Review Article
GSTT1 polymorphism and breast cancer risk in the Chinese population: an updated meta-analysis and review

Zhang-Sheng Xiao[1], Yun Li[1], Yan-Li Guan[2], Jia-Gen Li[1]

[1]Department of Oncological Surgery, Yinzhou Hospital Affiliated to Medical School of Ningbo University, Ningbo City 315100, Zhejiang Province, China; [2]Department of Cardiovascular, Yinzhou Hospital Affiliated to Medical School of Ningbo University, Ningbo City 315100, Zhejiang Province, China

Abstract: Background: Although a number of studies have been conducted on the association between GSTT1 polymorphism and breast cancer in China, this association remains elusive and controversial. To clarify the effects of GSTT1 polymorphism on the risk of breast cancer, an updated meta-analysis was performed in the Chinese population. Material/methods: Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) to up 28th January 2015. Pooled ORs and 95% CIs were used to assess the strength of the associations. Results: A total of 13 studies including 3387 breast cancer cases and 5085 controls were involved in this meta-analysis. Overall, a significant association (OR = 1.31, 95% CI: 1.02-1.67) was found between the null GSTT1 and breast cancer risk when all studies in Chinese population pooled into the meta-analysis. In subgroup analyses stratified by geographic areas and source of controls, it revealed the significant results in population-based studies (OR = 1.42, 95% CI: 1.23-1.65) and South China (OR = 1.47, 95% CI: 1.27-1.70). Conclusions: This meta-analysis showed that the null GSTT1 may be potential biomarkers for breast cancer risk in Chinese, and further studies with gene-gene and gene-environment interactions are required for definite conclusions.

Keywords: Meta-analysis, GSTT1, polymorphism, breast cancer

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458400) of the total cancer deaths in 2008 [1]. The age-standardized incidence and mortality rates of breast cancer in China in 2008 were 31.71 per 100,000 and 6.48 per 100000 respectively [2]. It also shows a continuously increasing trend in morbidity of breast cancer in China over recent years [1, 2]. The mechanism of breast carcinogenesis is still not fully understood. It has been suggested that low-penetrance susceptibility genes combining with environmental factors may be important in the development of cancer [3]. In recent years, several common low-penetrant genes have been identified as potential breast cancer sus-

ceptibility genes. An important one is glutathione S-transferase (GST), which consists of five distinct families, namely alpha (GSTA), sigma (GSTS), mu (GSTM), pi (GSTP), and theta (GSTT) [4]. Located on the long arm of chromosome 22 (22q11.23), the GSTT1 plays an important role in the xenobiotics' detoxification. The most common genotype of GSTT1 gene is homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity, increased vulnerability to cytogenetic damage and resulted in the increased susceptibility to cancer [5, 6]. An association between GSTT1 polymorphism and breast cancer was first reported by Bailey and co-workers in 1998 in Caucasian and African-American women [7], after which many studies analyzed the influence of GSTT1 polymorphism on breast cancer risk; no clear consensus, however, was reached. As previously reviewed [8], the preva-
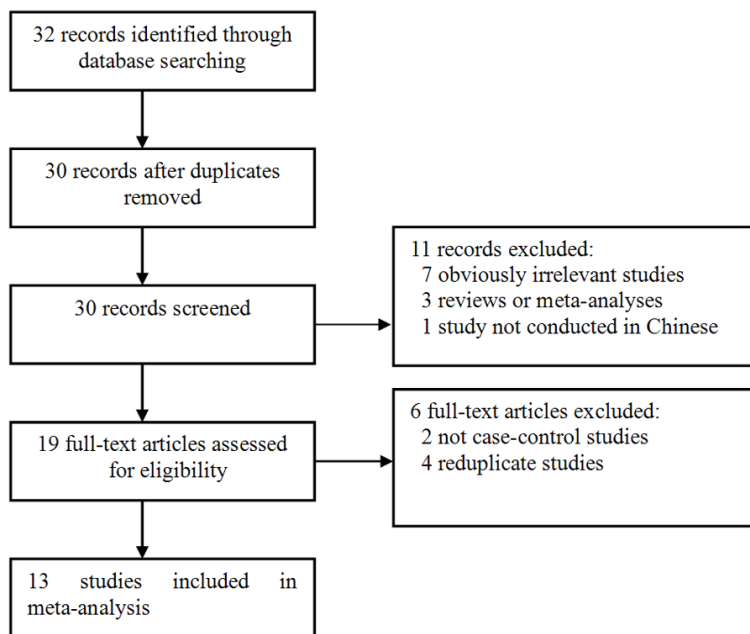
Figure 1. Flow diagram of the literature search.

lence of GSTT1 null status ranges from 20% in Caucasians to 60% among Asians. In order to lessen the impact of different genetic background, we performed this update meta-analysis to assess the relationship of GSTT1 polymorphism with risk of breast cancer in only Chinese population.

Materials and methods

Search strategy and selection criteria

The studies were searched using PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 28th January 2015. The key words used combination of the following terms: (1) GSTT1 or GST T1; (2) breast cancer or breast neoplasms; (3) polymorphism or variant or variation; and (4) Chinese or China or Taiwan. The search was performed without any restrictions on language and focused on studies conducted in humans. Besides, the references from retrieved articles were also searched. The criteria used to select studies for this meta-analysis were as follows: (1) independent cohort or case-control studies for human, (2) all patients with the diagnosis of breast cancer confirmed by pathological or histological examinations, (3) provides the distribution of

GSTT1 polymorphism in patients and controls, (4) all participants were Chinese. The reasons for exclusion of studies were: (1) duplicate publications, (2) incomplete data, (3) no control, (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Information was carefully extracted from all eligible publications independently by two authors according to the inclusion criteria. Disagreements were resolved through a discussion between the two authors. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data were extracted from the identified studies: the first author, publication year, source of controls, geographic area, sample size, and the number of subjects with two GSTT1 genotypes.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX). Odds ratios (ORs) with 95% confidence intervals (CIs) were used to determine the strength of association between the GSTT1 null genotype and breast cancer risk, and the significance of the pooled OR was determined by the Z test. Cochran's Q-statistic was used to assess between-study heterogeneity, and a significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies. If there was heterogeneity, then the random-effects model was chosen to pool the ORs with 95% CIs, otherwise the fixed-effects model was used. Sensitivity analyses were conducted by sequential omission of individual studies involved in the meta-analysis. Publication bias was investigated with the funnel plot, in which the Standard Error (SE) of log OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of

Table 1. Characteristics of studies included in the meta-analysis

Refence	Year	Source of controls	Area	Case number	Control number	Case		Control	
						Null genotype	Non-null	Null genotype	Non-null
Ceschi [9]	2005	PB	Singapore	256	667	100	156	282	385
Chang [10]	2006	PB	Taiwan	189	420	111	78	210	210
Cheng [11]	2005	PB	Taiwan	461	736	223	238	336	400
Cui [12]	2010	PB	Tianjin	315	360	147	168	78	282
Egan [13]	2004	PB	Shanghai	1136	1210	557	579	596	614
Fan [14]	2012	HB	Jiangsu	93	89	51	42	30	59
Gago-Dominguez [15]	2004	PB	Singapore	180	466	66	114	204	262
Li [16]	2008	PB	Sichuan	78	78	35	43	44	34
Luo [17]	2012	PB	Shanghai	353	701	186	167	364	337
Ma [18]	2007	HB	Tianjin	105	100	49	56	22	78
Wu [19]	2002	HB	Taiwan	60	60	27	33	26	34
Li [20]	2007	HB	Sichuan	91	128	51	40	56	72
Chang [21]	2008	HB	Hebei	70	70	38	32	30	40

HB, hospital-based; PB, population-based.

Egger's linear regression test. All the *P* values were two sided. *P* value less than 0.05 was considered statistically significant. In addition, subgroup analyses stratified by geographical location and source of controls were also performed.

Results

Description of included studies

According to the inclusion criteria, 13 case-control studies [9-21] were included and 54 articles were excluded. The publication year of involved studies ranged from 2002 to 2012. The flow chart of study selection is shown in **Figure 1**. In total, 3387 breast cancer cases and 5085 controls were involved in this meta-analysis, which evaluated the relationship between GSTT1 polymorphism and breast cancer risk in Chinese. The source of controls was mainly based on a healthy population. The characteristics of the included studies are summarized in **Table 1**.

Quantitative data synthesis

Overall analysis: The random-effects model was used in overall analysis due to between-study heterogeneity in all included studies ($\chi^2 =$ 86.78, P = 0.002). The results showed that the pooled OR with 95% CI for breast cancer in Chinese with null GSTT1 was 1.31 (CI 95%: 1.02-1.67, z = 2.15, P = 0.031) (**Figure 2A**). Therefore, the GSTT1 polymorphism was significantly related to breast cancer risk in Chinese. In addition, the finding from cumulative meta-analysis showed that there was a trend of more obvious association between GSTT1 null genotype and risk of breast cancer in Chinese as data accumulated by publication year (**Figure 2B**).

Subgroup analysis: In the subgroup analysis based on source of control, the results showed that the GSTT1 polymorphism was significantly related to breast cancer risk among hospital-based studies (OR = 1.90, 95% CI: 1.44-2.49), whereas not among population-based studies (OR = 1.12, 95% CI: 0.85-1.48) (**Table 2**). In addition, we also performed stratified analysis based on the geographic areas, it revealed the significant results in North China (OR = 2.67, 95% CI: 1.81-3.94) (**Table 2**).

Publication bias diagnosis and sensitive analysis: The Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. As showed in **Figure 3A**, the shape of the funnel plots did not reveal obvious asymmetry. Similarly, the Egger's test indicated that there was no evidence of obvious publication bias in the 13 reviewed studies (**Figure 3B**) (t = 1.56, *P* = 0.147). To estimate the sensitivity
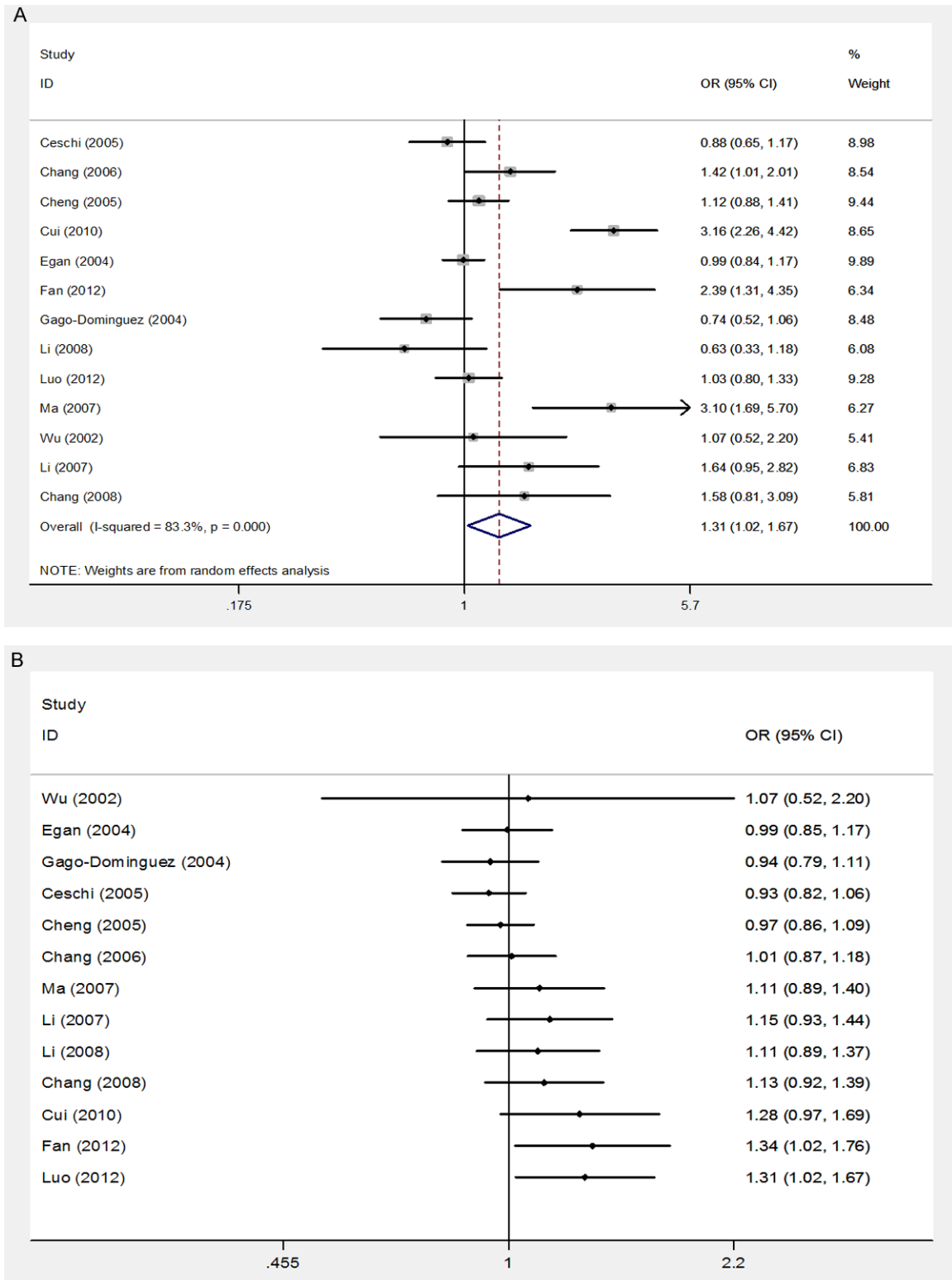
Figure 2. The forest plots of all selected studies on the association between GSTT1 polymorphism and breast cancer risk in Chinese (A: Meta-analysis; B: Cumulative meta-analysis).

of our meta-analysis, a leave-one-out sensitivity analysis was performed. The results did not substantially alter when any single study was deleted, suggesting that the results of this

Table 2. Main results in the total and subgroup analysis

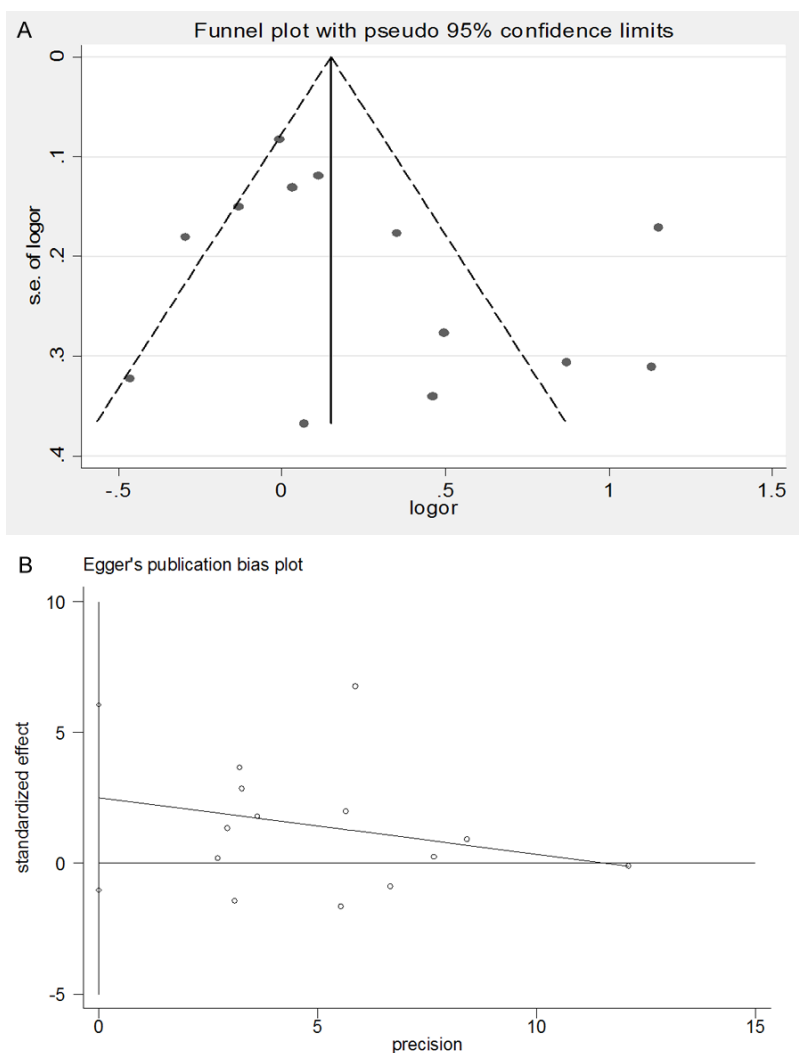| Subgroups	n	Random-effect model	Fixed-effect model	Heterogeneity	
		OR (95% CI)	OR (95% CI)	χ^2	P
Total analysis	13	1.31 (1.02-1.67)	1.17 (1.07-1.28)	71.67	0.000
Source of control					
Population-based	8	1.12 (0.85-1.48)	1.08 (0.98-1.18)	52.31	0.000
Hospital-based	5	1.88 (1.33-2.64)	1.90 (1.44-2.49)	6.06	0.195
Area					
South China	8	1.16 (0.96-1.39)	1.16 (0.96-1.39)	15.46	0.030
North China	3	2.67 (1.81-3.94)	2.67 (1.81-3.94)	3.42	0.181

Figure 3. Publication bias assessment of GSTT1 polymorphism and breast cancer risk in Chinese (A: Begg's funnel plot, B: Egger's test).

meta-analysis were relatively stable and credible (**Figure 4**).

Discussion

The GSTT1 enzyme is responsible for the metabolism of reactive electrophilic intermediates, including environmental pollutants and other polycyclic aromatic hydrocarbons, which are potent carcinogenic agents. Thus, impaired GSTT1 function may lead to serious DNA damage and carcinogenesis. Considering that the GSTT1 null genotype caused a complete loss of GSTT1 enzyme activity, it is biologically plausible that the GSTT1 null genotype may increase risk of cancers, including breast cancer. Till date, a series of studies in China have focused on the relation between GSTT1 polymorphism and breast cancer risk. Nevertheless, the results were inconclusive and inconsistent. Some papers have reported that a statistically significant correlation was found between null GSTT1 and breast cancer risk. Conversely, the results from other studies suggested that the null GSTT1 was not associated with breast cancer risk. Therefore, we conducted this update meta-analysis by critically reviewing 13 individual case-control studies on GSTT1 gene polymorphism with breast cancer risk in the Chinese population. In the meta-analysis, we found that the GSTT1 null variant was significantly associated with breast cancer risk in Chinese (**Figure 2A**). The finding from cumulative meta-analysis showed that there was a trend of more obvious associa-
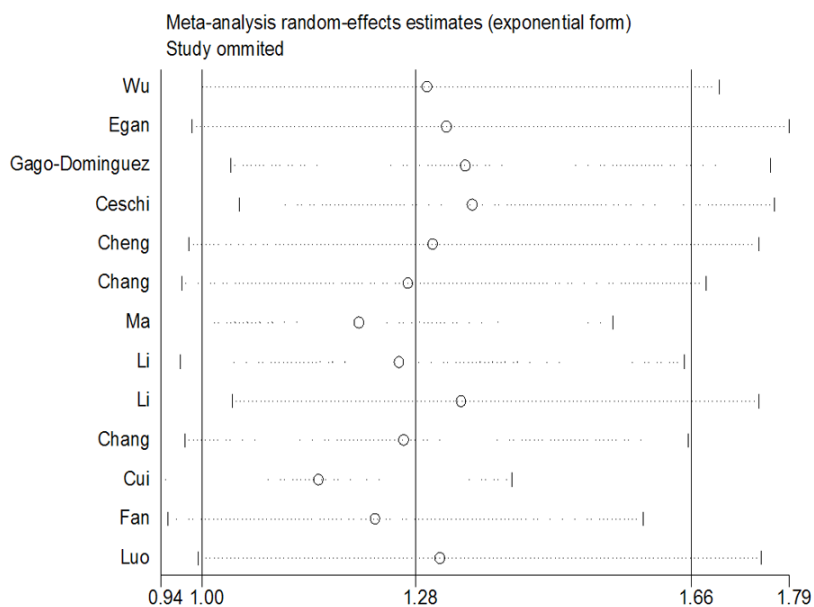
Figure 4. Sensitivity analysis to evaluate the stability of the meta-analysis.

ther factors concerned. Most of all, small sample size for the subgroups may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate [25].

The pathways of carcinogen metabolism are complex, mediated by the activities of multiple genes. The effect of any single gene might have a limited impact on breast cancer risk than have so far been anticipated. The knowledge of environmental determinants and large studies with detailed exposure information are crucial to evaluate reliably any moderate genetic effects. Many controversial data are present in literature. Positive associations were found in certain populations and not confirmed in others. In addition to an expected interethnic variability in allele frequencies, variability has also been found within an ethnic group, resulting in heterogeneity in association studies. Gene-environment interactions could be a confounding factor in these studies, with controversial findings on cancer risk. This study has some limitations. First, in the subgroup analyses, the number of studies was relatively small, not having enough statistical power to explore the real association. Second, our results were based on unadjusted estimates, while the confounding factors might influence the estimates. In spite of these limitations, our meta-analysis also had some advantages. First, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, a funnel plot and Egger's linear regression test were used to assess publication bias. Third, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Most of the important, impact of different genetic background was minimized by including the studies performed in Chinese only. Therefore, the 13 studies would appear to be comparable in all respects relevant to our meta-analysis.

tion between GSTT1 null genotype and risk of breast carcinoma in Chinese as data accumulated by publication year (**Figure 2B**). Therefore, GSTT1 null genotype is significantly associated with increased risk of breast carcinoma in Chinese. The results were inconsistent with previously published meta-analyses [13, 22-24], which indicated the significant associations in Caucasians, in non-Chinese populations, or no significant associations. However, these previously published meta-analyses included a smaller number of studies which were conducted in Chinese populations than ours did. And they did not calculate pooled ORs for all studies in Chinese population.

When stratified by geographical locations and source of controls, significant association with susceptibility for the development of breast cancer was found in North China and hospital-based studies. There might be some reasons could be explained that. First, the relationship between genes and breast cancer might be susceptible in different ethnicity. And we didn't perform subgroup analysis on nationality and other ethnicity history, because of the lack of sufficient data. In addition, genetic backgrounds and the environment they lived in play an important role in susceptibility to breast cancer. There are different living habits in South and North China. Third, gene-gene or gene-environmental interactions would be the fur-

In conclusion, this meta-analysis suggests that the GSTT1 null genotype may be associated with breast cancer in the Chinese population. The null genotype increased susceptibility to breast cancer both in North China and hospital-based studies. Further studies with gene-gene and gene-environment interactions are required. Such studies taking these factors into account may eventually lead to have a better, comprehensive understanding of the association between the GSTT1 polymorphism and breast cancer risk.

Disclosure of conflict of interest

None.

Address correspondence to: Jia-Gen Li, Department of Oncological Surgery, Yinzhou Hospital Affiliated to Medical School of Ningbo University, Ningbo City 315100, Zhejiang Province, China. E-mail: Jiagen-Li@126.com

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