RESEARCH ARTICLE

Glutathione S-transferase M1 Null Genotype and Hepatocellular Carcinoma Susceptibility in China and India: Evidence from an Updated Meta-analysis

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Abstract

Background: Glutathione S-transferase M1 (GSTM1) have been reported to be associated with hepatocellular carcinoma. However, the effect of the GSTM1 null genotype was divergent in the literature and we therefore performed the present meta-analysis to explore the relationship in detail. Materials and Methods: Reported studies were searched from 1990 to March 1, 2014 in PubMed and Wanfang Med Online. The total odds oatio (OR) and 95% CI were calculated and analyzed by Review Manager 5.1 and STATE 12. Results: Total OR was calculated from 26 articles with 3,769 cases and 5,517 controls and the association proved significant (OR [95%CI]=1.50 [1.25, 1.80], *P*<0.05) in the Chinese population. However, there was no significant association between hepatocellular carcinoma risk among subjects carrying the GSTM1 null genotype (OR [95%CI]=1.20 [0.88-1.64], *P*=0.24) in subgroups of publication in English and in Indian populations (OR [95%CI]=1.80 [0.80-4.20], *P*=0.15). Conclusions: The GSTM1 deletion polymorphism might not have a significant effect on the susceptibility of hepatocellular carcinoma overall.

Keywords: Glutathione S-transferase M1 gene (GSTM1) - null polymorphism - hepatocellular carcinoma

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Introduction

Liver cancer was the most common cancer and a serious fatal disease and had caused serious damage to human health (Yu et al., 2011). The etiloogy of liver cancer was chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) (Jeng et al., 2014). However, some studies were about genetic polymorphisms and suggested that GSTM1 deletion polymorphism was involved in liver cancer risk in China (Wang et al., 2010; Yu et al., 2011; Chen et al., 2012; Liu et al., 2013). However, only a minority of subjects who carried GSTM1 null genotype developed liver cancer. This phenomenon suggested that other risk factors, such as other genes polymorphisms, were related to susceptibility to liver cancer (Lakkakula et al., 2013). Many studies had discussed about GSTM1 null genotype and the results were not consistent. What's more, the researches were not performed by eliminating publication bias and irrelevant conclusions were made (Wang et al., 2010; Yu et al., 2011; Chen et al., 2012; Liu et al., 2013). We doubted that GSTM1 null genotype was the etiology of liver cancer.

Glutathione-S-transferases (GSTs) were coded by glutathione S-transferase mu 1 (GSTM1), glutathione S-transferase theta-1 (GSTT1) and other genes. GSTM1 was hypothesized to protect against toxins. However, many enzymes, such as cytochrome P450 (CYP450), microsomal epoxide hydrolase, and N-acetyltransferase, were involved in detoxification of carcinogens. We doubt that GSTM1 null genotype was the etiology of liver cancer. Therefore, we did this meta-analysis to investigate the effect of GSTM1 null genotype in etiology of liver cancer by subgroup analysis of publication language.

We enlarged the number of cases and controls to do an undated meta-analysis, and we ruled out publication bias by using subgroup analysis of publication language to make the conclusion more convincing.

Materials and Methods

Literature inclusion criteria

(1) The subjects of literature must be Chinese and Indian; (2) The papers should include the risk of hepatocellular carcinoma and GSTM1 null genotype; (3) Only case-control and cohort studies were considered; (4) The papers must provide the sample size, the OR values and 95% confidence interval or provide the related information such as genotype frequency that can calculate OR and 95%CI; (5) When more than one paper used the same study population, we included a recent literature.

Literature exclusion criteria

(1) There was no controls; (2) Duplicated data; (3) The articles were reviews; (4) Controls were with other malignancies.

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Search strategy

PubMed and Wanfang Med Online were searched by using key words: "liver cancer"; "GSTM1"; "glutathione S-transferase M1"; "hepatocellular carcinoma"; "polymorphism". The date of the search interval was from 1990 to March 1, 2014 and the scope of the search was all papers consisted of journals and dissertations.

Study selection and data extraction

According to pre-established criteria of inclusion and exclusion, a double-check procedure was carried out to make sure the accuracy of the data entry. The following information was extracted from the studies: first author, year, publication language, country, the data of total and exposure number in cases and control groups. A standardized procedure was performed to estimate Odds Ratio of cases and controls. Characteristics of studies were summarized.

Statistical analysis methods

Statistical analysis was did by using Review Manager5.1 and STATA 12. Adjusted OR value and 95%CI were calculated for each study, and crude OR value should be calculated if adjusted OR value was not available. The Cochrane Q statistics test and I^2 were performed for heterogeneity in this meta-analysis. A fixed effects model was used when $p>0.10$ and $I^2<50\%$, simultaneously, while a random effects model was selected when $p<0.10$ or $I^2>50\%$. The funnel plot was drawn to evaluate publication bias. Egger's test and Begg's test were also done to check the publication bias. All the tests were two-sided, a P value of 0.05 for any test or model was considered to be statistically significant.

Results

Overview of included studies

According to the search strategy, 29 papers were selected in Figure 1. We had read all 29 the papers and 16 papers about Chinese were published by Chinese and 10 papers were published by English and 3 studies were about Indian in Table 1.

Table 1. Literature Inclusion and Exclusion

First author	Year	Country	Publication language	Cases		Controls		Remark
				Null	Total	Null	Total	
Yu	1995	China	English	16	30	95	150	exclusion (duplication of data)
Bian	1996	China	Chinese	44	65	50	106	exclusion (duplication of data)
Dong	1997	China	Chinese	62	110	50	112	inclusion
Dong	1997	China	Chinese	33	54	26	54	exclusion (duplication of data)
Hu	1997	China	Chinese	37	45	104	147	inclusion
Yu	1999	China	English	42	84	216	375	inclusion
Wu	2000	China	Chinese	38	54	62	136	inclusion
Bian	2001	China	English	36	63	37	88	inclusion
Deng	2001	China	Chinese	102	162	92	177	exclusion (duplication of data)
Sun	2001	China	English	26	69	77	128	inclusion
Zhu	2001	China	Chinese	34	52	41	100	inclusion
Chen	2002	China	English	60	101	19	35	inclusion
Chen	2005	China	English	322	577	231	389	inclusion
Mcglynn	2003	China	English	134	231	124	256	inclusion
Deng	2005	China	English	117	181	172	360	inclusion
Liu	2002	China	Chinese	56	84	69	144	inclusion
Wei	2003	China	Chinese	70	100	64	135	exclusion (duplication of data)
Li	2004	China	Chinese	122	207	118	207	inclusion
Deng	2005	China	Chinese	117	181	172	360	exclusion (duplication of data)
He	2005	China	Chinese	68	105	77	151	exclusion (duplication of data)
He	2007	China	Chinese	68	105	77	151	exclusion (duplication of data)
He	2008	China	Chinese	68	105	77	151	inclusion
Long	2005	China	Chinese	92	140	254	536	exclusion (duplication of data)
Ma	2005	China	Chinese	37	63	29	73	inclusion
Zhu	2005	China	Chinese	56	91	61	130	inclusion
Guo	2005	China	Chinese	67	95	52	103	inclusion
Zhang	2005	China	Chinese	37	60	28	73	inclusion
Long	2006	China	English	179	257	312	649	inclusion
Yang	2009	China	Chinese	59	100	41	60	inclusion
Wei	2010	China	Chinese	118	181	305	641	inclusion
Kao	2010	China	English	54	102	211	386	inclusion
Xiao	2011	China	Chinese	126	210	40	75	inclusion
Tang	2012	China	Chinese	76	150	77	150	inclusion
Chen	2012	China	Chinese	15	21	25	68	inclusion
Li	2012	China	English	244	476	211	481	inclusion
Asim	2010	India	English	152	254	157	525	inclusion
Kiran	2008	India	English	16	63	38	169	inclusion
Sarma	2012	India	English	45	68	75	123	inclusion

Meta-analysis Results

We observed a significant association between GSTM1 null genotype and hepatocellular carcinoma in total Chinese population [OR= 1.50, 95%CI: 1.25-1.80, p<0.0001; P_Q<0.00001 and I^2=74%] in Figure 2. As shown in Table 2, we performed subgroup analysis of publication languages to eliminate the publication bias. There was a significant association between GSTM1 null genotype and hepatocellular carcinoma in Chinese population published by Chinese [OR= 1.74, 95%CI: 1.42-2.14, p<0.00001; P_Q=0.008 and I^2=52%] in Figure 3 (still significant after Bonferroni correction), but not in subgroup of published by English [OR= 1.20, 95%CI: 0.88-1.64, p=0.24; P_Q<0.00001 and I^2=84%] in Figure 4.

However, there is no significant association between GSTM1 null genotype and hepatocellular carcinoma in Indian population [OR = 1.80, 95%CI: 0.80-4.02, p=0.15; P_Q=0.0009 and I^2=86%] in Figure 5.

We caught a conclusion that there was no significant association between single GSTM1 null genotype and hepatocellular carcinoma in Indian population and Chinese population published by English.

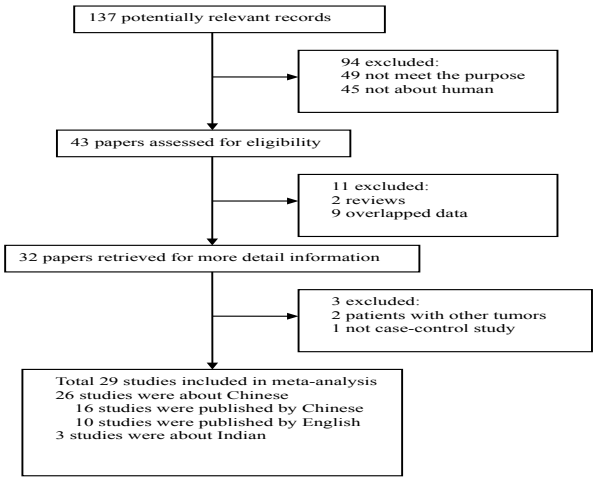

Figure 1. The Flow Chart of the Included Studies for a Meta-analysis of GSTM1 Null Genotype and Hepatocellular Carcinoma

Test of heterogeneity

Q test and I^2 were calculated to test the heterogeneity in Table 2. P value was less than 0.10, so we analyzed the pooled ORs with random effects model. Many factors might lead to heterogeneity. The distribution of GSTM1 null genotype was different in various regions; the selection of control group was different among studies;

Table 2. Pooled Measures for the Association between GSTM1 Null and Susceptibility to Hepatocellular Carcinoma

Country	Data	No.			Heterogeneity		Effect size		Model
		Studies	cases	controls	I^2(%)	p	OR (95%CI)	p	
China	Overall	26	3769	5517	74	<0.00001	1.50[1.25,1.80]	<0.0001	Random model
	Publication in Chinese	16	1628	2370	52	0.008	1.74[1.42,2.14]	<0.00001	Random model
	Publication in English	10	2141	3147	84	<0.00001	1.20[0.88,1.64]	0.24	Random model
India	Publication in English	3	385	817	86	0.0009	1.80[0.80,4.02]	0.15	Random model

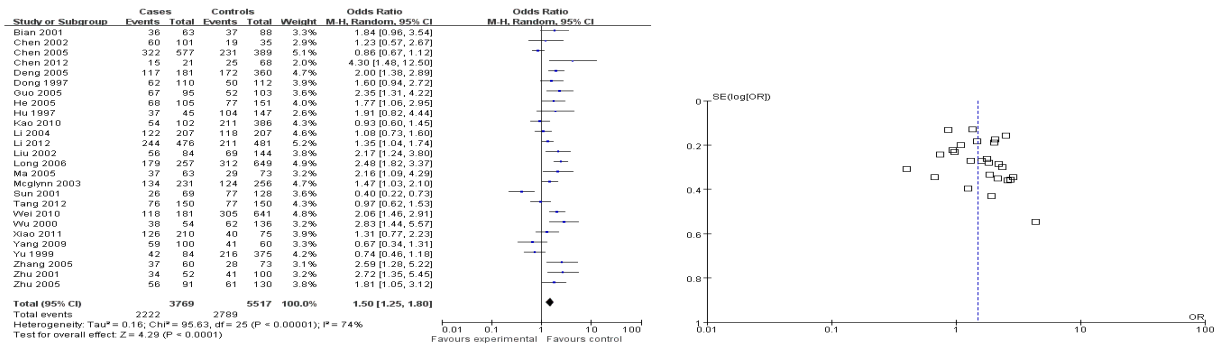

Figure 2. Forest Plot and Funnel Plot for the Association between GSTM1 null Genotype and Hepatocellular Carcinoma in Over all Chinese Population

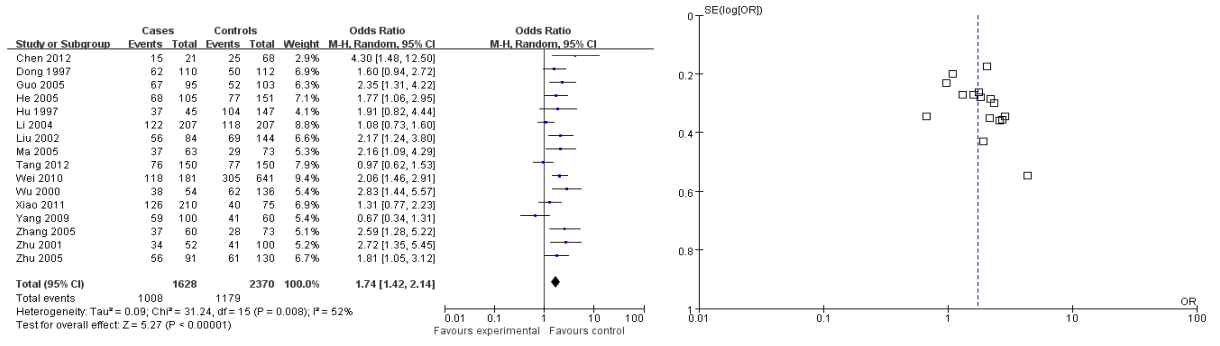

Figure 3. Forest Plot and Funnel Plot for the Association between GSTM1 Null Genotype and Hepatocellular Carcinoma in Chinese Population by Publication in Chinese

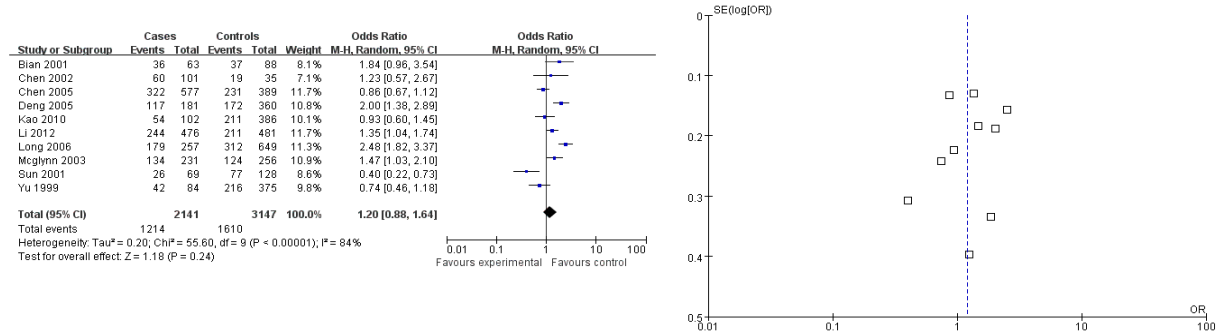

Figure 4. Forest Plot and Funnel Plot for the Association between GSTM1 Null Genotype and Hepatocellular Carcinoma in Chinese Population by Publication in English

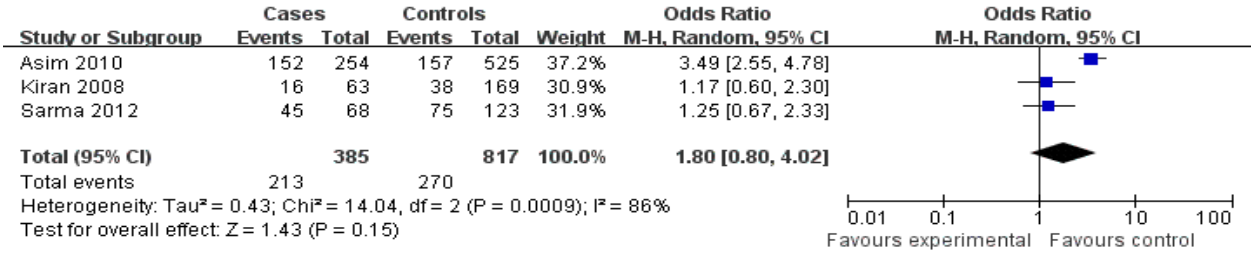

Figure 5. Forest Plot for the Association between GSTM1 Null Genotype and Hepatocellular Carcinoma in Indian Population

Table 3. Publication Bias for all Analysis

Country	Data	*p* value	
		Egger's test	Begg's test
China	overall	0.131	0.094
	Publication in Chinese	0.085	0.034
	Publication in English	0.773	1.000
India	Publication in English	0.451	0.296

smoking and subtypes of liver cancer also could lead to heterogeneity. However, this information could not collect completely.

Publication bias

Funnel plots was performed to assess the publication bias in Figure 2, Figure 3 and Figure 4. In addition, the Egger's test and Begg's test were also selected to test publication bias in Table 3. The PBegg's test of studies published in Chinese was 0.034<0.05, so publication bias was existent. The rest of Begg's tests were $p>0.05$, so it indicated that there was no publication bias in other analysis. Sensitivity analysis was performed by sequential omission of individual studies, and the results also indicated that the pooled result was robust.

Discussion

According to this meta-analysis, an interesting finding that GSTM1 null genotype was significant association with over all studies about China (OR=1.50, 95%CI=1.25–1.80, $p<0.0001$) was observed. The homozygous deletion of GSTM1 could result in a lack of enzyme activity, so failure to deal with toxins might lead to the development of liver cancer. However, this hypothesis had a precondition that GSTM1 was the major metabolic gene or GSTM1 was the only participator in metabolize carcinogens. As we all known that there were many metabolic genes, such as cytochrome P450 (CYP450), microsomal epoxide hydrolase, and N-acetyltransferase, could metabolize carcinogens. CYP450 might have a more important role in detoxification of carcinogens, and CYP450 could compensate the non-function of GSTM1 null genotype (Liu et al., 2013). We doubt that GSTM1 null genotype was the etiology of liver cancer.

Therefore, we analyzed the results by subgroup analysis. We observed that there was no significant association between GSTM1 null genotype and hepatocellular carcinoma risk in subgroup of publication in English (OR=1.20, 95%CI=0.88–1.64, $p=0.24$). This result was conflict with overall result. The power of test was enough because of 2141 cases and 3147 controls. However, there was significant association between GSTM1 null genotype and hepatocellular carcinoma risk in subgroup of publication in Chinese (OR=1.74, 95%CI=1.42–2.14, $p<0.00001$). Many reasons could lead to these inconsistent results. Positive results were easy to publish in Chinese journals, and this could lead to publication bias. Funnel plot, Egger's test and Begg's test were selected to test publication bias and the $P_{Begg's}$ test of studies published in Chinese was 0.034<0.05, so publication bias was existent. This result indicated the subgroup analysis of publication in English were more convincible than subgroup analysis of publication in Chinese. Besides, duplicate data were published among Chinese journals and publication bias was inevitable. Meta-analysis between GSTM1 null genotype and hepatocellular carcinoma risk in Indian population was performed. However, there were only 3 studies and no significant association was observed.

The heterogeneity was not negligible and it was difficult to eliminate. The distribution of GSTM1 null genotype was different in various regions; the selection of control group was different among studies; smoking and subtypes of liver cancer also could lead to heterogeneity. However, this information could not collect completely.

There were some limitations in this meta-analysis.

First, only published papers were included in this meta-analysis, and it would cause publication bias. Second, there were a few cases and controls in Indian population in this meta-analysis. Third, heterogeneity was difficult to exclude and this indicates that further analysis needs to gather complete data which includes gender, age, smoking and type of liver cancer. In spite of these limitations, there were some advantages in this study. First, 3769 cases and 5517 controls included in this meta-analysis were eligible and had greater statistical power. Second, we conducted separate meta-analyses for different publication language and we derived a different and convincible conclusion of the relationship between GSTM1 and null genotype and the risk of developing liver cancer.

In a word, we found that there was no significant association between GSTM1 null genotype and the susceptibility of liver cancer by subgroup analysis of publication in English.

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