Is there association between *Glutathione S Transferases* polymorphisms and cataract risk: a meta-analysis?

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**Abstract**

**Background:** *Glutathione S transferase* (GST) polymorphisms have been considered as risk factors for age-related cataracts, but the results remain controversial. In this study, we have performed a meta-analysis to evaluate the association between polymorphisms of *GSTM1* and *GSTT1* and cataract risk.

**Methods:** Published literature from PubMed and other databases were retrieved. The case–control studies regarding the association between *GSTM1* or *GSTT1* polymorphism and cataract risk were included. Pooled odds ratio (OR) and 95 % confidence interval (CI) were calculated using random- or fixed-effects model.

**Results:** Fifteen studies on *GSTM1* (3,065 patients and 2,105 controls), and nine studies on *GSTT1* (2,374 patients and 1,544 controls) were included. By pooling all the studies, *GSTM1* null polymorphism was not associated with cataract risk, and this negative association maintained in subgroup analyses. However, *GSTT1* null polymorphism was significantly associated with increased risk of posterior subcapsular (OR, 1.42; 95 % CI, 1.04–1.94) but not other subtypes of cataract. Stratified analyses demonstrated an association of *GSTT1* null genotype with increased risk of cataract in Asian (OR, 1.44; 95 % CI, 1.14–1.83) but not Caucasian populations. In addition, seven pooled studies showed no association of cataract risk with the combined *GSTM1* and *GSTT1* null genotypes.

**Conclusions:** This meta-analysis suggests that *GSTT1* null polymorphism is associated with increased risk of posterior subcapsular cataract. Given the limited sample size, the association between *GSTT1* null polymorphism and cataract risk in Asian awaits further investigation.

**Keywords:** *Glutathione S Transferases*, Polymorphisms, Cataract, Meta-analysis

**Background**

Cataract is the opacification of eye lens with the breakdown of the lens protein microarchitecture, which adversely affects the transmission of light onto the retina [1]. Recent data suggest that cataract remains the leading cause of blindness worldwide, and the age-related cataract accounts for approximately 50 % of blindness cases [2]. Epidemiologic studies have revealed some environmental risk factors for age-related cataract, including ultraviolet B light exposure, ionizing radiation, smoking, and use of steroids [3]. Recently, genetic factors have been found to play important roles in the pathogenesis of age-related cataract [4]; furthermore, gene polymorphisms have been reported to be associated with age-related cataract risk [5, 6].

It has been reported that oxidative stress contributes to development of age-related cataract [7]. Biochemical evidence demonstrates that generation of excessive reactive oxygen species (ROS) results in abnormal degradation, cross linking, and aggregation of lens proteins, and is involved in cataractogenesis [8]. The oxidative damage during cataractogenesis can be alleviated by cellular defense mechanisms, including catalase, superoxide dismutase, glutathione peroxidase, and glutathione *S* transferases (GSTs) in the eye [9]. Among them, GSTs are a superfamily of enzymes that play important roles in the detoxification, elimination of xenobiotics and...

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antioxidation, such as carcinogens, toxins, oxidants and drugs [10]. This enzymatic superfamily is composed of three different families: mitochondrial, microsomal and cytosolic. The cytosolic family of GSTs are classified in seven classes based on chromosomal location and on sequence similarity: alpha (GSTA), mu (GSTM), pi (GSTP), theta (GSTT), kappa (GSTK), zeta (GSTZ) and omega (GSTOP) [11].

Previous studies have identified numerous variants in GST genes, and some of these polymorphisms are functional, e.g., GSTT1 and GSTM1 null polymorphisms [12]. In fact, the deletion of GSTT1 or GSTM1 results in dysfunction of their enzyme activity [12], and these polymorphisms of GST are associated with increased risks of various pathologies including cancers [13] and ophthalmologic problems such as glaucoma [14]. The relationships between GST polymorphisms and risks of age-related cataract have been studied for many years, and an early meta-analysis suggested that GSTM1 and GSTT1 null genotypes were associated with increased risk for senile cataract in Asians but not Caucasians [6]. However, recent studies showed that GSTM1 positive (GSTM1+/+) genotype was associated with a susceptibility to age-related cortical cataract in Asians [15], while GSTM1 or GSTT1 null genotype was associated with age-related cataract risk in Caucasians [16, 17]. These inconsistent results may be due to the relatively small size of study populations from each individual study, or limited studies included by the previous meta-analysis; therefore, in this study we have conducted an update meta-analysis to reevaluate the associations between GSTM1 and GSTT1 polymorphisms and age-related cataract risk.

Methods
Identification of eligible studies
To identify all articles that evaluated the association of GST polymorphism with cataract, we carried out a literature search in the PubMed databases up to December

![Fig. 1 Flow diagram of studies identification](image-url)
2014 with the following MeSH terms and keywords: “cataract”, “glutathione S transferase", and “polymorphism”. The manual search was conducted to identify additional studies from other sources (e.g., Embase, Web of Knowledge, China National Knowledge Infrastructure), review articles on this topic or references to original studies. The inclusion criteria for eligible studies included in this meta-analysis as follows: (a) a study evaluating the association between GSTM1 or GSTT1 null polymorphism and cataract, (b) a case-control study, (c) an unrelated study, if studies had partly overlapped subjects, only the one with a larger sample size was selected, (d) a study with available genotype frequency, and (e) a study with sufficient data for estimating odds ratio (OR) and 95 % confidence interval (CI). Our meta-analysis was in accordance with PRISMA guidelines.

Because the data included in this study were retrieved from the literatures, written informed consent for participation and ethical approval have been provided by original studies. Thus, all investigations analyzed in this meta-analysis have been carried out in compliance with the Helsinki Declaration.

**Data extraction**

Two investigators (W.S. and L.S) independently assessed the articles for inclusion, and reached a consensus on data extracted. For each study, the following information was extracted: the first author name and publication year of the article; ethnicity (country) of study subjects; gene polymorphisms and genotype frequencies; sample size (numbers of cases and controls); sources of controls; subtypes of cataract classified. The missing data and information of included studies were obtained by contacting the study authors through email.

**Statistical analysis**

The association between GSTM1, or GSTT1 polymorphism and cataract was estimated by calculating pooled OR.

### Table 1 Characteristics of literatures included in the meta-analysis

| Author/ Year | Country       | Ethnicity | Sample size Cases/controls | Source of controls | Cataract subtype |
|--------------|---------------|-----------|----------------------------|--------------------|------------------|
| GSTM1        |               |           |                            |                    |                  |
| Sekine 1995  | Japan         | Asian     | 138/62 (101/30)            | PB                 | Not classified   |
| Alberti 1996 | United States | Caucasian | 202/98 (99/49)             | HB                 | NC/CC/M          |
| Pi 1996      | China         | Asian     | 59/112 (41/57)             | HB                 | Not classified   |
| Hao 1999     | China         | Asian     | 77/76 (41/35)              | HB                 | Not classified   |
| Juronen 2000 | Estonia       | Caucasian | 503/202 (240/111)          | HB                 | CC/NC/PSC/M      |
| Saadat 2004  | Iran          | Caucasian | 150/150 (90/58)            | HB                 | Not classified   |
| Saadat 2006  | Iran          | Caucasian | 95/95 (56/36)              | HB                 | Not classified   |
| Guven 2007   | Turkey        | Caucasian | 195/136 (105/58)           | HB                 | CC/NC/PSC/M      |
| Xu 2007      | China         | Asian     | 120/118 (81/60)            | HB                 | Not classified   |
| Azeem 2009   | Egypt         | Caucasian | 53/73 (23/46)              | HB                 | Not classified   |
| Zhou 2010    | China         | Asian     | 279/145 (171/95)           | PB                 | Not classified   |
| Sireesha 2012| India         | Caucasian | 455/205 (177/94)           | PB                 | CC/NC/PSC/M      |
| Saadat 2012  | Iran          | Caucasian | 186/195 (104/89)           | HB                 | Not classified   |
| Jiang 2012   | China         | Asian     | 422/312 (176/173)          | CC                 |                 |
| Chandra 2014 | India         | Caucasian | 124/126 (43/68)            | HB                 | Not classified   |
| GSTT1        |               |           |                            |                    |                  |
| Juronen 2000 | Estonia       | Caucasian | 503/202 (73/36)            | HB                 | CC/NC/PSC/M      |
| Saadat 2004  | Iran          | Caucasian | 150/150 (49/46)            | HB                 | Not classified   |
| Guven 2007   | Turkey        | Caucasian | 195/136 (29/22)            | HB                 | CC/NC/PSC/M      |
| Azeem 2009   | Egypt         | Caucasian | 53/73 (16/21)              | HB                 | Not classified   |
| Zhou 2010    | China         | Asian     | 279/145 (146/60)           | PB                 | CC/NC/PSC        |
| Sireesha 2012| India         | Caucasian | 455/205 (123/40)           | PB                 | CC/NC/PSC/M      |
| Saadat 2012  | Iran          | Caucasian | 186/195 (49/57)            | HB                 | Not classified   |
| Jiang 2012   | China         | Asian     | 422/312 (221/138)          | CC                 |                 |
| Chandra 2014 | India         | Caucasian | 131/126 (18/5)             | HB                 | Not classified   |

Abbreviations: PB population-based, HB hospital-based, CC cortical cataract, NC nuclear cataract, PSC posterior sub-capsular cataract, MC mixed cataract

*The number of null genotype cases or controls was presented in parenthesis*
Table 2 Association between GSTM1 or GSTT1 polymorphism and cataract risk

| Groups          | N\(^a\) | Statistical method\(^b\) | OR (95 % CI)       | P     |
|-----------------|---------|--------------------------|--------------------|-------|
| GSTM1 All       | 15      | Random (P < 0.001)       | 1.17 (0.88–1.57)   | 0.288 |
| Caucasian       | 9       | Random (P < 0.001)       | 1.07 (0.75–1.53)   | 0.712 |
| Asian           | 6       | Random (P < 0.001)       | 1.37 (0.79–2.40)   | 0.266 |
| Study design    |         |                          |                    |       |
| Population-based| 3       | Random (P = 0.001)       | 1.17 (0.58–2.33)   | 0.666 |
| Hospital-based  | 12      | Random (P < 0.001)       | 1.18 (0.84–1.65)   | 0.350 |
| Gender          |         |                          |                    |       |
| Male            | 5       | Random (P = 0.035)       | 0.89 (0.58–1.37)   | 0.598 |
| Female          | 5       | Random (P < 0.001)       | 1.02 (0.44–2.32)   | 0.970 |
| Subtype         |         |                          |                    |       |
| Cortical        | 4       | Random (P = 0.086)       | 0.85 (0.59–1.23)   | 0.386 |
| Nuclear         | 4       | Random (P = 0.084)       | 0.97 (0.62–1.52)   | 0.904 |
| Posterior subcapsular | 3   | Fixed (P = 0.242)       | 0.98 (0.72–1.32)   | 0.879 |
| Mixed           | 4       | Random (P = 0.040)       | 0.94 (0.60–1.48)   | 0.792 |
| GSTT1 All       | 9       | Random (P = 0.049)       | 1.20 (0.96–1.51)   | 0.105 |
| Caucasian       | 7       | Random (P = 0.058)       | 1.11 (0.83–1.49)   | 0.474 |
| Asian           | 2       | Fixed (P = 0.653)        | 1.44 (1.14–1.83)   | 0.003 |
| Study design    |         |                          |                    |       |
| Population-based| 2       | Fixed (P = 0.952)        | 1.54 (1.16–2.05)   | 0.003 |
| Hospital-based  | 7       | Random (P = 0.063)       | 1.10 (0.84–1.45)   | 0.498 |
| Gender          |         |                          |                    |       |
| Male            | 5       | Fixed (P = 0.984)        | 1.29 (0.98–1.70)   | 0.073 |
| Female          | 5       | Fixed (P = 0.359)        | 1.28 (0.97–1.69)   | 0.078 |
| Subtype         |         |                          |                    |       |
| Cortical        | 4       | Fixed (P = 0.186)        | 1.09 (0.82–1.45)   | 0.555 |
| Nuclear         | 4       | Random (P = 0.062)       | 0.92 (0.52–1.62)   | 0.774 |
| Posterior subcapsular | 4  | Fixed (P = 0.219)   | 1.42 (1.04–1.94)   | 0.026 |
| Mixed           | 3       | Random (P = 0.097)       | 1.21 (0.66–2.20)   | 0.535 |

\(^a\)N: The number of included studies
\(^b\)A random-effects or fixed-effects model was used in presence (P < 0.10) or absence (P > 0.10) of heterogeneity of included studies and the P value was presented in parenthesis

and 95 % CI. The significance of the pooled OR was determined by Z test, in which the P < 0.05 was considered statistically significant. The risk of GSTM1 or GSTT1 null genotype on cataract was evaluated by comparing to wild type homozygote as their reference. Stratified analyses were also performed by ethnicity of study populations, the source of controls, gender of subjects, and cataract subtype. Considering the possible additive effect of different GST genotypes, we next evaluated the association between the genotype profile and cataract risk, in which the individuals with two putative low-risk genotypes, i.e., the presence of functional GSTM1 and GSTT1 alleles, were used as reference group [18]. For the quantitative synthesis analysis, the environmental effects were not adjusted due to the lack of information from the original study. The I²-based Q statistic test was applied to examine variations due to heterogeneity rather than chance. A random-effects (DerSimonian-Laird method) model or fixed-effects (Mantel-Haenszel method) model was applied to calculate pooled effect estimates in the presence (P ≤ 0.10) or absence (P > 0.10) of heterogeneity. The Egger’s test [19] and the Begg’s [20] test were applied to detect publication bias for the overall pooled analysis of GSTM1 or GSTT1 null genotypes. Additionally, the Begg’s funnel plot was obtained, in which an asymmetry of the funnel plot indicates a potential publication bias. The one-way sensitivity analysis was performed when one single study was excluded each time, and the new pooled results reflect the influence of the study deleted to the overall OR. All analyses were carried out with Stata software (version 11.0; Stata Corp LP, College Station, TX), and the two-sided P values were applied.

Results

Characteristics of studies

By searching PubMed, fifteen abstracts were retrieved through the search “cataract” “glutathione S transferase” and “polymorphism”, and nine studies meeting the inclusion criteria were identified as eligible [15–18, 21–25]. Out of the fifteen, one was meta-analysis [6] and one was laboratory study [26]. One article was excluded due to investigation on an association of presenile cataracts with heterozygosity for galactosaemic states and with riboflavin deficiency [27]. We excluded two articles on the relationship between GST polymorphisms and risk of age-related macular degeneration [28] or primary open-angle glaucoma [29]. We also excluded one article that examined the association of GSTO polymorphisms with cataract risk [30]. In addition, we included six eligible articles with manual searching [31–36]. As a result, a total of fifteen articles on GSTM1 or GSTT1 polymorphisms meeting the inclusion criteria were identified as eligible studies (Fig. 1).

Fifteen studies on GSTM1 (3,065 cases and 2,105 controls), and nine studies on GSTT1 (2,374 cases and 1,544 controls) were included in this meta-analysis. For the ethnicities, six studies of Asians and eight studies of Caucasians were included on the GSTM1 genotype. As to GSTT1, two studies of Asians and six studies of Caucasians were included. We also grouped studies with different
sources of controls (i.e., population-based or hospital-based), gender (male or female) and subtypes of cataracts (e.g., cortical, nuclear, posterior subcapsular or mixed cataract). In addition to the study by Juronen et al. [25] that determined the GSTM1 and GSTT1 phenotypes by enzyme-linked immunosorbent assay (ELISA), the genotyping for GSTM1 or GSTT1 was determined by polymerase chain reaction (PCR) assay in all other studies. The Table 1 presents the detailed characteristics of each study included in the meta-analysis.

Quantitative synthesis

Table 2 shows the results of the meta-analysis on the association of GSTM1 or GSTT1 null polymorphism with cataract risk. When pooling all the studies, we found that GSTM1 null polymorphism was not associated with cataract risk (Fig. 2a), and this negative association maintained in either Caucasian or Asian populations (Table 2). When stratified by the source of controls, gender, or cataract subtype, no association was found between GSTM1 null polymorphism and cataract risk.

For GSTT1, the overall result showed that GSTT1 null polymorphism was significantly associated with increased risk of cataract in Asian (OR, 1.44; 95 % CI, 1.14–1.83) but not Caucasian populations (Table 2). The positive association of GSTT1 null polymorphism with increased risk of cataract was found when pooling studies with population-based (OR, 1.54; 95 % CI, 1.16–2.05) but not hospital-based controls. However, there was no association between GSTT1 null polymorphism and cataract risk in male or female subjects. Interestingly, GSTT1 null polymorphism was associated with risk of posterior subcapsular (OR, 1.42; 95 % CI, 1.04–1.94) but not other subtypes of cataract.

We next investigated the effects of the profiles of GST genotypes on the risk of cataract, and examined the association between combinations of GSTM1 and GSTT1 null genotypes and cataract risk. Table 3 displays cataract risk associated with combinations of GST null genotypes, and the trend in risk associated with each putative high-risk null genotype. The results showed no association between the combined GSTM1 and GSTT1 null genotypes and cataract risk in all population, Caucasian or Asian population. When stratified by source of controls, pooled two studies with population-based controls showed that combination of GSTM1 null and GSTT1 positive (GSTT1+/+) genotypes played a protective role in cataract risk (OR, 0.71; 95 % CI, 0.54–0.92), but combination of GSTM1 positive and GSTT1 null, or GSTM1 and GSTT1 null genotypes was not associated with cataract risk. The other sub-group analyses showed no association between combination of GSTM1 and GSTT1 polymorphisms and cataract risk.

Potential publication bias and sensitivity analysis

We firstly detected the publication bias by the Begg’s test for the overall pooled analyses of GSTM1 and GSTT1 null genotype, and found symmetric distribution of corresponding funnel plots for GSTM1 genotype with a P value of 0.138, and GSTT1 genotype with a P value of 0.754 (Fig. 3). However, the Egger’s test showed that the P values for GSTM1 and GSTT1 null genotype were 0.037 and 0.908 respectively, suggesting a publication bias for studies on GSTM1 but not GSTT1 genotype.

Sensitivity analysis showed that exclusion of each study did not influence the result in specific genotype comparison for GSTM1 and GSTT1 polymorphism (Fig. 4), suggesting that the results of synthetic analysis were robust.
| Groups                        | Number$^a$ | Statistical method$^b$ | OR (95% CI)     | P    |
|-------------------------------|------------|------------------------|-----------------|------|
| All                           |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 7          | Random (P < 0.001)     | 0.83 (0.56–1.23) | 0.356|
| GSTM1 positive + GSTT1 null   | 7          | Fixed (P = 0.240)      | 1.20 (0.95–1.53) | 0.134|
| GSTM1 null + GSTT1 null       | 7          | Random (P = 0.010)     | 1.16 (0.71–1.89) | 0.545|
| Ethnics                       |            |                        |                 |      |
| Caucasian                     |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 6          | Random (P < 0.001)     | 0.85 (0.52–1.37) | 0.494|
| GSTM1 positive + GSTT1 null   | 6          | Fixed (P = 0.658)      | 1.00 (0.74–1.34) | 0.983|
| GSTM1 null + GSTT1 null       | 6          | Random (P = 0.008)     | 1.27 (0.67–2.38) | 0.466|
| Study design                  |            |                        |                 |      |
| PB                            |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 2          | Fixed (P = 0.591)      | 0.71 (0.54–0.92) | 0.009|
| GSTM1 positive + GSTT1 null   | 2          | Fixed (P = 0.334)      | 1.03 (0.69–1.53) | 0.899|
| GSTM1 null + GSTT1 null       | 2          | Random (P = 0.036)     | 0.87 (0.34–2.18) | 0.760|
| HB                            |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 5          | Random (P < 0.001)     | 0.88 (0.47–1.65) | 0.697|
| GSTM1 positive + GSTT1 null   | 5          | Fixed (P = 0.196)      | 1.32 (0.97–1.79) | 0.073|
| GSTM1 null + GSTT1 null       | 5          | Random (P = 0.024)     | 1.38 (0.71–2.69) | 0.336|
| Gender                        |            |                        |                 |      |
| Male                          |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 2          | Fixed (P = 0.990)      | 0.88 (0.49–1.59) | 0.676|
| GSTM1 positive + GSTT1 null   | 2          | Fixed (P = 0.476)      | 0.84 (0.28–2.50) | 0.749|
| GSTM1 null + GSTT1 null       | 2          | Fixed (P = 0.672)      | 1.48 (0.52–4.21) | 0.463|
| Female                        |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 2          | Random (P < 0.001)     | 0.79 (0.06–10.87) | 0.858|
| GSTM1 positive + GSTT1 null   | 2          | Fixed (P = 0.767)      | 0.62 (0.27–1.43) | 0.264|
| GSTM1 null + GSTT1 null       | 2          | Random (P = 0.074)     | 0.91 (0.15–5.57) | 0.919|
| Cataract type                 |            |                        |                 |      |
| Cortical                      |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 3          | Fixed (P = 0.745)      | 0.82 (0.62–1.10) | 0.181|
| GSTM1 positive + GSTT1 null   | 3          | Fixed (P = 0.131)      | 1.39 (0.99–1.96) | 0.061|
| GSTM1 null + GSTT1 null       | 3          | Fixed (P = 0.171)      | 1.03 (0.72–1.48) | 0.855|
| Nuclear                       |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 2          | Random (P = 0.030)     | 1.00 (0.39–2.56) | 0.994|
| GSTM1 positive + GSTT1 null   | 2          | Random (P = 0.081)     | 0.67 (0.11–4.24) | 0.668|
| GSTM1 null + GSTT1 null       | 2          | Fixed (P = 0.868)      | 1.16 (0.56–2.38) | 0.694|
| Posterior subcapsular         |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 2          | Random (P = 0.038)     | 1.20 (0.42–3.39) | 0.734|
| GSTM1 positive + GSTT1 null   | 2          | Fixed (P = 0.157)      | 1.15 (0.59–2.26) | 0.682|
| GSTM1 null + GSTT1 null       | 2          | Fixed (P = 0.399)      | 1.97 (0.98–3.97) | 0.059|
| Mixed                         |            |                        |                 |      |
| GSTM1 null + GSTT1 positive   | 2          | Random (P = 0.019)     | 0.81 (0.25–2.61) | 0.724|
Discussion

Before inclusion of studies, we briefly searched PubMed, Embase, Web of Science and China National Knowledge Infrastructure, and found that most of studies examined association of GSTM1 or GSTT1 polymorphisms with cataract risk while very limited studies were related to other GST polymorphisms, e.g., GSTM3, GSTO or GSTP polymorphisms. Thus, this meta-analysis only evaluated the effects of GSTM1 and GSTT1 polymorphisms on cataract risk. Our data showed that GSTT1 but not GSTM1 null polymorphism was associated with cataract risk in Asians. Although different subtypes of cataract have their own pathogenesis and clinical characteristics, our meta-analysis data indicate that GSTT1 null polymorphism may contribute to increased risk of posterior subcapsular cataract.

In 1995, Sekine and colleagues for the first time reported possible correlation of GSTM1 null genotype frequency with cataract risk [36]. However, the following studies showed inconsistent results [18, 21–25, 32–35]. By pooling these early studies, previous meta-analysis by Sun et al., did not find an association of GSTM1 null genotype with cataract risk [6]. Even including three more studies, we did not find positive relationship between GSTM1 null genotype and cataract risk. To be noted, although previous meta-analysis indicated an association of GSTM1 null genotype and increased risk of cataract in Asians [6], our data did not confirm this association when including one more study on Asians.

For GSTT1 polymorphism, pooled four early studies on Caucasian showed no association [18, 22, 24, 25] while one study on Asians [21] showed positive association between GSTT1 null genotype and cataract risk; however, by pooling these five studies, no association was found [6]. By including four recent studies, our meta-analysis showed positive association of GSTT1 polymorphism with increased risk of cataract in all populations, and this association remained in Asians when two studies were pooling [15, 21]. Previous studies reported gender-dependent effects of GSTT1 null polymorphism on cataract risk [18, 22, 24]; however, recent two studies showed negative results [15, 16]. We performed a subgroup analysis stratified by gender with all five studies, and results showed no significant association, which was consistent with previous meta-analysis data based on three studies [6]. In addition, our data showed positive association of GSTT1 null polymorphism with increased risk of posterior subcapsular cataract although previous pooled study indicated that this association did not reach significant (OR, 1.21; 95 % CI, 0.96–1.53) [6]. Since the studies included for subgroup analyses were still limited, future studies are required to validate the association between GSTT1 null polymorphism and cataract risk.

To the best of our knowledge, the association between combination of GST polymorphisms and susceptibility to cataract has been assessed for the first time by our meta-analysis. The study by Juronen et al., firstly reported that the GSTM1 positive phenotype frequency was significantly higher in the cataract group than in the controls, and the cataract risk associated with the GSTM1 positive phenotype was increased in

### Table 3 Association between GSTM1 and GSTT1 polymorphisms and cataract risk (Continued)

| GSTM1 positive + GSTT1 null | Fixed ($P = 0.130$) | 1.22 (0.68–2.21) | 0.505 |
|----------------------------|---------------------|------------------|--------|
| GSTM1 null + GSTT1 null    | Fixed ($P = 0.523$) | 1.44 (0.74–2.79) | 0.279  |

*N: The number of included studies

*A random-effects or fixed-effects model was used in presence ($P \leq 0.10$) or absence ($P > 0.10$) of heterogeneity of included studies and the $P$ value was presented in parenthesis

![Fig. 3](image-url) Funnel plots showed symmetric distribution. Log OR is plotted against the standard error of log OR for studies on GSTM1 (a) or GSTT1 null (b) polymorphism. The dots represent specific studies for the indicated association.
carriers of the combined GSTM1 positive and GSTT1 positive phenotypes [25]. However, a later study by Saadat et al., showed that individuals with the null genotypes for GSTM1 and GSTT1, or combination of GSTT1 positive and GSTM1 null genotypes were at a significantly higher risk for developing cataract than individuals with both the genes positive genotypes [24]. The following studies consecutively presented inconsistent results [15, 16, 18, 22]. By pooling seven studies, our meta-analysis results did not show a significant association between each combination of GSTM1 and GSTT1 genotypes and cataract risk. Two pooled studies with population-based controls showed that combination of GSTM1 null and GSTT1 positive genotypes played a protective role in cataract risk [16, 25]; however, this positive association was not found in other stratified analyses. Thus, the result should be interpreted with caution.

When compared to individual studies, the meta-analysis has a vital advantages. However, some potential limitations in our study should be considered. First, the inclusion of studies might not be sufficient since we only included published papers with language in English, or Chinese. It is possible that some papers published in other languages may not indexed by the database (e.g. PubMed, Embase, Web of Science). Thus, the publication bias for GSTM1 polymorphism detected in our study might be due to insufficient inclusion of published studies. Second, this meta-analysis was limited by the small sample size, especially in subgroup analyses aforementioned (e.g., studies on GSTT1 polymorphism in Asians), and this need further investigation. Third, basic methodological differences among the studies, e.g., ELISA vs. PCR assay for genotyping, might have affected the results. Fourth, most of the studies included did not categorize the cataract patients as cortical, nuclear, posterior subcapsular and mixed cataract. Although we found positive association between GSTT1 null polymorphism and increased risk of posterior subcapsular cataract, however, only four studies with available data were pooled [16, 18, 21, 25], and thus this association awaits further confirmation. Fifth, the primary outcome measure was calculated based on individual unadjusted ORs, which might affect the evaluation precision of the study. The lack of detailed data in each study prevented multiple testing for combined effects of gene-environment factors on cataract risk, and thus future studies should address this point. Last, the Caucasian and Asian subjects from different countries might have been genetically heterogeneous, e.g., different lifestyle and environment (e.g., European vs. Arabian). These factors may explain the heterogeneity in this meta-analysis for Caucasian subjects.

**Conclusion**

In summary, the present meta-analysis showed that the association between GSTM1 null polymorphism and cataract risk was either negative or evidence limited. The GSTT1 null polymorphism was significantly associated with increased risk of posterior subcapsular cataract. Given the limited study populations, more studies with large study population are suggested to further validate the relationship between GST polymorphisms and genetic predisposition to cataract, e.g., association of GSTT1 null polymorphism with cataract risk in Asian.
Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Conceived and designed the study: WS, GC. Acquisition of data: WS, LS. Analysis and interpretation of data: YS, YC. Drafting the manuscript: WS, GC. Revising the manuscript critically for important intellectual content: WS, LS, YS, YC, GC. All authors read and approved the final manuscript.

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