

Association of glutathione S-transferase T1, M1, and P1 polymorphisms in the breast cancer risk: a meta-analysis

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Background: Several case-control studies investigating the relationship between genetic polymorphisms of glutathione S-transferase (GST) M1, GSTT1, and GSTP1 (rs1695) and the risk of breast cancer have reported contradictory results. We therefore performed a meta-analysis to clarify this issue.

Materials and methods: An updated meta-analysis using PubMed and Web of Knowledge databases for the eligible case-control studies was performed. Random- or fixed-effects model was used.

Results: A total of 10,067 cancer cases and 12,276 controls in 41 independent case-control studies from 19 articles were included in this meta-analysis. Significant increase in risk of breast cancer for Asians was found in GSTM1-null genotype ($P=0.012$, odds ratio [OR]=1.17, 95% confidence interval [CI]=1.04–1.32) and GSTT1-null genotype ($P=0.039$, OR=1.19, 95% CI=1.01–1.41). In addition, our results showed that the GSTP1 (rs1695) polymorphisms can significantly increase the risk among Caucasians ($P=0.042$, OR=1.16, 95% CI=1.01–1.34). Sensitivity analysis and publication bias further confirmed the dependability of the results in this meta-analysis.

Conclusion: Our results demonstrate that both GSTM1- and GSTT1-null polymorphisms are associated with an increased risk of breast cancer in Asians and that GSTP1 Val105Ile (rs1695) polymorphism is associated with an increased breast cancer risk in Caucasians.

Keywords: GSTM1, GSTT1, GSTP1, polymorphism, breast cancer, meta-analysis

Background

Breast cancer, one of the most common cancers, has shown a steady increase in incidence worldwide in recent years. It remains the major cause of cancer-related mortality among women.^{1,2} According to earlier reports, there are ~1.15 million breast cancer patients diagnosed every year, and the highest incidence of breast cancer is found in Europe and USA.^{3,4} In the People's Republic of China, the incidence of breast cancer has been growing rapidly. Patients with breast cancer, meanwhile, tend to be younger.^{5,6} Its pathogenesis is still unclear, although some studies have shown that breast cancer is caused by environmental and genetic factors.^{7,8}

As a vital Phase II isoenzyme, the glutathione S-transferase (GST) family can identify environmentally hazardous materials and regulate the level of other enzymes and proteins in the cell. Thus, it plays an important role in many basic physiological processes of the human body.^{9–11} According to their distinct isoelectric points, human GSTs can be divided into seven classes, alpha (α), mu (μ), omega (ω), pi (π), sigma (σ), theta (θ), and zeta (ζ). There are also microsomal GST isoenzymes.¹² It is reported that there are at least three genes of them with common functional polymorphisms, which

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are GSTT1 (θ), GSTM1 (μ), and GSTP1 (π). Every mutation in each of them may potentially lead to a loss of enzymatic function.^{13,14} Many researchers have shown that GSTs are crucial to cellular protection from a great deal of damage, and the polymorphism of GSTs could result in cancers of the esophagus,¹⁵ kidney,¹⁶ and liver,¹⁷ and glioma.¹⁸

A large number of studies have indicated that the GSTT1, GSTM1, and GSTP1 (rs1695) polymorphisms are associated with breast cancer.^{8,11–38} However, the results of these studies are inconclusive. Therefore, we performed this meta-analysis of published case–control studies to solve the conflicting results and draw a relatively reliable conclusion.

Materials and methods

Literature search

All related studies published before May 31, 2015, were identified independently by two reviewers through a computer-based search of PubMed (www.ncbi.nlm.nih.gov/pubmed) and Web of Knowledge (<http://isiknowledge.com/>) databases. The search terms used in this study were as follows: (“glutathione *S*-transferase” OR “GST” OR “GSTT1” OR “GSTM1” OR “GSTP1”) AND (“breast cancer” OR “breast neoplasm” OR “breast carcinoma”) AND “polymorphism”. There was no language restriction. For this meta-analysis, the included studies had to meet the following criteria: 1) a case–control study on the polymorphism of GSTT1, GSTM1, or GSTP1 polymorphism and the risk of breast cancer; 2) reported genotype frequencies of cases and controls; and 3) the genotypes of control subjects in accordance with the Hardy–Weinberg equilibrium (HWE).

Data extraction

Two investigators extracted carefully the relevant information independently, and any discrepancy was settled by consensus. The following data were extracted from articles: first author’s name, year, country, ethnicity, the source of controls, and the genotype attribution of cases and controls.

Statistical analysis

The odds ratio (OR) and their 95% confidence interval (CI) were adopted to evaluate the strength of association between the polymorphism of GSTT1, GSTM1, and GSTP1 (rs1695) and the risk of breast cancer. First, we examined GSTT1 and GSTM1 genotypes using the null vs present model. Then, the relationship between the GSTP1 (rs1695) polymorphism and risk of breast cancer was estimated with allelic (V vs I) model, the recessive (VV vs II + VI), the dominant (VV + VI vs II), and the codominant (VV vs II). The statistical

significance of the pooled OR was determined by the *Z*-test, and a $P < 0.05$ was considered statistically significant. HWE was estimated using the chi-squared test among controls, where $P < 0.05$ was considered a significant departure from HWE. We evaluated heterogeneity among included studies with chi-squared-based *Q*-test and *I*² statistic. If the heterogeneity was obvious, with $P < 0.1$, random-effects model was used to calculate the pooled OR; otherwise, the fixed-effects models were adopted. Moreover, subgroup analysis was conducted by ethnicity.

We performed sensitivity analysis by omitting single study every time to assess the robustness of the results. Funnel plots and Egger’s tests were used to explore the potential publication bias; $P > 0.05$ was considered to indicate no significant publication bias. All *P*-values were based on two-sided tests.

Results

Study characteristics

Our meta-analysis was conducted according to guidelines of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement (checklist)³⁹ and “Meta-analysis on Genetic Association Studies” statement (checklist).⁴⁰ The flowchart is illustrated in Figure 1. A total of 171 potentially relevant articles were found by the literature search, and among these 121 articles were excluded because of obvious irrelevance after a preliminary screening of the titles and abstracts. In addition, after full-text reviews

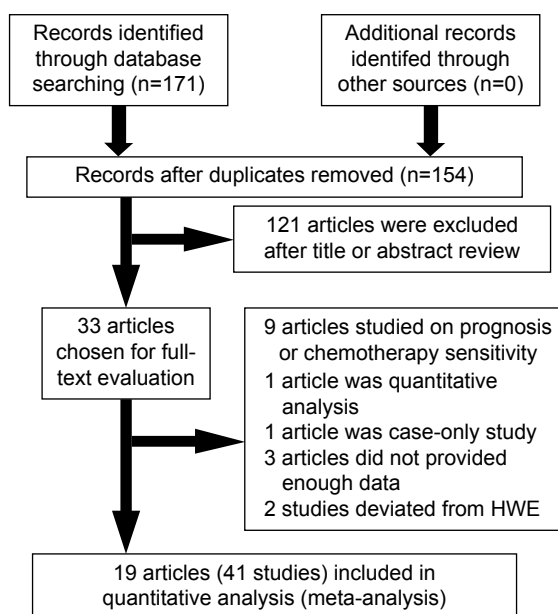


Figure 1 Flowchart of study selection in this meta-analysis. Abbreviation: HWE, Hardy–Weinberg equilibrium.

of the remaining 33 articles, 14 articles were excluded for the following reasons: articles were based on studies on prognosis or chemotherapy sensitivity ($n=9$), article was a quantitative analysis ($n=1$), article was a case report ($n=1$), articles had insufficient data ($n=3$), and studies deviated from HWE ($n=2$). Articles reporting data for different kinds of GST ethnicity were treated as independent studies. Finally, 19 articles^{8,19–36} involving 41 independent case–control studies with 10,067 cancer cases and 12,276 controls completely met the inclusion criteria. The detailed data collected from the included studies are summarized in Table 1.

Association of GSTM1-null polymorphism with breast cancer risk

Seventeen studies including 4,046 cases and 5,344 controls studied the association between GSTM1-null polymorphism and breast cancer.^{8,19,21–26,28,30–31,33–36} Our meta-analysis showed that there was no significant association of GSTM1-null polymorphism with breast cancer risk (OR =1.13, 95% CI =0.97–1.32) (Table 2). When stratifying for ethnicity, we found that GSTM1-null polymorphism could increase the breast cancer risk for Asians (OR =1.17, 95% CI =1.04–1.32) (Figure 2). However, no significant association was found for Caucasians (OR =1.13, 95% CI =0.85–1.52) or mixed ethnicity (OR =0.90, 95% CI =0.62–1.30) (Table 2).

Association of GSTT1-null polymorphism with breast cancer risk

Fourteen studies including 2,788 cases and 3,686 controls studied the association of GSTT1-null polymorphism with breast cancer.^{8,19,21–23,25,28,30–31,34–36} Totally, our meta-analysis showed that there was no significant association between GSTT1-null polymorphism and the risk of breast cancer (OR =1.15, 95% CI =0.93–1.42) (Table 2). When stratifying for ethnicity, similarly, we found that GSTT1-null polymorphism could increase breast cancer risk among Asians (OR =1.19, 95% CI =1.01–1.41) (Figure 3). However, we found that there was no significant association of GSTT1-null polymorphism with breast cancer risk for Caucasians (OR =1.17, 95% CI =0.96–1.42) or mixed ethnicity (OR =0.88, 95% CI =0.57–1.34) (Table 2).

Association of GSTP1 Val105Ile polymorphism with breast cancer risk

Ten studies including 3,233 cases and 3,246 controls studied the association between GSTP1 Val105Ile (rs1695) polymorphism and breast cancer.^{20,23–24,27,29–32,34,36} In the allelic model, our meta-analysis showed that GSTP1 Val105Ile (rs1695)

polymorphism was not associated with breast cancer risk overall (OR =1.21, 95% CI =0.99–1.48) (Table 2). When stratifying for ethnicity, similarly, we found that GSTP1 Val105Ile polymorphism could increase breast cancer risk for Caucasians (OR =1.16, 95% CI =1.01–1.34) (Figure 4). However, we found that there was no significant association between GSTP1 Val105Ile (rs1695) polymorphism and breast cancer risk for Asians (OR =1.26, 95% CI =0.91–1.75) (Table 2).

In the recessive model, we found that GSTP1 Val105Ile (rs1695) polymorphism was not associated with breast cancer risk overall (OR =1.16, 95% CI =0.83–1.62) (Table 2). When stratifying for ethnicity, we found that GSTP1 Val105Ile (rs1695) polymorphism had no significant association with the risk of breast cancer for Caucasians (OR =1.14, 95% CI =0.86–1.52) (Table 2) or for Asians (OR =1.28, 95% CI =0.70–2.35) (Table 2).

Similarly, we did not find any significant association of GSTP1 Val105Ile (rs1695) polymorphism with breast cancer risk overall (OR =1.19, 95% CI =0.93–1.52) and for Caucasians (OR =1.03, 95% CI =0.85–1.25) or Asians (OR =1.34, 95% CI =0.94–1.93) (Table 2) in the dominant model.

In codominant model, we found that there was no significant association of GSTP1 Val105Ile (rs1695) polymorphism with breast cancer risk overall (OR =1.24, 95% CI =0.81–1.89) and for Caucasians (OR =1.14, 95% CI =0.84–1.57) or Asians (OR =1.45, 95% CI =0.69–3.05) (Table 2).

Sensitivity analysis

A single study was excluded each time to reflect the effect of an individual study on the pooled OR and 95% CI. The deletion of any single study did not qualitatively alter the corresponding pooled ORs; these findings confirmed the stability of our meta-analysis results (data not shown).

Publication bias

We performed both Begg's and Egger's tests and generated a funnel plot to evaluate any potential publication bias. The symmetry of the funnel plots indicated no statistical evidence of publication bias in this meta-analysis (data not shown).

Discussion

Large-scale epidemiological studies on gene polymorphisms can contribute to uncovering the role and the corresponding mechanism of genes in the development of many diseases. To the best of our knowledge, this is the most comprehensive meta-analysis that evaluated the association of GSTM1-null, GSTT1-null, and GSTP1 Val105Ile (rs1695) polymorphisms with the risk of breast cancer. The obvious strength

Table 1 Characteristics of the literature included in the meta-analysis

First author	Year	Country	Ethnicity	Sample size (cases/controls)	GSTMI				GSTTI				GSTPI				P _{HWE}		
					Cases		Controls		Cases		Controls		Cases		Controls				
					Null	Present	Null	Present	Null	Present	Null	Present	Ile/Ile	Ile/Val	Val/Val	Ile/Ile		Ile/Val	Val/Val
Bailey et al ¹⁹	1998	USA	Caucasian	164/162	91	73	100	62	47	117	44	118	-	-	-	-	-		
Bailey et al ¹⁹	1998	USA	Mixed	59/59	20	39	24	35	12	47	17	42	-	-	-	-	-		
Zhao et al ²⁰	2001	USA	Caucasian	155/332	-	-	-	-	-	-	-	-	-	-	-	-	-		
Amorim et al ²¹	2002	Brazil	Caucasian	79/123	33	46	65	58	15	64	31	92	87	58	10	170	133	29	
Amorim et al ²¹	2002	Brazil	Mixed	128/256	50	78	103	153	32	96	65	191	-	-	-	-	-	-	
Sohail et al ²²	2013	Pakistan	Asian	100/102	43	57	45	57	27	73	32	70	-	-	-	-	-	-	
Zgheib et al ²³	2013	Lebanon	Asian	227/98	111	115	47	51	43	183	20	78	117	94	16	49	39	10	0.74
Sakoda et al ²⁴	2008	People's Republic of China	Asian	615/878	321	294	428	450	-	-	-	-	378	215	20	569	277	30	0.15
Chang et al ²⁵	2006	People's Republic of China	Asian	189/421	107	82	227	193	111	78	210	210	123	53	13	288	114	19	0.1
Ambrosone et al ²⁶	1999	USA	Caucasian	282/343	145	137	172	171	-	-	-	-	-	-	-	-	-	-	-
Saxena et al ²⁷	2012	India	Asian	215/215	-	-	-	-	-	-	-	-	81	89	45	101	75	39	0
Syamala et al ²⁸	2007	India	Asian	347/250	119	228	63	187	56	291	23	227	186	140	21	125	109	16	0.28
Mohamad ²⁹	2014	Saudi Arabia	Asian	100/48	-	-	-	-	-	-	-	-	58	40	2	28	18	2	1.000
Van Emburgh et al ³⁰	2008	USA	Caucasian	391/466	206	185	268	198	69	322	82	384	160	183	42	179	179	35	0.35
Rangel et al ³¹	2015	Mexico	Caucasian	243/118	117	124	34	79	32	211	22	92	58	105	79	35	53	30	0.27
Ge et al ³²	2013	People's Republic of China	Asian	920/783	-	-	-	-	-	-	-	-	540	325	55	519	230	34	0.2
Luo et al ⁸	2012	People's Republic of China	Asian	353/701	207	146	414	286	186	167	364	337	-	-	-	-	-	-	-
Christine et al ³³	1998	French	Caucasian	361/437	201	160	224	213	-	-	-	-	-	-	-	-	-	-	-
Hashemi et al ³⁴	2012	Iran	Asian	134/152	86	48	71	81	18	116	12	140	36	72	26	97	52	3	0.29
Zheng et al ³⁵	2002	USA	Caucasian	273/657	100	102	249	232	39	113	62	263	-	-	-	-	-	-	-
Ramalhinho et al ³⁶	2012	Portugal	Caucasian	101/121	66	35	45	76	47	54	24	97	54	35	12	55	48	16	0.31

Abbreviations: GST, glutathione S-transferase; Ile, isoleucine; Val, valine; "-", no data; HWE, Hardy-Weinberg equilibrium.

Table 2 Meta-analysis of the association between GSTM1, GSTT1, and GSTP1 polymorphisms and breast cancer risk

Comparisons	Odds ratio	95% CI	P-value	Heterogeneity		Effects model
				I ² (%)	P-value	
GSTM1						
Overall	1.13	0.97–1.32	0.019	66.00	<0.001	Random
Caucasian	1.13	0.85–1.52	0.398	79.50	<0.001	Random
Asian	1.17	1.04–1.32	0.012	41.40	0.115	Fixed
Mixed	0.9	0.62–1.30	0.567	0.00	0.584	Fixed
GSTT1						
Overall	1.15	0.93–1.42	0.189	60.00	0.002	Random
Caucasian	1.17	0.96–1.42	0.127	76.40	0.001	Random
Asian	1.19	1.01–1.41	0.039	43.30	0.117	Fixed
Mixed	0.88	0.57–1.34	0.544	0.00	0.378	Fixed
GSTP1						
V vs I						
Overall	1.21	0.99–1.48	0.066	81.30	<0.001	Random
Caucasian	1.16	1.01–1.34	0.042	25.40	0.259	Fixed
Asian	1.26	0.91–1.75	0.159	88.60	<0.001	Random
VV vs VV + VI						
Overall	1.16	0.83–1.62	0.38	57.40	0.012	Random
Caucasian	1.14	0.86–1.52	0.355	0.00	0.42	Fixed
Asian	1.28	0.70–2.35	0.429	73.00	0.002	Random
VV + VI vs II						
Overall	1.19	0.93–1.52	0.159	79.10	<0.001	Random
Caucasian	1.03	0.85–1.25	0.76	35.70	0.198	Fixed
Asian	1.34	0.94–1.93	0.11	85.80	<0.001	Random
VV vs II						
Overall	1.24	0.81–1.89	0.32	71.10	<0.001	Random
Caucasian	1.14	0.84–1.57	0.388	30.40	0.23	Fixed
Asian	1.45	0.69–3.05	0.324	81.30	<0.001	Random

Abbreviations: GST, glutathione S-transferase; CI, confidence interval; I, Ile; Ile, isoleucine; V, Val; Val, valine.

of meta-analysis is based on the accumulation of published data, providing a greater amount of information to find significant differences. In total, the meta-analysis involved 41 independent case-control studies of 19 articles comprising 10,067 cancer cases and 12,276 controls.

Our results demonstrate that the GSTM1-null, GSTT1-null, and GSTP1 Val105Ile (rs1695) polymorphisms are not significantly associated with breast cancer risk in the overall

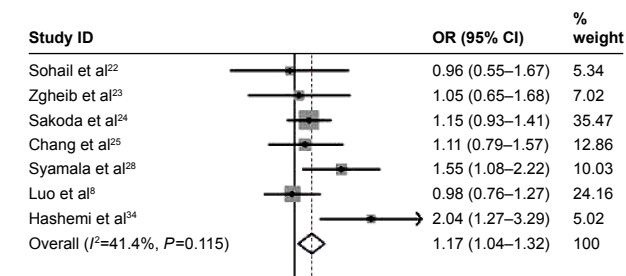


Figure 2 Forest plot for the association of GSTM1 null polymorphism and breast cancer risk for Asians.

Abbreviations: GSTM1, glutathione S-transferase M1; OR, odds ratio; CI, confidence interval.

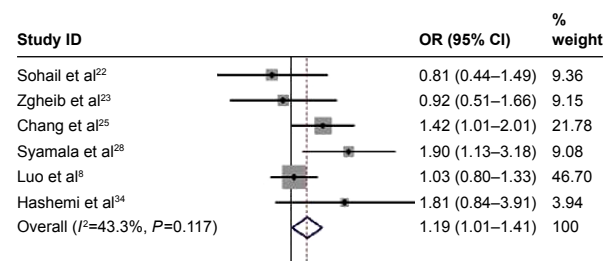


Figure 3 Forest plot for the association of GSTT1 null polymorphism and breast cancer risk for Caucasians.

Abbreviations: GSTT1, glutathione S-transferase T1; OR, odds ratio; CI, confidence interval.

populations. However, in the stratified analysis by ethnicity, significant associations were found in Asians for GSTM1-null and GSTT1-null polymorphisms. Significant result was also obtained for GSTP1 Val105Ile (rs1695) polymorphism among Caucasians. However, no significant associations were found among Caucasian and mixed populations for GSTM1-null and GSTT1-null polymorphism. Similarly, no significant associations were found among Asians for GSTP1 Val105Ile (rs1695) polymorphism.

In 2013, Liu et al³⁷ performed a meta-analysis, which showed that GSTP1 Val105Ile (rs1695) polymorphism was associated with the susceptibility of breast cancer in Asians under the allelic and recessive model. In another meta-analysis study, the GSTM1 and GSTP1 polymorphisms (under allelic and dominant model) were found to be associated with increased breast cancer risk Asian population, especially in East Asians, and that the GSTT1 polymorphism might not be associated with breast cancer.³⁸ These differences between different meta-analyses might have been due to the relatively small number of samples in each study.

There are several possible causes for the differences between different ethnicities. First of all, the frequencies of the genotype vary sharply between different ethnicities. For instance, the homozygous null genotype distributions of the GSTT1 polymorphism change greatly between Asian and Caucasian populations, with a prevalence of 79.6% and

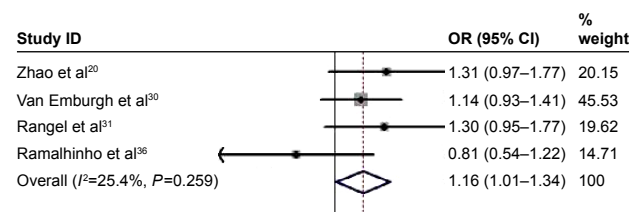


Figure 4 Forest plot for the association of GSTP1 Val105Ile (rs1695) polymorphism and breast cancer risk for Caucasians.

Abbreviations: GSTP1, glutathione S-transferase P1; OR, odds ratio; CI, confidence interval.

19.0%, respectively.^{23,41} Therefore, more studies with larger sample sizes are needed to further confirm ethnic difference in the association between these polymorphisms and breast cancer risk. Second, different lifestyles may explain partially the ethnic difference, as Asians and Caucasian adopt different food preferences. Previous studies have demonstrated that high intake of certain fruits, vegetables, milk, and eggs may have important effects on breast cancer risk.^{42–44} Different lifestyles, such as maintaining body mass index, physical exercise, and intake of sugary drinks, red meat, and alcohol, also have important influence in breast cancer susceptibility.^{45,46} Finally, the finding of an increasing breast cancer risk only in Asians is a chance of finding because of the relatively small number of the studies among each ethnicity included in this meta-analysis.

GSTs are important Phase II detoxification enzymes involved in the metabolism of a large number of potential carcinogens. Mutations in all of the three GST genes may lead to oxidative stress and the accumulation of reactive quinone intermediates in cells. In the GST family, it is well known that the proteins GSTM1, GSTT1, and GSTP1 (rs1695) have important influence on the modification of some vital enzymes. Many studies have shown that these enzymes may combine with glutathione and affect the detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins, and products of oxidative stress.^{47,48}

Limitations

Several limitations of our study should be acknowledged when interpreting the results. First, due to the failure in acquiring detailed original information, all the results of this meta-analysis is based on single-factor calculation without adjustment by other important co-variables, such as menopausal state, age of menarche, tobacco smoking habit, lifestyle factors, and family history. Second, some heterogeneity was observed in this study due to uncontrolled confounding factors and selection bias. We solved this problem by adopting a random-effects model and performing sensitivity analysis. Third, only articles published and written in English were included this meta-analysis, which might have resulted in some degree of publication bias. However, no significant publication bias was detected, indicating that no noticeable harm was done by potential publication bias.

Conclusion

Our meta-analysis demonstrates that GSTM1- and GSTT1-null polymorphisms can increase breast cancer risk for Asians, and GSTP1 Val105Ile (rs1695) polymorphism can increase breast cancer risk for Caucasians.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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