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 I^2 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 MMP9-1562 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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Table 1. Genotype Counts of the Analyzed Polymorphisms of Studies Included in the Meta-analysis

Gene	Year	Ethnicity	Source of control	Case				Control				Genotyping method	*p*
				N	XX	Xx	xx	N	XX	Xx	xx		
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
JiHye 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&dHPL C	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													
Jianhui 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&dHPL C	0.82
Shun ji	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
ShunjiMatsumura	2004	Asian	HB	215	101	88	26	166	88	61	17	PCR-RFLP	0.319

X/x 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

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, genotype 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, I^2 also was used to assess the heterogeneous. We considered heterogeneity to be present if the I^2 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 2. Associations between MMP Polymorphisms and Gastric Cancer Risk

Variables	N[a]	CASE	Control	Dominant genetic model[b] (BB+AB versus AA)				Recessive genetic model[b] (BB versus AB+AA)				Allelic contrast[b] (B versus A)			
				OR (95% CI)	P^c	P^d	I^2	OR (95% CI)	P^c	P^d	I^2	OR (95% CI)	P^c	P^d	I^2
MMP2-1306C>T															
Ethnicity															
Asian	6	1712	3220	0.741(0.497-1.103)[e]	0.74	0.001	85.6	1.177(0.451-3.071)[e]	0.739	0.064	52	1.093(0.396-3.017)[e]	0.864	0.041	56.9
European	2	224	227	0.925(0.611-1.400)	0.714	0.801	0	0.704(0.262-1.893)	0.487	0.692	0	0.772(0.278-2.141)	0.618	0.742	0
Total	8	1926	3844	0.776(0.556-1.077)[e]	0.13	0.001	80.7	0.851(0.536-1.361)	0.508	0.134	37	1.042(0.496-2.186)	0.914	0.107	40.7
MMP7-181 A>G															
Ethnicity															
Asian	4	622	1305	1.550(1.194-2.012)	0.001	0.438	0	2.130(1.297-3.499)	0.003	0.807	0	2.016(1.131-3.595)	0.018	0.86	0
European	1	79	169	0.495(0.283-0.866)	0.014	0	0	1.007(0.415-2.444)	0.987	0	0	0.637(0.246-1.646)	0.352	0	0
Total	5	701	1474	1.239(0.774-1.984)[e]	0.372	0.003	74.8	1.768(1.153-2.712)	0.009	0.54	0	1.452(0.895-2.355)	0.397	0.297	18.6
MMP9-1562 C>T															
Total	4	636	1480	0.897(0.728-1.105)	0.308	0.612	0	1.761(0.958-3.240)	0.069	0.846	0	1.615(0.872-2.991)	0.127	0.847	0
MMP1-1607 1G/2G															
Total	2	398	516	0.993(0.621-1.589)[e]	0.978	0.085	66.3	0.890(0.589-1.345)	0.58	0.234	29.4	0.927(0.480-1.791)[e]	0.822	0.134	55.5

[a]The number of comparisions; [b]Dominant model, AB & BB versus AA; recessive model, BB versus AB & BB , allelic contrast (A represents wild allele, B represents mutant allele); [c]*P* value for Z test; [d]*P* value for Q test; [e]Random effect model was used

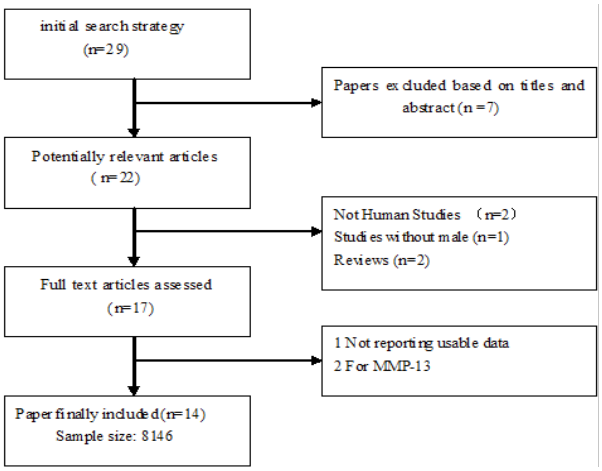

Figure 1. Flow Chart of Studies Identified, Included and Excluded

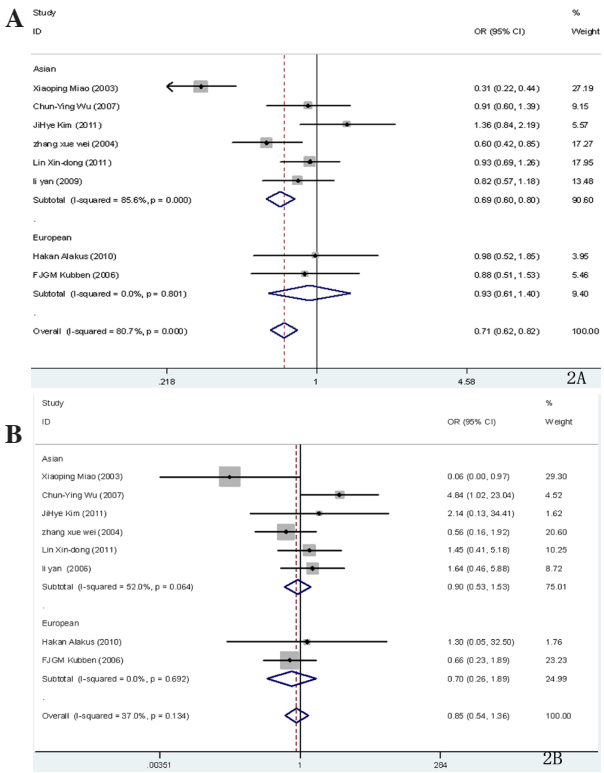

Figure 2. Meta-analysis for MMP2-1, 306 C/T Polymorphism and Gastric Cancers Susceptibility in Different Genetic Models. (A) in Dominant model; (B) b in recessive model

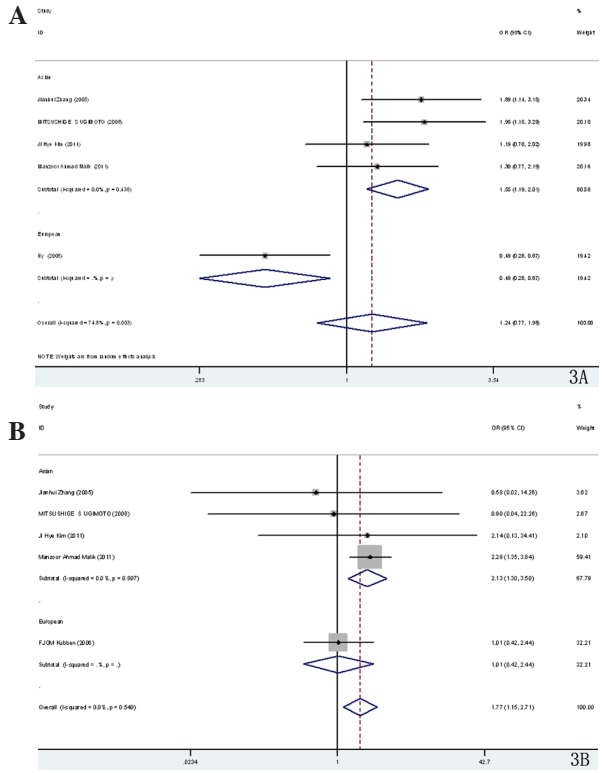

Figure 3. Meta-analysis for MMP7- 181 A/G Polymorphism and Gastric Cancers Susceptibility in Different Genetic Models. (A) in dominant model; (B) in Recessive Model

Table 1. The frequencies of age and sex were matched between cases and controls in each study. No studied had a deviation from Hardy–Weinberg equilibrium in controls at a statistical significance level of 0.01 (Table 1). The reasons for exclusion were described in Figure 1.

Overall, as shown in Table 2, we observed that the MMP-7 (-181A>G). polymorphism increased the gastric cancer risk in recessive model GG vs. AA/AG, OR=1.768, 95% CI =1.153-2.712). when all the eligible studies were pooled into the meta-analysis (Table 2). In the subgroup analysis, we found that the MMP-7 (-181A>G). polymorphism in Asian elevates gastric cancer risk in all the three models (GG vs. AA, OR =2.016, 95% CI=1.131-3.595; GG/AG vs. AA, OR=1.550, 95% CI=1.194-2.012; GG vs. AA/AG, OR=2.130, 95% CI=1.297-3.499) (Figure 3).

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, I^2=80.7%; recessive, OR=0.851, 95%CI 0.534-1.356, p=0.138, I^2=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 MMP2-735 C/T, MMP2-1306 C/T or MMP9-1562 C/T (Hu et al., 2013). Another meta-analysis based on 9 published case–control studies, found that MMP2-1306 C/T increased the risk of breast cancer. However, there was no association with polymorphisms of MMP1-1607 1G/2G, MMP3-1171 5A/6A and MMP9-1562 C/T (Zhou et al., 2011).

In some research, the polymorphism of MMP1 promoter could increase the risk of digestive cancers significantly and indicating its role in the development of many carcinomas was stimulative (Li et al., 2013). It may be contributed to 2G allele creates an E26 (Ets). transcription factor binding site and increases transcription capacity (Rutter et al., 1998). However, our meta-analysis indicated no significant association between the MMP1 polymorphism and gastric cancer risk.

Seveal studies have evaluated associations for the polymorphisms of MMP7 (– 181). with risk of gastric cancer. For MMP7 (– 181), individuals with -181G allele had a higher risk of gastric cancer under the recessive model, no association was found under the dominant model. Individuals with excess MMP-7 activity by harboring the -181G allele may predispose to malignant transformation through the 'sheddase' activity of MMP-7 protein, via recently described substrates such as tumor necrosis factor-α, E-cadherin and Fas ligand. These substrates have been known to play important roles in signal transduction, cell-cell adhesion and apoptosisthis (Carneiro et al., 2004; Fingleton et al., 2001; Noe et al., 2001). Subgroup analyses by ethnicity showed there was no association between MMP7 (–181). polymorphism and gastric cancer risk in European under all genetic models but MMP7 (–181). polymorphism was associated with increased risk of gastric cancer in Asian under the three model.

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 evalation 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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