RESEARCH ARTICLE

Lack of Association Between the Matrix Metalloproteinase-2 -1306C>T Polymorphism and Breast Cancer Susceptibility: a Meta-analysis

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Abstract

Background: Since inconsistent results have been reported regarding the relation between the matrix metalloproteinase-2 (MMP-2) -1306C>T polymorphism and susceptibility for breast cancer, we performed a meta-analysis to investigate the issue. Materials and Methods: An internet search of PubMed and EMBASE was performed to identify eligible studies. Pooled odds ratios (ORs) with their corresponding confidence intervals (CIs) were calculated to evaluate any association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility. Results: Nine case-control studies were included in the meta-analysis, involving 9,858 cases and 10,871 controls. Overall, there was no evidence of any association between the MMP-2 -1306C>T polymorphism and breast cancer susceptibility in different genetic models (T-allele *vs* C-allele: OR=0.95, 95%CI, 0.82-1.10, *p*=0.49; TT *vs* CC: OR=1.03, 95%CI, 0.90-1.19, *p*=0.66; TT+TC *vs* CC: OR=0.93, 95%CI, 0.78-1.10, *p*=0.38; TT *vs* TC+CC: OR=1.02, 95%CI, 0.89-1.17, *p*=0.77). In the subgroup analysis by ethnicity, CC was associated with a significant increase in breast susceptibility among Latin-Americans in the dominant model (OR=0.61, 95%CI, 0.40-0.93, *p*=0.02), but the association disappeared in other models. No significant association was observed among Europeans, East Asians and others in different genetic models. In the subgroup analysis by their source of controls, no significant association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility was noted among population-based studies and hospital-based studies in different genetic models. Conclusions: The results of this meta-analysis suggest that MMP-2 -1306C>T polymorphism is not associated with breast cancer susceptibility, although the association among Latin-Americans in the dominant model was significant.

Keywords: MMP-2 - polymorphism - breast cancer - meta-analysis

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Introduction

Breast cancer is the most frequent cancer and the principal cause of cancer-related death in female population around the world, accounting for 23% of new cases and 14% of total deaths globally (Jemal et al., 2011). Factors that are associated with increased risk of breast cancer include nulliparity (Hulka and Moorman 2001), postmenopausal hormone therapy (Hulka and Moorman 2001), alcohol consumption (Baan et al., 2007), high birth weight (Silva Idos et al., 2008) and so on. Although many environmental factors have been identified, the association between many genetic factors and breast cancer risk is still unclear and breast cancer is still lethal since many patients are presented with advanced stage at diagnosis (O'Shaughnessy 2005). Thus, early detection through gene indicators for breast cancer is valuable.

Matrix metalloproteinases (MMPs) are a family of endopeptidases, capable of degrading both extracellular matrix and basement membrane, two barriers that play key roles in separating the tumor cells from normal surrounding tissues (Stamenkovic 2000; Yadav et al., 2014). MMP-2 is a member of the MMP family and is capable of hydrolyzing gelatine and type IV collagen, these being the major structural components of the epithelial basement membrane (Nagase and Woessner, 1999). Numerous studies have shown that MMP-2 is overexpressed in breast cancer, whereas normal breast tissue and benign breast lesions have rarely been found to express MMP-2 (Brummer et al., 1999; Garbett et al., 1999; Baker et al., 2002). MMP-2 promoter C to T transition at -1306 (rs243865) abolishes the Sp1-binding site and results in lower transcriptional activities (Price et al., 2001; Yu et al., 2004), suggesting MMP-2 -1306C>T polymorphism may have an interactive effect on MMP-2 transcription. Many studies have showed that MMP-2 -1306C>T polymorphism may be associated with the risk of varieties of cancers, including colorectal cancer

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(Saeed et al., 2013b), gastric cancer (Miao et al., 2003), and esophageal squamous cell carcinoma (Li et al., 2010). Over the last decade, a number of case-control studies were conducted to investigate the association between MMP-2 -1306C>T polymorphism and breast cancer risk. But results of these studies conflicted. Reasons for the conflicting results might largely be the low power from a single study and the small sample size. The evidence from meta-analysis is deemed to be powerful for this association.

Although several previous meta-analyses have been performed to explore the association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility, results are conflicting. For instance, two meta-analyses found no significant association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility (McColgan and Sharma 2009; Peng et al., 2010). However, the meta-analysis by Zhou et al. showed that MMP-2 -1306C>T polymorphism may be a risk factor in developing breast cancer (Zhou et al., 2011). Moreover, these meta-analyses included only 4 studies and more studies which addressed the association have been published. With the aim of investigating comprehensively whether the MMP-2 -1306C>T polymorphism is associated with breast cancer susceptibility, we conducted this carefully designed meta-analysis of case-control studies.

Materials and Methods

Search Strategy

An internet search of PubMed and EMBASE was performed for eligible studies on the association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility in December 2013. The following terms were used for searching: "Matrix metalloproteinase-2", "MMP-2", "-1306C>T", "rs243865", "polymorphism", "breast cancer", "BC". The references of identified articles were also searched and examined for eligible studies. In the case of publications involving the overlapping cohort, only the updated and largest report was included in the analysis.

Inclusion criteria

The relevant studies were included if they met the following criteria: (1) they were case-control studies; (2) they investigated the association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility; (3) they reported sufficient data for estimating odds ratios (ORs) and their 95% confidence intervals (CIs).

Data extraction

Two investigators (Y.L. and L.N.) independently extracted the data with disagreements resolved by the third reviewer (X.XM.) until a consensus was reached. For each study, the following data were collected: the first author's last name, year of publication, country of origin, study design, ethnicity, genotyping methods, source of controls, total numbers of cases and controls, the frequencies of MMP-2 polymorphism in both cases and controls, and the Hardy-Weinberg equilibrium (HWE) in the controls.

Statistical analysis

The STATA software (version 12.0) was used for all analyses. HWE in the control group of each study was assessed by the chi-square goodness-of-fit test and a $P < 0.05$ was considered significant. The odds ratios (ORs) and the associated 95% confidence intervals (CIs) were used to assess the strength of the association between the MMP-2 -1306C>T polymorphism and breast cancer susceptibility. The association was evaluated under four models: the allele model (T-allele versus C-allele), the homozygous model (TT versus CC), the dominant model (TT+TC versus CC), and the recessive model (TT versus CC+TC). Subgroup analyses by ethnicity and sources of controls were conducted. Sensitivity analysis was also performed to evaluate the stability of the results. Between-study heterogeneity was evaluated by the Q statistic (Higgins et al., 2003). When $P_{heterogeneity}<0.10$ or $I^2> 50\%$, heterogeneity of the results between studies was considered statistically significant. Random-effect model was used if heterogeneity was statistically significant (DerSimonian and Laird 1986) and otherwise fixed-effect model was used (Mantel and Haenszel 1959). Potential publication bias was assessed by the Begg's funnel plots and the Egger's test (Begg and Mazumdar 1994; Egger et al., 1997). All reported P values were two-sided.

Results

Characteristics of the included studies

A total of 9 case-control studies were eligible (Zhou et al. 2004; Lei et al. 2007; Roehe et al. 2007; Delgado-Enciso et al. 2008; Beeghly-Fadiel et al. 2009; Ledwoń et al. 2013; Saeed et al. 2013a; Slattery et al. 2013; Zagouri et al. 2013). The flow chart of study selection is shown in Figure 1. The main characteristics of these studies are listed in Table 1. These studies involved a total of 9858 cases and 10871 controls. The total number of sample size of each study ranged from 182 to 7775. For ethnicity distribution, there were 3 studies of Europeans (Lei et al. 2007; Ledwoń et al. 2013; Zagouri et al. 2013), 2 studies of East Asians (Zhou et al. 2004; Beeghly-Fadiel et al. 2009), 2 studies of Latin-Americans (Roehe et al. 2007; Delgado-Enciso et al. 2008), 1 study of Arabians (Saeed et al. 2013a) and 1 study of mixed people (Slattery et al. 2013). All the studies were reported in full text.

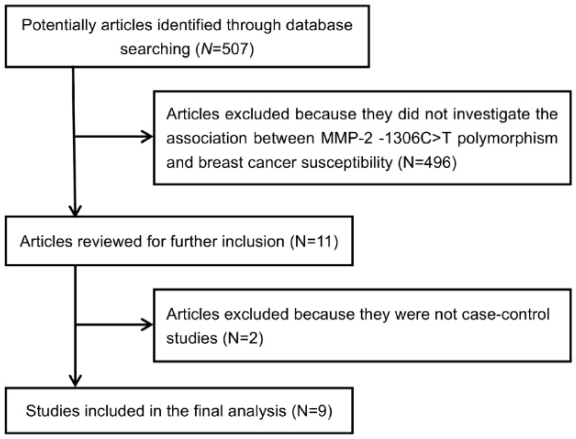

Figure 1. Flow Chart of Study Identification Process

Table 1. Characteristics of the 9 Studies Included in This Meta-Analysis

Study	Country	Ethnicity	Source of controls	Genotyping method	P_{HWE}	Sample size case/control
Zhou et al. 2004	China	East Asian	Population	PCR+sequencing	0.18	462/509
Roehe et al. 2007	Brazil	Latin-American	Hospital	Sequencing	0.4	89/100
Lei et al. 2007	Sweden	European	Population	TaqMan	0.52	959/952
Delgado-Enciso et al. 2008	Mexico	Latin-American	Hospital	PCR	0.18	90/96
Beeghly-Fadiel et al. 2009	China	East Asian	Population	PCR	0.99	3039/3027
Zagouri et al. 2013	Greece	European	Hospital	PCR	0.96	113/124
Saeed et al. 2013a	Saudi Arabia	Arabian	Hospital	TaqMan+sequencing	0.27	90/92
Slattery et al. 2013	US	Mixed	Hospital	PCR	0.62	3592/4183
Ledwoń et al. 2013	Poland	European	Population	TaqMan	0.33	1424/1788

*HWE, Hardy-Weinberg equilibrium; PCR, polymerase chain reaction

Table 2. Results of Overall and Subgroup Meta-analyses

Variables	N	T-allele vs C-allele		TT vs CC		TT+TC vs CC		TT vs TC+CC	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Total	9	0.95 (0.82, 1.10)	<0.01	1.03 (0.90, 1.19)	0.12	0.93 (0.78, 1.10)	<0.01	1.02 (0.89, 1.17)	0.17
Ethnicity									
European	3	1.04 (0.88, 1.22)	<0.10	0.95 (0.76, 1.18)	0.12	1.02 (0.91, 1.13)	0.22	0.94 (0.75, 1.17)	0.16
East Asian	2	0.71 (0.38, 1.34)	<0.01	0.80 (0.19, 3.38)	0.07	0.67 (0.34, 1.32)	<0.01	1.29 (0.88, 1.91)	0.11
Latin-American	2	0.71 (0.50, 1.03)	0.13	1.07 (0.36, 3.24)	0.13	0.61 (0.40, 0.93)	0.22	1.29 (0.43, 3.88)	0.16
Others	2	1.36 (0.72, 2.54)	0.04	1.05 (0.85, 1.29)	0.25	0.39 (0.72, 2.66)	0.05	1.02 (0.83, 1.26)	0.29
Source of controls									
Population-based	4	0.87 (0.72, 1.05)	<0.01	0.98 (0.81, 1.20)	0.11	0.84 (0.67, 1.06)	<0.01	0.99 (0.81, 1.20)	0.11
Hospital-based	5	1.11 (0.79, 1.54)	<0.01	1.09 (0.89, 1.33)	0.17	1.06 (0.72, 1.57)	<0.01	1.06 (0.87, 1.29)	0.25

*N, number of studies; OR, odds ratio; CI, confidence interval; *P*, *P* value of Q-test for heterogeneity test; Random-effect model was used if $P_{heterogeneity}$ <0.10, and otherwise fixed-effect model was used

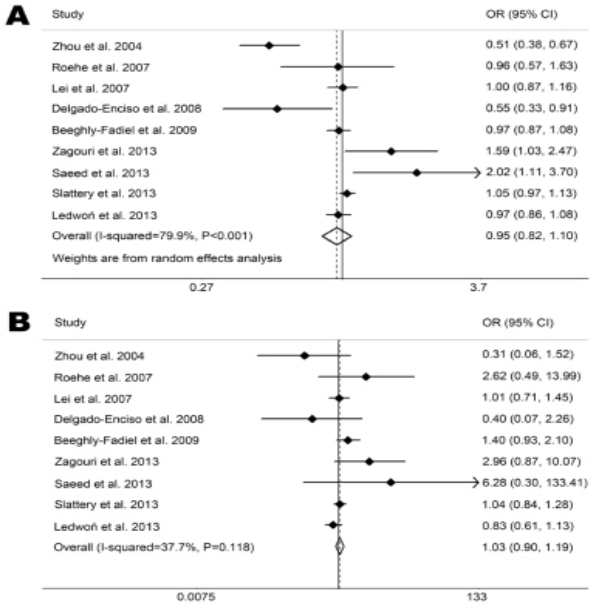

Figure 2. Forest Plots of MMP-2 -1306C>T Polymorphism and Breast Cancer Susceptibility under. A) allele model (T-allele versus C-allele); **B)** homozygous model (TT versus CC)

The genotype distributions of MMP-2 -1306C>T in the controls were in agreement with HWE. The information extracted by the two researchers achieved excellent consistency (kappa=0.99).

Meta-analysis

The results of the meta-analysis of the association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility are shown in Table 2. Overall, there was no evidence of an association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility in different genetic models (T-allele *vs* C-allele: OR=0.95, 95%CI, 0.82-1.10, *p*=0.49, Figure 2A; TT *vs* CC: OR=1.03, 95%CI, 0.90-1.19, *p*=0.66, Figure 2B; TT+TC *vs* CC: OR=0.93, 95%CI, 0.78-1.10, *p*=0.38, Figure 3A; TT *vs* TC+CC: OR=1.02, 95%CI, 0.89-1.17, *p*=0.77, Figure 3B). Random-effect models were used in the allele model and the dominant model since between-study heterogeneity was significant, and fixed-effect models were used in the homozygous model and the recessive model (Table 2).

In the subgroup analysis by ethnicity, CC was associated with a significant increase in breast susceptibility among Latin-Americans in the dominant model (OR=0.61, 95%CI, 0.40-0.93, *p*=0.02; fixed-effect model). However, the association among Latin-Americans was limited in the dominant model and disappeared in other models. No significant association was observed among Europeans, East Asians and others in different genetic models (Table 2). No significant association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility was noted among population-based studies and hospital-based studies in different genetic models (Table 2).

Sensitivity analysis

Sensitivity analysis was carried out by exclusion of a particular trial from the analysis. In neither case were the pooled ORs substantially altered. The pooled ORs were not significantly altered when any study was excluded.

Publication bias

We used the extensive search strategy to minimize the potential publication bias. The symmetry Begg's funnel

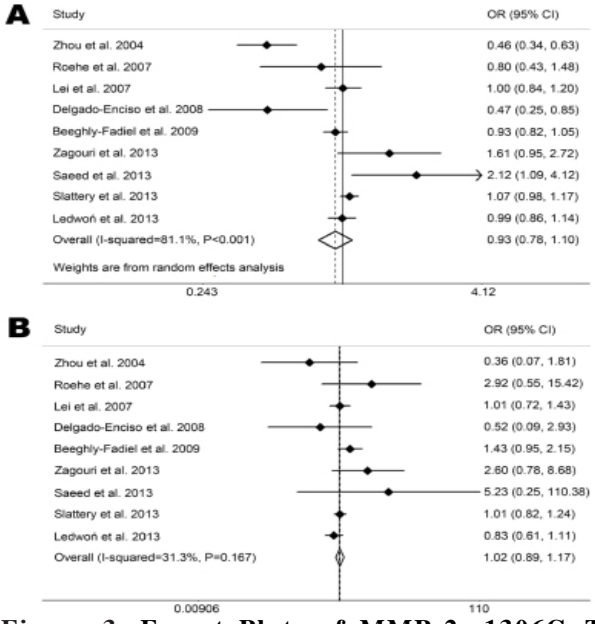

Figure 3. Forest Plots of MMP-2 -1306C>T Polymorphism and Breast Cancer Susceptibility under. A) dominant model (TT+TC versus CC); **B)** recessive model (TT versus CC+TC)

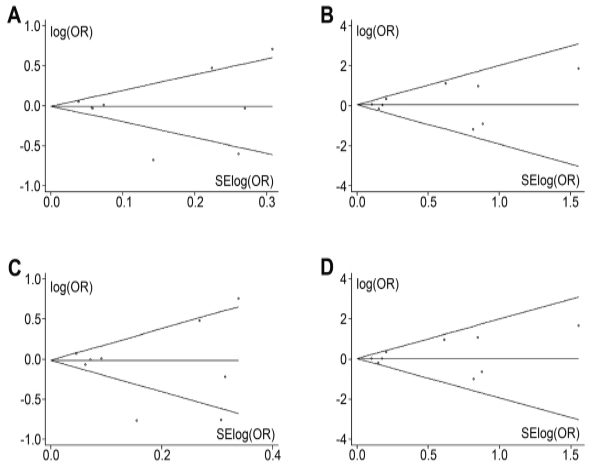

Figure 4. Begg's Funnel Plots in A) Allele Model (T-allele *versus* C-allele); B) Homozygous Model (TT *versus* CC); C) Dominant Model (TT+TC *versus* CC); D) Recessive Model (TT *versus* CC+TC).

plots indicated that there was no evidence of publication bias in the meta-analysis (Figure 4). The potential publication bias was further assessed by the Egger's test and the results also suggested the absence of publication bias (p=0.66 for T-allele *vs* C-allele; p=0.58 for TT *vs* CC; p=0.54 for TT+TC versus CC; p=0.44 for TT versus CC+TC).

Discussion

In this study we investigated the association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility. Overall, the results of this meta-analysis suggest that MMP-2 -1306C>T polymorphism is not associated with breast cancer susceptibility.

The case-based study by Grieu et al. suggested that MMP-2 -1306 T allele was associated with a significantly different prognosis according to estrogen receptor (ER) status. MMP-2 -1306 TT was associated with poor survival compared with CC or CT for patients with ER(-) tumors, whereas MMP-2 -1306 TT was associated with a trend towards good survival for those with ER(+) tumors (Grieu et al. 2004). The study indicates that MMP-2 -1306 C>T polymorphism may affect the prognostic of patients. Thus, it is reasonable to assume that MMP-2 -1306 C>T polymorphism is associated with breast cancer susceptibility. However, the results of our study showed that there was no evidence of relation between them, which is inconsistent with the meta-analysis reported by Zhou et al. (Zhou et al. 2011). Since our study combined a total of 9858 cases and 10871 controls from 9 case-control studies, our results are more convincing.

Subgroup analyses by ethnicity or sources of controls allowed us to look for potential differences in the association. Notably, the -1306 T-allele frequency differs across ethnicities: Saudi (0.10), Chinese (0.12), Brazilian (0.18), Greek (0.18), Australian (0.24), Polish (0.24), Mexican (0.26), Swedish (0.26) (Grieu et al. 2004; Zhou et al. 2004; Lei et al. 2007; Roehe et al. 2007; Delgado-Enciso et al. 2008; Beeghly-Fadiel et al. 2009; Ledwoń et al. 2013; Saeed et al. 2013a; Zagouri et al. 2013). However, when subgroup analysis by ethnicity was performed, we could only find that CC was associated with a significant increase in breast susceptibility among Latin-Americans in the dominant model and the association disappeared in other models. However, there were only two small studies with limited sample size and the power to support an association is undermined. The MMP-2 -1306C>T polymorphism is not associated with breast cancer susceptibility in Europeans or Chinese or others. Among population-based studies and hospital-based studies, no significant association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility was observed in different genetic models. Sensitivity analysis did not alter the results, implying that the results were robust.

The strength of this meta-analysis is that it only included case-control studies. We selected studies strictly to minimize potential bias and errors. All of the studies included in the meta-analysis meet our selection criteria and publication bias was not found. In spite of these, several limitations in this analysis should be mentioned when the results are interpreted. First, the controls were not homogenously defined. Population-based controls and hospital-based controls have different risks of evolving breast cancer. Second, although publication bias was not found according to Begg's funnel plots and Egger's test, we only screened studies in English, which probably provided additional bias. Third, the meta-analysis was performed at the study level. For lack of sufficient data, we were unable to conduct subgroup analyses based on other clinical factors such as age, hormone receptor status, or menopausal status. Fourth, there were only two studies of Chinese and two studies of Latin-Americans in the subgroup analysis. The small sample size of different ethnic populations may result in lack of power in investigating the association. Therefore, caution is needed when the results of the study are interpreted.

In conclusion, our meta-analysis shows that MMP-2

-1306C>T polymorphism is not associated with breast cancer susceptibility. Future well-designed studies involving different ethnic populations are needed to further investigate the role of MMP-2 -1306C>T polymorphism in breast cancer, and other clinical factors should be taken into account that may affect the association between MMP-2 -1306C>T polymorphism and breast cancer susceptibility.

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