RESEARCH ARTICLE

Current Evidence on Associations Between the MMP-7 (-181A>G) Polymorphism and Digestive System Cancer Risk

Pan Ke, Zhong-De Wu, Hua-Song Wen, Miao-Xiong Ying, Huo-Cheng Long, Liu-Guo Qing*

Abstract

Matrix metalloproteinases (MMPs) degrade various components of the extracellular matrix and functional polymorphisms in encoding genes may contribute to genetic susceptibility to many cancers. Up to now, associations between MMP-7 (-181A>G) and digestive system cancer risk have remained inconclusive. To better understand the role of the MMP-7 (-181A>G) genotype in digestive cancer development, we conducted this comprehensive meta-analysis encompassing 3,518 cases and 4,596 controls. Overall, the MMP-7 (-181A>G) polymorphism was associated with higher digestive system cancer risk on homozygote comparison (GG vs. AA, OR=1.21, 95% CI = 1.12-1.60) and in a dominant model (GG/GA vs. AA, OR=1.16, 95% CI =1.03-1.46). On subgroup analysis, this polymorphism was significantly linked to higher risks for gastric cancer (GG vs. AA, OR=1.22, 95% CI = 1.02-1.46; GA vs. AA, OR=1.82, 95% CI =1.16-2.87; GG/GA vs. AA, OR=1.13, 95% CI =1.01-1.27; GG vs. GA/AA, OR= 1.25, 95% CI = 1.06-2.39. We also observed increased susceptibility to colorectal cancer and esophageal SCC in both homozygote (OR = 1.13, 95% CI = 1.06-1.26) and heterozygote comparisons (OR = 1.45, 95% CI = 1.11-1.91). In the stratified analysis by controls, significant effects were only observed in population-based studies (GA vs. AA, OR=1.16, 95% CI=1.08-1.50; GA/AA vs. GG, OR=1.10, 95% CI=1.01-1.72). According to the source of ethnicity, a significantly increased risk was found among Asian populations in the homozygote model (GG vs. AA, OR=1.40, 95% CI=1.12–1.69), heterozygote model (GA vs. AA, OR=1.26, 95% CI=1.02–1.51), and dominant model (GG/GA vs. AA, OR=1.18, 95% CI=1.08–1.55). Our findings suggest that the MMP-7 (-181A>G) polymorphism may be a risk factor for digestive system cancer, especially among Asian populations.

Keywords: MMP-7 - polymorphism - digestive cancer - meta-analysis - ethnic variation

Asian Pacific J Cancer Prev, **14 (4)**, 2269-2272

Introduction

The matrix metalloproteinase (MMPs) family comprise of more than 20 enzymes that are capable of degrading extracellular matrix proteins (Li et al., 2006; Singh et al., 2008; Wu et al., 2011). MMPs not only play important roles in physiological ECM remodelling, such as wound repair, tissue regeneration and embryo development, but are also associated with pathological conditions, such as arthritis, atherosclerosis and autoimmune blistering disorders of the skin. There is also growing evidence suggesting that MMPs can degrade various components of the extracellular matrix and are involved in cancer development by modulating cell proliferation, apoptosis, angiogenesis, and so on (Li et al., 2006; Singh et al., 2008).

MMP7, localised on chromosome 11q21-q22, is one of the smallest members of the MMPs family, which can degrade elastin, proteogylcans, fibronectin and type IV collagen. It also cleaves non-matrix substrates from the cell surface, such as E-cadherin, pro-tumour necrosis factor and Fas ligand. An A to G transition at -181 base pair position upstream of the transcription start site of MMP7 gene has been reported. The G allele has greater basal transcriptional activity than A allele in vitro experiment (Jormsjo et al., 2001). Over-expression of MMP7 has been shown to occur in a wide variety of cancers, including tumours of the oesophagus, stomach, colorectal, kidney and breast (Greenwald et al., 2002; Hodi et al., 2003), and this is correlated with tumor size, lymph node involvement and decreased survival.

Recently, Many studies indicating that the common MMP-7 (-181A>G) genetic polymorphism was correlated with cancer risk in many cancer types (Ghilardi et al., 2003; Zhang et al., 2005; Lievre et al., 2006; Kubben et al., 2006; Vairaktaris et al., 2007; Woo et al., 2007; Li et al., 2008; Sugimoto et al., 2008; Qiu et al., 2008; de Lima et al., 2009; Ohtani et al., 2009; Fang et al., 2010; Dziki et al., 2011; Kim et al., 2011; Malik et al., 2011; Malik et al., 2011). However, this relationship remains controversial in digestive system cancer, this meta-analysis was performed to evaluate the association between the MMP-7 (-181A>G) genetic polymorphism and cancer risk.

*Department of General Surgery, Xiang-Ya 2nd Hospital, Central South University, Chang-Sha, Hunan, China *For correspondence: lgqonline@126.com*

Table 1. Main Characteristics of Included Studies in the Meta-analysis

Author	Year	Cancer type	Country	Ethnicity	Genotype assay	Source of Control	Case/Control	$P^{\ddagger}$
Zhang	2005	Gastric	China	Asian	PCR-RFLP	Population	201/350	Yes
Kim	2011	Gastric	Korea	Asian	PCR-RFLP	Hospital	153/326	Yes
Malik	2011	Gastric	India	Asian	PCR-RFLP	Population	108/195	Yes
Sugimoto	2008	Gastric	Japan	Asian	PCR-RFLP	Hospital	160/434	Yes
Kubben	2006	Gastric	Holland	European	PCR-RFLP	Population	79/169	Yes
Li	2008	Gastric	China	Asian	PCR-RFLP	Population	338/380	Yes
Zhang	2005	ESCC	China	Asian	PCR-RFLP	Population	258/350	Yes
Malik	2011	ESCC	India	Asian	PCR-RFLP	Population	135/195	Yes
Lievre	2006	Colorectal	France	European	Tagman	Population	596/565	Yes
Dziki	2011	Colorectal	Poland	European	PCR-RFLP	Hospital	184/205	Yes
Ohtani	2009	Colorectal	Japan	Asian	PCR-RFLP	Hospital	119/67	Yes
Ghilardi	2003	Colorectal	Italy	European	Sequencing	Population	58/111	Yes
Woo	2007	Colorectal	Korea	Asian	PCR-RFLP	Population	185/304	Yes
Fang	2010	Colorectal	China	Asian	PCR-RFLP	Population	252/237	Yes
de Lima	2009	Colorectal	Brazil	South America	PCR-RFLP	Hospital	108/113	Yes
Vairaktaris	2007	Oral	Germany, Greek	European	PCR-RFLP	Population	159/120	No
Qiu	2008	Hepatocellular	China	Asian	PCR-RFLP	Population	425/475	Yes

$^{\ddagger}P$ value of Hardy-Weinberg equilibrium in controls; ESCC, esophageal squamous cell carcinoma

Table 2. Results of Meta-analysis for MMP-7 (-181A>G) Polymorphism and Digestive Cancer Risks

Study groups	N *	GG vs. AA		GA vs. AA		GG/GA vs. AA		GG vs. GA/AA	
		OR (95% CI)	$P_{\$}$	OR (95% CI)	$P_{\$}$	OR (95% CI)	$P_{\$}$	OR (95% CI)	$P_{\$}$
Total	17	1.21(1.12-1.60)‡	<0.001	1.06 (0.99-1.36)	0.536	1.16 (1.03-1.46)‡	<0.001	1.12 (0.95-1.31)‡	<0.001
Cancer type									
Hepatocellular	1	1.43 (1.10-1.87)	0.851	1.29 (0.99-1.68)	0.771	1.36 (0.92-1.75)	0.796	1.17 (0.96-1.37)	0.92
Gastric	6	1.22 (1.02-1.46)	0.523	1.82 (1.16-2.87)	0.704	1.13 (1.01-1.26)	0.711	1.25 (1.06 -2.39)	0.642
Colorectal	7	1.13 (1.01-1.26)‡	0.02	0.805 (0.50-1.30)‡	0.006	0.86 (0.54-1.35)‡	0.006	1.08 (0.80- 1.45)	0.215
Esophagus	2	1.00 (0.24-4.30)‡	<0.001	1.45 (1.11-1.91)	0.146	1.19 (0.48-2.96)‡	0.002	0.81 (0.27-2.39)‡	<0.001
Oral	1	0.73 (0.38-1.39)	0.312	1.09 (0.26 -4.55)‡	0.013	1.012 (0.30-3.45)‡	0.026	0.88 (0.56-1.36)	0.478
Ethnicity									
Asian	12	1.40 (1.12- 1.69)‡	<0.001	1.26 (1.02- 1.51)‡	<0.001	1.18 (1.08-1.55)‡	<0.001	1.14 (0.96 -1.36)‡	<0.001
European	5	1.13 (0.60-1.97)‡	0.07	0.98 (0.69-1.37)‡	0.07	1.11 (0.76-1.52)‡	0.029	1.01 (0.73 -1.51)	0.154
Source of Control									
Population-based	5	1.19 (0.91 -1.90)‡	<0.001	1.16 (1.08-1.50)‡	0.029	1.10 (1.01-1.72)‡	<0.001	0.95 (0.68-1.73)‡	<0.001
Hospital-based	12	1.25 (1.01 -1.74)‡	0.001	1.15 (0.88- 1.50)‡	<0.001	1.14 (0.84-1.54)‡	<0.001	0.97 (0.82 -1.39)	0.15

CI, confidence interval; OR, odds ratio; *Studies of comparison; $^{\$}P$-value of Q-test for heterogeneity test; ‡Random model was used

Materials and Methods

Search strategy and data extraction

In this analysis, a literature research of the Pub Med database, ISI Web of Knowledge, Medline, Embase and Google Scholar Search (up to date as of October, 2012) were conducted using the search terms including (''MMP7'' or ''matrix metalloproteinase 7''), ''polymorphisms'' , ''cancer'', to obtain all genetic studies on the relationship of MMP-7 (-181A>G) polymorphism and cancer. We also used the combined phrases and a hand search of references of original studies on this topic.

Data extraction was carried out independently by two investigators. We record the following information of each eligible study: the first author, year of publication, country of origin, genotyping methods, source of controls, number of cases and controls with different groups.

Statistical analysis

The strength of relationship between MMP-7 (-181A>G) polymorphism and cancer was assessed by using Crude OR with 95% CI. We examined the association between the MMP-7 (-181A>G) polymorphism and digestive cancer risk using homozygote comparison (GG vs. AA), heterozygote comparison (GA vs. AA), dominant genetic model (GG + GA vs. AA) and recessive genetic model (GG vs. GA + AA). Between-study heterogeneity was evaluated by Q-test. Fixed effects model was used to pool the data when the P-value of Q-test ≥ 0.05, otherwise, random-effects model was selected. Egger's test was used to assess the publication bias. ($P<0.10$ was considered representative of statistical significance). All statistical analyses were performed using STATA11.0 software and Review Manage (v.5; Oxford, England).

Results

Eligible studies

The main characteristics of these studies are shown in Table 1. Genotype distribution of the MMP-7 (-181A>G) polymorphism among cancer cases and controls of the 16 studies are shown in Table 2. The genotyping method contains the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, DNA sequencing, Affymetrix and Taqman. Among all the studies, seven colorectal cancer studies, six gastric cancer studies, two esophageal squamous cell carcinoma studies, one oral carcinoma and one hepatocellular carcinoma

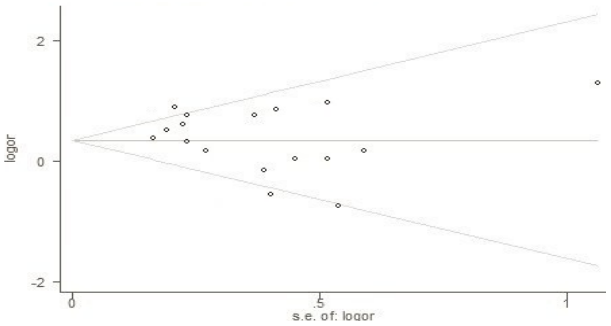

Figure 1. Beggs Funnel Plot with 95% Confidence Limits

were included. Twelve studies were Asian descent, four studies were Caucasian descent and one study was South America descent. Hospital based controls were carried out in 5 studies, while population based controls were carried out in twelve studies.

Meta-analysis

Overall, as shown in Table 2, we observed that the MMP-7 (-181A>G) polymorphism increased the digestive system cancer risk in homozygote comparison (GG vs. AA, OR=1.21, 95% CI = 1.12-1.60) and dominant model (GG/GA vs. AA, OR=1.16, 95% CI =1.03-1.46) 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 elevates gastric cancer risk in all the four models (GG vs. AA, OR =1.22, 95% CI=1.02-1.46; GA vs. AA, OR=1.82, 95% CI=1.16-2.87; GG/AG vs. AA, OR=1.13, 95% CI=1.01-1.26; GG/AG vs. AA, OR=1.25, 95% CI=1.06-2.39; Furthermore, we found significant association of MMP-7 (-181A>G) polymorphism with ESCC and colorectal cancer in heterozygote comparison (GA vs. AA, OR=1.45, 95% CI=1.11-1.91) and homozygote comparison (GG vs. AA, OR=1.13, 95% CI=1.01-1.26) respectively. Compared with gastric cancer, ESCC and colorectal cancer, no significant associations were found in oral carcinoma and hepatocellular carcinoma.

We then evaluated the effects of the MMP-7 (-181A>G) polymorphism according to different ethnicities and different source of control. As shown in Table 2, in the stratified analysis by ethnicity, a significantly increased risk was found among Asian populations in heterozygote model (GA vs. AA, OR=1.26, 95% CI=1.02-1.51), homozygote model (GG vs. AA, OR=1.40, 95% CI=1.12-1.69), and dominant model (GG/AG vs. AA, OR=1.18, 95% CI=1.08-1.55). According to source of controls, significant effects were observed in population-based studies (GA vs. AA, OR=1.16, 95% CI=1.08-1.50,GG/AA vs. GG, OR=1.10, 95% CI=1.01-1.72).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis (Figure 1 shows the funnel plot of overall GG vs. AA). Then Egger's test was performed to assess the publication bias of the literature. The results did not present any obvious evidence of publication bias in the subgroup analyses: for GG vs. AA *P*=0.58, GA vs. AA P=0.87, GG+GA vs. AA *p*=0.68, GG vs. GA+AA *P*=0.72.

Discussion

The result of this meta-analysis involving 3,518 cases and 4,596 controls suggested that the MMP-7 -181A/G polymorphism was overall significantly associated with digestive system cancer risk, especially in Asian population.

Recently, Malik et al. (2011) conducted one study indicating that individuals who living in the Kashmir Valley carrying -181 GG genotype were related to high risk of gastric cancer. Besides, Ghilardi et al. (2003) observed the -181A/G polymorphism was associated with increased risk of colorectal cancer development. However, Peng et al. (2010) performed a meta-analysis and suggested the association between MMP7 -181 A>G and increased cancer risk was found in the gastric cancer subgroup, no significant difference was found for colorectal cancer.

In this meta-analysis, significant association was found between the MMP7 -181 A>G polymorphism and risk of gastric cancer. Besides, the association was more significant in the recessive model compared with the dominant model. Functional analysis in vitro has shown that nuclear proteins bind with higher affinity to the -181 G allele than to the -181 A allele and promoter activity variation of the -181G allele was about 2-3 times than that of the -181 A allele, which may induce elevation of the protein expression, so individuals with GG genotype could have a higher risk of the gastric cancer than with GA genotype. For ESCC and colorectal cancer, the significant associations were just found in the dominant model and homozygote model respectively. We also found Asians with GG genotype had higher risk of cancer compared to Caucasians. Several factors such as environmental factors and different genetic backgrounds might contribute to the difference. Furthermore, inconsistent results were observed between hospital-based studies and population-based studies. Controls in population-based studies were more representative of general population than controls from hospital-based studies.

As in all research, our study has limitations. First, the controls were not uniformly defined. Second, studies involved in different ethnicities are warranted to estimate the effects of this functional polymorphism on digestive system cancer risk. Third, due to the original data of the eligible studies are not available. It is difficult to evaluate the roles of diet, alcohol consumption, and smoking status in digestive cancer development.

In conclusion, our meta-analysis suggested that the MMP7 -181 A>G polymorphism may be a risk factor in digestive system cancer development, especially among Asian population. Large well-designed studies are needed to validate our findings in the future.

Acknowledgements

The author(s) declare that they have no competing interests.

References

Bo P, Lihuan C, Xiaopin M, et al (2010). Meta-analysis of association between matrix metalloproteinases 2, 7 and 9 promoter polymorphisms and cancer risk. *Mutagenesis*, **25**, 371-9.

de Lima JM, de Souza LG, da Silva ID, et al (2009). E-cadherin and metalloproteinase-1 and -7 polymorphisms in colorectal cancer. *Int J Biol Markers*, **24**, 99-106.

Dziki L, Przybylowska K, Majsterek I, et al (2011). A/G Polymorphism of the MMP-7 Gene Promoter Region in Colorectal Cancer. *Pol Przegl Chir*, **83**, 622-6.

Fang W-L, Liang W-B, He H, et al (2010). Association of Matrix Metalloproteinases 1, 7, and 9 Gene Polymorphisms with Genetic Susceptibility to Colorectal Carcinoma in a Han Chinese Population. *DNA Cell Biol*, **29**, 657-61.

Ghilardi G, Biondi ML, Erario M, et al (2003). Colorectal carcinoma susceptibility and metastases are associated with matrix metalloproteinase-7 promoter polymorphisms. *Clin Chem* ,**49**, 1940-2.

Greenwald RJ, Oosterwegel MA, van der Woude D, et al (2002). CTLA-4 regulates cell cycle progression during a primary immune response. *Eur J Immunol*, **32**, 366-73.

Hodi FS, Mihm MC, Soiffer RJ, et al (2003). Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Natl Acad Sci USA*, **100**, 4712-17.

Jormsjo S, Whatling C, Walter DH, et al (2001). Allele specific regulation of matrix metalloproteinase-7 promoter activity is associated with coronary artery luminal dimensions among hypercholesterolemic patients. *Arterioscler Thromb Vasc Biol,* **21**, 1834-39.

Kim JH, Pyun JA, Lee KJ, et al (2011). [Study on association between single nucleotide polymorphisms of MMP7, MMP8, MMP9 genes and development of gastric cancer and lymph node metastasis]. *Korean J Gastroenterol*, **58**, 245-51.

Kubben FJGM, Sier CFM, Meijer MJW, et al (2006). Clinical impact of MMP and TIMP gene polymorphisms in gastric cancer. *Br J Cancer*, **95**, 744-51.

Li JY, Tian MM, Zhao AL (2008). Polymorphism in the promoter region of the metalloproteinase-7 increases susceptibility and risk of metastasis of gastric adenocarcinoma. *Gastroenterology*, **134**, A603.

Li Y, Jin X, Kang S, et al (2006). Polymorphisms in the promoter regions of the matrix metalloproteinases-1, -3, -7, and -9 and the risk of epithelial ovarian cancer in China. *Gynecol Oncol*, **101**, 92-6.

Lievre A, Milet J, Carayol J, et al (2006). Genetic polymorphisms of MMP1, MMP3 and MMP7 gene promoter and risk of colorectal adenoma. *BMC Cancer*, **6**, 270.

Malik MA, Sharma KL, Zargar SA, et al (2011). Association of matrix metalloproteinase-7 (-181A>G) polymorphism with risk of esophageal squamous cell carcinoma in Kashmir Valley. *Saudi J Gastroenterol*, **17**, 301-6.

Malik MA, Zargar SA, Mittal B (2011). Role of the metalloproteinase-7 (181A>G) polymorphism in gastric cancer susceptibility: a case control study in Kashmir valley. *Asian Pac J Cancer Prev*, **12**, 73-6.

Ohtani H, Maeda N, Murawaki Y (2009). Functional polymorphisms in the promoter regions of matrix metalloproteinase-2,-3,-7,-9 and TNF- alpha genes, and the risk of colorectal neoplasm in Japanese. *Yonago Acta Medica*, **52**,47-56

Qiu W, Zhou G, Zhai Y, et al (2008). No association of MMP-7, MMP-8, and MMP-21 polymorphisms with the risk of hepatocellular carcinoma in a Chinese population. *Cancer Epidemiol Biomarkers Prev*, **17**, 2514-8.

Singh H, Jain M, Mittal B (2008). MMP-7 (–181A>G) promoter polymorphisms and risk for cervical cancer. *Gynecol Oncol*, **110**, 71-5.

Sugimoto M, Furuta T, Kodaira C, et al (2008). Polymorphisms of matrix metalloproteinase-7 and chymase are associated with susceptibility to and progression of gastric cancer in Japan. *J Gastroenterol*, **43**,751-61.

Vairaktaris E, Serefoglou Z, Yapijakis C, et al (2007). High gene expression of matrix metalloproteinase-7 is associated with early stages of oral cancer. *Anticancer Res*, **27**, 2493-8.

Woo M, Park K, Nam J, et al (2007). Clinical implications of matrix metalloproteinase-1, -3, -7, -9, -12, and plasminogen activator inhibitor-1 gene polymorphisms in colorectal cancer. *J Gastroenterol Hepatol*, **22**, 1064-70.

Wu S, Lu S, Tao H, et al (2011). Correlation of polymorphism of IL-8 and MMP-7 with occurrence and lymph node metastasis of early stage cervical cancer. *J Huazhong Univ Sci Technol*, **31**, 114-9.

Zhang J (2005). The functional polymorphism in the matrix metalloproteinase-7 promoter increases susceptibility to esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma and non-small cell lung carcinoma. *Carcinogenesis*, **26**, 1748-53.