

RESEARCH ARTICLE

Lack of Association of the Cyclooxygenase-2 Gene 8473T>C Polymorphism with Breast Cancer Risk: a Meta-analysis

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Abstract

Background: Associations between the 8473T>C polymorphism (rs5275) in the cyclooxygenase-2 (COX-2) gene and breast cancer (BC) risk are still inconclusive and ambiguous. The aim of this meta-analysis was to comprehensively estimate the genetic risk of 8473T>C polymorphism in the COX-2 gene for BC. **Materials and Methods:** We searched PubMed, Web of Science, Medline, Chinese biomedical (CBM), Weipu, China national knowledge infrastructure (CNKI), and Wanfang databases, covering all publications (last search was updated on Aug 17, 2014). Statistical analyses were performed using Revman 5.3 and STATA 10.0 software. **Results:** A total of 6,720 cases and 9,794 controls in 12 studies were included in this study. The results indicated no significant associations between the 8473T>C polymorphism of the COX-2 gene and BC risk for the CC+TC vs TT model (pooled odds ratio (OR)=0.97, 95% confidence interval (CI)=0.90-1.03, and $p=0.29$). On subgroup analysis, we also found that subdivision on ethnicity among Caucasians, Asians and others also revealed no relationship with BC susceptibility. With the study design (CC+TC vs TT), no significant associations were found in either population-based case-control studies (PCC), or hospital-based case-control studies (HCC). **Conclusions:** This present meta-analysis suggests that the 8473T>C polymorphism in the COX-2 gene is not a conspicuous low-penetrant risk factor for developing BC.

Keywords: Cyclooxygenase-2 (COX-2) - breast cancer - polymorphism - meta-analysis

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Introduction

Breast cancer (BC) is one of the most severe diseases which can cause increasing morbidity and mortality every year in women around the world. According to the comprehensive overview of current cancer statistics in the United States, it is the first most common cancer and the second leading cause of cancer in females (Siegel et al., 2014). In 2014, about 232,670 women were diagnosed with BC and approximately 72,330 women died of the disease in the United States (Siegel et al., 2014). The development of BC is a complex and multi-factorial disease including environmental exposures, genetic variations, and gene-environment interactions (Dong et al., 2008; Yu et al., 2010; Zhu et al., 2010). Age, personal or family history of breast disease, reproductive factors, genetic difference and environmental factors had been documented to an increased risk of the development of female BC (Shah et al., 2014). Recently, the association of genetic variants with BC susceptibility has drawn considerable attentions in numerous published studies (Gao et al., 2014; Markkula et al., 2014). And among them, cyclooxygenase-2 (COX-2) gene has been extensively studied.

COX-2, an inducible isoform of cyclooxygenase

(COX), only up-regulated by growth factors, cytokines, and tumor promoters, is often undetectable in most normal tissues, whereas in many tumor tissue specimens its expression is extensively higher (Smith et al., 1996; Bakhle, 2001; Cao and Prescott, 2002; Simmons et al., 2004; Pan et al., 2011; Peng et al., 2011; Turk et al., 2012; Shalaby et al., 2014). Studies have revealed that cellular expression of COX-2 could participate in carcinogenesis, angiogenesis, apoptosis inhibition, immune response suppression, and tumor cell invasion and metastasis (Langsenlehner et al., 2006; Kalalinia et al., 2012; Tabriz et al., 2013; He et al., 2014; Xu et al., 2014; Zhao et al., 2014). COX-2 overexpression is detected in BC, and it is associated with parameters of poor prognosis, including lymph node metastasis, poor differentiation, lower survival, and large tumor size (Harris et al., 2003; Denkert et al., 2004). Furthermore, genetic polymorphisms in COX-2 have been shown to alter its expression and influence the susceptibility to BC, such as 8473T>C (rs5275), -765G>C (rs20417), -1195G>A (rs689465), -1759G>A (rs3218625), -202C>T (rs2745557), and -1290A>G (rs689466) (Cox et al., 2007). To the best of our knowledge, the most extensively studied polymorphisms with BC risk is 8473T>C (rs5275) in the

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3'UTR of COX-2.

A number of the current molecular epidemiological studies have been conducted to examine the association between the 8473T>C polymorphism in the COX-2 gene and the susceptibility of BC, but the results remain inconclusive and controversial (Gallicchio et al., 2006; Cox et al., 2007; Fawzy et al., 2013). Although, two meta-analyses regarding this issue have been respectively reported by Zhu et al. and Yu et al., it is regrettably that some eligible and latest studies with larger sample sizes were not included in these reports, thereby might bias the results and make their conclusions questionable (Yu et al., 2010; Zhu et al., 2010; Gao et al., 2014). Therefore, we conducted this current meta-analysis to be more precise estimate the BC risk associated with the 8473T>C polymorphism of COX-2 gene.

Materials and Methods

Selection of studies

PubMed, Web of Science, Medline, Chinese biomedical (CBM), Weipu, China national knowledge infrastructure (CNKI), and Wanfang database were searched using the search terms (last search was updated on Aug 17, 2014): "COX-2 or COX 2 or cyclooxygenase-2 or cyclooxygenase 2 or PTGS2 or prostaglandin endoperoxide synthase 2" and "breast cancer or neoplasm" in combination with "genetic variant or polymorphism or mutation". The search was limited to English and Chinese language papers. Studies in our meta-analysis were included if they met the following criteria: (1) evaluation of the 8473T>C polymorphism of COX-2 gene and BC risk; (2) sufficient data (genotype distributions for cases and controls) to estimate odds ratio (OR) with its 95% confidence interval (CI) and *p* value; (3) the design had to be a case-control design published in a journal; (4) conforming Hardy-Weinberg equilibrium (HWE) in the control group. Studies were excluded if one of the following existed: (1) no controls; (2) genotype frequencies or number not reported; (3) reviews, abstracts, and repeat studies.

Data extraction

Information was carefully extracted from all eligible publications independently by two of the investigators (XY and FZ). And the two independent reviewers reached a consensus on all items. In case of disagreement, a third author would adjudicate the disagreements. The following items were extracted from each study if available: first author's name, publication year, original country, ethnicity, genotype number in cases and controls, study design (population- or hospital-based case-control study), and genotyping methods.

Statistical analysis

Crude ORs with their 95% CI was used to estimate the strength of association between the 8473T>C polymorphism of COX-2 gene and BC risk. We first assessed the risk of dominant model (CC+TC vs TT), and then estimated the risks of (CC vs TT+TC, CC vs TT, TC vs TT, C vs T, respectively). The pooled OR was calculated by a fixed-effects model or a random-effects model according

to the heterogeneity. Heterogeneity assumption was checked by a χ^2 -based Q statistic among the studies and $p < 0.10$ was considered statistically significant. If the result was $p > 0.10$, the fixed-effects model was used to calculate the pooled ORs; otherwise, the random effect model was used. The statistical significance of OR was analyzed by Z test, and $p < 0.05$ was considered as statistically significant. To evaluate the ethnicity-specific and study design-specific effects, we performed stratification analyses on ethnicity and study design. For the subgroup analysis by ethnicity, different ethnicity descents were categorized as Caucasian, Asian, African, or Mixed that involved more than one ethnic descent (if it was difficult to discriminate the ethnicity of participants according to the data presented, the study was termed "Mixed"). Moreover, subjects were stratified into different classifications according to study design: population-based case-control (PCC) study or hospital-based case-control (HCC) study.

Sensitivity analyses were performed to estimate the stability of the results (Zhang et al., 2010). The potential publication bias was assessed visually in a Begg's funnel plot and the degree of asymmetry was tested using Egger's test ($p < 0.05$ considered representative of statistical significance) (Begg and Mazumdar, 1994; Egger et al., 1997).

HWE was tested by using an internet-based program (Zhang et al., 2010). All of the statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Oxford, England) and STATA 10.0 software.

Results

Study characteristics

As illustrated in Figure 1, the initial search identified 120 studies from the selected electronic databases. After reading the titles and abstracts, 42 potential articles were included for full-text view. After reading the full texts, 32 studies were excluded for being irrelevant to BC risk and COX-2-8473T>C polymorphism gene. Finally, a total of 12 studies in 10 publications which met our inclusion criteria were identified, including 6720 cases and 9794 controls. Table 1 lists the main characteristics of studies identified for 8473T>C polymorphism based meta-analysis. Of those, there are 7 studies of Caucasians group

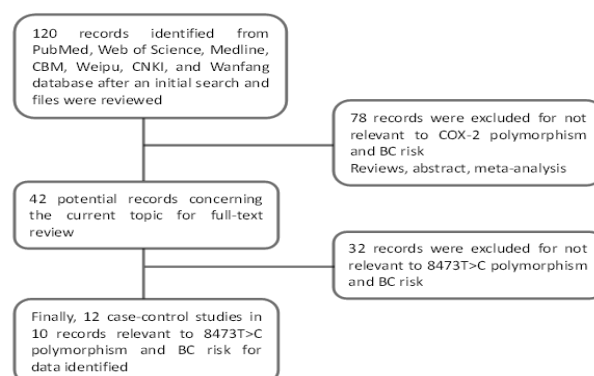


Figure 1. Flow Diagram of Included/Excluded Studies. BC, breast cancer

(Gallicchio et al., 2006; Langsenlehner et al., 2006; Cox et al., 2007; Vogel et al., 2007; Brasky et al., 2011), 2 of Asians group (Gao et al., 2007; Gao et al., 2014), and 3 of other groups (2 Mixed and 1 African) (Shen et al., 2006; Piranda et al., 2010; Fawzy et al., 2013). Among 12 studies in this article, 10 studies were performed in PCC study (Gallicchio et al., 2006; Langsenlehner et al., 2006; Shen et al., 2006; Cox et al., 2007; Vogel et al., 2007; Piranda et al., 2010; Brasky et al., 2011; Festa-Vasconcellos et al., 2012) and 2 in HCC study (Gao et al., 2007; Gao et al., 2014). In addition, genotype and allele distribution for each study were summarized in Table 2.

Quantitative data synthesis

All studies: As shown in Figure 2, the heterogeneity

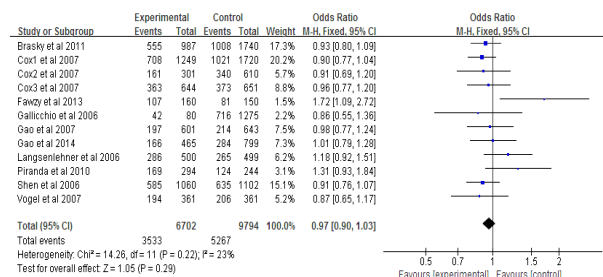


Figure 2. Meta-analysis with a Fixed-Effects Model for the Association between Breast Cancer Risk and the COX-2-8473T>C Polymorphism (TC+CC vs TT). CI, confidence interval; OR, odds ratio

of (CC+TC vs TT) for all 12 studies was estimated and the value of χ^2 was 14.26 with 11 degree of freedom and $p=0.22$ in a fixed-effects model. Moreover, the I-square, which is another index of the test of heterogeneity, was 23%, suggesting a mild heterogeneity. Therefore, we chose the fixed-effects model to synthesize the data. Overall, pooled OR was 0.97 (95% CI=0.90-1.03), and the test for overall effect Z value was 1.05 ($p=0.29$) for (CC+TC vs TT) model (Figure 2). The results indicated that no significant associations were observed between 8473T>C polymorphism of COX-2 gene and BC risk. Table 3 presents, in detail, the all results of meta-analyses. We also found no significant results between this polymorphism and BC risk in other genetic models when all studies were pooled into the meta-analysis (CC vs TT+TC pooled OR=1.08, 95% CI=0.86-1.35, and $p=0.52$; CC vs TT pooled OR=1.07, 95% CI=0.85-1.36, and $p=0.55$, TC vs TT pooled OR=0.97, 95% CI=0.90-1.05, and $p=0.49$, C vs T pooled OR=1.02, 95% CI=0.93-1.11, and $p=0.57$).

Subgroup analyses: We carried out a subgroup meta-analysis of 8473T>C polymorphism in ethnic group and study design under various genetic models (Table 3). Stratified by ethnic group in (CC+TC vs TT) model, no obvious associations were found among Caucasian group (pooled OR=0.94, 95% CI=0.87-1.02, and $p=0.14$), Asian group (pooled OR=0.99, 95% CI=0.84-1.17, and $p=0.92$), and other groups (pooled OR=1.03, 95% CI=0.89-1.19, and $p=0.68$) (Figure 3A). However, significantly increased

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

First author	Year	Country	Ethnicity	Study design	No. (Cases/Controls)	Genotyping method
Gallicchio et al	2006	USA	Caucasian	PCC	80/1275	TaqMan
Langsenlehner et al	2006	Austria	Caucasian	PCC	500/499	TaqMan
Shen et al	2006	USA	Mixed	PCC	1060/1102	TaqMan
Cox1 et al	2007	USA	Caucasian	PCC	1249/1720	TaqMan
Cox2 et al	2007	USA	Caucasian	PCC	301/610	TaqMan
Cox3 et al	2007	USA	Caucasian	PCC	644/651	TaqMan
Gao et al	2007	China	Asian	HCC	601/643	TaqMan
Vogel et al	2007	Denmark	Caucasian	PCC	361/361	PCR*
Piranda et al	2010	Brazil	Mixed	PCC	294/244	DHPLC/PCR-RFLP
Brasky et al	2011	USA	Caucasian	PCC	987/1740	RT-PCR
Fawzy et al	2013	Egypt	African	PCC	160/150	PCR-RFLP
Gao et al	2014	China	Asian	HCC	465/799	TaqMan

*PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; DHPLC, PCR-based denaturing high-performance liquid chromatography; Population-based case-control study (PCC); Hospital-based case-control study (HCC)

Table 2. Distribution of COX-2-8473T>C Genotype and Allele among Breast Cancers and Controls

Author	Cases(n)			Controls(n)			Cases(n)		Controls(n)		HWE ^a for control	
	TT	TC	CC	TT	TC	CC	T	C	T	C	P	χ^2
Gallicchio et al	38	31	11	559	583	133	107	53	1701	849	0.29	1.1
Langsenlehner et al	214	224	62	234	232	33	652	348	700	298	0.1	6.03
Shen et al	475	585*	NA	467	635*	NA	NA	NA	NA	NA	NA	NA
Cox1 et al	541	567	141	699	808	213	1649	849	2206	1234	0.38	0.76
Cox2 et al	140	131	30	270	259	81	411	191	799	421	0.13	2.24
Cox3 et al	281	296	67	278	294	79	858	430	850	452	0.92	0.008
Gao et al	404	179	18	429	194	20	987	215	1052	234	0.73	0.11
Vogel et al	167	150	44	155	165	41	484	238	475	247	0.77	0.08
Piranda et al	125	149	20	120	99	25	399	189	339	149	0.49	0.46
Brasky et al	432	447	108	732	782	226	1311	663	2246	1234	0.44	0.57
Fawzy et al	53	71	36	69	67	14	177	143	205	95	0.69	0.15
Gao et al	299	132	34	515	244	40	730	200	1274	324	0.11	2.45

*HWE, Hardy-Weinberg equilibrium; *Numbers of TC+CC; NA, not available

Table 3. The Meta-analysis for the Associations between COX-2-8473T>C Polymorphism and Risk of Breast Cancer

Variables (No.studies)	CC+TC VS TT		CC VS TT+TC		CC VS TT		TC VS TT		C VS T	
	OR (95% CI)	P ^a	OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b
Total (12)	0.97 [0.90, 1.03]	0.29	1.08 [0.86, 1.35]	0.52	1.07 [0.85, 1.36]	0.55	0.97 [0.90, 1.05]	0.49	1.02 [0.93, 1.11]	0.57
Subgroup by study design										
HCC(2)	0.99 [0.84, 1.17]	0.92	1.27 [0.84, 1.93]	0.26	1.26 [0.84, 1.88]	0.27	0.96 [0.80, 1.14]	0.62	1.03 [0.89, 1.19]	0.70
PCC(10)	0.96 [0.90, 1.03]	0.27	1.05 [0.82, 1.35]	0.69	1.05 [0.81, 1.37]	0.71	0.98 [0.90, 1.06]	0.59	0.98 [0.92, 1.04]	0.44
Subgroup by ethnicity										
Caucasian(7)	0.94 [0.87, 1.02]	0.14	1.00 [0.80, 1.25]	0.97	0.96 [0.77, 1.21]	0.76	0.95 [0.87, 1.03]	0.20	0.95 [0.90, 1.01]	0.12
Asian(2)	0.99 [0.84, 1.17]	0.92	1.27 [0.84, 1.93]	0.26	1.26 [0.84, 1.88]	0.27	0.96 [0.80, 1.14]	0.62	1.03 [0.89, 1.19]	0.70
Others(3)	1.03 [0.89, 1.19]	0.68	1.34 [0.31, 5.72]	0.70	1.59 [0.38, 6.73]	0.53	1.42 [1.07, 1.90]	0.02	1.30 [1.06, 1.59]	0.01

*CC+TC vs TT dominant model; CC vs TC+TT, recessive model; Population-based case-control study (PCC), Hospital-based case-control study (HCC); ^aP value for Z test for all studies; ^bP value for Z test for those studies excluding shen et al. The bold values mean that their association is significant

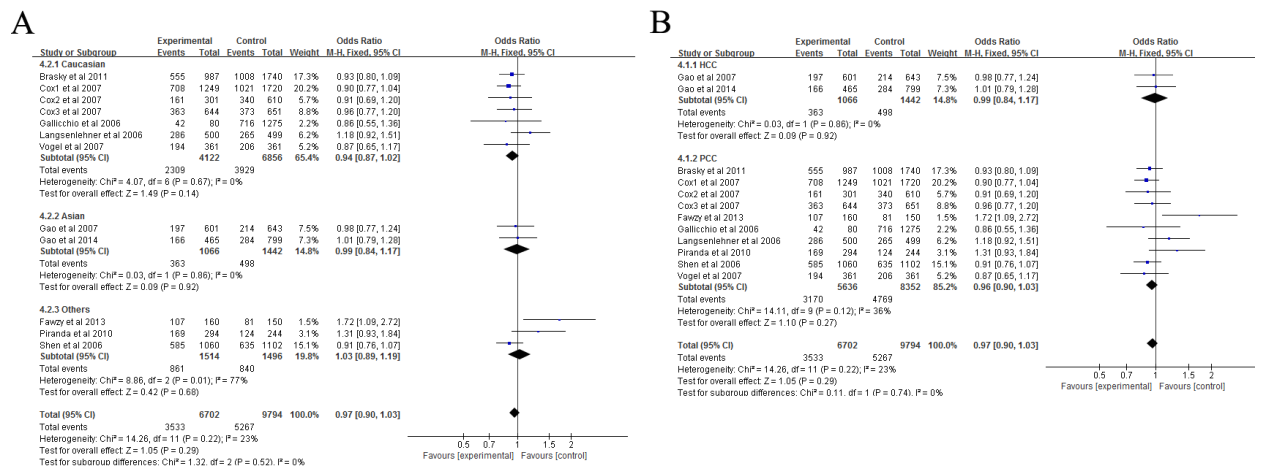


Figure 3. Meta-analysis with a Fixed-effects Model for the Association between Breast Cancer Risk and the COX-2-8473T>C Polymorphism (TC+CC vs TT): A, Subgroup Analysis by Ethnicity; B, Subgroup Analysis by Study Design. CI, confidence interval; OR, odds ratio

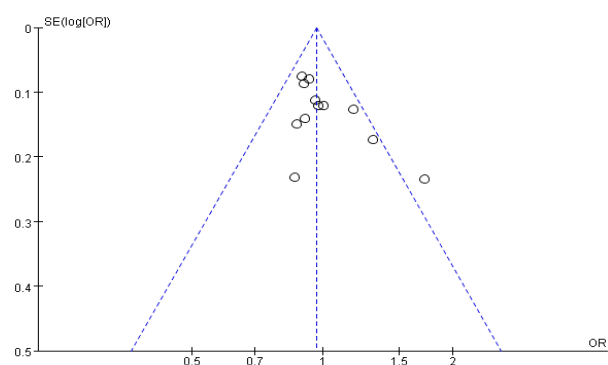


Figure 4. Begg's Funnel Plot for Publication Bias in Selection of Studies on the COX-2-8473T>C Polymorphism (TC+CC vs. TT). OR, odds ratio

risks were found in other groups for (TC vs TT) model (pooled OR=1.42, 95% CI=1.07-1.90, and $p=0.02$) and (C vs T) model (pooled OR=1.30, 95% CI=1.06-1.59, and $p=0.01$). For the subgroup analysis by study design, we found that the HCC study (pooled OR=0.99, 95% CI=0.84-1.17, and $p=0.92$) and PCC study (pooled OR=0.96, 95%

CI=0.90-1.03, and $p=0.27$) had no relationship with BC risk in (CC+TC vs TT) model (Figure 3B). Moreover, in other genetic models, no significant associations were observed in HCC study and PCC study.

Sensitivity analysis

To evaluate the stability of the results of the meta-analysis, we performed a sensitivity analysis through sequentially excluded individual studies. No individual study affected the overall OR dominantly, statistically similar results were observed for (CC+TC vs TT) (all $p>0.05$), suggesting the stability of this meta-analysis (Data not shown).

Publication bias

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The graphical funnel plot of 12 studies of the 8473T>C polymorphism of COX-2 gene did not reveal any evidence of obvious asymmetry in the (CC+TC vs TT) model (Figure 4), and the Egger's test indicated the absence of publication bias ($p>0.05$).

Discussion

Cyclooxygenases (COXs) are key enzymes that mediate production of prostaglandins from arachidonic acid (Gallicchio et al., 2006). Two isoforms of cyclooxygenase (COX-1 and COX-2) are known: the constitutive form, COX-1 is present in many tissues and synthesizes prostaglandins; and the inducible form, COX-2, is not detected in most normal tissues, and rapidly induced by growth factors, cytokines, and various carcinogens (Smith et al., 1996). Many studies found that COX-2 overexpression has been ruled in the pathogenesis of BC development (Gallicchio et al., 2006; Gao et al., 2007). Moreover, genetic polymorphisms in COX-2 gene altering the level of protein expressed, which encodes for the COX-2 enzyme, would be related to cancers of the breast (Langsenlehner et al., 2006; Li et al., 2009).

Genetic variations in the 8473T>C polymorphisms of COX-2 gene may contribute to increased stability of mRNA and the synthesis of COX-2 (Piranda et al., 2010). Researchers from Cox et al. have reported three separate studies in the American population to test the hypothesis that polymorphisms in COX-2 are associated with BC risk (Cox et al., 2007). The results indicated that 8473T>C polymorphism (rs5275) of COX-2 gene was associated with a decrease in BC risk. This reduced BC risk was still confirmed by Zhu et al. in a meta-analysis based on 5 studies (Zhu et al., 2010). However, Vogel et al. have reported that no significant associations were found between COX-2-8473T>C genotype and BC susceptibility (Vogel et al., 2007). Yu et al. have also observed no significant associations between 8473T>C genotype of COX-2 and BC risk in a meta-analysis based on 9 studies (Yu et al., 2010), which include more eligible and large sample size studies compared with Zhu's meta-analysis. Recently, other interesting results in this field have been reported by Fawzy et al., who found obvious increases of the variant alleles COX-2-8473T>C in Egyptian women of BC (Fawzy et al., 2013). To date, the association between 8473T>C in the COX-2 gene and BC risk is still ambiguous. Therefore, we performed a meta-analysis and provided the most powerful conclusion to specifically estimate the association based on 12 studies.

Our results based on 6720 cases and 9794 controls suggested that 8473T>C polymorphism was not significantly associated with BC risk in the (CC+TC vs TT) genetic model. In addition, in other genetic models, we also found no significant associations between this polymorphism and BC risk. It is important to point out that, the results of this study are in accordance with the previous Yu's report, which pooled the relationship between three SNPs (rs5275, rs20417 and rs5277) and BC, and concluded that no significant associations were observed in dominant model (CC+TC vs TT) between 8473T>C polymorphism of COX-2 gene and BC risk (pooled OR=0.97, 95% CI=0.91-1.04) (Yu et al., 2010). Thus, it is possible that the susceptibility of BC may be affected by several polymorphisms, rather than one individual polymorphism (Gao et al., 2007). This implies that the COX-2-8473T>C polymorphism might influence plasma levels of COX-2 but not in a substantial way.

Considering the property of genetic background may influence the results of genetic association studies, we conducted subgroup analysis by ethnicity and study design. In this meta-analysis, we observed that ethnicity among Caucasian group, Asian group, and other groups had no relationship with BC susceptibility in (CC+TC vs TT) model. Significantly increased risks were found in other groups for (TC vs TT) model and (C vs T) model, while among Caucasian group and Asian group showed no statistically significant, suggesting a possible role of ethnic differences in genetic backgrounds. For all genetic models, no significant associations were found in PCC study and HCC study. So it is likely that the study design detect a slight effect on the combined outcomes. Owing to studies with small sample size may have insufficient statistical power, additional studies are warranted to further validate ethnic and study design in the effect of 8473T>C polymorphism on BC susceptibility.

Compared with previous 2 meta-analyses, our study has some advantages. Firstly, it updates the recent data for 8473T>C polymorphism and BC risk. Secondly, we did not observe any publication bias suggesting that the whole pooled results should be unbiased. Finally, we were carefully investigated the methodological issues for meta-analysis, such as heterogeneity, publication bias, and stability of results. In spite of these, our meta-analysis still had some limitations. First, all eligible studies in this meta-analysis were published reports written in English or in Chinese language indexed by the selected database. Thus, it is possible that some potential published studies in other languages or unpublished studies could be missed. Second, some studies were excluded owing to lack of original data by email or phone from the corresponding author, which may lead to a selection bias. Third, lack of original data of each study limited more detailed analyses, including joint effects of gene-gene or gene-environment factors. And the last, the overall results were based on individual unadjusted ORs, whereas a more precise evaluation should be conducted by other potentially suspected factors such as age and family history.

In summary, this meta-analysis suggests a lack of association between 8473T>C polymorphism (rs5275) of COX-2 gene and BC risk. Our results, subgroup analysis by ethnicity and study design, indicated that COX-2-8473T>C polymorphism was no significant associations with BC susceptibility in (CC+TC vs TT) model. Regarding some limitations of this study, additional scientific and rigorous studies with large sample sizes are warranted to validate our findings. Moreover, more sophisticated gene-gene and gene-environment interactions should also be display the association between the 8473T>C polymorphism in COX-2 gene and BC risk.

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