Association of hOGG1 polymorphism with hepatocellular carcinoma susceptibility in East Asian populations: evidence from a meta–analysis

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Abstract

Oxidative DNA damage caused by reactive oxygen species plays an important role in cancer development. Several research groups have investigated the influence of the human 8-oxoguanine DNA glycosylase 1 (hOGG1) Ser326Cys polymorphism on hepatocellular carcinoma (HCC) susceptibility. However, the results remain inconclusive and controversial. In this work, a meta-analysis was performed to derive a more precise estimation of the relationship. Literature databases were searched for all cases dated until May 2013. Crude odds ratios with 95% confidence intervals were used to assess the strength of the association between hOGG1 Ser326Cys polymorphism and HCC risk. A total of 7 studies (1,546 cases and 1,620 controls) fulfilled our inclusion criteria in this meta-analysis. Overall no significant associations were observed in all genetic models in East Asian populations after excluding the studies that deviated from the Hardy–Weinberg equilibrium (HWE). However, on performance of a subgroup meta-analysis by Chinese population, significant associations were found (homozygous model: OR = 1.99, 95% CI = 1.44–2.75, I^2 =41.4%, P = 0.163 for heterogeneity; recessive model: OR=1.42, 95% CI = 1.08–1.87, I^2 =0.0%, P = 0.591 for heterogeneity) after excluding 2 studies not in agreement with HWE. Thus, this meta-analysis finds the hOGG1 Ser326Cys polymorphism to be a risk factor for HCC in Chinese. However, given the limitation of the studies included in the meta-analysis, large-scale investigations is needed in order to illuminate the differences in HCC susceptibility among these East Asian populations.

Keywords: Hepatocellular carcinoma; Risk; hOGG1; Genetic polymorphism

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Introduction

According to the International Agency for Research on Cancer, liver cancer is the leading cause of cancer deaths for men and women worldwide [1,2]. Hepatocellular carcinoma (HCC) is the most common form of liver cancer. The incidence of HCC varies across the world. The highest overall incidence of HCC is in East Asia, which accounts for about 76% of all cases in the whole world. In parts of China the age-adjusted incidence rate (AAIR) exceeds 30/100,000/year [3]. The etiology of HCC is still poorly understood. Besides chronic infection with hepatitis viruses, alcoholism, aflatoxin and other carcinogens established as major risk factors contribute to liver carcinogenesis, host factors, including genetic polymorphisms, have been growing interest in the study of the tumorigenesis of HCC [2,4,5].

DNA damage, which is associated with carcinogenesis, can be removed or repaired through different repair systems. The base excision repair pathway, which is composed of many DNA repair genes, mainly removes DNA damage caused by reactive oxidative species and ionizing radiation [6-8].

The human 8-oxoguanine DNA glycosylase 1 (hOGG1) gene, a crucial multi–functional gene involved in base excision repair pathway, plays a role in repairing damaged DNA. It can release 8-hydroxydeoxyguanine (8–OHdG), cleave the damaged DNA base site and repair 8-oxoguanine that is one of the highly mutagenic lesions in oxidative DNA damage [6,9]. Several single–nucleotide polymorphisms have been identified and evaluated in the hOGG1 gene, all of which were localized on chromosome 3p26[10]. Among these polymorphisms, the most extensively studied is the Ser326Cys polymorphism (also referred to as rs1052133), which is characterized by an amino acid substitution of serine (Ser) with cysteine (Cys) at codon 326 in the 1a-specific exon 7 of hOGG1 gene [11], and the Ser326Cys polymorphism has been reported to reduces DNA repair activity [12] and to be associated with susceptibility of different cancers, such as endometrium [13], gallbladder [14] and colorectum cancer [15] .

Up to now, virtually all of the epidemiologic studies investigating the association of hOGG1 gene polymorphism with HCC risk were conducted in East Asian populations. However, the available evidence is weak at present, due to sparseness of data or disagreements among the reported investigations. Meta-analysis is a useful method to overcome the disadvantages of individual studies, thereby increasing the statistical power and the precision of effect estimates. This meta-analysis was performed to investigate whether the hOGG1 gene polymorphism was associated with the risk of HCC occurrence in East Asian population.

Methods

Literature and search strategy

Literature databases including PubMed, ISI Web, Embase, China National Knowledge Infrastructure, China Biological Medicine and Wanfang data were searched using the following keywords: (hOGG1 or OGG1 or OGG or human 8-oxoguanine DNA glycosylase or rs1052133) and (allete or mutation or variant or variation or polymorphism) and (hepatoma or hepatocellular cancer or hepatocellular carcinoma or HCC or liver cell carcinoma). There were no language restrictions. The literature search was updated on May 31, 2013. Review articles and reference cited in the searched studies were examined to identify additional published articles. The listed articles were assessed to determine whether they should be included in the meta-analysis. For studies with overlapping data published by same investigators, only the most recent or complete study was included. Conference abstracts, case reports, editorials, review articles, and letters were excluded.

Inclusion criteria and data extraction

Studies included in the meta-analysis were required to meet the following criteria: (1) using case-control design, (2) giving information about the distribution of hOGG1 genotypes in both cases and corresponding controls, and (3) there is an evaluation of the hOGG1 Ser326Cys polymorphism and hepatocellular carcinoma risk.

Information was carefully extracted from all eligible publications independently by two of the authors according to the above-listed inclusion criteria. An agreement was reached through a discussion between the two reviewers (Li H.J. and Wang X.M.) for cases with conflicting information. The following characteristics were collected from each study: the first author's name, publication year, country, and frequencies of allele or genotype in cases and controls.

Statistical analysis

STATA version 11.0 (STATA Corporation, College Station, Texas) was used for all statistical analyses. The combined odds ratios (OR), along with their corresponding 95% confidence intervals (CI), were used to calculate and assess the strength of the association between hOGG1 Ser326Cys polymorphism and HCC risk. The statistical significance of the overall OR was determined using a *Z*-test, $P < 0.05$ was considered statistically significant. Subgroup analyses were conducted by Chinese group. An appropriate continuity correction (addition of 0.5) was implemented for cases of zero cells [16].

Heterogeneity assumption was examined using the Chi-square (χ^2) test based on the *Q* statistic [17] and was considered statistically significant when $P < 0.10$. The heterogeneity was quantified by the I^2 metric, which is independent of the number of studies used in the meta-analysis ($I^2 < 25\%$, no

heterogeneity; I^2=25–50%, moderate heterogeneity; I^2 > 50%, extreme heterogeneity) [26].The pooled OR estimation of each study was calculated through a random-effects model (DerSimonian and Laird method) when $P < 0.10$; otherwise, a fixed-effects model was used (Mantel–Haenszel method) [18].

In addition, sensitivity analysis was performed by omitting each individual study to reflect the influence of the individual dataset on the pooled OR using the "metaninf" STATA command. The appropriate Chi-square goodness-of-fit test [19] was performed using the "genhwcci" STATA command to assess the deviation from Hardy–Weinberg equilibrium (HWE) only in control groups. Statistical significance for the interpretation of the Chi-square test was defined as $P < 0.05$.

Publication bias was evaluated through the Begg's and the Egger's Asymmetry tests [20] and through visual inspection of funnel plots, in which the standard error was plotted against the log (OR) to form a simple scatterplot. Statistical significance for the interpretation of the Egger's test was defined as $P < 0.10$.

Results

Study characteristics

The literature search identified a total of 41 potentially relevant articles. Of these, 25 were excluded after reading the title and abstract because of obvious irrelevance. In addition, 1 article was excluded since it was a review [21]; Another 2 articles were excluded because they were duplicated publications [22,23]; 6 articles were excluded as they did not provide sufficient data for calculation of OR and 95% CI [24-29]. Finally, 7 studies on Ser326Cys polymorphism met the inclusion criteria and were included in the meta-analysis [30-36]. The characteristics of the case–control studies included for the polymorphism are summarized in Table 1. A total of 1,546 HCC cases and 1,620 controls were identified for the Ser326Cys polymorphism of hOGG1 in East Asian populations. The Ser326Cys minor allele frequencies (MAF) in controls of different population were calculated. Among the included studies, the MAF of Ser326Cys polymorphism ranged from 0.11 to 0.53. The sample size ranged from 156 to 1,007. Almost all of the cases were confirmed by histological or pathological analysis. There were 6 studies on Chinese population [30, 32-36] and 1 study on Japanese population [31]. A classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was carried out in 4 of the 7 studies. The distribution of genotypes in the controls was consistent with HWE in all but 2 studies (P<0.05) [33,35]. A flow chart summarizing the process of study inclusion or exclusion is depicted in Figure 1.

Table 1 Main characteristics of studies included in Ser326Cys polymorphism of hOGG1 and hepatocellular carcinoma risk

Study	Year	Country	Genotyping method	Cases /controls	Genotype data (cases)					Genotype data (controls)					MAF	HWE (*P*)
					X	x	X/X	X/ x	x/ x	X	x	X/X	X/ x	x/ x		
Zhang et al [30]	2005	China	Sequencing	86/89	98	74	30	38	18	119	59	42	35	12	0.33	0.29
Sakamoto et al [31]	2006	Japan	PCR/RFLP	209/275	222	196	56	110	43	269	281	73	123	79	0.51	0.08
Wang et al [32]	2008	China	Sequencing	175/119	154	196	31	92	52	112	126	27	58	34	0.53	0.81
Ji et al [33]	2011	China	Taqman	500/507	754	246	357	40	103	905	109	427	51	29	0.11	<0.01
Tang et al [34]	2011	China	PCR/RFLP	150/150	229	71	94	41	15	220	80	81	58	11	0.27	0.89
Jiang et al [35]	2012	China	PCR/RFLP	76/80	70	82	16	38	22	93	67	22	49	9	0.42	0.02
Yuan et al [36]	2012	China	PCR/RFLP	350/400	351	349	67	217	66	494	306	144	206	50	0.38	0.07

X/x for Ser/Cys of Ser326Cys***; PCR-RFLP*** polymerase chain reaction-restriction fragment length polymorphism***; MAF*** minor allele frequency***; HWE*** Hardy–Weinberg equilibrium***; P*** value for HWE in control group.

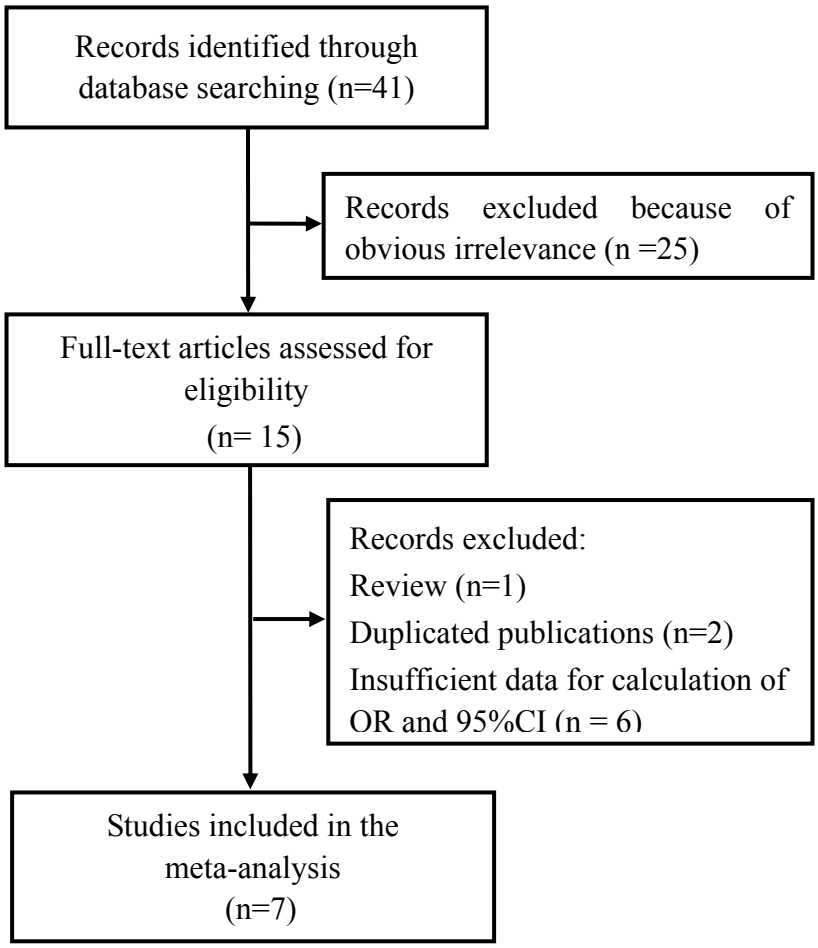

Fig. 1 Flow diagram of study selection and specific reasons for exclusion in the meta-analysis.

Meta-analysis results

We carried out a meta-analysis of the hOGG1 Ser326Cys polymorphism overall, and in subgroups according to Country under various genetic models. The pooled ORs, along with their 95% CIs, are presented in detail in Table 2. In the overall analysis, significant associations were observed only under homozygous model (Cys/Cys vs. Ser/ Ser: OR=1.91, 95%CI=1.09–3.35, P<0.001 for heterogeneity), and no significant association between this polymorphism and HCC was demonstrated in allele model (Cys vs. Ser: OR = 1.37, 95% CI = 0.97–1.92, I^2 =88.8%, P < 0.001 for heterogeneity), heterozygous model (Ser/Cys vs. Ser/Ser: OR = 1.20, 95% CI = 0.83–1.73, I^2 =72.2%, P = 0.001 for heterogeneity), dominant model (Ser/Cys + Cys/Cys vs. Ser/ Ser: OR = 1.43, 95% CI = 0.99–2.06, I^2 = 77.7%, P < 0.001 for heterogeneity), and recessive model (Cys/Cys vs. Ser/Ser + Ser/Cys: OR = 1.64, 95% CI = 0.94–2.86, I^2 =86.0%, P < 0.001 for heterogeneity). However, changes took place in the pooled results after excluding the two studies [30, 32] that deviated from HWE, and the results showed that there were no significant associations in all the genetic models. Due to the limited number of studies from Japanese population, we only carried out a subgroup analysis in Chinese group. In 6 Chinese populations, significant associations in HCC patients with hOGG1 Ser326Cys polymorphism were observed under the homozygous model (OR = 2.36, 95% CI = 1.53–3.64, I^2 =60.9%, P = 0.026 for heterogeneity), dominant model (OR = 1.54, 95% CI = 1.04–2.27, I^2 =76.2%, P = 0.001 for heterogeneity), and the recessive model (OR = 1.96, 95% CI = 1.20–3.20, I^2 =76.1 %, P = 0.001 for heterogeneity); Moreover, there was no significant association between this polymorphism and HCC under other genetic models. However, after excluding 2 studies [30, 32] that was not in agreement with HWE, the analyzed results changed slightly. Significant associations were still found (homozygous model: OR = 1.99, 95% CI = 1.44–2.75, I^2 =41.4%, P = 0.163 for heterogeneity; recessive model: OR=1.42, 95% CI = 1.08–1.87, I^2 =0.0%, P = 0.591 for heterogeneity) in Chinese populations. The forest plot for the association between the Ser326Cys polymorphism of hOGG1 and HCC risk under homozygous model and recessive model among Chinese population is shown in Figure 2 and 3.

Table 2 Results of meta-analysis for Ser326Cys polymorphism of hOGG1 and hepatocellular carcinoma risk

Genetic model	Study group	OR (95% CI)	I^2 (%)	P_h	Z	P_Z
Allele model (Cys vs. Ser)						
	All	1.37(0.97,1.92)	88.8	<0.001	1.79	0.073
	All in HWE	1.15(0.85,1.55)	79.5	0.001	0.90	0.366
	Chinese	1.49(1.07,2.08)	84.9	<0.001	2.37	0.018
	Chinese in HWE	1.25(0.93,1.69)	70.2	0.018	1.50	0.133
Homozygous model (Cys/Cys vs. Ser/ Ser)						
	All	**1.91(1.09,3.35)**	82.1	<0.001	2.26	0.024
	All in HWE	1.46(0.81,2.60)	75.7	0.002	1.27	0.205
	Chinese	**2.36(1.53,3.64)**	60.9	0.026	12.78	<0.001
	Chinese in HWE	**1.99(1.44,2.75)F**	41.4	0.163	4.2	<0.001
Heterozygous model (Ser/Cys vs. Ser/Ser)						
	All	1.20(0.83,1.73)	72.2	0.001	0.99	0.324
	All in HWE	1.28(0.80,2.07)	78.8	0.001	1.03	0.301
	Chinese	1.20(0.77,1.87)	76.6	0.001	0.82	0.410
	Chinese in HWE	1.31(0.70,2.46)	83.3	<0.001	0.86	0.392
Dominant mode l (Ser/Cys +Cys/Cys vs. Ser/ Ser)						
	All	1.43(0.99,2.06)	77.7	<0.001	1.94	0.052
	All in HWE	1.30(0.81,2.10)	81.3	<0.001	1.09	0.274
	Chinese	**1.54(1.04,2.27)**	76.2	0.001	2.16	0.031
	Chinese in HWE	1.40(0.78,2.53)	83.3	<0.001	1.13	0.258
Recessive model (Cys/Cys vs.Ser/Ser+Ser/Cys)						
	All	1.64(0.94,2.86)	86.0	<0.001	1.76	0.079
	All in HWE	1.17(0.77,1.76)	64.6	0.023	0.73	0.468
	Chinese	**1.96(1.20,3.20)**	76.1	0.001	2.70	0.007
	Chinese in HWE	**1.42(1.08,1.87)F**	0.0	0.591	2.49	0.013

All pooled ***ORs*** were derived from random-effect model except for cells marked with (fixed ^{F})

P_h *P*-value for heterogeneity based on ***Q*** test

P_Z *P*-value for statistical significance based on ***Z*** test

Bold values denote statistical significance

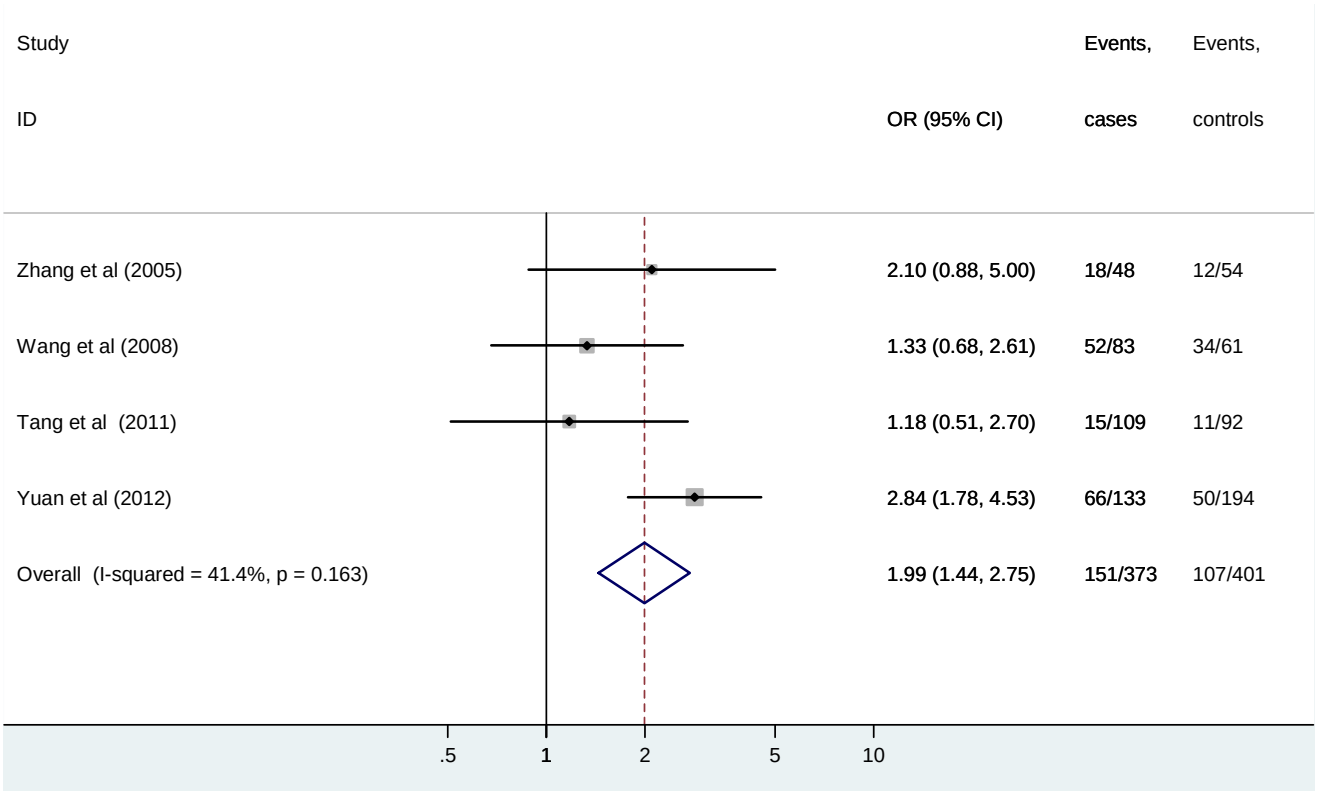

Fig. 2 Forest plot for the association between hOGG1 Ser326Cys polymorphism and hepatocellular carcinoma risk among Chinese populations in HWE under homozygous model.

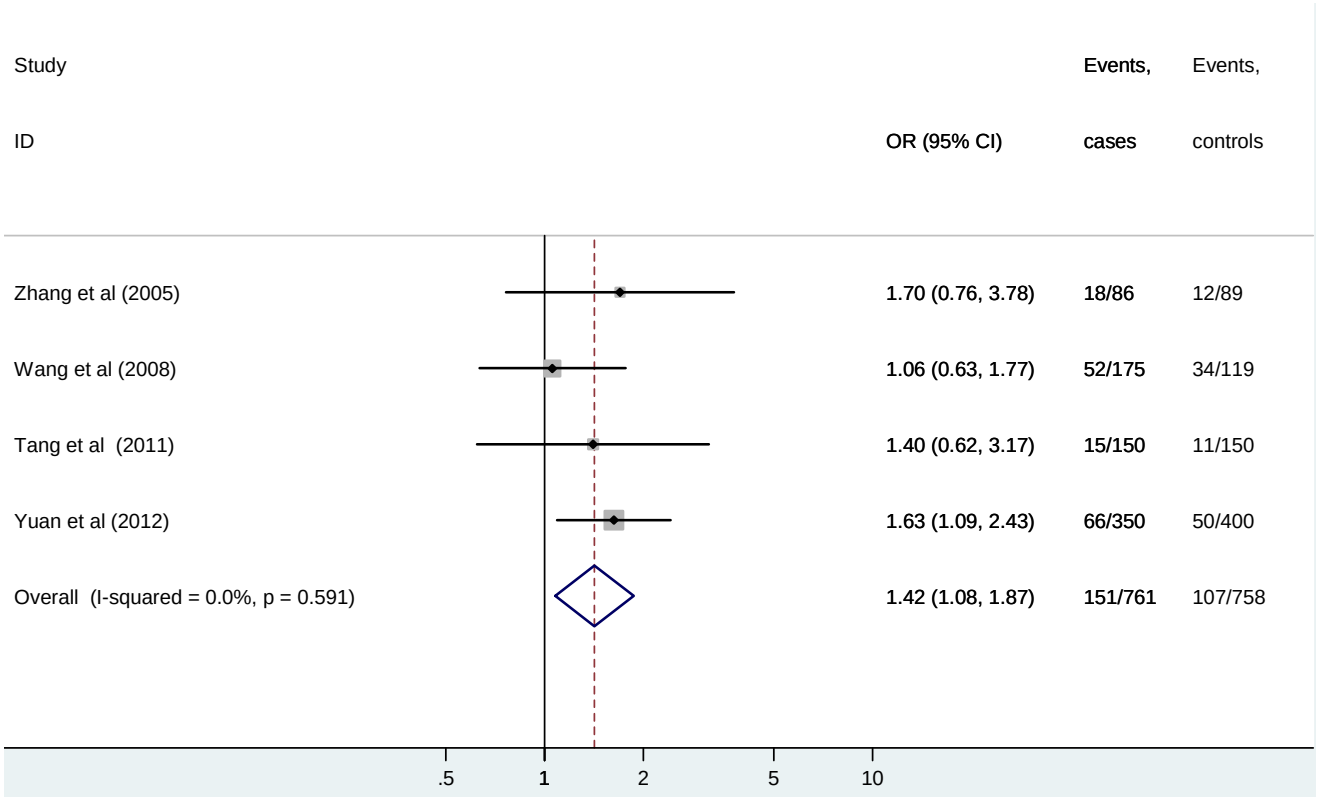

Fig. 3 Forest plot for the association between hOGG1 Ser326Cys polymorphism and hepatocellular carcinoma risk among Chinese populations in HWE under recessive model.

Sensitivity analysis and publication bias

In the sensitivity analysis, the influence of each study on the pooled OR was examined by repeating the meta-analysis while omitting each study, one at a time. Figure 4 demonstrates that no point estimate of the omitted individual study lay outside the CI of the combined analysis on the allele model. Similarly, no significant influence was observed when an analysis was conducted on the other models (figure not shown for reasons of brevity). These analyses suggest that no individual study affected the results in the meta-analysis.

Publication bias on the overall OR analysis was not detected at any comparison in East Asian population and in Chinese. In addition, neither the Begg's test nor the Egger's test provided any obvious evidence of publication bias in Chinese (Table 3, $P > 0.10$). The shapes of the funnel plots appeared to be roughly symmetrical in all genetic models.

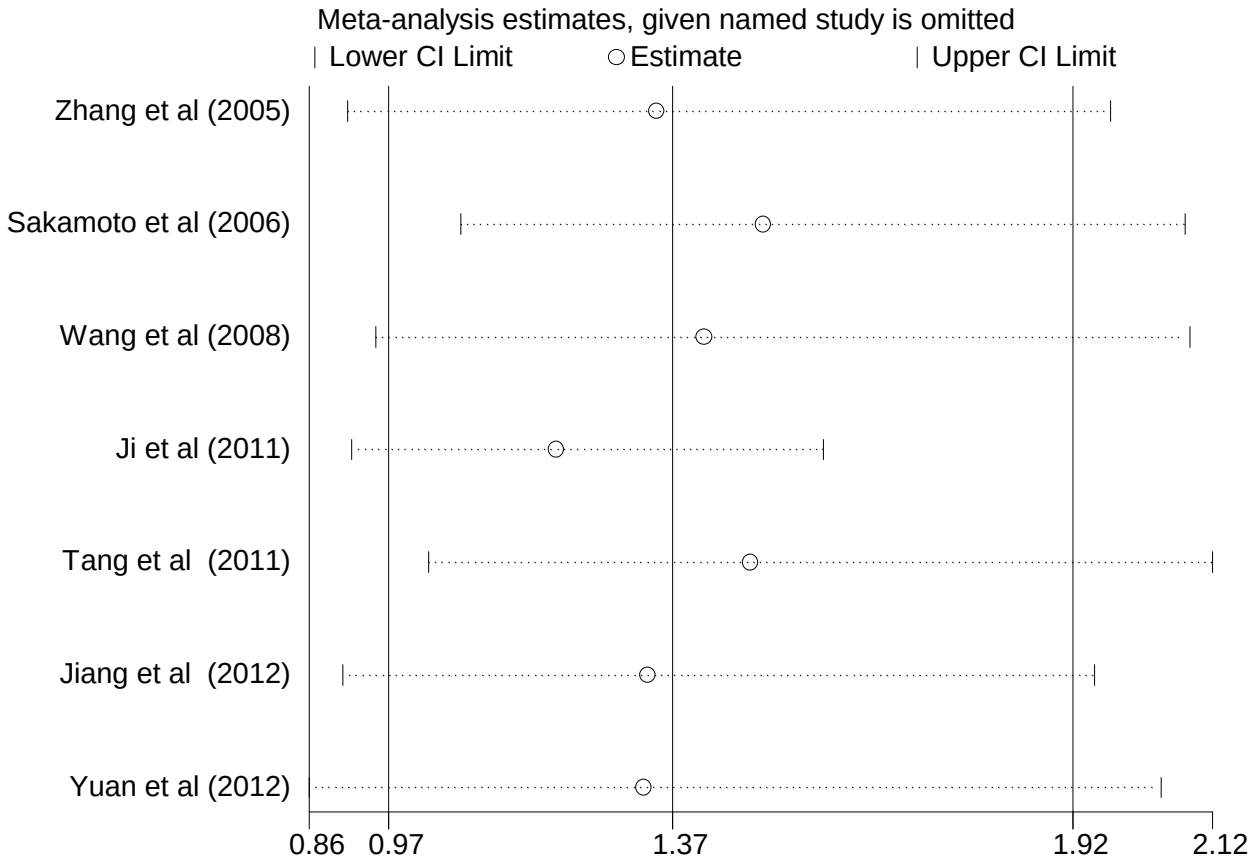

Fig. 4 Effect of individual studies on the pooled OR in the allele model for the Ser326Cys polymorphism of hOGG1 in hepatocellular carcinoma among East Asian populations.

Table 3 Results of Egger's test and Begg's test for Ser326Cys polymorphism of hOGG1 and hepatocellular carcinoma risk

Comparison	Egger's test				Begg's test	
	t	*P*	95% CI		*Z*	*P*
Allele model	-0.15	0.594	-15.453	10.586	-0.24	1.000
Homozygous model	-0.16	0.883	-14.332	12.954	-0.24	1.000
Heterozygous model	-0.89	0.440	-17.578	9.908	-0.24	1.000
Dominant model	-0.68	0.544	-19.667	12.727	-0.24	1.000
Recessive model	0.50	0.652	-8.0750	11.081	-0.24	1.000

Discussion

Hepatocellular carcinoma is becoming an increasingly important health problem and is the leading cause of cancer-related mortality worldwide, especially in East Asia. Recent years, the relationship between HCC susceptibility and genotypic polymorphism of DNA repair genes has attracted growing attentions. The hOGG1, which is a key gene generally involved in DNA repair process, also has been extensively studied. And the Ser326Cys polymorphism is reported to be a functional variation in the hOGG1 gene. The association between Ser326Cys polymorphism of hOGG1 and susceptibility to cancer has been evaluated in different cancers, including bladder [37], prostate [38], lung [39], head and neck [40], gastric [41], and breast cancers [42].

Since the original identification of the hOGG1 Ser326Cys polymorphism, several studies have investigated the genetic effect of this polymorphism on HCC susceptibility. Yuan et al. [36] found that individuals carrying hOGG1 Cys326Cys and Ser326Cys genotypes have significantly increased risk for the development of HCC compared with individuals with Ser326Ser genotype. In addition, some studies such as Sakamoto et al. [31] and Wang et al. [32] failed to demonstrate that any hOGG1 Ser326Cys variants has no effect on the genetic susceptibility to HCC. Considering conflicting and contradictory conclusions for the same type of cancer, the meta-analysis of the published case–control studies was been conducted.

To our knowledge, this is the first meta-analysis which comprehensively assessed the associations between Ser326Cys polymorphism of hOGG1 and HCC risk and quantify the potential between-study heterogeneity. The principal results indicated significant associations of hOGG1 Ser326Cys polymorphism with HCC susceptibility among the Chinese populations not among the overall East Asian populations.

Heterogeneity between studies is very common in the current meta-analysis of genetic association studies in East Asian populations, this may be due to not only differences in population characteristics, sample size, and deviation of allelic distributions from HWE, and also other confounding factors such as age, sex, family history, environmental factors and lifestyle. After assessing the source of heterogeneity compared by subgroup analysis based on Chinese group not on other confounding factors because of insufficient data in these included studies, Heterogeneity was not found for the polymorphism under homogeneous co-dominant model and recessive model among Chinese populations after excluding the studies that deviated from the HWE, suggesting the homogeneity of the included individual studies in Chinese populations. Moreover, there was no publication bias for the analysis in Chinese population. Therefore, the conclusion in this study for Chinese might be robust.

The present meta-analysis has some advantages compared with other individual studies, however it does have potential limitations. First, our meta-analysis was based primarily on unadjusted effect estimates and confidence intervals and the confounding factors were not controlled. Second, the effects of gene–gene and gene–environment interactions were not addressed. Third, the meta-analysis is based on few studies and a limited sample size, the results for Ser326Cys polymorphism of hOGG1 should be interpreted with caution. Fourth, the conclusions are not appropriate for all ethnicity because so far there was no study of other populations like Caucasian and African populations.

In conclusion, our meta–analysis indicated the significant association between Ser326Cys polymorphism of hOGG1 gene and hepatocellular carcinoma susceptibility in Chinese. However, given the limitation of the studies included in the meta-analysis, large-scale investigations is needed in order to elucidate the differences in HCC susceptibility among these East Asian populations.

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Conflict of interest statement

None of the authors have any potential financial conflict of interest related to this manuscript.

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