Journal of Breast Cancer

J Breast Cancer 2014 June; 17(2): 149-156 http://dx.doi.org/10.4048/jbc.2014.17.2.149

ORIGINAL ARTICLE

The Catechol-O-Methyltransferase Val158Met Polymorphism Contributes to the Risk of Breast Cancer in the Chinese Population: An Updated Meta-Analysis

Guo-Xing Wan*, Yu-Wen Cao*, Wen-Qin Li, Yu-Cong Li, Feng Li

Department of Pathology and the Key Laboratories for Xinjiang Endemic and Ethnic Diseases, Shihezi University School of Medicine, Shihezi, China

Purpose: Catechol-O-methyltransferase (COMT) enzyme plays a central role in estrogen-induced carcinogenesis. Emerging evidence from association studies has revealed that the functional Val158Met polymorphism (rs4680 G>A) of the Catechol-O-methyltransferase gene (*COMT*) has been implicated in susceptibility to breast cancer in the Chinese population, while results of individual published studies remain inconclusive and inconsistent. To assess this association in the Chinese population, a meta-analysis was performed. **Methods:** Eligible studies were searched on MEDLINE, Embase, Cochrane Library, China National Knowledge Infrastructure, and the Chinese Biomedicine Database. Odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were pooled to assess the association between *COMT* polymorphisms and the risk of breast cancer using RevMan 5.2 and Stata 12.0 software. **Results:** The meta-analysis included 14 eligible studies, with a total of 4,626 breast cancer cases and 5,637 controls. Overall, the *COMT* Val158Met polymorphism (rs4680 G>A) was significantly associated with an increased risk of breast cancer in several genetic models (A/A vs. G/G: OR, 1.59, 95% CI, 1.12–2.27; A/A vs. G/A+G/G: OR, 1.62, 95% CI, 1.14–2.29; A vs. G: OR, 1.15, 95% CI, 1.00–1.32), and a subgroup analysis according to menopausal status showed that this association was especially evident among premenopausal Chinese women (A/A vs. G/G: OR, 1.87, 95% CI, 0.99–3.54; A/A vs. G/A+G/G: OR, 1.94, 95% CI, 1.03–3.63). **Conclusion:** The results of this meta-analysis indicated that *COMT* Val158Met variants contribute to breast cancer susceptibility in the Chinese population, particularly among premenopausal women.

Key Words: *Breast neoplasms, Catechol-O-methyltransferase, Genetic, Meta-analysis, Polymorphism*

INTRODUCTION

Breast carcinoma is a major cause of cancer-specific mortality worldwide, and efforts are being made for its prevention and early detection, which is important. Breast cancer remains the most common cancer among the female population in China, with an age-standardized rate by world population of 21.6 per 100,000 [1]. In addition to the well-established risk factors for breast cancer, including age at first birth, menarche, and menopause; family history; ethnicity; and geographic variation [2], the significance of exposure to circulating estrogen has been widely accepted as an important factor in the development of breast cancer. Recent studies have shown that estrogen is capable of inducing the proliferation of breast epithelial cells, making them more susceptible to genetic errors during DNA replication; malignant phenotypes are frequently generated by uncorrected replication errors [3]. Therefore, genes that regulate the transcription and translation necessary for the biosynthesis and metabolism of estrogen may contribute to the function of estrogen and, consequently, influence the susceptibility to breast cancer [2].

Catechol-O-methyltransferase (COMT) is a phase II enzyme that inactivates catechol estrogen by methylation and may play a vital role in estrogen-induced carcinogenesis [4]. Aberrant expression of COMT has been observed in several malignancies, including breast carcinoma, in parallel with estrogen metabolism disorders. Recently, Catechol-O-methyltransferase gene (*COMT*) was found to be polymorphic in its participation

Correspondence to: **Feng Li**
Department of Pathology, Shihezi University School of Medicine, 59 North 2nd Road, Shihezi 832000, China
Tel: +86-0993-2057125, Fax: +86-0993-2057125
E-mail: fengli7855@126.com

*These authors contributed equally to this work.

Received: October 10, 2013 **Accepted:** April 11, 2014

http://ejbc.kr | pISSN 1738-6756
eISSN 2092-9900

in the development of breast cancer [3]. The polymorphism of *COMT* gene at codon 158 resulting in the amino acid substitution of Val with Met is designated as Val158Met, with *COMT-H* and *COMT-L* alleles. Individuals carrying the *COMT-Met* (*COMT-A*) allele are hypothesized to harbor a higher risk for breast cancer owing to the formation and accumulation of carcinogenic catechol estrogens [5]; this hypothesis is supported by several lines of evidence indicating that this amino acid substitution is responsible for a decrease in COMT activity and dysregulation of estrogen metabolism [6].

An increasing number of epidemiological studies conducted in the Chinese population have addressed the association between the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer. However, the results remain conflicting or even contradictory [3,7-19]. Moreover, previous studies with pooled analyses of the overall population regarding this issue have yielded different conclusions, possibly owing to the different sample sizes and different ethnicities of the populations investigated [2,20-22]. The discrepancies between previous overall meta-analyses and the inconclusive results of studies conducted in the Chinese population prompted us to perform a meta-analysis for a more precise estimation of the association between the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer in the Chinese population.

METHODS

Literature search strategy

Relevant papers included in the meta-analysis were systematically and electronically searched on MEDLINE, Embase, Cochrane Library, China National Knowledge Infrastructure, and the Chinese Biomedicine Database to identify association studies updated to July 2013 using the following limits: Humans, Chinese population, and article in English or Chinese. We developed a search strategy using the following query: ["*COMT*" or "Catechol-O-methyltransferase" or "Val158Met" or "rs4680"] and ["breast cancer" or "breast carcinoma"] and ["SNP" or "polymorphisms" or "polymorphism" or "variant"]. The reference lists of major textbooks, review articles, and all of the included articles identified by the search were then individually and manually reviewed to identify other potentially eligible studies for the meta-analysis. In cases of duplicate studies, only the one with the largest sample size was included.

Inclusion criteria

To be eligible for inclusion in the current meta-analysis, studies had to satisfy the following criteria: 1) case–control studies including nested case-control studies to evaluate the association between the *COMT* Val158Met polymorphism and the risk of breast cancer; 2) sufficient information provided for estimating odds ratios (ORs) with their 95% confidence intervals (CIs); 3) diagnoses of all patients with malignant tumors were confirmed by pathological or histological examination; 4) the frequencies of alleles or genotypes in case and control groups were able to be extracted.

Exclusion criteria

The following criteria were used to exclude studies from the analysis: 1) no control population was present; 2) they were not conducted in the Chinese population; 3) the outcomes of the study were not reported or were difficult to determine; 4) they were based on incomplete raw data or duplicated the results of previous publications; 5) they were abstracts, comments, letters, reviews, or editorial articles; 6) other necessary information for this meta-analysis were lacking, including studies based on families and those that did not specify the genotyping methods or provide appropriate references.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers to evaluate their eligibility for inclusion by first screening the title and abstract of each identified reference, and then establishing the eligibility of the included papers based on the full text when necessary. For each included study, the following information was collected: first author, year of publication, region, study design, sample size, source of control, genotyping method, allele or genotype frequencies, and evidence of Hardy-Weinberg equilibrium. Any discrepancy between the two reviewers was resolved by discussion and consultation with a third reviewer.

Statistical analysis

Individual or pooled OR and 95% CIs were calculated for the strength of the association between the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer using Review Manager version 5.2 software (provided by The Cochrane Collaboration, Oxford, UK; http://www.cochrane.org/software/revman.htm). The between-study heterogeneity was evaluated using both the Q test and the I^2 test; $p < 0.1$ and $I^2 > 50\%$ indicated heterogeneity [23]. The Q test was used to calculate the pooled OR if the between-study heterogeneity was significant across the included studies [24], and the random-effects model was selected; otherwise, the fixed-effects model (the Mantel-Haenszel method) was used [25]. The sources of heterogeneity were appraised using stratification analysis, based on study characteristics such as menopausal status and source of control. Sensitivity analysis was per-

http://dx.doi.org/10.4048/jbc.2014.17.2.149

formed by sequential omission of individual studies under various contrasts. The significance of the pooled OR was not influenced excessively, indicating the reliability of the results of the meta-analysis. Begger's funnel plots, in which the standard error (SE) of the log (OR) of each study was plotted against its log (OR), were drawn to estimate potential publication bias. An asymmetric plot suggested a possible publication bias; funnel plot asymmetry was assessed using Egger's linear regression test, and $p < 0.05$ was considered to be statistically significant [22]. The Begger's funnel plot and Egger's linear regression test were performed using Stata 12.0 software (Stata Corp., College Station, USA). All *p*-values generated were two-tailed.

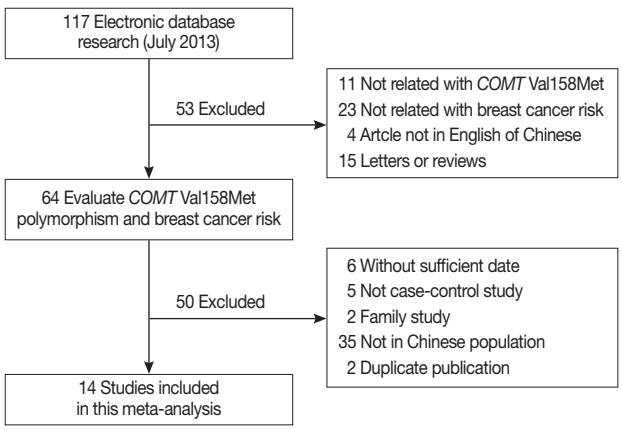

Figure 1. Flow chart of study selection procedure.
COMT = catechol-O-methyltransferase.

RESULTS

Study characteristics

A total of 117 potentially relevant publications focusing on the *COMT* Val158Met polymorphism and breast cancer were retrieved using our search strategy. However, only 14 studies were ultimately included, in accordance with the established inclusion criteria. After reading the titles and/or abstracts, 101 studies lacked indispensable information or were not conducted in Chinese population and were excluded. Of these, 53 articles were excluded because they were irrelevant (34 articles), the language was not Chinese or English (4 articles), or they were letters or reviews (15 articles). Forty-eight articles were excluded because they were not case-control studies (5 articles), not conducted in the Chinese population (35 articles), had insufficient data (6 articles) or were family-based studies (2 articles). Sixteen studies were subjected to a full text review, two of which were excluded due to duplication (1 study) and a lack of essential information (1 study). A flow chart summarizing study selection is shown in Figure 1. In total, 14 case-control studies involving 4,626 breast cancer cases and 5,637 controls were included in the final meta-analysis [3,7-19]. Eleven studies were reported in English and three were reported in Chinese. Nine of the included studies were population-based studies, and five had a hospital-based design. Five publications were concerned with the *COMT* Val158Met polymorphism and premenopausal breast cancer cases, and six were concerned with the *COMT* Val158Met polymorphism and postmenopausal breast cancer cases. Detailed characteristics of the included studies are summarized in Table 1.

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

First author, year	Region	SC	Genotyping method	Menopausal status	Genotypes distribution (case/control)			HWE test
					A/A	G/A	G/G	
Hu, 2007 [12]	Shanghai	PB	Sequencing	Pre-, post-	11/3	36/41	65/66	0.25
Cheng, 2005 [10]	Taiwan	HB	SEQUENOM	Mixed	35/58	197/262	237/420	0.06
Huang, 1999 [13]	Taiwan	HB	PCR-RFLP	Pre-, post-	12/4	35/55	66/65	0.06
Wang, 2010 [17]	Sichuan	PB	AS-PCR	Post-	34/14	62/66	80/96	0.58
Fan, 2007 [11]	Tianjin	HB	PCR-RFLP	Mixed	29/5	75/44	96/51	0.25
Wen, 2005 [18]	Shanghai	PB	PCR-RFLP	Pre-, post-	83/93	425/470	612/628	0.70
Shrubsole, 2009 [15]	Shanghai	PB	PCR-RFLP	Mixed	497/554*		596/615	NA
Lin SC, 2005 [14]	Taiwan	PB	PCR-RFLP	Mixed	6/23	35/138	58/205	0.97
Chang, 2006 [9]	Taiwan	HB	PCR-RFLP	Mixed	9/30	77/159	103/160	0.28
Lin WY, 2005 [3]	Taiwan	PB	PCR-RFLP	Mixed	5/18	31/133	51/190	0.39
Wang, 2011 [16]	Sichuan	PB	Sequencing	Pre-, post-	68/36	145/156	187/208	0.39
Wu, 2003 [19]	Unknown	PB	TaqMan	Mixed	14/15	67/78	97/106	0.90
Tan, 2003 [8]	Beijing	HB	PCR-RFLP	Pre-, post-	26/13	103/105	121/132	0.17
Xu, 2010 [7]	Shandong	PB	AS-PCR	Mixed	38/10	42/44	60/68	0.45

SC = source of control; HWE = Hardy-Weinberg equilibrium; PB = population-based; Pre- = premenopausal; Post- = postmenopausal; HB = hospital-based; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; AS-PCR = allele-specific-polymerase chain reaction; NA = not available.
*Number of A/A+G/A genotype in case and control, respectively.

Overall results of meta-analysis

As shown in Table 2, significant evidence of heterogeneity was detected in four genetic models ($p_h < 0.1$), all except the additive model ($p_h = 0.4$), and the random-effects model was used to calculate the pooled OR, in all except the additive model. Overall, the results of the meta-analysis showed that the *COMT* Val158Met polymorphism (rs4680 G > A) was significantly associated with an increased risk of breast cancer in the Chinese population in three genetic models (A/A vs. G/G: OR, 1.59, 95% CI, 1.12–2.27; A/A vs. G/A+G/G: OR, 1.62, 95% CI, 1.14–2.29; A vs. G: OR, 1.15, 95% CI, 1.00–1.32) (Table 2, Figure 2A, B). However, no significant association between the *COMT* Val158Met polymorphism and the risk of breast cancer was observed in the dominant model or the additive model (A/A+G/A vs. G/G: OR, 1.04, 95% CI, 0.93–1.17; G/A vs. G/G: OR, 0.98, 95% CI, 0.89–1.08, respectively). The results are shown in Table 2.

Results of subgroup analysis

According to the different menopausal status and sources of control, we also performed further subgroup analyses. In the subgroup analysis based on menopausal status, the polymorphism presented a significantly increased risk of breast cancer in a premenopausal group (A/A vs. G/G: OR, 1.87, 95% CI, 0.99–3.54; A/A vs. G/A+G/G: OR, 1.94, 95% CI, 1.03–3.63), but not in other genetic models. However, the postmenopausal group did not show a significantly increased risk of breast cancer in any model. The data were further stratified by the source of control, and the polymorphism only showed a significantly increased risk of breast cancer in population-based studies in the codominant model and the recessive model (A/A vs. G/G: OR, 1.69, 95% CI, 1.06–2.69; A/A vs. G/A+G/G: OR, 1.71, 95% CI, 1.10–2.66). Similarly, no significantly elevated risk of breast cancer was associated with this polymorphism in hospital-based studies in any of the genetic models. All the results are presented in Table 2.

Sensitivity analysis and publication bias

Since significant between-study heterogeneity was observed in the overall meta-analyses in some genetic models, we performed a sensitivity analysis by sequential omission of individual studies in an attempt to investigate the influence of

Table 2. Meta-analysis of the *COMT* Val158Met polymorphism on breast cancer susceptibility in Chinese population

Contrast	Study groups	No. of studies	OR (95% CI)	*p*-value	Heterogeneity		Effect model
					P_h	I^2 (%)	
A/A vs. G/G	Overall	13	1.59 (1.12–2.27)*	0.01*	<0.01	70	R
	Pre-	5	1.87 (0.99–3.54)*	0.05*	0.04	60	R
	Post-	6	1.71 (0.90–3.28)	0.10	0.01	65	R
	PB	8	1.69 (1.06–2.69)*	0.03*	<0.01	73	R
	HB	5	1.47 (0.77–2.80)	0.24	<0.01	71	R
G/A vs. G/G	Overall	13	0.98 (0.89–1.08)	0.70	0.40	5	F
	Pre-	5	0.91 (0.77–1.08)	0.29	1.00	0	F
	Post-	6	0.96 (0.80–1.16)	0.70	0.57	0	F
	PB	8	0.95 (0.85–1.08)	0.45	0.98	0	F
	HB	5	0.95 (0.72–1.25)	0.70	0.03	62	R
A vs. G	Overall	13	1.15 (1.00–1.32)*	0.05*	<0.01	69	R
	Pre-	5	1.07 (0.95–1.22)	0.27	0.15	41	F
	Post-	6	1.23 (0.09–1.51)	0.06	0.08	50	R
	PB	8	1.20 (0.98–1.47)	0.08	<0.01	75	R
	HB	5	1.08 (0.88–1.33)	0.46	0.03	61	R
A/A+G/A vs. G/G	Overall	14	1.04 (0.93–1.17)	0.48	0.06	40	R
	Pre-	5	1.00 (0.85–1.17)	0.98	0.71	0	F
	Post-	6	1.10 (0.93–1.31)	0.27	0.23	28	F
	PB	9	1.00 (0.91–1.10)	0.97	0.17	32	F
	HB	5	1.02 (0.79–1.31)	0.89	0.05	58	R
A/A vs. G/A+G/G	Overall	13	1.62 (1.14–2.29)*	<0.01*	<0.01	71	R
	Pre-	5	1.94 (1.03–3.63)*	0.04*	0.03	62	R
A/A vs. G/A+G/G	Post-	6	1.75 (0.90–3.38)	0.10	<0.01	69	R
	PB	8	1.71 (1.10–2.66)*	0.02*	<0.01	72	R
	HB	5	1.51 (0.79–2.92)	0.22	<0.01	74	R

COMT = catechol-O-methyltransferase; OR = odds ratio; CI = confidence interval; P_h = *p*-value for heterogeneity; I^2 = quantitative estimate for heterogeneity; Pre- = premenopausal; Post- = postmenopausal; PB = population-based; HB = hospital-based; R = random effects model; F = fixed effects model.
*The values indicates a significant difference.

http://dx.doi.org/10.4048/jbc.2014.17.2.149

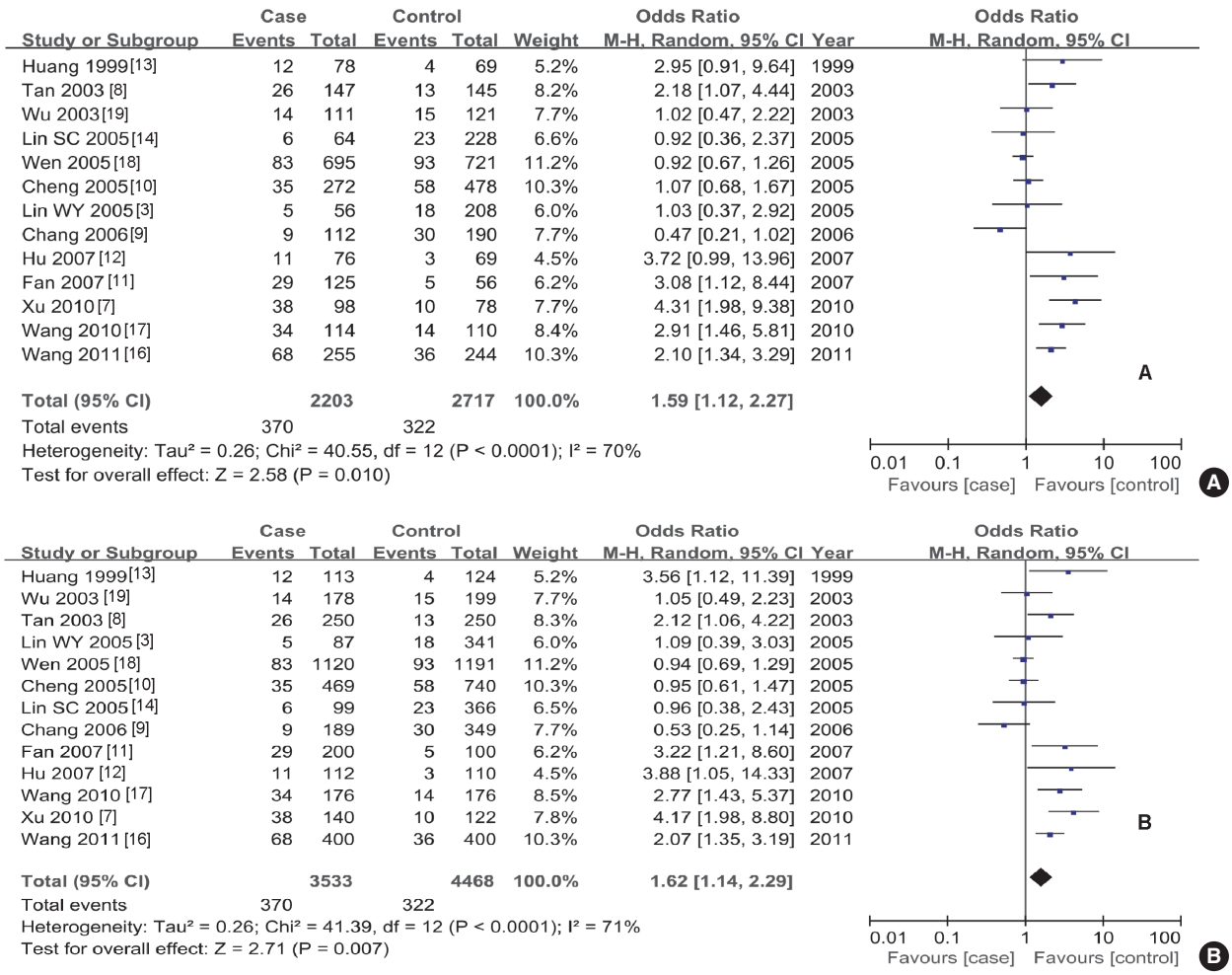

Figure 2. Forest plots for the association of catechol-O-methyltransferase Val158Met polymorphism with breast cancer risk in Chinese population. (A) A significant association was observed under A/A versus G/G contrast. (B) A significant association was observed under A/A versus G/A+G/G contrast. CI = confidence interval.

Table 3. Sensitivity analysis by sequential omission

Study omitted	A vs. G model		Effect model
	p-value	OR (95% CI)	
Huang, 1999 [13]	0.05	1.16 (1.00–1.34)	R
Tan, 2003 [8]	0.09	1.14 (0.98–1.33)	R
Wu, 2003 [19]	0.04	1.17 (1.00–1.35)	R
Lin WY, 2005 [3]	0.04	1.17 (1.01–1.35)	R
Cheng, 2005 [10]	0.08	1.15 (0.98–1.35)	R
Wen, 2005 [18]	0.03	1.18 (1.02–1.37)	R
Lin SC, 2005 [14]	0.04	1.17 (1.01–1.35)	R
Chang, 2006 [9]	<0.01	1.19 (1.04–1.37)	R
Hu, 2007 [12]	0.07	1.14 (0.99–1.32)	R
Fan, 2007 [11]	0.08	1.14 (0.98–1.32)	R
Xu, 2010 [7]	0.13	1.10 (0.97–1.25)	R
Wang, 2010 [17]	0.12	1.12 (0.97–1.29)	R
Wang, 2011 [16]	0.10	1.13 (0.97–1.31)	R

OR = odds ratio; CI = confidence interval; R = random effects model.

each study on the overall OR. As a result, the significance of the pooled OR in all genetic models was not affected excessively, with the exception of the allele contrast model. We found a slight fluctuation of the *p*-value around 0.05 indicating a significant association of A versus G with the risk of breast cancer in the sensitivity analysis, the result of which is shown in Table 3. Nevertheless, a significant association of this polymorphism with the risk of breast cancer was suggested by most results of sequential omission in the sensitivity analysis. Publication bias of the literature on the association between the *COMT* Val158Met polymorphism (rs4680 G>A) and the risk of breast cancer was assessed by Begger's funnel plot and Egger's linear regression test. The graphical funnel plot shown in Figure 3 seemed symmetrical, suggesting no evident publication bias; this was also supported by the results of Egger's test (A/A+G/A vs. G/G, $p = 0.44$; A vs. G, $p = 0.284$; G/A vs. G/G, $p = 0.362$; A/A vs. G/A+G/G, $p = 0.129$; A/A vs.

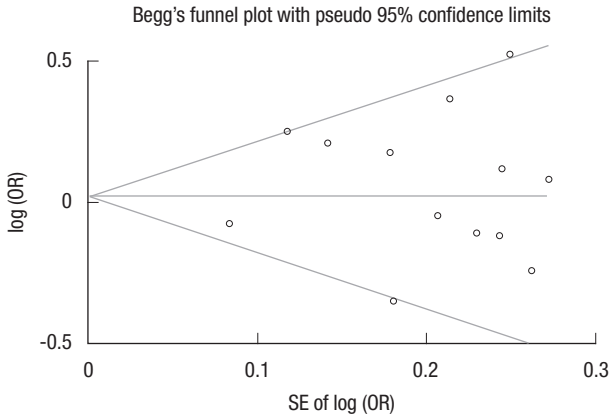

Figure 3. Begger's funnel plot of the overall analysis of breast cancer risk and catechol-O-methyltransferase Val158Met polymorphism in Chinese population revealed no evident publication bias under A/A+G/A versus G/G contrast.
SE = standard error; OR = odds ratio.

G/G, $p = 0.165$, all $p > 0.05$).

DISCUSSION

The present meta-analysis assessing the association between the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer in the Chinese population was based on data from all available studies published to date, representing the largest study so far. Our results suggest that the *COMT* Val158Met polymorphism (rs4680 G > A) is significantly associated with an increased risk of breast cancer in the Chinese population, particularly in premenopausal women.

The preponderance of data from epidemiological and animal studies indicates that estrogen signaling is central in breast carcinogenesis. The levels of estrogen are partially regulated by its catabolism. However, the participation of the genes involved in estrogen catabolism in carcinogenesis and the extent to which estrogen exposure modifies the associations of these genes with the risk of breast cancer require further investigation. Several molecular epidemiologic studies conducted worldwide have reported the potential role of the functional polymorphism, *COMT* Val158Met (rs4680 G > A), in determining the risk of breast cancer. An amino acid substitution yielded by a single G to A base pair change in the *COMT* gene is believed to result in a 2- to 3-fold decrease in the enzymatic activity of COMT, which was suggested to contribute to the susceptibility of breast cancer through its role in estrogen signaling [20,26,27]. To date, although many epidemiological studies conducted in the overall population have evaluated the association of the *COMT* Val158Met polymorphism with breast cancer, the results remain inconsistent; some original studies conducted in the Chinese population demonstrated an association between the *COMT* Val158Met polymorphism and the risk of breast cancer [8,10,13], whereas others reported contrasting results [3,17,18]. We undertook the present meta-analysis to achieve a more precise estimation of the association between the *COMT* Val158Met polymorphism and the risk of breast cancer in the Chinese population. To our knowledge, this is the most comprehensive meta-analysis with the largest sample size focusing on the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer in the Chinese population.

Previous epidemiological studies conducted in the Chinese population obtained discrepant results. Huang et al. [13] and Cheng et al. [10] found a trend toward an increasing risk for developing breast cancer in women who harbored low-activity *COMT* (*COMT* L/L or A/A) genotypes. Similarly, a study by Tan et al. [8] showed that the elevated risk of breast cancer associated with the *COMT* A/A genotype was only evident among premenopausal women, but not among postmenopausal women. In contrast, Wang et al. [17] suggested that postmenopausal women carrying the *COMT* A/A genotype may possess a higher risk of breast cancer. However, Lin et al. [3] and Wen et al. [18] found no overall association between the *COMT* genotype and individual susceptibility to breast cancer.

In the current meta-analysis, we found evidence of a significant association between the *COMT* Val158Met polymorphism and the risk of breast cancer in the Chinese population on the overall analysis of 14 case-control studies involving 4,626 cases and 5,637 controls. In line with most individual studies conducted in the Chinese population, a significant association between the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer was found in several genetic models (A/A vs. G/G: OR, 1.59, 95% CI, 1.12–2.27; A/A vs. G/A+G/G: OR, 1.62, 95% CI, 1.14–2.29; A vs. G: OR, 1.15, 95% CI, 1.00–1.32), suggesting a contribution of the *COMT* Val158Met variant genotype to an increased risk of breast cancer in the Chinese population. Furthermore, subgroup analysis based on menopausal status and the source of control showed that the variant genotype was also significantly associated with an elevated risk of breast cancer in premenopausal cases (A/A vs. G/G: OR, 1.87, 95% CI, 0.99–3.54; A/A vs. G/A+G/G: OR, 1.94, 95% CI, 1.03–3.63) and in population-based studies (A/A vs. G/G: OR, 1.69, 95% CI, 1.06–2.69; A/A vs. G/A+G/G: OR, 1.71, 95% CI, 1.10–2.66). However, the results of present meta-analysis were not in accordance with previous analyses. He et al. [20] and Ding et al. [21] reported a decreased risk of breast cancer among European populations in the recessive model, with borderline signifi-

http://dx.doi.org/10.4048/jbc.2014.17.2.149

cance (OR, 0.96, 95% CI, 0.92–1.00; OR, 0.90, 95% CI, 0.90–1.00, respectively), but not in Asians. In contrast, the studies conducted by Qin et al. [2] and Mao et al. [22] both demonstrated no association between the *COMT* Val158Met polymorphism and the risk of breast cancer in an overall analysis and in subgroup analysis according to ethnicity, menopausal status, or control source. Moreover, although He et al. [20] performed a more comprehensive analysis compared to previous reports, several more recent studies conducted in the Chinese population with larger sample sizes involving 2,006 cases and 2,018 controls have been reported since that study; these studies also failed to show any association in Asians (only 2,674 cases and 3,619 controls in the Chinese population, as well as 1,609 cases and 1,580 controls in other Asian populations), indicating that sample size or geographical variation were possible influences on the assessment of this association. Additionally, in premenopausal women, we found that the *COMT* Val158Met polymorphism was significantly associated with an increased risk of breast cancer in the Chinese population; this may be due to the interaction between the *COMT* polymorphism and menopausal status, which may play a critical role in catechol estrogen metabolism in breast cancer etiology, depending on the levels of circulating estrogens. Therefore, in a higher estrogen environment, such as that typically observed in premenopausal women, the presence of higher circulating levels of the catechol compounds of estradiol generated in an environment with low COMT activity may result in higher circulating levels of potentially mutagenic compounds, such as estrogens, leading to a relatively high risk of breast cancer in premenopausal women. These results were, at least in part, different from those of previously published studies, and this mechanism may account for these disparities. First, the discrepancies indicated that sample size was likely significant for the assessment regarding the association between the *COMT* Val158Met polymorphism and the risk of breast cancer. Second, the same polymorphism played different roles in breast cancer susceptibility among different regions or ethnic populations; since cancer is a complicated, multigenetic disease, diverse genetic backgrounds and environmental exposures may result in different influences on the risk of breast cancer through gene-gene and gene-environment interactions [28]. In the stratification analysis based on control source, we found a borderline significant increase in the risk of breast cancer among studies using population-based controls but not in those using hospital-based controls. The reason behind this difference may be that the controls were retrieved from an ill-defined reference population associated with the genotype investigated under the disease condition. Therefore, using a suitable and representative control population may contribute to a more reliable and robust result. Furthermore, heterogeneity is a potential problem that may affect the interpretation of the results. Obvious between-study heterogeneity was found in the overall comparison of this meta-analysis. However, the observed heterogeneity was not significantly reduced by subgroup analysis, suggesting a possibility that other limitations may partially contribute to the observed heterogeneity.

Despite the considerable efforts to explore the possible association between the *COMT* Val158Met polymorphism (rs4680 G > A) and the risk of breast cancer, some limitations need to be addressed when interpreting the results of this meta-analysis. First, the association of the *COMT* Val158Met polymorphism with the risk of breast cancer has been reported to be modified by related factors such as the consumption of soy isoflavones, consumption of green tea, duration from menarche to the first full-term pregnancy, and body mass index. Because of a lack of necessary data, the use of unadjusted estimates was unavoidable in this meta-analysis. Second, potential interactions of other important genes with *COMT* in similar biological pathways involved in the risk of breast cancer were not assessed because of the lack of original data. Third, the controls were not defined uniformly, and therefore, non-differential misclassification was possible.

In summary, our meta-analysis demonstrated that the *COMT* Val158Met polymorphism (rs4680 G > A) was significantly associated with an increased risk of breast cancer, particularly among premenopausal women, in the Chinese population. In order to verify our findings, the interaction of estrogen metabolism-related factors and genes in similar biological pathways in the development of breast cancer with *COMT* should be evaluated for their influence on the susceptibility to breast cancer in additional well-designed studies with a larger sample size and an adequate methodological quality to properly control for possible confounding factors.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Wang YC, Wei LJ, Liu JT, Li SX, Wang QS. Comparison of cancer incidence between China and the USA. Cancer Biol Med 2012;9:128-32.
2. Qin X, Peng Q, Qin A, Chen Z, Lin L, Deng Y, et al. Association of COMT Val158Met polymorphism and breast cancer risk: an updated meta-analysis. Diagn Pathol 2012;7:136.
3. Lin WY, Chou YC, Wu MH, Jeng YL, Huang HB, You SL, et al. Polymorphic catechol-O-methyltransferase gene, duration of estrogen exposure, and breast cancer risk: a nested case-control study in Taiwan.

Cancer Detect Prev 2005;29:427-32.
4. Lajin B, Hamzeh AR, Ghabreau L, Mohamed A, Al Moustafa AE, Alachkar A. Catechol-O-methyltransferase Val 108/158 Met polymorphism and breast cancer risk: a case control study in Syria. Breast Cancer 2013;20:62-6.
5. Wen W, Ren Z, Shu XO, Cai Q, Ye C, Gao YT, et al. Expression of cytochrome P450 1B1 and catechol-O-methyltransferase in breast tissue and their associations with breast cancer risk. Cancer Epidemiol Biomarkers Prev 2007;16:917-20.
6. Yager JD. Catechol-O-methyltransferase: characteristics, polymorphisms and role in breast cancer. Drug Discov Today Dis Mech 2012; 9:e41-46.
7. Xu YJ, Ge YL, Zhang JY, Li FN, Zheng Z. Polymorphism of COMT, p21 and NuMA in sporadic breast cancer. Chin J Clin 2010;4:591-6.
8. Tan W, Qi J, Xing DY, Miao XP, Pan KF, Zhang L, et al. Relation between single nucleotide polymorphism in estrogen-metabolizing genes COMT, CYP17 and breast cancer risk among Chinese women. Zhonghua Zhong Liu Za Zhi 2003;25:453-6.
9. Chang TW, Wang SM, Guo YL, Tsai PC, Huang CJ, Huang W. Glutathione S-transferase polymorphisms associated with risk of breast cancer in southern Taiwan. Breast 2006;15:754-61.
10. Cheng TC, Chen ST, Huang CS, Fu YP, Yu JC, Cheng CW, et al. Breast cancer risk associated with genotype polymorphism of the catechol estrogen-metabolizing genes: a multigenic study on cancer susceptibility. Int J Cancer 2005;113:345-53.
11. Fan Y, Feng Y, Wang L, Wang Y, Fu L. The relationship between catechol-O-methyltransferase (COMT) polymorphisms and the development of breast cancer. Chin J Clin Oncol 2007;34:430-3.
12. Hu Z, Song CG, Lu JS, Luo JM, Shen ZZ, Huang W, et al. A multigenic study on breast cancer risk associated with genetic polymorphisms of ER Alpha, COMT and CYP19 gene in BRCA1/BRCA2 negative Shanghai women with early onset breast cancer or affected relatives. J Cancer Res Clin Oncol 2007;133:969-78.
13. Huang CS, Chern HD, Chang KJ, Cheng CW, Hsu SM, Shen CY. Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes CYP17, CYP1A1, and COMT: a multigenic study on cancer susceptibility. Cancer Res 1999;59:4870-5.
14. Lin SC, Chou YC, Wu MH, Wu CC, Lin WY, Yu CP, et al. Genetic variants of myeloperoxidase and catechol-O-methyltransferase and breast cancer risk. Eur J Cancer Prev 2005;14:257-61.
15. Shrubsole MJ, Lu W, Chen Z, Shu XO, Zheng Y, Dai Q, et al. Drinking green tea modestly reduces breast cancer risk. J Nutr 2009;139:310-6.
16. Wang Q, Li H, Tao P, Wang YP, Yuan P, Yang CX, et al. Soy isoflavones, CYP1A1, CYP1B1, and COMT polymorphisms, and breast cancer: a case-control study in southwestern China. DNA Cell Biol 2011;30:585-95.
17. Wang Q, Wang YP, Li JY, Yuan P, Yang F, Li H. Polymorphic catechol-O-methyltransferase gene, soy isoflavone intake and breast cancer in postmenopausal women: a case-control study. Chin J Cancer 2010;29:683-8.
18. Wen W, Cai Q, Shu XO, Cheng JR, Parl F, Pierce L, et al. Cytochrome P450 1B1 and catechol-O-methyltransferase genetic polymorphisms and breast cancer risk in Chinese women: results from the shanghai breast cancer study and a meta-analysis. Cancer Epidemiol Biomarkers Prev 2005;14:329-35.
19. Wu AH, Tseng CC, Van Den Berg D, Yu MC. Tea intake, COMT genotype, and breast cancer in Asian-American women. Cancer Res 2003; 63:7526-9.
20. He XF, Wei W, Li SX, Su J, Zhang Y, Ye XH, et al. Association between the COMT Val158Met polymorphism and breast cancer risk: a meta-analysis of 30,199 cases and 38,922 controls. Mol Biol Rep 2012;39: 6811-23.
21. Ding H, Fu Y, Chen W, Wang Z. COMT Val158Met polymorphism and breast cancer risk: evidence from 26 case-control studies. Breast Cancer Res Treat 2010;123:265-70.
22. Mao C, Wang XW, Qiu LX, Liao RY, Ding H, Chen Q. Lack of association between catechol-O-methyltransferase Val108/158Met polymorphism and breast cancer risk: a meta-analysis of 25,627 cases and 34,222 controls. Breast Cancer Res Treat 2010;121:719-25.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
25. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
26. Goodman JE, Jensen LT, He P, Yager JD. Characterization of human soluble high and low activity catechol-O-methyltransferase catalyzed catechol estrogen methylation. Pharmacogenetics 2002;12:517-28.
27. Dawling S, Roodi N, Mernaugh RL, Wang X, Parl FF. Catechol-O-methyltransferase (COMT)-mediated metabolism of catechol estrogens: comparison of wild-type and variant COMT isoforms. Cancer Res 2001;61:6716-22.
28. Srivastava K, Srivastava A. Comprehensive review of genetic association studies and meta-analyses on miRNA polymorphisms and cancer risk. PLoS One 2012;7:e50966.

http://dx.doi.org/10.4048/jbc.2014.17.2.149