Int J Clin Exp Med 2016;9(7):13268-13280
www.ijcem.com /ISSN:1940-5901/IJCEM0021837

Review Article

Genetic polymorphisms of glutathione S-transferase (GSTM1, GSTT1 and GSTP1) with esophageal cancer risk: a meta-analysis

Yabiao Zheng[1*], Xiaoling Ni[2*], Yang Jiao[3], Fangyuan Shen[4], Hua Jiang[5], Minghua Wang[4], Guohua Hu[2], Shiheng Tao[1]

[1]Bioinformatics Center, Northwest A&F University, Yangling, Shaanxi, P. R. China; [2]Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, P. R. China; [3]State Key Laboratory of Military Stomatology, School of Stomatology, The Fourth Military Medical University, Xi'an, Shaanxi, P. R. China; [4]Department of Biochemical and Molecular Biology, Medical College, Soochow University, Suzhou, Jiangsu, P. R. China; [5]Internal Medicine, The Second People's Hospital of Xiangcheng District, Suzhou, Jiangsu, P. R. China. [*]Equal contributors.

Received December 14, 2015; Accepted May 19, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Glutathione S-transferases (GSTs) are important phase II enzymes and play a crucial role in the elimination of electrophilic carcinogens. Numerous studies have investigated the association between *GST*s gene variations with esophageal carcinoma risk, but a final conclusion has not been made. Then we searched PubMed, Web of Knowledge and China National Knowledge Infrastructure (CNKI) for relevant articles until June, 2015. We totally extracted and analyzed the pooled data form 43 published articles about *GSTM1* null genotype, *GSTT1* null genotype and *GSTP1* Ile105Val polymorphism (rs1695) with esophageal carcinoma risk. *GSTM1* null genotype and *GSTT1* null genotype could significantly increase esophageal cancer risk (OR=1.27, 95% CI=1.11-1.44; OR=1.12, 95% CI=1.05-1.39 respectively). The subgroup analysis showed that the two mutations most likely contribute to esophageal squamous cell carcinoma susceptibility. And Asians carrying the homozygous null genotype were at higher esophageal cancer risk than Caucasians. While *GSTP1* Ile105Val variants showed no significant effect to esophageal cancer risk. This meta-analysis provides evidence to support that *GSTM1* and *GSTT1* null genotypes could increase esophageal cancer risk, which would benefit the diagnosis and prevention of esophageal cancer.

Keywords: Esophageal cancer, GSTM1, GSTT1, GSTP1, meta-analysis

Introduction

The malignant tumors, accounting for one-fourth of all deaths, is a very serious public health issue throughout the world. Among the malignant tumors, esophageal cancer, a kind of malignant digestive tumor, is the sixth most common malignancy worldwide, and the incidence and mortality rates of esophageal cancer have increased in recent years with 5-year survival rate less than 10% [1]. Although the mechanism of esophageal cancer is still unclear, studies revealed that the incidence of esophageal cancer has obvious regional distribution difference and patients have some familial aggregation, indicating that environmental and genetic factors have impacts on the occurrence of esophageal cancer.

Glutathione S-transferases (GSTs) are important phase II enzymes and mainly eliminate electrophilic carcinogens in the body through catalyzing the conjugation with glutathione [2]. Glutathione S-transferase M1 (*GSTM1*), T1 (*GSTT1*) and P1 (*GSTP1*) are the main members among *GST*s gene family, all of which have high expression in esophageal mucosa in humans [3]. The genes of *GSTM1* and *GSTT1* mainly present the entire gene deletion variants and *GSTP1* gene presents an A313G substitution (rs1695) resulting Ile105Val [4-6]. Though numerous studies have examined these mutations within *GST*s and esophageal cancer risk, these results were inconclusive and inconsistent because of the limitation of sample size for individual study and different regions of sample population, thus the exact influences of these

variants have not been fully understood. A meta-analysis which incorporates all these case-control studies and could draw an overall conclusion should be conducted. With the publications of some new case-control studies, it is urgent to perform a new and comprehensive meta-analysis. In the current meta-analysis using the large-scale integration of data, we aim to illuminate the effect of *GSTM1* and *GSTT1* deletion mutations (homozygote with whole deletion of genes), and *GSTP1* Ile105Val polymorphism within esophageal cancer development.

Materials and methods

Identification of eligible studies

A comprehensive literature search in the following databases: PubMed (www.ncbi.nlm.nih.gov/pubmed), Web of Science (www.webofknowledge.com) and China National Knowledge Infrastructure (CNKI, www.cnki.net) was conducted. These key words were used in combination to search published studies before June 2015: 'esophageal cancer', 'esophageal carcinoma', 'glutathione S-transferases', '*GSTM1*', '*GSTT1*', '*GSTP1*', 'null genotype' and 'polymorphism'. The key words were used in Chinese in the CNKI database. References of the retrieved articles were also checked to identify more relevant studies.

The further literature selection was subject to such criteria: (I) studies should be case-control designed; (II) cases are clearly diagnosed with esophageal cancer and controls are cancer-free; (III) studies should contain available population data about genotype distributions of *GSTM1*, *GSTT1* or *GSTP1* gene mutations. When two or more studies conducted in the same project or research institution have overlapping data, the latest study or the study involving the largest population was selected and included in our analysis.

Data extraction

The data were carefully extracted from all the eligible studies independently by two investigators. Only the data which they reached an agreement on were used in the following analysis. For each study, the following data were collected: the first author's name, the ethnicity of the study population, cancer type, the publication year, the publication language, the number of cases and controls, and corresponding genotype distribution. As many studies didn't take environmental factors into account or the definitions of exposed environmental factors in these studies were not consistent which could cause great heterogeneity in the meta-analysis, so the environmental effects weren't collected and we didn't bring environmental factors into analysis.

Statistical analysis

For *GSTP1* Ile105Val polymorphic site, we first tested the Hardy-Weinberg equilibrium (HWE) of genotype distribution in control group for each article using χ^2 test. The associations between these variants and esophageal cancer risk were measured using odds ratio (OR) with 95% confidence interval (95% CI). As *GSTP1* Ile105Val mutation has three genotypes in population, we then evaluated the associations in three genetic models including dominant model (W for major allele, V for minor allele; W/W vs. W/V+V/V), recessive model (W/W+W/V vs. V/V) and allelic model (W vs. V). Heterogeneity among these studies was checked by the Q-test [7]. *P*-value less than 0.1 for Q-test indicates the existence of significant heterogeneity among the studies, then the summary OR was calculated through the random effect model. Otherwise, the fixed effect model was used.

The sensitivity analysis and stratified analysis were further performed. The sensitivity analysis is a method that can find which included studies will cause the greatest heterogeneity and avoid a single study causing great deviation to the overall results. The sensitivity analysis was conducted by sequentially excluding each study and performing meta-analysis on other studies to observe whether there is great deviation. In the stratified analysis, these studies were divided into subgroups according to participants' ethnicity (Caucasians and Asians) and cancer subtypes (esophageal squamous cell carcinoma, ESCC and esophageal adenocarcinoma, EAC), respectively, aiming to examine the heterogeneity and the genetic effect in each subgroup.

Finally, funnel plot and Egger's linear regression test were used to evaluate potential publication bias. *P* value for Egger's test below 0.05

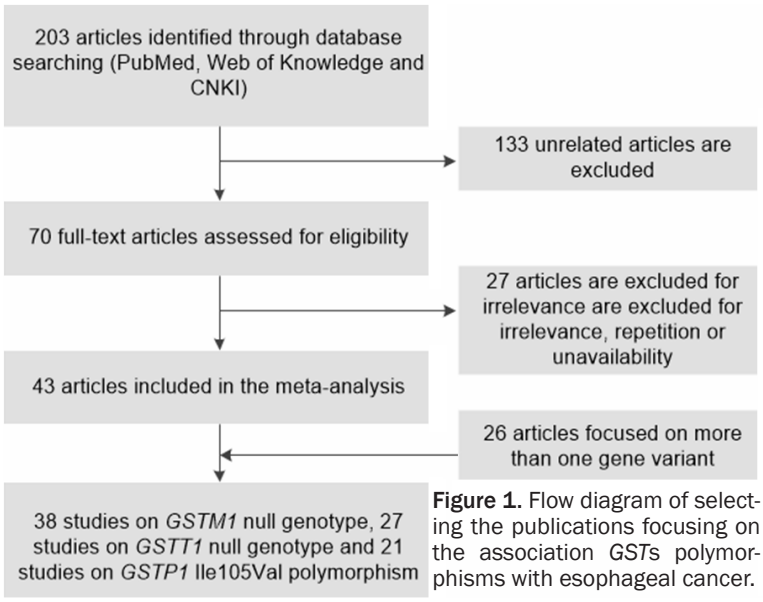

Figure 1. Flow diagram of selecting the publications focusing on the association *GST*s polymorphisms with esophageal cancer.

was considered statistically significant and there was publication bias among the studies. All statistical tests were performed with Review Manager Version 5.2 (Cochrane Collaboration) and R (version 2.15.2).

Results

Study characteristics

202 articles concerning *GST*s and esophageal cancer were first retrieved through computerized literature search. We excluded 133 irrelevant articles through reading abstracts and then abandoned 27 articles because of unrelated, duplicated or unavailable data after reviewing full texts. Finally, a total of 43 articles were acquired [8-44]. The flow diagram of literature search was given in **Figure 1**. The characteristics of the studies in the meta-analysis are presented in **Table 1**. These studies were carried out between 1997 and 2015, most of which were conducted among Asians and Caucasians. Many articles concentrated on more than one mutation among *GST* gene families or incorporated with both ESCC and EAC types, so we treated these articles as separate studies in subgroup analysis. In total, 38 studies were focused on the association between *GSTM1* null genotype and esophageal cancer, 27 studies on *GSTT1* null genotype and 21 studies on *GSTP1* Ile105Val polymorphic site.

GSTM1 null genotype and esophageal cancer risk

The overall meta-analysis showed that *GSTM1* null genotype could significantly increase esophageal cancer risk (OR=1.27, 95% CI=1.11-1.44) with high heterogeneity (*P*-value < 0.10) in the random effects model (**Figure 2**). The overall result was stable and randomly excluding one study couldn't bring great deviation to the overall result through the sensitivity analysis (**Figure 3**). The subgroup analyses showed that *GSTM1* null genotype could increase ESCC risk with the combined OR being 1.19 (95% CI=1.02-1.39) in the random effect model from 21 studies. While for EAC subgroup, the result was insignificant (OR=1.00, 95% CI=0.83-1.20). According to races, *GSTM1* null genotype exerted different influences on esophageal cancer risk between the two populations. The null genotype could increase esophageal cancer risk among Asians (OR=1.31, 95% CI=1.11-1.55), whereas the effect was null among Caucasians (OR=1.00, 95% CI=0.84-1.19). The detailed data were shown in **Table 2**.

The funnel plot and Egger's test were carried out to assess publication bias (**Figure 4A**). In the meta-analysis, the publication bias was not evident as the funnel plot was approximately symmetrical and the Egger's test (*P*-value=0.14) also confirmed the result.

GSTT1 null genotype and esophageal cancer risk

27 case-control studies about *GSTT1* null genotype were collected and included in the meta-analysis. The overall result has shown that *GSTT1* null genotype could significantly increase esophageal cancer risk (OR=1.22, 95% CI=1.05-1.41) (**Figure 5**). And the sensitivity analysis proved that the result is robust and reliable (**Figure 6**).

Subgroup analyses stratified by histology and ethnicity were further conducted and the

Table 1. Characteristics of eligible studies on the polymorphisms of *GST*s and esophageal cancer risk

Study	Year	Ethnic group	Cancer type	Published language	GSTM1 (Case/Control)		GSTT1 (Case/Control)		GSTP1 Ile105Val (Case/Control)			*P*-value for HWE
					Present	Null	Present	Null	Ile/Ile	Ile/Val	Val/Val	
Hori H	1997	Asians	ESCC	English	53/41	41/29						
Morita S	1997	Asians	ESCC	English	30/77	23/55						
Nimura Y	1997	Asians	EC	English	42/74	47/63						
Lin DX	1998	Asians	EC	English	25/24	20/21	26/22	19/23	29/22	12/11	1/3	0.656
Morita S	1998	Asians	ESCC	English					61/113	5/48	0/3	0.714
Lieshout EM	1999	Caucasians	EC[a]	English	17/119	17/128	28/198	6/49	10/146	21/89	3/12	0.946
			EAC		9/119	12/128	17/198	4/49	5/146	15/89	1/12	
			ESCC		8/119	5/128	11/198	2/49	5/146	6/89	2/12	
Shao GZ	2000	Asians	ESCC	Chinese	39/56	68/55						
Tan W	2000	Asians	ESCC	English	104/74	46/76	90/91	60/59	93/83	48/55	9/8	0.960
Gao CM	2002	Asians	EC	English	35/90	106/133	67/104	74/119				
Shi Yun	2002	Asians	EC	Chinese	31/69	67/51						
Yokoyama A	2002	Asians	ESCC	English	131/313	103/321						
Casson AG	2003	Caucasians	EAC	English	19/20	26/25	37/33	8/12	19/26	22/12	4/7	0.063
Ribeiro P	2003	Mixed	EAC	English	13/42	19/26	26/53	6/15				
Wang LD	2003	Asians	ESCC	English	35/19	27/19	28/18	34/20	29/24	30/13	3/1	0.886
Abbas A	2004	Caucasians	EC[a]	English	29/61	39/59	56/85	14/30	31/59	33/56	6/9	0.682
			EAC		13/61	12/59	25/85	1/30	10/59	12/56	3/9	
			ESCC		16/61	27/59	31/85	13/30	21/59	21/56	3/9	
Roth MJ	2004	Asians	ESCC	English	89/309	41/145	54/211	77/243	86/283	38/142	7/29	0.163
Wang AH	2004	Asians	EC	English	53/57	74/44						
Han YB	2005	Asians	ESCC	Chinese	43/51	46/48						
Yin LH	2005	Asians	EC	Chinese	37/45	69/61	60/55	46/51				
Cai L	2006	Asians	ESCC	English					143/265	58/116	3/12	0.987
Casson AG	2006	Caucasians	EAC	English	22/41	34/54	42/80	14/15	18/40	27/44	11/11	0.978
Jain M	2006	Asians	EC[a]	English	50/86	35/51	62/100	23/37	50/72	27/56	8/9	0.912
			EAC		4/86	5/51	6/100	3/37	4/72	4/56	1/9	
			ESCC		46/86	30/51	56/100	20/37	46/72	23/56	7/9	
Lu XM	2006	Asians	ESCC	English	72/344	44/310						
Dong CX	2007	Asians	EC	Chinese	44/69	76/51						
Murphy	2007	Caucasians	EAC	English					83/86	100/112	24/25	0.441
Rossini A	2007	Mixed	ESCC	English	74/153	51/99	110/192	15/60	42/116	65/108	18/28	0.931
Wideroff	2007	Mixed	EAC	English	30/87	37/121	59/173	8/35	32/91	23/94	12/21	0.901
Deng J	2008	Asians	EC	Chinese	42/89	45/73	36/75	51/87				
Li Y	2008	Asians	ESCC	Chinese	48/70	77/55						
Zhang LW	2009	Asians	ESCC	Chinese			31/39	57/33				
Zendehdel K	2009	Caucasians	EC[a]	English	87/230	85/239	150/394	22/76	70/208	84/207	18/38	0.399
			EAC		52/230	43/239	80/394	15/76	44/208	42/207	8/38	
			ESCC		35/230	42/239	70/394	7/76	26/208	42/207	10/38	
Ji R	2010	Asians	ESCC	Chinese	78/127	111/98	91/122	98/94				
Li DP	2010	South Africans	ESCC	English	206/200	133/80	125/178	113/102	90/106	111/134	37/40	0.975
Liu R	2010	Asians	ESCC	English	43/65	54/32	34/57	63/40	66/61	29/27	0/3	0.999
Malik	2010	Asians	EC	English	67/116	68/79	110/146	25/49	72/111	48/75	15/9	0.712
Moaven O	2010	Asians	ESCC	English	83/78	65/58	112/105	36/31	84/74	50/54	14/8	0.903
Matejcic M	2011	South Africans	ESCC	English			375/648	153/228	148/245	267/433	139/224	0.497
Chen Y	2012	Asians	EC	Chinese	31/96	68/90						
Gao P	2012	Asians	EC	Chinese	18/35	22/45	17/56	23/24				
Dura P	2013	Caucasians	EC[a]	English	204/273	228/318	335/463	97/128	167/246	199/261	56/84	0.550
			ESCC		48/273	57/318	87/463	18/128	48/246	42/261	15/84	
			EAC		156/273	171/318	248/463	79/128	119/246	157/261	41/84	
Sharma A	2013	Asians	EC	English	186/297	129/139	233/373	82/63				
Talukdar FR	2013	Asians	ESCC	English	68/90	44/40	66/93	46/37				
Makhdoomi	2015	Asians	ESCC	English	328/328	164/164	306/367	186/125				

EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; HWE, Hardy-Weinberg equilibrium test; [a]Articles including both types of esophageal cancer: EAC and ESCC.

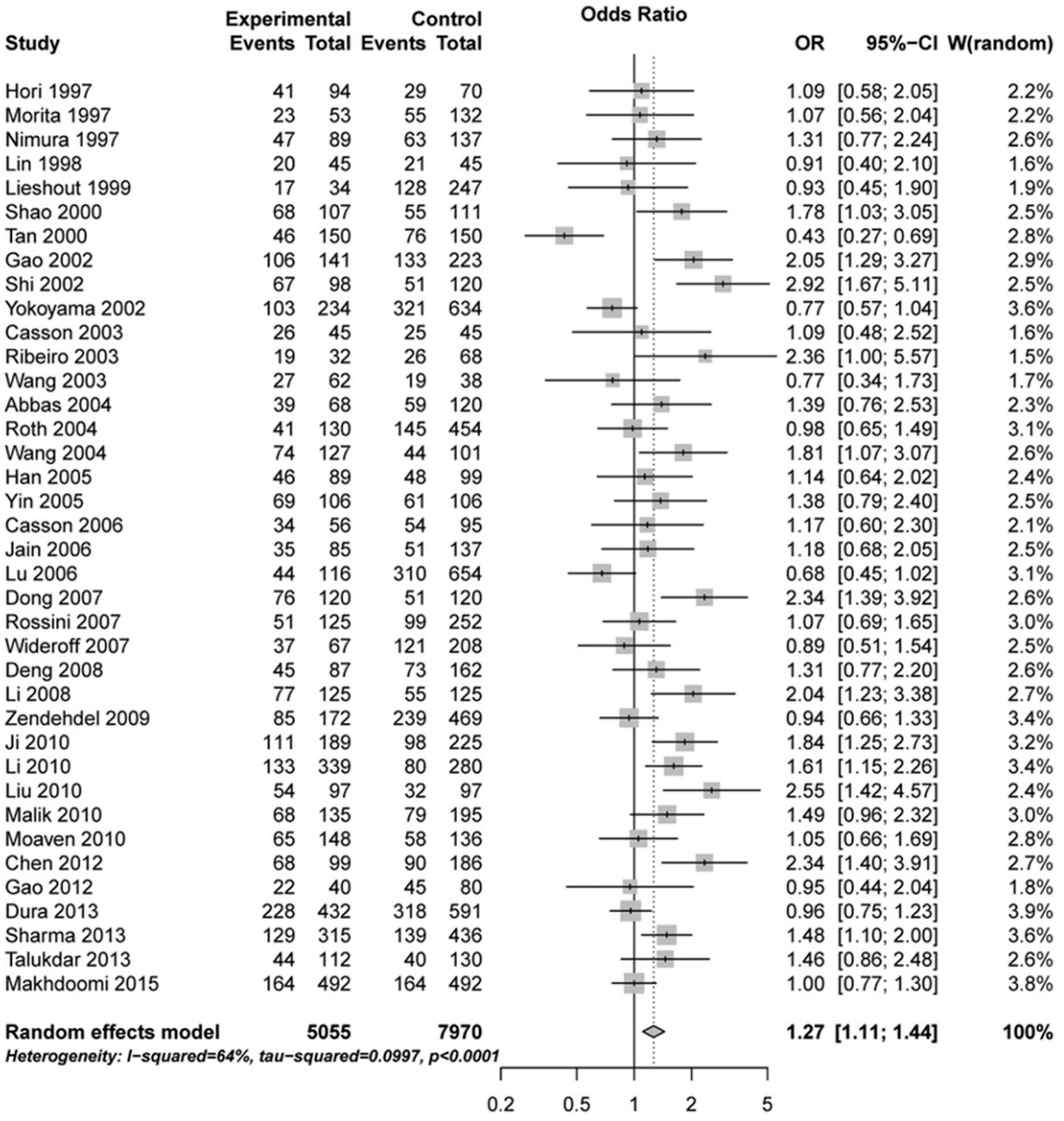

Figure 2. Forest plot of the meta-analysis for *GSTM1* null genotype and esophageal cancer susceptibility. Grey boxes represent the ORs of individual studies, and horizontal lines represent the 95% CI. The diamond is the overall OR.

results of subgroup analysis were summarized in **Table 3**. The combined OR of *GSTT1* null genotype with ESCC was 1.30 (95% CI=1.10-1.54). And *GSTT1* null genotype significantly increased esophageal cancer in Asians (OR=1.33, 95% CI=1.10-1.61), while the null genotype has null effect on Caucasian subgroup (**Table 3**). At last, the funnel plot and the Egger's test (*P*-value=0.22) revealed that there was no publication bias (**Figure 4B**).

GSTP1 Ile105Val polymorphism and esophageal cancer risk

GSTP1 Ile105Val mutation data were available from 21 studies containing 3108 cases and 5208 controls. The genotype distribution of controls from all studies were in Hardy-Weinberg equilibrium (*P*-value > 0.05). The result of *GSTP1* Ile105Val polymorphic site and esophageal cancer risk was presented in **Table 4**.

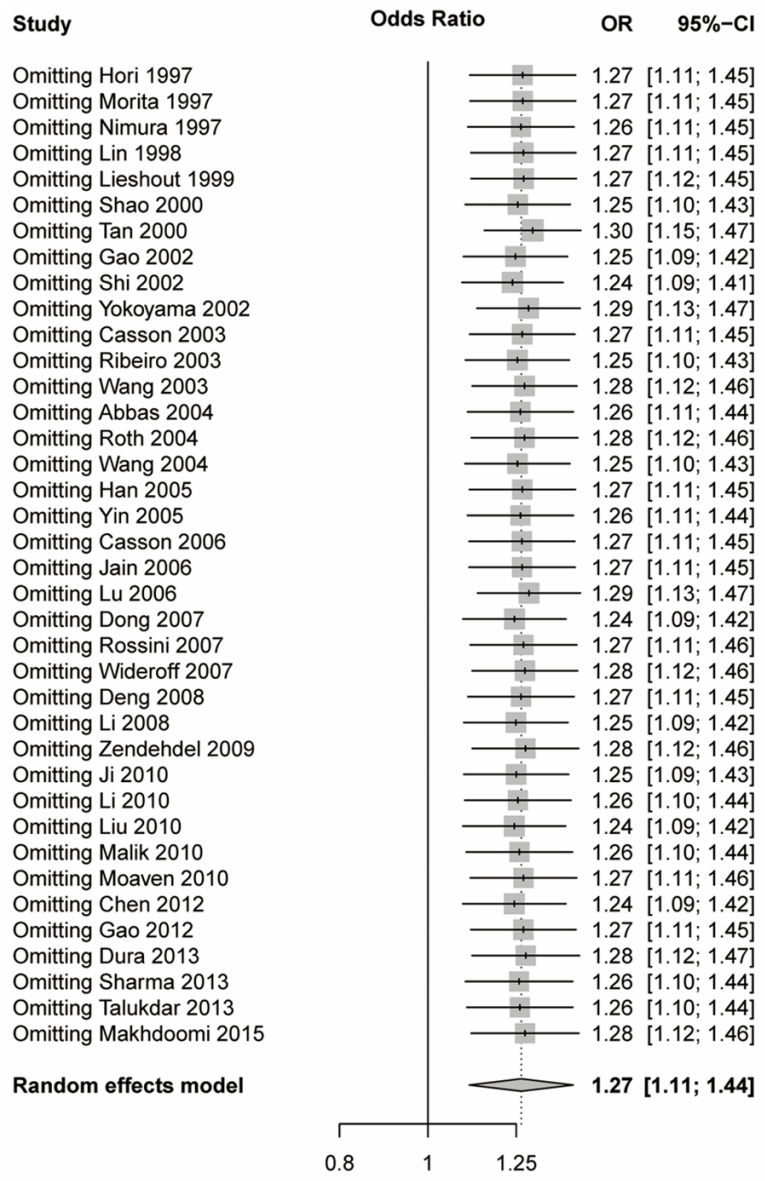

Figure 3. Sensitivity analysis for the studies of *GSTM1* null genotype and esophageal cancer risk.

Table 2. Meta-analysis of *GSTM1* null genotype with esophageal cancer risk

GSTM1 null genotype	Number of studies	Sample size (cases/controls)	OR (95% CI)	*P*-value of Q-test
Overall	38	5055/7970	1.27 (1.11-1.44)	0.000
Cancer Types				
ESCC	21	2826/5493	1.19 (1.02-1.39)	0.001
EAC	9	677/1980	1.00 (0.83-1.20)	0.549
Ethnic Groups				
Asians	28	3685/5595	1.31 (1.11-1.55)	0.000
Caucasians	6	807/1567	1.00 (0.84-1.19)	0.890

There were no significant associations between *GSTP1* Ile105Val mutation and esophageal cancer under three genetic models including the dominant, recessive and allelic models, respectively.

In the ESCC and EAC subgroup analyses including 15 studies and 9 studies respectively, *GSTP1* Ile105Val mutation has null effect on cancer risk. When it came to the subgroup analysis according to ethnicity, there were also no significant associations in the subgroups concerning Asians and Caucasians (**Table 4**).

The shapes of funnel plot and *P*-values of Egger's test (dominant model, *P*-value= 0.91; recessive model, *P*-value=0.94; allelic model, *P*-value=0.86) indicated no obvious publication bias existing (**Figure 7**).

Discussion

In the present study, we conducted the meta-analysis using the comprehensive published data and explored the effect of *GSTM1* null genotype, *GSTT1* null genotype and *GSTP1* Ile105Val polymorphism on esophageal carcinoma susceptibility. A total of 43 articles were incorporated into this analysis, which has been the largest scale meta-analysis concerning *GST*s so far.

Glutathione S-transferases regulate some metabolic pathways and prevent damage from a variety of carcinogens and environmental toxins that can lead cancer development [2]. GSTM1 and GSTT1 are the main types of GSTs. The whole deletion of these two

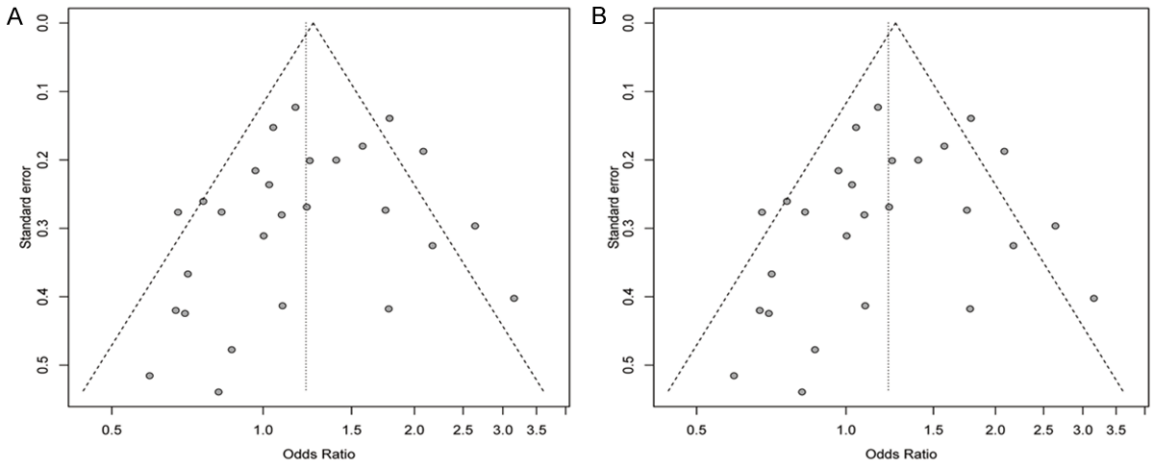

Figure 4. Funnel plot for publication bias of *GSTM1* and *GSTT1* polymorphisms and esophageal cancer risk. A. *GSTM1* polymorphism. B. *GSTT1* polymorphism.

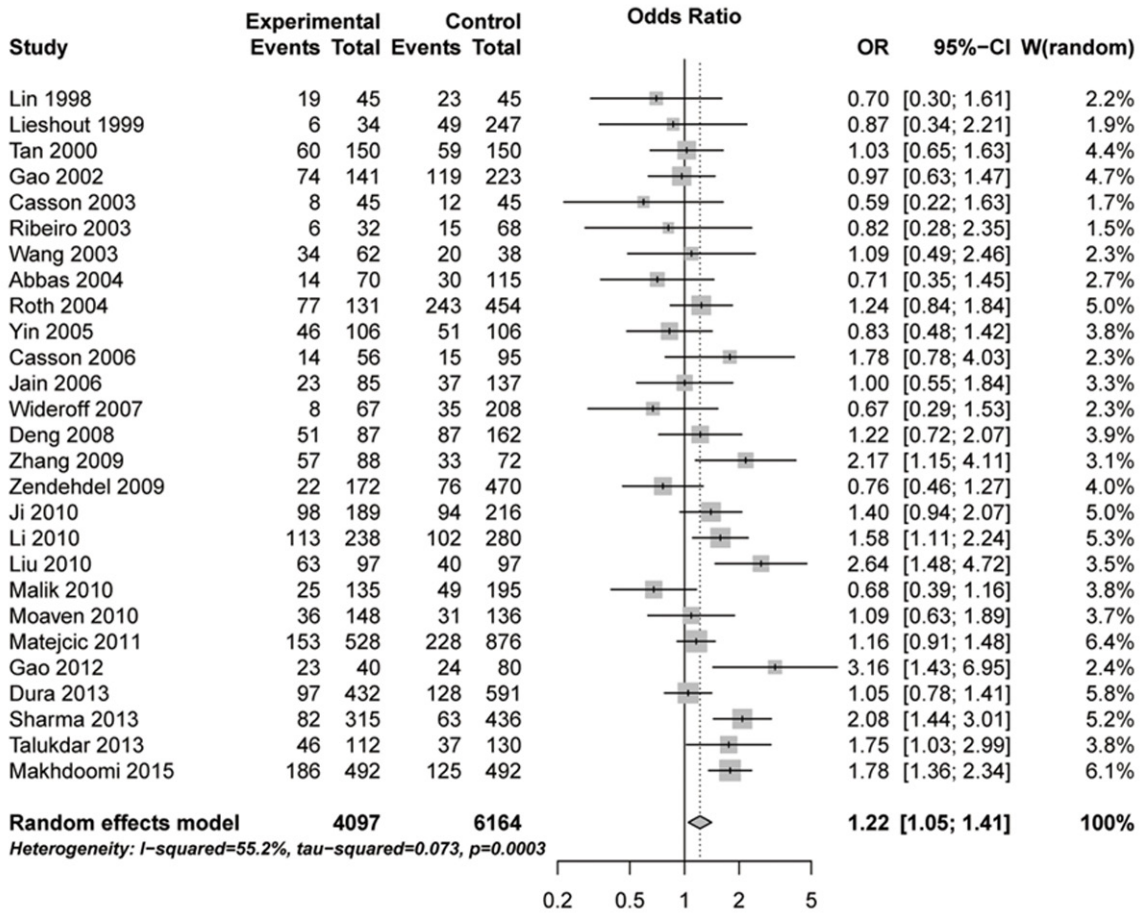

Figure 5. Forest plot of the meta-analysis for *GSTT1* null genotype and esophageal cancer susceptibility. Grey boxes represent the ORs of individual studies, and horizontal lines represent the 95% CI. The diamond is the overall OR.

genes could lead to the loss of functional activities and researchers have explored their roles in cancer development. Previous studies have suggested that the null genotypes were associ-

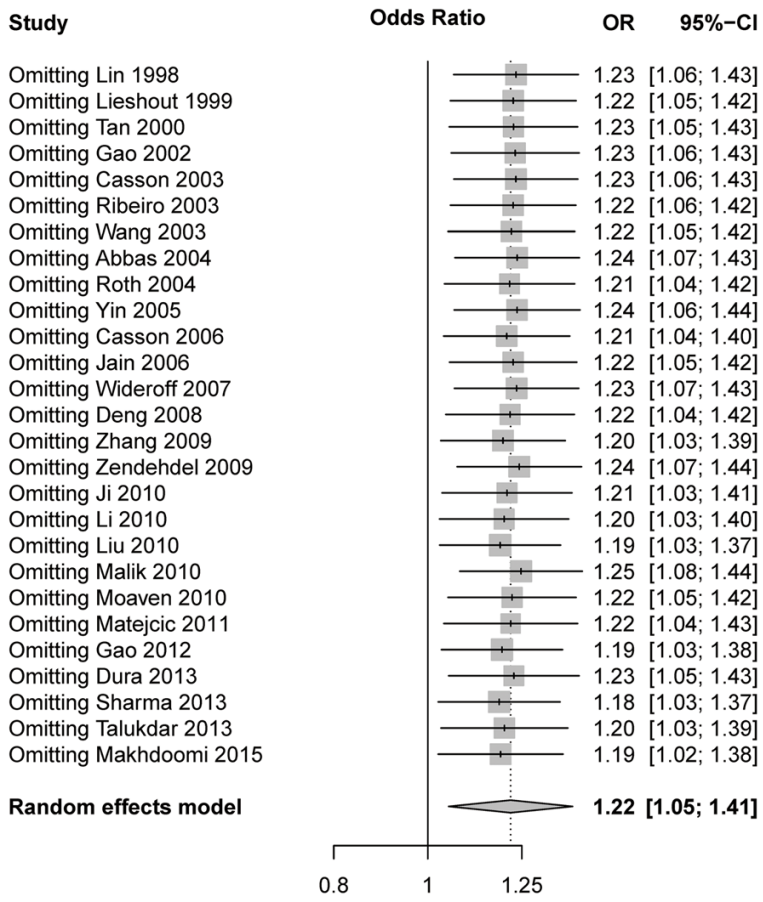

Figure 6. Sensitivity analysis for the studies of *GSTT1* null genotype and esophageal cancer risk.

Table 3. Meta-analysis of *GSTT1* null genotype with esophageal cancer risk

GSTT1 null genotype	Number of studies	Sample size (cases/controls)	OR (95% CI)	*P*-value for Q-test
Overall	27	4097/6164	1.22 (1.05-1.41)	0.0003
Cancer Types				
ESCC	16	2550/4501	1.30 (1.10-1.54)	0.019
EAC	9	678/1976	0.99 (0.74-1.31)	0.313
Ethnic Groups				
Asians	17	2423/3169	1.33 (1.10-1.61)	0.001
Caucasians	6	809/1563	0.95 (0.76-1.18)	0.428

ated with increased risk of various cancer types. One study has shown that the two *GST* null genotype polymorphisms would increase hepatocellular carcinoma susceptibility in a Chinese population [45]. Chen conducted a meta-analysis and proved that *GSTM1* null genotype could increase lung cancer risk in Chinese population [46]. In our analysis, *GSTM1* and *GSTT1* null genotypes are both associated with an increased risk of esophageal carcinoma.

Subgroup analyses according to histological and ethnic stratifications indicated a significantly increased association for *GSTM1* and *GSTT1* null genotypes and cancer risk in ESCC and Asian subgroups. The ESCC development has a high correlation with carcinogens from outside the body such as alcohol and nicotine, while the correlation with carcinogens is weaker for EAC. As GSTs prevent cancer and protect our health mainly through the clearage of carcinogens, the physiological difference may result in the non-significant association between *GST* polymorphisms and EAC observed in our analysis. At the same time, *GSTM1* and *GSTT1* null genotypes expressed different influences among Caucasians and Asians. We then calculated the percentages of homozygous deletion of *GSTM1* and *GSTT1* in Asians and Caucasians using the data from included studies. For *GSTM1* null genotype, the percentage of homozygous deletion in Caucasians (52.84%) was more than in Asians (47.27%). The distributions of *GSTT1* null genotype were reverse as the homozygous deletions among Asians (39.94%) were significantly more than among Caucasians (19.87%). The genotype distributions were different among the two races. And with the difference in daily foodconsumption and exposure situations across areas, as we have suspected, the interactions among epidemic factors and genetic susceptibility may differ the susceptibility to esophageal carcinoma across these populations [47].

Table 4. Meta-analyses of *GSTP1* Ile105Val polymorphism and esophageal cancer risk

GSTP1 Ile105Val polymorphism	Genetic model	Number of studies	Sample size (cases/controls)	OR (95% CI)	*P*-value for Q-test
Overall	Dominant	21	3108/5208	1.05 (0.91, 1.21)	0.008
	Recessive	21	3108/5208	1.09 (0.95, 1.26)	0.559
	Allelic	21	3108/5208	1.06 (0.95, 1.17)	0.017
Cancer types					
ESCC	Dominant	15	2090/4408	0.99 (0.82, 1.19)	0.008
	Recessive	15	2090/4408	1.07 (0.90, 1.26)	0.766
	Allelic	15	2090/4408	1.01 (0.88, 1.16)	0.012
EAC	Dominant	9	841/2121	1.17 (0.98, 1.38)	0.158
	Recessive	9	841/2121	1.08 (0.84, 1.40)	0.623
	Allelic	9	841/2121	1.10 (0.98, 1.25)	0.424
Ethnic groups					
Asians	Dominant	10	1118/1790	0.86 (0.69, 1.08)	0.070
	Recessive	10	1118/1790	1.12 (0.79, 1.60)	0.264
	Allelic	10	1118/1790	0.91 (0.74, 1.12)	0.031
Caucasians	Dominant	6	972/1531	1.14 (0.97, 1.34)	0.644
	Recessive	6	972/1531	1.04 (0.81, 1.34)	0.616
	Allelic	6	972/1531	1.08 (0.96, 1.22)	0.703

The *GSTP1* gene is also an important member of *GST*s family and its coding enzyme can eliminate DNA oxidative products of thymidine or uracil propenal [48]. Studies have proven that the Ile105Val polymorphic site could alter substrate binding site and catalytic activity thus affecting individual's cancer susceptibility [49]. While we didn't observe any remarkable roles that *GSTP1* Ile105Val plays in esophageal cancer risk in this analysis including 21 studies. To ensure study quality, we first considered Hardy-Weinberg equilibrium for genotype distribution in control groups. All included studies for *GSTP1* Ile105Val conformed to HWE. This non-significant association result was the same as the previous results of prostate cancer, lung cancer and colorectal cancer risks [50-53]. While Sundberg has stated that the individuals homozygous for Val allele had a high susceptibility to malignancy because of a decreased catalytic efficiency in the detoxication of carcinogens [49]. As *GSTP1* Ile105Val is not an independent dangerous factor of carcinogenesis and it modifies cancer susceptibility mainly through interacting with other environmental factors, so high-quality case-control studies with available information of daily habits should be performed to get more precise conclusion.

Our study has several limitations to be further addressed. Data on risk factors for individuals such as smoking and eating habits were not available. Further case-control researches are necessary to identify the possible gene-environmental interaction in esophageal cancer.

In conclusion, the meta-analysis confirmed that *GSTM1* null genotype and *GSTT1* null genotypes were significantly associated with esophageal cancer risk, especially among Asians. The homozygous null genotype carriers have more risk on esophageal cancer than the gene carriers. While *GSTP1* Ile105Val mutation has no obvious effect on esophageal cancer risk. This result suggests the polymorphisms in *GST*s can be used as clinical references and biomarkers for esophageal cancer diagnosis and treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Guohua Hu, Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, P. R. China. E-mail: hu.guohua@zs-hospital.sh.cn; Shiheng Tao, Bioinformatics Center, Northwest A&F University, Yangling, Shaanxi, P. R. China. E-mail: shihengt@nwsuaf.edu.cn

References

[1] Umar SB and Fleischer DE. Esophageal cancer: epidemiology, pathogenesis and preven-

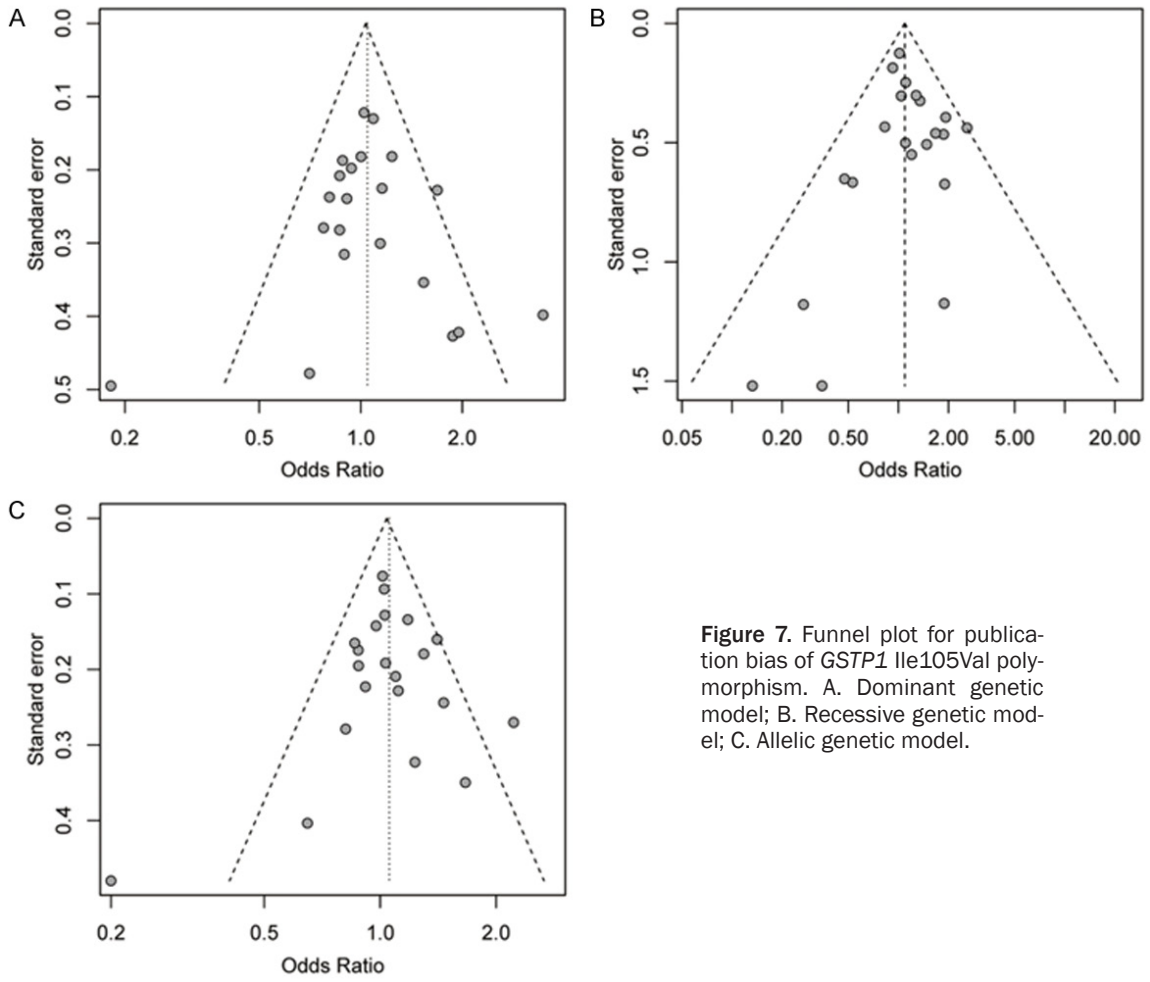

Figure 7. Funnel plot for publication bias of *GSTP1* Ile105Val polymorphism. A. Dominant genetic model; B. Recessive genetic model; C. Allelic genetic model.

tion. Nat Clin Pract Gastroenterol Hepatol 2008; 5: 517-526.

[2] Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1997; 6: 733-743.

[3] Chen YK and Lin LM. Immunohistochemical demonstration of epithelial glutathione S-transferase isoenzymes in normal, benign, premalignant and malignant human oral mucosa. J Oral Pathol Med 1995; 24: 316-321.

[4] Alexandrie AK, Rannug A, Juronen E, Tasa G and Warholm M. Detection and characterization of a novel functional polymorphism in the GSTT1 gene. Pharmacogenetics 2002; 12: 613-619.

[5] Ali-Osman F, Akande O, Antoun G, Mao JX and Buolamwini J. Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem 1997; 272: 10004-10012.

[6] Stosic I, Grujicic D, Arsenijevic S, Brkic M and Milosevic-Djordjevic O. Glutathione S-transferase T1 and M1 polymorphisms and risk of uterine cervical lesions in women from central Serbia. Asian Pac J Cancer Prev 2014; 15: 3201-3205.

[7] Handoll HH. Systematic reviews on rehabilitation interventions. Arch Phys Med Rehabil 2006; 87: 875.

[8] Hori H, Kawano T, Endo M and Yuasa Y. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and human esophageal squamous cell carcinoma susceptibility. J Clin Gastroenterol 1997; 25: 568-575.

[9] Morita S, Yano M, Shiozaki H, Tsujinaka T, Ebisui C, Morimoto T, Kishibuti M, Fujita J, Ogawa A, Taniguchi M, Inoue M, Tamura S, Yamazaki K, Kikkawa N, Mizunoya S and Monden M. CYP1A1, CYP2E1 and GSTM1 polymorphisms are not associated with susceptibility to squamous-cell carcinoma of the esophagus. Int J Cancer 1997; 71: 192-195.

[10] Nimura Y, Yokoyama S, Fujimori M, Aoki T, Adachi W, Nasu T, He M, Ping YM and Iida F.

Genotyping of the CYP1A1 and GSTM1 genes in esophageal carcinoma patients with special reference to smoking. Cancer 1997; 80: 852-857.

[11] Lin DX, Tang YM, Peng Q, Lu SX, Ambrosone CB and Kadlubar FF. Susceptibility to esophageal cancer and genetic polymorphisms in glutathione S-transferases T1, P1, and M1 and cytochrome P450 2E1. Cancer Epidemiol Biomarkers Prev 1998; 7: 1013-1018.

[12] Morita S, Yano M, Tsujinaka T, Ogawa A, Taniguchi M, Kaneko K, Shiozaki H, Doki Y, Inoue M and Monden M. Association between genetic polymorphisms of glutathione S-transferase P1 and N-acetyltransferase 2 and susceptibility to squamous-cell carcinoma of the esophagus. Int J Cancer 1998; 79: 517-520.

[13] van Lieshout EM, Roelofs HM, Dekker S, Mulder CJ, Wobbes T, Jansen JB and Peters WH. Polymorphic expression of the glutathione S-transferase P1 gene and its susceptibility to Barrett's esophagus and esophageal carcinoma. Cancer Res 1999; 59: 586-589.

[14] Tan W, Song N, Wang GQ, Liu Q, Tang HJ, Kadlubar FF and Lin DX. Impact of genetic polymorphisms in cytochrome P450 2E1 and glutathione S-transferases M1, T1, and P1 on susceptibility to esophageal cancer among high-risk individuals in China. Cancer Epidemiol Biomarkers Prev 2000; 9: 551-556.

[15] Gao CM, Takezaki T, Wu JZ, Li ZY, Liu YT, Li SP, Ding JH, Su P, Hu X, Xu TL, Sugimura H and Tajima K. Glutathione-S-transferases M1 (GSTM1) and GSTT1 genotype, smoking, consumption of alcohol and tea and risk of esophageal and stomach cancers: a case-control study of a high-incidence area in Jiangsu Province, China. Cancer Lett 2002; 188: 95-102.

[16] Yokoyama A, Kato H, Yokoyama T, Tsujinaka T, Muto M, Omori T, Haneda T, Kumagai Y, Igaki H, Yokoyama M, Watanabe H, Fukuda H and Yoshimizu H. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinogenesis 2002; 23: 1851-1859.

[17] Casson AG, Zheng Z, Chiasson D, MacDonald K, Riddell DC, Guernsey JR, Guernsey DL and McLaughlin J. Associations between genetic polymorphisms of Phase I and II metabolizing enzymes, p53 and susceptibility to esophageal adenocarcinoma. Cancer Detect Prev 2003; 27: 139-146.

[18] Ribeiro Pinto LF, Teixeira Rossini AM, Albano RM, Felzenszwalb I, de Moura Gallo CV, Nunes RA and Andreollo NA. Mechanisms of esophageal cancer development in Brazilians. Mutat Res 2003; 544: 365-373.

[19] Wang LD, Zheng S, Liu B, Zhou JX, Li YJ and Li JX. CYP1A1, GSTs and mEH polymorphisms and susceptibility to esophageal carcinoma: study of population from a high-incidence area in north China. World J Gastroenterol 2003; 9: 1394-1397.

[20] Abbas A, Delvinquiere K, Lechevrel M, Lebailly P, Gauduchon P, Launoy G and Sichel F. GSTM1, GSTT1, GSTP1 and CYP1A1 genetic polymorphisms and susceptibility to esophageal cancer in a French population: different pattern of squamous cell carcinoma and adenocarcinoma. World J Gastroenterol 2004; 10: 3389-3393.

[21] Roth MJ, Abnet CC, Johnson LL, Mark SD, Dong ZW, Taylor PR, Dawsey SM and Qiao YL. Polymorphic variation of Cyp1A1 is associated with the risk of gastric cardia cancer: a prospective case-cohort study of cytochrome P-450 1A1 and GST enzymes. Cancer Causes Control 2004; 15: 1077-1083.

[22] Wang AH, Sun CS, Li LS, Huang JY, Chen QS and Xu DZ. Genetic susceptibility and environmental factors of esophageal cancer in Xi'an. World J Gastroenterol 2004; 10: 940-944.

[23] Han Y, Li P and Niu Z. Case-control study on relationship of CYP1A1 and GSTM1 polymorphisms and susceptibility to esophageal squamous carcinoma. Chin J Publ Health 2005; 21: 3-6.

[24] Yin L, Song Y, Hu X, Liu Y and Kai H. Polymorphisms of susceptibility genes for esophageal cancer risk in Huaian population in Jiangsu province. Tumor J 2005; 25: 357-361.

[25] Cai L, Mu LN, Lu H, Lu QY, You NC, Yu SZ, Le AD, Zhao J, Zhou XF, Marshall J, Heber D and Zhang ZF. Dietary selenium intake and genetic polymorphisms of the GSTP1 and p53 genes on the risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15: 294-300.

[26] Casson AG, Zheng Z, Porter GA and Guernsey DL. Genetic polymorphisms of microsomal epoxide hydroxylase and glutathione S-transferases M1, T1 and P1, interactions with smoking, and risk for esophageal (Barrett) adenocarcinoma. Cancer Detect Prev 2006; 30: 423-431.

[27] Jain M, Kumar S, Rastogi N, Lal P, Ghoshal UC, Tiwari A, Pant MC, Baiq MQ and Mittal B. GSTT1, GSTM1 and GSTP1 genetic polymorphisms and interaction with tobacco, alcohol and occupational exposure in esophageal cancer patients from North India. Cancer Lett 2006; 242: 60-67.

[28] Lu XM, Yang T, Xu SY, Wen H, Wang X, Ren ZH, Zhang Y and Wang W. Glutathione-S-trans-

ferase M1 polymorphisms on the susceptibility to esophageal cancer among three Chinese minorities: Kazakh, Tajik and Uygur. World J Gastroenterol 2006; 12: 7758-7761.

[29] Murphy SJ, Hughes AE, Patterson CC, Anderson LA, Watson RG, Johnston BT, Comber H, McGuigan J, Reynolds JV and Murray LJ. A population-based association study of SNPs of GSTP1, MnSOD, GPX2 and Barrett's esophagus and esophageal adenocarcinoma. Carcinogenesis 2007; 28: 1323-1328.

[30] Rossini A, Rapozo DC, Soares Lima SC, Guimaraes DP, Ferreira MA, Teixeira R, Kruel CD, Barros SG, Andreollo NA, Acatauassu R, Matos HJ, Albano RM and Pinto LF. Polymorphisms of GSTP1 and GSTT1, but not of CYP2A6, CYP2E1 or GSTM1, modify the risk for esophageal cancer in a western population. Carcinogenesis 2007; 28: 2537-2542.

[31] Wideroff L, Vaughan TL, Farin FM, Gammon MD, Risch H, Stanford JL and Chow WH. GST, NAT1, CYP1A1 polymorphisms and risk of esophageal and gastric adenocarcinomas. Cancer Detect Prev 2007; 31: 233-236.

[32] Deng J GR, Yue H, Huang Z and Ma Y. A case-control study of the polymorphisms of phase I and phase II metabolic genes and esophageal carcinoma susceptibility. Pract J Card Cereb Pneumal Vasc Dis 2008; 16: 16-17.

[33] Zendehdel K, Bahmanyar S, McCarthy S, Nyren O, Andersson B and Ye W. Genetic polymorphisms of glutathione S-transferase genes GSTP1, GSTM1, and GSTT1 and risk of esophageal and gastric cardia cancers. Cancer Causes Control 2009; 20: 2031-2038.

[34] Zhang L IS, Wu M, Zhang Z, Li D and Liu Z. Study on relations between genetic polymorphisms in CYP2C19, GSTT1 and risk of Kazakh's esophageal cancer in Xinjiang. J Pract Oncol 2009; 24: 232-236.

[35] Li D, Dandara C and Parker MI. The 341C/T polymorphism in the GSTP1 gene is associated with increased risk of oesophageal cancer. BMC Genet 2010; 11: 47.

[36] Liu R, Yin L, Pu Y, Li Y, Liang G, Zhang J and Li X. Functional alterations in the glutathione S-transferase family associated with enhanced occurrence of esophageal carcinoma in China. J Toxicol Environ Health A 2010; 73: 471-482.

[37] Malik MA, Upadhyay R, Mittal RD, Zargar SA and Mittal B. Association of xenobiotic metabolizing enzymes genetic polymorphisms with esophageal cancer in Kashmir Valley and influence of environmental factors. Nutr Cancer 2010; 62: 734-742.

[38] Moaven O, Raziee HR, Sima HR, Ganji A, Malekzadeh R, A'Rabi A, Abdollahi A, Memar B, Sotoudeh M, Naseh H, Nekoui N, Razavipour A, Gholamin M, Dadkhah E, Farshchian M and Abbaszadegan MR. Interactions between Glutathione-S-Transferase M1, T1 and P1 polymorphisms and smoking, and increased susceptibility to esophageal squamous cell carcinoma. Cancer Epidemiol 2010; 34: 285-290.

[39] Matejcic M, Li D, Prescott NJ, Lewis CM, Mathew CG and Parker MI. Association of a deletion of GSTT2B with an altered risk of oesophageal squamous cell carcinoma in a South African population: a case-control study. PLoS One 2011; 6: e29366.

[40] Chen Y ZH, Yin D, Wang H, Wang Y, Deng Y and Ma Y. Relationship between GSTM1 gene polymorphism and interaction of gene-environment and susceptibility of esophageal cancer. Mod Prev Med 2012; 39: 110-113.

[41] Dura P, Salomon J, Te Morsche RH, Roelofs HM, Kristinsson JO, Wobbes T, Witteman BJ, Tan AC, Drenth JP and Peters WH. No role for glutathione S-transferase genotypes in Caucasian esophageal squamous cell or adenocarcinoma etiology: an European case-control study. BMC Gastroenterol 2013; 13: 97.

[42] Sharma A, Das BC, Sehgal A, Mehrotra R, Kar P, Sardana S, Phukan R, Mahanta J, Purkayastha J, Saxena S, Kapur S, Chatterjee I and Sharma JK. GSTM1 and GSTT1 polymorphism and susceptibility to esophageal cancer in high- and low-risk regions of India. Tumour Biol 2013; 34: 3249-3257.

[43] Talukdar FR, Ghosh SK, Laskar RS and Mondal R. Epigenetic, genetic and environmental interactions in esophageal squamous cell carcinoma from northeast India. PLoS One 2013; 8: e60996.

[44] Makhdoomi MA, Shah IA, Bhat GA, Amin S, Lone MM, Islami F and Dar NA. Association between GSTM1 and GSTT1 polymorphisms and esophageal squamous cell carcinoma: results from a case-control study in Kashmir, India. Tumour Biol 2015; 36: 2613-2619.

[45] Liu K, Zhang L, Lin X, Chen L, Shi H, Magaye R, Zou B and Zhao J. Association of GST genetic polymorphisms with the susceptibility to hepatocellular carcinoma (HCC) in Chinese population evaluated by an updated systematic meta-analysis. PLoS One 2013; 8: e57043.

[46] Chen XP, Xu WH, Xu DF, Xie XH, Yao J and Fu SM. GSTM1 polymorphisms and lung cancer risk in the Chinese population: a meta-analysis based on 47 studies. Asian Pac J Cancer Prev 2014; 15: 7741-7746.

[47] Denlinger CE and Thompson RK. Molecular basis of esophageal cancer development and progression. Surg Clin North Am 2012; 92: 1089-1103.

[48] Berhane K, Widersten M, Engstrom A, Kozarich JW and Mannervik B. Detoxication of base propenals and other alpha, beta-unsaturated al-

dehyde products of radical reactions and lipid peroxidation by human glutathione transferases. Proc Natl Acad Sci U S A 1994; 91: 1480-1484.

[49] Sundberg K, Johansson AS, Stenberg G, Widersten M, Seidel A, Mannervik B and Jernstrom B. Differences in the catalytic efficiencies of allelic variants of glutathione transferase P1-1 towards carcinogenic diol epoxides of polycyclic aromatic hydrocarbons. Carcinogenesis 1998; 19: 433-436.

[50] Wei B, Zhou Y, Xu Z, Ruan J, Cheng H, Zhu M, Hu Q, Jin K, Yan Z, Zhou D, Xuan F, Zhou H, Wang Z, Huang X and Wang Q. GSTP1 Ile105Val polymorphism and prostate cancer risk: evidence from a meta-analysis. PLoS One 2013; 8: e71640.

[51] Xu CH, Wang Q, Zhan P, Qian Q and Yu LK. GSTP1 Ile105Val polymorphism is associated with lung cancer risk among Asian population and smokers: an updated meta-analysis. Mol Biol Rep 2014; 41: 4199-4212.

[52] Tan Z, Feng M, Luo Y, Sun C, Fan Z, Tan Y, Fu B and Lang J. GSTP1 Ile105Val polymorphism and colorectal cancer risk: an updated analysis. Gene 2013; 527: 275-282.

[53] Pandith AA, Lateef A, Shahnawaz S, Hussain A, Malla TM, Azad N, Shehjar F, Salim M and Shah ZA. GSTP1 gene Ile105Val polymorphism causes an elevated risk for bladder carcinogenesis in smokers. Asian Pac J Cancer Prev 2013; 14: 6375-6378.