RESEARCH ARTICLE

Meta-analysis of Associations Between four Polymorphisms in the Matrix Metalloproteinases Gene and Gastric Cancer Risk

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Abstract

Background: Matrix metalloproteinases (MMPs) play important roles in pathogenesis and development of cancer. Recently, many studies have show associations between polymorphisms in the promoter regions of MMPs and risk of gastric cancer. The present meta-analysis was conducted in order to investigate the potential association between four polymorphisms in the MMP gene and gastric cancer risk. Methods: A computerized literature search was conducted in databases of Med-line, Embase, Science Citation Index and PubMed till June 2013 for any MMP genetic association study of gastric cancer. Odds ratios (ORs) and 95 % confidence intervals (CIs) were estimated for each gene under dominant and recessive models, and heterogeneity between studies was assessed using the Q test and I² value. Overall and subgroup analyses according to ethnicity were carried out with Stata 12.0. Results: 14 reports covering 8,146 patients (2,980 in the case group and 5,166 in the control group) were included in the present meta-analysis. We found that the MMP-7 (-181A>G) polymorphism increased the gastric cancer risk in therecessive model (GG vs. AA/AG, OR=1.768, 95% CI =1.153-2.712). For MMP2 −1306 C>T, MMP1-1607 1G/2G, and MMP9−1 562 C>T, there were no associations between these polymorphisms and the risk of gastric cancer under dominant or recessive models. Conclusion: This meta-analysis suggested that the MMP7-181 A>G polymorphism may contribute to gastric cancer susceptibility. More studies are needed, especially in Europeans, in the future.

Keywords: Matrix metalloproteinases (MMPs) - polymorphism - gastric cancer - risk - meta analysis

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Introduction

Gastric cancer is one of the major cancers in the world and has caused serious damages to human health. Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred (de Martel et al., 2012). In addition to the H. pylori strain, and various environmental factors which are major risk factors, genetic background also plays an important role (Companioni et al., 2013; Lee and Derakhshan, 2013). The matrix metalloproteinase (MMPs) family comprise of more than 20 enzymes that are capable of degrading extracellular matrix proteins (Ke et al., 2013). MMPs play an important role in several steps of cancer development by regulating cancer cell growth, differentiation, apoptosis, angiogenesis, invasion, and metastasis by degrading the extracellular matrix and basement membrane barriers (Sugimoto et al., 2008; Egeblad and Werb, 2002). The activity of MMPs is modulated by transcriptional regulation, as well as by their interaction with tissue inhibitors of metalloproteinases (TIMPs). MMPs and TIMPs play a crucial role in tumor dissemination and metastasis (Alakus et al., 2010).

MMP1, MMP2, MMP-7, and MMP-9 are important members of the MMP family. Four polymorphisms in the promoter region of these MMPs, which are MMP1-1607 1G/2G, MMP-2 1306 C>T, MMP7-181 A>G, and MMP9-1 562 C>T, have been reported to be functional and may contribute to genetic susceptibility to cancers (McColgan and Sharma, 2009; Peng et al., 2010). Many studies have showed that SNP of MMPs genes may be associated with gastric cancer risk. However, the associations between these polymorphisms and gastric risk remain inconclusive due to conflicting results from different case-control studies. Therefore, we performed a meta-analysis to clarify clinical impact of MMP gene polymorphisms in gastric cancer.

Materials and Methods

Search strategy

The literature search was aimed to find all relevant studies that examined the association of MMP-1, MMP-2, MMP-7, and MMP-9 polymorphisms with gastric cancer following electronic databases: the Med-line, Embase, Science Citation Index, and PubMed databases between August 1992 and June 2013. The following medical subject heading terms were used: “matrix metalloproteinase”,
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The inclusion criteria for the present meta-analysis were as follows: (1) patients included in the study were gastric cancer; (2) they used an unrelated case–control design; (3) availability of genotypes or allelic frequencies; and (4) they applied a useful genotyping method and presented sufficient data to calculate the odds ratio (OR) with a confidence interval (CI) and a P-value. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking control groups were excluded. The following studies or data were also excluded: 1) the outcomes and parameters of patients were not clearly reported; 2) it was impossible to extract the appropriate data from the published results; and 3) there was overlap between authors or centers in the published literature.

Data extraction

Details extracted from each report included the first author, published year, ethnicity of study population (Asian or European), numbers of case and controls, genotypetype distribution, genotyping methods, allele, etc. All data were extracted and registered into two databases independently by two reviewers (TF Yang and L Guo), to avoid bias in the data extraction process. Any disagreement between these two investigators was resolved by consensus or by consultation with additional reviewers (Wang Q).

Statistical analysis

First, we tested Hardy-Weinberg equilibrium (HWE), by comparing the expected and observed genotype frequencies of the control group using the Pearson chi-square test for goodness of fit. The association between the MMP polymorphisms and risk of gastric cancer was assessed by OR and 95% CI. Heterogeneity among the studies was assessed by the chi-square test. P value<0.05 was considered to be heterogeneous obviously. At the same time, I² also was used to assess the heterogeneous. We considered heterogeneity to be present if the I² statistic was >50%. P<0.05 was considered significant. Heterogeneity was to be explored by subgroup analysis or a random-effects model. Publication bias was quantitatively evaluated using funnel plots. The pooled ORs were performed on the dominant (Xx + xx versus XX), recessive model (xx versus XX + Xx), and allelic contrast (x versus X). respectively (X represented major allele, x represented minor allele). All analyses were conducted using STATA 12.0 (STATA Corporation, College Station, Texas), using two sided P values, and all tests were two sided.

Results

Selected studies

According to our criteria, there were 14 studies including 2980 cases and 5166 controls, gastric cancer was confirmed by histological or pathogenic method in each study. Genotype counts of the analyzed polymorphisms of studies included in the meta-analysis were showed in Table 1.

| Gene          | Year   | Ethnicity | Source          | Case                               | Control           | Genotyping method | p     |
|---------------|--------|-----------|----------------|------------------------------------|-------------------|-------------------|-------|
| MMP2-1306 C>T |         |           |                |                                    |                   |                   |       |
| Xiaoping Miao(10) | 2003   | Asian     | HB             | 356 312 44 0                       | 789 542 229 18    | PCR & dHPLC       | 0.741 |
| Chun-Ying Wu  | 2007   | Asian     | PB             | 240 191 41 8                       | 283 221 60 2      | PCR               | 0.06  |
| Hakan Alakus  | 2010   | European  | HB             | 135 82 52 1                        | 58 35 23 0        | PCR               | 0.018 |
| Ji Hye Kim    | 2011   | Asian     | HB             | 153 120 32 1                       | 326 271 54 1      | PCR               | 0.064 |
| Zhang xue-mei | 2004   | Asian     | HB             | 228 180 45 3                       | 774 536 220 18    | PCR & dHPLC       | 0.921 |
| FJGM Kubben   | 2006   | European  | HB             | 89 50 34 5                        | 169 102 53 14     | ARMS-PCR          | 0.803 |
| Lin Xin-dong  | 2011   | Asian     | HB             | 478 366 106 6                     | 461 347 110 4     | PCR               | 0.588 |
| Yan Li        | 2010   | Asian     | HB             | 257 207 46 4                       | 630 487 137 6     | PCR               | 0.44  |
| MMP7-181 A>G  |         |           |                |                                    |                   |                   |       |
| Junhui Zhang  | 2005   | Asian     | HB             | 201 167 34 0                       | 350 316 33 1      | PCR–RFLP          | 0.19  |
| Ji Hye Kim    | 2011   | Asian     | HB             | 153 128 24 1                       | 326 280 45 1      | PCR               | 0.913 |
| FJGM Kubben   | 2006   | European  | HB             | 79 34 37 8                        | 169 46 106 17     | ARMS-PCR          | 0.654 |
| MITSUSHIGE    | 2008   | Asian     | HB             | 160 133 27 0                      | 434 393 40 1      | PCR               | 0.244 |
| Manzoor       | 2010   | Asian     | HB             | 118 29 49 40                       | 195 63 92 40      | PCR               | 0.078 |
| MMP9-1562 C>T |         |           |                |                                    |                   |                   |       |
| Ji Hye Kim    | 2011   | Asian     | HB             | 152 85 58 9                       | 313 161 143 9     | PCR               | 0.829 |
| FJGM Kubben   | 2006   | European  | HB             | 79 59 19 1                        | 169 120 46 3      | ARMS-PCR          | 0.699 |
| Zhang xue-mei | 2004   | Asian     | HB             | 228 169 55 4                      | 774 584 183 7     | PCR & dHPLC       | 0.82  |
| Shunji        | 2005   | Asian     | HB             | 177 133 38 6                      | 224 156 63 5      | PCR               | 0.126 |
| MMP1-1607 1G/2G |       |           |                |                                    |                   |                   |       |
| Xia Jin       | 2005   | Asian     | HB             | 183 112 51 20                      | 350 194 105 51    | PCR               | 0.896 |
| Shunji Matsumura | 2004  | Asian     | HB             | 215 101 88 26                     | 166 88 61 17      | PCR–RFLP          | 0.319 |

X/xs for 1G/2G of MMP1, C/T of MMP2, A/G of MMP7, C/T of MMP9; HB, hospital-based; PB, population-based; HWE, Hardy–Weinberg equilibrium

"gastric cancer", “MMP", and“polymorphisms”. The “related articles” function was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. A manual search of the bibliographies of relevant journals was also carried out to identify trials for possible inclusion.

Selections of studies

About the enrollment criteria for the present meta-analysis were as follows: (1) patients included in the study were gastric cancer; (2) they used an unrelated case–control design; (3) availability of genotypes or allelic frequencies; and (4) they applied a useful genotyping method and presented sufficient data to calculate the odds ratio (OR) with a confidence interval (CI), and a P-value. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking control groups were excluded. The following studies or data were also excluded: 1) the outcomes and parameters of patients were not clearly reported; 2) it was impossible to extract the appropriate data from the published results; and 3) there was overlap between authors or centers in the published literature.
Table 2. Associations between MMP Polymorphisms and Gastric Cancer Risk

| Variables       | N  | CASE | Control |     |     |     |     |
|-----------------|----|------|---------|-----|-----|-----|-----|
|                 |    |      |         |     |     |     |     |
| MMP2-1306C>T    | 6  | 1712 | 3220    | 0.74| 0.001| 85.6| 1.177(0.451-3.071) |
| Asian Ethnicity |    |      |         |     |     |     |     |
|                 | 8  | 1926 | 3844    | 0.74| 0.001| 80.7| 0.851(0.536-1.361)  |
| European Ethnicity |    |      |         |     |     |     |     |
|                 |    |      |         |     |     |     |     |
| MMP7-181 A>G    | 4  | 622  | 1305    | 1.55| 0.001| 74.8| 1.761(0.958-3.240)  |
| Ethnicity       |    |      |         |     |     |     |     |
|                 | 5  | 701  | 1474    | 0.49| 0.014| 66.3| 0.927(0.480-1.791)  |
| MMP9-1562 C>T   | 4  | 636  | 1480    | 0.89| 0.001| 74.8| 2.130(1.297-3.499)  |
| MMP1-1607 1G/2G | 2  | 398  | 516     | 0.999| 0.001| 74.8| 2.130(1.297-3.499)  |

The number of comparisons; Dominant model, AB & BB versus AA; recessive model, BB versus AB & BB; allelic contrast (A represents wild allele, B represents mutant allele); P value for Z test; P value for Q test; Random effect model was used.

Figure 1. Flow Chart of Studies Identified, Included and Excluded

Figure 2. Meta-analysis for MMP2-1, 306 C/T Polymorphism and Gastric Cancers Susceptibility in Different Genetic Models. (A) in dominant model; (B) in recessive model

Figure 3. Meta-analysis for MMP7-181 A/G Polymorphism and Gastric Cancers Susceptibility in Different Genetic Models, (A) in dominant model; (B) in recessive model
MMP2 −1306 C>T There were eight studies for MMP2 −1306 C>T when analyzed on the overall and subgroup analysis, there was no association between the risk of gastric cancer and this polymorphism under the dominant and recessive models (Table 2). (dominant, OR=0.776, 95%CI 0.556-1.077, p=0.0001, I²=80.7%; recessive, OR=0.851, 95%CI 0.534-1.356, p=0.138, I²=36.4%). (Figure 2).

MMP-9 − 1562 C>T and MMP1-1607 1G/2G In overall comparison, there was no association between these two polymorphisms and risk of gastric cancer under the dominant and recessive models (Table 2). Because of the limited data, we did not analyze the data based on the ethnicity study population for these two polymorphisms.

Discussion

This meta-analysis of 17 studies involving 7983 cases and 7382 controls was performed to investigate the relationship between four polymorphisms in MMP gene and gastric cancer risk. We found that MMP7 (−181) polymorphism increased this risk. In contrast, no significant difference was found in any genotype of MMP-1, MMP-2 or MMP-9.

The associations between SNP of MMPs genes and other cancers have been investigated by many studies. A meta-analysis based on 17 studies published case–control studies, including 7983 cases and 7382 controls, found that MMP1-1607 1G/2G polymorphism may contribute to lung cancer susceptibility, but no significant difference was found in any genotype of MMP-1, MMP-2 or MMP-9.

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Several studies have reported that MMP2 and MMP9 are highly expressed in tumor tissues compared to normal tissues, polymorphisms of MMP2 (−1306), and MMP9 (−1562), play significant roles in cancer development. Previous studies showed that C allele of MMP2 (−1306), had higher promoter activity than T allele, (Price et al., 2001), and C allele of MMP9 (−1562), had lower promoter activity than T allele (Zhang et al., 1999). However, our meta-analysis had included several literatures, the pooled OR results demonstrated that there was no association with risk of gastric cancer for these two polymorphisms.

The two genetic variants were not a major risk factor for the development of gastric cancer. Whether environment factors participated in pathogenesis of gastric cancer for these two polymorphisms should be clarified in further studies.

Different MMP polymorphisms result in different associations with gastric cancer risk. Several reasons might explain this problem. First, population for each study came from different regions and ethnicity, different genetic backgrounds and environmental factors could influence the result. Second, the molecular mechanism of the relation ship of SNP of MMPs genes and gastric cancer risk were different.

There are also some shortcomings needed to be discussed. Firstly, the inclusion of few studies with relatively small sample size and poor validation was a main limitation of the meta-analysis. Secondly, lack of available information prevented a more precise evalution with adjusted ORs by age, gender, smoking status and different histological types of gastric cancer, etc. Although it is difficult for us to analyze the interaction between gene and environment, it is necessary to evaluate the roles of some special environmental factors and life styles such as diet, alcohol consumption, and smoking status in developing gastric cancer. Thirdly, while all of these studies were reported on European and Asians, more studies are required in other population types such as Africans.

In conclusion, this meta-analysis suggested that MMP7-181 A>G polymorphism may contribute to gastric cancer susceptibility. Future studies are needed to confirm this association and to focus on the possible mechanisms.

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