Int J Clin Exp Med 2016;9(11):21334-21345
www.ijcem.com /ISSN:1940-5901/IJCEM0029240

Original Article

Glutathione S-transferase M1 polymorphism and susceptibility to colorectal cancer: an updated meta-analysis

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Received March 27, 2016; Accepted June 21, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Objective: To provide a more precise meta-analysis of glutathione S-transferase M1 *(GSTM1)* polymorphism in estimating the risk of colorectal cancer (CRC). Methods: We conducted a comprehensive literature search in Science, PubMed, and Embase for reports on *GSTM1* genetic deficiency and susceptibility to CRC up to Oct 11, 2015. Odds ratios (ORs) with 95% confidence intervals (CIs) were adopted to evaluate results. Statistical analysis was performed using SAS software and RevMan 5.0. Results: The present meta-analysis included 17,050 cases and 23,704 controls from 51 independent case-control studies. The data indicated an overall OR of 1.13 (95% CI, 1.06 to1. 21, $P_{heterogeneity}$<0.00001), which suggested that CRC risk may increase in the individuals with GSTM1 null genotype. In subgroup by race, a positive relationship between GSTM1 null polymorphism and CRC risk was observed in Caucasians (OR=1.14, 95% CI, 1.04 to 1.24) and Asians (OR=1.12, 95% CI, 1.03 to 1.21). The CRC incidence was significantly higher in the colon than in the rectum (OR=1.17, 95% CI, 1.04 to 1.32). However, we did not identify positive correlations in sex, smoking status, and tumor subset. The results of sensitivity analysis were stable and there was no publication bias. Conclusions: GSTM1 null genotype may increase CRC risk.

Keywords: Glutathione S-transferase M1, polymorphism, colorectal cancer, risk, meta-analysis

Introduction

Colorectal cancer (CRC) has already been the third most prevalent malignant tumor worldwide, being ranked after lung and gastric cancer [1]. CRC is a leading etiology of morbidity and mortality in the world because approximately 1.2 million have it and over 0.6 million died of it every year [2].

Although some patients have a family history of CRC, the majority of CRC cases are sporadic. Epidemiological evidence suggests that external environmental factors combined with genetic factors may play important roles in the development of sporadic CRC [3]. Environmental carcinogens such as polycyclic aromatic hydrocarbons (PAH), heterocyclic amines and nitrosamines, are typically absorbed due to poor dietary habits, tobacco smoking, and excessive alcohol consumption [4]. Efficient metabolism of those carcinogens is protective against CRC [5-7]. However, the capacity to eliminate carcinogens from the human body varies among individuals. Deficiencies in the critical enzymes for the metabolism of carcinogens may lead to the development of cancer [8, 9]. For example, the glutathione S-transferase (GST, chromosome 1p13.3) proteins are a super-family of proteins that perform phase II detoxification reactions of PAHs and other carcinogens [10]. GSTs include seven cytosolic isoenzymes, and GSTM, GSTT, and GSTP are the three most common cytosolic isoenzymes. Glutathione S-transferase M 1 (GSTM1) genetic polymorphisms lead to altered activity levels of enzymes involving in the metabolism of PAHs, thus affecting carcinogen clearance [6, 7, 10]. Hence, the studies above have demonstrated that variance in enzyme activity induced by gene polymorphisms may lead to different CRC risk in individuals.

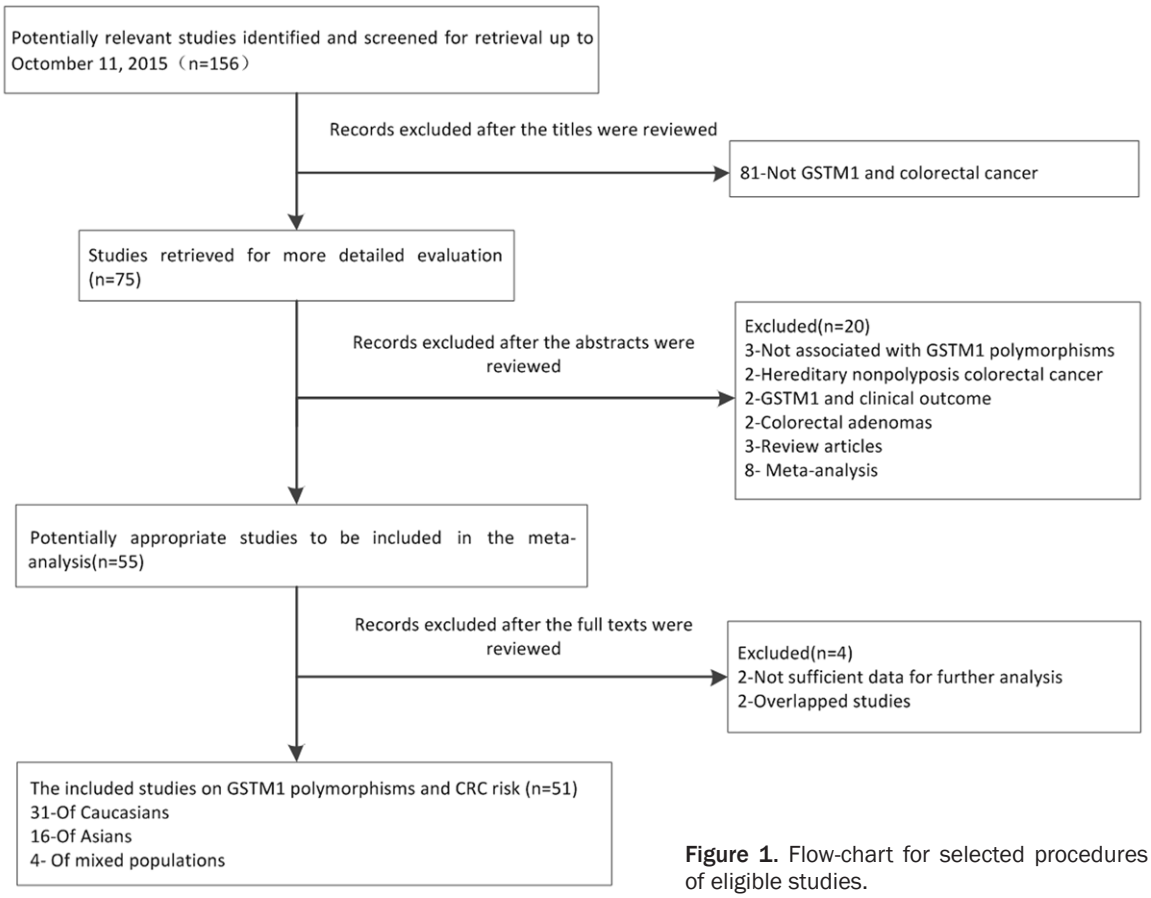

Figure 1. Flow-chart for selected procedures of eligible studies.

The deletion of both alleles of the GSTM1 gene is regarded as the GSTM1-null genotype, which is a common polymorphism of the GSTM1 gene [11, 12]. Since the relevance between GSTM1 polymorphism and CRC risk was raised for the first time in 1993 [13], many studies about it have been reported. However, these results are controversial. To provide a more precise assessment for the association between GSTM1 null genotype and CRC risk, we conducted the present meta-analysis.

Materials and methods

Literature search

We implemented a comprehensive literature search of Science, PubMed, and Embase using search terms as follows: “colorectal cancer”, “CRC”, “colorectal neoplasm”, “colorectal carcinoma”, “colon cancer”, “colonic neoplasm”, “rectum neoplasm”, “rectal cancer”, “GSTM1”, “glutathione s-transferase M1”, “glutathione s-transferase null 1”, “genotype”, “genetic polymorphism” or “polymorphism”. To identify potentially pertinent studies, an extensive manual search was conducted by reviewing the references of studies enrolled in this study and relevant reviews.

Selection of eligible studies and selection criteria

In total, 156 papers were identified by our search. By reviewing the titles of these papers, 81 papers were excluded, and 75 articles were retrieved for more detailed evaluation. Twenty studies were excluded after the abstracts were reviewed. The full texts of 55 papers were reviewed. Among those papers, two did not provide sufficient data [14, 15]. In addition, the data in four papers overlapped [16-19], so two of the four papers were excluded based on the criteria described below [18, 19]. Finally, 51 papers were included in this meta-analysis [13, 16, 17, 20-67]. The details of selected procedures for the 51 papers are presented in **Figure 1**.

Table 1. Characteristics of studies included in the meta-analysis

First author	Year	Country	Racial descent	Source of controls	Genotype distribution			
					Case		Control	
					Null	Present	Null	Present
Zhong [13]	1993	UK	Caucasian	HB†	110	86	94	131
Chenevix-Trenh [20]	1995	Australia	Caucasian	NR‡	64	68	101	99
Katoh [21]	1996	Japan	Asian	PB	56	47	55	71
Deakin [22]	1996	UK	Caucasian	HB	135	117	316	261
Gou [23]	1996	China	Asian	PB§	7	12	6	17
Gertig [24]	1998	USA	Caucasian	PB	114	97	117	104
Edmund [25]	1998	Japan	Asian	HB	128	172	89	94
Slattery [26]	1998	America	Caucasian	PB	808	759	1004	885
Abdel-Rahman [27]	1999	Egypt	Asian	HB	37	26	30	15
Welfare [28]	1999	UK	Caucasian	PB	102	94	90	88
Zhang [29]	1999	Sweden	Caucasian	PB	44	50	55	54
Gawronskazklarz [30]	1999	Poland	Caucasian	NR	46	24	72	73
Butler [31]	2001	Australia	Caucasian	HB	106	97	108	92
Loktionov [32]	2001	UK	Caucasian	PB	133	73	208	147
Saadat [33]	2001	Iran	Asian	NR	25	21	53	78
Tiemersma [34]	2002	Netherlands	Caucasian	PB	58	44	285	252
Ye [35]	2002	UK	Caucasian	NR	20	21	33	49
Sachse [36]	2002	UK	Caucasian	PB	206	284	291	302
Laso [37]	2002	Spain	Caucasian	HB	133	114	158	138
Sgambato [38]	2002	Italy	Caucasian	HB	32	12	53	47
Nascimento [39]	2003	Brazil	Mixed	HB	50	52	134	166
Slattery [40]	2003	America	Mixed	PB	404	397	546	467
van der Hel [41]	2003	Netherlands	Caucasian	PB	88	124	369	396
van der Logt [42]	2004	Hungary	Caucasian	HB	291	209	242	258
Ates [43]	2004	Netherlands	Caucasian	PB	184	186	203	212
Kiss [44]	2005	Turkey	Asian	HB	98	83	88	116
Huang [45]	2006	America	Mixed	PB	257	297	371	503
Little [46]	2006	UK	Caucasian	PB	131	110	221	162
Martinez [47]	2006	Spain	Caucasian	PB	87	55	149	180
Probst-Hensch [16]	2006	Singapore	Asian	PB	132	168	525	643
Skjelbred [48]	2007	Norway	Caucasian	PB	55	53	151	148
Yeh [17]	2007	China	Asian	HB	402	321	410	323
Yoshida [49]	2007	Japan	Asian	PB	36	30	62	59
Csejtei [50]	2008	Hungary	Caucasian	HB	60	42	46	51
Pande [51]	2008	America	Caucasian	PB	52	68	113	144
Matakova [52]	2009	Slovakia	Caucasian	PB	100	83	220	202
Zupa [53]	2009	Italy	Caucasian	HB	61	31	68	53
Epplein [54]	2009	America	Caucasian	PB	91	82	147	166
Cleary [55]	2010	Canada	Caucasian	PB	616	550	684	608
Hlavata [56]	2010	Czech	Caucasian	HB	267	228	241	254
Wang [57]	2010	India	Asian	HB	100	202	76	215
Yang [58]	2010	China	Asian	PB	189	133	731	522
Darazy [59]	2011	Lebanon	Asian	PB	25	32	12	58
Nisa [60]	2012	Japan	Asian	PB	549	1506	567	1767
Hezova [61]	2012	Czech	Caucasian	PB	100	97	101	117

Rudolph [62]	2012	Germany	Caucasian	PB	932	822	923	844
Ebrahimkhani [63]	2012	Iran	Asian	HB	1	268	1	281
Vogtmann [64]	2013	China	Asians	PB	201	134	379	259
Djansugurova [65]	2014	Kazakhstan	Mixed	NR	125	124	87	158
Procopciuc [66]	2014	Romania	Caucasian	HB	90	60	65	97
Kassab [67]	2014	Tunisia	Asian	HB	104	43	87	41

†Hospital-based study; ‡Population-based study; §Not reported.

Table 2. Main results of all ORs in the present meta-analysis

	Null versus present			
	N*	OR	95% CI	*P*#
Total	8,242	1.13	1.06-1.21	<0.00001
Ethnicity				
Caucasian	5,608	1.14	1.04-1.24	<0.0001
Asian	2,125	1.12	1.03- 1.21	0.02
African	83	1.45	1.02- 2.07	0.69
Sex				
Male	1,756	1.02	0.93-1.12	0.16
Female	1,536	0.94	0.85-1.03	0.06
Smoking status				
Nonsmokers	1,419	1.09	0.94-1.26	0.04
Smokers	1,501	1.01	0.92-1.12	0.15
Tumor location				
Colon	2,738	1.17	1.04-1.32	0.006
Rectum	1,006	1.19	0.95-1.48	0.009
Subset				
Proximal	658	1.01	0.78-1.30	0.009
Distal	936	1.09	0.97-1.22	0.02

*Number of cases. #*P*-value for heterogeneity.

The inclusion criteria were as follows: (a) case-control or prospective study in humans; (b) investigated the relationships between GSTM1 polymorphism and CRC risk, (c) sufficient data which includes odds ratios (ORs) and 95% confidence intervals (CIs), and (d) full-text article written in English. If multiple publications were available for overlapping populations, we selected the publication that provided the most detailed information or had the largest sample size.

Data extraction

To minimize bias, all data were extracted independently and cross-checked by two researchers. For each eligible study, information was extracted as follows: year of publication, first author's surname, country of the participants, study design (categorized as hospital-based case-control studies, population-based case-control studies or cohort studies), sex of the participants, smoking status, tumor location, tumor subset, and number of participants with the GSTM1 null genotype or an intact GSTM1 gene (number of cases and controls).

Statistical analysis

ORs with 95% CIs were adopted to estimate the association between CRC risk and GSTM1 polymorphisms. A chi-square-based Q-statistical test and the I^2 score were applied to quantify the between-study heterogeneities [68]. When the heterogeneity was considered to be of significance ($P<0.05$), a random-effect model (RE) was applied, as previously described by Der Simonian and Laird [69]. In contrast, a fixed-effect model (FE) was used when the heterogeneity was insignificant, as previously described by Mantel and Haenszel [70]. The results of these two models were similar, indicating the lack of between-study heterogeneity. Then, analyses were stratified according to ethnicity, sex, smoking status, tumor location, and tumor subset. Additionally, the sensitivity analysis was applied to assess the stability of our results.

The publication bias was measured by Begg's funnel plot and Egger's regression test [71]. All statistical tests were conducted using the Review Manager (v.5.0; Oxford, England), STATA (v.12.1; STATA Corp. College Station, TX, USA) and Statistical Analysis System software (v.9.1.3; SAS Institute, Cary, NC). All statistical tests were 2-sided. $P<0.05$ was considered statistically significant.

Results

Eligible studies [13, 16, 17, 20-67]

A total of 51 studies with 17,050 patients and 23,704 controls were selected to evaluate the

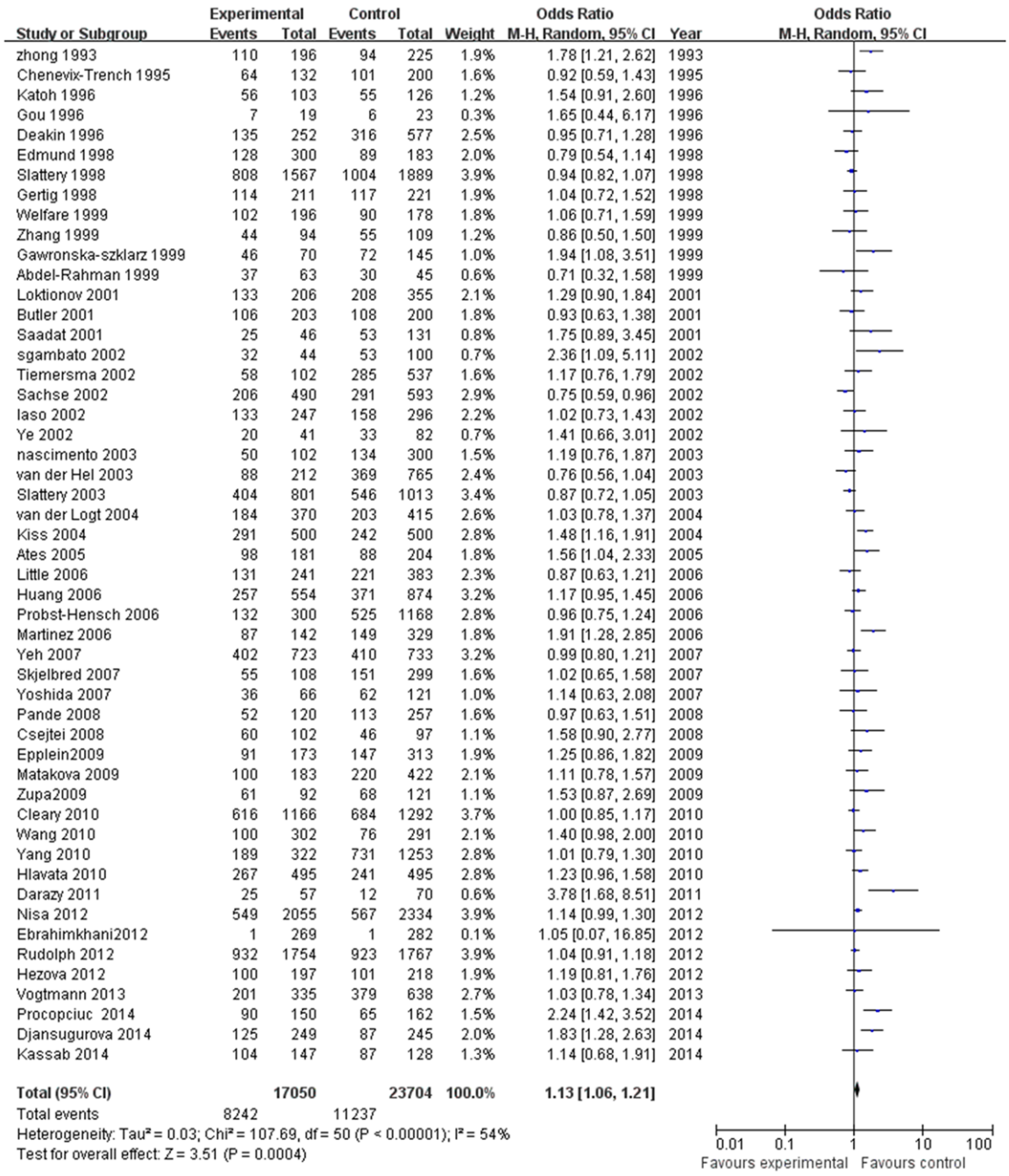

Figure 2. Forest plot of the association between the GSTM1 null polymorphism and colorectal cancer risk in the overall population. Note: GSTM1: *Glutathione S-transferase M 1.*

association between CRC risk and GSTM1 polymorphism [13, 16, 17, 20-67]. All eligible studies were English publication. The main characteristics of these eligible studies are shown in **Table 1** including 16 studies from Asians, 31 studies from Caucasians, and 4 studies from mixed populations. Of the 4 studies from mixed populations, only 2 studies were performed in African population [39, 45]. Additionally, among the 51 studies, 28 were population-based, 18 were hospital-based, and the other 5 did not report the study design. For all eligible studies, the distribution of genotypes was in accordance with Hardy-Weinberg equilibrium (HWE).

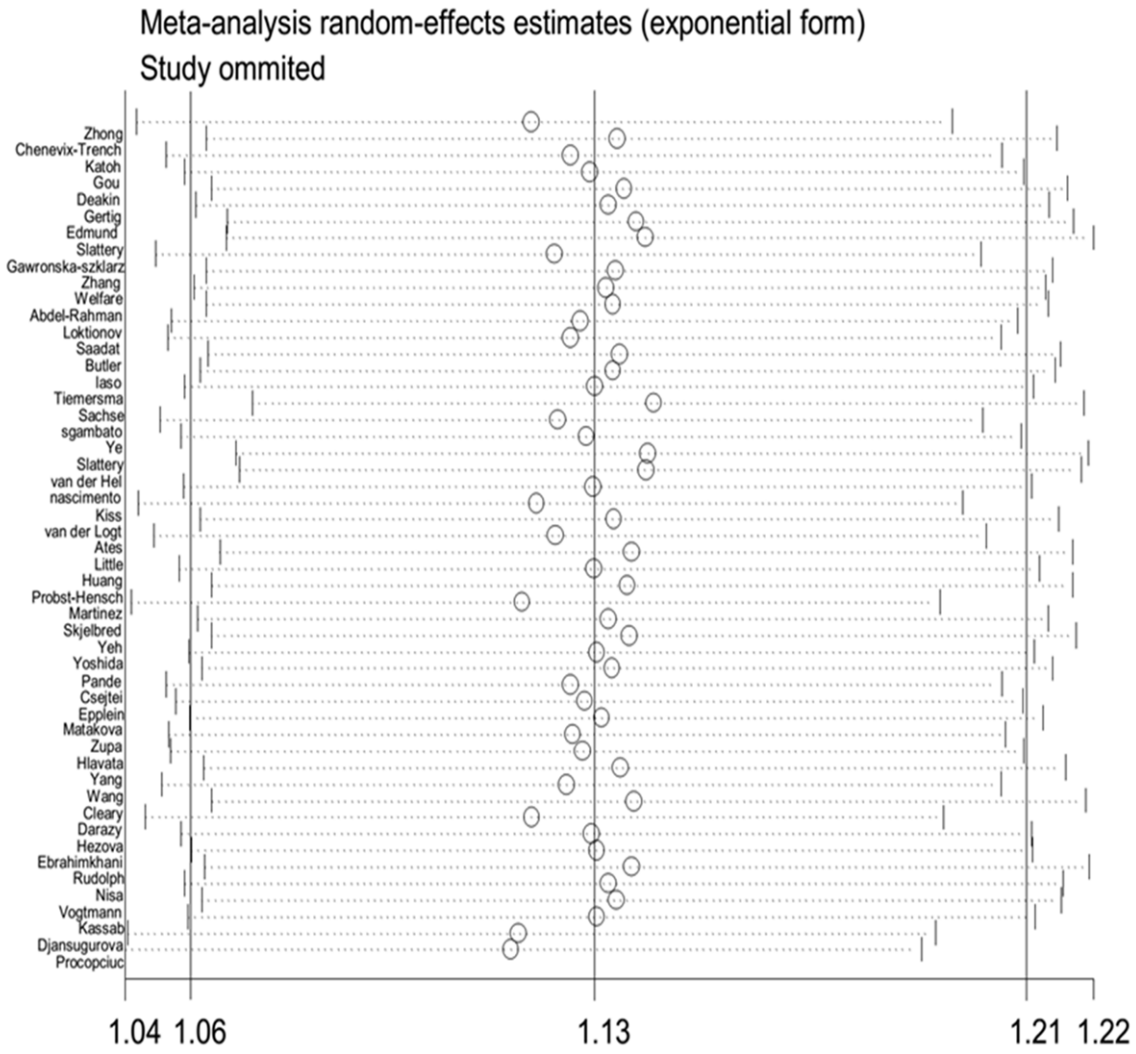

Figure 3. Sensitivity analysis of the present meta-analysis.

Overall

The main outcome of the heterogeneity test and our meta-analysis are shown in **Table 2**. The ORs were calculated for the GSTM1 null genotype versus intact GSTM1 genotypes. CRC risk was significantly higher in the individuals with GSTM1 null genotype than in the individuals with GSTM1 gene (OR=1.13, 95% CI=1.06-1.21, $P_{heterogeneity}$<0.00001, RE model, **Figure 2**).

Subgroup meta-analysis

In subgroup analysis by race, a significantly increased association between GSTM1 null polymorphism and CRC risk was obtained in Caucasians (OR=1.14, 95% CI=1.04-1.24) and Asians (OR=1.12, 95% CI=1.03-1.21). The number of African patients is so small and it may not reach adequate sample size. A sensitivity analysis was performed and indicated no significant difference. This suggested that each study or all studies enrolled in this study did not affect overall results of this study, namely that results obtained by this study possessed statistical stability (**Figure 3**).

In the subgroup analysis by tumor location, the GSTM1 null genotype was associated with an increased risk of CRC in the colon (OR=1.17, 95% CI=1.04-1.32) but not in the rectum (OR=1.19, 95% CI=0.95-1.48). However, in the analyses stratified by sex, tumor subset and smoking status, no significant association with the GSTM1 null genotype was found. The main

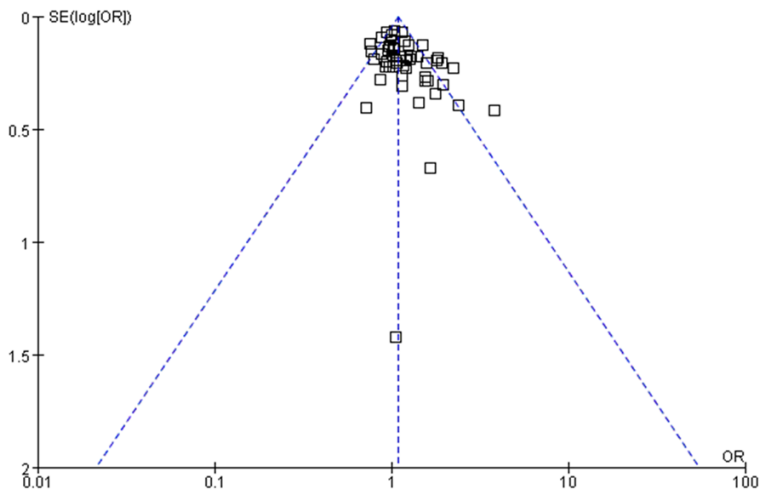

Figure 4. Funnel plots of publication bias in the meta-analysis of the association between genetic polymorphisms of GSTM1 and CRC risk.

outcomes of the heterogeneity test and our meta-analysis are presented in **Table 2**.

Publication bias

Begg's funnel plot and Egger's regression test were carried out to estimate publication biases of all eligible literatures. As depicted in **Figure 4**, the shape of the funnel plot for the overall population is symmetrical, which suggested no publication bias. The results of the Egger's test provided statistical evidence for funnel plot symmetry.

Discussion

Genetic polymorphisms have been reported to alter enzyme activity and lead to individual variation in the risk of cancer [14, 72-75]. Since the first report in the UK of an association of the GSTM1 gene deletion with an increased risk to CRC, approximately 1,800 articles have attempted to identify the relationship between GSTM1 genotypes and cancers, for example, breast cancer, lung cancer, gastric cancer, and prostate cancer, over the past 22 years [10]. However, the results of those studies are contradictory, especially for the studies on colorectal carcinoma [6, 13, 16, 17, 20-67]. We performed an updated meta-analysis that included 51 studies with 17,050 cases and 23,704 control subjects. Based on the cumulative evidence, this study may be a more comprehensive meta-analysis regarding the relationship between the GSTM1variant allele and CRC risk. The main findings of the present meta-analysis suggest that the GSTM1 null genotype contributes to CRC risk in the overall populations, which is consistent with previous studies [76, 77]. Our results also further indicate that GSTM1 plays a key role in CRC carcinogenesis. This is conducive to understanding the correlation between GSTM1 and risk of CRC.

In subgroup analysis by race, we found that the GSTM1 null genotype increased CRC risk in Caucasians and Asians, and this result is consistent with the results obtained by earlier studies [13, 30, 38, 44, 47, 65, 66, 76, 77]. We also found that the OR for Africans was slightly higher than that for Asians and Caucasians. These findings indicate that GSTM1 polymorphisms may play different roles on CRC risk in different ethnic groups [78, 79]. However, only 2 of the 51 included studies explored the effect of GSTM1 polymorphisms in Africans. Owing to the limited number of African subjects examined (249 cases and 627 controls), larger, well-designed, precise epidemiological studies are required to verify our results.

In the subgroup analysis by tumor location, we observed a significantly higher to risk of colon cancer in individuals with GSTM1-null genotype. Similar results were reported by other previous studies [13, 38, 53]. However, other studies reported no correlation between GSTM1 genotype and colon cancer location [20, 22, 24]. This inconsistency may be due to differences in the expression level of GSTM1 genes in different cell types along the human gastrointestinal tract [79].

In the analyses stratified by sex, smoking status, and tumor subset, no significant association between GSTM1 polymorphism and CRC risk was identified. However, some studies have demonstrated that increases in CRC risk is associated with those variables in the individuals with the GSTM1 null genotype [13, 21, 27,

32, 49]. Various studies failed to draw the same conclusion regarding the possible association between GSTM1 deletion and distal CRC [17, 20, 21, 24, 26, 29, 35, 37-39, 42, 62, 65]. This may be due to the relatively small sample sizes in these studies, and different ethnicities, different high-risk gene frequencies and different sources of control subjects among these studies. Moreover, there was potential for misclassification of smoking status and tumor subset in our study. Smoking status and tumor subset were reported only in 2920 cases and 1594 cases among 8242 cases, respectively. This may also contribute to different results. Similar to previous meta-analyses, various limitations of our study should be taken into account. First, CRC is a consequence of the interaction of multiple risk factors, such as unhealthy diet, physical inactivity, gender, and age. However, owing to the limited data in the included studies, we were unable to make a more precise assessment by excluding those confounding factors. Furthermore, the pathogenesis of CRC is only partially understood, and researchers intend to explore the interactions of multiple genes encoding enzymes involved in the metabolism of carcinogens and the involvement of those interactions in CRC pathogenesis [66]. Second, in some of the subgroup analyses, the sample size seemed to be relatively small. Thus, the subgroup analyses may not have adequate power to detect true relationships. Finally, our meta-analysis only included published studies, which may potentially have biased the findings.

Overall, the updated meta-analysis demonstrated that the GSTM1 null genotype may contribute to CRC risk in the overall population. Owing to the limitations mentioned above, additional randomized controlled trials or larger epidemiological studies that are, well-designed are warranted to verify our findings.

Disclosure of conflict of interest

None.

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