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Glutathione S-transferase P1 rs1695 A>G polymorphism and breast cancer risk: evidence from a meta-analysis

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ABSTRACT. Breast cancer (BC) is the most widespread cause of cancer-related deaths in women. Many published studies have assessed the association between the glutathione S-transferase P1 (*GSTP1*) rs1695 polymorphism and BC risk. However, the effect of the *GSTP1* rs1695 polymorphism on BC risk has remained controversial. Therefore, this meta-analysis was conducted to obtain a comprehensive estimation of this association. A total of 20,615 cases and 20,481 controls from thirty-six case-control trials were extracted from an online literature survey. The meta-analysis indicated that the *GSTP1* rs1695 A>G polymorphism did not contribute to the susceptibility of

BC when the overall population was considered. However, intriguingly, this polymorphism was significantly associated with increased risk of BC in Asian women [GG *vs* AA: odds ratio (OR) = 1.4, 95% confidence interval (CI): 1.06-1.88, P = 0.02; AG *vs* AA: OR = 1.08, 95%CI = 1.00-1.16, P = 0.05; GG/AG *vs* AA: OR = 1.11, 95%CI = 1.04-1.19, P = 0.00]. Moreover, a subgroup analysis based on the source of control groups showed a marked increase in BC susceptibility in hospital-based control subjects (GG *vs* AA: OR = 1.28, 95%CI = 1.10-1.48, P= 0.00; GG *vs* AG/AA: OR = 1.22, 95%CI = 1.06-1.41, P = 0.00; GG/AG *vs* AA: OR = 1.10, 95%CI = 1.02-1.18, P = 0.00). In conclusion, our study indicated that the *GSTP1* rs1695 A>G polymorphism was correlated with elevated BC risk in Asian women. Our results must be validated with further research.

Key words: *GSTP1*; Polymorphism; Breast cancer; Meta-analysis

INTRODUCTION

BC is the most common type of cancer that is widespread among women. It is also the major cause of cancer-related deaths in women (Ferlay et al., 2010). Cancer is a multi-step complex process influenced by risk factors such as reproduction, age, and family history. However, only a third of all BC cases is related to these factors (Coates and Tracey, 2001). Additional risk factors include the genetic background and lifestyle of a person, as well as environmental factors (Ermolenko et al., 2010). Exposure to estrogen was also believed to be associated with fortified risk of BC development (Yager and Davidson, 2006). The mechanism of estrogen-induced carcinogenesis is intricate. Estrogens are primarily metabolized by the catechol estrogen metabolism pathway (CEMP). This pathway produces reactive oxygen species (ROS) and adducts that may contribute to mutations and DNA damage, which may act as the trigger for neoplasm development (Ball and Knuppen, 1980). Estrogens are hydroxylated in CEMP, producing 2-hydroxycatechol estrogen (2-OH CE) or 4-hydroxycatechol estrogen (4-OH CE). These two catechol estrogens (CEs) are oxidized into CE semiquinones, and subsequently into catechol estrogen quinones (CE-Qs) if CEs are not inactivated by O-methylation catalyzed by *COMT* (Russo and Russo, 2006).

These CE-Qs can then be conjugated to glutathione (GSH) by the members of the glutathione S-transferase (GST) family, preventing DNA damage. The most well-characterized GST classes include á (*GSTA*), ð (*GSTP*), ì (*GSTM*), and è (*GSTT*). GSTP1, the paramount GST enzyme found in the breast, plays an important role in suppressing tumorigenesis (Raftogianis et al., 2000). CE-Qs conjugated with glutathione is known to prevent DNA damage. In contrast, CE-Qs may cause mutations and initiate BC (Yager and Davidson, 2006). *GSTP1* is a polymorphic gene located on chromosome 11q13. One of the functional genetic variants identified in this gene is the point mutation at nucleotide 313, a polymorphic site at codon 105 (exon5), which is an A-G substitution. This brings about a single amino acid transformation from isoleucine (Ile) to valine (Val) (Board et al., 1989). This causes a decrease in enzymatic activity and an increase in cancer munity (Zimniak et al., 1994). Previous studies have reported that the *GSTP1* rs1695 G allele increases the risk of developing bladder, testicular, and lung cancers (Cavalieri et al., 2000). Conversely, the expression of the A allele is favorable in

prostate and lung cancer (Ryberg et al., 1997).

The epidemiological studies conducted so far have explored the association between *GSTP1* rs1695 and breast cancer risk (Liu et al., 2013), with limited success, that is, the outcome remains uncertain. The accuracy of these results might be induced by limitations such as individual studies and sparse data, or discordance among the reported original studies. Meta-analysis is a valuable instrument to evaluate and explain the results from different clinical trials, and may offer a precise evaluation. Here, we have performed a meta-analysis of 36 published case-control studies to estimate the association between the *GSTP1* rs1695 A>G polymorphism and BC risk.

MATERIAL AND METHODS

Identification and eligibility of relevant studies

We performed an electronic search of PubMed using the search terms "rs1695", "*GSTP1*", "polymorphism" and "breast cancer". The search was limited to English papers. Additionally, we performed a manual search of the relevant references in extracted studies to identify additional studies. Studies that satisfied the following criteria were included in our meta-analysis: a) case-control studies, b) genotype frequencies for both patients and control populations, or odds ratio (OR) and 95% confidence interval (CI) of the relevant genetic models available, and c) studies that evaluated the association between *GSTP1* rs1695 polymorphism and breast cancer risk.

Selection of trials and data collection

Two investigators independently extracted the data. The following data was considered in each study: the first author's name, ethnicity, country of origin, source of controls (healthy or hospital-based controls), number of genotyped cases and controls, and ORs and 95%CIs of relevant genetic models. People with different ethnicities were grouped into European, Asian, and African populations. Data from different ethnic groups was extracted separately in studies with individuals from different ethnic groups whenever possible.

Statistical analysis

OR and the 95%CI was used to measure the intensity of association between the *GSTP1* rs1695 polymorphism and breast cancer risk. The codominant [GG *vs* AA (homozygote comparison); AG *vs* AA (heterozygote comparison)], dominant (AG/GG *vs* AA), and recessive models (GG *vs* AG/AA) were used to assess the risk. The Q statistic test for heterogeneity was performed (Handoll, 2006). A Q-test P value <0.05 indicates a lack of heterogeneity among studies; therefore, the fixed-effects model (Mantel-Haenszel method) was used to pool the data (DerSimonian and Laird, 1986). On the other hand, the random effects model (DerSimonian and Laird method) was used when $P > 0.05$ (Mantel and Haenszel, 1959).Potential publication bias was tested by the funnel plot; the linear regression test ($P < 0.05$) indicates statistical significance (Egger et al., 1997). A Chi square test was applied to assess the conformance of the distribution of genotypes in the controls with the Hardy-Weinberg equilibrium (HWE) in all studies ($P < 0.05$ was considered to be significant) (Zhang et al., 2011). All statistical

analyses were performed using the Stata software (v.8.2; Stata Corp LP, College Station, TX, USA), using two-sided P values.

RESULTS

Description of included studies

Thirty-six case-control studies, including 20,615 cases and 20,481 controls were selected. The primary features of these studies are shown in Table 1. The extracted publications included 21 studies from Europe, 12 from Asia, 2 from Africa, and 3 with a mixed population. Ten of these studies were performed on premenopausal women and 13 on postmenopausal women. Fifteen were hospital-based studies and 19 were population-based studies.

Table 1. Main characteristics of literatures included in the meta-analysis.

First author	Country	Ethnicity	Control source	Case			Case total	Control			Control total
				AA	AG	GG		AA	AG	GG	
Martínez-Ramírezetal.	UK	Caucasians	Healthy	40	39	71	150	43	66	41	150
Cerne et al.	Slovenia	Caucasians	Hospital	233	243	54	530	130	101	39	270
Ermolenko et al.	Russian	Caucasians	Hospital	448	390	94	932	213	209	48	470
Reding et al.	UK	Caucasians	Healthy	382	417	92	891	366	390	119	875
Zhang et al.	China	Asian	Healthy	-	-	-	3062	-	-	-	3075
Cerne et al.	Slovenia	Caucasians	Hospital	233	297		530	130	139		269
Ramalhinho et al.	Portugal	Caucasian	Hospital	39	-	-	85	48	-	-	102
Kaushal et al	India	Asian	Hospital	62	48	7	117	108	62	4	174
Pongtheerat et al.	Thailand	Asian	Healthy	30	-	-	43	32	-	-	53
McCarty et al.	America	Mix	Healthy	427	-	-	837	426	-	-	912
Reding et al.	America	Mix	Healthy	382	417	92	891	366	390	119	875
Saxena et al.	India	Asian	Healthy	147	193	66	406	200	171	32	403
Antognelli et al.	Italy	Caucasian	Healthy	315	217	15	547	128	340	76	544
Kadouri et al.	England	Caucasian	Hospital	121	74	16	211	76	29	3	108
Van Emburgh et al.	America	Mix	Hospital	174	212	55	441	204	218	48	470
		African		14	29	13	56	25	39	13	77
		Caucasian		160	183	42	385	179	179	35	393
Sakoda et al.	America	Asian	Healthy	378	215	20	613	569	277	30	876
Lee et al.	China	Asian	Hospital	1950	953	123	3026	2003	949	85	3037
Torresan et al.	Brazil	Caucasian	Healthy	46	43	13	102	61	38	3	102
Unlu et al.	Turkey	Caucasian	NR	28	26	11	65	51	37	20	108
Rajkumar et al.	India	Asian	NR	118	103	29	250	230	219	51	500
Syamala et al.	India	Asian	Hospital	186	140	21	347	125	109	16	250
Steck et al.	America	Mix	Healthy	496	-	-	988	512	-	-	1040
Spurdle et al.	Australia	Caucasian	Healthy	539	545	148	1232	283	286	80	649
Edvardsen et al.	Norway	Caucasian	Healthy	119	123	30	272	105	118	45	268
Chang et al.	Taiwan	Asian	Healthy	123	-	-	189	288	-	-	421
Ceschi et al.	Singapore	Asian	Healthy	161	87	9	257	442	199	27	668
Sarmanova et al.	Czech	Caucasian	Hospital	95	111	30	236	146	132	31	309
Egan et al.	China	Asian	Healthy	723	363	53	1139	809	371	31	1211
Kim et al.	Korea	Asian	Hospital	122	44	5	171	113	52	6	171
Gudmundsdottir et al.	Iceland	Caucasian	Hospital	202	225	73	500	177	172	46	395
Mitrunen et al.	Finland	Caucasian	Healthy	283	178	22	483	266	181	34	481
Zhao et al.	America	Caucasian	Healthy	87	58	10	155	170	133	29	332
Millikan et al.	America	Mix	Healthy	239	286	91	616	195	304	96	595
		African		61	131	56	248	54	135	58	247
		Caucasian		178	155	35	368	141	169	38	348
Curran et al.	Australia	Caucasian	Hospital	63	55	11	129	59	64	6	129
Helzlsouer et al.	America	Caucasian	Hospital	41	54	15	110	56	48	9	113
Harries et al.	England	Caucasian	Hospital	25	32	5	62	79	66	10	76

GSTP1 rs1695 polymorphism and BC risk

The main results of this meta-analysis and the heterogeneity tests are shown in Table 2. Unfortunately, we found no significant association between the *GSTP1* rs1695 A>G polymorphism and breast cancer risk in the overall population in all genetic models (codominant model GG *vs* AA: OR = 1.07, 95%CI = 0.85-1.35, P = 0.56; AG *vs* AA: OR = 1.01, 95%CI = 0.89-1.14, P = 0.88; recessive model GG *vs* AA/AG: OR = 1.08, 95%CI = 0.89-1.30, P = 0.45; for dominant model GG/AG *vs* AA: OR = 0.98, 95%CI = 0.87-1.11, P = 0.79).

Table 2. Association of *GSTP1* rs1695 A>G gene polymorphism with risk of breast cancer.

	GG *vs* AA OR (95%CI)	P*	GA *vs* AA OR (95%CI)	P*	GG/GA *vs* AA OR (95%CI)	P*	GG *vs* GA/AA OR (95%CI)	P*
Total	1.07 (0.85-1.35)	0.56	1.01 (0.89-1.14)	0.88	0.98 (0.87-1.11)	0.79	1.08 (0.89-1.30)	0.45
Source of control								
healthy based	0.90 (0.61-1.32)	0.60	0.93 (0.75-1.15)	0.50	0.93 (0.88-0.98)	0.01	0.98 (0.72-1.34)	0.90
Hospital based	1.28 (1.10-1.48)	0.00	1.07 (0.99-1.15)	0.10	1.10 (1.02-1.18)	0.01	1.22 (1.06-1.41)	0.01
Ethnicity								
Asian	1.41 (1.06-1.88)	0.02	1.08 (1.00-1.16)	0.05	1.11 (1.04-1.19)	0.00	0.91 (0.70-1.19)	0.51
Caucasians	0.98 (0.72-1.33)	0.90	0.98 (0.81-1.20)	0.85	1.00 (0.84-1.20)	0.97	0.99 (0.77-1.27)	0.94
Menopausal status								
Premenopausal	1.01 (0.61-1.66)	0.97	0.85 (0.67-1.07)	0.17	0.88 (0.67-1.14)	0.32	1.12 (0.72-1.74)	0.62
Postmenopausal	0.92 (0.61-1.39)	0.69	0.92 (0.69-1.21)	0.54	0.94 (0.86-1.02)	0.16	0.93 (0.69-1.24)	0.60

*P value: Q test for heterogeneity.

Subgroup analysis

Menopausal status

We further assessed this association by stratifying the studies according to the menopausal status, ethnicity, and the source of control groups. The results of this analysis are shown in Table 2. Ten studies provided data on premenopausal subgroups based on the codominant and dominant models. Data from recessive models was extracted from nine studies. However, we did not find any significant association between the *GSTP1* rs1695 A>G polymorphism and BC risk. Among the postmenopausal subgroups, thirteen studies offered data on the codominant model, while twelve and eleven studies provided data regarding the dominant and recessive models. The P value of data pertaining to postmenopausal patients was greater than 0.05. That is we detected no significant association between the *GSTP1* rs1695 A>G polymorphism and BC risk in all genetic models by menopausal status.

Ethnicity

Differences in the ethnicity may lead to heterogeneity in the relationship between *GSTP1* rs1695 A>G polymorphism and BC risk. As only 2 eligible trials were performed in the African population, we have not taken this subgroup analysis into consideration. The population was divided into the Asian and Caucasian populations, according to the original data. Asian women showed significantly increased risk of BC (Figure 1 for GG *vs* AA: OR = 1.4, 95%CI = 1.06-1.88, P = 0.02; AG *vs* AA: OR = 1.08, 95%CI = 1.00-1.16, P = 0.05; GG/AG *vs* AA: OR = 1.11, 95%CI = 1.04-1.19, P = 0.00). However, no association was detected in the Caucasian population (Table 2).

Source of control groups

The data was also stratified according to the source of the control group; we found the existence of a bias between hospital-based and population-based studies. *GSTP1* rs1695 polymorphism was associated with increased BC risk in hospital-based studies (GG *vs* AA: OR 1.28, 95%CI = 1.10-1.48, P = 0.00; GG *vs* AG/AA: OR 1.22, 95%CI = 1.06-1.41, P = 0.01; GG/GA *vs* AA: OR 1.10, 95%CI = 1.02-1.18, P = 0.01; Figure 2), but not in population-based studies. Details are shown in Table 2.

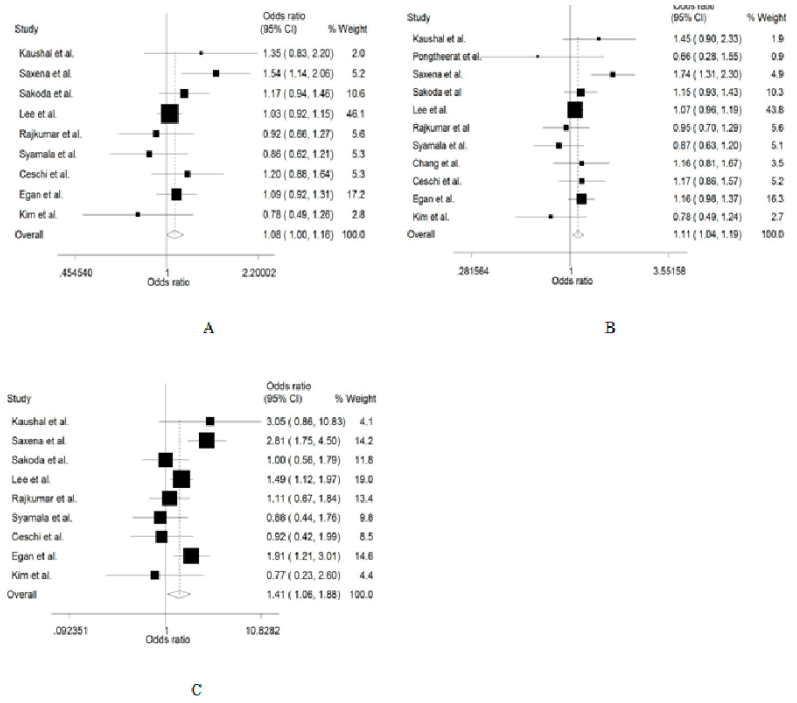

Figure 1. Genetic model in Asian women: **A.** GG+GA *vs* AA; **B.** GA *vs* AA; **C.** GG *vs* AA.

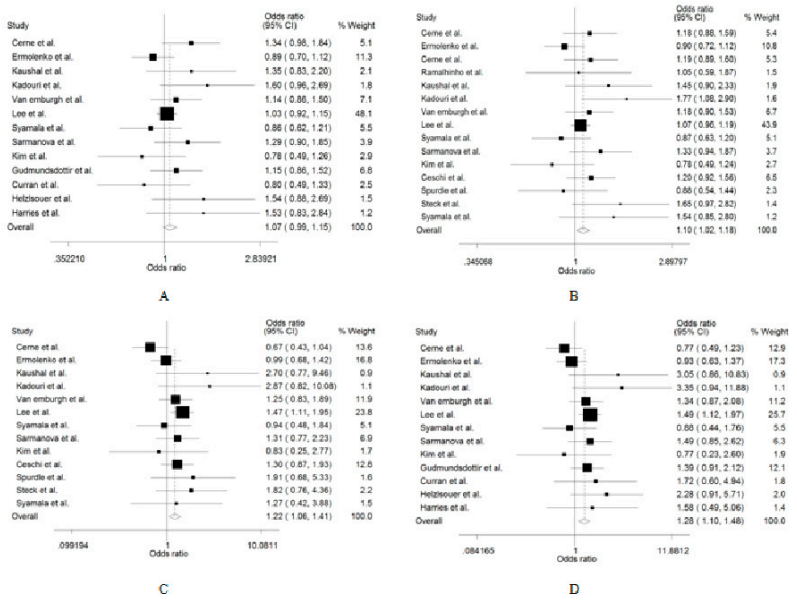

Figure 2. Genetic model in hospital-based studies: **A.** AG *vs* AA; **B.** GG+AG *vs* AA; **C.** GG *vs* AA+GA; **D.** GG *vs* AA.

The publication bias was assessed in the overall publication by a funnel plot; the shape of the funnel plots in codominant genetic models (AG *vs* AA) revealed no significant funnel asymmetry (Figure 3). The Egger tests indicated that there was statistical evidence of publication bias (P > 0.01 in all genetic models).

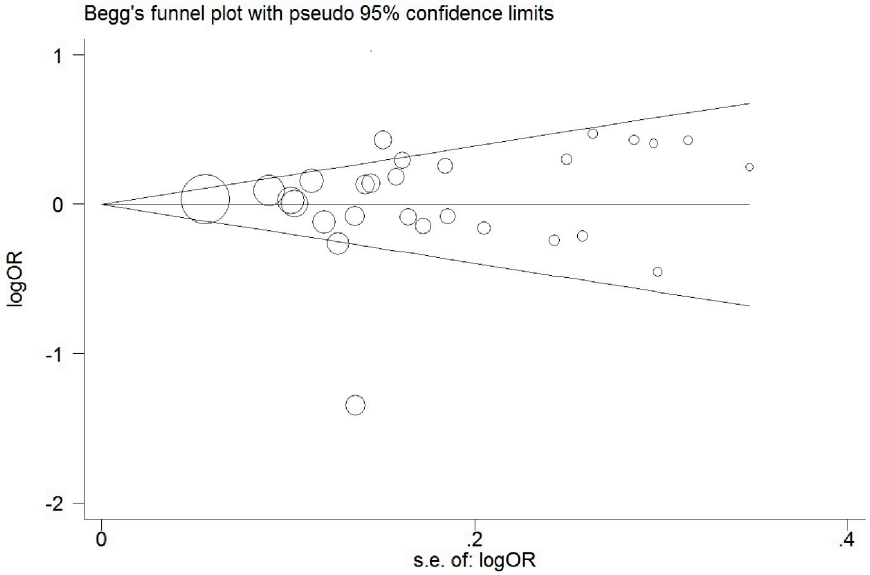

Figure 3. Begg's funnel plot with pseudo 95% confidence limits of publication bias test for *GSTP1* rs1695 polymorphism (AG *vs* AA). Each point represents a separate study for the indicated association. Log[OR], natural logarithm of odds ratio. Horizontal line, mean effect size.

DISCUSSION

This meta-analysis showed that the *GSTP1* rs1695 A>G polymorphism has no significant association with breast cancer susceptibility in the population. Intriguingly, we found a significant association in the Asian population, in the subgroup analysis according to ethnicity. When stratified according to the menopausal status, we detected no significant association either in the postmenopausal or premenopausal groups. A positive link was ascertained in hospital-based studies. This non-conformity between hospital-based and population-based subgroups may prove that population-based studies are more representative of the general population than controls from hospital-based studies.

The completion of the Human Genome Project (HGP) has expedited the identification of inherited genetic variants. These inherited genetic variants change the susceptibility to multifactorial and polygenic diseases such as cancer. The recognition of inherited genetic variants is a widely researched and highly difficult topic (Hunter et al., 2005). Hereditary factors including high- and moderate-penetrance genes have been identified in only about 20% of the total cases of BC (Stratton and Rahman, 2008); that is, most cases of BC are closely bound with common mutations in low penetrance genes. Also, interactions between carcinogenic agents such as estrogen are related to BC (Lynch et al., 2008; Palacios et al.,

2008; Hemel and Domchek, 2010). CEMP plays an important role in the estrogen metabolism process. GST is a superfamily of multifunctional enzymes, which play an important role in phase II metabolism, and the detoxification of therapeutic drugs and various carcinogens via conjugation with glutathione (GSH). GSTs keep cells from free radicals, peroxides, and numerous xenobiotics (Cebrian et al., 2006). CE semiquinones and quinones are responsible for the formation of reactive estrogen metabolites within the CEMP. They damage DNA by the formation of superoxide radicals and depurination DNA adducts (Cavalieri et al., 1997). The *GSTP1* enzyme also plays a significant role in the metabolism of estradiol derivatives (Cavalieri et al., 2000). In CEMP, GSH conjugates with catechol estrogen quinones. This process is catalyzed by GSTs. The reactive intermediates of estrogen metabolism bind to DNA and protect the cells from DNA damage and adduct formation (Ketterer, 1988). Studies have reported the expression of *GSTP1* in many human tissues including breast epithelium (Forrester et al., 1990).

This meta-analysis was performed as the exact correlation between the *GSTP1* rs1695 A>G polymorphism and breast cancer risk remains to be elucidated. In our study, we observed a considerable association between *GSTP1* rs1695 polymorphism and breast cancer risk in homozygous mutations and dominant genetic models in Asian women (Figure 1). We found no significant association in Caucasians in all genetic models. The difference in outcomes between Asian and Caucasian populations are unknown. Lee et al. (2008) reported that the association between cruciferous vegetable intake and breast cancer risk may be modified by *GSTP1* rs1695, which led us to infer the role of differences in environmental exposure and lifestyle factors Asian and Caucasian populations in affecting BC risk. This contributes to the difference in association between BC risk and *GSTP1* rs1695 polymorphism.

When stratified according to the menopausal status, we observed no significant association in both groups. James et al. (2015) reported that a higher fat content in the body is a major risk factor for post-menopausal breast cancer. In contrast, it is generally accepted that a higher body mass index (BMI) is associated with lower risk of developing breast cancer in premenopausal women; however, the molecular mechanism of this association remains poorly understood (Cowan et al., 1981). We inferred that a higher body fat content may affect the relationship between BC risk and *GSTP1* rs1695 in both premenopausal and postmenopausal women. Because of the lack of original BMI data, we did not stratify and analyze the data according to the BMI. This may cause differences in the results, to a certain degree. Cerne et al. (2011) reported that the *MnsoD47* T>C polymorphism resulting from long-term hormone replacement therapy (HRT) may decrease the risk of postmenopausal breast cancer. This is paradoxical with the results of previous studies, where the use of HRT for over 5 years was found to be related to a small but significant increase in the risk of breast cancer (Anderson et al., 2004). Despite the inconsistency in results, we doubted the possibility that HRT may also modify the relationship between rs1695 variants and breast cancer risk in people with different menopausal status, as well as in the overall population.

Our results provide greater confidence because of the larger number of studies included than that in previous relative meta-analyses (Liu et al., 2013). However, some limitations must be taken into consideration. Firstly, there is an increased risk of BC because of the presence of endogenous and exogenous estrogen exposure. The ovulatory cycles of women influence endogenous estrogen, while the use of hormonal contraceptives and hormone replacement therapy affects exogenous estrogen. Nulliparity and tardy first childbirth are also associated with an increased risk for BC (Beral and Million Women Study Collaborators,

2003). Moreover, the original data pertaining to age of menarche and menopause and the use of exogenous estrogen is not provided in the included articles. Our outcomes cannot take these factors into consideration. Secondly, recent studies have suggested that genetic variants may interact with others and confer an elevated breast cancer risk (Ermolenko et al., 2010). There is also crescent evidence regarding the risk genotypes of different cancer pathways, including DNA repair, cell cycle, and immune system. These pathways may interact with each other and lead to an increase in breast cancer risk (Onay et al., 2006). This would imply that estrogen metabolism genotypes and other BC-related genotypes may work together to increase BC risk, even though the specific mechanism remains to be understood. However, we observed no combined effects of gene-gene interactions on the susceptibility of BC. Despite this, the number of potential interactions between SNPs associated with cancer can be plentiful. Investigations into such gene-gene interactions are subject to new statistical challenges. It is yet to be determined if SNPs in genes within the catechol estrogen metabolism pathway altered the risk of breast cancer alone or in combination. Thirdly, some published studies reported the effect of smoking on BC incidence (Kaushal et al., 2010). However, as we did not have sufficient data pertaining to the relationship between smoking and breast cancer, this factor has not been taken into account in the subgroup analysis (similar to data pertaining to BMI, age, HRT, and gene-gene interactions).

In summary, the results of our meta-analysis suggests that the *GSTP1* rs1695 A>G polymorphism increases breast cancer risk in Asian women. Understanding the components of CEMP molecular links may provide an avenue for preventive and therapeutic strategies to reduce cancer risk and mortality. Further investigations are required to characterize the association between the *GSTP1* A>G polymorphism and breast cancer risk, and a greater number of original studies should be investigated to verify our results in the future.

Conflicts of interest

The authors declare no conflict of interest.

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