RESEARCH ARTICLE

Lack of Any Association of GST Genetic Polymorphisms with Susceptibility to Ovarian Cancer - a Meta-analysis

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Abstract

Objective: Epidemiology studies have reported conflicting results between glutathione S-transferase Mu-1 (GSTM1), glutathione S-transferase theta-1 (GSTT1) and glutathione S-transferase pi-1 (GSTP1) and ovarian cancer (OC) susceptibility. In this study, an updated meta-analysis was applied to determine whether the deletion of GSTM1, GSTT1 and GSTP1 has an influence on OC susceptibility. Methods: A published literature search was performed through PubMed, Embase, Cochrane Library, and Science Citation Index Expanded database for articles published in English. Pooled odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated using random or fixed effects models. Heterogeneity between studies was assessed using the Cochrane Q test and I^2 statistics. Sub-group analysis was conducted to explore the sources of heterogeneity. Sensitivity analysis was employed to evaluate the respective influence of each study on the overall estimate. Results: In total, 10 published studies were included in the final analysis. The combined analysis revealed that there was no significant association between GSTM1 null genotype and OC risk (OR=1.01, 95%CI: 0.91-1.12). Additionally, there was no significant association between GSTT1 genetic polymorphisms and OC risk (OR=0.98, 95% CI: 0.85-1.13). Similalry, no significant associations were found concerning the GSTP1 rs1695 locus and OC risk. Meanwhile, subgroup analysis did not show a significant increase in eligible studies with low heterogeneity. However, sensitivity analysis, publication bias and cumulative analysis demonstrated the reliability and stability of the current meta-analysis. Conclusions: These findings suggest that GSTs genetic polymorphisms may not contribute to OC susceptibility. Large epidemiological studies with the combination of GSTM1 null, GSTT1 null and GSTP1 Ile105Val polymorphisms and more specific histological subtypes of OC are needed to prove our findings.

Keywords GSTM1- GSTT1 - GSTP1 - polymorphisms - ovarian cancer - meta - analysis

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Introduction

Ovarian cancer (OC), a malignant cancer faced by females both in the developed and developing countries (Sagae et al., 2002), is a lethal gynecologic malignancy due to cancerous growth arising from the epithelial cells, stromal cells and germ cells in ovary tissue. There is no doubt the increased trend of OC within the Asian Pacific countries (Sagae et al., 2002). The origin and pathogenesis of OC is poorly understood (Permuth-Wey et al., 2009; Kurman et al., 2010; Buys et al., 2011). The early symptoms of OC are not obvious, but mainly consisted of increased abdominal size, bloating, pelvic pain, difficulty eating, constipation/diarrhea and urinary frequency. It is the fifth leading cause of death from cancer among women, and the estimated mortality rate of OC was 42.7 per 100000 in Europe in 2012 (Hetland et al., 2012; Ferlay et al., 2013).

Previous epidemiologic studies, including case-control or cohort studies, showed that the combined effect of environmental factors and genetic factors plays a critical role in the development of carcinoma and complex diseases (Lichtenstein et al., 2000; Clayton et al., 2001). There are evidences suggesting that family history, infertility and age are risk factors for OC, while increased parity, oral contraceptive use, hysterectomy and tubal ligation are protective factors (Booth et al., 1989; Whittmore et al., 1992; Risch et al., 1994; Rosenberg et al., 1994; Purdie et al., 1995; Riman et al., 1998; Riman et al., 2002; Lukanova et al., 2005). However, the majority of risk factors of OC are not clear, and the existing screening methods for OC such as serum CA 125, pelvic examination and transvaginal sonography (TVS) are not reliable in any risk group (Van Nagell et al., 1995; Bell et al., 1998; Jayde et al., 2012).

The glutathione S-transferases (GSTs) enzymes are an important phase II isoenzyme group which can catalyze the conjugation of glutathione with a variety of electrophilic compounds (Whalen et al., 1998). Enzymes of the GST family in eukaryotic species are composed

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of multiple cytosolic and membrane-bound isoenzymes, among them GSTM1, GSTT1 and GSTP1 belong to human GSTs and have been proven to play an important role in human carcinogenesis. It has been assumed that GST functional variants that are related to a less effective detoxification of potential carcinogens may contribute to increased cancer susceptibility (Strange et al., 1998).

Salinas-Sanchez et al. (2011) showed that GSTM1 null genotype is a risk factor for bladder cancer and dual GSTM1-GSTT1 null genotype increases the bladder cancer risk. Additionally, Ye et al found that GSTM1 deletion and GSTT1 deficiency were important risk factors for head and neck cancer from population-based and hospital-based studies (Ye et al., 2004). Chen et al revealed a relationship between GSTM1 genetic polymorphism and increasing susceptibility to gastric cancer (Chen et al., 2010). Liu et al also demonstrated that null genotype of GSTM1 and GSTT1 were linked to increased risk in developing hepatocellular carcinoma (Liu et al., 2013). While by the means of meta-analysis, Jie Peng et al indicated that GSTM1 null genotype had a significant effect on the susceptibility of oral cancer in the Indian population (Peng et al., 2014). Archana Krishna Murthy et al discovered a significant relationship for the GSTM1 and GSTT1 null genotypes and nasopharyngeal cancer risk (Murthy et al., 2013).

Various epidemiological research including case-control and cohort studies have been carried out on the association between GSTs genetic variants and OC risks in the general population and specific occupational groups, but the results are inconsistent. In addition, most of these studies had either small sample sizes or design limitations. Given that meta-analysis is an efficient and powerful statistical method to combine different studies, we carry out an updated meta-analysis to determine whether the deletion of GSTM1, GSTT1 and/or GSTP1 has an influence on OC susceptibility.

Materials and Methods

Literature and search strategy

We searched PubMed, Cochrane Library, Embase, and Science Citation Index Expanded databases for case-control and cohort studies on GSTs polymorphisms and OC susceptibility in English. The following search terms were used: ("glutathione S-transferase" or "GST" or "GSTM1" or "GSTT1" or "GSTP1") and ("ovarian cancer" or "oophoroma" or "ovarian carcinoma" or "carcinoma of ovary"). In addition, reference lists were also reviewed manually. The latest research was performed on February 28, 2014.

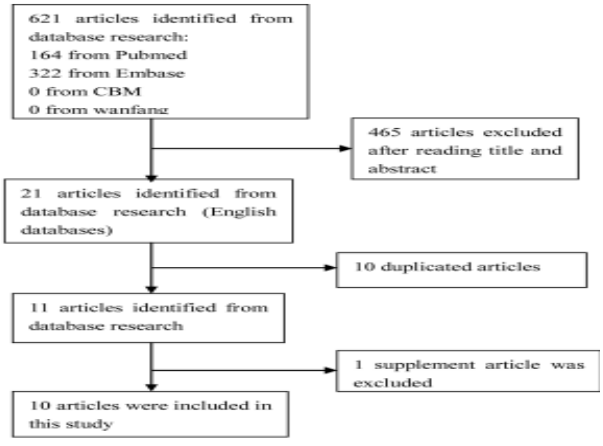

Figure 1. Flow Chart of Study Selection

Inclusion and exclusion criteria

In order for articles to be included in our study, the following criteria must be met: 1) case-control or cohort studies; 2) evaluating the relationship between GSTM1, GSTT1 or GSTP1 and OC risk; 3) providing raw data, or relevant information which could be used to calculate an odds ratios (ORs) with 95% confidence intervals (CI); 4) genotype distribution in controls were in Hardy-Weinberg equilibrium. The exclusion criteria included: 1) repeated reports; 2) the genotype frequency was not reported; 3) case reports, editorials, review articles, conference papers and meta-analysis.

Data extraction and synthesis

All publications retrieved from the databases were examined by two independent reviewers (Liyuan Han and Kui Liu) and disagreements were solved by a third researcher (Jinshun Zhao). For each eligible study, the following characteristics were collected: first author, year of publication, the relevant polymorphisms, study design, sample size, ethnicity and geographical location of the populations, sources of control, characteristics of cases and controls.

Statistics and analysis

Meta-analysis using STATA software (version 11; Stata Corporation, College Station, Texas) was conducted. The Z test was used to calculate the P value of the overall effect for the meta-analysis. Heterogeneity assessment employed the Cochran's Q test and I^2 test. If the *P* value of the Q test was above 0.1 ($P>0.1$), the fixed-effect model was used to evaluate the pooled ORs and 95% CIs, otherwise, the random-effect model was used. Subgroup analysis (<200 vs.≥200, the source of controls: hospital-based *vs* population-based studies), sensitivity analysis and cumulative meta-analysis were performed to assess the heterogeneity and change trends in all inclusive articles. Publication bias was assessed by Begg's funnel plot and Egger's linear regression. The leave-one-out sensitivity was performed, in which the meta-analysis estimates were computed each time that a study was omitted. All P values are two-tailed with a significant level at 0.05.

Results

Study characteristics

A total of 10 published articles regarding the relationship between GSTs and ovarian cancer were identified by applying the inclusion criteria (Figure 1) (Sarhanis et al., 1996; Hengstler et al., 1998; Lallas et al., 2000; Baxter et al., 2001; Spurdle et al., 2001; Morari et al., 2006; Delort et al., 2008; Gates et al., 2008; Khokhrin et al., 2012; Oliveira et al., 2012), 10 articles documented GSTM1 (2578 cases and 3423 controls) (Sarhanis et al.,

Table 1. Characteristics of the Studies Correlating with the Effects of GSTs Genetic Polymorphisms on OC Risks

No	Study(ref.)	Area	Source of controls	Case group	Control group	Null GSTM1		Null GSTT1		GSTP1Ile105Val				
						Group number		Group number		Case			Control	
						Case	Control	Case	Control	AA	AG	GG	AA	AG	GG
1	Sarhanis P 1996	UK(northern European)	Hospital	84 cases	325 controls with benign disease	47/84	192/312	13/81	61/325						
2	Hengstler JG 1998	German (Mainz)	Hospital	103 cases	115 controls	47/103	44/115	17/103	16/115						
3	LallasTA 2000	USA (Iowa)	Population	146 cases	80 controls without consanguineous relationship	70/146	45/80								
4	Baxter SW 2001	UK (South east England)	Population	293 cases	219 healthy controls	173/293	107/219								
5	Spurdle AB 2001	Australia (Queensland)	Population	285 cases	299 unrelated monozygotic female twin of controls matched on the date of birth distribution	159/285	162/297	57/285	56/295	121/282	130/282	31/282	114/292	135/292	43/292
6	Morari EC 2006	Brazil (Sao Paulo Campinas)	Population	69 cases	222 controls without consanguineous relationship	38/69	100/222	8/69	43/222	33/69	26/69	10/69	98/222	94/222	30/222
7	Delort L 2008	France (Auvergne)	Population	51cases with no BRCA mutation and no family history	1000 healthy woman controls					26/51	20/51	5/51	459/1000	434/1000	107/1000
8A	Gates MA (NECC) 2008	USA (Massachusetts)	Population	1175 cases	1202 controls matched on age and state of residence	594/1167	628/1195	247/1166	257/1195						
8B	Gates MA (NHS) 2008	USA (Massachusetts)	Population	210 cases	600 controls	93/195	285/553	36/193	118/557						
10	Khokhrin DV 2012	Russia (Kursk, etc)	Population	104 cases	298 health controls	47/104	134/298	18/104	44/298	10/104	53/104	41/104	36/298	128/298	134/298
11	Cristiane Oliveira 2012	Brazil (Southeastern)	Hospital	132 cases	132 controls	48/132	42/132	39/132	34/132	76/132	42/132	14/132	60/132	59/132	13/132

1996; Hengstler et al., 1998; Whalen et al., 1998; Lallas et al., 2000; Baxter et al., 2001; Clayton et al., 2001; Riman et al., 2002; Gates et al., 2008; Oliveira et al., 2012), 8 articles studied GSTT1 (2133 cases and 3141 controls) (Sarhanis et al., 1996; Hengstler et al., 1998; Spurdle et al., 2001; Morari et al., 2006; Gates et al., 2008; Khokhrin et al., 2012; Oliveira et al., 2012) and 5 articles reported GSTP1 rs1695 (641 cases and 1949 controls) (Spurdle et al., 2001; Morari et al., 2006; Delort et al., 2008; Khokhrin et al., 2012; Oliveira et al., 2012). More details of these studies were summarized in (Supplementary Table 1).

The results of meta-analysis

GSTM1 null genotype with OC risk

Using the fixed-effect model, meta-analysis showed no significant association between the GSTM1 null genotype and OC risk (OR=1.01, 95% CI: 0.91 to 1.12, P =0.16) (Table 2), the forest plot was shown in Figure 2.

GSTT1 null genotype with OC risk

The meta-analysis showed no significance association between the GSTT1 and OC risk (OR=0.98, 95% CI: 0.85 to 1.13, P=0.75) under the fixed-effect model (Table 3), the forest plot was shown in Figure 3.

The genotypes of GSTP1 genetic polymorphisms with OC risk

Analysis using the available data of GSTP1 genotypes also revealed no statistical significant association between: (a) A allele *vs* G allele (OR=1.15, 95% CI: 0.99 to 1.34, P=0.95); (b) AA *vs* AG+GG (OR=1.21, 95% CI: 0.98 to 1.50, P=0.58); (c) AG *vs* AA+GG (OR=0.93, 95% CI: 0.76 to 1.14, P=0.14); (d) GG *vs* AA+GG (OR=0.84, 95% CI: 0.64 to 1.10, P=0.85).

Subgroup analysis and sensitivity analysis

Considering the small sample size of GSTP1 meta-analysis, we only performed subgroup analysis in GSTM1 and GSTT1 groups by the number of OC cases (<200 vs.≥200) and the source of controls (hospital-based *vs* population-based studies). The subgroup analysis results showed no significant associations (Table 2 and Table 3). Meanwhile, we checked the pooled ORs in each study by excluding sequentially one article each time with sensitivity analysis, the pooled ORs did not change significantly.

The cumulative meta-analysis

Cumulative meta-analyses were also conducted via assortment of studies by

Table 2. Subgroup Analysis of GSTM1 and OC Risk

Polymorphism	Null *vs* present	No of studies (cases/controls)	Odds ratio 95%CI	*P*	Model	Heterogeneity I^2 (%)	P_H	P_E
GSTM1	All studies	9(2578/3423)	1.01(0.91-1.12)	0.16	Fixed	30.7	0.16	0.51
Subgroup analysis by number of case								
	<200	6(833/1712)	0.99(0.83-1.18)	0.92	Fixed	14.9	0.32	0.38
	≥200	3(1745 /1711)	1.10(0.84-1.45)	0.48	Random	65.9	0.05	0.4
Subgroup analysis by source of control								
	Hospital-based	3(319/559)	1.08(0.80-1.48)	0.62	Fixed	18	0.3	0.27
	Population-based	6(2259/2864)	1.00(0.89-1.12)	0.98	Fixed	42	0.11	0.65

Table 3. Subgroup Analysis of GSTT1 and OC Risk

Polymorphism	Null *vs* present	No of studies (cases/controls)	Odds ratio 95%CI	*P*	Model	Heterogeneity I^2 (%)	P_H	P_E
GSTT1	All studies	7(2133/3139)	0.98(0.85-1.23)	0.75	Fixed	0	0.75	0.73
Subgroup analysis by number of case								
	<200	6(682/1649)	0.95(0.75-1.20)	0.67	Fixed	0	0.54	0.7
	≥200	2(1451 /1490)	1.00(0.83-1.19)	0.97	Fixed	0	0.72	-
Subgroup analysis by source of control								
	Hospital-based	3(316/572)	1.08(0.75-1.54)	0.69	Fixed	0	0.63	0.89
	Population-based	4(1817/2567)	0.96(0.83-1.12)	0.63	Fixed	0	0.55	0.5

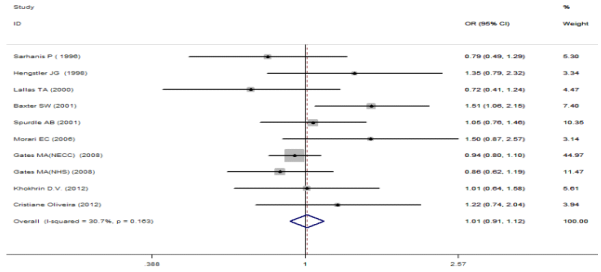

Figure 2. Association between GSTM1 Null Genotype and OC Risk Analyzed by Forest Plot

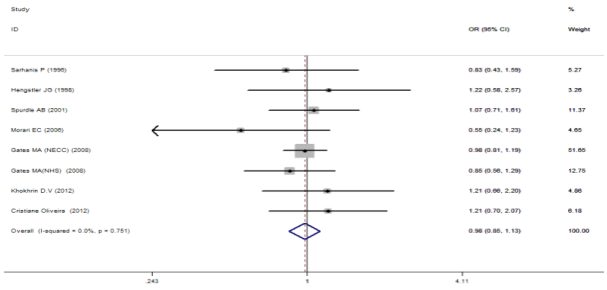

Figure 3. Association between GSTT1 Null Genotype and OC Risk Analyzed by Forest Plot

chronological order. The GSTM1 cumulative meta-analysis tended to gradually become more consistent after the 2008 studies were added. Similarly, the GSTT1 cumulative meta-analysis tended to be more consistent with the addition of studies added after 2006. The cumulative analysis showed that the results tended to remain stable over time. The results of cumulative meta-analysis for GSTM1 and GSTT1 were shown in (Supplementary Figure 4).

Potential publication bias

Publication bias was measured by Begg's and Egger's test. The outlines of funnel plots did not demonstrate any asymmetry in all comparison models by Begg's test (data not shown). Furthermore, we used Egger's test to supplement statistical evidence of funnel plot symmetry. The results were shown in Tables 2 and Table 3.

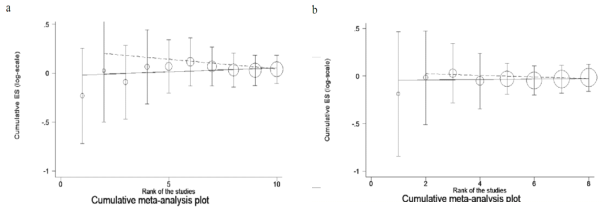

Figure 4. The Cumulative Meta-Analysis of GSTM1 and GSTT1. (A) the metatrend test of GSTM1 by public time, **(B)** the metatrend test of GSTT1 by public time

Discussion

In order to reflect new developments and produce more powerful estimation on the associations between the GSTs gene polymorphisms and OC susceptibility, an updated systematic meta-analysis with more available data was conducted in this study. Consistent with the conclusion in a previous published meta-analysis (its latest searching time was 2009) (Economopoulos et al., 2010), our results also show no significant associations between the GSTs gene polymorphisms and OC susceptibility.

Baxter et al reported an excess of GSTM1 null genotype in Caucasian OC patients when compared to controls in England (Whalen et al., 1998). Gates et al found that GSTT1 null genotype was associated with OC in a particular group of women using genital talc (Gates et al., 2008). Cristiane et al showed that the GSTM1 null, GSTT1 null and GSTP1 Ile/Ile genotypes, especially in combination, constitute significant inherited OC determinants in subjects from Southeastern Brazil, which indicated that GSTs may act synergistically in OC development (Lallas et al., 2000). Therefore, it is more likely that the combination of GST genes may increase the OC susceptibility. In addition, Spurdle et al reported that GSTM1 null genotype was associated with endometrioid/

clear cell invasive cancer risk, due to the fact that GSTT1 and GSTM1 were more common in both endometrioid and cell OC histological subtypes, which indicates that the GST null genotypes may specifically increase the risk of OC histological subtypes (Hengstler et al., 1998).

Associations of GSTM1, GSTT1, and GSTP1 genotype have not been observed in most studies. Considering the fact that the difference in sample sizes and control sources in certain studies could influence the stability of the conclusions, we performed subgroup analysis for GSTM1 and GSTT1 genetic polymorphism and OC risk, and the results still showed no significance differences. Then, we further performed sensitivity analysis and cumulative meta-analysis to observe the heterogeneity of these articles, the conclusion of non-significant association between GSTM1 genetic variants and OC risk didn't change. The cumulative analysis showed that the results tended to be stable over time. The funnel plots were all symmetric for GSTM1, GSTT1 and GSTP1, suggesting no publication bias (data not shown). Additionally, Egger's test didn't show significance of publication bias.

There are some limitations in this meta-analysis that are worth noting in explaining the results. 1) Limited number and scale of studies may influence the stability of the conclusion and there were no data on the Asian and African population in the available studies, which may affect the conclusion; 2) The range of our literature searching only included English, which would result in the language selection bias; 3) The control subjects of three articles were from hospital-based population, which may differ from the population-based controls; 4) Available studies did not provide sufficient data about specific histological subtypes of OC, so we could not conduct a further analysis on the relationship between the specific OC histological subtypes and GSTs polymorphisms; This is significant, because Maliheh Arab et al found that histological subtypes affected OC patient's survival (Arab et al., 2009). 5) Complex environmental factors also played critical roles in developing carcinoma, we could not evaluate the interactive between genes and environment in our meta-analysis. These may all be factors that could affect the results of this meta-analysis.

In summary, our meta-analysis revealed no association between the GSTs gene polymorphisms and OC susceptibility, but the roles of GSTM1 null, GSTT1 null and GSTP1 Ile105Val polymorphisms in combination for OC risk is still unclear. Perhaps the combination of GSTM1 null, GSTT1 null and GSTP1 Ile105Val polymorphisms may confer a greater risk to OC, future studies designed to investigate the combinations is a promising area. Besides, studies that examine associations between the specific histological types and OC susceptibility are also very important for future research (Sagae et al., 2002). In order to provide a more precise evaluation between the GSTs gene polymorphisms and OC susceptibility, well designed epidemiological and molecular biology studies should be performed in general populations especially in Asian and African. Marzieh Rohani-Rasaf et al demonstrated that OC had a positive correlation with socio-economic position in Iran (Rohani-Rasaf et al., 2013), therefore given the difference of inheritance and living habits in various ethnicities, future studies should also give balanced attention to different ethnicity groups (Hamajima et al., 2002). In addition, identification of microRNAs may be helpful for disclosing the molecular mechanisms of OC and exploring the new treatments of OC (Wan et al., 2012).

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