

Association between promoter polymorphisms of matrix metalloproteinase-1 and risk of gastric cancer

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Abstract: Growing evidences show that matrix metalloproteinase-1 (*MMP1*) plays important roles in tumorigenesis and cancer metastasis. The interactions between *MMP1*-1607 1G>2G polymorphism and risk of gastric cancer (GC) have been reported, but results remained ambiguous. To determine the association between *MMP1*-1607 1G>2G polymorphism and risk of GC, we conducted a meta-analysis and identified the outcome data from all the research papers estimating the association between *MMP1*-1607 1G>2G polymorphism and GC risk, which was based on comprehensive searches using databases such as PubMed, Elsevier Science Direct, Excerpta Medica Database (EMBASE), and Chinese National Knowledge Infrastructure (CNKI). The fixed-effects model was used in this meta-analysis. Data were extracted, and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. In this meta-analysis, six studies involving 1,377 cases and 1,543 controls were included. We identified the significant association between *MMP1*-1607 1G>2G polymorphism and GC risk for allele model (OR = 1.05; 95% CI, 1.01–1.08), for dominant model (OR = 1.11; 95% CI, 1.08–1.15), and for recessive model (OR = 1.06; 95% CI, 0.98–1.14). In summary, our analysis demonstrated that *MMP1*-1607 1G>2G polymorphism was significantly associated with an increased risk of GC.

Keywords: *MMP1*, gene polymorphisms, gastric cancer

Introduction

Gastric cancer (GC) is the fourth most common cancer and second leading cause of cancer-related deaths worldwide.¹ The mechanism of gastric carcinogenesis remains elusive. Environmental and genetic factors possibly play a role in the etiology of the disease.^{2,3} However, these risk factors cannot fully explain the development of GC, since only a minority of exposed population finally developed GC, indicating possible interplay between risk factors and personal background including genetic susceptibility.⁴ Matrix metalloproteinases (MMPs) are a group of proteolytic enzymes involved in physiological and pathological extracellular matrix processing, capable of degrading essentially all extracellular matrix components.^{5,6}

MMPs are divided into five structural families, including collagenases, gelatinases, stromelysins, matrilysins, and membrane-type MMPs. More evidence indicates that many MMPs are involved in tumorigenesis by modulating cell proliferation, apoptosis, and angiogenesis.⁷ *MMP1*, located on 11q22.3, is one member of the MMP family and degrades interstitial collagen types I, II, and III. The expression level of *MMP1* gene is at low level in normal cells under physiological conditions;^{8,9} however, *MMP1* expression is dramatically increased in many malignancies.^{5,10} It has been reported that the promoter of *MMP1* can regulate *MMP1* gene transcription,

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in which there is a functional single nucleotide polymorphism (SNP), *MMP1*-1607 1G>2G (rs1799750),^{11,12} which contains a guanine insertion/deletion polymorphism at position -1607¹³ and leads to higher expression of *MMP1*. In the current study, we performed a meta-analysis of hospital-based studies to determine the association between the *MMP1*-1607 1G>2G polymorphism and GC risk.

Materials and methods

Study strategy

A systematic computerized search in all the electronic databases that could search for literatures, including PubMed, Chinese National Knowledge Infrastructure (CNKI), EMBASE and Elsevier Science Direct etc, was conducted to collect all case-control studies evaluating *MMP1* and GC in humans published until August 2014. The search was developed without any language restriction and searching for the following terms: (matrix metalloproteinase-1 OR *MMP1*), (polymorphism OR polymorphisms OR variant OR variants OR genotype), and (cancer OR carcinoma OR neoplasm). To expand our research, we also performed the search in the CNKI database using terms in Chinese, such as *MMP1*, gastric cancer risk OR GC risk, and polymorphism. The references for all identified publications were hand-searched for additional studies.

Statistical methods

We used odds ratios (ORs) and 95% confidence intervals (CIs) to measure the strength of association between *MMP1*-1607 1G>2G polymorphism and GC risk. Pooled ORs and 95% CIs were calculated for an allele mode, a dominant model (variant homozygote + heterozygote vs wild-type homozygote), and a recessive model (variant homozygote vs heterozygote + wild-type homozygote).

Then, we assessed an estimate of potential publication bias using the funnel plot, in which the standard error of log (SEL) of every study was plotted against its log (OR), and an asymmetric plot indicated a potential publication bias. We assessed funnel plot asymmetry using Egger's linear regression test, a linear regression method of evaluating funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined using the *t*-test suggested by Egger, and $P < 0.05$ was considered representative of statistically significant publication bias. All of the statistical tests were performed using STRATA version 12.0 (StrataCorp, College Station, TX, USA).

Data extraction

The following basic data were collected from the studies that met the inclusion criteria: first author's name, tumor

type, year of publication, country, ethnicity of study population, number of cases and controls, and genotyping method. Two independent investigators conducted data extraction work, and they resolved discrepancies through discussion. Study qualities were judged according to the criteria modified from a previously published study¹⁴ (Table S1).

Results

Eligible study characteristics

A total of 649 publications, all written in English or Chinese and all extracted from the PubMed, MEDLINE, EMBASE, and CNKI databases, were reviewed. Finally, six articles^{15–20} containing six studies, including 1,377 GC cases and 1,543 non-cancer controls were included in the current meta-analysis. A flowchart shows the study selection procedure (Figure 1). The main characteristics of the studies are listed in Table 1. Sample sizes and *MMP1*-1607 1G>2G allele and genotype distributions in the studies considered in the present meta-analysis are shown in Table 2.

Quantitative synthesis

The fixed-effects model is used in the current meta-analysis. The association between the *MMP1*-1607 1G>2G polymorphism and cancer risk was estimated with the following models: an allele model (2G vs 1G), a dominant model (2G/2G + 1G/2G vs 1G/1G), and a recessive model (2G/2G vs 2G/1G + 1G/1G). The evaluations of the association of *MMP1*-1607 1G>2G with cancer risk are shown in Table 3. In the allele model (2G vs 1G), the overall pooled effect showed that the 2G allele was associated with an increased overall cancer risk, compared with the 1G allele (OR = 1.05; 95% CI, 1.01–1.08) (Figure 2A). In the recessive model (2G/2G vs 2G/1G + 1G/1G), the overall pooled effect showed that the 2G/2G homozygote was not associated with an overall cancer risk, compared with the 2G/2G + 1G/1G homozygote (OR = 1.06; 95% CI, 0.98–1.14) (Figure 2B). In the dominant model (2G/2G + 1G/2G vs 1G/1G), the overall pooled effect demonstrated that the 2G/2G + 1G/2G genotypes were associated with a significantly increased overall cancer risk, compared with the 1G/1G homozygote (OR = 1.11; 95% CI, 1.08–1.15) (Figure 2C).

Heterogeneity analysis

Heterogeneity was assessed using the χ^2 -based *Q*-test among studies in the overall comparisons analysis. Heterogeneity was found in the pooling models ($P < 0.1$ in all models); thus, the fixed-effects model was used to produce an extended pool of studies with 95% CIs. No significant heterogeneity can be

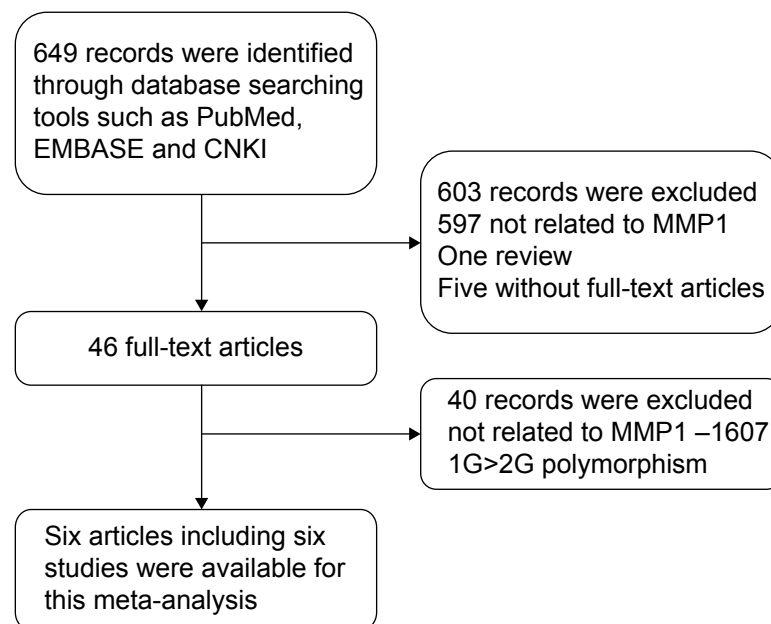


Figure 1 Flowchart of study selection procedure of this meta-analysis.

Abbreviations: EMBASE, Excerpta Medica Database; CNKI, Chinese National Knowledge Infrastructure; *MMP1*, matrix metalloproteinase-1.

seen among the six comparisons using the dominant model, recessive model, or allelic contrast.

Publication bias

For *MMP1*-1607 1G>2G, Begg's funnel plot and Egger's test provided no evidence of publication bias in an allele model (2G vs 1G, Egger's test: 95% CI, -4.65 to -4.81, $P=0.964$; Begg's test: $P=0.851$). Similarly, there was no evidence of publication bias for *MMP1*-1607 1G>2G in a dominant model (2G/2G + 1G/2G vs 1G/1G, Egger's test: 95% CI, -6.78 to -3.50, $P=0.425$; Begg's test: $P=0.75$), and in a recessive model (2G/2G vs 1G/2G + 1G/1G, Egger's test: 95% CI, -7.48 to -6.22, $P=0.81$; Begg's test: $P=0.851$) (Figure 3). These findings demonstrated that publication bias, if any, did not significantly affect the results of our current meta-analysis for the association between *MMP1*-1607 and GC risk.

Discussion

MMPs can degrade the extracellular matrix and basement membrane, which is an important event in many physiological and pathological processes, including tumor invasion and metastasis. MMP expression has been found in a variety of human tumors and is significantly correlated with tumor invasion, metastasis, and therapeutic response.²¹ However, certain members of the MMP family exert contradicting roles at different stages during cancer progression, depending upon other factors and upon the tumor stage, tumor site, enzyme localization, and substrate profile.²²

The expression level of the *MMP1* gene was found to be increased in various tumors and was related to a poor prognosis in several types of cancers. *MMP1* expression can be regulated by the *MMP1* promoter. The polymorphism at position -1607 among the *MMP1* promoters determined the increased *MMP1* transcriptional level, which is attributed to its 2G allele generating a core-binding site for the E26 transformation-specific (ETS) transcription factor family, leading to the increased *MMP1* expression.²³

There were six articles^{15–20} containing six studies, including 1,377 GC cases and 1,543 non-cancer controls used in the present meta-analysis. The procedure of meta-analysis was performed by using STRATA version 12.0 software. We found that individuals with the 2G allele and 1G/2G + 2G/2G genotypes had a higher risk of GC for all models, including allele and dominant models. Interestingly, in a recessive model, there was no significant difference between 2G/2G genotype and 1G/2G + 1G/1G genotypes. These results indicated that 2G allele and heterozygote 2G might affect the individual's phenotype more than other genotypes; the 2G allele or 1G/2G genotype carriers therefore seemed more susceptible to cancer development than 1G allele genotype carriers, or 1G/1G genotype carriers.

In the past several years, other studies have also found that the 2G allele is associated with an increased risk of other cancers. Zhang et al¹² have reported that the *MMP1*-1607 1G>2G polymorphism is associated with an increased risk of head and neck cancer. Hu et al's results showed that the *MMP1* rs1799750 polymorphism is associated with a decreased risk

Table 1 Characteristics of individual studies included in the current meta-analysis

First author's name (year)	Country	Genotype method	Selection/characteristics of cases	Selection/characteristics of controls	Ref
Matsumura et al (2004)	Japan	PCR-RFLP	215 gastric cancer patients, 153 males and 62 females (median age 67.7±11.4 years), including 122 patients with an intestinal type of gastric cancer and 93 patients with a diffuse type	166 healthy control subjects, 95 males and 71 females	20
Jin et al (2005)	People's Republic of China	PCR	183 patients with gastric cardiac adenocarcinoma, 134 males and 49 females, average age 55.0±10.5 years	350 healthy individuals, 229 males and 121 females, average age 51.7±10.7 years	19
Fang et al (2013)	People's Republic of China	PCR-RFLP	246 gastric cancer patients, 163 males and 83 females, average age 57.9±11.8 years	252 normal controls, 167 males and 85 females, average age 58.8±11.2 years	18
Devulapalli et al (2014)	India	PCR-RFLP	166 gastric cancer patients, 118 males and 48 females, 82.53% ≥50 years	202 normal controls, 132 males and 70 females, 62.37% ≥50 years	16
Dey et al (2014)	India	PCR	145 gastric cancer patients, 112 males and 33 females, range 42.6–65.8 years	145 normal controls, 81 males and 64 females, range 34.5–62.5 years	17
Hua et al (2014)	People's Republic of China	PCR	422 gastric cancer patients, 237 males and 185 females, range 42.2±5.6 years	428 gastric cancer patients, range 43.3±4.6 years	15

Note: Equations show data are presented as mean ± standard deviation.

Abbreviations: PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

Table 2 Sample sizes and *MMP1* –1607 IG>2G allele and genotype distributions in the studies considered in the present meta-analysis

Gene	First author's name (year)	Cases				Controls				HWE of control (P-value)	Frequency of IG allele in controls	Quality*				
		Cases		Controls												
		N	2G/2G	IG/2G	IG/IG	2G	IG	N	2G/2G				IG/2G	IG/IG	2G	IG
MMP1-1607 IG/2G	Matsumura et al ²⁰ (2004)	215	101	88	26	290	140	166	88	61	17	237	95	Y (0.1953)	0.713855	7
	Jin et al ¹⁹ (2005)	183	112	51	20	275	91	350	194	105	51	493	207	N (0.0000)	0.704286	7
	Fang et al ¹⁸ (2010)	246	155	85	6	395	97	252	161	78	13	400	104	Y (0.3826)	0.793651	7
	Devulapalli et al ¹⁶ (2014)	166	46	114	6	206	126	202	50	130	22	230	174	N (0.0000)	0.569307	7
	Dey et al ¹⁷ (2014)	145	56	66	23	178	112	145	53	72	20	178	112	Y (0.2713)	0.613793	6
	Hua et al ¹⁴ (2014)	422	186	187	49	559	285	428	158	195	75	511	345	Y (0.5686)	0.596963	7

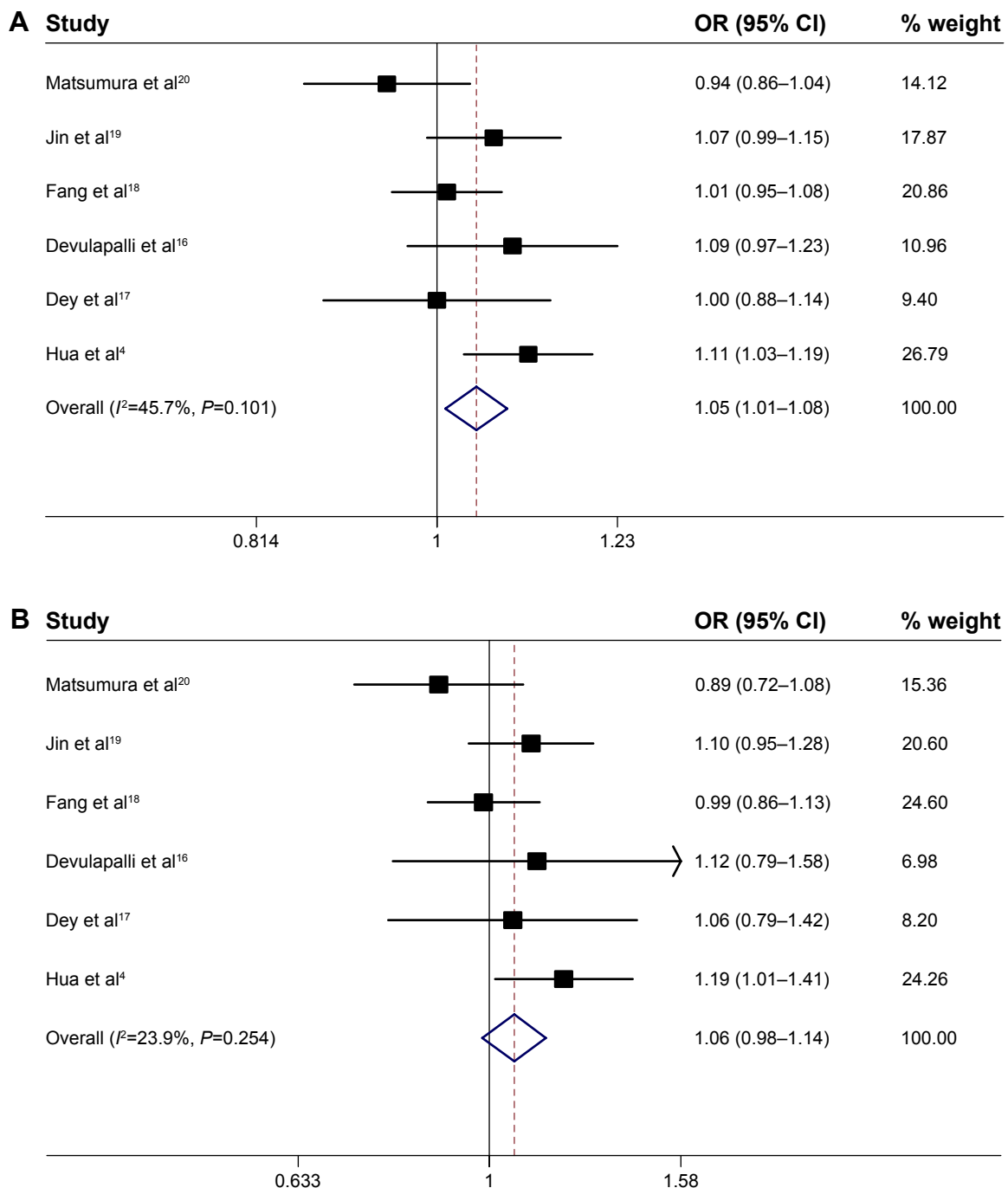
Note: *Represents the confidence of the study.

Abbreviations: *MMP1*, matrix metalloproteinase-1; HWE, Hardy–Weinberg equilibrium; N, number of subjects.

Table 3 Meta-analysis of the association between the studied *MMP1* alleles and GC in different populations

Gene	Genotypes	Group	Fixed-effects model				Heterogeneity	
			OR (95% CI)	Z	P	χ^2	I^2 (%)	P_{Q-test}
MMP1-1607	2G vs 1G	Total	1.05 (1.01–1.06)	2.49	0.013	9.21	45.7	0.101
	1G/2G	Total	1.06 (0.989–1.14)	1.52	0.129	6.57	23.9	0.254
	2G/2G + 2G/1G vs 1G/1G	Total	1.11 (1.08–1.15)	6.14	0.000	4.51	0	0.478

Abbreviations: GC, gastric cancer; *MMP1*, matrix metalloproteinase-1; OR, odds ratio; CI, confidence interval; vs, versus.

**Figure 2** (Continued)

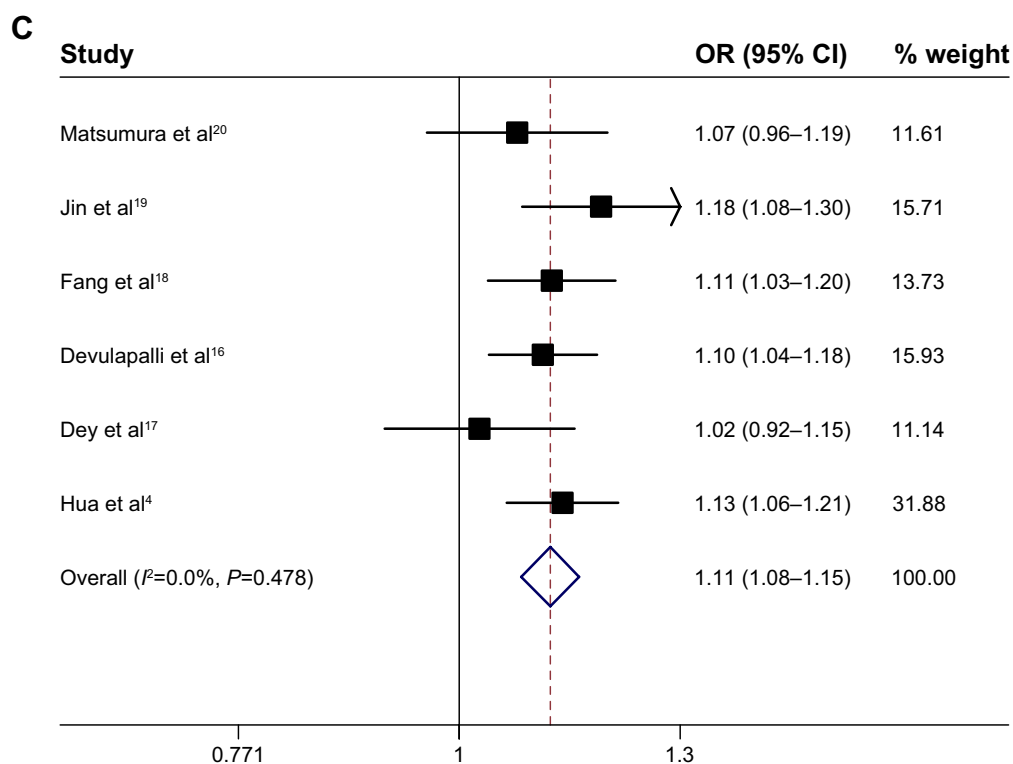


Figure 2 Meta-analysis of the association between GC and the *MMP1*–1607 IG>2G polymorphisms.

Notes: (A) *MMP1*–1607 IG>2G allele model (2G vs 1G), among all populations in the fixed-effects model. (B) *MMP1*–1607 IG>2G recessive model (2G/2G vs 1G/2G + 1G/1G), among all populations in the fixed-effects model. (C) *MMP1*–1607 IG>2G dominant model (2G/2G + 1G/2G vs 1G/1G), among all populations in the fixed-effects model.

Abbreviations: OR, odds ratio; CI, confidence interval; *MMP1*, matrix metalloproteinase-1; GC, gastric cancer; vs, versus.

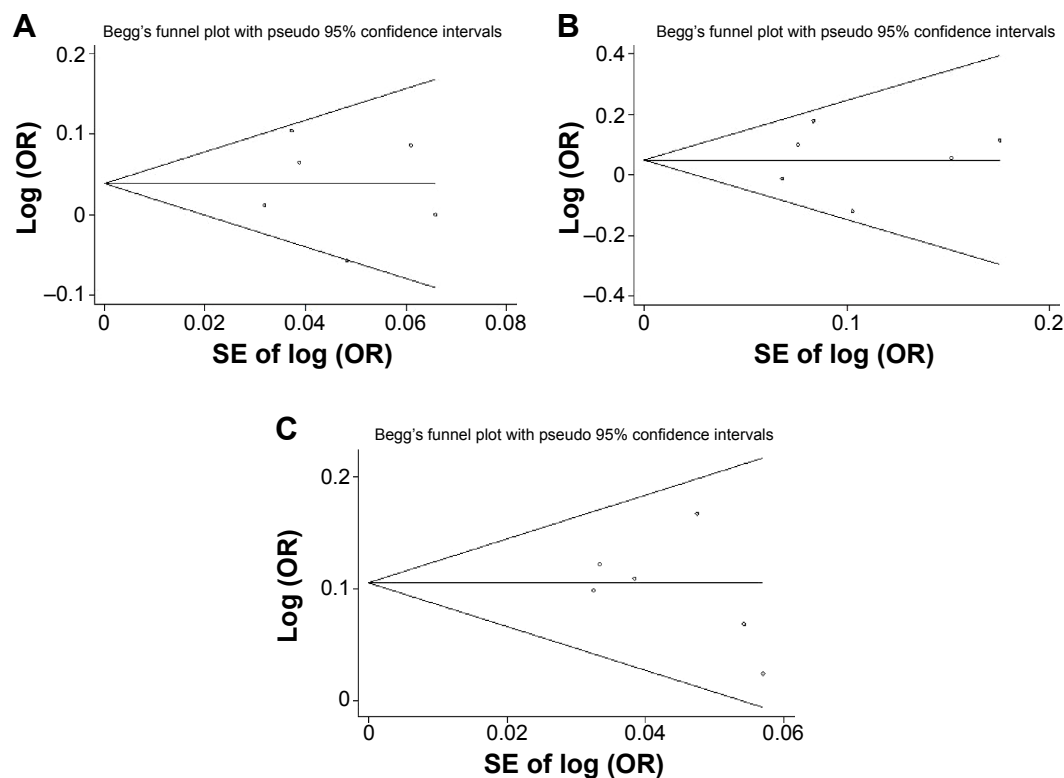


Figure 3 Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log (OR) is the natural logarithm of OR. Horizontal line is the effect size.

Notes: (A) *MMP1*–1607 IG>2G, 2G vs 1G; (B) *MMP1*–1607 IG>2G, 2G/2G vs 1G/2G + 1G/1G; (C) *MMP1*–1607 IG>2G, 2G/2G + 1G/2G vs 1G/1G.

Abbreviations: SE, standard error; OR, odds ratio; *MMP1*, matrix metalloproteinase-1; vs, versus.

of lung cancer in Asian, but not in Caucasian subjects.²⁴ Taken together, the relationship between *MMP1* rs1799750 polymorphism and cancer risk may be disease-specific and may depend on other factors, such as race, age, habits, etc. There are another two studies that relate to GC and *MMP1*, included in Li et al (2013)²⁵ and Yang et al (2014).²⁶ Meanwhile, Li's study^{14,25} gathered data before August 2011, and Yang's before June 2013. In our results, there are four more studies involved, indicating the advantages of our study compared to previously published similar studies.

Recently, multiple therapeutic agents named matrix metalloproteinase inhibitors (MMPis) have been developed to target MMPs and to control their enzymatic activity.²² *MMP1*-1607 1G>2G polymorphism may be regarded as a target of MMPis in treatment of GC in the future.

Study limitations

There are some limitations to the current study. First, we have collected all eligible studies, but the study number was not large and the numbers of patients examined were small. Second, we did not assess the potential effects of other factors such as differences in race. Third, only one SNP in *MMP1* was included in this study. Some other SNPs in *MMP1* also could contribute to susceptibility to GC. The effects of these SNPs and the interaction or network among these related genes should also be studied in the future.

Conclusion

In conclusion, our present meta-analysis indicates that *MMP1*-1607 1G>2G polymorphism is associated with GC risk. However, our results should be further validated with larger samples and in different ethnic populations, due to the limited study numbers and relatively small sample sizes.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Scale for methodological quality assessment

Criteria	Score
1. Representativeness of cases	
Gastric cancer diagnosed according to acknowledged criteria	2
Mentioned the diagnosed criteria but not specifically described	1
Not mentioned	0
2. Source of controls	
Population or community-based	3
Hospital-based GC-free controls	2
Healthy volunteers without total description	1
GC-free controls with related diseases	0.5
Not described	0
3. Sample size	
>300	2
200–300	1
<200	0
4. Quality control of genotyping methods	
Repetition of partial/total tested samples with a different method	2
Repetition of partial/total tested samples with the same method	1
Not described	0
5. Hardy–Weinberg equilibrium (HWE)	
Hardy–Weinberg equilibrium in control subjects	1
Hardy–Weinberg disequilibrium in control subjects	0

Abbreviation: GC, gastric cancer.

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