ORIGINAL RESEARCH

Relationship between single-nucleotide polymorphism of matrix metalloproteinase-2 gene and colorectal cancer and gastric cancer susceptibility: a meta-analysis

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Background: Recently, the published data on the association between matrix metalloproteinase-2 (MMP-2) (C-1306T) polymorphism and colorectal cancer (CRC) and gastric cancer (GC) (gastrointestinal cancer) risk remained controversial. The aim of this study is to investigate the relationship between the risk of CRC and GC and single-nucleotide polymorphism of MMP-2(C-1306T).

Methods: Medline, Embase, Science Citation Index, and PubMed were thoroughly searched to identify relevant studies. Odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of the association.

Results: We performed a meta-analysis of 14 studies including 642 cases and 692 controls for CRC and 1,936 cases and 3,490 controls for GC. The result indicates that there is significant relationship between MMP-2(C-1306T) polymorphism and CRC risk in recessive model and codominant model (TT vs CC/CT: OR: 2.39, 95% CI: 1.30–4.37, P=0.005; TT vs CC: OR: 2.36, 95% CI: 1.29–4.34, P=0.006). In subgroup analysis according to ethnicity, significant associations were found in Caucasians (TT vs CC/CT: OR: 2.87, 95% CI: 1.43–5.78, P=0.003; TT vs CC: OR: 2.86, 95% CI: 1.41–5.80, P=0.003), but we did not find significant evidence with GC in all genetic models, and in stratified analysis according to ethnicity, no significant risk was found in the subgroup too.

Conclusion: This meta-analysis considered that the MMP-2(C-1306T) polymorphism is a risk factor for CRC susceptibility, especially in Caucasians, but it does not support any relationship to GC, and further studies are needed to explore the association.

Keywords: matrix metalloproteinase-2, colorectal cancer, gastric cancer

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Introduction

The incidence of gastrointestinal cancer has increased year by year, with approximately 2 million new cases diagnosed worldwide and approximately 1.2 million patients dying per year. Gastrointestinal cancer ranked in the top five in cancer mortality rankings, the leading cause of cancer death.[1,2] Moreover, various environmental factors are major risk factors, especially genetic background.[3] Matrix metalloproteinases (MMPs) are a multigene family of zinc-dependent endopeptidases that share a similar structure and collectively have the capacity to degrade essentially all extracellular matrix components.[4] Matrix metalloproteinase-2 (MMP-2) is an important member of the family, and the main effect of the MMP-2 is to degrade type IV collagen which is an important part of the cell layer of basement membrane,[5] which is involved in the breakdown of extracellular matrix in normal

physiological processes, such as embryonic development, reproduction, angiogenesis,[6–8] and tissue remodeling, as well as in disease processes, tumor invasion, and metastasis. A number of researches have demonstrated the role of MMP-2 in colorectal cancer (CRC) and gastric cancer (GC).[9–13] Single-nucleotide polymorphism (SNP) is the most common type of genetic variation, and small part of these polymorphisms has function. Most of the functional polymorphisms are located in the promoter region of the gene and are therefore considered to influence gene expression.[14–17] Human MMP-2 promoter has been proved to contain several cis-acting regulatory elements. Among them, functional SNP in the promoter region of the MMP-2 (the C-1306T/rs 243865) that disrupts an Sp1-type promoter site (CCACC box) affects MMP-2 expression or activity and may predispose to disease conditions.[18] Moreover, transient transfection experiment had shown that MMP-2 expression is ~1.4- to twofold higher with the C allele than with the T allele.[19] Many studies have shown that SNP of MMP-2-(C-1306T) genes may be associated with gastrointestinal cancer risk. However, as a result of conflicting results from various studies, the relationship between the polymorphisms and gastrointestinal risk remains inconclusive. Hence, we performed a meta-analysis to clarify clinical impact of MMP-2(C-1306T) polymorphism on CRC and GC.

Materials and methods
Search strategy

Medline, Embase, Science Citation Index, and PubMed were thoroughly searched with the terms "metalloproteinases" or "MMPs", "polymorphism" or "polymorphisms", "risk", "susceptibility", and "colorectal cancer" or "gastric cancer" or "gastrointestinal cancer" (till July 2014). We got more relevant articles by literature references backtracking, and only the publications with full text available were included. Additionally, abstracts and unpublished reports were not considered.

Selections of studies

The following are included in the inclusion criteria: (1) independent case-control design was used to evaluate the association between MMP-2(C-1306T) and the risk of CRC or GC; (2) genotype distribution of the control population that conformed to Hard–Weinberg equilibrium (HWE); (3) the study presented sufficient data to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

The exclusion criteria included the following: (1) there is no comparison, just the study of case or noncancer;

(2) literature data that are not complete; (3) the genotype distribution of the control population that did not accord with HWE; (4) if finding overlaps studies, only the most recent or complete study was included in this meta-analysis.

Data extraction

Two investigators read all the included literatures carefully, and then extracted all data such as the first author, published year, ethnicity of study population (Asian or Caucasian), numbers of case and controls, genotype distribution, genotyping methods, and allele independently. If two investigators had divergent idea on any data, another investigator would be asked to check and to reach consensus on the data.

Statistical analysis

HWE was assessed by using the goodness-of-fit χ^2 test for control group, and bias was considered when $P<0.05$. Crude ORs with their corresponding 95% CIs were used to evaluate the strength of relationship between the MMP-2(C-1306T) and the risk of CRC and GC. The pooled ORs were evaluated in codominant model (CT vs CC, TT vs CC), dominant model (CT/TT vs CC), and recessive model (TT vs CC/CT). Subgroup analyses were performed by ethnicity. Moreover, we performed sensitivity analysis to assess the accuracy and stability of the results by excluding a single study each time. Q-test was used to check heterogeneity among the studies. If $P<0.1$, it is considered as heterogeneity and statistically significant. We used the random-effects model to calculate the pooled OR. Otherwise, the fixed-effects model was used.[20,21] Potential publication bias was assessed by Begg's funnel plot[22] and Egger's test,[23] if $P<0.05$ was considered as statistically significant. Data analysis was performed using Revman 5.1 (Cochrane Collaboration) and Stata 11.0 (Stata Corporation, College Station, TX, USA).

Results
Study characteristics

According to the search strategy, 67 publications were found. Among these studies, 12 articles were irrelevant; 20 were letters, review articles, and meta-analysis; 13 studies were relevant to other members of the MMP family or other polymorphisms of MMP-2; and eight studies were duplicate of a previous study. So, 14 studies were finally included in this meta-analysis (Figure 1).[24–37] Fourteen studies which consist of six CRC studies[24–29] (642 cases and 692 controls) and eight GC studies[30–37] (1,936 cases and 3,490 controls) were included. As illustrated in Table 1, among these studies, nine were Asians and five were Caucasians. In no study
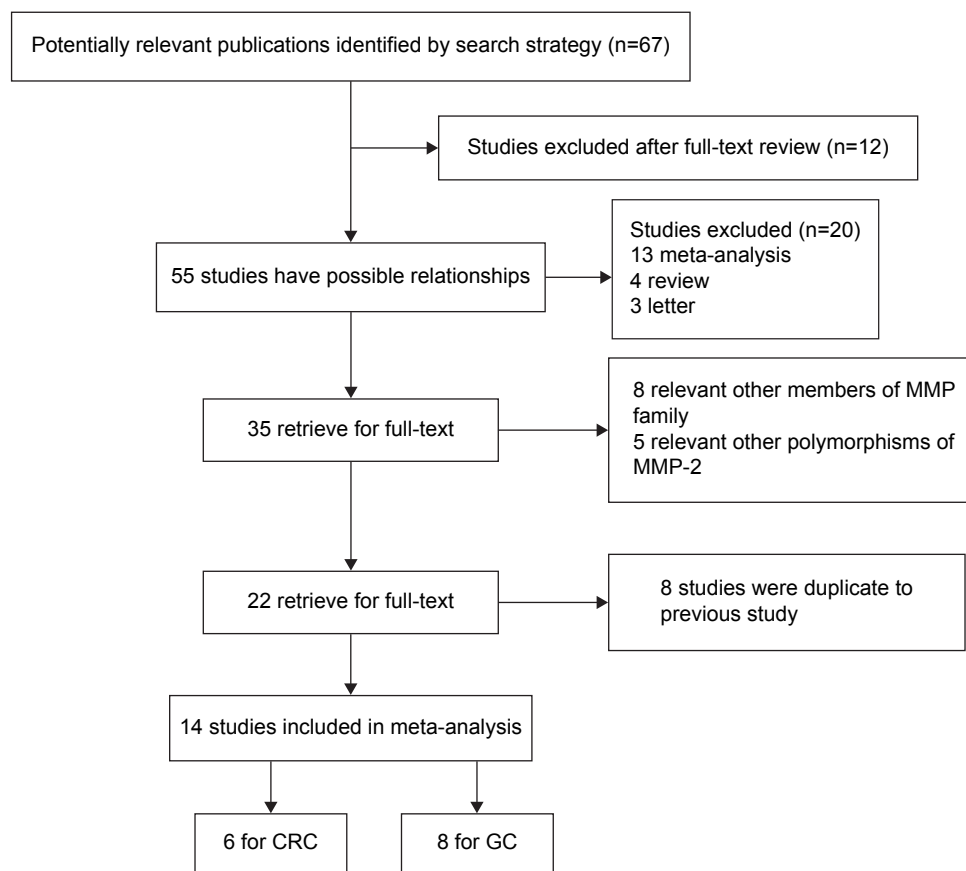
Figure 1 Study flow chart explaining the selection of the 14 studies included in the meta-analysis.
Abbreviations: CRC, colorectal cancer; GC, gastric cancer; MMP, matrix metalloproteinase.

was the genotypic distribution of the controls deviated from HWE ($P>0.1$).

Meta-analysis results

As shown in Table 2, we found that there is significant relationship between MMP-2(C-1306T) polymorphism and CRC risk in recessive model and codominant model (TT vs CC/CT: OR: 2.39, 95% CI: 1.30–4.37, $P=0.005$; TT vs CC: OR: 2.36, 95% CI: 1.29–4.34, $P=0.006$; Figures 2 and 3). No significance was found between the other genetic models and CRC. In subgroup analysis according to ethnicity, the results indicated that there is a positive relationship between the MMP-2(C-1306T) polymorphism and CRC risk in Caucasians (TT vs CC/CT: OR: 2.87, 95% CI: 1.43–5.78, $P=0.003$; TT vs CC: OR: 2.86, 95% CI: 1.41–5.80, $P=0.003$), but there is no association in Asians. However, when eight GC studies were pooled into the meta-analysis, we found that there is no significant association between MMP-2(C-1306T) polymorphism and GC risk in all genetic models. Therefore, the stratified analysis was performed according to ethnicity; still, no relationship was found between the two subgroups in all genetic models.

Heterogeneity analysis

As shown in Table 3, significant heterogeneity was found between the MMP-2(C-1306T) polymorphism and CRC risk in the dominant model (CT/TT vs CC: $\chi^2=11.83$, $I^2=58\%$, $P_H=0.04$). To explore the sources of heterogeneity, the stratified analysis was performed according to ethnicity. We found that heterogeneity still exists in the dominant model among Asians (CT/TT vs CC: $\chi^2=6.18$, $I^2=68\%$, $P_H=0.05$). In order to find further sources of heterogeneity, Galbraith plot analysis was performed to identify which study may result in the heterogeneity. As illustrated in Figure 4, all studies were inside the CI of the regression line. It indicates that overall heterogeneity in dominant model is not significant.[38] In addition, there was moderate heterogeneity between MMP-2(C-1306T) polymorphism and GC risk in the codominant model and dominant model (CT vs CC: $\chi^2=33.55$, $I^2=79\%$, $P_H<0.05$; CT/TT vs CC: $\chi^2=38.97$, $I^2=82\%$, $P_H<0.05$). Heterogeneity was found among Asians in the same genetic models according to stratified analysis (CT vs CC: $\chi^2=28.9$, $I^2=82\%$, $P_H<0.05$; CT/TT vs CC: $\chi^2=35.23$, $I^2=86\%$, $P_H<0.05$). As illustrated

Table 1 Characteristics of included studies in this meta-analysis

| Author	Year	Country	Ethnicity	Matching criteria	Source of control	Genotyping methods	CC (case/control)	TT (case/control)	CT (case/control)	HWE (P-value)
Colorectal cancer										
Kang et al[24]	2011	Korea	Asian	Sex, age	HB	PCR-RFLP	39/42	4/2	7/6	0.018
Xu et al[25]	2004	People's Republic of China	Asian	Sex, age	HB	RT-PCR	106/92	1/2	19/32	0.678
Elander et al[26]	2006	Sweden	Caucasian	Regional	PB	PCR-RFLP	69/109	9/10	49/89	0.125
Saeed et al[27]	2014	Saudi	Caucasian	Age	PB	RT-PCR	92/103	12/2	21/20	0.382
Hesham et al[28]	2013	Saudi	Caucasian	Sex, age	PB	RT-PCR	66/92	5/1	24/23	0.689
Ohtani et al[29]	2009	Japan	Asian	NC	HB	PCR	107/64	1/0	11/3	0.851
Gastric cancer										
Wu et al[30]	2007	People's Republic of China	Asian	Age, data	PB	PCR	191/221	8/2	41/60	0.337
Kubben et al[31]	2006	the Netherlands	Caucasian	NC	PB	ARMS-PCR	50/102	5/14	34/53	0.069
Li et al[32]	2010	People's Republic of China	Asian	Sex, age, habit, family history	HB	PCR	207/487	4/6	46/137	0.283
Kim et al[33]	2011	Korea	Asian	NC	HB	PCR	120/271	1/1	32/54	0.322
Alakus et al[34]	2010	Germany	Caucasian	NC	HB	PCR	82/35	1/0	52/23	0.060
Zhang et al[35]	2004	People's Republic of China	Asian	Age	HB	PCR-dHPLC	180/536	3/18	45/220	0.409
Lin et al[36]	2011	People's Republic of China	Asian	Sex, nation, regional, age	HB	PCR	366/347	6/4	106/110	0.138
Miao et al[37]	2003	People's Republic of China	Asian	Sex, age	HB	PCR-dHPLC	312/542	44/229	0/18	0.279

Abbreviations: HWE, Hardy–Weinberg equilibrium; HB, hospital-based studies; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT, reverse transcription; PB, population-based studies; ARMS, amplification refractory mutation system; dHPLC, denaturing high performance liquid chromatography; NC, not clear.

**Table 2** Associations between MMP-2(C-1306T) polymorphism and CRC and GC

Variables	CT vs CC		TT vs CC		CT/TT vs CC		TT vs CC/CT	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Colorectal cancer								
Total	0.97 (0.74–1.27)	0.81	2.36 (1.29–4.34)	0.006	1.18 (0.77–1.83)	0.45	2.39 (1.30–4.37)	0.005
Asian	0.78 (0.48–1.28)	0.33	1.30 (0.38–4.45)	0.67	1.08 (0.41–2.84)	0.88	1.32 (0.39–4.54)	0.65
Caucasian	1.06 (0.77–1.48)	0.71	2.86 (1.41–5.80)	0.003	1.31 (0.86–2.01)	0.21	2.87 (1.43–5.78)	0.003
Gastric cancer								
Total	0.80 (0.58–1.01)	0.16	0.80 (0.51–1.28)	0.36	0.80 (0.57–1.13)	0.21	0.85 (0.54–1.36)	0.51
Asian	0.72 (0.50–1.04)	0.08	1.00 (0.40–3.02)	0.86	0.76 (0.49–1.17)	0.21	0.90 (0.53–1.53)	0.71
Caucasian	1.15 (0.76–1.74)	0.52	0.77 (0.28–2.12)	0.62	0.92 (0.69–1.24)	0.6	0.70 (0.26–1.89)	0.49

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; OR, odds ratio; CI, confidence interval; MMP-2, matrix metalloproteinase-2.
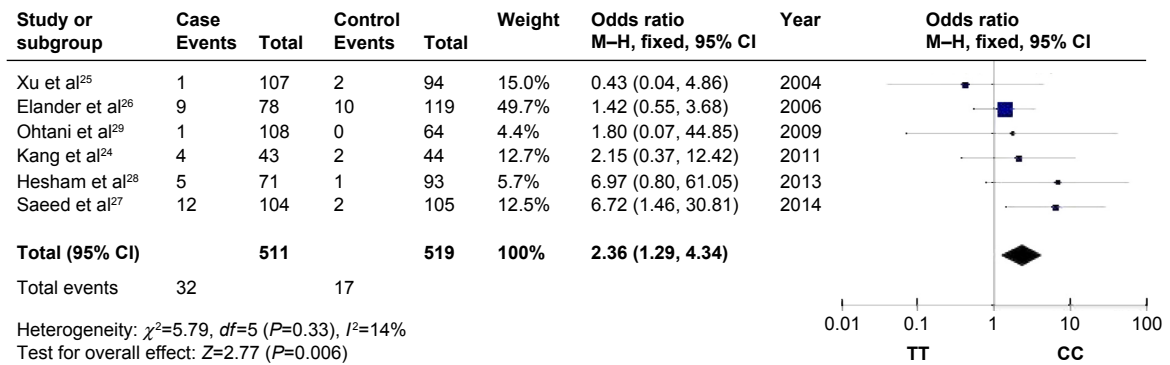
Figure 2 Meta-analysis of MMP-2(C-1306T) polymorphism and CRC susceptibility in codominant model (TT vs CC).
Abbreviations: CRC, colorectal cancer; CI, confidence interval; MMP-2, matrix metalloproteinase-2; M–H, Mantel–Haenszel test.
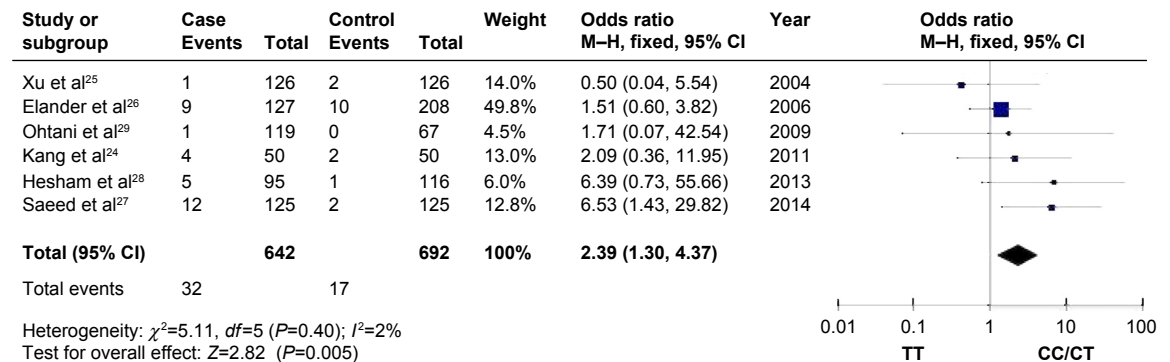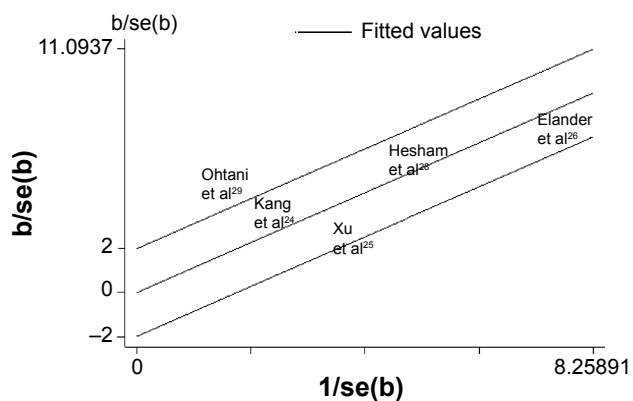

Figure 3 Meta-analysis of MMP-2(C-1306T) polymorphism and CRC susceptibility in recessive model (TT vs CC/CT).
Abbreviations: CRC, colorectal cancer; CI, confidence interval; MMP-2, matrix metalloproteinase-2; M–H, Mantel–Haenszel test.

Table 3 The Q-test for heterogeneity in various researches and its P_H value

Variables	CT vs CC			TT vs CC			CT/TT vs CC			TT vs CC/CT		
	χ^2 value	P_H value	I^2 (%)	χ^2 value	P_H value	I^2 (%)	χ^2 value	P_H value	I^2 (%)	χ^2 value	P_H value	I^2 (%)
Colorectal cancer												
Total	7.51	0.19	33	5.77	0.33	14	11.83	0.04	58	5.11	0.4	2
Asian	4.66	0.1	57	1.15	0.56	0	6.18	0.05	68	0.92	0.63	0
Caucasian	1.70	0.43	0	3.94	0.14	49	3.55	0.17	44	3.49	0.17	43
Gastric cancer												
Total	33.55	<0.05	79	11.80	0.11	41	38.97	<0.05	82	11.11	0.13	37
Asian	28.9	<0.05	82	11.61	0.07	48	35.23	<0.05	86	10.42	0.06	50
Caucasian	0.51	0.47	0	0.11	0.74	0	1.29	0.26	23	0.16	0.69	0

Figure 4 Galbraith plots of MMP-2(C-1306T) polymorphism and CRC risk in dominant model CT/TT vs CC.
Abbreviations: CRC, colorectal cancer; MMP-2, matrix metalloproteinase-2.
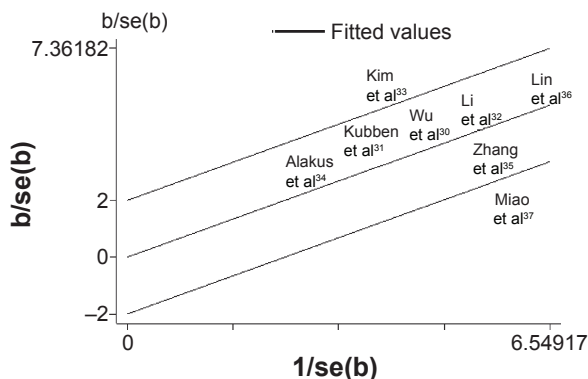
Figure 6 Galbraith plots of MMP-2(C-1306T) polymorphism and GC risk in dominant model CT/TT vs CC.
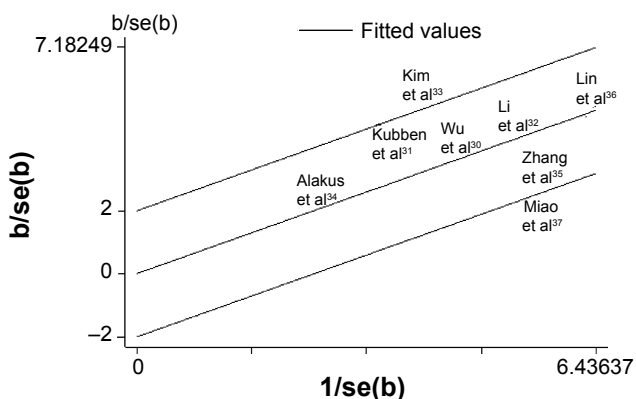**Note:** The studies of Kim et al and Miao et al were spotted as outliers.
Abbreviations: GC, gastric cancer; MMP-2, matrix metalloproteinase-2.

in Figures 5 and 6, the studies by Kim et al[33] and Miao et al[37] were outliers in codominant model and dominant model from the Galbraith plot analysis, and all I^2 values decreased obviously, and P_H values were more than 0.10 after removing the two studies in all genetic comparison models in the overall populations (CT vs CC: I^2=19%, P_H=0.29; CT/TT vs CC: I^2=17%, P_H=0.30), Asians (CT vs CC: I^2=0%, P_H=0.42; CT/TT vs CC: I^2=30%, P_H=0.23). The significance of MMP-2(C-1306T) polymorphism in different genetic models in overall population and stratified analysis were not influenced by excluding the two studies.

Sensitivity analysis

As the sample size for case and control in all studies is not the same, which ranged from 50 to 789, we gradually removed the small sample size, and corresponding overall results were not qualitatively altered.

Publication bias

No publication bias could be discovered in any genetic models by Begg's funnel plot and Egger's test. All P-values of Egger's tests were more than 0.05, which present statistical evidence of the funnel plots symmetry (Figure 7 and Table 4).

Discussion

MMP was classified as a large family of zinc-containing proteases, and this family is proven to be of relevance for cancer development and prognosis in various systems.[39,40] As MMP-2 is an enzyme with proteolytic activity against matrix and non-matrix proteins, particularly basement membrane constituents, and has type IV collagenolytic activity, it is considered to be an important member in the family. It is expressed by great majority of connective tissue cells. Furthermore, researches have also demonstrated that MMPs

Figure 5 Galbraith plots of MMP-2(C-1306T) polymorphism and GC risk in codominant model CT vs CC.
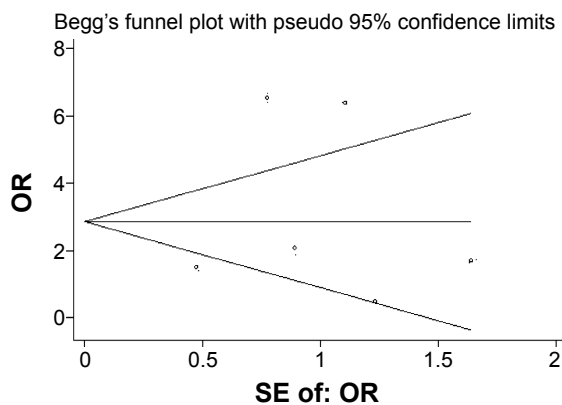**Note:** The studies of Kim et al and Miao et al were spotted as outliers.
Abbreviations: GC, gastric cancer; MMP-2, matrix metalloproteinase-2.

Figure 7 Funnel plots for publication bias of the meta-analysis of the association between MMP-2(C-1306T) polymorphism and CRC risk of the overall populations (recessive model TT vs CC/CT).
Abbreviations: CRC, colorectal cancer; SE, standard error; OR, odds ratio; MMP-2, matrix metalloproteinase-2.

Table 4 The Egger's test for publication bias in different genetic models and its P_E value

Variables	CT vs CC	TT vs CC	CT/TT vs CC	TT vs CC/CT
Colorectal cancer				
Coefficient	2.2316	1.9846	1.973	1.7139
95% CI	−1.6394 to 6.1026	−8.3366 to 12.305	−1.8439 to 5.7899	−7.8053 to 11.233
P_E value	0.185	0.622	0.225	0.643
Gastric cancer				
Coefficient	3.4371	0.7689	3.2950	0.8045
95% CI	−2.2084 to 9.0826	−3.8764 to 5.4142	−2.6797 to 9.2697	−4.0528 to 5.6618
P_E value	0.187	0.700	0.226	0.699

Abbreviation: CI, confidence interval.

are associated with the angiogenic switch; it was reliably recapitulated in the model of tumor progression. This switch is the earliest stage that involves in the tumor growth and progression, and MMP-2 was shown to play a key role in the development of the angiogenic phenotype.[41] MMP promoter SNPs affecting the gene transcription and expression are associated with malignant cancers susceptibility. SNP is the most common type of genetic variation, and genetic variation in MMP-2 may contribute to matrix membrane damage and angiogenesis, thus increasing cancer risk. The number of SNPs in the human genome is huge, but only a very small part of these polymorphisms have functional properties. Most of the functional polymorphisms are situated in the promoter region of the gene. MMP-2(C-1306T) was deemed to be an important polymorphism in the promoter region of the MMP-2 gene, and it was reported that the polymorphism 1306C→T disrupts an Sp1-type promoter site (CCACC box). Multifunctional protein which can directly interact with the basal transcriptional complex for the MMP-2 proximal promoter may contribute to interindividual diversity in susceptibility to cancer and many complex diseases leading to strikingly lower promoter activity with the T allele.[19,42]

In this study, the significant relationship between MMP-2(C-1306T) polymorphism and CRC risk was found in recessive model and codominant model (TT vs CC/CT: OR: 2.39, 95% CI: 1.30–4.37, P=0.005; TT vs CC: OR: 2.36, 95% CI: 1.29–4.34, P=0.006), and this positive relationship is more meaningful in European populations after subgroup analysis according to ethnicity (TT vs CC/CT: OR: 2.87; 95% CI: 1.43–5.78, P=0.003; TT vs CC: OR: 2.86, 95% CI: 1.41–5.80, P=0.003). Among the eligible publications, there are three studies that took Europeans as an object of study. Elander et al[26] did not find any evidence for the associations regarding CRC and MMP-2(C-1306T) polymorphism. However, this was different from Saeed et al's and Hesham et al's studies;[27,28] they all found that MMP-2(C-1306T) polymorphism might increase the risk of CRC. Furthermore, Hesham

also found that both the homozygous TT and T alleles were significantly associated with higher risk of colorectal cancerogenesis in males and old-aged patients. But both Saeed's and Hesham's researches took Saudi population as an object of study, so further investigations are needed to confirm and clarify whether this observation is only due to different regions. In Asians, no significant relationship was found between the risk of developing CRC and MMP-2(C-1306T) polymorphism from Kang's and Ohtani's studies.[24,29] In contrast to this, Xu's study[25] suggested that MMP-2(C-1306T) polymorphism may be associated with CRC development, and found that CRCs with CC genotype were more common with serosa/adventitia layer invasiveness compared with other genotypes (OR: 1.959, 95% CI: 1.055–3.637).

However, when eight GC studies were pooled into the meta-analysis, we found that there is no significant association between MMP-2(C-1306T) polymorphism and GC risk in all genetic models; the same result appeared in the stratified analysis. Our results were consistent with those reports from Wu et al's, Kubben et al's, Li et al's, Kim et al's, Alakus et al's, and Lin et al's studies;[30–34,36] they all did not find significant difference in distribution of MMP-2(C-1306T) polymorphism between GC patients and controls. In addition, in contrast to Alakus's study,[34] Kubben's study[31] showed that tumor of patients with the CC genotype contained significantly more MMP-2 antigen than tumor of patients with the CT/TT genotypes. The different methods used to determine antigen levels of MMP-2 in the different studies may contribute to these different results.[43] Further investigations are needed to clarify these different findings. Nevertheless, Zhang et al's and Miao et al's studies[35,37] found that subjects with the CC genotype had increased risk of developing GC compared with other genotypes. Finally, we exclude Liu et al's study to include 344 GC patients and 324 controls because only the data of TT/CT genotype and CC genotype were presented in the study. Liu et al suggested that MMP-2(C-1306T) polymorphism is an important risk factor for GC and the multifactor

interactions (OR: 3.07, 95% CI: 2.09–4.50).[44] Therefore, if we include their study, our conclusion may be changed.

We also found six recent meta-analyses focused on the gastrointestinal cancer risk and MMP-2(C-1306T) polymorphism.[10,45–49] Only Langers et al's study reported that the association between MMP-2(C-1306T) polymorphism and gastrointestinal cancer risk is not unidirectional (OR: 2.77, 95% CI: 1.27–6.04).[49] The remaining studies did not find an association between the polymorphism and CRC, but those meta-analyses did not include two studies that reported that the MMP-2(C-1306T) genotype was associated with a significant increase in CRC susceptibility. In the Saeed's and Hesham's study[27,28] cohort of 220 CRC patients and 241 control patients, samples of these different areas may significantly affect the results. Moreover, Peter et al's study[48] includes one duplicate of a previously published study, which may affect the accuracy of the conclusion. Yang et al's study found that there was no association between the risk of GC and this polymorphism in dominant and recessive models;[46] none of the other studies found similar results.[10,45,49] Li's meta-analyses included the study that suggested that MMP-2(C-1306T) polymorphism is an important risk factor for GC and the multifactor interactions (OR: 0.68, 95% CI: 0.47–0.99).[44] Moreover, Peng's result of meta-analysis showed that MMP-2(C-1306T) TT and TC genotype carriers were less susceptible to GC compared with CC genotype carrier. The meta-analyses of Peng and Langers included four studies, a relatively small number for studying the influence of gene polymorphisms on cancer susceptibility. This may explain the discordant results between the different studies and illustrates the need for larger sample sizes.

This meta-analysis might have several limitations. First, the controls were not uniformly defined. Most of them were common hospital-based case-control studies; other controls were population based. Hence, selection bias cannot be fully excluded. It would therefore be important to confirm these findings in a population-based prospective study. Second, our study has high heterogeneity in some genetic models; this may have insufficient statistical power to check the association. In addition, because of data limitations, this study is unable to adjust other environmental risk factors such as age, alcohol consumption, and pathogenic infections.

In summary, this meta-analysis indicates that the MMP-2(C-1306T) polymorphism is a risk factor for CRC susceptibility, especially in Caucasians, but it does not support any relationship to GC. However, because of data limitations, this study may not be particularly perfect. Therefore, further large sample studies are needed to estimate the effect of gene–gene

and gene–environment interactions, and studies including more samples with different ethnicities, environmental factors, and sufficient biological evidence for the SNP functions may lead to a better, comprehensive understanding of the association between the MMP-2(C-1306T) polymorphism and gastrointestinal cancer risk.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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