Association of Glutathione S-Transferases Polymorphisms (*GSTM1* and *GSTT1*) with Senile Cataract: A Meta-analysis

Lei Sun,[1,2] *Bo Xi,*[2,3] *Lei Yu,*[2,4] *Xiang-Chun Gao,*[1] *De-Jing Shi,*[1] *Yin-Kun Yan,*[5] *Dong-Jiang Xu,*[6] *Qing Han,*[*,1] *and Chunyu Wang*[*,7]

Purpose. Glutathione S-transferase (GST) polymorphisms have been considered risk factors for the development of senile cataract. However, the results are not consistent. In this study, the authors conducted a meta-analysis to assess the association between *GSTM1* and *GSTT1* null genotypes and the risk for senile cataract.

Methods. Published literature from PubMed, EMBASE, and other databases were retrieved. All studies evaluating the association between *GSTM1/GSTT1* polymorphisms and senile cataract were included. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using fixed- or random-effects model.

Results. Eleven studies on *GSTM1* (1871 cases and 1267 controls) and five studies on *GSTT1* (1180 cases, 706 controls) were included. Overall analysis showed that the association between *GSTM1* null genotype and risk for senile cataract is not statistically significant (OR, 1.39; 95% CI, 0.99–1.94; $P = 0.054$) and that the association between *GSTT1* null genotype and risk for senile cataract is not significant (OR, 1.09; 95% CI, 0.87–1.36; $P = 0.454$). Subgroup analysis showed that the association between *GSTM1* null genotype and risk for senile cataract is statistically significant in Asians (OR, 1.66; 95% CI, 1.03–2.67; $P = 0.039$) but not in Caucasians (OR, 1.21; 95% CI, 0.74–1.96; $P = 0.443$). Similar results were observed for the association between *GSTT1* null genotype and risk for senile cataract.

Conclusions The present meta-analysis suggested that *GSTM1* and *GSTT1* null genotypes are associated with increased risk for senile cataract in Asian populations but not in Caucasian populations. Given the limited sample size, the finding on GST polymorphisms merits further investigation. (*Invest Ophthalmol Vis Sci.* 2010;51:6381–6386) DOI:10.1167/iovs.10-5815

Recent data from the World Health Organization suggest that there are 37 million blind people worldwide; cataract is one of the major causes.[1] Epidemiologic studies have shown that cataract is associated with many environmental factors such as ultraviolet B light exposure,[2] smoking,[3] alcohol consumption,[4,5] and use of steroids.[6] Recently, genetic factors have been found to play important roles in the development of senile cataract.[7–9] Twin studies have demonstrated that heritability is responsible for approximately 50% of cases of senile cataract.[10,11]

Oxidative stress as a result of increased generation of reactive oxygen species and free radicals in the lens has been considered one of the main causes of senile cataract.[12,13] The toxic effects of oxidative stress during cataractogenesis can be alleviated by cellular defense mechanisms. The reducing compound glutathione is one of the essential antioxidants.[14,15] Glutathione S-transferases (GSTs) are a superfamily of cytosolic soluble detoxification enzymes that can catalyze the conjugation of reduced glutathione to various xenobiotics and endobiotics. GSTs play important roles in cellular protection against oxidative stress. Homozygous deletion of GST genes (null genotype) could result in decreased enzyme activity, which will impede detoxification and ultimately increase the risk for many diseases.[16] Although many studies have investigated the relationship between *GSTM1* and *GSTT1* polymorphisms and senile cataract, thus far the association has been inconsistent. Individual studies are usually underpowered in detecting the effect of low penetrance genes; therefore, in this study we conducted a meta-analysis to investigate the association between *GSTM1* and *GSTT1* null genotypes and the risk for senile cataract.

Materials and Methods

Literature and Search Strategy

We searched the literature databases including PubMed (1950–2010), EMBASE (1966–2010), ISI web of science (1975–2010), Japana Centra Revuo Medicina (1983–2010, in Japanese), J-Stage (1957–2010, in Japanese), China National Knowledge Infrastructure (1979–2010, in Chinese), and Wanfang Data (1982–2010, in Chinese).

We used a search strategy to identify all possible studies by combinations of the following key words: *glutathione S-transferase* or *GST* and *cataract* or *senile cataract* or *age-related cataract*. The search was conducted on human subjects, with no restriction on language.

From the Departments of [1]Ophthalmology and [4]Infectious Disease, the Fourth Hospital of Harbin Medical University, Harbin, People's Republic of China; [3]Department of Maternal and Child Health Care, School of Public Health, Shandong University, Jinan, People's Republic of China; [5]Department of Epidemiology, Capital Institute of Pediatrics, Beijing, People's Republic of China; [6]Department of Physiology and Pathophysiology, Peking Union Medical College, Beijing, People's Republic of China; and [7]Baylor College of Medicine and The University of Texas MD Anderson Cancer Center, Houston, Texas.

[2]These authors contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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*Each of the following is a corresponding author: Qing Han, Department of Ophthalmology, the Fourth Hospital of Harbin Medical University, Harbin, China; hqeye@yahoo.com.cn.

Chunyu Wang, Baylor College of Medicine and The University of Texas MD Anderson Cancer Center, Houston, TX 77030; chunyuwang2000@gmail.com.

The reference lists of retrieved articles were hand-searched. If more than one article was published using the same case series, only the study with the largest sample size was selected. The literature search was updated on March 30, 2010.

Inclusion Criteria and Data Extraction

The studies used for meta-analysis had to meet all the following inclusion criteria: evaluation of the association between *GSTM1* or *GSTT1* null genotypes and senile cataract; case-control design; number of null genotypes of *GSTM1* or *GSTT1* in cases and controls presented to calculate odds ratio (OR) with confidence interval (CI). For each study, the following information was extracted: name of the first author; publication year; ethnicity (country); number of cases and controls; number of null genotypes for *GSTM1 or GSTT1* in cases and controls. Two authors (BX and CW) independently assessed the articles for inclusion/exclusion, resolved disagreements, and reached consistency.

Statistical Analysis

The association between *GSTM1* or *GSTT1* polymorphism and senile cataract was estimated by calculating pooled ORs and 95% CIs. The significance of the pooled OR was determined by *Z* test ($P < 0.05$ was considered statistically significant). The I^2-based Q statistic test was performed to evaluate variations due to heterogeneity rather than chance. A random-effects (DerSimonian-Laird method[17]) or fixed-effects (Mantel-Haenszel method[18]) model was used to calculate pooled effect estimates in the presence ($P \leq 0.10$) or absence ($P > 0.10$) of heterogeneity. Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detecting bias or systematic heterogeneity.[19] An asymmetric funnel plot indicated a relationship between effect and study size, which suggested the possibility of either publication bias or a systematic difference between smaller and larger studies (small study effects). Furthermore, publication bias was assessed by Egger's test[20] ($P < 0.05$ was considered statistically significant). Studies were categorized into subgroups based on ethnicity, sex, and subtypes of senile cataract, and data analysis was performed (STATA, version 10; StataCorp LP, College Station, TX).

Results

Characteristics of Studies

The literature search identified 60 potentially relevant studies. Eleven studies met the inclusion criteria.[21–31] Eleven case-control studies[21–31] were included in the meta-analysis of *GSTM1* genotype (1871 cases, 1267 controls). Five case-control studies[21,23,25,28,31] were included in the meta-analysis of *GSTT1* genotype (1180 cases, 706 controls). For the meta-analysis of *GSTM1*, six studies on Caucasians[21–23,25,27,28] and five studies on Asians[24,26,29–31] were included. For the meta-analysis of *GSTT1*, four studies on Caucasians[21,23,25,28] and one study on Asians[31] were included. Study characteristics included in the meta-analysis are presented in Table 1.

Meta-analysis Results

The forest plot of the meta-analysis of *GSTM1* is shown in Figure 1. Because of the heterogeneity among studies ($P_Q = 0.000$; $I^2 = 79\%$), a random-effects model was used. The overall result showed that the association between *GSTM1* null genotype and risk for senile cataract was not statistically significant (OR, 1.39; 95% CI, 0.99–1.94; $P = 0.054$). The forest plot of the meta-analysis of *GSTT1* is shown in Figure 2. The association between *GSTT1* null genotype and risk for senile cataract was not significant (OR, 1.09; 95% CI, 0.87–1.36; $P = 0.454$).

Next, subgroup analyses were performed based on ethnicity, sex, and subtype of senile cataract. The result showed that the association between the *GSTM1* null genotype and risk for senile cataract is statistically significant in Asians (OR, 1.66; 95% CI, 1.03–2.67; $P = 0.039$) but not in Caucasians (OR, 1.21; 95% CI, 0.74–1.96; $P = 0.443$; Fig. 3; Table 2). Only one study evaluated *GSTT1* in Asians. The result showed a significant association between *GSTT1* null genotype and risk for senile cataract in Asians (OR, 1.56; 95% CI, 1.04–2.33; $P = 0.033$) but not in Caucasians (OR, 0.93; 95% CI, 0.71–1.22; $P = 0.592$; Fig. 4; Table 2). Subgroup analyses by sex and subtypes of senile cataract did not reveal any significant association between *GSTM1* and *GSTT1* polymorphisms and risk for senile cataract (Table 2).

Potential Publication Bias

Begg's funnel plots were generated to assess potential publication bias for *GSTM1* (Fig. 5) and *GSTT1* (Fig. 6). No publication bias was detected for *GSTM1* (Egger's test, $P = 0.196$) or *GSTT1* ($P = 0.653$).

Table 1. Characteristics of Studies Included in the Meta-analysis

First Author	Year	Ethnicity (country)	Sample Size		No. of Null Genotype		Reference
			Cases	Controls	Cases	Controls	
GSTM1							
Sekine	1995	Asian (Japan)	138	62	101	30	29
Alberti	1996	Caucasian (Italy)	202	98	99	49	22
Pi	1996	Asian (China)	59	112	41	57	26
Hao	1999	Asian (China)	77	76	41	35	24
Juronen	2000	Caucasian (Estonia)	503	202	240	111	25
Saadat	2004	Caucasian (Iran)	150	150	90	58	28
Saadat	2006	Caucasian (Iran)	95	95	56	36	27
Guven	2007	Caucasian (Turkey)	195	136	105	58	23
Xu	2007	Asian (China)	120	118	81	60	30
Abdel Azeem	2009	Caucasian (Egypt)	53	73	23	46	21
Zhou	2010	Asian (China)	279	145	171	95	31
GSTT1							
Juronen	2000	Caucasian (Estonia)	503	202	73	36	25
Saadat	2004	Caucasian (Iran)	150	150	49	46	28
Guven	2007	Caucasian (Turkey)	195	136	29	22	23
Abdel Azeem	2009	Caucasian (Egypt)	53	73	16	21	21
Zhou	2010	Asian (China)	279	145	146	60	31

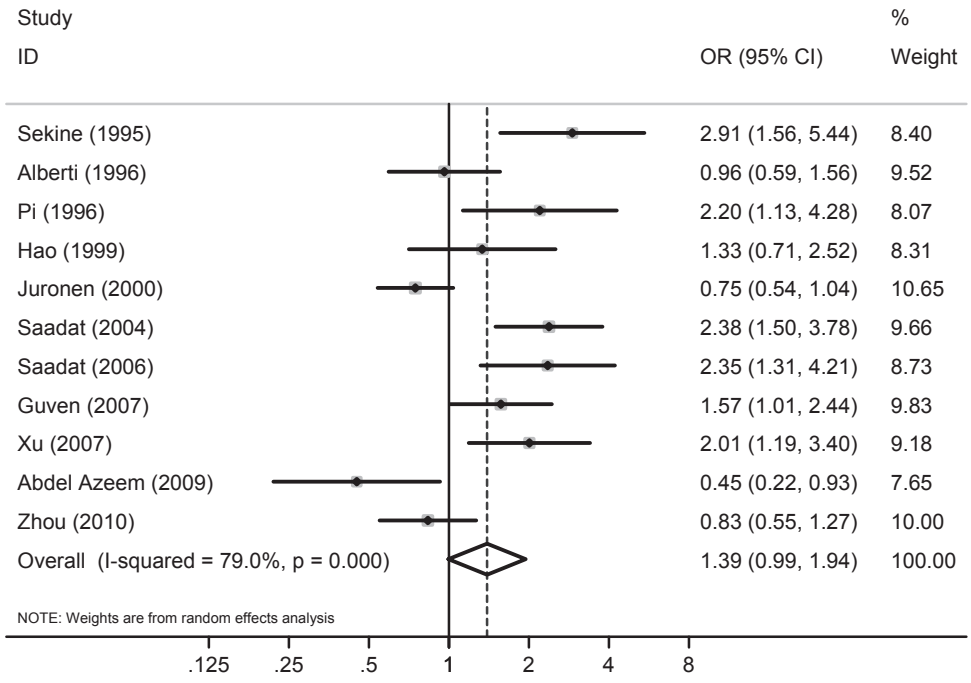

FIGURE 1. Forest plot of the association between *GSTM1* polymorphism (null vs. positive genotype) and risk for senile cataract using a random-effects model.

DISCUSSION

Genetic factors are considered the most important factors in the development of senile cataract. Previously, many studies investigated the association between *GSTM1* and *GSTT1* polymorphisms and senile cataract. However, the association has been controversial. Some studies reported that the null genotypes are positively correlated, inversely correlated, or not correlated with the risk for senile cataract in different ethnic populations. These discrepancies could have been due to limited sample numbers and ethnic differences. Therefore, we conducted a meta-analysis of 11 published case-control studies to investigate the role of GST polymorphisms in senile cataract. To our knowledge, this is the first meta-analysis assessing the association between GST polymorphisms and senile cataract. The meta-analysis results showed that the association between *GSTM1* and *GSTT1* null genotypes and the risk for senile cataract is statistically significant in Asians but not in Caucasians.

Many studies, including ours,[32–34] have reported on the effect of ethnic differences on genetic predisposition to human diseases. For example, the odds of having posterior subcapsular cataract are 1.5 times greater among Caucasians than among African Americans.[35] In addition, the data showed that the allele frequencies of both *GSTM1* and *GSTT1* null genotypes are higher in Asians (*GSTM1*, 0.54; *GSTT1*, 0.41) than in Caucasians (*GSTM1*, 0.47; *GSTT1*, 0.22). In the present study, we found that the association between *GSTM1* and *GSTT1* null genotypes and the risk for senile cataract is statistically significant in Asians but not in Caucasians. The reasons may be differences in lifestyle, nutrition, environmental factors, and genetic factors (given that the *GSTM1* and *GSTT1* null alleles may be causative, the

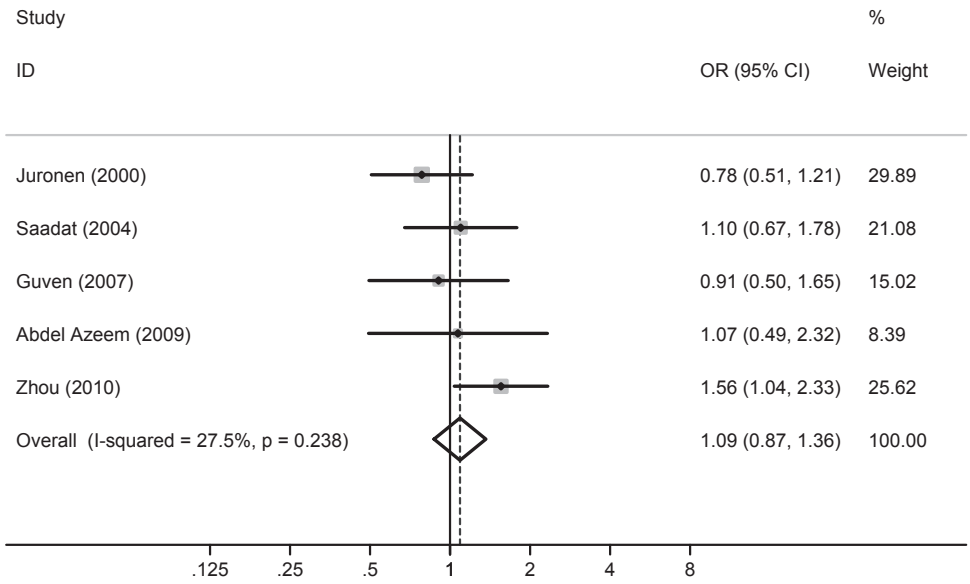

FIGURE 2. Forest plot of the association between *GSTT1* polymorphism (null vs. positive genotype) and risk for senile cataract using a fixed-effects model.

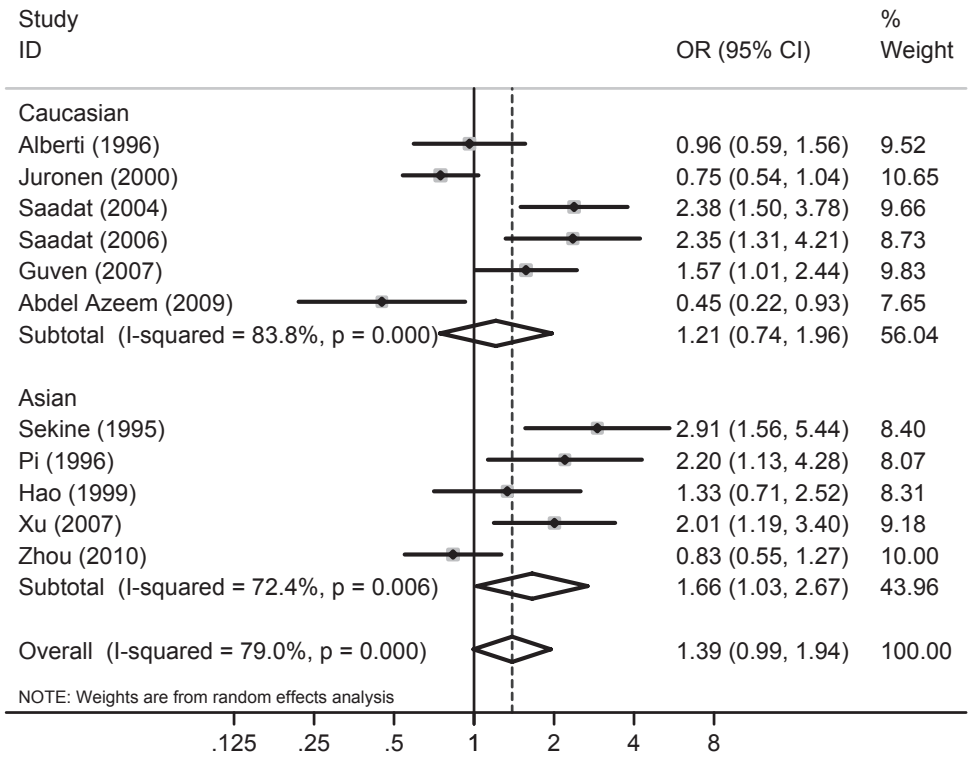

Figure 3. Subgroup analysis of the association between *GSTM1* polymorphism and risk for senile cataract stratified by ethnicity.

reasons were unlikely to be differences in the haplotype block structure of the populations).

The studies by Saadat,[28] Guven,[23] and Abdel Azeem[21] reported the effect of gender differences on the association between GST polymorphisms and senile cataract. Interestingly, all these three studies found that the association was significant in females but not in males, which might reflect gender-related differences in the expression of GST isoenzymes. Gender differences have also been observed in the studies of other tissues.[36–38] Therefore, we conducted a subgroup analysis stratified by gender. However, no significant result was found, possibly because the study by Abdel Azeem[21] reported an inverse correlation in females.

Although meta-analysis has a vital advantage compared with individual studies, some potential limitations in our study should be considered and our results should be interpreted with caution. First, our meta-analysis was based on unadjusted estimates. Because of the lack of detailed data, it was not

Table 2. Subgroup Analysis of the Association between *GSTM1* and *GSTT1* Polymorphisms and the Risk for Senile Cataract

Groups	No. of Studies	Statistical Method	OR (95% CI)	*P*	References
GSTM1					
All studies	11	Random	1.39 (0.99–1.94)	0.054	21–31
Ethnicity					
Caucasian	6	Random	1.21 (0.74–1.96)	0.443	21–23,25,27,28
Asian	5	Random	1.66 (1.03–2.67)	0.039	24,26,29–31
Sex					
Male	3	Fixed	1.10 (0.90–1.34)	0.342	21,23,28
Female	3	Random	1.24 (0.61–2.52)	0.550	21,23,28
Subtype					
Cortical	3	Random	0.91 (0.69–1.20)	0.508	22,23,25
Nuclear	3	Fixed	1.07 (0.90–1.27)	0.460	22,23,25
Posterior subcapsular	2	Random	1.03 (0.72–1.46)	0.881	23,25
GSTT1					
All studies	5	Fixed	1.09 (0.87–1.36)	0.454	21,23,25,28,31
Ethnicity					
Caucasian	4	Fixed	0.93 (0.71–1.22)	0.592	21,23,25,28
Asian	1	—	1.56 (1.04–2.33)	0.033	31
Sex					
Male	3	Fixed	1.11 (0.76–1.62)	0.595	21,23,28
Female	3	Fixed	0.94 (0.68–1.31)	0.729	21,23,28
Subtype					
Cortical	3	Fixed	1.07 (0.86–1.33)	0.536	23,25,31
Nuclear	3	Random	0.76 (0.41–1.42)	0.387	23,25,31
Posterior subcapsular	3	Fixed	1.21 (0.96–1.53)	0.110	23,25,31

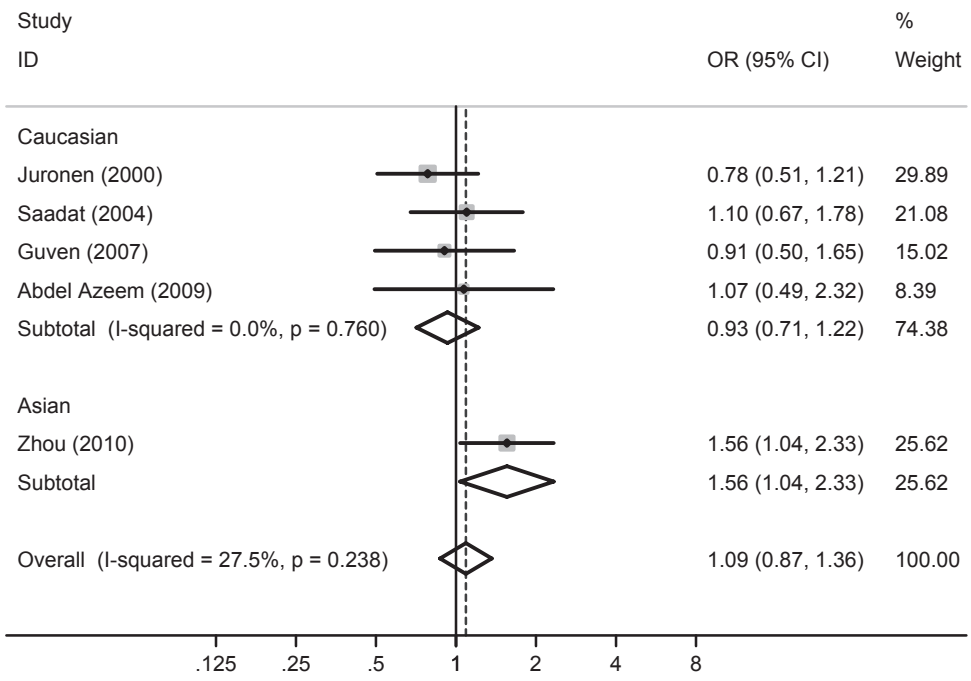

FIGURE 4. Subgroup analysis of the association between *GSTT1* polymorphism and risk for senile cataract stratified by ethnicity.

possible to conduct multiple testing of the various groups of patients and cataracts. Second, this meta-analysis was limited by thee small sample size, especially in subgroup analysis. Nonsignificant findings in cataract subtype analyses are likely to be confounded by small sample size and ethnicity. Third, basic methodological differences among the studies might have affected the results. All studies used PCR methods for genotyping, but the study by Juronen et al.[25] used enzyme-linked immunosorbent assay. The conclusion did not change after the exclusion of this study. Fourth, the studies differed in their procedure for assessing phenotypes. Not all the studies used a certified cataract grading system to identify cases and controls; only three studies[22,23,31] used Lens Opacities Classification System II (LOCSII), and six studies used slit lamp examination.[21–24,30,31] This might have introduced considerable variability in the quality of the studies selected for the meta-analysis. Fifth, the Caucasian group might have been genetically heterogeneous, with differences in terms of lifestyle and environment. These factors may explain the heterogeneity in study results and the lack of significant findings in Caucasian populations. Sixth, gene-environment interactions were not addressed in our meta-analysis. The pathogenesis and development of senile cataract has a genetic and environmental basis because GST polymorphisms usually exert their effects through interaction with environmental exposures (e.g., ultraviolet-B exposure, cigarette smoking, alcohol consumption).[39] However, most studies did not provide the null genotypes of GST polymorphisms stratified by these confounding factors. This issue should be considered in future studies.

In summary, the present meta-analysis suggested that *GSTM1* and *GSTT1* null genotypes are both associated with increased risk for senile cataract in Asian populations but not in Caucasian populations. More epidemiologic studies are necessary to further ascertain the relationship between

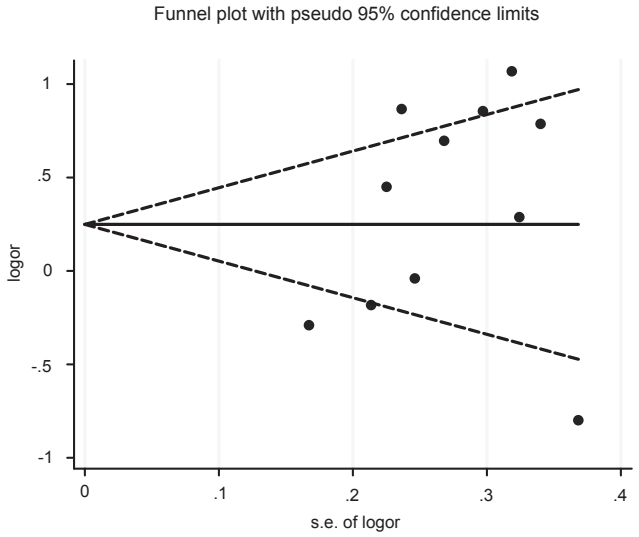

FIGURE 5. Funnel plot of the meta-analysis of *GSTM1* polymorphism and risk for senile cataract.

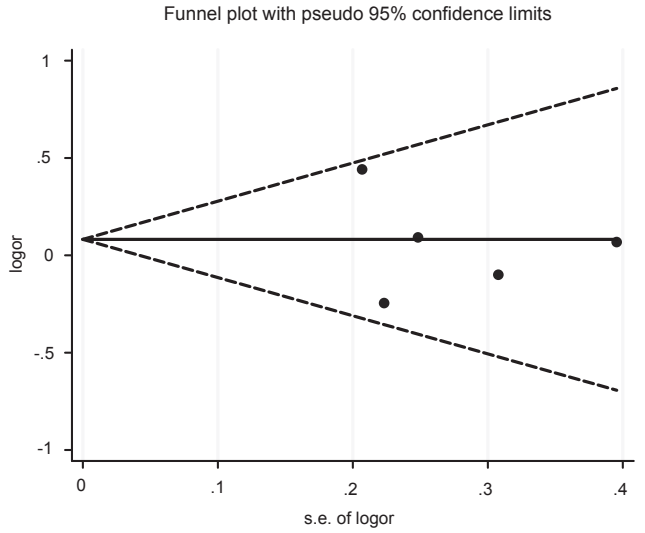

FIGURE 6. Funnel plot of the meta-analysis of *GSTT1* polymorphism and risk for senile cataract.

GST polymorphisms and genetic predisposition to senile cataract.

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