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BRIEF ARTICLE

GST polymorphisms are associated with hepatocellular carcinoma risk in Chinese population

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Abstract

AIM: To investigate the association between *GSTM1* and *GSTT1* polymorphisms and the risk of hepatocellular carcinoma (HCC) in Chinese population.

METHODS: Literature databases including PubMed, ISI web of science and other databases were searched. Pooled odds ratio (OR) and 95% CI were calculated using random- or fixed- effects model. Subgroup analysis and sensitivity analysis were also performed.

RESULTS: Nineteen studies of *GSTM1* (2660 cases and 4017 controls) and 16 studies of *GSTT1* (2410 cases and 3669 controls) were included. The *GSTM1*/*GSTT1* null genotypes were associated with increased risk of HCC in Chinese population (for *GSTM1*, OR = 1.487, 95% CI: 1.159 to 1.908, *P* = 0.002; for *GSTT1*, OR = 1.510, 95% CI: 1.236 to 1.845, *P* = 0.000). No publication bias was detected. In subgroup analysis, glutathione S-transferases polymorphisms were significantly associated with HCC risk among the subjects living in high-incidence areas, but not among the subjects living in low-incidence areas.

CONCLUSION: The present meta-analysis suggests that *GSTM1*/*GSTT1* null genotypes are associated with increased risk of HCC in Chinese population.

Key words: *GSTM1*; *GSTT1*; Polymorphism; Hepatocellular carcinoma; Liver cancer

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INTRODUCTION

Liver cancer is one of the most common types of cancer and one of the most common causes of cancer-related

death[1]. The death rates have increased for both men and women with liver cancer over the past two decades[2]. The incidence and mortality rates of liver cancer vary considerably among racial and ethnic groups[3]. Asians, particularly Chinese, have a high risk of developing liver cancer[4]. About 80%-90% of all cases of primary liver cancer are hepatocellular carcinoma (HCC).

The pathogenesis of HCC may have a genetic and environmental basis[5,6]. Epidemiological studies have shown that HCC is associated with many environmental factors, including alcoholism, chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), and dietary exposure to aflatoxin B1 (AFB1)[7]. These hepatocarcinogens result in increased generation of reactive oxygen species and free radicals that cause liver damage and repair. Thus the accumulated multistage genetic mutations may lead to liver carcinogenesis[8-11].

During liver carcinogenesis, cellular defense mechanisms can alleviate the effects of oxidative stress and exogenous toxins. One of the essential antioxidant is the reducing compound glutathione. Reduced glutathione can be conjugated to various xenobiotics and endobiotics by glutathione S-transferases (GST), a superfamily of cytosolic soluble detoxification enzymes. In humans, cytosolic soluble GSTs are encoded by seven distinct genes: Alpha, Mu, Omega, Pi, Sigma, Theta and Zeta[12-14]. GSTs play an important role in cellular protection against oxidative stress and exogenous toxins. Homozygous deletion of GST genes (null genotype) results in decreased enzyme activity, which will impede detoxification and may ultimately increase the risk of many diseases, including HCC[13-16]. *GSTM1* and *GSTT1* have been the most extensively studied GST genes. While many studies have investigated the relationship between *GSTM1* and *GSTT1* polymorphisms and HCC risk, so far the results have been inconsistent.

Recently, a meta-analysis result did not suggest a statistically significant increased risk of HCC with the *GST* null genotypes[17]. However, a large number of studies were not reported in that meta-analysis (which included only 9 studies of *GSTM1* and 8 studies of *GSTT1* in Chinese population)[17]. Since the ethnic background and the environmental exposures may vary greatly across populations in different geographic regions, the conclusion could not be drawn[17]. During the preparation of this paper, another meta-analysis was published showing that the null genotypes of *GSTM1* and *GSTT1* are both associated with an increased HCC risk[18]. However, these investigators omitted some important data and introduced some incorrect information[18]. For example, Indians are mainly of Indo-European and Dravidian ancestries, which should be distinguished from East Asian population[18]. Many studies, including our previous studies[16,19-22], have reported on the effects of ethnic differences on genetic predisposition to human diseases. In addition, it is important to note that the allele frequencies and the genotype distributions for GST genes differed significantly across ethnic groups[23]. For example, the frequency of *GSTM1* null genotype is about 0.53 in Caucasians/Asians and about 0.28 in Africans; and the frequency of *GSTT1* null genotype is about 0.20 in Caucasians and about 0.52 in Asians[23]. Therefore, heterogeneity was introduced in that meta-analysis, which may not accurately assess the effects of *GSTM1* and *GSTT1* null genotypes on the risk of HCC[18]. In this study, we reinvestigated the relationship between *GSTM1*/*GSTT1* polymorphisms and the risk of HCC. We focused on the association between GST polymorphisms and the risk of HCC in Chinese population, because Chinese are at a much greater risk of developing HCC compared to other ethnic groups. A total of 19 studies of *GSTM1* (2660 cases and 4017 controls) and 16 studies of *GSTT1* (2410 cases and 3669 controls) were included. This meta-analysis has a much greater number of subjects and thus a much greater statistical power; therefore, it may define the effects of GST gene polymorphisms on the risk of HCC more precisely.

MATERIALS AND METHODS

Literature and search strategy

We searched the literature databases including PubMed (1950 to 2010), ISI web of science (1975 to 2010), Embase (1966 to 2010), Chinese Biomedical Database (1978 to 2010), China National Knowledge Infrastructure (1979 to 2010, in Chinese) and Wanfang Data (1982 to 2010, in Chinese).

The search strategy to identify all possible studies involved use of combinations of the following key words: ("glutathione S-transferase" or "GST" or "GSTM1" or "GSTT1") and ("hepatocellular carcinoma" or "liver cancer" or "HCC") and ("China" or "Chinese"). The reference lists of reviews and retrieved articles were also searched. Supplementary data were searched for missing data points. If more than one article were published using the same case series, only the study with largest sample size was selected. The literature search was updated on Oct. 20th, 2010.

Inclusion criteria and data extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluating the association between *GSTM1* or *GSTT1* null genotypes and HCC risk; (2) case-control design; (3) in Chinese population; and (4) sufficient data for calculation of odds ratio (OR) with CI. The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) language of publication; (4) residence area of the subjects; (5) source of control subjects; (6) numbers of cases and controls; (7) numbers of null genotypes for *GSTM1* and *GSTT1* in cases and controls; and (8) OR and 95% CI. The authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision.

Statistical analysis

The association between *GSTM1*/*GSTT1* polymorphisms and the risk of HCC was estimated by calculating pooled

Table 1 Characteristics of studies included in the meta-analysis of *GSTM1*

Ref.	Language of publication	Residence area of subjects	Case			Control			Source of control	OR (95% CI)	Earlier or smaller reports
			Null	Positive	Total	Null	Positive	Total			
Dong *et al*[28], 1997	Chinese	Jiangsu, Guangxi and Hebei	62	48	110	50	62	112	Population	1.602 (0.943-2.721)	[29,30]
Yu *et al*[31], 1999	English	Taiwan	42	42	84	216	159	375	Hospital	0.736 (0.458-1.183)	[32-37]
Wu *et al*[38], 2000	Chinese	Hu'nan	38	16	54	62	74	136	Population	2.835 (1.444-5.565)	NA
Sun *et al*[39], 2001	English	Taiwan	26	43	69	77	51	128	Population	0.400 (0.219-0.731)	NA
Zhu *et al*[40], 2001	Chinese	Guangdong	34	18	52	41	59	100	Hospital	2.718 (1.354-5.455)	NA
Chen *et al*[41], 2002	English	Taiwan	60	41	101	19	16	35	Hospital	1.232 (0.568-2.674)	NA
Liu *et al*[42], 2002	Chinese	Jiangsu	56	28	84	69	75	144	Population	2.174 (1.243-3.803)	[43-46]
McGlynn *et al*[47], 2003	English	Jiangsu	NA	NA	231	NA	NA	256	Population	0.830 (0.570-1.210)	[48-50]
Li *et al*[51], 2004	Chinese	Jiangsu	122	85	207	118	89	207	Population	1.083 (0.733-1.600)	NA
Chen *et al*[52], 2005	English	Taiwan	322	255	577	231	158	389	Population	0.864 (0.666-1.121)	[53]
Deng *et al*[54], 2005	English	Guangxi	117	64	181	172	188	360	Hospital	1.998 (1.383-2.888)	[55-58]
Guo *et al*[59], 2005	Chinese	Henan	67	28	95	52	51	103	Population	2.347 (1.306-4.218)	NA
He *et al*[60], 2005	Chinese	Guangxi	68	37	105	77	74	151	Hospital	1.766 (1.059-2.947)	[61, 62]
Long *et al*[63], 2005	Chinese	Guangxi	92	48	140	254	282	536	Hospital	2.128 (1.444-3.137)	[64]
Ma *et al*[65], 2005	Chinese	Guangxi	37	25	62	29	44	73	Population	2.246 (1.125-4.481)	NA
Zhang *et al*[66], 2005	Chinese	Hubei	37	23	60	28	45	73	Hospital	2.585 (1.281-5.219)	NA
Zhu *et al*[67], 2005	Chinese	Zhejiang	56	35	91	61	69	130	Hospital	1.810 (1.049-3.121)	NA
Long *et al*[68], 2006	English	Guangxi	179	78	257	312	337	649	Hospital	2.479 (1.823-3.370)	NA
Yang *et al*[69], 2009	Chinese	Guangxi	59	41	100	41	19	60	Hospital	0.667 (0.340-1.309)	NA

NA: Not available; OR: Odds ratio.

OR and 95% CI. The significance of the pooled OR was determined by Z test with $P < 0.05$ considered statistically significant. Q test was performed to evaluate whether the variation was due to heterogeneity or by chance. A random- (DerSimonian-Laird method[24]) or fixed- (Mantel-Haenszel method[25]) effects model was used to calculate pooled effect estimates in the presence ($P \leqslant 0.10$) or absence ($P > 0.10$) of heterogeneity, respectively. Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detecting bias or systematic heterogeneity[26]. An asymmetric funnel plot indicates a relationship between effect and study size, which suggests the possibility of either publication bias or a systematic difference between smaller and larger studies ("small study effects"). Publication bias was assessed by Begg's test and Egger's test[27] with $P < 0.05$ considered statistically significant. Subgroup analyses were performed to examine the effect of heterogeneity on meta-analysis results. The following subgroup comparisons were analyzed: residence area of the subjects (high-incidence area *vs* low-incidence area), number of cases (< 100 *vs* ⩾ 100), and source of controls (population-based *vs* hospital-based). To evaluate the stability of results, sensitivity analysis was performed by removing one study at a time and calculating the overall homogeneity and effect size. Data analysis was performed using STATA version 10 (StataCorp LP, College Station, Texas, USA).

RESULTS

Characteristics of the studies

The literature search identified a total of 137 potential relevant papers. The full text articles were retrieved and carefully reviewed to assess the eligibility according to the inclusion criteria. Forty-three papers met the inclusion criteria[28-70]. However, 23 papers were excluded because they were earlier or smaller reports from the same groups[29,30,32-37,43-46,48-50,53,55-58,61,62,64]. Nineteen studies of *GSTM1* (2660 cases and 4017 controls) and 16 studies of *GSTT1* (2410 cases and 3669 controls) were included in the meta-analysis, respectively. Most of the cases and controls included in this meta-analysis were HBV carriers. The characteristics of the included studies are listed in Tables 1 and 2.

Meta-analysis results of the association between GSTM1 polymorphisms and HCC

Nineteen studies of *GSTM1*, including 2660 cases and 4017 controls, were included in the meta-analysis. The relative frequency of *GSTM1* null genotype among control groups ranged from 0.384 to 0.683 in Chinese population. Using a random-effects model, the overall meta-analysis result showed that there was a statistically significant association between *GSTM1* null genotype and HCC risk in Chinese population (OR = 1.487, 95% CI: 1.159 to 1.908, $P = 0.002$). The forest plot is shown in Figure 1.

Meta-analysis results of the association between GSTT1 polymorphisms and HCC

Sixteen studies of *GSTT1*, including 2410 cases and 3669 controls, were included in the meta-analysis. The relative frequency of *GSTT1* null genotype among control groups ranged from 0.183 to 0.602 in Chinese population. Using a random-effects model, the overall meta-analysis result showed that there was a statistically significant association between *GSTT1* null genotype and HCC risk in Chinese

Table 2 Characteristics of studies included in the meta-analysis of *GSTT1*

Ref.	Language of publication	Residence area of subjects	Case			Control			Source of control	OR (95% CI)	Earlier or smaller reports
			Null	Positive	Total	Null	Positive	Total			
Dong *et al*[28], 1997	Chinese	Jiangsu, Guangxi and Hebei	63	47	110	42	70	112	Population	2.234 (1.305-3.825)	[29,30]
Yu *et al*[31], 1999	English	Taiwan	41	42	83	181	194	375	Hospital	1.046 (0.650-1.683)	[32-37]
Sun *et al*[39], 2001	English	Taiwan	30	37	67	77	51	128	Population	0.537 (0.295-0.976)	NA
Liu *et al*[42], 2002	Chinese	Jiangsu	34	50	84	36	108	144	Population	2.040 (1.146-3.630)	[43-46]
McGlynn *et al*[47], 2003	English	Jiangsu	NA	NA	231	NA	NA	256	Population	0.880 (0.590-1.310)	[48-50]
Liu *et al*[70], 2003	Chinese	Guangxi	28	23	51	18	35	53	Population	2.367 (1.072-5.227)	NA
Li *et al*[51], 2004	Chinese	Jiangsu	108	99	207	97	110	207	Population	1.237 (0.841-1.820)	NA
Chen *et al*[52], 2005	English	Taiwan	298	279	577	199	190	389	Population	1.020 (0.788-1.319)	[53]
Deng *et al*[54], 2005	English	Guangxi	108	73	181	154	206	360	Hospital	1.979 (1.377-2.845)	[55-58]
Guo *et al*[59], 2005	Chinese	Henan	58	37	95	45	58	103	Population	2.020 (1.146-3.562)	NA
He *et al*[60], 2005	Chinese	Guangxi	43	62	105	50	101	151	Hospital	1.401 (0.836-2.347)	[61,62]
Long *et al*[63], 2005	Chinese	Guangxi	82	58	140	234	302	536	Hospital	1.825 (1.251-2.660)	[64]
Ma *et al*[65], 2005	Chinese	Guangxi	35	27	62	21	52	73	Population	3.210 (1.573-6.551)	NA
Zhang *et al*[66], 2005	Chinese	Hubei	38	22	60	34	39	73	Hospital	1.981 (0.986-3.982)	NA
Long *et al*[68], 2006	English	Guangxi	146	111	257	297	352	649	Hospital	1.559 (1.165-2.086)	NA
Yang *et al*[69], 2009	Chinese	Guangxi	33	67	100	11	49	60	Hospital	2.194 (1.010-4.765)	NA

NA: Not available; OR: Odds ratio.

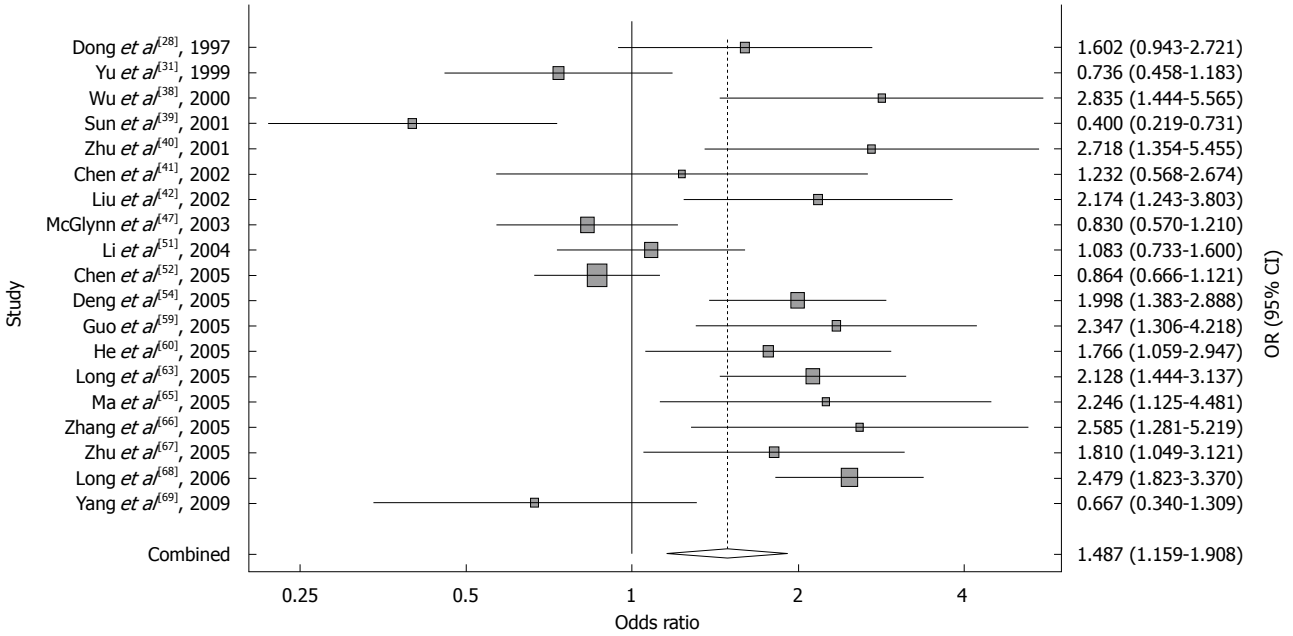

Figure 1 Forest plot of the meta-analysis of the association between *GSTM1* polymorphism and hepatocellular carcinoma risk.

population (OR = 1.510, 95% CI: 1.236 to 1.845, P = 0.000). The forest plot is shown in Figure 2.

Subgroup analysis

To examine the effect of heterogeneity between studies on meta-analysis results, we conducted subgroup analyses stratified by the following: residence area of the subjects (high-incidence area vs low-incidence area), number of cases (< 100 *vs* ≥ 100), and source of controls (population-based vs hospital-based). GST polymorphisms were significantly associated with HCC risk among the subjects living in high-incidence areas (Jiangsu, Zhejiang, Guangxi and Guangdong provinces), but not among the studies living in low-incidence areas. The result of subgroup analysis is shown in Tables 3 and 4.

Sensitivity analysis

Sensitivity analysis was performed by excluding each study at a time. The analysis confirmed the stability of the association between *GSTM1* and *GSTT1* polymorphisms and HCC risk (data not shown).

Potential publication bias

Begg's funnel plots were generated to assess potential publication bias (Figure 3 for *GSTM1* and Figure 4 for *GSTT1*). No publication bias was detected (Egger's test,

Table 3 Subgroup analysis of the association between *GSTM1* polymorphism and hepatocellular carcinoma risk

Group	No. of studies (cases/controls)	Statistical method	OR (95% CI)	*P*
All studies	19 (2660/4017)	Random	1.487 (1.159-1.908)	0.002
Residence area of the subjects				
High-incidence area	11 (1510/2666)	Random	1.659 (1.264-2.177)	0.000
Low-incidence area	7 (1040/1239)	Random	1.235 (0.753-2.026)	0.402
Mixed areas	1 (110/112)	-	1.602 (0.943-2.721)	0.081
No. of cases				
< 100	9 (651/1262)	Random	1.676 (1.061-2.649)	0.027
⩾ 100	10 (2009/2755)	Random	1.365 (1.005-1.853)	0.046
Source of controls				
Population-based	9 (1489/1548)	Random	1.316 (0.915-1.892)	0.139
Hospital-based	10 (1171/2469)	Random	1.675 (1.251-2.243)	0.001

OR: Odds ratio.

Table 4 Subgroup analysis of the association between *GSTT1* polymorphism and hepatocellular carcinoma risk

Group	No. of studies (cases/controls)	Statistical method	OR (95% CI)	*P*
All studies	16 (2410/3669)	Random	1.510 (1.236-1.845)	0.000
Residence area of the subjects				
High-incidence area	10 (1418/2489)	Random	1.641 (1.328-2.027)	0.000
Low-incidence area	5 (882/1068)	Random	1.152 (0.777-1.707)	0.483
Mixed areas	1 (110/112)	-	2.234 (1.305-3.825)	0.003
Number of cases				
< 100	7 (502/949)	Random	1.617 (1.035-2.528)	0.035
⩾ 100	9 (1908/2720)	Random	1.457 (1.173-1.810)	0.001
Source of controls				
Population-based	9 (1484/1465)	Random	1.441 (1.039-1.997)	0.028
Hospital-based	7 (926/2204)	Fixed	1.635 (1.391-1.921)	0.000

OR: Odds ratio.

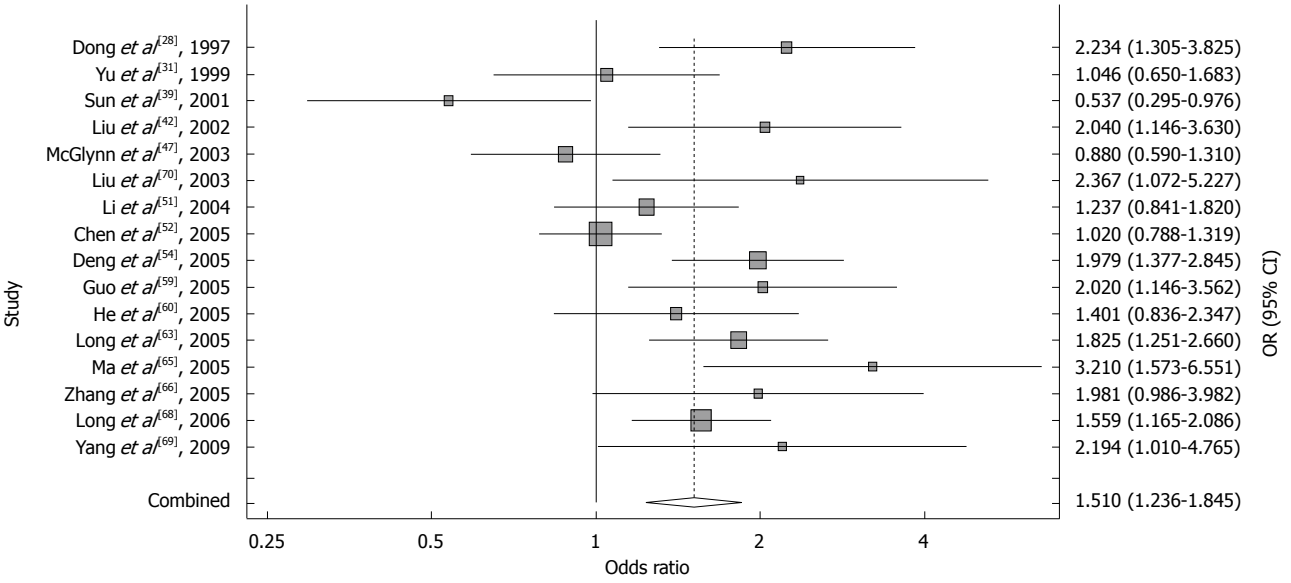

Figure 2 Forest plot of the meta-analysis of the association between *GSTT1* polymorphism and hepatocellular carcinoma risk.

P = 0.542 for *GSTM1* and *P* = 0.136 for *GSTT1*; Begg's test, *P* = 0.677 for *GSTM1* and *P* = 0.299 for *GSTT1*).

DISCUSSION

GST polymorphisms are implicated in the development of HCC. In the present study, we investigated the relationship between *GSTM1* and *GSTT1* polymorphisms and the risk of HCC in Chinese population. To minimize language bias, all available studies published in both English and Chinese languages were assessed, including a total of 19 studies of *GSTM1* (2660 cases and 4017

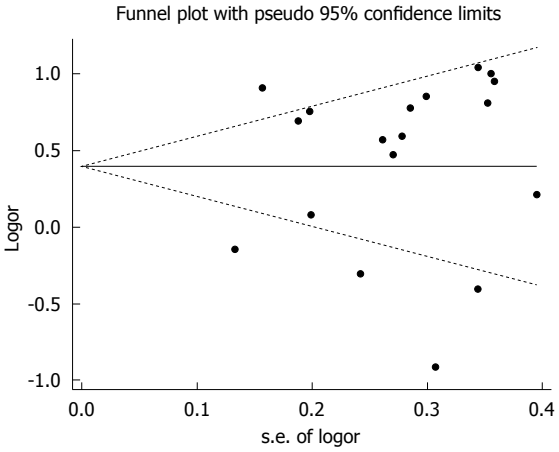

Figure 3 Funnel plot of the meta-analysis of the association between *GSTM1* polymorphism and hepatocellular carcinoma risk.

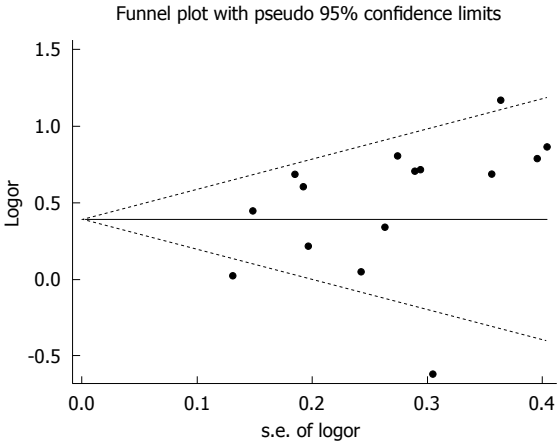

Figure 4 Funnel plot of the meta-analysis of the association between *GSTT1* polymorphism and hepatocellular carcinoma risk.

controls) and 16 studies of *GSTT1* (2410 cases and 3669 controls). The present meta-analysis has a much greater number of subjects and thus a much greater statistical power; therefore, it can define the effect of GST genes polymorphisms on HCC risk more precisely. The pooled analysis of two genes produced similar risk estimates (for *GSTM1*, OR = 1.487, 95% CI: 1.159 to 1.908, P = 0.002; for *GSTT1*, OR = 1.510, 95% CI: 1.236 to 1.845, P = 0.000), suggesting that both *GSTM1* and *GSTT1* null genotypes are associated with an increased risk of HCC in Chinese population.

The difference between our meta-analysis and the previous metaanalysis may be due to language bias introduced in the previous metaanalysis, which was based primarily on reports in English[17]. Therefore, all available studies published in both English and Chinese languages were assessed in the current meta-analysis. Another recent meta-analysis suggested that null genotypes of *GSTM1* and *GSTT1* were both associated with increased risk of HCC[18]. However, these investigators omitted some data and included some studies with incorrect information[52,53,59,65,69]. Therefore, the effects of *GSTM1* and *GSTT1* null genotypes on HCC was not assessed accurately[18]. Considering that Chinese people are at a much greater risk of developing HCC, we focused on the relationship between GST polymorphisms and HCC risk in Chinese population, thereby minimizing ethnic/racial differences. In the subgroup analysis, GST polymorphisms were significantly associated with HCC risk among the subjects living in high-incidence areas, but not among the subjects living in low-incidence areas. This result suggests that the effect of GST polymorphisms on HCC risk may be enhanced by environmental risk factors, such as dietary exposure to AFB1. Since sample size could influence the results, we also performed subgroup analysis stratified by sample size of cases. The results showed that the studies with either large (number of cases $\geqslant$ 100) or small sample size (number of cases $<$ 100) had similar risk estimates, indicating that small study effects may not exist in this meta-analysis. In addition, we generated Begg's funnel plots and found no publication bias among the studies included in this meta-analysis (Begg's test and Egger's test, $P > 0.1$).

The current meta-analysis has vital advantages compared to other studies; however, it does have some limitations. First, the present meta-analysis was based on unadjusted effect estimates and confidence intervals due to insufficient data available for most of the studies. Although the cases and controls were matched on age, sex and residence in all studies, these confounding factors might slightly modify the effect estimates. Second, the effect of gene-environment interactions was not studied in this meta-analysis. Alcoholism, HBV/HCV infections, and dietary exposure to AFB1 may be environmental risk factors that modify the effect estimates. Third, although most primary liver cancer cases are HCC, some of the included studies did not state whether the primary liver cancer patients were histologically confirmed to be HCC. Fourth, the heterogeneity between studies was not well addressed by subgroup analysis, suggesting there were other potential confounding factors in the included studies. Fifth, the results of subgroup analysis should be interpreted with caution because of limited statistical power. We anticipate these issues will be addressed in future studies.

In summary, our research suggests that *GSTM1*/*GSTT1* null genotypes are associated with increased risk of HCC in Chinese population. Considering the increasing prevalence of HCC in China and other countries worldwide, our finding may have important clinical and public health implications. More epidemiological and mechanistic studies are needed to further elucidate the role of GST polymorphisms in HCC and other liver cancers.

COMMENTS

Background

Asians, particularly Chinese, have a high risk of developing liver cancer. About 80%-90% of all cases of primary liver cancer diagnosed are hepatocellular carcinoma (HCC). Previous studies suggest that glutathione S-transferase (GST)

polymorphisms (*GSTM1* and *GSTT1*) may be risk factors for HCC. However, recent findings have been inconsistent.

Research frontiers

Meta-analysis was performed to assess the association between *GSTM1* and *GSTT1* polymorphisms and HCC risk in Chinese population.

Innovations and breakthroughs

The meta-analysis provided new evidence for the association between *GSTM1* and *GSTT1* polymorphisms and HCC risk in Chinese population. The results of this meta-analysis show that the *GSTM1* and *GSTT1* null genotypes are both associated with increased risk of HCC in Chinese population, suggesting that *GSTM1*/*GSTT1* null genotype carriers have 1.5 fold higher risk of developing HCC.

Applications

Since *GSTM1*/*GSTT1* polymorphisms are implicated in the pathogenesis of HCC, population-based genetic screening in future may help to identify the individuals at high risk of developing liver cancers.

Terminology

Meta-analysis, which combines the results of several studies that address a set of related research hypotheses, is an important component of a systematic review procedure.

Peer review

This meta-analysis provided new insights into liver cancer research.

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