publications. If two or more studies described the same cases, the more informative one would be selected.

Data extraction

The following data were extracted from each original study by two investigators individually: first author's name, year of publication, country, ethnicity, control source, genotyping method, number of cases and controls, genotype frequency and *P* values for Hardy-Weinberg equilibrium (HWE). When studies contained more than one ethnic group or control source, the data were selected separately. Any inconformity would be resolved via discussion.

Statistical analysis

To assess whether *hOGG1* Ser326Cys polymorphism was involved in HCC, we calculated the pooled ORs with corresponding 95% CIs under five genetic models: GG vs. CC, GG + CG vs. CC, GG vs. CG + CC, Allele G vs. Allele C and CG vs. CC. According to ethnicity and control source,

subgroup analyses were conducted to specifically analyze the relationship. Z test was used to check whether the pooled ORs were significant. $P < 0.05$ was considered statistically significant. The between-study heterogeneity was examined by χ^2 -based Q test. $P > 0.05$ indicates no heterogeneity, then the fixed-effect model was adopted to calculate pooled ORs; otherwise, the random-effect model was selected. Begg's funnel plot and Egger's test were used to test potential publication bias. We conducted sensitivity analysis to assess the effects of each individual dataset on the pooled results by extracting each single study sequentially. HWE was checked in controls by χ^2 test. Statistical analyses were performed with STATA software (V.12.0, STATA Corp).

Results

Characteristics of studies

As shown in **Figure 1**, there were 109 records altogether obtained by databases and other sources, among which 34 full texts were considered potentially eligible. In the 34 studies, 19 were excluded for being unpublished and 6 for studying the same population. Finally, nine case-control publications were included in this meta-analysis [14, 15, 17-23]. Main characteristics of the included studies are presented in **Table 1**. Among these eligible studies, eight studies were conducted in Asians and one in Caucasians. Meanwhile, six studies involved hospital based (HB) population and three were population based (PB). The distributions of genotypes in the controls were in accordance with HWE except the article of Ji Long et al [22].

HOGG1 Ser326Cys polymorphism and HCC

Table 2. ORs and heterogeneity results on the association of *hOGG1* -Ser326Cys polymorphism with risk of HCC

	GG vs. CC		GG + CG vs. CC		GG vs. CG + CC		Allele G vs. Allele C		CG vs. CC	
	OR [95% CI]	P_h	OR [95% CI]	P_h	OR [95% CI]	P_h	OR [95% CI]	P_h	OR [95% C]	P_h
Asian population	2.17 [1.49, 3.17]	<0.05	1.13 [1.03, 1.25]	<0.05	1.96 [1.41, 2.73]	<0.05	1.15 [0.94, 1.42]	<0.05	1.09 [0.97, 1.23]	0.88
Caucasian population	10.41 [4.84, 22.39]	0	1.08 [0.77, 1.51]	0	10.55 [4.99, 22.31]	0	1.15 [0.86, 1.55]	0	1.03 [0.72, 1.47]	0
Hospital control	2.31 [1.50, 3.56]	<0.05	1.14 [0.94, 1.39]	<0.05	2.17 [1.44, 3.28]	<0.05	1.18 [0.89, 1.57]	<0.05	1.03 [0.89, 1.19]	0.99
Population control	2.80 [1.16, 6.77]	0	1.15 [0.98, 1.36]	0.48	2.39 [1.08, 5.30]	<0.05	1.12 [0.92, 1.36]	0.13	1.20 [0.99, 1.45]	0.61
Total	2.51 [1.67, 3.78]	<0.05	1.13 [1.03, 1.24]	0.08	2.27 [1.57, 3.30]	<0.05	1.15 [0.96, 1.39]	<0.05	1.09 [0.97, 1.22]	0.92

P_h : *P*-value of heterogeneity test.

HOGG1 Ser326Cys polymorphism and HCC

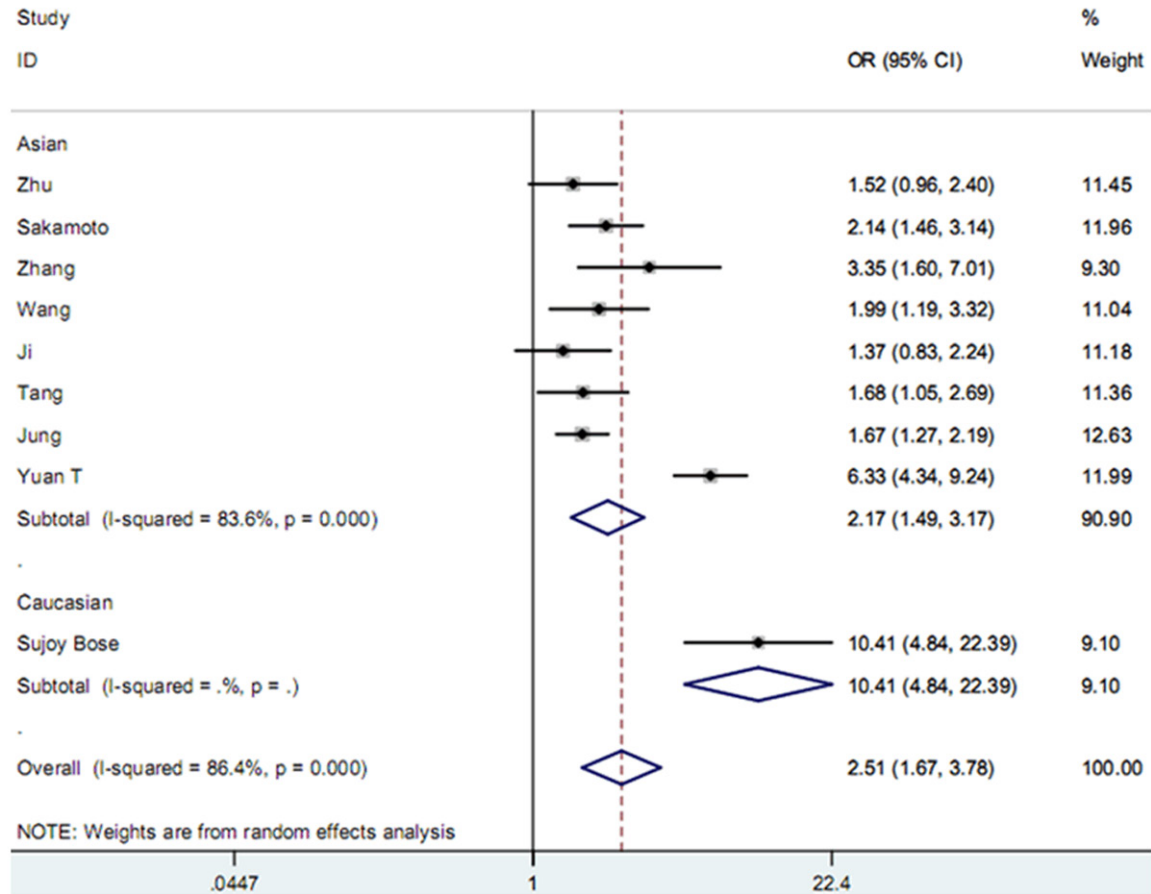


Figure 2. Forest plot of *hOGG1* Ser326Cys polymorphism involved in HCC risk under the GG versus CC genetic model by ethnicity. The squares and horizontal lines accord to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Meta analysis results

Table 2 exhibited ORs and heterogeneity results of the meta-analysis, and **Figures 2** and **3** showed the forest plots on the association of *hOGG1* Ser326Cys polymorphism with HCC risk based on ethnicity and control source respectively. Overall, we found that GG or GG + CG genotypes carriers were more likely to suffer HCC (GG versus CC: OR=2.51, 95% CI=1.67-3.78; GG versus CG + CC: OR=2.27, 95% CI=1.57-3.30; GG + CG versus CC: OR=1.13, 95% CI=1.03-1.24). In the subgroup analysis by ethnicity, the results revealed that *hOGG1* Ser326Cys polymorphism was associated with high risk of HCC in Asians (GG versus CC: OR=2.17, 95% CI=1.49-3.17; GG versus CG + CC: OR=1.96, 95% CI=1.41-2.73; GG + CG versus CC: OR=1.13, 95% CI=1.03-1.25). Results of subgroup analysis based on source of control showed that there existed significant rela-

tionship of GG genotype with elevated risk for HCC in HB and PB population (HB: GG versus CC: OR=2.31, 95% CI=1.50-3.56; GG versus CG + CC: OR=2.17, 95% CI=1.44-3.28; PB: GG versus CC: OR=2.80, 95% CI=1.16-6.77; GG versus CG + CC: OR=2.39, 95% CI=1.08-5.30).

Sensitivity analysis

We deleted each single study in the sensitivity analysis to check whether the selected study had influence on the combined results. The pooled ORs were not materially altered, which indicated that our meta-analysis results were highly stable.

Publication bias

Begg's funnel plot and Egger's test were used to check the potential publication bias of the present study. We could see though **Figure 4**

HOGG1 Ser326Cys polymorphism and HCC

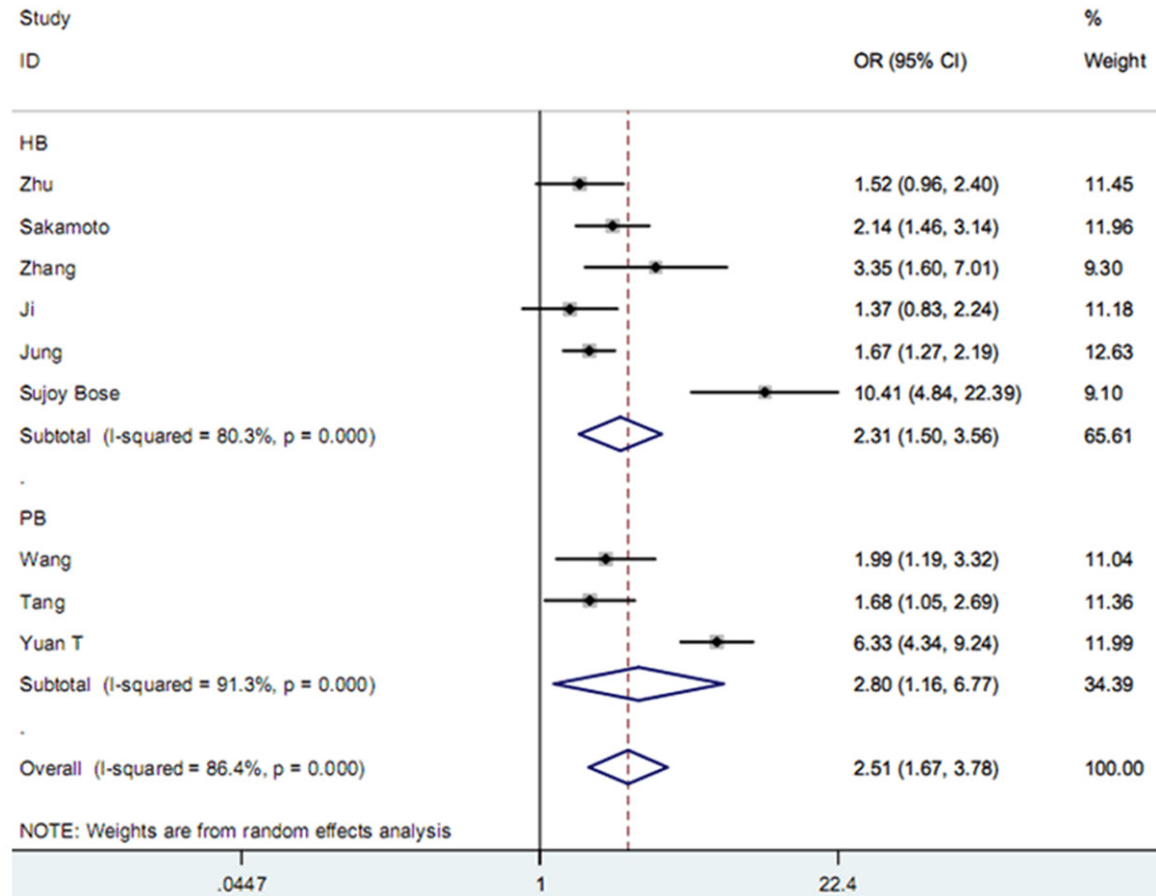


Figure 3. Forest plot of *hOGG1*-Ser326Cys polymorphism involved in HCC risk under the GG versus CC genetic model by source of control.

that the shape of the funnel plot seemed symmetric under CG versus CC genetic model. Moreover, Egger's test showed no evident publication bias ($P=0.56$), which suggested that even there is subtle bias from publications; it might not materially alter the results of our meta-analysis.

Discussion

DNA damage, mainly caused by environmental factors and normal metabolic process in cells, occurs at a rate of 10,000 to 1,000,000 molecular lesions per cell per day [24]. It may generate cancerogenic substances once tumor suppress genes are inactive or oncogenes are activated [25]. Genetic polymorphisms resulting from DNA damage or the insertion or deletion of segments of DNA by mobile genetic elements may lead to discernible changes in the observable characteristics of an organism, thus play crucial roles in both normal and

abnormal biological processes especially in cancer [26-28]. In recent years, the relationship between genetic polymorphisms and risk of HCC has been broadly studied and some confounding findings have been obtained [29, 30].

One of the single nucleotide polymorphisms (SNPs) of *hOGG1* gene, Ser326Cys polymorphism has been reported to affect the functions of *hOGG1* and may be associated with the risk for lung, colon, stomach and esophageal cancers, but not breast cancer [31-33]. Moreover, Yuan et al. found that *hOGG1* Ser326Cys polymorphism could work together with environmental factors of smoking, drinking and HBV infection in the pathogenesis of HCC [15]. However, several investigations provided null association between *hOGG1* Ser326Cys and HCC susceptibility [17, 18]. Meanwhile, Cardin Romilda et al. pointed out that Ser326Cys polymorphism was not in rela-

HOGG1 Ser326Cys polymorphism and HCC

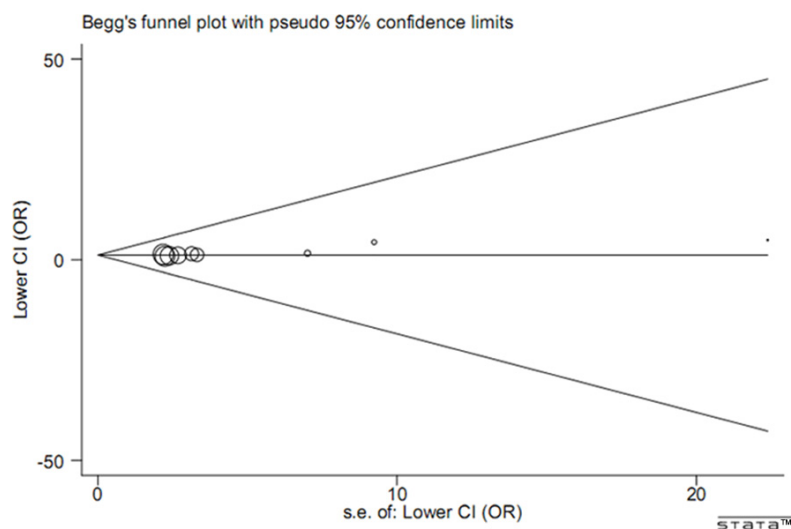


Figure 4. Begg's funnel plot of publication bias test under the GG versus CC genetic model. Each point represents a single study for the indicated association.

tion to the development of HCC and CG and/or GG genotypes were not observed in HCC samples [34]. The divergent findings for the association may result from the difference in sample size, environmental and genetic backgrounds in the studies. In view of this, with comparatively larger sample size, we conducted a meta-analysis to comprehensively evaluate the association.

According to our meta-analysis, overall, increased risk of HCC was in relation with *hOGG1* Ser326Cys polymorphism, especially the GG genotype. Moreover, in the subgroup analysis by ethnicity and source of control, high risk for HCC was found among Asians with GG or GG + CG genotypes. Besides, GG genotype was also observed to be related with HCC in HB and PB population.

Overall, the results of our meta-analysis were reliable, however, there are still some limitations. First, HCC is a multi-factorial disease and caused by various genetic and environmental factors. In our meta-analysis, we only studied the association between one single polymorphism with HCC, not considering the influence of gene-gene or gene-environment interaction, which may reach a unilateral conclusion. Second, the genotyping method and selection criteria of controls in the studies were not the same, which may introduce in some biases into our analysis. Finally, most of the included stud-

ies were conducted among Asians. Therefore, more studies concerning Caucasians should be gathered.

In conclusion, despite some limitations, our meta-analysis demonstrated that *hOGG1* Ser326Cys polymorphism was related with increased risk for HCC. Well-designed studies considering gene-gene or gene-environment risk factors are needed to clarify this issue in the future.

Disclosure of conflict of interest

None.

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