Association between Four MMP-9 Polymorphisms and Breast Cancer Risk: A Meta-Analysis

Xiaoli Zhang
Guoyin Jin
Jianfeng Li
Linxi Zhang

Corresponding Author: Linxi Zhang, e-mail: zlxwxl@163.com
Source of support: Self financing

Background: The role of matrix metalloproteinase 9 (MMP-9) polymorphisms in breast cancer risk remains unclear. The purpose of this study was to evaluate the association between MMP-9 variants and breast cancer susceptibility.

Material/Methods: Case-control studies were searched on electronic databases to retrieve related articles published between 2000 and 2014 concerning the role of MMP-9 variants in breast cancer risk. Pooled odds ratios (OR) with correlative 95% confidence intervals (CI) were employed to assess this association.

Results: Ten articles were screened out, including 6177 breast cancer patients and 6726 matched-controls. For rs3918242 (-1562 C/T), 6 studies contained 1435 patients and 1446 controls. Although the frequency of risk allele C was higher in breast cancer patients than in controls, only TT genotype in recessive model was significantly associated with increased risk of breast cancer (TT vs. CT+CC: OR=1.55, 95% CI=1.12–2.16, P=0.009) in a fixed-effects model. This significant relationship was not observed in other genetic models (P>0.05). No significant association was found between breast cancer risk and rs17576, rs2250889, and rs3787268 under any genetic models.

Conclusions: Our results show that TT genotype of MMP-9–1562 C/T polymorphism might be a risk factor for breast cancer. More studies are needed to further explore this association.

MeSH Keywords: Breast Diseases • Matrix Metalloproteinase 9 • Meta-Analysis • Polymorphism, Genetic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893890
Background

Breast cancer, a global health concern, is the most common cancer worldwide, and ranks as the fifth leading cause of cancer-related death [1]. It represents 22.9% of total female cancers [2]. Approximately 232,670 new cases and 40,000 deaths are expected to occur in 2014 among women in the United States [3]. The incidence rates in more developed countries and less developed countries were 71.7 and 29.3 per 100,000 persons per year, respectively, and the corresponding mortality rates were 17.1 and 11.8, with 5-year relative survival rate ranging from 12% to 90% [4]. The introduction of population-based screening using mammography and the systemic use of adjuvant therapies contribute to observed improvements in breast cancer survival. A meta-analysis showed that identification of risk factors for breast cancer might be useful for personalized mammography screening [5]. Thus, it is important to discuss the risk factors, explore the mechanism underlying this disease, and identify the best diagnostic marker to diagnose early-stage breast carcinogenesis.

In recent decades, gene mutations were shown to be risk factors for breast cancer occurrence [6] and an independent prognostic marker for patients who received adjuvant therapy [7]. Matrix metalloproteinase (MMPs) are a multifunctional family of endopeptidases participating in the degradation of extracellular matrix and basement membrane barriers [8] and also play key roles in separating the tumor cells from normal surrounding tissues [9,10]. MMP-9, also known as 92-kD type IV collagenase or gelatinase B, is a member of the MMPs family and is a zinc-dependent peptidase. It regulates inflammation in cancer tissues and diseases [11]. Differential expression in breast cancer cells of MMP-9 affects the degree of cellular differentiation and is closely correlated with the most aggressive subtypes [12]. Genetic variation may influence MMP-9 expression, resulting in development of cancer susceptibility. The human MMP-9 gene is located on chromosome region 20q11.2–q13.1 [13]. Several single-nucleotide polymorphisms (SNPs) have been reported to be associated with tumor progression. MMP-9–1562 C/T polymorphism (rs3918242), a C to T substitution at -1562bp, was the most studied and is associated with increased risk of deep vein thrombosis [14] and colorectal cancer [15] in cancer patients. MMP-9 P574R (rs2250889, a G to A substitution at -1562bp, was the most studied and is associated with increased risk of deep vein thrombosis [14] and colorectal cancer [15] in cancer patients. MMP-9 P574R (rs2250889, a G to A substitution in exon 10) and R279Q (rs17576, a G to A substitution in exon 6) functional polymorphisms are biomarkers for the occurrence and metastasis of primary lung cancer [16]. MMP-9 rs3787268, a G to A substitution, was shown to have strongest association with breast cancer among the Native American women [17].

Although research has been performed to explore the effect of MMP-9 polymorphisms in breast cancer susceptibility, results are inconclusive. Grieu et al. found that patients with MMP-9–1562 CT or TT genotypes showed marginally better prognosis compared to CC homozygotes [18] but Roeh et al. found no significant association between MMP-9–1562C/T polymorphism and breast cancer risk [19]. Furthermore, the breast cancer incidence rates vary by country. Therefore, we conducted this meta-analysis to investigate the relationship between MMP-9 polymorphisms and breast cancer risk.

Material and Methods

Search strategy

We conducted a literature search using the online electronic databases of EBSCO (PubMed and Medline) and China (China National Knowledge Internet and Wanfang) to retrieve related articles published between 2000 and 2014. The MeSH (Medical Subject Headings) search terms were “breast cancer or carcinoma or neoplasms”, “matrix metalloproteinase 9 or MMP-9 or gelatinase B”, and “polymorphism or variant or mutation”, as well as their combinations. The references of identified articles were also searched manually to discover additional eligible studies. When the same authors or laboratory reported several publications on the same issue, only the most recent study was included.

Inclusion criteria

Eligibility criteria were: 1) case-control study; 2) cases were histopathologically confirmed and the controls were age-matched; 3) evaluating the association between MMP-9 polymorphisms and breast cancer risk; 4) results presented as odds ratio (ORs) with 95% confidence intervals (CIs); and 5) genotype information of patients and controls can be extracted.

Data extraction

Two experts independently assessed the extracted data of the included studies. The following items from each study were extracted: first author name, publication year, country, ethnicity, total number of breast cancer cases and controls, genotyping method, study design (hospital-based or population-based case-control studies), and the genotype information.

Statistical analysis

Pooled ORs with associated 95% CIs were employed to assess the strength of the association between MMP-9 polymorphisms and breast cancer susceptibility. Four genetic models were calculated to evaluate this association: the allele model, the homozygous model, the dominant model, and the recessive model. Statistical heterogeneity between studies was measured by using the Q statistic. A random-effects model...
was used when the P value was less than 0.1 or I² more than 50%, which was considered statistically significant; otherwise, a fixed-effects model was used. Review Manager 5.2 (the Cochrane Collaboration, Oxford) was used for conducting the statistical analyses. All tests were 2-sided.

Results

Study characteristics

We identified 42 articles that contained our key words. After applying the inclusion and exclusion criteria, we selected 10 articles, including 6177 breast cancer cases and 6726 matched controls. Figure 1 shows the selection process. Of the 10 selected articles, 1 was written in Chinese [20] and 9 in English [17,19,21–27]. Four polymorphisms of MMP-9 were assessed in the present meta-analysis: rs3918242, rs17576, rs2250889, and rs3787268. Table 1 presents the main information of included studies. Table 2 lists the distribution of allele and genotype information for each variant in the included studies.

Meta-analysis

Table 3 shows the results of statistical analysis for each polymorphism of MMP-9. For rs3918242, 6 studies included 1435 breast cancer cases and 1446 controls. The results showed that the frequency of risk allele C was higher in breast cancer.
### Table 2. Alleles and genotypes distribution for each SNP among included studies.

| First author | Cases | Controls |
|--------------|-------|----------|
| rs3918242    |       |          |
| Holliday DL  | 10    | 3        |
| Lei HX       | 10    | 3        |
| Roehe AV     | 76    | 20       |
| Sadeghi M    | 57    | 28       |
| Chiranjeevi P| 75    | 66       |
| Wang XW      | 46    | 30       |
| Chahil JK    | 50    | 26       |
| Fu FM        | 139   | 98       |
| Resler AJ    | 338   | 393      |
| rs17576      |       |          |
| Chahil JK    | 1     | 18       |
| Fu FM        | 154   | 87       |
| rs2250889    |       |          |
| Chahil JK    | 1     | 18       |
| Fu FM        | 154   | 87       |
| rs3787268    |       |          |
| Slattery ML  | 2479  | 1074     |

### Table 3. Meta-analysis of polymorphisms on MMP9 and breast cancer risk.

| SNP        | N | Comparison | OR (95% CI) | P   | Ph  | I² | Model |
|------------|---|------------|-------------|-----|-----|----|-------|
| rs3918242  | 6 | T vs. C    | 1.36 (0.91, 2.02) | 0.13 | 0.002 | 79% | R     |
| rs17576    | 3 | A vs. G    | 0.88 (0.58, 1.34) | 0.55 | 0.001 | 85% | R     |
| rs2250889  | 2 | AA vs. GG  | 0.71 (0.27, 1.98) | 0.49 | 0.003 | 82% | R     |
| rs3787268  | 2 | AA+GA vs. GG | 0.96 (0.64, 1.43) | 0.84 | 0.02  | 73% | R     |

N – number of included studies for a certain polymorphism; F – fixed-effect model; R – random-effect model; P – p-value of included studies; Ph – heterogeneity among included studies.
This insignificant association was also found in the homozygous model (TT vs. CC: OR = 1.43, 95% CI = 0.72–2.86, P = 0.30) and the dominant model (TT + CT vs. CC: OR = 1.38, 95% CI = 0.88–2.16, P = 0.16). TT genotype in the patients than in controls (20.8% vs. 17.7%); however, the C allele was not associated with breast cancer risk (T vs. C: OR = 1.36, 95% CI = 0.91–1.30, P = 0.13). This insignificant association was also found in the homozygous model (TT vs. CC: OR = 1.43, 95% CI = 0.72–2.86, P = 0.30) and the dominant model (TT + CT vs. CC: OR = 1.38, 95% CI = 0.88–2.16, P = 0.16). TT genotype in the
For rs17576, 3 articles, containing 1176 patients and 1142 controls, were included. Overall, no significant association was found between rs17576 of MMP-9 and breast cancer susceptibility under any genetic model (A vs. G: OR=0.88, 95% CI=0.58–1.34, P=0.55; AA vs. GG: OR=0.71, 95% CI=0.27–1.89, P=0.49; AA+GA vs. GG: OR=0.72, 95% CI=0.31–1.71, P=0.46) in a random-effects model (Figure 3).

For rs2250889, we identified 2 articles, including 331 cases and 335 controls. There was no evidence of an association between MMP-9 rs2250889 and breast cancer susceptibility in different genetic models (G vs. C: OR=0.61, 95% CI=0.27–1.36, P=0.49; AA vs. GG: OR=0.96, 95% CI=0.64–1.43, P=0.84; AA+GA vs. GG: OR=0.72, 95% CI=0.31–1.71, P=0.46) in a random-effects model (Figure 3).
Figure 4. Association between MMP-9 rs2250889 and breast cancer risk in dominant model (A: GG+CG vs. CC) and recessive model (B: GG vs. CG+CC).

Figure 5. Forest plot of MMP-9 rs3787268 in breast cancer risk under dominant model (AA+GA vs. GG).

For rs3787268, 2 articles were assessed, including 3804 cases and 4387 controls. No significant relationship was found between GG+GA genotype and breast cancer risk in the dominant model (AA+GA vs. GG: OR=0.95, 95% CI=0.71–1.27, P=0.74) (Figure 5).

Sensitivity analysis and publication bias

We deleted each included study 1 at a time to observe whether the single study influenced the overall results. We found that the significance of pooled ORs was not changed when any individual study was omitted, indicating no bias was present. A funnel plot showed no obvious asymmetry (Figure 6), further indicating that there was no possible publication bias.
MMP-9 plays an important role in the malignancy and the growth of the tumor [29], and has been linked to cancer cell proliferation, tumor invasion, and epithelial-to-mesenchymal transformation [30]. Rosella et al. summarized and analyzed the role of MMP-9 in different phases of the tumorigenic process, and found that MMP-9 has vital tumor-suppressing functions, promoting inflammatory anti-tumor activity, producing endogenous angiogenesis inhibitors, and inducing apoptosis [31]. Studies have demonstrated that MMP-9 is involved in breast cancer progression and metastasis due to its ability to degrade denatured collagens and type IV collagen, which is associated with the disruption of basement membranes [32].

Merdad et al. showed that MMP-9 is a reliable potential candidate diagnostic biomarker and drug target in breast cancer [33]. Expression of MMP-9 is up-regulated in breast cancer [34], and higher concentrations of MMP-9 proteins were detected in breast cancer tissue compared to normal breast tissue [29]. MMP-9 was also constitutively expressed in some breast tumor cell lines but not in normal breast epithelial cells [35]. MMP-9 expression has prognostic value of overall survival and relapse-free survival in breast cancer patients. Johanna et al. reported that positive stromal MMP-9 expression indicates poor survival in hormone-responsive small tumors, but that MMP-9 expression favors survival in carcinoma cells [36]. A meta-analysis by Song et al. suggested that positive MMP-9 expression confers a higher risk of relapse and worse survival in patients with breast cancer [37].

MMP-9 variants that influence expression may contribute to cancer susceptibility. The -1562 C/T variant was shown to play a functional role in gene transcription, resulting in the loss of binding of a nuclear protein to this region and an increase in transcriptional activity in macrophages. Przybylowksa et al. showed that the T allele of MMP-9–1562 C/T was associated with the malignance and the growth of the tumor [29]. MMP-9 R279Q polymorphism was shown to influence the malignant potential of renal cell carcinoma in a Japanese population [38]. However, Beeghly-Fadiel et al. suggested that common genetic variation of MMP-9 was not significantly associated with breast cancer susceptibility among participants of the Shanghai Breast Cancer Genetics Study [39].

The present meta-analysis has several limitations. First, the number of eligible articles was small, which may affect the reliability of the results. Secondly, MMP-9 may act by interacting with other MMPs or their inhibitors. Thirdly, we only analyzed studies from a few populations, so future research needs to include more ethnic groups.

Conclusions

Our results found that TT genotype of MMP-9–1562 C/T polymorphism in the recessive model was significantly associated with increased the risk of breast cancer. However, no significant association was found between other MMP-9 polymorphisms and breast cancer risk. Further well-designed studies with larger populations are needed to further explore the role of MMP-9 polymorphism in breast cancer risk.

Acknowledgement

We thank colleagues in our department for valuable discussions about this study.

Conflict of interest

The authors declared no conflict of interest.

References:

1. Curado MP: Breast cancer in the world: incidence and mortality. Salud Publica Mex, 2011; 53(5): 372–84
2. Ferlay J, Soerjomataram I, Dikshit R et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015; 136(5): E359–86
3. Siegel R, Ma J, Zou Z, Jemal A: Cancer statistics, 2014. Cancer J Clin, 2014; 64(1): 9–29
4. Youliden DR, Cramb SM, Dunn NA et al: The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. Cancer Epidemiol, 2012; 36(3): 237–48
5. Nelson HD, Zakhler B, Cantor A et al: Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med, 2012; 156(9): 635–48
6. Ren HF, Wang XJ, Kang HF et al: Associations between C1772T polymorphism in hypoxia-inducible factor-1α gene and breast cancer: a meta-analysis. Med Sci Monit, 2014; 20: 2578–83
7. Zhang X, Pu Z, Ge J et al: Association of CYP2D6* 10, OATP1B1 A388G, and OATP1B1 T521C polymorphisms and overall survival of breast cancer patients after tamoxifen therapy. Med Sci Monit, 2015; 21: 563–69
8. Sotiriou C, Pusztai L: Gene-expression signatures in breast cancer. N Engl J Med, 2009; 360(8): 790–800
9. Yadav L, Puré N, Rastogi V et al: Matrix metalloproteinases and cancer – roles in threat and therapy. Asian Pac J Cancer Prev, 2014; 15(3): 1085–91
10. Nessler MB, Puchala J, Chrpausta A et al: Levels of plasma matrix metalloproteinases (MMP-2 and MMP-9) in response to INTEGRA® dermal regeneration template implantation. Med Sci Monit, 2014. 20: 91–96
11. Wang X, Yu YY, Lieu S et al: MMP9 regulates the cellular response to inflammation after skeletal injury. Bone, 2013; 52(1): 111–19
12. Yousef EM, Tahir MR, St-Pierre Y, Gaboury IA: MMP-9 expression varies according to molecular subtypes of breast cancer. BMC Cancer, 2014; 14: 609
13. St Jean PL, Zhang XC, Hart BK et al: Characterization of a dinucleotide repeat in the 92 kDa type IV collagenase gene (CLG4B), localization of CLG4B to chromosome 20 and the role of CLG4B in aortic aneurysmal disease. Ann Hum Genet, 1995; 59(Pt 1): 17–24
14. Malaponte G, Police J, Candido S et al: IL-6-174 G > C and MMP-9-1562 C > T polymorphisms are associated with increased risk of deep vein thrombosis in cancer patients. Cytokine, 2013; 62(1): 64–69
15. Li X, Qu L, Zhong Y et al: Association between promoters polymorphisms of matrix metalloproteinases and risk of digestive cancers: a meta-analysis. J Cancer Res Clin Oncol, 2013; 139(9): 1433–47
16. Hu Z, Huo X, Lu D et al: Functional polymorphisms of matrix metalloproteinase-9 are associated with risk of occurrence and metastasis of lung cancer. Clin Cancer Res, 2005; 11(15): 5433–39
17. Slattery ML, John E, Torres-Mejia G et al: Matrix metalloproteinase genes are associated with breast cancer risk and survival: the Breast Cancer Health Disparities Study. PLoS One, 2013; 8(5): e63165
18. Griew F, Li WQ, Iacopetta B: Genetic polymorphisms in the MMP-2 and MMP-9 genes and breast cancer phenotype. Breast Cancer Res Treat, 2004; 88(3): 197–204
19. Roehe AV, Frazzon AP, Agnes G et al: Detection of polymorphisms in the promoters of matrix metalloproteinases 2 and 9 genes in breast cancer in South Brazil: preliminary results. Breast Cancer Res Treat, 2007; 102(1): 123–24
20. Wang X et al: Association between MMP-2 and MMP-9 polymorphisms and breast cancer risk in Chinese female population. Maternal and Child Health Care of China, 2014; 29(7): 1094–97
21. Lei H, Hemminki K, Altieri C et al: Promoter polymorphisms in matrix metalloproteinases and their inhibitors: few associations with breast cancer susceptibility and progression. Breast Cancer Res Treat, 2007; 103(1): 61–69
22. Fu F, Wang C, Chen LM et al: The influence of functional polymorphisms in matrix metalloproteinase 9 on survival of breast cancer patients in a Chinese population. DNA Cell Biol, 2013; 32(5): 274–82
23. Chiranjeevi P, Spurthi KM, Rani NS et al: Gelatinase B (MMP-9) polymorphism in tumor progression and invasion of breast cancer. Tumour Biol, 2014; 35(2): 1351–56
24. Holliday DL, Hughes S, Shaw JA et al: Intrinsic genetic characteristics determine tumor-modifying capacity of fibroblasts: matrix metalloproteinase-3 SA/SA genotype enhances breast cancer cell invasion. Breast Cancer Res, 2007; 9(5): R67
25. Resler AI, Malone KE, Johnson LG et al: Genetic variation in TLR or NFkappaB pathways and the risk of breast cancer: a case-control study. BMC Cancer, 2013; 13: 219
26. Chahil JK, Munretnam K, Samsudin N et al: Genetic polymorphisms associated with breast cancer in Malaysian cohort. Int J Clin Biochem, 2014; 1–6
27. Sadeghi M, Motovali Bashir M, Hojati Z: MMP-9 promoter polymorphism associated with tumor progression of breast cancer in Iranian population. International Journal of Integrative Biology, 2009; 6(1): 33–37
28. Zhou P, Du LF, Lv GQ et al: Current evidence on the relationship between four polymorphisms in the matrix metalloproteinases (MMP) gene and breast cancer risk: a meta-analysis. Breast Cancer Res Treat, 2011; 127(3): 813–18
29. Przybylsowska K, Kluczna A, Zadrozný M et al: Polymorphisms of the promoter regions of matrix metalloproteinases genes MMP-1 and MMP-9 in breast cancer. Breast Cancer Res Treat, 2006; 95(1): 65–72
30. Baldyuk M, Zerimech F, Gouyer V et al: Specific expression of matrix metalloproteinases 1, 3, 9 and 13 associated with invasiveness of breast cancer cells in vitro. Clin Exp Metastasis, 2000; 18(2): 171–78
31. Farina AR, Mackay AR: Gelatinase B/MMP-9 in tumour pathogenesis and progression. Cancers, 2014; 6(1): 240–96
32. Jones JL, Walker RA: Control of matrix metalloproteinase activity in cancer. J Pathol, 1997; 183(4): 377–79
33. Merdad A, Karim S, Schultz HJ et al: Expression of matrix metalloproteinases (MMPs) in primary human breast cancer: MMP-9 as a potential biomarker for cancer invasion and metastasis. Anticancer Res, 2014; 34(3): 1355–66
34. Liu D, Guo H, Li Y et al: Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of breast cancer metastasis: a meta-analysis. PLoS One, 2012; 7(2): e31251
35. Bartsch JE, Staren ED, Appert HE: Matrix metalloproteinase expression in breast cancer. J Surg Res, 2003; 110(2): 383–92
36. Pellikainen JM, Ropponen KM, Kataja V et al: Expression of matrix metalloproteinase (MMP)-2 and MMP-9 in breast cancer with a special reference to activator protein-2, HER2, and prognosis. Clin Cancer Res, 2004; 10(22): 7621–28
37. Song J, Su H, Zhou YY, Guo LL: Prognostic value of matrix metalloproteinase-9 expression in breast cancer patients: a meta-analysis. Asian Pac J Cancer Prev, 2013; 14(3): 1615–21
38. Awakura Y, Ito N, Nakamura E et al: Matrix metalloproteinase-9 polymorphism and renal cell carcinoma in a Japanese population. Cancer Lett, 2006; 241(1): 59–63
39. Beeghly-Fadiel A, Lu W, Shu XO et al: MMP9 polymorphisms and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study. Breast Cancer Res Treat, 2011; 126(2): 507–13