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Meta-analysis on the relationship between the SNP of MMP-2-1306 C>T and susceptibility to breast cancer

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Abstract. – OBJECTIVE: Current conclusions on the potential influence of the single nucleotide polymorphism (SNP) of Matrix metalloproteinase-2 (MMP)-2-1306 C>T on Breast cancer (BCa) susceptibility remain controversial. This study aims to accurately clarify their relation.

MATERIALS AND METHODS: The relevant literature on the relation between genetic variation of MMP-2 and BCa susceptibility was searched in PubMed, Web of School, VIP, and CNKI published before March 2019. The keywords used were as follows: "MMP-2, breast/mammary cancer/carcinoma/tumor" or "SNPs of MMP-2, breast/mammary cancer/carcinoma/tumor". Odds ratio (OR) and 95% CI of extracted data from eligible literature were calculated.

RESULTS: A total of 7 studies involving 1823 BCa patients and 1899 healthy controls were included. All control genes were consistent with HWE (p>0.05). Different genetic models were utilized to clarify the potential influence of MMP-2-1306 C>T (rs243865) on BCa susceptibility. No significant correlation was identified between the SNP of MMP-2-1306 C>T and BCa susceptibility based on the calculated OR and 95% CI in different genotypes: CC *vs.* CT&TT: p=0.54, OR=0.88 (95% CI=0.58-1.33); TT *vs.* CC&CT: p=0.67, OR=1.07 (95% CI=0.79-1.44); CC *vs.* TT: p=0.73, OR=0.95 (95% CI=0.70-1.29); C Allele *vs.* T Allele: p=0.93, OR=1.02 (95% CI=0.70-1.47).

CONCLUSIONS: The SNP of MMP-2-1306 C>T did not correlate to the susceptibility to BCa.

Key Words:
MMP-2, SNP, BCa susceptibility.

Introduction

Breast cancer (BCa) is one of the most prevalent malignancies among women worldwide. It is estimated that there were 1.67 million newly diagnosed cases of BCa in 2012 throughout the world, accounting for 25% of all cancers[1]. About 11% of females suffer from BCa, and over 130,000 women die of BCa annually[2]. The pathogenesis of BCa involves both genetic mutations and environmental risk factors. Researches conducted in different populations indicated that genetic factors influence the individual susceptibility to BCa, especially single nucleotide polymorphisms (SNPs)[3].

Matrix metalloproteinases (MMPs) are a class of endopeptidases that degrade extracellular matrices and basement membranes. These two barriers contribute to separate tumor cells from surrounding normal tissues[4,5]. Increasing evidence has identified that MMPs are closely related to malignant phenotypes of tumors. MMPs could serve as prognostic indicators for some certain types of malignancies, including lymphoma[6]. As a member of the MMP family, MMP-2 hydrolyzes the major structural components of the epithelial basement membrane (gelatin and type IV collagen)[7]. MMP-2 gene is located on chromosome 16 at position 12.2[8], which affects cell junctions[9,10]. It contains additional extracellular matrix (ECM) and non-ECM substrates, which also participates in pathological processes, including inflammation, angiogenesis and malignant proliferation[11,12]. Compared with matched normal tissues, protein or mRNA level of MMP-2 is upregulated in primary BCa[13-15]. Moreover, increased serum level of MMP-2 is correlated to poor prognosis or expression levels of relevant prognostic markers of BCa[16,17].

Genetic variations that mediate MMP-2 expression may result in individual differences in cancer susceptibility. MMP-2 promoter SNPs-1306 C/T (rs243865) abolishes the Sp1 binding site and decreases its transcriptional activity, suggesting that the SNP of MMP-2-1306 C>T may have an interaction with MMP-2 transcription[18,19]. The relation between SNPs of MMP-2 and cancer susceptibility has been identified. However, their conclusions remain controversial. So far, researches on evalu-

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ating the influence of genetic variations of MMP-2 on BCa susceptibility are rare, and only concern about a single SNP rs243865[10,20-22]. Previous studies[23-25] have reported contradictory relations between the SNP of MMP2-1306 C>T and BCa susceptibility. This meta-analysis was conducted to explore the potential influence of the SNP of MMP-2-1306 C>T on BCa susceptibility.

Materials and Methods

Literature Searching

The relevant literature on the relation between genetic variation of MMP-2 and BCa susceptibility was searched in PubMed, Web of School, VIP and CNKI published before March 2019. The keywords used were as follows: "MMP-2, breast/mammary cancer/carcinoma/tumor" or "SNPs of MMP-2, breast/mammary cancer/carcinoma/tumor". No limitations were set on languages. Citations in each literature were manually reviewed.

Inclusive and Exclusive Criteria

Inclusive criteria: 1) Case-control studies in human without language limitations; 2) BCa patients were pathologically diagnosed; 3) Literature provided complete data of genotype distribution or raw data that could calculate the genotype frequencies; 4) Studies on the relation between the SNP of MMP-2-1306 C>T and BCa susceptibility; 5) Genotype frequencies were consistent to HWE (Hardy-Weinberg equilibrium) (p>0.05).

Exclusive criteria: 1) Reviews, comments, animal experiments, researches on the mechanism and case reports; 2) Replicate literature; 3) Literature with inadequate data; 4) The latest studies or those with a larger sample size were selected in case of overlapping data.

Flow diagram of literature searching was depicted in Figure 1.

Data Extraction

Data were independently searched by two researchers, and the third one was responsible for solving any disagreement. Extracted data included: 1) Baseline data of literature, including publication origin, first author, year or publication, etc.; 2) Basic characteristics of subjects, including sample size, research country, genotype number and distribution, HWE in control group, etc.

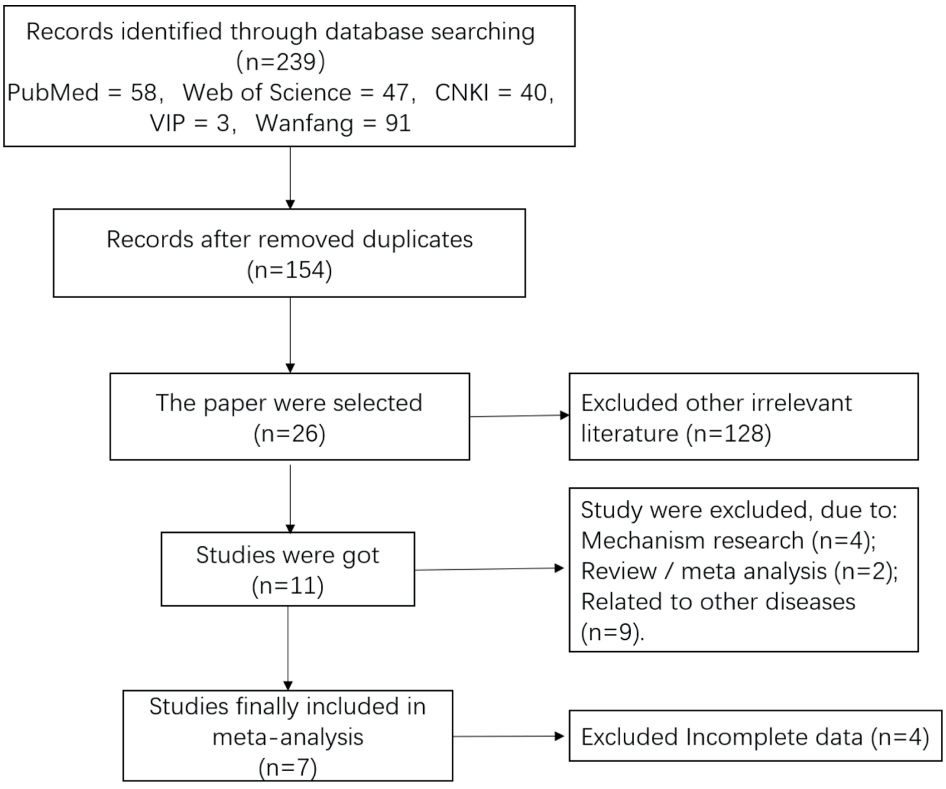

Figure 1. Flow diagram of the selection process.

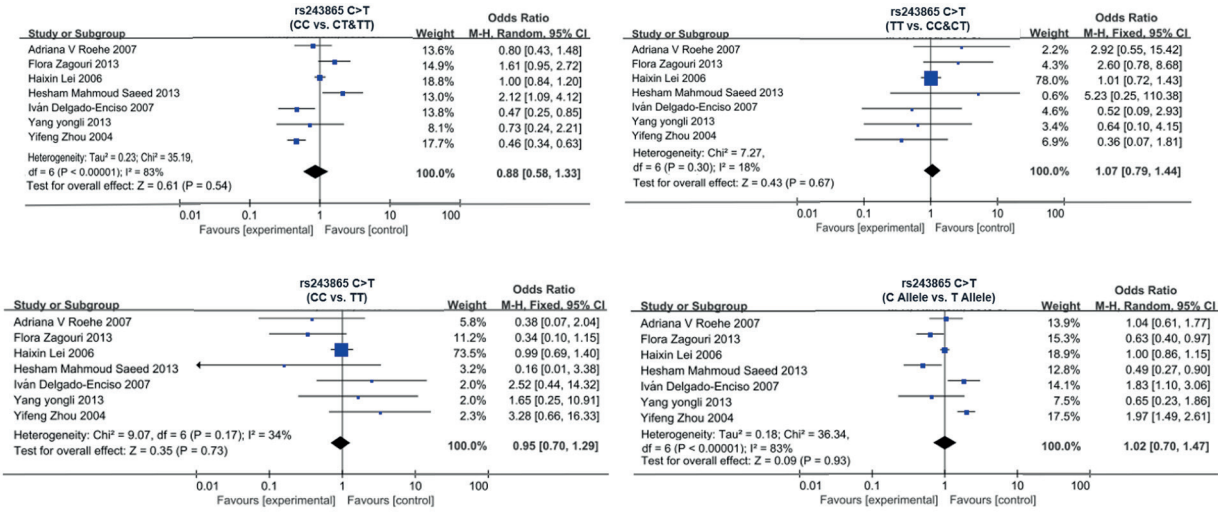

Figure 2. Forest map of the relation between the SNP of MMP-2 rs243865 and susceptibility to breast cancer.

Statistical Analysis

Heterogeneity test was conducted by calculating OR and the 95% CI with the I^2 test and the Q test. The pooled OR in studies lacking the heterogeneity was calculated by the fix-effects model; otherwise, a random-effects model was used. Sensitivity analysis was performed by removing one study each time and analyzing the remaining in a combined way. The χ^2 test was conducted to assess the HWE of control genotype distribution and $p<0.05$ considered as inequivalent. Publication bias was evaluated by funnel plots and Egger's test. Data analyses were carried out using RevMan 5.3 and STATA12.0.

Results

Baseline Characteristics of Enrolled Studies

239 relevant literatures were initially searched from PubMed, Web of Science, CNRI, Wanfang and VIP databases. 85 duplicates and 128 irrelevant literatures were first excluded. For the remaining 26 studies, 4 researches on the mechanism, 2 reviews, 4 literatures without complete data and 9 others were excluded. At last, 7 eligible literatures were enrolled in this study (Figure 2).

Baseline characteristics of enrolled studies were shown in Table I. They were case-control studies published from 2004 to 2013, with 6 literatures published in English-language journals and 1 in a Chinese-language journal. Genotyping methods were conducted using PCR-RFLP, PCR-ABI PRISM, PCR-sanger or Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)-MegaBace. Control groups in these eligible studies did not deviate from HWE ($p>0.05$).

Relationship Analysis

A total of 7 studies involving 1823 BCa patients and 1899 healthy controls were included. All control genes were consistent with HWE ($p>0.05$). Different genetic models were utilized to clarify the potential influence of MMP-2-1306 C>T rs243865 on BCa susceptibility. However, no evidence proved their relation. The specific results were as follows: CC *vs.* CT&TT: $p=0.54$, OR=0.88 (95% CI=0.58-1.33); TT *vs.* CC&CT: $p=0.67$, OR=1.07 (95% CI=0.79-1.44); CC *vs.* TT: $p=0.73$, OR=0.95 (95% CI=0.70-1.29); C Allele *vs.* T Allele: $p=0.93$, OR=1.02 (95% CI=0.70-1.47).

According to the heterogeneity test results, a random-effects model was used to analyze the genotype of CC *vs.* CT&TT and C Allele *vs.* T Allele ($I^2>50\%$, $p<0.05$); whereas the genotype of TT *vs.* CC&CT and CC *vs.* TT was analyzed using a fixed-effects model ($I^2<50\%$, $p>0.05$).

Heterogeneity Test and Sensitivity Analysis

Heterogeneity test was conducted by calculating OR and the 95%CI with the I^2 test and the Q test. Significant heterogeneity was identified in the genetic model of CC *vs.* CT&TT and C Allele *vs.* T Allele ($I^2>50\%$, $p<0.05$). Sensitivity analysis was performed by removing one study each time and analyzing the remaining in a combined way.

Table I. The included studies in this meta-analysis.

Author	Year origin	Country	Journal name/ publicationmethods	Genotyping	SNP loci (PHWE)	Sample size	Control	Sample	NOA
Zhou et al	2004	China	Carcinogenesis	PCR-RFLP	(rs 243865 PHWE=0.18)	462	509	Blood	
Lei et al	2007	North Sweden	Breast Cancer Res Treat	PCR-ABI PRISM	(rs 243865 PHWE= 0.52)	959	952	Blood	
Delgado et al	2008	Mexican	Gynecologic Obstetric	PCR-sanger	(rs 243865)	90	96	Blood	
Adriana et al	2007	Brazil	Breast Cancer Res Treat	PCR-RFLP	(rs 243865)	89	100	Blood	
Zagouri et al	2013	Greece	Mol Biol Rep	PCR-RFLP	(rs 243865 PHWE=0.96)	113	124	Blood	
Saeed et al	2013	Saudi Arabia	ABP	RT-PCR-MegaBace	(rs 243865 PHWE=0.27)	90	92	Blood	
Yang et al	2013	China	Shandong Medicine	PCR-RFLP	(rs 243865)	30	30	Cancerous tissue	

SNP = Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; pHWE = p-value of Hardy-Weinberg equilibrium test in controls for each locus; PCR = polymerase chain reaction; NOS = Newcastle-Ottawa Scale.

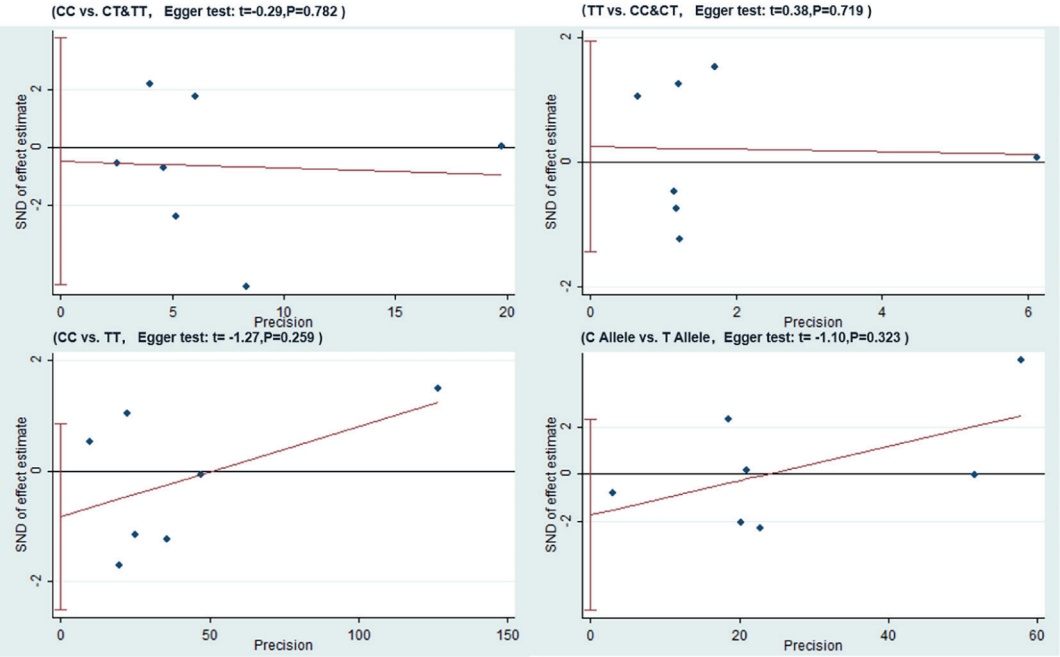

Figure 3. Publication bias on the relation between the SNP of MMP-2 rs243865 and susceptibility to breast cancer.

The heterogeneity did not disappear by removing a single study (data not shown), indicating stable and reliable results.

Publication Bias

A wide range of searching strategies was performed to minimize potential publication bias. Here, Egger's test was used to assess the potential bias between MMP-2 rs243865 and BCa susceptibility. The data were applied as follows: CC *vs.* CT+TT, p=0.728; TT *vs.* CC+CT, p=0.719; CC *vs.* TT, p=0.259; C Allele *vs.* T Allele, p=0.323. Therefore, our results showed no evidence of publication bias (Figure 3).

Discussion

The morbidity and mortality of BCa remain high in Chinese women[26]. MMPs, as endopeptidases that can degrade collagen from ECM, are important proteolytic enzymes for tumor invasion and metastasis[27]. Based on different substrates they target, MMPs are divided into collagenase, gelatinase (MMP-2 and MMP-9), stromelysin and membrane-type MMPs[28]. Researchers[19,22,29] have found that MMP-2-1306 C>T greatly increases the risk of multiple types of malignant tumors, which is closely related to the invasiveness and metastases of tumors.

So far, the potential influence of MMP-2-1306C/T on BCa susceptibility is rarely reported and the conclusion is uncertain. A small sample size that lacks statistical power could be a major reason for contradictory conclusions. Meta-analysis is a useful tool to provide convincing evidence from different investigations, thus obtaining an accurate conclusion. In this study, we confirmed no relation between the SNP of MMP-2-1306C/T and BCa susceptibility.

Unlike our results, some studies have shown that MMP-2-1306 C>T affects BCa susceptibility. Grieu et al[30] reported that T allele of MMP-2-1306 is related to BCa patients with either ER (-) or ER (+). ER (-) BCa patients with the genotype of MMP-2-1306 TT present a worse survival than those with MMP-2-1306 CC or MMP-2-1306 CT. For BCa patients with ER (+), MMP-2-1306 TT indicates a good prognosis[30]. A relevant study[31] conducted in Tunisian population reported that MMP-2-1306 CT or MMP-2-1306 TT is associated with a reduced BCa risk. They suggested that variant alleles present in the MMP-2 promoter may be a protective factor for BCa. Similar conclusions are validated in Chinese, Saudi and Mexican populations[10,21,22].

This research included carefully selected case-control studies to minimize potential biases and errors. All studies were eligible and no publication bias was found. Despite these advantages, there were several limitations that should be noteworthy. First of all, the source of control group was inconsistent. Population-based and hospital-based controls had different susceptibilities to BCa. Secondly, studies providing complete data may lead to potential bias. Thirdly, subgroups based on age, hormone receptors or menopausal status were lacking.

Conclusions

The data of this study demonstrated that MMP-2-1306 C>T did not associate with BCa susceptibility in different putative genetic models. A large-sample study is required for further verification, and other clinical factors that may influence their relation should be considered.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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