Review Article

Is There Any Association between Glutathione S-transferases M1 and Glutathione S-transferases T1 Gene Polymorphisms and Endometrial Cancer Risk? A Meta-analysis

Abstract

Epidemiological evidence on the association between genetic polymorphisms in glutathione S-transferases M1 (GSTM1) and T1 (GSTT1) genes and risk of endometrial cancer (EC) has been inconsistent. In this meta-analysis, we seek to investigate the relationship between GSTM1 and GSTT1 polymorphisms and the risk of EC. We searched Medline, PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure database, and Chinese Biomedical Literature database to identify eligible studies. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) for the association were determined using a fixed- or random-effect model. Tests for heterogeneity of the results and sensitivity analyses were performed. A total of six case–control studies were included in the final meta-analysis of GSTM1 (1293 cases and 2211 controls) and GSTT1 (1286 cases and 2200 controls) genotypes. Overall, GSTM1 null genotype was not significantly associated with an increased risk of EC (OR = 1.00, 95% CI = 0.76–1.30, P = 0.982). Similarly, for GSTT1 deletion genotype, we observed no association under the investigated model in the overall analysis (OR = 0.91, 95% CI = 0.64–1.30, P = 0.619). Subgroup analysis also showed no significant association between the GSTM1 null genotype and EC risk in hospital-based design (OR = 1.26, 95% CI = 0.93–1.71, P = 0.131) and no relationship between GSTT1 null genotype with EC risk in population-based design (OR = 1.18, 95% CI = 0.79–1.76, P = 0.407). However, GSTM1 null genotype contributed to an increased EC risk in population-based design (OR = 0.76, 95% CI = 0.60–0.97, P = 0.027), while null GSTT1 in hospital-based studies (OR = 0.70, 95% CI = 0.52–0.93, P = 0.015). The present meta-analysis suggested that GSTs genetic polymorphisms may not be involved in the etiology of EC. Large epidemiological studies with the combination of GSTM1 null, GSTT1 null, and design-specific with the development of EC are needed to prove our findings.

Keywords: *Endometrial cancer, glutathione S-transferases M1, glutathione S-transferases T1, meta-analysis, susceptibility*

Xiuxiu Yin, Jie Chen[1]

Department of Scientific Research, Jining No. 1 People's Hospital, Jining, China, [1]Department of Maternal and Child Health, School of Public Health, Shandong University, Jinan 250012, China

Introduction

Endometrial cancer (EC) is the most common type of uterine cancer and gynecologic cancer worldwide. Conventionally, the classification of EC risks is major composed of prolonged unopposed estrogen stimulation, partial estrogen against drugs such as tamoxifen, late menopause, nulliparity, and obesity.[1] However, epidemiologic studies showed that the combined effect of environmental factors and genetic factors plays a critical role in the development of EC. Recent evidence, mainly from molecular genetic analyses, suggests that invasive cancer has a substantial hereditary component.

The glutathione S-transferases (GSTs) enzymes are important phase II isoenzyme group which conjugate a broad range of electrophilic xenobiotic and carcinogenic compounds to glutathione.[2] 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.[3] Meanwhile, cytosolic GSTs (glutathione S-transferases M1 [GSTM1] and glutathione S-transferases T1 [GSTT1]) play a significant role in human carcinogenesis.

Endometrial carcinoma is a common malignant tumor in women, in which relatively little attention has been given to genetic susceptibility factors. In 1997, Esteller *et al*. first reported the GSTM1 and GSTT1 polymorphisms as potential

Access this article online

Website:
www.ijpvmjournal.net/www.ijpm.ir

DOI:
10.4103/ijpvm.IJPVM_346_15

Quick Response Code:

How to cite this article: Yin X, Chen J. Is there any association between glutathione s-transferases m1 and glutathione s-transferases t1 gene polymorphisms and endometrial cancer risk? a meta-analysis. Int J Prev Med 2017;8:47.

molecular markers and found that GSTM1 null genotype was associated with an increased risk of endometrial carcinoma.[4] However, Doherty *et al.* confirmed that GSTT1 but not GSTM1 null genotype was associated with the risk of EC.[5] Subsequently, several studies also reported the potential association between GSTM1 and GSTT1 polymorphisms and the EC risk.[6-9] However, the data show conflicting results that remain to be further clarified. Therefore, we conducted this meta-analysis to determine whether the deletion of GSTM1, GSTT1 has an impact on EC susceptibility.

Methods

Literature search and selection criteria

We searched PubMed, Embase, ISI Web of Science, China National Knowledge Infrastructure database, and Chinese Biomedical Literature database to identify relevant publications. The following search terms were used: ("glutathione S-transferase" OR "GST" OR "GSTM1" OR "GSTT1") and ("endometrial cancer" OR "endometrial carcinoma"). Relevant studies of GSTM1 or GSTT1 polymorphism and EC risk published in English or Chinese were all retrieved. In addition, the related articles of the reference lists were also screened for useful data. The literature search was updated on June 30, 2016.

To get all eligible articles, the following inclusion criteria must be met: (a) cohort or case–control studies; (b) evaluating the relationship between GSTs (GSTM1 and GSTT1) and EC risk; (c) providing sufficient information to calculate pooling odds ratios (ORs) with 95% confidence intervals (CIs); (d) the published language must be in English or Chinese. The following information was extracted from each study: (a) name of the first author; (b) year of publication; (c) country of origin. Two authors independently assessed the articles for compliance with the inclusion criteria and resolved discrepancies by discussion until a consistent decision was reached. We used the modified Newcastle–Ottawa quality scale (NOS)[10] to assess the quality of each study.

Statistical analysis

The association between GSTM1 and GSTT1 polymorphisms and risk of EC was estimated by calculating pooled ORs with 95% CI under an additive model. The significance of pooled ORs was checked using the Z-test. Heterogeneity between studies was measured by Q statistic ($P < 0.05$ represented significant results) and I^2 statistic ($I^2 < 25\%$, no heterogeneity; $25\% < I^2 < 50\%$, moderate heterogeneity; $50\% < I^2 < 75\%$, large heterogeneity, and $75\% < I^2 < 100\%$, extreme heterogeneity).[11] A random-(DerSimonian–Laird method)[12] or fixed-(Mantel–Haenszel method)[13] effect model was used to calculate the pooled OR in the presence ($P < 0.05$) or absence ($P > 0.05$) of heterogeneity, respectively. The

following categories were conducted to find the source of heterogeneity: source of controls, ethnicity, study numbers, and quality score of the papers (NOS). The leave-one-out sensitivity analysis was performed to assess the stability of results. Publication bias was assessed by funnel's plot[14] and Egger's linear regression[15] ($P < 0.05$ was considered statistically significant). Statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX, USA).

Results

Characteristics of the studies

A total of six published articles were identified to be eligible to be included for the final meta-analysis. A flowchart summarizing the selection details is depicted in Figure 1.

Of the six studies, three studies were population-based design, and the other three were based on the hospital. All studies investigated both GSTM1 and GSTT1 polymorphism and were based on Caucasians, except for one on Asians. For genotyping methods, three articles adopt polymerase chain reaction (PCR), while the other three were real-time PCR, PCR-restriction fragment length polymorphism, and multi-PCR, respectively. More detailed characteristics of the included studies are presented in Table 1.
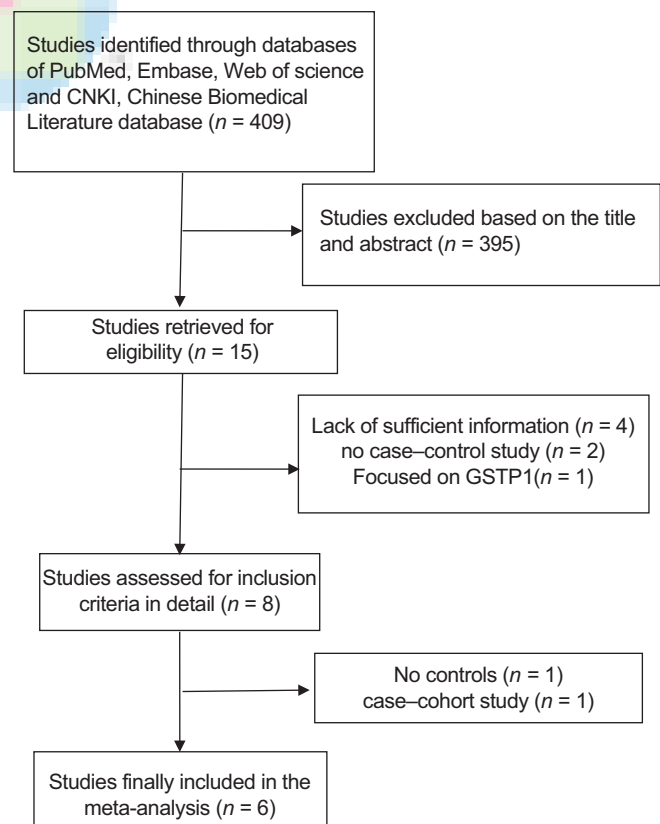

Studies identified through databases of PubMed, Embase, Web of science and CNKI, Chinese Biomedical Literature database (*n* = 409)

Studies excluded based on the title and abstract (*n* = 395)

Studies retrieved for eligibility (*n* = 15)

Lack of sufficient information (*n* = 4) no case–control study (*n* = 2) Focused on GSTP1(*n* = 1)

Studies assessed for inclusion criteria in detail (*n* = 8)

No controls (*n* = 1) case–cohort study (*n* = 1)

Studies finally included in the meta-analysis (*n* = 6)

Figure 1: Flowchart of study selection

Quantitative synthesis

Glutathione S-transferases M1 polymorphism

The association of GSTM1 polymorphism with risk of EC was estimated in 1293 cases and 2211 controls. The overall results showed no significant association of null GSTM1 carries with the EC risk (OR = 1.00; 95% CI = 0.76–1.30) [Figure 2a]. There was heterogeneity in studies (I^2 = 64.8%, P = 0.014), and a random-effects model was used [Table 2].

Glutathione S-transferases T1 polymorphism

As for GSTT1 polymorphism, a total of 1286 cases and 2200 controls from the six studies were included. The overall results also showed no significant association between GSTT1 null genotype and EC risk (OR = 0.91, 95% CI = 0.64–1.30) [Figure 2b]. A random-effects model was introduced as there was significant heterogeneity in studies (I^2 = 70.4%, P = 0.005) [Table 2].

Subgroup analysis

We performed meta-regression with the introduction of ethnicity (Caucasians vs. Asians), study design (population-based vs. hospital-based), number of cases (≥200 vs. <200), and the score quality of the papers (≥6 vs. ≤6) to identify the potential source of heterogeneity. Results showed that the study design was the only source that contributed to the heterogeneity. For GSTM1 null genotype, subgroup analysis results showed no significant association with EC in hospital-based design (OR = 1.26, 95% CI = 0.93–1.71, P = 0.131) [Figure 3a], whereas results showed no association of GSTT1 deletion with EC in population-based design (OR = 1.18, 95% CI = 0.79–1.76, P = 0.407) [Figure 3b]. Moreover, the heterogeneity dropped in both groups. However, there were significant associations of EC with the null of genotype GSTM1 in population-based studies

Table 1: Characteristics of the publications identified for the meta-analysis

Study, country	Ethnicity	Study design	Sample size (case/control)	Genotyping method	GSTM1 (null)	GSTM1 (present)	GSTT1 (null)	GSTT1 (present)	NOS
Esteller et al., 1997, Spain	Caucasian	Hospital	80/60	PCR	51/28	29/32	19/12	61/48	5
Doherty et al., 2005, USA	Caucasian/ African-Americans	Population	371/420	PCR-RFLP	181/220	190/200	78/61	293/359	5
Ashton et al., 2010, Australia	Caucasian	Population	191/286	PCR	84/161	107/125	33/47	158/239	8
Du et al., 2010, China	Asian	Hospital	171/201	Multi-PCR	109/114	62/87	70/109	101/92	7
Karageorgi et al., 2011, USA	Caucasian	Hospital	441/1237	Real-time PCR	232/621	195/556	64/239	356/927	5
Ozerkan et al., 2012, Turkey	Caucasian	Population	53/67	PCR	28/38	25/29	14/22	39/45	6

PCR=Polymerase chain reaction, RFLP=Restriction fragment length polymorphism, NOS=Newcastle-Ottawa quality scale, GSTM1=Glutathione S-transferases M1, GSTT1=Glutathione S-transferases T1
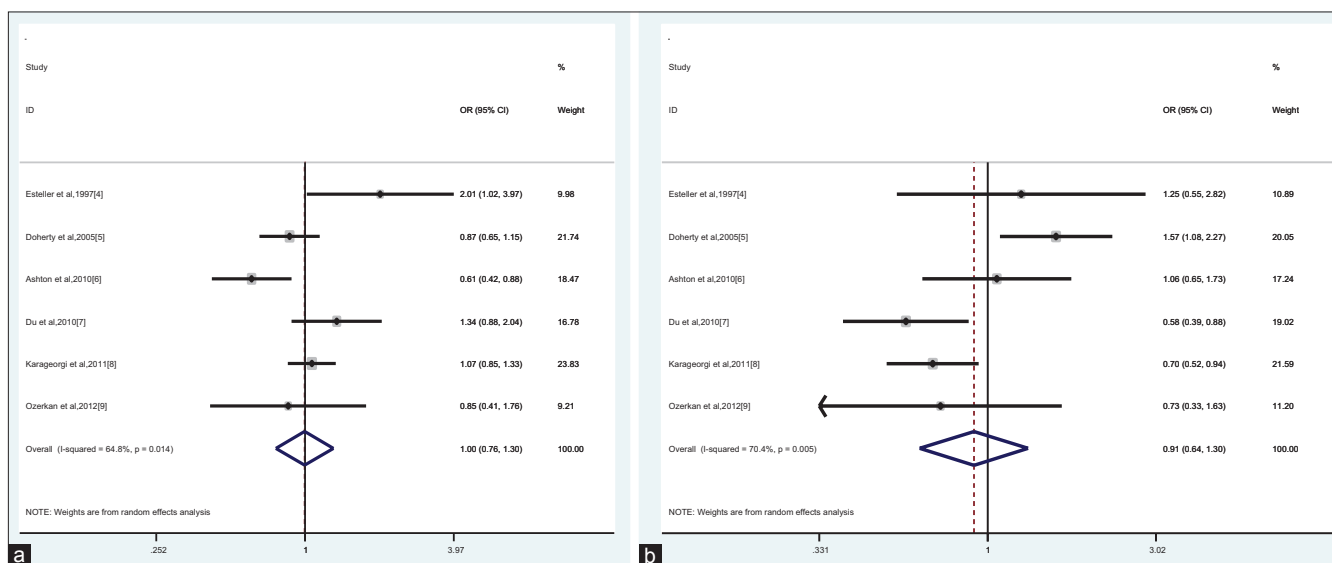

Figure 2: (a) Forest plot for the overall association between glutathione S-transferases M1 null genotype and endometrial cancer risk. (b) Forest plot for the overall association between glutathione S-transferases T1 null genotype and endometrial cancer risk

Table 2: Meta-analysis of the association between glutathione S-transferases M1, glutathione S-transferases T1 polymorphisms, and the risk of endometrial cancer

SNP	Null versus present	Study sample (case/control)	OR	95% CI	Heterogeneity I^2 (%)	P	P_Z	P_E	P_B
GSTM1	Total	1293/2211	1.00	0.76-1.30	64.80	0.014*	0.982	0.677	0.707
Subgroup-analysis	Hospital-based	678/1438	1.26	0.93-1.71	43.10	0.173	0.131	0.093	0.296
	Population-based	615/773	0.76	0.60-0.97	13.00	0.317	0.027*	0.759	1.000
GSTT1	Total	1286/2200	0.91	0.64-1.30	70.40	0.005*	0.619	0.641	0.707
Subgroup-analysis	Hospital-based	671/1427	0.70	0.52-0.93	24.20	0.268	0.015*	0.317	1.00
	Population-based	615/773	1.18	0.79-1.76	44.10	0.167	0.407	0.163	0.296

*Statistical significance. P_z=P for Z-test, P_E=P for Egger's test, P_B=P for Begg's test. SNP=Single nucleotide polymorphism, OR=Odds ratio, 95% CI=95% confidence interval, GSTM1=Glutathione S-transferases M1, GSTT1=Glutathione S-transferases T1
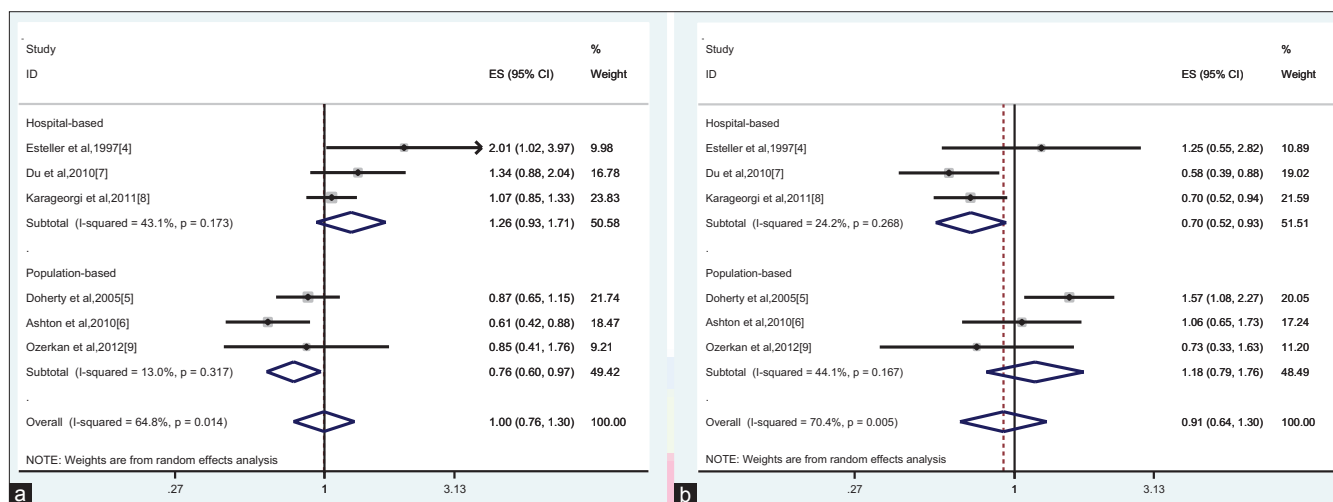
Figure 3: (a) Relationship between glutathione S-transferases M1 null genotype and endometrial cancer risk by study design. (b) Relationship between glutathione S-transferases T1 null genotype and endometrial cancer risk by study design

(OR = 0.76, 95% CI = 0.60-0.97, P = 0.027) and with the null genotype of GSTT1 polymorphism in hospital-based studies (OR = 0.70, 95% CI = 0.52-0.93, P = 0.015). More details are presented in Table 2.

Sensitivity analysis and potential publication bias

We performed a sensitivity analysis by excluding sequentially one study at a time to inspect the stability and reliability of our meta-analysis results. The recalculated ORs and 95% CIs did not change significantly, suggesting the results were robust and convincing. Publication bias was measured by both funnel plot and Egger's test. Results are shown in Figure 4a and b. The outlines did not reveal any evidence for publication bias (all $P > 0.05$). Details are shown in Table 2.

Discussion

The facts that the GSTs have broad and overlapping substrate specificities and that allelic variants associated with less effective detoxification of potential carcinogens may confer an increased susceptibility to cancer.[16,17] Previous research showed conflicting results that cannot reach an agreement.[4-9] We performed this meta-analysis to clarify new developments and produce more powerful estimation on the association between the GSTs gene polymorphisms and EC susceptibility. With more comprehensive data, the analysis showed no significant association between the GSTs and EC susceptibility.

Ozerkan et al. reported that GSTM1 and GSTT1 null genotype was not related with EC and no association could be demonstrated between GSTM1 and GSTT1 polymorphisms and clinical stages of EC as well.[9] Karageorgi et al. found that GSTM1 copy did not influence EC risk.[8] Esteller et al. showed that GSTT1 null genotype did not significantly increase the EC risk.[4] Interestingly, Ashton et al. found that the deletion of GSTM1 was associated with a decrease in EC risk. It is believed that the null genotypes decrease the enzymatic activity and have been proposed to increase cancer risk due to the inability to detoxify metabolites of estrogen.[6] Our studies revealed no association between GSTM1/GSTT1 and EC risk. The sensitivity analysis results showed the pooled ORs of the GSTs were compatible, representing that the present results were statistically robust. Notably, there was considerable between-study heterogeneity, and subgroups analyses were conducted in different study design. Then, we found a similar nonsignificant relationship between GSTM1 null genotype in population-based design and GSTT1 deletion
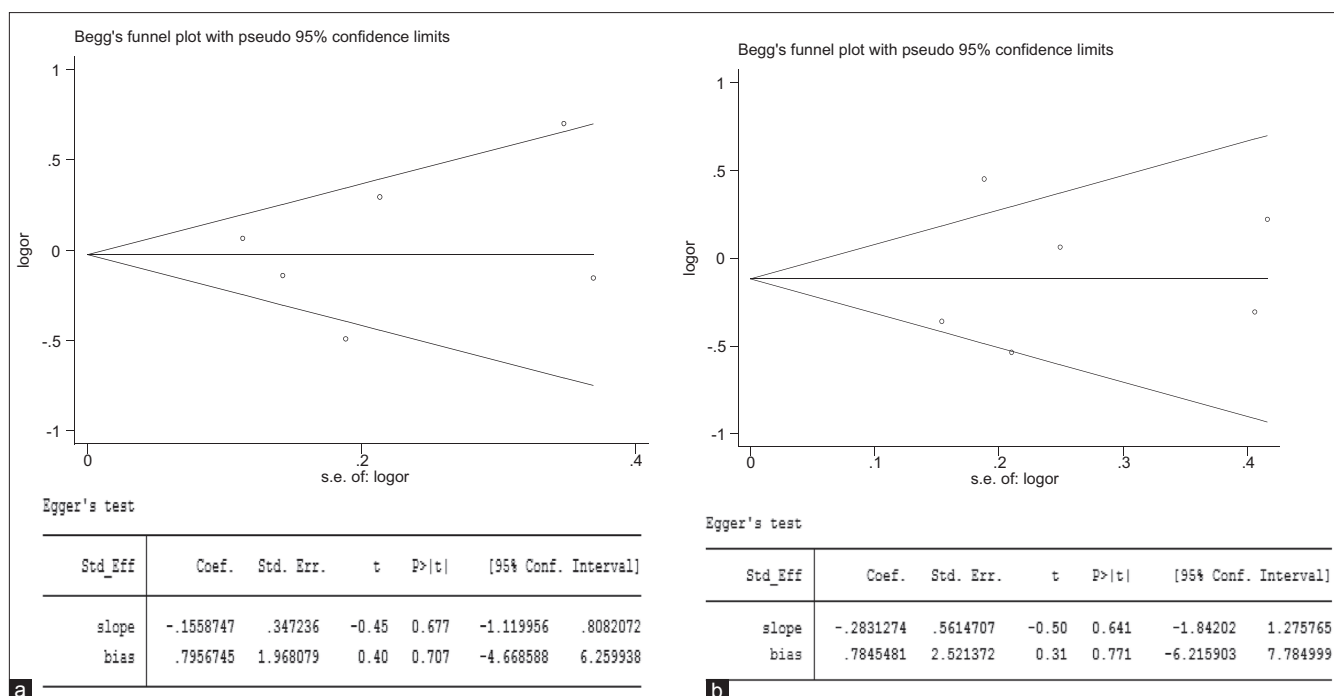
Figure 4: (a) Funnel plot for glutathione S-transferases M1 gene polymorphism and endometrial cancer risk. (b) Funnel plot for glutathione S-transferases T1 gene polymorphism and endometrial cancer risk

in hospital-based design, and the heterogeneity dropped in both subgroups. The results were similar to some previous studies and simultaneously inconsistent to other studies. Therefore, it is more likely that the inconsistent results among those studies were attributed to study design.

The present meta-analysis included 1307 cases and 2271 controls, which increased the statistical power. Pooled results revealed that GSTs had no association with the risk of EC, which was consistent with the reports from Ozerkan *et al*.[9] To determine the potential causes for the instability of the results, we performed subgroup analysis by source of the control. Results showed similar nonsignificant differences in hospital-based design of GSTM1 deletion and population-based design of GSTT1 deletion. However, results also showed that GSTM1 null polymorphism was significantly associated with EC risk in population-based design, while GSTT1 null genotype was related to EC risk in hospital-based design. The exact mechanisms of all GSTs are not clear; however, it appears that GSTs deactivate metabolites of estrogen formed during phase II estrogen metabolism. The null genotypes decrease the enzymatic activity and have been proposed to increase cancer risk due to the inability to detoxify metabolites of estrogen.[18] Moreover, the GSTs consist of seven classes and 60% of them are homology; therefore, it is possible that other GSTs catalyze the conjugation of glutathione of a wide variety of metabolites.[19-20] In other words, the nonsignificant relationship between GSTM1 and GSTT1 deletion genotype and EC implies that a role of functional genes might also be involved in activating compounds acted as endometrial carcinogens.[21] In addition, the effects

might also be blinded by chance or other unidentified factors involved in the endometrial carcinogenesis. Hence, our results should be interpreted with caution.

However, our study also has limitations. First, the subjects were mainly Caucasians, which may impose restrictions on applied to other ethnicities. Second, due to the limited sample size, it might not provide sufficient power to detect the weak association between the null GSTM1 and GSTM1 polymorphism and EC risk. Third, complex environmental factors also played critical roles in developing carcinoma, but we could not evaluate the interactive effect between genes and environment in our meta-analysis. Fourth, the present meta-analysis found no association between the GSTs genetic polymorphisms that may contribute to EC risk, but subgroup analysis did, and there were heterogeneity in the overall results and subgroup analysis, which might impair the stability of the study. In addition, the presence of other unidentified causal factors involved in the EC development, a more precise evaluation needs to be adjusted by other covariants if available. All those potential factors might affect the results of our meta-analysis.

Conclusions

On the basis of the statistical evidence, results from this meta-analysis showed that both GSTM1 genotype and GSTT1 genotype had no significant association with the development of EC. However, stratifying analysis by study design showed GSTM1 null genotype has a moderately strong association with EC risk in population-based design, while GSTT1 null genotype shows moderately increased risk for EC with no heterogeneity (both $I^2 < 25\%$).

Furthermore, epidemiological studies considering large sample size, well-matched controls, standardized unbiased genotyping methods would be required to precisely estimate the effect size of the association between EC risk and GSTM1 and GSTT1 polymorphisms.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

References

1. Cavalieri E, Frenkel K, Liehr JG, Rogan E, Roy D. Estrogens as endogenous genotoxic agents – DNA adducts and mutations. J Natl Cancer Inst Monogr 2000;(27):75-93.

2. Beckett GJ, Hayes JD. Glutathione S-transferases: Biomedical applications. Adv Clin Chem 1993;30:281-380.

3. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, Mariani A, Dowdy SC. Current issues in the management of endometrial cancer. Mayo Clin Proc 2008;83:97-112.

4. Esteller M, García A, Martínez-Palones JM, Xercavins J, Reventós J. Susceptibility to endometrial cancer: Influence of allelism at p53, glutathione S-transferase (GSTM1 and GSTT1) and cytochrome P-450 (CYP1A1) loci. Br J Cancer 1997;75:1385-8.

5. Doherty JA, Weiss NS, Freeman RJ, Dightman DA, Thornton PJ, Houck JR, et al. Genetic factors in catechol estrogen metabolism in relation to the risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev 2005;14:357-66.

6. Ashton KA, Proietto A, Otton G, Symonds I, McEvoy M, Attia J, et al. Polymorphisms in genes of the steroid hormone biosynthesis and metabolism pathways and endometrial cancer risk. Cancer Epidemiol 2010;34:328-37.

7. Du Y, Li L, Li Y, Zhang N, Cheng J. GSTM1 and GSTT1 gene polymorphism and endometrial cancer susceptibility. Chin J Pract Gynecol Obstet 2010;26:623-6.

8. Karageorgi S, Prescott J, Wong JY, Lee IM, Buring JE, De Vivo I. GSTM1 and GSTT1 copy number variation in population-based studies of endometrial cancer risk. Cancer Epidemiol Biomarkers Prev 2011;20:1447-52.

9. Ozerkan K, Atalay MA, Yakut T, Doster Y, Yilmaz E, Karkucak M. Polymorphisms of glutathione-s-transferase M1, T1, and P1 genes in endometrial carcinoma. Eur J Gynaecol Oncol 2013;34:42-7.

10. Wells GA, Shea B, O'connell D. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses [Ottawa Hospital Research Institute Web Site]; 2013. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Last cited on 2013 Nov 29].

11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

13. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.

14. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.

15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

16. Hengstler JG, Kett A, Arand M, Oesch-Bartlomowicz B, Oesch F, Pilch H, et al. Glutathione S-transferase T1 and M1 gene defects in ovarian carcinoma. Cancer Lett 1998;130:43-8.

17. Spurdle AB, Webb PM, Purdie DM, Chen X, Green A, Chenevix-Trench G. Polymorphisms at the glutathione S-transferase GSTM1, GSTT1 and GSTP1 loci: Risk of ovarian cancer by histological subtype. Carcinogenesis 2001;22:67-72.

18. Zhuo X, Cai L, Xiang Z, Li Q, Zhang X. GSTM1 and GSTT1 polymorphisms and nasopharyngeal cancer risk: An evidence-based meta-analysis. J Exp Clin Cancer Res 2009;28:46.

19. Pearson WR, Vorachek WR, Xu SJ, Berger R, Hart I, Vannais D, et al. Identification of class-mu glutathione transferase genes GSTM1-GSTM5 on human chromosome 1p13. Am J Hum Genet 1993;53:220-33.

20. Webb G, Vaska V, Coggan M, Board P. Chromosomal localization of the gene for the human theta class glutathione transferase (GSTT1). Genomics 1996;33:121-3.

21. Wilkinson J 4th, Clapper ML. Detoxication enzymes and chemoprevention. Proc Soc Exp Biol Med 1997;216:192-200.