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Current Evidence on the Association between Four Polymorphisms in the Matrix Metalloproteinases (MMP) Gene and Breast Cancer Metastasis

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Abstract

The matrix metalloproteinases (MMP) can degrade various components of the extracellular matrix and its functional genetic polymorphisms may be associated with cancer metastasis. However, this relationship remains inconclusive in breast cancer. To better understand the roles of MMP polymorphisms in breast cancer metastasis, we conducted this comprehensive meta-analysis encompassing 1,165 cases and 3,418 controls. Four polymorphisms including MMP1 (-1607 1G/ 2G), MMP2 (-1575 G.A), MMP3 (1612 5A/6A), and MMP9 (-1562 C.T) were studied in this meta-analysis. Crude odds ratios (OR) with 95% confidence intervals (CI) were used to assess the strength of association. We found significant association between MMP1 (-1607 1G/2G) and breast cancer metastasis (for the recessive model 2G/2G vs. 1G/2G+1G/1G: OR 1.81, 95% CI 1.32–2.48; for the dominant model 2G/2G+1G/2G vs. 1G/1G: OR 1.60, 95% CI 1.02–2.50). For the MMP3, significant association between MMP3 (-1171 5A/6A) and breast cancer metastasis was also detected under the dominant model (6A/6A+5A/6A vs. 5A/5A: OR 0.55, 95% CI 0.37-0.80). In conclusion, our results demonstrate that MMP1 may contribute the risk of breast cancer metastasis, while MMP3 played a protective role in breast cancer metastasis. Further studies are needed to evaluate these associations with breast cancer metastasis.

Keywords: Matrix metalloproteinases; Polymorphism; Breast cancer; Metastasis; Meta-analysis

Introduction

Breast cancer is the most common female cancer in the world and constitutes nearly 30% of all cancers diagnosed in women [1]. In 2007 alone, about 537,000 women died due to breast cancer. It is clear that Cancer is a multi-factorial disease that results from complex interactions between environmental and genetic factors [2]. In breast cancer, the genetic factors contribute more to the causation of cancer than do lifestyle or environmental factors. More and more studies investigating the relationship between genetic polymorphisms and breast cancer susceptibility and progression are being reported. The MMPs are a subfamily of the metzincin superfamily, consisting of 26 related zinc-dependent endopeptidases [3]. Based on the structure and substrate specificity, MMPs can be divided into five groups: collagenases, gelatinases, stromelysins, matrilysins and membrane MMPs [4]. Studies have shown that MMPs are key mediators of (i) growth factor activation, bioavailability and receptor signaling, (ii) cell adhesion and motility, (iii) apoptosis and survival mechanisms, (iv) angiogenesis, and (v) inflammatory responses and immune surveillance [5-7]. Besides, MMPs have been implicated in tumor progression, and high levels of expression have been related to more aggressive tumor behavior and poorer patient prognosis [8-10].

Over the past few years, there have been a variety of studies showing evidence of functional SNPs in the promoters of MMP genes in relation to disease susceptibility and in particular to cancer risk [11,12]. For instance, polymorphisms in MMP1 (-1607 1G/ 2G), MMP2 (-1575 G.A), MMP3 (1612 5A/6A), and MMP9 (-1562 C.T), have been associated with several cancers, such as: lung cancer, head and neck cancer, renal cancer, oesophageal cancer and colorectal cancer. However, results for different MMP polymorphisms with breast cancer metastasis are inconsistent [13-17]. Therefore, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association to better understand its possible influence on breast cancer metastasis.

Search strategy

In this meta-analysis, a comprehensive literature research of the US National Library of Medicine's Pub Med database, ISI Web of Knowledge, Medline, Embase and Google Scholar Search (update to August, 2011) were conducted using the search terms including ("MMPs" or "matrix metalloproteinase"),"polymorphisms" , "breast cancer", "metastasis", and the combined phrases in order to obtain all genetic studies on the relationship of MMP polymorphisms and breast cancer metastasis. We also used a hand search of references of original studies or reviewed articles on this topic to identify additional studies. The following criteria was used to select the eligible studies: (1) a case–control study on the association between MMP polymorphisms and breast cancer metastasis, (2) detailed number of different genotypes for estimating an odds ratio (OR) with 95% confidence interval (3) when several publications reported on the same population data, the largest or most complete study was chosen. As a result, 5 eligible case–control studies were included in our meta-analysis.

Data extraction

Two investigators independently extracted data. For each eligible study, the following information was recorded: the first author's name, the year of publication, country of origin, genotyping methods, racial descent of the study population, number of cases and number of controls with different genotypes, and results of studies.

Statistical analysis

The strength of relationship between MMP polymorphisms and breast cancer metastasis was assessed by using Crude OR with 95% CI. The dominant model (Zz+zz vs. ZZ) and the recessive model (zz

vs. ZZ+Zz) were used in this study to evaluate the risk. Between-study heterogeneity was evaluated by Q-test. Fixed effects model was used to pool the data when the P-value of Q-test ≥ 0.05, otherwise, random-effects model was selected. Both funnel plot and Egger's test were used to assess the publication bias. (P<0.10 was considered representative of statistical significance). All statistical analyses were performed using STATA11.0 software and Review Manage (v.5; Oxford, England).

Results

Eligible studies

By the inclusion and exclusion criteria, 25 articles were found, but only 12 studies were preliminarily identified for further evaluation. After carefully evaluating the quality of the 12 remained articles, we excluded 7 studies, of which 2 studies had overlapped data and 5 studies did not report detailed genotype data or genotype frequency information for metastasis-positive/ negative cases. Finally, 5 relevant studies addressing four polymorphisms in four MMP genes involving 1,165 cases and 3,418 controls were selected in this meta-analysis (Figure 1). The main characteristics of these studies are shown in Table 1. Genotype distribution of the four MMP polymorphisms among breast cancer cases and controls of the 5 studies are shown in Table 2. None of the studies in controls had a deviation from Hardy-Weinberg equilibrium at a statistical significance level of 0.01 (Table 2).

Meta-analysis

The main results of this meta-analysis and the heterogeneity tests are shown in Table 3. For the MMP1, we found significant association between MMP1 (-1607 1G/2G) and breast cancer metastasis (for the recessive model 2G/2G vs. 1G/2G+1G/1G: OR 1.81, 95% CI 1.32–2.48; for the dominant model 2G/2G+1G/2G vs. 1G/1G: OR 1.60, 95% CI 1.02–2.50). For the MMP3, significant association between MMP3 (-1171 5A/6A) and breast cancer metastasis was also detected under the dominant model (6A/6A+5A/6A vs. 5A/5A: OR 0.55, 95% CI 0.37-0.80). However, the association was not found under the recessive model (Table 3). For the MMP2 (-1306 C/T) and MMP9 (-1562 C/T), no association was found between these two polymorphisms and breast cancer metastasis under both dominant model and recessive model (Table 3). Both Begg rank correlation method and Egger's test were performed to assess the publication bias of the literature. Neither Begg rank correlation method (p = 0.69) nor Egger's test (p = 0.55) detected any obvious evidence of publication bias.

Discussion

We conducted this meta-analysis encompassing 5 studies involving 1,165 cases and 3,418 controls in order to investigate the potential association between four polymorphisms in the four MMP genes and breast cancer metastasis. Our main finding was that both MMP1 (-1607 1G/2G) and MMP3 (-1171 5A/6A) were significantly associated with the risk of breast cancer metastasis. No significant difference was detected in MMP2 (-1306 C/T) and MMP9 (-1562 C/T). MMP1 is one of the most widely expressed metalloproteinases and overexpression of MMP1 is implicated in tumor invasion and metastasis in a number of cancers. Nishioka et al. [18] showed that SNP of MMP-1 promoter might influence the ability in cervical cancer invasion. In a study of Italian cases (n = 60) and controls (n = 164), Ghilardi et al. [19] observed an association of the MMP1 -1607 2G allele and increased metastasis of colorectal cancer. In breast cancer, the study conducted by Przybylowska et al. [15] demonstrated that an increased risk of lymph node metastasis in breast cancer patients carrying the 2G allele (OR : 1.68, 95% CI, 1.19–2.39), particularly those of the 2G/2G

genotype (OR : 2.14, 95% CI , 1.24–3.69). Our analysis demonstrated significant association between MMP1 (-1607 1G/2G) and breast cancer metastasis (for the recessive model 2G/2G vs. 1G/2G+1G/1G : OR 1.81, 95% CI 1.32–2.48; for the dominant model 2G/2G+1G/2G vs. 1G/1G : OR 1.60, 95% CI 1.02–2.50).

To date, MMP2 and MMP9 have been the most extensively studied metalloproteinases in cancer patients. It has been shown that MMP2 expression is increased in cancer patients compared with controls. Moreover, increased expression has been associated with advanced stages of disease and worse prognosis [19]. In our study, we did not find significant association between MMP2 (-1306 C/T) and breast cancer metastasis. Because there is only one study for MMP2, the negative result does not mean that there was no association with metastasis. There is evidence indicating that a C/T polymorphism located at nucleotide position -1562 in the MMP9 gene promoter has an effect on MMP9 expression, with the T allele having 1.5-fold higher promoter activity than the C allele [20]. In a study of 270 patients with breast cancer and 300 controls, Przybylowska et al. [15] found that the T allele was associated with poor differentiation, tumor size but not with lymph node involvement. Besides, a study with 959 Swedish cases and 952 controls showed an increased risk of developing breast cancer in TT homozygotes but no genotypic effect on lymph node metastasis or differentiation [21]. Consistent with these studies, we did not find any association between MMP9 (-1562 C/T) and the risk of breast cancer metastasis. The promoter region of MMP3 is characterized by a 5A/6A polymorphism located at nucleotide position -1171 relative to the transcriptional start site, with one allele having six ad enosines (6A) and the other having five adenosines (5A) at the polymorphic site [22]. In vitro experiments showed that the 5A allele has approximately twofold higher promoter activity than the 6A allele [23-25]. Ghilardi et al. [13] reported a higher risk of metastasis in 5A homozygotes, which is in line with the results of Krippl et al. [14] who observed a higher propensity of lymph node involvement among patients with the 5A/5A genotype. In our study we found that the MMP3 can play a protective role in the breast cancer metastasis. In our meta-analysis, between-study heterogeneity from various factors including diversity in population characteristics, different sample size and genotyping methods. As in all research, our study has limitations. First, the controls were not uniformly defined. Second, there is only one study among Asians and the sample size is relatively small, studies involved in different ethnicities especially among Asians and Africans
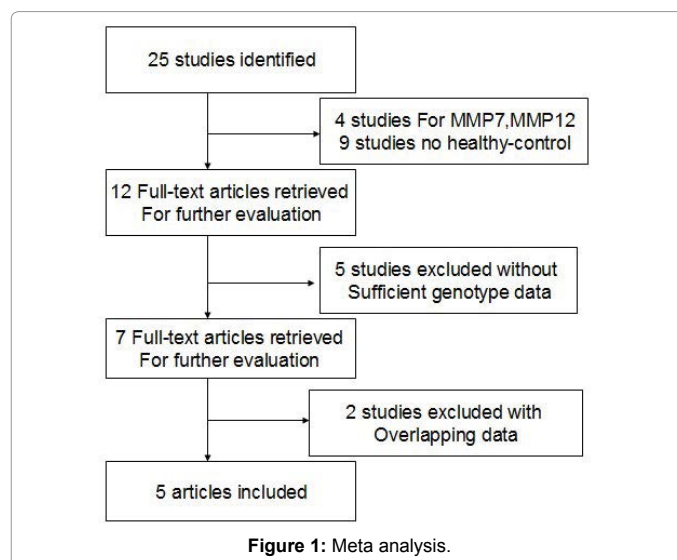

Figure 1: Meta analysis.

Authors	Country	Year	Genes	Cases	Controls	Genotyping method
Przybylowska	Poland	2006	MMP-1 (-1607 1G/2G)	52	88	PCR
Hughes	England	2007	MMP-1 (-1607 1G/2G)	141	129	PCR
Lei	Sweden	2007	MMP-2 (-1306 C/T)	241	1305	PCR-RELP
Hughes	England	2007	MMP-3 (-1171 5A/6A)	50	85	PCR
Krippl	Austria	2004	MMP-3 (-1171 5A/6A)	216	259	PCR-RELP
Ghilardi	Italy	2002	MMP-3 (-1171 5A/6A)	40	15	PCR
Lei	Sweden	2007	MMP-9 (-1562 C/T)	241	1301	PCR-RELP
Hughes	England	2007	MMP-9 (-1562 C/T)	43	76	PCR
Przybylowska	Poland	2006	MMP-9 (-1562 C/T)	141	129	PCR

Abbreviations: MMP matrix metalloproteinase, PCR polymerase chain reaction, RFLP restriction fragment length polymorphism

Table 1: Characteristics of studies included in the meta-analysis.

Authors	Genes	ZZ(case)	Zz(case)	zz(case)	ZZ(control)	Zz(control)	zz(control)	HWE
Przybylowska	MMP-1 (-1607 1G/2G)	33	57	51	44	58	27	0.38
Hughes	MMP-1 (-1607 1G/2G)	12	20	20	26	43	19	0.72
Lei	MMP-2 (-1306 C/T)	126	91	24	732	479	94	0.07
Hughes	MMP-3 (-1171 5A/6A)	16	29	5	23	44	18	0.63
Krippl	MMP-3 (-1171 5A/6A)	59	103	54	43	146	70	0.51
Ghilardi	MMP-3 (-1171 5A/6A)	15	0	25	9	0	37	0.27
Lei	MMP-9 (-1562 C/T)	174	62	5	927	332	42	0.17
Hughes	MMP-9 (-1562 C/T)	35	0	8	74	0	2	0.32
Przybylowska	MMP-9 (-1562 C/T)	83	56	2	90	38	1	0.41

Abbreviations: Z/z for 2G/1G of MMP-1, C/T of MMP-2, 6A/5A of MMP-3, C/T of MMP-9; HWE Hardy–Weinberg equilibrium

Table 2: Genotype distribution of the analyzed four MMP polymorphisms included in the meta-analysis.

Genes	Polymorphisms	Genetic model	Cases	Controls	OR(95% CI)	p-value1
MMP-1	(-1607 1G/2G)	Dominant	193	217	1.603(1.02-2.50)	0.69
		Recessive	193	217	1.813(1.32-2.48)	0.43
MMP-2	(-1306 C/T)	Dominant	241	1305	1.17(0.89-1.54) -	
		Recessive	241	1305	1.43(0.88-2.28) -	
MMP-3	(-1171 5A/6A)	Dominant	306	390	0.553(0.37-0.80)	0.53
		Recessive	306	390	0.73(0.51-1.04)	0.17
MMP-9	(-1562 C/T)	Dominant	425	1506	1.632(0.78-3.42)	0.01
		Recessive	425	1506	1.992(0.34-11.67)	0.02

Abbreviations: CI, confidence interval; OR, odds ratio. MMP, matrix metalloproteinase
[1]P-value for heterogeneity test; [2] Random effect model was used; [3] Statistically significant results.

Table 3: Results of this meta-analysis for the four MMP polymorphisms and the risk of breast cancer metastasis.

are warranted to estimate the effects of these functional polymorphisms on breast cancer metastasis. Third, due to the original data of the eligible studies are unavailable. We did not perform the analysis adjusted for some covariates such as: age, tumor size and steroid hormone receptor status. In conclusion, our results demonstrate that MMP1 could contribute the risk of breast cancer metastasis, while MMP3 played a protective role in breast cancer metastasis. Further studies are needed to evaluate these associations with breast cancer metastasis and their possible mechanisms.

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