Glutathione S-transferase M1 polymorphism and esophageal cancer risk: An updated meta-analysis based on 37 studies

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Supported by Science and Technology Project of The Health Department of Henan Province, China, No. 510102050432.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Data sharing statement: No additional data are available.

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Received: March 31, 2015
Peer-review started: April 1, 2015
First decision: June 19, 2015
Revised: October 6, 2015
Accepted: November 13, 2015
Article in press: November 13, 2015
Published online: February 7, 2016

Abstract

AIM: To evaluate the relationship between glutathione S-transferase M1 (GSTM1) polymorphism and susceptibility to esophageal cancer (EC).

METHODS: A comprehensive search of the United States National Library of Medicine PubMed database and the Elsevier, Springer, and China National Knowledge Infrastructure databases for all relevant studies was conducted using combinations of the following terms: “glutathione S-transferase M1”, “GSTM1”, “polymorphism”, and “EC” (until November 1, 2014). The statistical analysis was performed using the SAS software (v.9.1.3; SAS Institute, Cary, NC, United States) and the Review Manager software (v.5.0; Oxford, England); crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association between the GSTM1 null genotype and the risk of EC.

RESULTS: A total of 37 studies involving 2236 EC cases and 3243 controls were included in this meta-analysis. We observed that the GSTM1 null genotype
was a significant risk factor for EC in most populations (OR = 1.33, 95%CI: 1.12-1.57, \( P_{\text{heterogeneity}} < 0.000001, \) and \( I^2 = 77.0\% \)), particularly in the Asian population (OR = 1.53, 95%CI: 1.26-1.86, \( P_{\text{heterogeneity}} < 0.000001, \) and \( I^2 = 77.0\% \)), but not in the Caucasian population (OR = 1.02, 95%CI: 0.87-1.19, \( P_{\text{heterogeneity}} = 0.97, \) and \( I^2 = 0\% \)).

CONCLUSION: The GSTM1 null polymorphism may be associated with an increased risk for EC in Asian but not Caucasian populations.

Key words: Meta-analysis; Glutathione S-transferase M1; Polymorphism; Esophageal cancer; Deletions

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Core tip: Many previous studies have investigated the association between the glutathione S-transferase M1 (GSTM1) null genotype and the risk of esophageal cancer (EC), but these studies have provided controversial findings. The present study represents the largest meta-analysis to estimate the association between the GSTM1 polymorphism and EC risk. We investigated these two genotypes (GSTM1 null or GSTM1 present) in terms of EC morbidity.

Lu QJ, Bo YC, Zhao Y, Zhao EJ, Sapa WB, Yao MJ, Duan DD, Zhu YW, Lu QJ, Li QJ, Yuan L. Glutathione S-transferase M1 and esophageal cancer risk: A meta-analysis. World J Gastroenterol 2016; 22(5): 1911-1918 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i5/1911.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i5.1911

INTRODUCTION

Esophageal cancer (EC), which is the sixth leading cause of cancer-associated death worldwide, has two major histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EADC)[1]. The five-year survival rate for EC is less than 20%[2]. A growing body of epidemiological evidence suggests that environmental factors together with genetic factors play important roles in the risk of developing EC[3,4]. The major risk factors for EC include alcohol consumption, smoking tobacco, and micronutrient deficiency[5]. Various factors and multiple processes lead to EC development. In addition to the above mentioned factors, genetic factors also account for EC cases.

Previous studies have suggested that glutathione S-transferases (GSTs) are phase II metabolizing enzymes that detoxify free radicals and other carcinogens[6]. Therefore, individual variation in phases II enzyme activity may contribute to varying susceptibility to EC progression. The GST family plays an important role in the detoxification of a variety of electrophilic carcinogens through conjugation with glutathione, and there is a widely variable organ distribution of the four classes of GSTs, although all of these display esophageal expression: GSTA (a), GSTM (m), GSTP (p), and GSTT (t)[7]. Homozygous deletions of GSTM1 have been associated with the loss of enzymatic activity for the detoxification of carcinogens, which consequently confers a risk for some cancers, such as colorectal, pancreatic, esophageal, and head and neck cancers[9-12]. Therefore, the null genotype of GSTM1 might be associated with an increased risk of EC[13]. Many previous studies have investigated the association between the GSTM1 null genotype and the risk of EC, but these studies have provided controversial findings[8,14-18]. It remains uncertain whether the GSTM1 polymorphism is a risk factor for EC. Considering these controversial results, we conducted a meta-analysis summarizing reported case-control or prospective studies to assess the risk of EC.

MATERIALS AND METHODS

Search strategy

We conducted a comprehensive search of the US National Library of Medicine PubMed database and the Elsevier, Springer, and China National Knowledge Infrastructure databases for all relevant studies using combinations of the following terms: “glutathione S-transferase M1”, “GSTM1”, “polymorphism”, and “EC” (until November 1, 2014). Additional eligible studies were identified through references that were cited in the relevant articles. The full text of each potentially relevant paper was scrutinized to ensure that the following inclusion criteria were met: (1) the articles clearly described studies concerning the association of EC with GSTM1 polymorphism; (2) The study design should be observational (case-control or prospective); (3) Sufficient data for estimating the odds ratios (ORs) and 95% confidence intervals (CIs) were present; and (4) If more than one publication reported on the same population, we selected the study with the largest sample size.

Data extraction

Two researchers independently extracted the following data from each study that met the inclusion criteria: first author’s surname, year of publication, country, ethnicity of the subjects (stratified into Asian, Caucasian, and African populations), sources of the controls (categorized as population-based studies and hospital-based studies), histological type (adenocarcinoma and squamous cell carcinoma), number of different genotypes in cases and controls, smoking status, and the frequency of different genotypes in the cases and controls. Individuals with “present” genotype were defined as carriers with at least one of the functional alleles in accordance with the definition used in most studies, whereas individuals...
Table 1  Characteristics of the studies included in this meta-analysis

| Ref. | Year | Ethnicity | Country       | Source of controls | Genotype distribution | Case | Control |
|------|------|-----------|---------------|-------------------|-----------------------|------|---------|
|      |      |           |               |                   |                       | Null| Present |         |         |         |
| Morita et al[38] | 1997 | Asian | Japan         | PB                | 23                     | 30  | 55      | 77     |
| Nimura et al[39] | 1997 | Asian | China         | HB                | 47                     | 42  | 63      | 74     |
| Horii et al[40]  | 1997 | Asian | Japan         | HB                | 41                     | 53  | 196     | 232    |
| Lin et al[41]    | 1998 | Asian | China         | PB                | 20                     | 25  | 21      | 24     |
| Shao et al[42]   | 1999 | Asian | China         | HB                | 68                     | 40  | 55      | 57     |
| van Lieshout et al[34] | 1999 | Caucasian | The Netherlands | PB | 17 | 17 | 128     | 119    |
| Tan et al[43]    | 2000 | Asian | China         | PB                | 46                     | 104 | 76      | 74     |
| Shi et al[44]    | 2002 | Asian | China         | HB                | 67                     | 31  | 51      | 69     |
| Yokoyama et al[45] | 2002 | Asian | Japan         | HB                | 103                    | 131 | 321     | 313    |
| Gao et al[46]    | 2002 | Asian | China         | PB                | 106                    | 35  | 133     | 90     |
| Cassner et al[47] | 2003 | Caucasian | Canada      | PB                | 26                     | 19  | 25      | 20     |
| Wang et al[48]   | 2003 | Asian | China         | PB                | 27                     | 35  | 19      | 19     |
| Wang et al[49]   | 2004 | Asian | China         | HB                | 74                     | 53  | 44      | 57     |
| Abbas et al[50]  | 2004 | Caucasian | France    | PB                | 39                     | 29  | 59      | 61     |
| Roth et al[51]   | 2004 | Asian | China         | HB                | 41                     | 90  | 145     | 309    |
| Han et al[52]    | 2005 | Asian | China         | HB                | 46                     | 43  | 48      | 51     |
| Lu et al[53]     | 2005 | Asian | China         | PB                | 36                     | 68  | 4       | 100    |
| Yin et al[54]    | 2005 | Asian | China         | HB                | 69                     | 37  | 61      | 45     |
| Cassner et al[55] | 2006 | Caucasian | Canada    | HB                | 34                     | 22  | 54      | 41     |
| Jain et al[56]   | 2006 | Asian | India         | HB                | 39                     | 61  | 51      | 86     |
| Dong et al[57]   | 2007 | Asian | China         | HB                | 76                     | 44  | 51      | 69     |
| Wideroff et al[58] | 2007 | Caucasian | United States | PB | 37 | 30 | 121     | 87     |
| Rossini et al[59] | 2007 | Caucasian | Brazil   | HB                | 51                     | 74  | 99      | 153    |
| Li et al[60]     | 2008 | Asian | China         | PB                | 77                     | 48  | 55      | 70     |
| Zemrehdel et al[61] | 2009 | Caucasian | Sweden     | PB                | 85                     | 85  | 230     | 239    |
| Ji et al[62]     | 2010 | Asian | China         | PB                | 111                    | 78  | 98      | 127    |
| Malik et al[63]  | 2010 | Asian | India         | HB                | 68                     | 67  | 79      | 116    |
| Liu et al[64]    | 2010 | Asian | China         | PB                | 54                     | 43  | 32      | 65     |
| Moaven et al[65] | 2010 | Asian | Iran          | HB                | 65                     | 83  | 58      | 78     |
| Li et al[66]     | 2010 | Black | Africa        | HB                | 33                     | 206 | 80      | 200    |
| Gao et al[67]    | 2012 | Asian | China         | HB                | 22                     | 18  | 45      | 35     |
| Chen et al[68]   | 2012 | Asian | China         | HB                | 68                     | 31  | 90      | 96     |
| Liu et al[69]    | 2013 | Asian | China         | HB                | 47                     | 63  | 74      | 146    |
| Talukdar et al[70] | 2013 | Asian | India         | PB                | 44                     | 68  | 40      | 90     |
| Sharma et al[71] | 2013 | Asian | India         | PB                | 129                    | 186 | 139     | 297    |
| Dura et al[72]   | 2013 | Caucasian | The Netherland | PB | 228 | 204 | 318     | 273    |
| Djansugurova et al[73] | 2013 | Asian | Kazakhstan    | PB | 72 | 43 | 24      | 76     |

PB: Population-based study; HB: Hospital-based study.

were performed using the SAS (v.9.1.3; SAS Institute, Cary, NC, United States) and Review Manager software (v.5.0; Oxford, England) with two-sided P values and a 0.05 significance level.

RESULTS

Eligible studies

A total of 37 studies involving 2236 EC cases and 3243 controls were finally included in this meta-analysis[8,12-18,23-51]. The main characteristics of these studies are presented in Table 1. Among these studies, one case-control study was nested within a cohort study[51], and 25 studies provided data of the histological type of the EC cases. The smoking statuses of the cases and controls were recorded in six studies.

Meta-analysis

Considering the obvious heterogeneity among the 37

Statistical analysis

Crude ORs with 95%CI s were used to estimate the strength of the relationship between the GSTM1 polymorphism and EC risk. The pooled ORs were evaluated for null vs present genotypes. The heterogeneity was assessed using a χ² analysis based on the Q-test[19]. The heterogeneity was considered significant for P < 0.05. In the presence of significant heterogeneity, a random-effects model (the DerSimonian and Laird method)[20] was used to calculate pooled estimates; otherwise, a fixed-effects model (the Mantel-Haenszel method) was used[21]. These two models provided similar results in the absence of heterogeneity. The potential publication bias was assessed using a funnel plot and linear regression asymmetry test[22]. The statistical analyses
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| Study or subgroup | Case Events | Control Events | Total Events | Total Weight | Odds ratio M-H, random, 95%CI | Odds ratio M-H, random, 95%CI |
|------------------|-------------|----------------|-------------|--------------|-------------------------------|-------------------------------|
| Abbas 2004       | 39          | 68             | 97          | 2.5%         | 1.39 [0.76, 2.53]             |                              |
| CHEN 2012        | 68          | 99             | 167         | 2.8%         | 2.34 [1.40, 3.91]             |                              |
| Djansugurova 2013| 72          | 115            | 187         | 2.6%         | 5.30 [2.93, 9.61]             |                              |
| Dong 2007        | 76          | 120            | 196         | 2.8%         | 2.34 [1.39, 3.92]             |                              |
| Dura 2013        | 228         | 432            | 650         | 3.5%         | 0.96 [0.75, 1.23]             |                              |
| FRSCC 2006       | 34          | 56             | 90          | 2.4%         | 1.17 [0.60, 2.30]             |                              |
| FRSCC 2003       | 26          | 45             | 71          | 2.0%         | 0.99 [0.48, 2.52]             |                              |
| Gao 2002         | 106         | 141            | 247         | 2.9%         | 2.05 [1.29, 3.27]             |                              |
| GAO 2012         | 22          | 40             | 62          | 2.1%         | 0.95 [0.44, 2.04]             |                              |
| HAN 2005         | 46          | 89             | 135         | 2.6%         | 1.14 [0.64, 2.02]             |                              |
| Hori 1997        | 41          | 94             | 135         | 3.0%         | 0.92 [0.58, 1.44]             |                              |
| Jain 2006        | 39          | 100            | 139         | 2.7%         | 1.08 [0.63, 1.83]             |                              |
| Ji 2010          | 111         | 189            | 300         | 3.1%         | 1.84 [1.25, 2.73]             |                              |
| Li 2010          | 33          | 239            | 272         | 3.0%         | 0.40 [0.26, 0.63]             |                              |
| Li 2008          | 77          | 125            | 202         | 2.8%         | 2.04 [1.23, 3.38]             |                              |
| Lin 1998         | 20          | 45             | 65          | 2.0%         | 0.91 [0.40, 2.10]             |                              |
| Liu 2010         | 54          | 97             | 151         | 2.6%         | 2.55 [1.42, 4.57]             |                              |
| Liu 2013         | 47          | 110            | 157         | 2.9%         | 1.47 [0.92, 2.36]             |                              |
| Lu 2005          | 36          | 104            | 140         | 1.5%         | 13.24 [4.50, 38.89]           |                              |
| Malik 2010       | 68          | 135            | 203         | 3.0%         | 1.49 [0.96, 2.32]             |                              |
| Moaven 2010      | 65          | 148            | 213         | 2.9%         | 1.05 [0.66, 1.69]             |                              |
| MORITA 1997      | 23          | 55             | 78          | 2.4%         | 1.07 [0.56, 2.04]             |                              |
| Nimura 1997      | 47          | 89             | 136         | 2.7%         | 1.31 [0.77, 2.24]             |                              |
| Rossini 2007     | 51          | 125            | 176         | 3.0%         | 1.07 [0.69, 1.65]             |                              |
| Roth 2004        | 41          | 131            | 172         | 3.0%         | 0.97 [0.64, 1.48]             |                              |
| Shao 1999        | 68          | 108            | 176         | 2.7%         | 1.76 [1.03, 3.02]             |                              |
| Sharma 2013      | 129         | 315            | 444         | 3.3%         | 1.48 [1.10, 2.00]             |                              |
| Shi 2002         | 67          | 98             | 165         | 2.7%         | 1.92 [1.67, 5.11]             |                              |
| Talukdar 2013    | 44          | 112            | 156         | 2.7%         | 1.46 [0.86, 2.48]             |                              |
| Tan 2000         | 46          | 150            | 196         | 2.9%         | 0.40 [0.27, 0.69]             |                              |
| Van Lieshout 1999| 17          | 34             | 51          | 2.2%         | 0.93 [0.45, 1.90]             |                              |
| Wang 2003        | 27          | 62             | 89          | 2.0%         | 0.77 [0.34, 1.73]             |                              |
| Wang 2004        | 74          | 127            | 191         | 2.7%         | 1.81 [1.07, 3.07]             |                              |
| Wideroff 2007    | 37          | 67             | 104         | 2.7%         | 0.89 [0.51, 1.54]             |                              |
| Yin 2005         | 69          | 106            | 175         | 2.7%         | 1.38 [0.79, 2.40]             |                              |
| Yokoyama 2002    | 103         | 234            | 337         | 3.3%         | 0.77 [0.57, 1.04]             |                              |
| Zendehdel 2009   | 85          | 170            | 255         | 3.2%         | 1.04 [0.73, 1.48]             |                              |

Total events: 2236, Total (95%CI): 4572, 7377 (100.0%), 1.33 [1.12, 1.57]

Heterogeneity: Tau² = 0.20, I² = 154.38, df = 36 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.27 (P = 0.001)

Figure 1 Forest plot for the association between the glutathione S-transferase M1 polymorphism and esophageal cancer risk.

Included studies (P < 0.001, I² = 77%), the random-effects model (DerSimonian-Laird method) was used to calculate the pooled ORs for the GSTM1 null vs GSTM1 present genotypes. Individuals with GSTM1 null genotypes were significantly associated with an increased risk for EC compared those carrying the GSTM1 present genotype (OR = 1.33, 95%CI: 1.12-1.57, Figure 1). In the sensitivity analysis, individual studies were sequentially removed. The results indicated that no individual study significantly affected the pooled OR, suggesting that these results were statistically robust.

In the subgroup analysis based on ethnicity, a positive correlation was observed between the GSTM1 null genotype and the EC risk in the Asian population (OR = 1.53, 95%CI: 1.26-1.86) but not in the Caucasian population (OR = 1.02, 95%CI: 0.87-1.19). However, the results of the stratified analysis based on histological type showed that the GSTM1 null genotype increased the risk of EC in patients whose histological type was unknown, but no statistically significant association was observed for either the ESCC or the EADC patients. Moreover, the heterogeneity was significantly reduced among Caucasian populations and studies based on the histological type of adenocarcinoma. Because only one study (14EADC, 137 ESCC) reported an association between the GSTM1 polymorphism and EADC in Asian populations, we only analyzed the data according to ESCC and EADC in Caucasian populations, and the results showed no statistically significant association between the GSTM1 polymorphism and...
ESCC or EADC. The main results of this meta-analysis and the heterogeneity test are shown in Table 2.

**Publication bias**
A funnel plot was used to graphically estimate the publication bias of the literature. As shown in Figure 2, the shape of the funnel plot was symmetrical in the overall population, suggesting the absence of publication bias. The results of Egger's test showed statistical evidence for funnel plot symmetry (t = 1.76, P = 0.0873).

**DISCUSSION**
GSTM1 is a member of the family of cytosolic GSTs, which are phase II xenobiotic-metabolizing enzymes. These enzymes play a crucial role in the detoxification and elimination of electrophilic carcinogens through conjugation with glutathione[12]. Many studies have investigated the association between the GSTM1 null genotype and various types of cancer, such as colorectal carcinoma, lung cancer, liver cancer, and EC, but the findings are controversial, particularly those obtained for EC[52,53]. The results of this meta-analysis showed that the GSTM1 null genotype is significantly associated with an increased risk of EC in the overall population. Furthermore, in the subgroup analysis by ethnicity, we detected a significant association between the GSTM1 polymorphism and EC risk in Asians but not in Caucasians, suggesting that the GSTM1 null polymorphism might contribute to increased susceptibility to EC in Asians. Similar results have been obtained in several previous meta-analyses[54,55]. However, other studies have shown conflicting results. A pooled analysis of 20 studies from the Archives of Medical Research revealed that there was no evidence of increased risk of EC associated with the GSTM1 null genotype[56]. The result might reflect a relatively small sample size and, to a lesser extent, different ethnicities, different histological types and the source of the controls.

In the present meta-analysis, most of the included studies concerned Asian populations. This phenomenon might be attributed to the occurrence of EC, which displays a remarkable geographical difference. Specifically, the “EC belt”, which stretches from North Central China westward through Central Asia and northern Iran, exhibits a particularly high EC incidence in Asian populations[57], which explains why many of the studies were conducted in Asian countries.

In the subgroup analysis based on histological type, no significant association was detected between the GSTM1 polymorphism and ESCC or EADC risk, indicating that histological type might affect the statistical correlation between the GSTM1 polymorphism and EC. Similar results have been reported in previous studies[23,55,58], indicating that further clarification of the histological type might avoid the interference of some confounding factors.

Several potential limitations of the present meta-analysis should also be acknowledged. Only one of the included studies was conducted in Africa, and it did not provide sufficient data for the subgroup analysis based on ethnicity. Therefore, we could not include the African population in the subgroup analysis based on ethnicity. Moreover, only published studies were included in the present meta-analysis, which might have biased the results.

In conclusion, this meta-analysis demonstrated that the GSTM1 null polymorphism might be associated with an increased risk for EC in Asian populations but not in Caucasian populations. Larger well-designed epidemiological studies are warranted to verify these findings.

| Table 2  Main results of the pooled odds ratios in this meta-analysis |
|-----------------------------|----------------|------------------|-----------------|
|                           | Null vs present |                |                |
|                           | No. of studies | OR               | 95%CI           | P  value       |
| Total                     | 37             | 1.33             | 1.12-1.57       | 0.00001        |
| Ethnicity                 |                |                  |                 |                |
| Asian                     | 27             | 1.53             | 1.26-1.86       | 0.00001        |
| Caucasian                 | 8              | 1.02             | 0.87-1.19       | 0.97           |
| Histological type         |                |                  |                 |                |
| ESCC                      | 22             | 1.15             | 0.91-1.45       | 0.00001        |
| EADC                      | 8              | 0.98             | 0.81-1.18       | 0.93           |
| NR                        | 12             | 1.82             | 1.58-2.09       | 0.007          |
| Smoking status            |                |                  |                 |                |
| Smokers                   | 6              | 0.97             | 0.53-1.77       | 0.00001        |
| Nonsmokers                | 6              | 0.97             | 0.57-1.64       | 0.001          |
| Histological type of     |                |                  |                 |                |
| Caucasian                 |                |                  |                 |                |
| ESCC                      | 5              | 1.15             | 0.91-1.45       | 0.33           |
| EADC                      | 8              | 0.98             | 0.81-1.18       | 0.93           |

The P value for heterogeneity. ESCC: Esophageal squamous cell carcinoma; EADC: Esophageal adenocarcinoma; NR: Not reported.

Figure 2  Funnel plot evaluating the risk of publication bias in this meta-analysis.
Esophageal cancer (EC), which is the sixth leading cause of cancer-associated death worldwide, has two major histological types: esophageal squamous cell carcinoma and esophageal adenocarcinoma. The five-year survival rate for EC is less than 20%. Previous studies have suggested that glutathione S-transferase (GSTs) are phase II metabolizing enzymes that detoxify free radicals and other carcinogens. Therefore, individuals with low phase II activity might have a higher risk of developing cancer. The GST family plays an important role in the detoxification of a variety of electrophilic carcinogens through conjugation with glutathione, and there is a widely variable organ distribution of the four classes of GSTs, namely, GSTA (α), GSTM (μ), GSTP (π), and GSTT (h), although all show esophageal expression.

Research frontiers
A growing body of epidemiological evidence suggests that environmental factors together with genetic factors play important roles in the risk of developing esophageal carcinoma: alcohol consumption, smoking tobacco, and micronutrient deficiency are considered the major risk factors for EC. The GSTM1 null genotype has been associated with an increased risk of EC. Many previous studies have investigated the association between the GSTM1 null genotype and the risk of esophageal carcinoma, but these studies provide controversial findings.

Innovations and breakthroughs
The results of the present study indicated that the GSTM1 null polymorphism might be associated with an increased risk of EC in Asian populations but not in Caucasian populations, which would be helpful for the identification of individuals at an increased risk of developing EC.

Applications
The present study enhances the current understanding of the effects of GSTM1 on EC. Larger well-designed epidemiological studies are warranted to confirm the precise mechanism underlying the involvement of the GSTM1 gene in EC progression.

Terminology
GSTM1 is a primary member of the GST family, which comprises enzymes that play important roles in the detoxification of a variety of electrophilic carcinogens through conjugation with glutathione. Homozygous deletions of GSTM1 might disrupt enzymatic detoxification of carcinogens and consequently confer risk for some cancers, such as colorectal, pancreatic, esophageal, and head and neck cancers.

Peer-review
The present study analyzed the effect of the GST1 polymorphism on EC risk. The meta-analysis of 37 studies showed that the GSTM1 null polymorphism is associated with a significantly increased risk of EC.

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