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Review Article

The Association between GSTM1, GSTT1 Genetic Variants and Gastric Carcinoma Susceptibility in Chinese: A Systematic Review Article

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Abstract

Background: Glutathione S-transferases (*GSTs*) have been investigated as potential carcinoma susceptible genes. However, the relationship between GSTs (*GSTM1*, *GSTT1*) variants and gastric carcinoma (GC) risk has been controversial in Chinese population.

Methods: A comprehensive literature search strategy (PubMed, Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Wan fang Database, etc.) was launched. Crude odds ratios (ORs) and confidence intervals (95% CI) were applied to estimate the strength of the association.

Results: Significant associations between GSTs genetic polymorphisms and GC were evidenced under random-effects model (OR_{GSTM1}=1.56, 95% CI: 1.39 to 1.76, I^2=50.7%, P<0.0001; OR_{GSTT1}=1.24, 95% CI: 1.10 to 1.39, I^2=43.6%, P=0.014; $OR_{GSTM1\text{-}GSTT1}$=1.51, 95% CI: 1.26 to 1.81, I^2=59.7%, P=0.004). The pooled ORs were not qualitatively changed when any single study was omitted by sensitivity analysis.

Conclusion: Our results indicated an increased GC risk in Chinese population with *GSTM1* and *GSTT1* null genotype and *GSTM1-GSTT1* dual null genotype. Further multi-center studies are needed to investigate the gene-gene and gene-environment interactions on the susceptibility of GC.

Introduction

Gastric carcinoma (GC) is one of the most common malignant tumors and is the second leading cause of cancer-related death across the worldwide (1). GC is a major health issue in China (2); its incidence is high, accounts for over 40% of all new GC cases (3).

Studies involved in twins, familial clustering, and different ethnicities have identified that genetic factors contributed to GC susceptibility (4). Glutathione S-transferases (*GSTs*) family, known as phase II isoenzymes, has proved to be involved in detoxifying several carcinogens and plays a critical role in the deactivation of toxic and carcinogenic electrophile (5-7). The *GST* family included four gene subfamilies (*GSTA, GSTM, GSTT,* and *GSTP*), *GSTM1* and *GSTT1* arelocated in 1p13.3 and 22q11.23 in the human chromosome, and has been studied widely (8-11). Polymorphisms within *GSTM1* and *GSTT1* genes either decrease or abolish their enzyme activities (12). The most common variant of *GSTM1* and *GSTT1* genes is homozygous deletion (null geno-

type), which can detoxify several xenobiotics and lower the defense against oxidative stress (8, 13-14).

A meta-analysis involved in 46 studies observed evidence for GSTT1 null polymorphism and GC risk in East Asians and Indians, but not in Caucasian, and Middle Eastern and African populations (15). Another meta-analysis with 8,203 GC cases and 13,866 controls showed that GSTT1 null allele was associated with increased risk of GC in Europeans and Asians (16). Whereas, no statistical significance was observed for the GSTT1, GSTM1 genotypes and GC risk in Taiwanese (17). The above indicate that these associations vary in different populations.

Substantial studies have investigated the associations between *GSTM1* and *GSTT1* genetic polymorphisms and GC risk in Chinese population. However, the results have been controversial. Therefore, we performed a meta-analysis to explore the above association with increased sample size and statistical power.

Methods

Literature review

Two reviewers independently conducted a comprehensive literature search in PubMed, EMBASE, Web of science, Chinese Biomedical Database, Chinese National Knowledge Infrastructure and Wan fang Data, up to Apr 2016 without language restriction. Besides, we also searched two websites (http://www.baidu.com and http://scholar.google.com). The reference lists of available articles were also retrieved simultaneously. The following search strategies were used: ("glutathione s-transferase" or "GST" or "*GSTM1*" or "*GSTT1*") AND ("gastric" or "stomach ") AND ("cancer" or "carcinoma" or "tumo(u) r" or "neoplasm") AND ("China" or "Chinese" or "Taiwan"). When there was more than one article published, only the latest and /or the most comprehensive one would be adopted.

Inclusion and exclusion criteria

All inclusive studies should comply with the following criteria: 1) case–control or cohort studies; 2) the articles provided raw data or sufficient information to calculate odds ratios (ORs) with 95% confidence intervals (CIs); 3) if studies contained overlapping data, only the one with the largest sample size was included.

Exclusion criteria were: 1) not related case–control or cohort studies; 2) abstract, case report, review article, and other meta-analysis; and 3) studies that contained overlapping data.

Data extraction and synthesis

According to the inclusion criteria, relevant data were extracted from the included studies by two independent reviewers. Discrepancy was resolved by discussion among all reviewers. The following data were extracted: first author, years of publication, geographical location, study time, criteria of pathologic diagnosis, source of control, characteristic of cases and controls, genotype frequencies of null *GSTM1*, null *GSTT1* and dual null *GSTM1-GSTT1* in cases and controls (Table 1). Meanwhile, sub-group analyses based on geographical location, number of cases, source of control and test material were also performed.

Statistical analysis

1) ORs and 95% CIs were applied to evaluate the strength of associations between the GSTs and gastric carcinoma risk; 2) statistical heterogeneity was calculated by Q and I^2 statistics (18). The Q test and I^2 were used to evaluate the proportion of the total variation from heterogeneity (19), When *P* value of heterogeneity tests was ($P \leq 0.1$), a random-effect model was performed. Otherwise, a fixed-effect model was used (20). Heterogeneity was divided into high heterogeneity ($I^2 \geq 50\%$) and low heterogeneity ($I^2 < 50\%$); 3) in order to explore the potential heterogeneity, subgroup analysis were also performed by geographical location (Northeast China, North China, East China, Central China, South China, Southwest China, Northwest China, and Taiwan), number of cases (<100 vs. ≥100), and sources of control (population-based, hospital-based, mixed); 4) Sensitivity analysis was used to determine the stability of the results after removing one study at a time. Galbraith plot was also performed to identify the potential heterogeneity; 5)

The potential publication bias was assessed using Begg's funnel plot (21) and Egger's linear regression test (22), and $P<0.05$ was regarded as representative of statistically significant; and 6) all analyses were performed by STATA version 12.0 (Stata Corporation, College station, TX, USA), and all *P* values were two-sided.

Results

The selection and characteristics of studies

After a comprehensive search of the above databases, a total of 142 articles were identified, 46 irrelevant articles were excluded by reviewing their abstracts, 16 articles were excluded for overlapping data, 36 articles were excluded for meta-analysis, review, only cases and other populations, and other 7 articles were excluded due to unavailable information. Finally, the remaining 37 full-text publications (18-54) were used to evaluate the associations of *GSTM1* and *GSTT1* genetic polymorphisms with gastric carcinoma susceptibility (Fig. 1).

The characteristics of the included studies were shown in Table 1. There were 34 studies concerning about *GSTM1* and GC susceptibility (4841 cases and 7608 controls) (23-35,37,39-57,59), 23 articles about *GSTT1* (3865 cases and 5915 controls) (23,26,28-29,32-39,41,45,50-58), and 12 articles about both *GSTM1* and *GSTT1* (1577 cases and 2982 controls) (23,28,33,35,37,39,51,53-57).

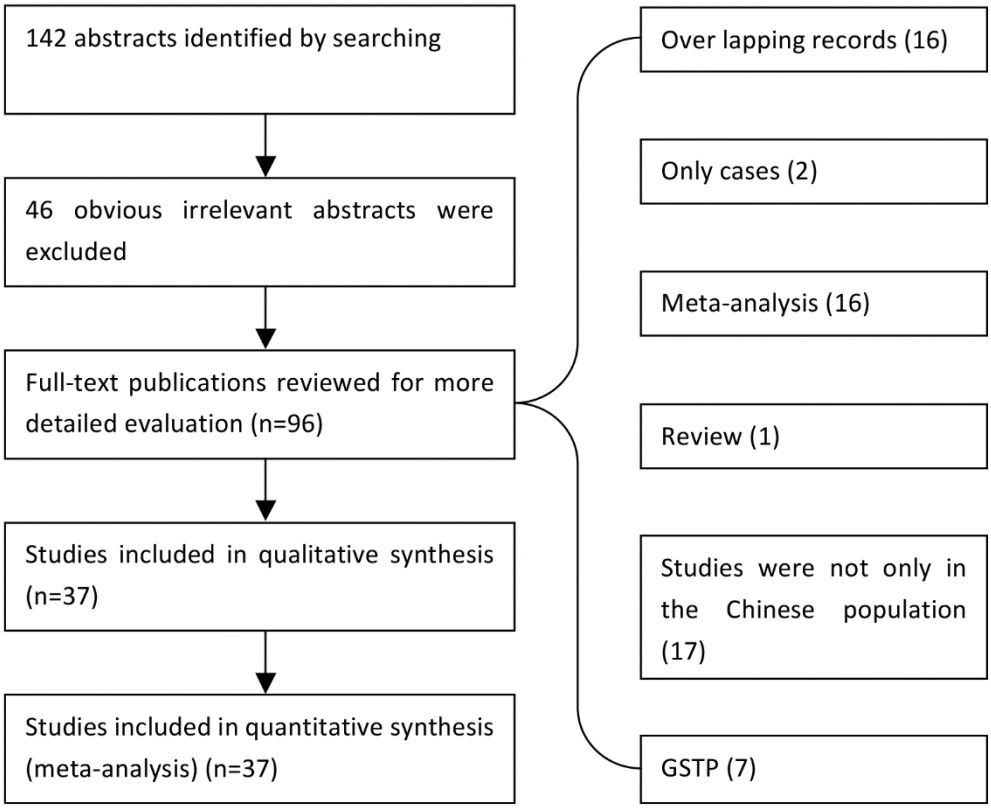

Fig. 1: Flow chart of study selection

In order to explore the potential heterogeneity, sub-group analyses concerning geographical location (Northeast China (24,25,27), North China (49), East China (23,26,28-33,35,38,39,41-43,45,46,48,50,52,53), Central China (36,37,39,40,54), South China (47,51,55,59), Southwest China (56), Northwest China (57,58), and Taiwan (34,44), case number (≥100 (29,31-34,37,41-48,50,52-56,58,59) and <100 (23-28,30,35,36,38,39,40,49,51,57).), and sources of control (population-based (23,25,26,28-33,35,35-38,40,43,46-49,51,53-59) and hospital-based (24,27,34,39,41,42,44,45,50,52)) were performed.

Results of Overall Meta-analysis

- ***GSTM1* null genotype with GC risk:** A total of 34 studies showed a significant association between the *GSTM1* null genotype and GC risk in Chinese population under random-effect model (OR=1.56, 95% CI: 1.39-1.76, I^2=50.7%, *P*<0.000) (Fig. 2a).
- ***GSTT1* null genotype with GC risk:** A total of 23 studies controls demonstrated that *GSTT1* null genotype was significantly related with GC risk in Chinese population under random-effect model (OR=1.24, 95% CI: 1.10 to 1.39, I^2=43.6%, *P*=0.014) (Fig. 2b).
- **2.3. Dual-null genotype of *GSTM1-GSTT1* with GC risk:** Dual-null genotype of *GSTM1-GSTT1* had a significant association with GC in Chinese population under random-effect model (OR=1.51, 95% CI: 1.26 to 1.81, I^2=59.7%, *P*=0.004) (Fig. 2c).

Results of Sub-group analysis

We did not detect significant increased risk for GC in either North or Taiwan in GSTM1 meta-analysis or in the East or Taiwan in GSTT1 meta-analysis. Cases number <100 had a higher risk than cases number ≥100 in both GSTM1 and GSTT1 meta-analysis. In addition, population-based studies had a higher risk than hospital-based studies in GSTM1 meta-analysis. The heterogeneity test demonstrated that studies from Taiwan were major sources of heterogeneity for *GSTM1* meta-analysis (I^2=71.2%).

In the analysis of the relationship between *GSTM1-GSTT1* genetic polymorphisms and GC risk, significant associations were found in South China, Northwest of China and hospital-based studies, however, we observed high heterogeneities in South China (I^2=71.4%).

Galbraith plot and sensitivity analysis

In this meta-analysis, Galbraith plot was used to identify the possible sources of heterogeneity. Three articles, two articles and two articles were identified as outliers by Galbraith plot in *GSTM1, GSTT1* and *GSTM1-GSTT1* meta-analysis, respectively. (Data not shown). After omitting those studies, the heterogeneity was reduced (OR_{GSTM1}=1.57, 95% CI: 1.41-1.76, *P*<0.001, I^2=39.4%; OR_{GSTT1}=1.29, 95% CI: 1.15 -1.43, *P*<0.001, I^2=30.6%; $OR_{GSTM1\text{-}GSTT1}$=1.46, 95% CI: 1.29-1.64, *P*<0.001, I^2=37.4%). Meanwhile, sensitivity analysis did not change the results of each meta-analysis (Fig. 3).

Potential publication bias

Begg's funnel plots and Egger's tests were applied to assess the potential publication bias for *GSTM1* meta-analysis (Fig. 4a and Fig. 4b), *GSTT1* meta-analysis (Fig. 4c and Fig. 4d), and dual-null genotype of *GSTM1-GSTT1* meta-analysis (Fig. 4e and Fig. 4f). The fail-safe number was taken to evaluate further the publication bias.

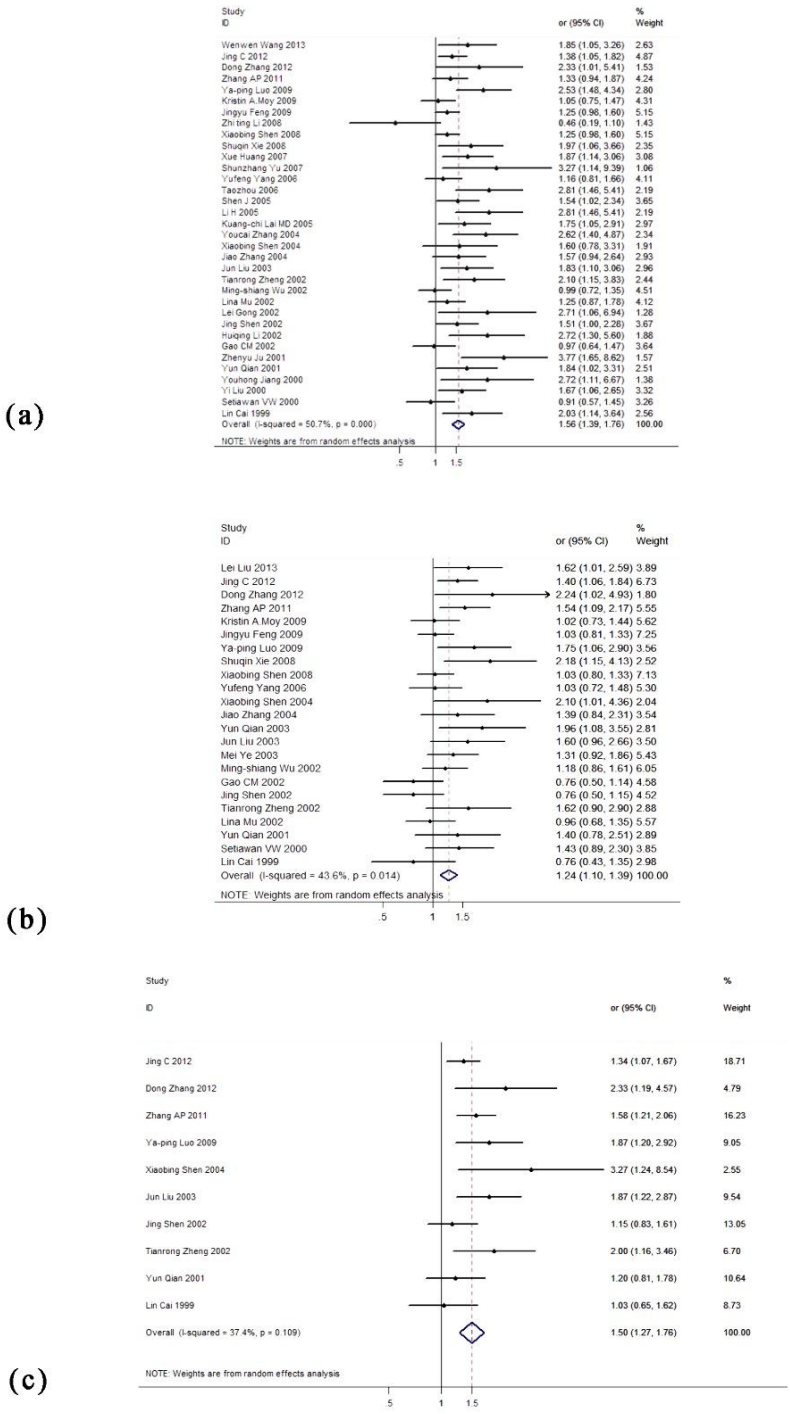

Fig. 2: (a) Forest plot for *GSTM1* meta-analysis; (b) Forest plot for *GSTT1* meta-analysis;(c) Forest plot for *GSTM1-GSTT1* meta-analysis

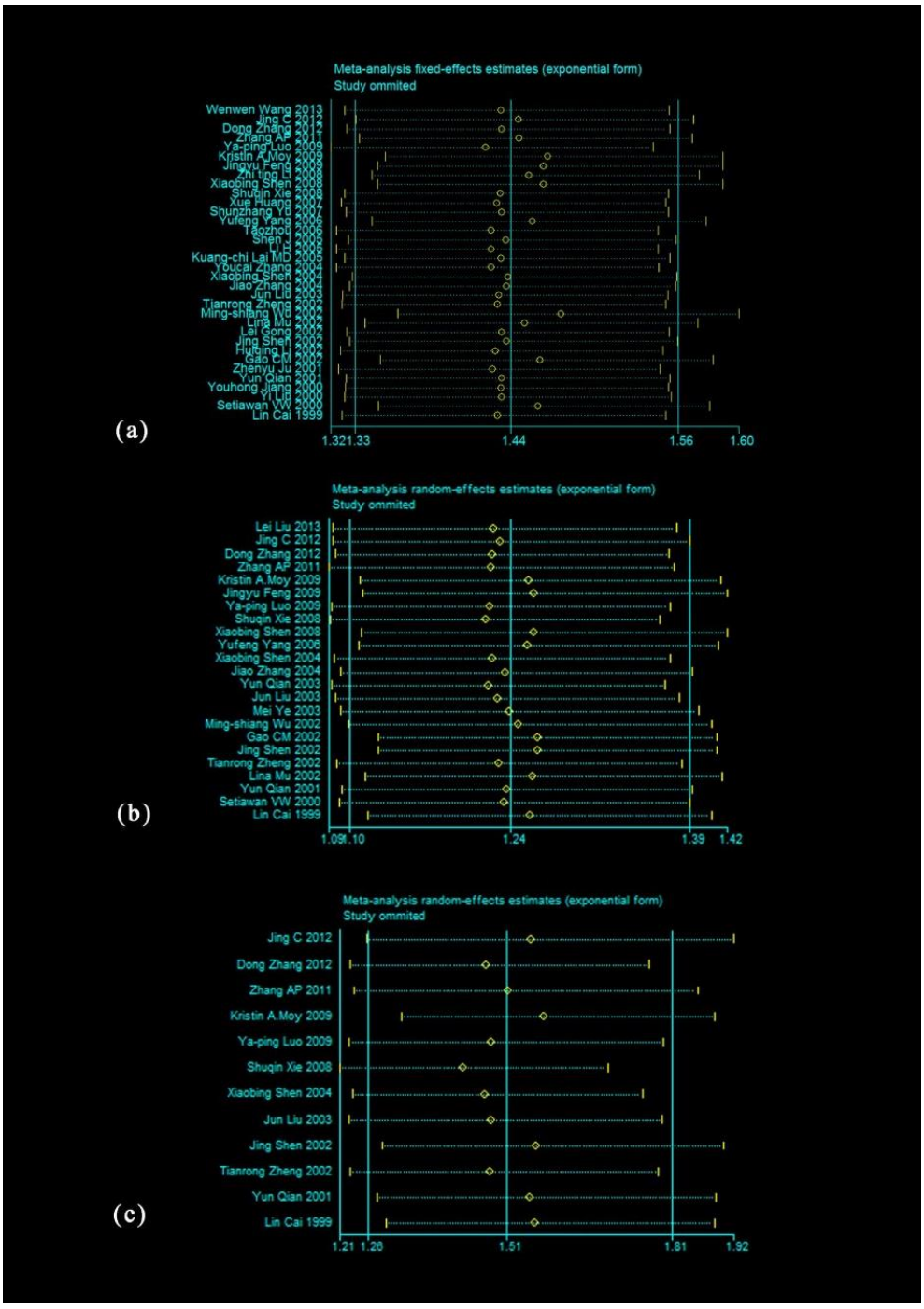

Fig. 3: (a) Sensitivity analysis for *GSTM1* meta-analysis; (b) Sensitivity analysis for *GSTT1* meta-analysis; (c) Sensitivity analysis for *GSTM1-GSTT1* meta-analysis

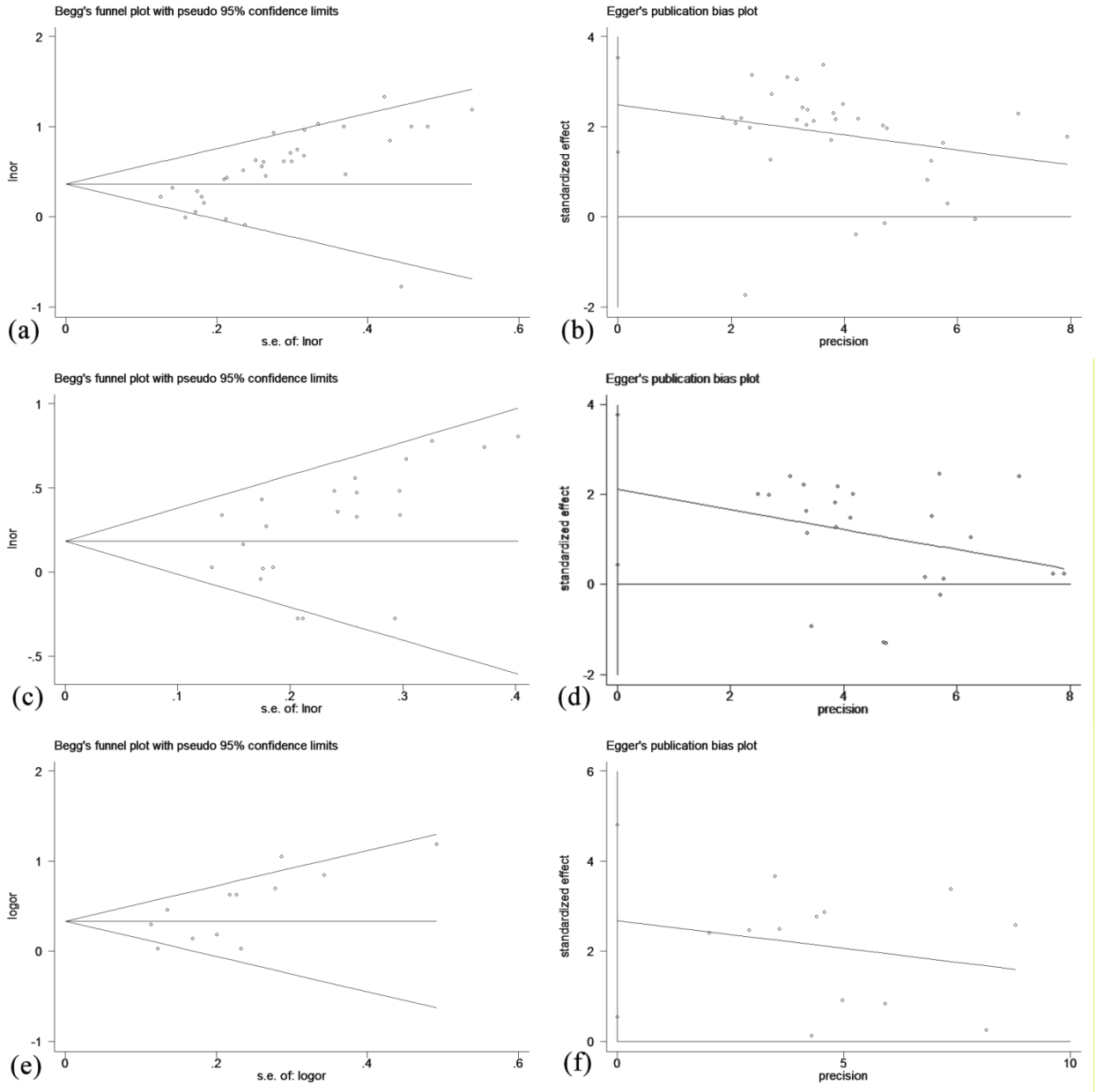

Fig. 4: Begg's funnel plot was used to detect potential publication bias qualitatively, and Egger's linear regression test was used to quantify the potential presence of publication bias. (a)(b) Publication bias for *GSTM1* meta-analysis. (c)(d) Publication bias for *GSTT1* meta-analysis. (e)(f) Publication bias for *GSTM1-GSTT1* meta-analysis.

Publication bias was evidenced (*GSTM1*: P_B<0.001, P_E<0.001; *GSTT1:* P_B=0.007, P_E=0.015; *GSTM1-GSTT1:* P_B=0.024, P_E=0.019). However, after we omitted the outliers' articles according to the Galbraith plot, no publication bias was observed by Egger's test in *GSTM1-GSTT1* meta-analysis.

The fail-safe number ($N_{fs0.05}$) was 1000 and 248 in *GSTM1* and *GSTT1* meta-analysis respectively, which indicated that if we want to turn the results, at least 1000 and 248 non-statistically significant studies should be further included in relevant meta-analysis. Therefore, our results were robust and reliable.

Discussion

The pooled and sub-group analysis identified a positive association between *GSTM1*, *GSTT1* and *GSTM1-GSTT1* genetic polymorphisms and GC susceptibility in Chinese population. This is consistent with previous studies. A meta-analysis showed homozygous deletion in *GSTM1* increased risk of GC in different ethnics (including Japanese, Chinese, Indians, Caucasians and Africans) (60).

However, significant heterogeneity was noticed. Studies from East China and Taiwan were the main heterogeneity for *GSTM1* meta-analysis. The eastern region is rich in seafood, which is typically high in salt for longer storage. Fujian, an eastern coastal region, is a representative high-risk area for GC. Inhabitants' diet includes dried shrimp sauce and pickled fish (48, 61). As well known, a high salt diet is a significant risk factor for the development of GC. The high osmotic pressure caused by dietary salt can damage the gastric mucosa, which will lead to extensive diffuse hyperemia, necrosis, hemorrhage etc. (62) and then accelerate the potential carcinogenicity of carcinogenic compounds. Meanwhile, studies in Chinese have confirmed that pickled food is rich in amine, which can synthesize a hard carcinogenic substance (N-nitroso compound) in the stomach. Thus, traditional Asian pickled vegetables have been classified as possible human carcinogen by the International Agency for Research on Cancer (IARC) (63, 64).

Furthermore, the population from East China, such as Fujian, Shanghai, and Southern Jiangsu, favors of sweet food. Available nutrition epidemiological studies have considered sugar as a vital risk factor for GC. Increasing daily sugar intake was responsible for the susceptibility of stomach cancer in both male and female in island residents (65). Diet with high sugar can damage the gastric mucosa, thus accelerate the absorption of carcinogenic substances (66).

To further explore the potential heterogeneity, we performed Galbraith plot analysis. In the *GSTM1* meta-analysis, three studies were identified as potential heterogeneous sources (27, 34, 49). These three studies with small sample size might contribute to potential bias. While in the *GSTT1* meta-analysis, two studies were spotted as outliers (29, 43), no statistical significant heterogeneity was observed after omitted those two studies (I^2=30.6%).

Due to the heterogeneity and publication bias, the following limitations should be claimed: 1) studies included in our meta-analysis were mainly hospital-based studies, which were not as representative as population-based studies; 2) our meta-analysis included few studies with relatively small sample size, which might contribute to potential publication bias; 3) the sample size included in our meta-analysis is not very large, which may not have sufficient statistical power to evaluate the relevant associations; 4) we did not assess the gene-gene and gene–environment interactions due to unavailable data; 5) we spotted publication bias, but the fail-safe number illustrated the impact of publication bias was negligible, and the conclusion was reliable.

Conclusion

The findings indicate that GSTs genetic polymorphisms are associated with the increased GC risk in Chinese. However, larger sample size and multi-center studies are needed to confirm our findings, and gene-gene and gene-environment interactions should be explored further in the future.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Table 1: Characteristics of the studies evaluating the effects of *GSTM1* and *GSTT1* polymorphisms on the risk of GC

No.	Study (ref.)	Area	Study time	[c]Pathologic diagnosis	Source of controls	Case group	Control group	Null *GSTM1* /Group number		Null *GSTT1* /Group number		Dual Null /Group number	
								case	control	case	control	case	control
[a]1	(59)	Hainan	2005-2010	ALL	Population	130 cases	138 controls	39/130	26/138				
[a]2	(58)	Ningxia (Hui)	2009.1-2012.3	ALL	Population	110cases(GCA,87 men,23women,mean age56.27±7.39 yr)	220 controls(154 men,66 women, mean age 58.80±7.43 yr)			49/110	73/220		
[b]3	(56)	Chengdu	2007.4-2011.4	ALL	Population	410cases	410 population controls matched by gender and age	240/410	207/410	236/410	202/410	131/410	98/410
[a]4	(57)	Ningxia (Hui)	2006.1-2010.10	ALL	Population	40cases(GCA,27 men,13women,mean age57.24±6.43 yr)	80 controls(46 men,34 women, mean age 56.77±7.21 yr)	30/40	45/80	19/40	23/80	14/80	12/80
[b]5	(55)	Southern (China)	2007.1-2011.1	ALL	Population	194 cases(age 40-75 yr)	412 controls(age 35-77yr)	105/194	194/412	114/194	198/412	67/194	90/412
[b]6	(53)	Shanghai	1986.1.1-2002.9	PARTIAL	Population	312cases	936 controls matched by date of birth (within 2 yr), date of biospecimen collection(within 1 month) and neighborhood of residence at recruitment. Individual matching by 1:3.	98/170	415/735	97/170	415/735	55/170	231/735
[a]7	(52)	Nanjing (Han)	NA	ALL	Hospital	374cases(273men,101 women, Mean age 61.15±12.61yr, rang 18-90 yr)	374 controls matched by residence, sex, age (with in 5 yr)	OR=1.251,(95%CI:0.976-1.604)c		OR=1.033,(95%CI:0.805-1.326)c			
[a]8	(54)	NA	2006.7-2007.8	NA	Population	123 cases(72 men, 51 women, mean age 55.2±10.6 yr)	129 controls(80 men,49 women, mean age 53.7±12.3 yr)	93/123	71/129	77/123	63/129	41/123	23/129
[a]9	(49)	Tangshan	2006.1-2007.10	NA	Population	42 cases (31 men, 11 women, age 58.9 yr, rang 42-71.)	42 controls matched by sex and age	18/42	26/42				
[a]10	(51)	Guangxi (Zhuang)	2006.8-2007.5	ALL	Population	70 cases(AC,55 men,15women, mean age 56.6±14.4 yr, rang 27-84.)	100 controls (72 men, 28 women, mean age 53.3±12.4 yr, rang 23-84.)	39/70	39/100	48/70	50/100	28/70	14/100
[a]11	(50)	Nanjing (Jiangsu, Han)	NA	ALL	Hospital	503 cases (366 men, 137women,mean age:61.60±12.25yr, rang 21-90)	503 controls matched by residence ,sex, age(within 5 yr)	245/503	217/503	219/503	215/503		
[a]12	(47)	Guangxi (Han, Zhuang)	2005.7-2006.11	ALL	Population	121cases(AC,92 men,29women,mean age:52.66±13.35 yr, rang 34-75, 67Zhuang people,	138 controls(106 men,32 women, mean age 49.6±14.31 yr, rang 28-72,76 Zhuang people,62 Han people)	66/121	54/138				

						54 Han people)						
[a]13	(48)	Changle (Fujian)	1996-1998	ALL	Population	101 cases	101 controls matched by residence ,sex, age(within 3 yr)	OR=3.27(95%CI:1.14-9.39)c				
[a]14	(46)	Shang-dong (Han)	NA	ALL	Population	100 cases	62 controls	67/100	26/62			
[a]15	(45)	Nanjing (Jiangsu, Han)	NA	ALL	Hospital	244 cases (177men, 67 women, Mean age 60.22±11.77 yr, rang 40-70 .)	244 controls matched by residence, sex, age(within 5 yr)	117/244	108/244	110/244	108/244	
[b]16	5(44)	Taiwan	2000.1-2002.12	ALL	Hospital	123 cases(AC)	121 unrelated healthy individuals from this hospital	73/123	55/121			
[b]17	(42)	Shang-dong	1998.1-2000.1	ALL	Hospital	102 cases(86 males and 16 females)	62 controls(33 males and 29 females) had normal gastrointestinal mucous membrane	67/100	26/62			
[b]18	(43)	Yang-zhong (Han)	1997.1-1998.12	ALL	Population	114 cases(76 men,38 women, age 59.4±9.9 yr)	693 controls(290 case's siblings(150 men,140women),403non-blood relatives(160 men,243 women))	71/111	361/675			
[a]19	(40)	Hubei(Han)	NA	ALL	Population	72cases(Gastric cardiacadenocarcinoma, GCA.49 men, 23women, age 55.2 yr,rang31-70.7 Early stage,65advanced stage.11withhigh differentiation,35 With middle differentiation, 26 were with low differentiation.	114 controls(78 men,36 women, age 53.8 yr, rang 25-73	44.997/72	53.039/114			
[a]20	(39)	Nanjing	2002-2003	ALL	Hospital	60cases(age58±11.9 yr,44men,16 women)	60 controls matched by age(±5 yr),sex, ethnicity, residence and residence time	31/60	24/60	37/60	26/60	OR=3.27(95%CI:1.24-8.54)c
[a]21	(41)	Nanjing (Jiangsu)	2002.5-2003.12	ALL	Hospital	121 cases(87 men, 34 women, mean age 59.65±12.53yr, rang 40-70.)	121 controls matched by ethnicity, residence , residence time, sex, age (within 5 yr)	54/121	41/121	64/121	54/121	
[a]22	(38)	Jintan, Huaian (Jiangsu)	NA	ALL	Population	90 cases	90 controls matched by sex, ethnicity, residence, age (within 5 yr)			54/90	39/90	

[a]23	(37)	Hubei	NA	ALL	Population	127cases(AC,39 early stage,88advanced stage.76intestinal type,51 diffuse type)	114 controls	78/127	53/114	76/127	55/114	48/127	23/114
[a]24	(36)	Hubei(Han)	NA	ALL	Population	56cases(AC,42 men,14women, mean age 57.6, rang 22-79.)	56 controls matched by sex(39 men,17 women),age(mean age 58.0,rang 26-86)			33.992/56	25.984/56		
[b]25	(34)	Taiwan	1996-1999	ALL	Hospital	356cases(AC,218 men,138women),age 62.0±13.3(rang 25-87)	278 unaffected controls(156 men,122 women),age 61.6±13.1(rang 22-86)	173/356	136/278	181/356	130/278		
[b]26	(29)	Huaian (Jiangsu)	1987-2000.12	ALL	Population	153 cases(ones were from hospital aged 40-81 yr, the others were from the regional cancer registry)	223 controls matched by sex, ethnicity and age	90/153	133/223	71/153	119/223		
[a]27	(31)	Shang-dong	1998.1-2000.1	ALL	Population	102 cases	62 controls	OR=2.72,(95%CI:1.3-5.6)c					
[a]28	(33)	Yang-zhong	1997.1-1998.12	ALL	Population	112 cases	675 controls	71/112	361/675	43/110	309/675	30/107	161/662
[a]29	(30)	An-hui(Han)	NA	ALL	Population	32cases(19men, 13 women, age 36-74 yr)	88 controls(46 men,42 women, age 32-79 yr)	25/32	50/88				
[a]30	(35)	Fuzhou (Fujian)	NA	PARTIAL	Population	92 cases	92 controls matched by ethnicity, residence, age (within 5 yr)	64/92	48/92	49/92	38/92	30/92	15/92
[a]31	(32)	Taixing (Jiangsu)	NA	NA	NA	197 cases	393 controls	128/197	235/393	94/197	192/393		
[a]32	(27)	Shengyang	1999.9-1999.12	ALL	Hospital	50 cases	50 controls matched by age(±5 yr),sex, ethnicity	33/50	17.05/50				
[a]33	(28)	Jintan (Jiangsu)	1998.4-1999.7	PARTIAL	Population	89 cases	94 controls matched by age(±5 yr),sex	55/89	44/94	51/89	46/94	34/89	30/94
[b]34	(26)	Yang-zhong (Jiangsu)	1995.1.1-1995.6.30	ALL	Population	91 cases	429 controls	42/87	212/419	44/81	190/418		
[a]35	(25)	NA	NA	ALL	Population	99 cases	364 controls	63/99	186/364				
[a]36	(24)	Benxi	1999.9-1999.12	ALL	Hospital	41 cases	41 controls matched by ethnicity, sex, age(within 2 yr)	24/41	14/41				
[a]37	(23)	Changle (Fujian)	NA	ALL	Population	95 cases	94 controls matched by ethnicity, residence, sex, age(within 3 yr)	60/95	43/94	41/95	47/94	27/95	26/94

[a] Articles published in Chinese; [b]: Articles published in English;/ [c] Pathologic diagnosis: ALL: Gastric cases were confirmed by pathologic diagnosis; PARTIAL: part of Gastric cases were confirmed by pathologic diagnosis; NA: relative data were not available in original studies.