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EDITORIAL

Single-nucleotide polymorphisms of matrix metalloproteinases and their inhibitors in gastrointestinal cancer

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Abstract

Matrix metalloproteinases (MMPs) are implicated in cancer development and progression and are associated with prognosis. Single-nucleotide polymorphisms (SNPs) of MMPs, most frequently located in the promoter region of the genes, have been shown to influence cancer susceptibility and/or progression. SNPs of MMP-1, -2, -3, -7, -8, -9, -12, -13 and -21 and of the tissue inhibitor of metalloproteinases (TIMPs) TIMP-1 and TIMP-2 have been studied in digestive tract tumors. The contribution of these polymorphisms to the cancer risk and prognosis of gastrointestinal tumors are reviewed in this paper.

Key words: Matrix metalloproteinase; Tissue inhibitor of metalloproteinase; Single nucleotide polymorphism; Promoter region; Digestive tract; Cancer

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INTRODUCTION

The matrix metalloproteinases (MMPs) belong to a metzincin superfamily of zinc-containing proteinases. Other members of this superfamily are the ADAM (a disintegrin and metalloproteinase) family and the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family, which have also been reported to be implicated in cancer progression[1,2]. MMP as well as ADAM/ADAMTS family members are inhibited by tissue inhibitors of metalloproteinases(TIMP)s. RECK (reversion-inducing, cysteine-rich protein with Kazal motifs) is a membrane-anchored inhibitor of MMPs and ADAMs[3]. Even though ADAM, ADAMTS, and RECK are closely related to the MMPs and TIMPs, their single-nucleotide polymorphisms (SNPs) in gastrointestinal cancer have not yet been studied and are therefore not included in this review.

MMPs have proven to be of relevance for cancer development and prognosis in various organ systems. The 23 members of this family of endopeptidases all share a catalytic domain, a pro-peptide and a hemopexin-like C-terminal domain. According to their structure and major function or substrates, the MMPs are subdivided in the following subgroups: collagenases (MMP-1, -8 and -13), stromelysins (MMP-3, -10 and -11), matrilysins (MMP-7 and -26), gelatinases (MMP-2 and -9), membrane-type MT-MMPs (MMP-14, -15, -16, -17, -24 and -25), and others[4-6]. The most firmly established function of MMPs is the degradation/remodeling of extracellular matrix. By cleavage of receptors and their ligands they also influence various growth and signaling pathways in normal and pathological

conditions[6]. In cancer, MMPs are involved in angiogenesis by regulating the bio-availability of vascular endothelial growth factor (VEGF) (e.g. MMP-9) and the cleavage of matrix-bound VEGF (MMPs -3, -7, -9 and -16)[7]. On the other hand, cleavage of plasminogen by MMP-2, -9 and -12 leads to the production of angiostatin, an inhibitor of angiogenesis[8,9]. Furthermore, MMPs have been suggested to interfere in the balance between growth signals and growth-inhibiting signals [e.g. by modulating the transforming growth factor-β (TGF-β) pathway and activation of the epidermal growth factor (EGF) receptor], to regulate the induction of apoptosis by cleavage of Fas ligand (by MMP-7), to play a role in the creation of a metastatic niche (MMP-3, -9 and -10), and to control inflammation (MMP-2, -3, -7, -8, -9, -12) and invasive processes (MMP-1, -2, -3, -7, -13 and -14), see Figure 1[6,10]. It has become increasingly clear that MMPs are not always detrimental since they also show anti-tumor effects, as illustrated by the inhibiting effects on angiogenesis described before[11]. MMPs are secreted as inactive pro-enzymes that need activation to exert their proteolytic properties. Their actions can be counteracted by specific inhibitors, i.e. the TIMPs.

Single-Nucleotide Polymorphism is the most common type of genetic variation. The estimated number of SNPs in the human genome is 10 million, but only a small part of these polymorphisms are functionally relevant. Most of the functional SNPs are located in the promoter region of the gene and are therefore expected to influence gene expression (Table 1)[12-30]. In this paper, we review the association of SNPs in the MMP and TIMP genes with the risk, the phenotype, and prognosis of gastrointestinal tumors.

LITERATURE SEARCHE

Data sources

Electronic literature searches using PubMed, Embase and Web of Science were used to identify published papers concerning SNPs of MMPs, TIMPs, ADAMs, ADAMTS and RECK in gastrointestinal cancer up to September 2010. Search terms used included the MeSH heading "digestive system neoplasm" as well as all different types of gastrointestinal tumors mentioned separately, in combination with the MeSH heading "matrix metalloproteinases", as well as all individual MMPs mentioned separately, combined with the MeSH heading "polymorphism, genetic" or synonyms of the term SNP. Papers were included when written in English or in any other language, provided that an English abstract was available. Full papers, as well as letters and abstracts, were included in this review. Publications concerning *in vitro* or animal studies only were excluded. Results are arranged by tumor type.

Software

To generate the forest plot, IBM SPSS statistics 17.0 was used.

ESOPHAGEAL CANCER

The incidence of esophageal cancer shows great geographical variation. This tumor is more common in Southern Africa and Eastern Asia than in Europe and Northern America (source: GLOBOCAN; http://globocan.iarc.fr). In the Asian population almost all cases of esophageal cancer are squamous cell cancers, whereas in the Western world adenocarcinoma occurs more often and its incidence has risen over recent decades. Because the pathophysiology and risk factors of squamous cell cancer and adenocarcinoma are different, we will discuss these two tumor types separately. An overview of the studies included in this paragraph is shown in Table 2[31].

ESOPHAGEAL ADENOCARCINOMA

Only two papers describe the relationship between polymorphisms of MMPs and esophageal adenocarcinoma (EA). One of these studies focused on the protective effect of *Helicobacter pylori* (*H. pylori*) infection in patients with different genotypes of MMP-1 (-1607 1G/2G), MMP-2 (-1306 C/T), MMP-3 (-1171 6A/5A) and MMP-12 (-82 A/G)[32]. In individuals with an MMP-2-1306 CC (wild-type) genotype, *H. pylori* infection (at any time during life) strongly protects against EA [adjusted odds ratio (OR) 0.29, 95% confidence interval (CI) 0.1-0.7]. In persons with a CT or TT genotype, the esophageal cancer risk was not influenced by *H. pylori* infection. To a lesser extent, the protective effect of *H. pylori* infection on the development of EA was also seen in carriers of the MMP-3 wild-type (6A/6A) and MMP-12 wild-type (-82 AA). However, no association between any of the studied MMP polymorphisms and overall risk of EA was found. The second paper, published by the same group, investigated the polymorphisms of MMP-1 (-1607 1G/2G), MMP-3 (6A/5A), and MMP-12 (-82 A/G) in relation to the risk and overall survival of EA[33]. In a cohort of 313 cancer patients and 455 controls, they found an increased cancer risk in 2G-allele carriers of the MMP-1 -1607 1G/2G polymorphism [2G/2G *vs* 1G/1G: adjusted OR 1.83 (95% CI: 1.2-2.8), $P = 0.005$]. 5A-allele carriers of the MMP-3 polymorphism also had an increased risk of developing EA in the same patient population (5A/5A *vs* 6A/6A, OR 1.61, 95% CI: 1.0-2.5, $P = 0.03$). The various genotypes of the MMP-12-82 A/G polymorphism were not associated with an EA risk. There was no difference in survival of the patients in relation to any of the above mentioned polymorphisms.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Matrix metalloproteinase-2 is overexpressed in esophageal squamous cell cancer (ESCC)[34-37]. There are two known functionally important SNPs in the promoter region of the MMP-2 gene, MMP-2-1306 C/T and MMP-2-735 C/T.

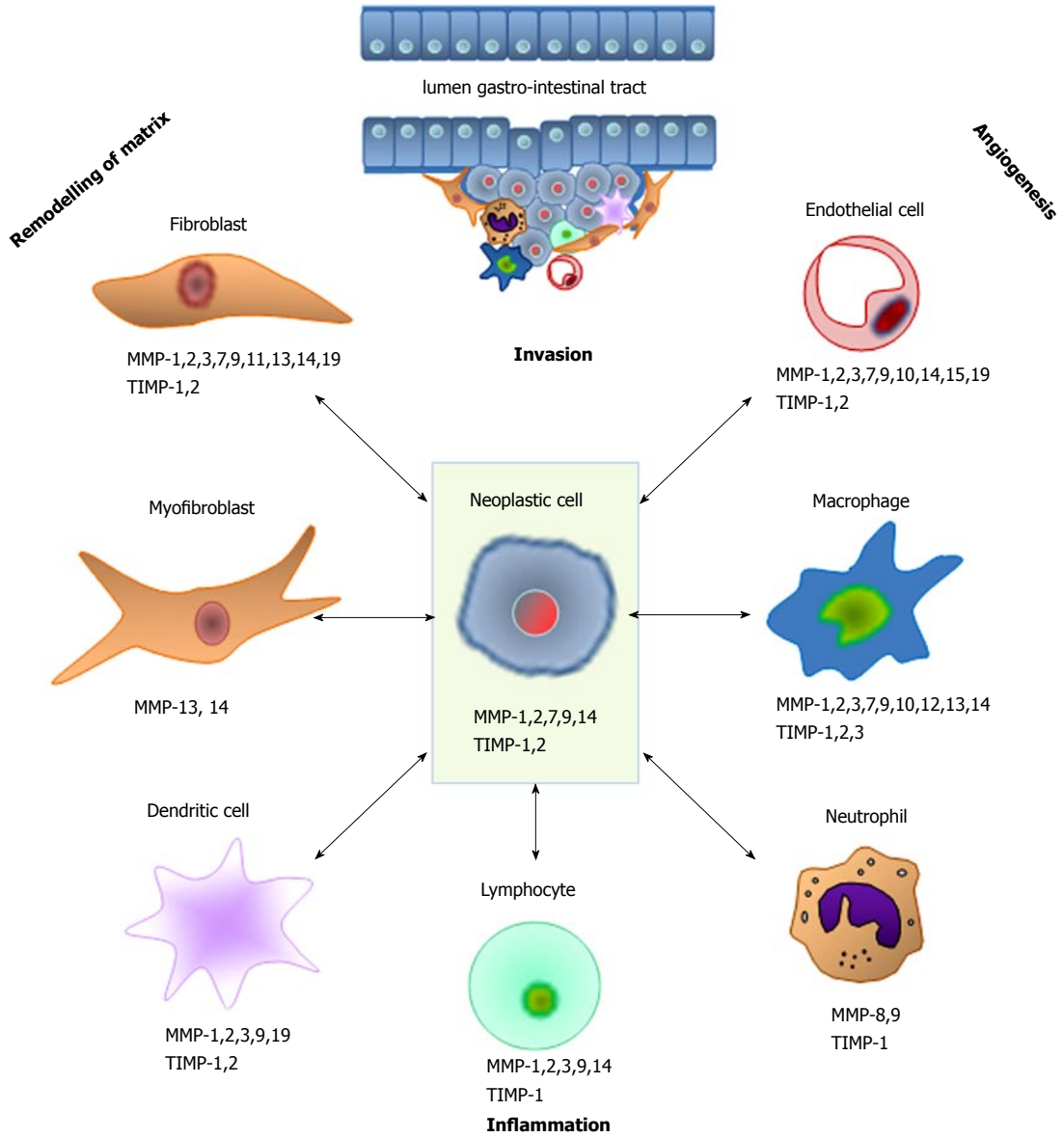

Figure 1 Schematic overview of the various types of matrix metalloproteinase-producing cells that are involved in the different processes during the various stages of cancer. MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase.

The C to T transition at the -1306 position disrupts a Sp-1 transcription factor binding site and thereby reduces promoter activity[22] (Table 1). The allele frequency of the minor (T) allele is significantly lower in the Asian population (13.6%) than in the European population (23.3%)[38]. Increased risk of developing ESCC in individuals with -1306 CC genotype (compared to CT+TT genotype) has been reported in two large cohorts of Chinese patients (Figure 2)[15,39]. In Mongolian patients, the association between the different genotypes and incidence of ESCC did not reach statistical significance[40]. A recent meta-analysis showed that the -1306 CC genotype, which is the genotype with the highest transcriptional activity[22], is associated with an increased overall cancer risk and this association was maintained in the subgroup analysis of ESCC patients[38]. These findings suggest an important role for the MMP-2 -1306 C/T polymorphism in cancer development, which led us to the idea of plotting the results for this MMP-2 polymorphism derived from all the publications included in this review. Figure 2 illustrates that in gastrointestinal cancers the association between MMP-2 -1306 C/T polymorphism and cancer risk is not unidirectional.

The reports on the association of the MMP-2 -735 C/T polymorphism are more dispersed. T allele carriers of this polymorphism show a lower transcriptional activity[15], which could explain the trend towards increased cancer risk in CC carriers compared to CT+TT carriers, which was reported in a Chinese population (OR 1.30, 95% CI: 1.04-1.63, P =0.056)[15]. However, these results were not confirmed in another large Chinese cohort[39] and a Mongolian study even found the opposite, higher ESCC cancer risk in TT carriers compared to CC, OR = 4.82, 95% CI: 1.59-14.60[40].

No association between the different promoter polymorphisms of MMP-1 (-1607 C/T), MMP- 9 (-1562 C/T), MMP-12 (-82 A/G), MMP-13 (-77 A/G) or be-

Table 1 Effects of matrix metalloproteinases single nucleotide polymorphisms on promoter activity

MMP	SNP	Effect of mutation	Influence on promoter activity *in vitro*	Ref.
MMP-1	-1607 1G/2G	Extra Guanine (2G) creates a binding site for transcription factor Ets-1	Increased in 2G allele (4-fold)	Rutter *et al*[18]
MMP-2	-1306 C/T	C to T substitution disrupts Sp-1 binding site	Decreased in T-allele	Price *et al*[22]
MMP-2	-735 C/T	C to T substitution influences Sp-1 binding site	Decreased in T-allele	Yu *et al*[15]
MMP-2	-790 T/G	Three transcription factors[1] bind to T (but not G) allele sequence	Decreased in G allele[2]	Vasku *et al*[28]
MMP-2	-955 A/C	Unknown	Effect unclear	Price *et al*[22]
MMP-2	-1575 G/A	G to T substitution decreases estrogen receptor α binding	Decreased in A allele	Harendza *et al*[27]
MMP-3	-1171 5A/6A[3]	Transcription suppressor binds with higher affinity to 6A allele	Decreased in 6A allele (2-fold)	Ye *et al*[19]
MMP-3	Lys45Glu	Lys to Glu substitution in exon 2 of gene	Effect unclear	Ouyang *et al*[16]
MMP-7	-181 A/G	Nuclear proteins bind with higher affinity to G allele	Increased in G allele[4] (2- to 3- fold)	Jormsjö *et al*[17]
MMP-7	-153 C/T	T allele binds additional nuclear proteins compared with C allele affinity for proteins that bind to both alleles higher in C allele	Increased in T allele[4] (2- to 3- fold)	Jormsjö *et al*[17]
MMP-8	-799 C/T	Influences binding of transcription factor?	Increased in T allele[5]	Wang *et al*[23]
MMP-8	17 C/G	Influences binding of transcription factor?	Increased in G allele[5]	Wang *et al*[23]
MMP-9	-90 CA(n)	Number of repeats influences strength of nuclear binding	Increased in n = 21 *vs* n = 14, n = 18	Shimajiri *et al*[12]
MMP-9	-1562 C/T	C to T substitution disrupts nuclear protein binding site	Increased in T allele	Zhang *et al*[20]
MMP-9	R279Q	Arg to Gln substitution in fibronectin type II domains	Effect unclear[6]	Wu *et al*[13]
MMP-9	P574R	Pro to Arg substitution in hemopexin domain	Effect unclear[6]	Wu *et al*[13]
MMP-9	R668Q	Arg to Gln substitution in hemopexin domain	Effect unclear[6]	Wu *et al*[13]
MMP-12	-82 A/G	A to G substitution results in decreased affinity for transcription factor AP-1	Decreased in G allele	Jormsjö *et al*[21]
MMP-12	1082 A/G	Asn to Ser substitution at coding region of hemopexin domain	Effect unclear	Joos *et al*[25]
MMP-13	-77 A/G	A to G substitution results in decreased affinity for transcription factor AP-1	Decreased in G allele (2-fold)	Yoon *et al*[24]
MMP-21	C572T	Ala to Val substitution in enzymes catalytic domain	Effect unclear	Shagisultanova *et al*[29]
TIMP-1	372 C/T	Unknown, located in exon 5, no effect on transcription or amino-acid sequence	Effect unclear	Hinterseher *et al*[26]
TIMP-2	-418 G/C	G to C substitution results in disruption of Sp-1 binding site	Decreased in C allele[2]	Hirano *et al*[30]
TIMP-2	303C/T	Unknown, located in exon 3, no effect on transcription or amino-acid sequence	Effect unclear	Kubben *et al*[14]

[1]The three transcription factors are: GKLF (Gut-enriched Krueppel-like factor), S8 and Evi1 (ectopic viral integration site 1 encoded factor); [2]Not confirmed; [3]Formerly known as -1612 5A/6A; [4]Only in combination MMP-7 -181G/-153T; [5]Only in combination MMP-8 -799T/-381G/+17G, in cells resembling chorion cytotrophoblasts; [6]Probably influences substrate binding and inhibitor binding. MMP: Matrix metalloproteinase; SNP: Single-nucleotide polymorphisms; TIMP: Tissue inhibitor of metalloproteinase.

tween a polymorphism in the catalytic domain of MMP-9 (R279Q) or R668Q and the occurrence of ESCC has been found[13,39,41-43]. A polymorphism of MMP-3, located in the promoter region at position -1171 (5A/6A) was not associated with the overall risk of developing ESCC. However, the cancer risk was lower in smokers with a 6A/6A genotype (cancer risk 5A/6A *vs* 6A/6A: OR = 2.12, 95% CI: 1.16-3.90) and the risk of lymph node metastases was lower in 6A allele carriers (risk of lymph node metastases 5A/6A *vs* 6A/6A: OR = 2.24, 95% CI: 1.07-4.69)[44]. An increase in ESCC was also observed in AG and GG carriers of the MMP-7-181 A/G polymorphism (AG+GG *vs* AA: OR = 1.83, 95% CI: 1.12-2.99)[45]. MMP-7 is one of the smallest MMPs and has the capability of degrading a variety of extracellular matrix components, including elastin, type Ⅳ collagen, fibronectin, vitronectin, aggrecan and proteoglycans[46]. In various cancer types, including esophageal cancer, MMP-7 is over-expressed and associated with worse prognosis[47-49]. The G-allele of -181A/G is associated with higher basal transcriptional activity *in vitro*[17], which could explain the contribution of MMP-7 over-expression to prognosis.

In summary, the association between genotype and esophageal cancer susceptibility is most prominent for the MMP-2 -1306 C/T polymorphism with an increased risk of squamous cell cancer and an *H. pylori* protection against adenocarcinoma in the CC genotype carriers. In an Asian population, ESCC risk is increased in G-allele carriers of the MMP-7 -181 A/G polymorphism. No clear association was found between any of the investigated SNPs and disease progression or prognosis.

GASTRIC CANCER

Gastric cancer is the second largest cause of global cancer related mortality. The World Health Organization reported 803.000 deaths worldwide in 2004. There is a male preponderance and known risk factors are *H. pylori* infection and tobacco smoking[50]. Most of the data concerning polymorphisms of MMPs in gastric cancer concern the Asian population, reflecting the much higher incidence of gastric tumors in the Eastern world compared to Western Europe and the United States. Table 3 gives an overview of the studies discussed in this paragraph.

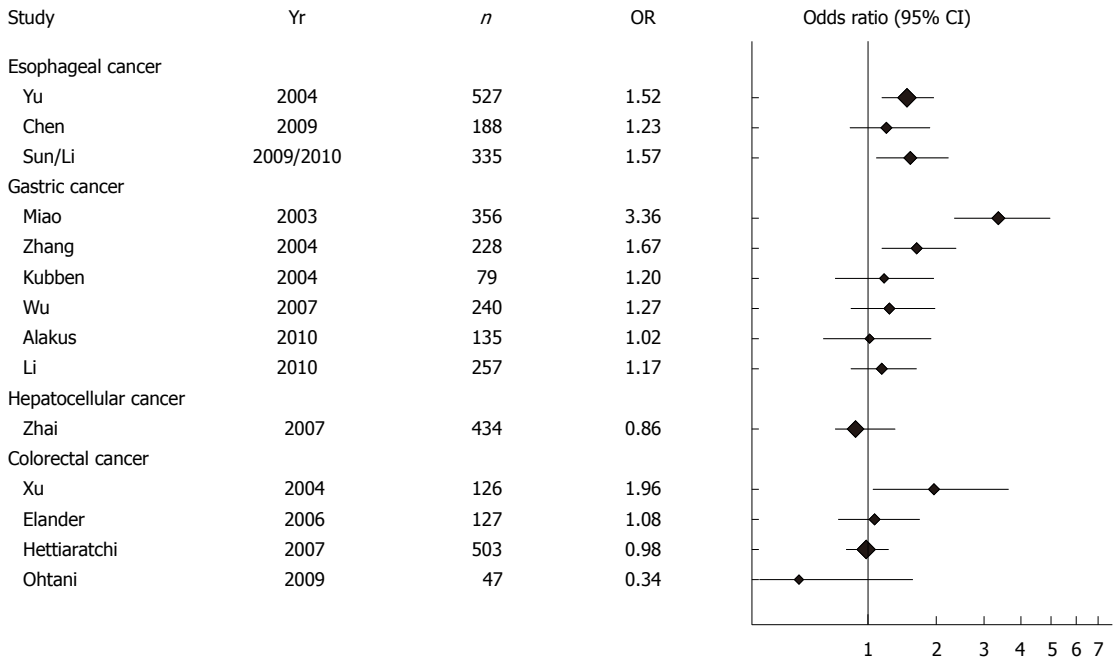

Figure 2 Forest plot of gastrointestinal cancer risk associated with the MMP-2 -1306 C/T polymorphism. Results are expressed as Odds ratios ± 95% confidence interval (CI) for CC *vs* CT+TT. The size of the diamonds indicates the size of the study cohort.

The gelatinases MMP-2 and MMP-9 are upregulated in gastric cancer and increased MMP-2 and MMP-9 protein levels in tumor tissue of gastric cancer patients are associated with poor prognosis[51,52]. Two papers reported a significant increase in gastric cancer risk in -1306 CC carriers of the MMP-2 SNP[53,54], while four other studies did not find such a correlation (Figure 2)[14,39,55,56]. In a recent meta-analysis, the MMP-2 -1306 CC genotype was associated with a significant increase in gastric cancer susceptibility[38], but this meta-analysis did not include two studies that reported no difference in cancer risk between the different genotypes[14,56]. Survival was not influenced by the -1306 C/T polymorphism in any of these studies. However, Wu *et al* detected an increase in lymphatic and venous invasion in individuals with a CC genotype[55]. A second functional polymorphism of MMP-2 is a C to T transition at position -735 in the promoter region of the gene. This substitution influences a Sp1 transcription factor binding site, resulting in lower promoter activity in T allele carriers[15], similar to the C to T transition at position -1306. There is a trend towards increased cancer risk in MMP-2-735 CC individuals, and this correlation is particularly significant in smokers.

The C to T substitution at position -1562 of the promoter region of MMP-9 results in the loss of binding to this region of a repressor nuclear protein, resulting in an increase in transcriptional activity in macrophages[20]. T-allele carriers of this polymorphism had deeper submucosal infiltration, more frequent lymphatic invasion and more advanced stage cancer compared to non-T allele carriers[57]. Nevertheless, none of the four publications describing the MMP-9 -1562 C/T polymorphism in gastric cancer found an association between the various genotypes and cancer risk[14,53,57,58]. In addition, Kubben *et al* did not find an association between the MMP-9 polymorphisms and tumor-related survival[14]. Two non-synonymous SNPs located in an exon of MMP-9, R279Q and P574R, were both associated with the risk of lymph node metastases in gastric cancer (higher risk in the RR and PP genotype, respectively), but did not show a relationship with gastric cancer risk[59].

MMP-7 over-expression has been demonstrated in various forms of cancer. In gastric cancer, MMP-7 expression has been linked to cancer progression and survival[60-62]. The genotype distribution of the -181 A/G polymorphism of MMP-7 is significantly different in various parts of the world; the frequency of the minor G-allele being 8.8% in the Asian population and 42.0% in the European population[38]. An increased risk of gastric cancer in G-allele carriers of the MMP-7 -181A/G polymorphism, who have a higher transcriptional activity, was reported in three studies[45,63,64]. These findings are in line with the observations in esophageal squamous cell cancers, as described above. Patients with the GG and AG genotype had a more advanced cancer stage. Interestingly, these findings are in contrast with two other papers, where either no correlation between the MMP-7 polymorphisms and gastric cancer risk was found[56] or there was even an inverse correlation, i.e. a higher percentage of MMP-7 -181 AA genotype in the gastric cancer group compared to the control group[14]. The discrepancy between these findings might be explained by a difference in ethnicity: in the first three papers all patients had an Asian background, whereas the latter two papers concern Caucasian patients.

The SNPs of MMP-1 (-1607 1G/2G), MMP-3 (-1171 5A/6A), MMP-7 (-153 C/T), MMP-8 (17 C/G) and MMP-8 (-799 C/T) are reported not to be associated with gastric cancer risk or prognosis[14,42,44,65]. Smokers with the

Table 2 Polymorphisms of tissue inhibitor of matrix metalloproteinases in esophageal cancer

Gene	SNP	Ref.	Cancer type	Ethnicity	Case/control	Outcome parameter	Results	Parameter OR	OR	95% CI	*P* value
MMP-1	-1607 1G/2G	Bradbury[33]	EA	Caucasian	313/455	Cancer risk	Increased cancer risk in 1G/2G and 2G/2G	2G/2G *vs* 1G/1G	1.83	1.2-2.8	0.005
						Overall survival	No difference in overall survival				
		Fruh[32]	EA	Caucasian	101/101	Cancer risk	No difference in cancer risk				
		Jin[42]	ESCC	Chinese	234/350	Cancer risk	No difference in cancer risk				
						LN metastases	No difference in LN metastases				
MMP-2	-735 C/T	Li[39]	ESCC	Chinese	335/624	Cancer risk	No difference in cancer risk				
		Yu[15]	ESCC	Chinese	527/777	Cancer risk	Increased cancer risk in CC (trend)	CC *vs* CT+TT	1.30	1.04-1.63	0.056
		Sun[31]	ESCC	Chinese	335/624	Cancer risk	No difference in cancer risk				
		Chen[40]	ESCC	Mongolian	188/324	Cancer risk	Increased cancer risk in TT	TT *vs* CC	4.82	1.59-14.60	
MMP-2	-1306 C/T	Fruh[32]	EA	Caucasian	101/101	Cancer risk	No difference in cancer risk				
						Cancer risk and HP	HP infection protects against EA in CC	CC *vs* CT+TT	0.29	0.1-0.7	
		Chen[40]	ESCC	Mongolian	188/324	Cancer risk	No difference in cancer risk				
		Li[39]	ESCC	Chinese	335/624	Cancer risk	Increased cancer risk in CC	CC *vs* CT+TT	1.57	1.10-2.23	0.010
		Yu[15]	ESCC	Chinese	527/777	Cancer risk	Increased cancer risk in CC	CC *vs* CT+TT	1.52	1.17-1.96	0.001
		Sun[31]	ESCC	Chinese	335/624	Cancer risk	Increased cancer risk in CC	CC *vs* CT+TT	1.57	1.10-2.23	
MMP-3	-1171 6A/5A	Bradbury[33]	EA	Caucasian	313/455	Cancer risk	Increased cancer risk in 6A/5A and 5A/5A	5A/5A *vs* 6A/6A	1.61	1.0-2.5	0.030
						Overall survival	No difference in overall survival				
		Fruh[32]	EA	Caucasian	101/101	Cancer risk	No difference in cancer risk				
						Cancer risk and HP	HP infection protects against EA in 6A/6A	6A/6A *vs* 5A/5A + 5A/6A	0.04	0.002-0.9	0.040
		Zhang[44]	ESCC	Chinese	234/350	Cancer risk	No difference in cancer risk				
						Cancer in smoker	Increased cancer risk in 5A allele in smokers	5A/5A + 5A/6A *vs* 6A/6A	1.95	1.08-3.53	
						LN metastases	Increased risk of LN metastases in 5A allele	5A/5A *vs* 6A/6A	2.24	1.07-4.69	0.030
						Infiltration depth	No difference in infiltration depth				
MMP-3	Lys45Glu	Ouyang[16]	ESCC	Chinese	227/378	Cancer risk	No difference in cancer risk				
MMP-7	-181 A/G	Zhang[45]	ESCC	Chinese	258/350	Cancer risk	Increased cancer risk in AG and GG	AG+GG *vs* AA	1.83	1.12-2.99	
						LN metastases	No difference in LN metastases				
MMP-9	R279Q	Wu[13]	ESCC	Chinese	132/132	Cancer risk	No difference in cancer risk				
MMP-9	P574R	Wu[13]	ESCC	Chinese	132/132	Cancer risk	Increased cancer risk in RR	RR *vs* PP	4.08	1.58-10.52	0.000
MMP-9	R668Q	Wu[13]	ESCC	Chinese	132/132	Cancer risk	No difference in cancer risk				
MMP-9	-1562 C/T	Xia[43]	ESCC	Chinese		Cancer risk	No difference in cancer risk				
MMP-12	-82 A/G	Bradbury[33]	EA	Caucasian	313/455	Cancer risk	No difference in cancer risk				
						Overall survival	No difference in overall survival				
		Fruh[32]	EA	Caucasian	101/101	Cancer risk	No difference in cancer risk				
						Cancer risk and HP	HP infection protects against EA in AA	AA *vs* AG/GG	0.44	0.2-0.8	0.020
MMP-12	1082 A/G	Bradbury[33]	EA	Caucasian	313/455	Cancer risk	No difference in cancer risk				
						Overall survival	No difference in overall survival				
MMP-12	-82 A/G	Li[39]	ESCC	Chinese	335/624	Cancer risk	No difference in cancer risk				
						Cancer risk	No difference in cancer risk				
MMP-13	-77 A/G	Zhang[41]	ESCC	Chinese	316/609	Cancer risk	No difference in cancer risk				

SNP: Single nucleotide polymorphism; EA: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; LN: Lymph node; HP: *Helicobacter pylori*; OR: Odds Ratio; 95% CI: 95% confidence interval.

Table 3 Polymorphisms of matrix metalloproteinases in hepatocellular carcinoma

Gene	SNP	Ref.	Cancer type	Ethnicity	Case/control	Outcome parameter	Results	Parameter OR	OR	95% CI	*P* value
MMP-1	-1607 1G/2G	Matsumura[65]	Gastric	Japanese	215/166	Cancer risk	No difference in cancer risk				
						Clinicopathol. par.	No correlation with any clinicopath. par.				
		Jin[42]	GCA	Chinese	183/350	Cancer risk	No difference in cancer risk				
						LN metastases	No difference in LN metastases				
MMP-2	-1306 C/T	Zhang[53]	Gastric	Chinese	228/774	Cancer risk	Increased cancer risk in CC	CC *vs* CT/TT	1.67	1.17-2.38	
		Wu[55]	Gastric	Taiwanese	240/283	Cancer risk	No difference in cancer risk				
						LN metastases	Increased risk of lymphatic invasion in CC	CC *vs* CT+TT	2.77	1.27-6.04	0.01
						Venous invasion	Increased risk of venous invasion in CC	CC *vs* CT+TT	2.93	1.27-6.78	0.012
						Survival	No difference in survival				
		Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
		Alakus[56]	Gastric	Caucasian	135/58	Cancer risk	No difference in cancer risk				
						MMP-2 protein expression	No correlation with protein expression				
						Overall survival	No difference in overall survival				
		Li[39]	GCA	Chinese	257/624	Cancer risk	No difference in cancer risk				
		Miao[54]	GCA	Chinese	356/789	Cancer risk	Increased cancer risk in CC	CC *vs* CT+TT	3.36	2.34-4.97	
						Distant metastases	No difference in metastases				
MMP-2	-735 C/T	Li[39]	GCA	Chinese	257/624	Cancer risk	Trend towards increased cancer risk in CC	CC *vs* CT+TT	1.36	0.99-1.87	0.06
						Cancer risk in non-smoker	Increased cancer risk in CC in non-smoker	CC *vs* CT+TT	1.7	1.07-2.68	0.02
MMP-3	-1171 6A/5A	Zhang[44]	GCA	Chinese	183/350	Cancer risk	No difference in cancer risk				
						Cancer risk in smoker	No difference in cancer risk in smoker				
						LN metastases	No difference in LN metastases				
						Infiltration depth	No difference in infiltration depth				
MMP-8	-799 C/T	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
MMP-7	-181 A/G	Sugimoto[63]	Gastric	Japanese	160/434	Cancer risk	Increased cancer risk in G-allele carriers	AG+GG *vs* AA	2.32	1.24-4.35	0.009
						Cancer stage	Increased cancer stage in G allele carriers	AG+GG *vs* AA	3.66	1.54-8.73	0.003
		Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	More AA and less AG in cancer group	AG+GG *vs* AA	0.50	0.28-0.87	< 0.04
						Tumor-related survival	No difference in tumor-related survival				
		Li[64]	Gastric	Chinese	338/380	Cancer risk	Increased cancer risk in G allele carriers	AG+GG *vs* AA	1.95	1.24-3.05	0.004
						LN metastases	Increased risk of LN metastases in G allele	AG+GG *vs* AA			0.040
						Cancer stage	More advanced cancer stage in G allele	AG+GG *vs* AA			0.007
		Alakus[56]	Gastric	Caucasian	135/58	Cancer risk	No difference in cancer risk	AG+GG *vs* AA	1.06	0.69-1.64	0.79
						Overall survival	No difference in overall survival				
		Zhang[45]	GCA	Chinese	201/350	Cancer risk	Increased cancer risk in G allele carriers	AG+GG *vs* AA	1.96	1.17-3.29	
						LN metastases	No difference in LN metastases				
MMP-7	-153 C/T	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
MMP-8	17 C/G	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
MMP-9	R279Q	Tang[59]	Gastric	Chinese	74/100	Cancer risk	No difference in cancer risk				
						LN metastases	Increased risk of LN metastases in RR	RR *vs* QQ+RQ	5.74	1.59-13.43	
MMP-9	P574R	Tang[59]	Gastric	Chinese	74/100	Cancer risk	No difference in cancer risk				
						LN metastases	Increased risk of LN metastases in PP	PP *vs* RR+PR	4.17	1.39-11.78	

MMP-9	-1562 C/T	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
		Matsumura[57]	Gastric	Japanese	177/224	Cancer risk	No difference in cancer risk				
						Infiltration depth	Deeper submucosal infiltration in T allele	CT+TT *vs* CC	2.61	1.07-6.34	0.034
						Lymphatic invasion	Increased lymphatic invasion in T allele	CT+TT *vs* CC	2.27	1.09-4.74	0.028
						TNM classification	More advanced stage cancer in T allele	CT+TT *vs* CC	2.26	1.12-4.55	0.022
						Venous invasion	No difference in venous invasion	CT+TT *vs* CC	1.98	0.99-3.97	0.053
		Zhang[53]	Gastric	Chinese	228/774	Cancer risk	No difference in cancer risk				
		Wu[58]	Gastric	Taiwanese	263/354	Cancer risk	No difference in cancer risk				
MMP-12	-82 A/G	Li[39]	GCA	Chinese	335/624	Cancer risk	No difference in cancer risk				
						Cancer risk in smoker	No difference in cancer risk in smoker				
MMP-13	-77 A/G	Li[39]	GCA	Chinese	257/624	Cancer risk	No difference in cancer risk				
						Cancer risk in smoker	Decreased cancer risk in AG in smoker	AG *vs* AA/AG	0.47	0.28-0.8	0.01
		Zhang[41]	GCA	Chinese	243/609	Cancer risk	No difference in cancer risk				
						Cancer risk in smoker	Decreased cancer risk in AG in smoker				
TIMP-1	372 C/T	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
TIMP-2	-418 G/C	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	No difference in tumor-related survival				
		Wu[55]	Gastric	Taiwanese	240/283	Cancer risk	No difference in cancer risk				
						LN metastases	Increased risk of LN metastases in GG	GG *vs* CG+GG	2.87	1.22-6.76	0.16
						Venous invasion	Increased venous invasion in GG	GG *vs* CG+GG	2.65	1.08-6.49	0.033
						Survival	No difference in survival				
		Yang[66]	Gastric	China	206/206	Cancer risk	More C-alleles in cancer patients	CC+CG *vs* GG	1.51	1.00-2.26	0.049
						Clinicopathol. par.	No correlation with any clinicopath. par.				
TIMP-2	303 C/T	Kubben[14]	Gastric	Caucasian	79/169	Cancer risk	No difference in cancer risk				
						Tumor-related survival	Better survival in CC patients	CC *vs* CT/TT	4.45	1.81-10.9	0.001
		Alakus[56]	Gastric	Caucasian	135/58	Cancer risk	No difference in cancer risk				
						LN metastases	More LN metastases in CC				0.01
						Distant metastases	Increased risk of distant metastases in CC				0.022
						Survival	No difference in survival				

SNP: Single nucleotide polymorphism; GCA: Gastric Cardia Adenocarcinoma; LN: Lymph node; OR: Odds ratio; 95% CI: 95% confidence interval; Clinicopath. par.: Clinicopathological parameters. [1]Except histological subtype.

AG genotype of the MMP-13 -77A/G polymorphism were reported to have a decreased risk of developing gastric cancer[39,41]. A trend towards increased cancer risk was observed in individuals with the AG genotype of the MMP-12 -82 A/G polymorphism[39,41].

One of the mechanisms that regulates MMP activity, in addition to promoter polymorphisms, is the interaction with TIMPs. The contribution of gene polymorphisms of TIMP-1 and TIMP-2 has only been studied sporadically in gastric cancer. The 372 C/T polymorphism of TIMP-1 did not correlate with cancer risk or cancer-related survival[14]. The G to C substitution at position -418 in the promoter region of the TIMP-2 gene has been suggested to disrupt a Sp-1 binding site, presumably leading to decreased TIMP-2 transcription[30]. Yang *et al*[66] studied this TIMP-2 polymorphism in a group of 206 gastric cancer patients and 206 controls. The gastric cancer risk was elevated in C-allele carriers (CC + GC *vs* GG, adjusted OR = 1.51, 95% CI: 1.00-2.26, $P = 0.049$). Two other papers that described the contribution of this polymorphism on gastric cancer occurrence, did not find an association between the different genotypes and cancer risk[14,55]. In a cohort of 240 Taiwanese gastric cancer patients, Wu *et al*[55] found increased lymph node metastases, increased serosal invasion and increased venous invasion in patients with the TIMP-2 GG genotype. Despite these results, neither in the Taiwanese study, nor in a Dutch study, was an association with survival reported[14,55]. The function of the 303C/T polymorphism of TIMP-2, located in exon 3 of the gene, is unclear. Both Kubben *et al*[14] and Alakus *et al*[56] found no correlation between genotype and gastric cancer risk. The finding in the study of Alakus *et al* that patients with the TIMP-2 303CC genotype more often have lymphatic and distant metastases seems to contradict with the findings of Kubben *et al*, who showed a significantly better tumor-related survival in patients with the CC genotype. This discrepancy could possibly be due to the low number of patients with a CT or TT genotype in both studies.

To conclude, an increased gastric cancer susceptibility seems to be present in Asian (but not in Caucasian) G-allele carriers of the MMP-7 -181 A/G polymorphism, an association also seen with ESCC. While some studies reported an association between genotype and clinicopathological parameters or prognosis, these results were not confirmed by others and are thus not consistent, except for the finding that MMP-7-181 AG or GG genotype patients in the Asian population seem to have a more advanced tumor stage than patients with the AA genotype[63,64].

SMALL INTESTINAL CANCER

Tumors of the duodenum, jejunum and ileum are rare and there are in fact no data on the effect of functional polymorphisms of matrix metalloproteinases in these tumors. Only one paper describes MMP-2, -7, -9, -11 and -13 protein levels in 25 patients with a carcinoid tumor localized in the ileum. Except for MMP-2, none of the MMP protein levels were associated with survival[67]. Surprisingly, low MMP-2 expression in the primary carcinoid tumor is correlated with an unfavorable outcome of the disease. This finding, which contrasts with observations made in many other gastrointestinal tumors, might indicate that these neuro-endocrine tumors have a different proteolytic phenotype compared to the other tumors which are adenocarcinomas or (in case of proximal or mid-esophageal cancers) squamous cell carcinomas.

PANCREATIC CANCER

Over-expression of MMP-1, MMP-2, MMP-7 and MMP-9 protein in pancreatic cancer is associated with more advanced tumor stage and poor prognosis[68-74], whereas high glandular TIMP-2 expression is associated with better survival in pancreatic ductal adenocarcinoma[75]. However, until now, there are no reports on the functional polymorphisms of MMPs and TIMPs in malignant tumors of the pancreas.

CHOLANGIOCARCINOMA

Bile duct tumors are rare in the general population. Patients with primary sclerosing cholangitis (PSC) have an increased risk of developing cholangiocarcinoma. Wiencke *et al*[76] investigated the association of MMP-1 and MMP-3 promoter polymorphisms in 165 PSC patients. Fifteen of these patients developed cholangiocarcinoma; all of these were 1G-allele carriers of the MMP-1 -1607 1G/2G polymorphism, compared to 72% of the whole PSC population. This finding is somewhat surprising since the 2G allele of this SNP is associated with a higher level of transcription and in most cancers, as for example esophageal adenocarcinomas, associated with increased cancer risk or worse prognosis. The number of PSC patients in this study was too small to draw definite conclusions about the role of this promoter-SNP in PSC-associated cholangiocarcinoma.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the eighth in women worldwide[77]. The geographic distribution of this most common form of primary liver cancer follows the distribution of hepatitis B and C infection, as most of the patients have a background of liver cirrhosis or hepatitis B-infection. Several studies have looked into the effect of single nucleotide polymorphisms of MMPs on the incidence of HCC and its relation to survival of the patients (Table 4). None of the MMP gene polymorphisms that have been studied in HCC patients is correlated with cancer risk. In one paper, the number of 2G/2G homozygotes of the MMP-1 -1607 1G/2G polymorphism was slightly increased in HCC patients with a background of chronic hepatitis C virus (HCV)-related liver disease compared to patients with HCV-related chronic liver disease with-

Table 4 Polymorphisms of matrix metalloproteinases in hepatocellular carcinoma

Gene	SNP	Ref.	Ethnicity	Case/control	Parameter	Results	Parameter OR	OR	95% CI	*P* value
MMP-1	-1607 1G/2G	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
		Okamoto[78]	Japanese	95/83	Cancer risk	Increased risk of HCC in 2G/2G				0.002
					Clinicopath. par.	No correlation with any clinicopath. par.				
					Survival	No difference in survival				
		Okamoto[79]	Japanese	92/170	Cancer risk	No difference in cancer risk				
					Survival/ clinicopath. par.	No difference in survival/ clinicopath. par.				
MMP-2	-735 C/T	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
					Cancer risk	No difference in cancer risk				
MMP-2	-1306 C/T	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
		Wu[82]	Chinese	93/0	HCC recurrence after LTx	More CC in recurrence group	CT *vs* CC	0.42	0.18-0.99	< 0.05
MMP-3	-1171 5A/6A	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
		Okamoto[78]	Japanese	95/83	Cancer risk	No difference in cancer risk				
					HCC diameter at diagnosis	Larger diameter in 5A allele carriers				
					Survival	Decreased survival in 5A allele carriers				
		Okamoto[79]	Japanese	92/170	Cancer risk	Increased cancer risk in 5A allele carriers				
					Survival/ clinicopath. par.	Decreased survival in 5A allele carriers				0.035
MMP-7	-181 A/G	Qiu[81]	Chinese	434/480	Cancer risk	No difference in cancer risk				
MMP-8	-799 C/T	Qiu[81]	Chinese	434/480	Cancer risk	No difference in cancer risk				
MMP-9	-1562 C/T	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
		Wu[82]	Chinese	93/0	HCC recurrence after LTx	No difference in HCC recurrence				
		Okamoto[78]	Japanese	95/83	Cancer risk	No difference in cancer risk				
					Differentiation grade	Differentiation worse in T allele carriers		0.03		
					Survival	No difference in survival				
		Okamoto[79]	Japanese	92/170	Cancer risk	No difference in cancer risk				
					Survival/ clinicopath. par.	No difference in survival/ clinicopath. par.				
MMP-12	-82 A/G	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
MMP-13	-77 A/G	Zhai[80]	Chinese	434/480	Cancer risk	No difference in cancer risk				
MMP-21	C572T	Qiu[81]	Chinese	434/480	Cancer risk	No difference in cancer risk				
TIMP-2	-418 G/C	Okamoto[83]]	Japanese	92/70	Cancer risk HCC	No difference in cancer risk				
					Survival	No difference in survival				

SNP: Single nucleotide polymorphism; LN: Lymph node; Clinicopath. par.: Clinicopathological parameters; OR: Odds ratio; 95% CI: 95% confidence interval; HCC: Hepatocellular carcinoma; LTx: Liver transplantation.

out HCC[78]. However, when the same patient group was compared with healthy controls, this relationship was no longer present[79]. In hepatitis B virus (HBV) patients with or without HCC, the genotype distribution of the MMP-1 -1607 polymorphism was similar[80]. No association was found between the MMP-2 -1306 C/T polymorphism and the risk of hepatocellular carcinoma[80], although patients with the CC genotype did experience an increase in HCC recurrence after liver transplantation compared to patients with the CT genotype (CT *vs* CC, OR = 0.42, 95% CI: 0.18-0.99, $P < 0.05$; there were no TT patients in the cohort). When compared with healthy controls, HCV-infected patients with HCC were more often 5A-allele carriers of the -1171 5A/6A polymorphism[79]. However, when compared to HCV infected patients without HCC, no difference in genotype distribution was found[78], which might suggest that the 5A-allele interferes with the development of the underlying disease instead of with the development of HCC. 5A allele carriers did have larger tumor diameters at the time of diagnosis and a poorer prognosis[78,79]. The SNPs MMP-2 -735 C/T, MMP-7 -181 A/G, MMP-8 -799C/T, MMP-9 -1562 C/T, MMP-12 -82 A/G, MMP-13 -77 A/G and MMP-21 C572T were found not to be associated with an increased risk of developing HCC[78-82]. One paper which describes the impact of the TIMP-2 -418 G/C polymorphism in a group of 92 HCC patients and 70 patients with chronic liver disease without signs of HCC found no association with HCC occurrence or prognosis[83].

In conclusion, polymorphisms of MMPs are not associated with HCC susceptibility. MMP-genotype may possibly influence the course of the disease in HCC patients, as HCV-infected HCC patients carrying the 5A allele of the MMP-3 -1171 5A/6A polymorphism appear

to have worse survival rates[78,79]. In addition, it has been reported that HCC recurrence after liver transplantation is increased in MMP-2 -1306 CC genotype carriers when compared to CT patients[82].

COLORECTAL CANCER

Worldwide, colorectal cancer (CRC) is the fourth most common cancer in men and the third most common cancer in women[84]. Continents with a high incidence of colorectal cancer include Europe and North America. The lowest incidence is found in Asia, Africa and South America. In Eastern Europe and Japan, CRC incidence has increased over recent years, probably due to a "Westernization" of lifestyle[84]. The effect of MMP polymorphisms on lung, breast and colorectal cancer has been reviewed previously by Decock *et al*[85]. The studies that are included in the present review are shown in Table 5.

MMP-1, an interstitial collagenase, degrades fibrillar collagens type Ⅰ, Ⅱ, Ⅲ, Ⅴ, Ⅸ, and Ⅹ, that form the most abundant class of extracellular matrix proteins in the interstitium[86]. The MMP-1 gene is located on chromosome 11q22. Insertion of an extra guanine (G) at the -1607 promoter position creates an Ets-1 transcription factor binding site (5'-GGA-3') leading to a significant increase in transcription activity in normal fibroblasts[18]. Both alleles are common in the general population; the allele frequency of the 2G allele is 64% in the Asian population and 52% in the European population[87]. In the Caucasian population, the frequency of the homozygote -1607 2G/2G polymorphism is about 30%. Several papers reported an increased colorectal cancer susceptibility in either 2G/2G homozygotes or 2G-allele carriers of the MMP-1 -1607 polymorphism[88-93]. However, a number of other studies found no association between cancer risk and MMP-1 genotype[94-98]. With exception of the studies of Fang *et al* and Hettiaratchi *et al*, all studies included a relatively small number of patients, which could explain the differences in results. Hettiaratchi *et al* included the largest cohort (503 Australian CRC patients, 471 controls) of all studies so far[96]. Besides the lack of association between the genotype and CRC susceptibility, in this cohort the 5-year survival was increased in 2G/2G homozygotes. All other studies, which have either looked at survival or correlation with clinicopathological parameters, showed that the 2G/2G genotype is either associated with worse survival[99], with unfavourable clinicopathological parameters, like increased risk of metastases at time of diagnosis[92], a higher number of affected lymph nodes[89], or with earlier distant metastases[88]. Patient selection could possibly account for this discrepancy, since Hettiaratchi *et al* only included patients who did not have synchronous metastases at the time of diagnosis, and the influence of MMP-1 on the cancer process may change during different stages of cancer progression. De Lima *et al* reported a higher risk of lymph node metastases in patients carrying a 1G-allele, although this association was not significant with a *P* value of 0.09[95]. In all the other abovementioned papers, no association of MMP-1 gene polymorphisms and clinicopathological parameters was found. In two meta-analyses, 2G-allele carriers showed a significantly increased risk of developing colorectal cancer when compared with homozygous 1G allele carriers[87,100]. However, the large cohort of Hettiaratchi *et al*[96] was not included in these meta-analyses and inclusion of this study might lead to loss of significance.

Lièvre *et al*[101] studied the influence of genetic polymorphisms in the MMP-1 (-1607 1G/2G) gene in 295 patients with large adenomas and 302 patients with small adenomas, the premalignant condition to colorectal cancer, and in 568 polyp-free controls. No difference was found in the genotype distribution between patients with large adenomas and patients with small adenomas or healthy controls.

In a population of 126 CRC patients and 126 healthy controls, Xu *et al*[102] found an increase in CRC susceptibility in patients with the CC genotype of the MMP-2 -1306 C/T polymorphism. These findings were not supported by Hettiaratchi *et al*[96], Elander *et al*[90] and Ohtani *et al*[103], who found no influence of the MMP-2 genotype on the colorectal cancer risk (Figure 2). Difference in ethnicity (Australian *vs* European *vs* Japanese) or sample size might be the underlying cause of this discrepancy. Two meta-analyses, both including the study of Xu *et al*, showed no association between the MMP-2 -1306 C/T polymorphism and colorectal cancer susceptibility[87,100]. Xu *et al*[104] also reported that patients with the CC genotype had more frequent serosa/adventitia involvement, while none of the other studies described any correlation with clinicopathological parameters or survival, except for the study of Langers *et al*, where the TT genotype was shown to be an indicator of poor 10-year survival[89-93,96,97,99,103,105]. In the Xu *et al*[104] cohort of 126 CRC patients and 126 control patients, two other polymorphisms of MMP-2 (-790 T/G, -955 A/C) were not associated with cancer susceptibility or infiltration depth, while GG genotype carriers of the MMP-2 -1575 G/A polymorphism had an increased risk of developing CRC and more frequent serosa or adventitia invasion compared to the other genotypes, similar to that with the -1306 CC genotype[102]. The similarity in these observations are probably because the MMP-2 -1575 G/A, -1306 C/T, -790 G/T and -735 C/T polymorphisms have been found to be in almost complete pair-wise linkage (dis)equilibrium[28].

The most frequently studied MMP-9 polymorphism is the C to T substitution at position -1562 of the promoter region, which increases transcriptional activity. In a population of 185 Korean colorectal cancer patients and 304 controls, individuals with the CC genotype had an increased risk for developing CRC (OR = 1.7, 95% CI: 1.04-2.66, $P = 0.033$)[89]. None of the other studies found similar results[90,103-107]. A meta-analysis that included the studies of Elander *et al*[90], Xu *et al*[104,107], Woo *et al*[89] and Xing *et al*[106] showed no significant association of the -1562 C/T MMP-9 polymorphism and colorectal cancer[100]. The same conclusion was reached in a sec-

Table 5 Polymorphisms of matrix metalloproteinases in colorectal cancer

Gene	SNP	Ref.	Ethnicity	Case/control	Parameter	Results	Parameter OR	OR	95% CI	*P* value
MMP-1	-1607 1G/2G	Ghilardi[92]	Caucasian	60/164	Cancer risk	Increased cancer risk in 2G/2G	2G/2G *vs* 1G/1G + 1G/2G	2.21	1.17-4.16	0.014
					Distant metastases	Increased risk of metastases in 2G/2G	2G/2G *vs* 1G/1G + 1G/2G	4.73	1.46-15.26	0.008
		Zinzindohoue[99]	Caucasian	201/0	Survival	Overall survival worse in 2G/2G	2G/2G *vs* 1G/1G	5.4	2.0-14.7	0.001
		Hettiaratchi[96]	Australian	503/471	Cancer risk	No difference in cancer risk				
					Survival	Increased survival in 2G/2G	2G/2G *vs* 1G/2G + 1G/1G	0.43	0.19-0.96	0.040
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Woo[89]	Korean	185/304	Cancer risk	Increased cancer risk in 2G/2G and G-allele	2G/2G in patients *vs* controls	1.8	1.23-2.64	0.044
					LN metastases	More often >10 LN in 2G/2G				
		Fang[94]	Chinese	237/252	Cancer risk	No difference in cancer risk				
		Xu[97]	Chinese	126/126	Cancer risk	No difference in cancer risk				
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Przybylowska[98]	Caucasian	33/52	Cancer risk	No difference in cancer risk				
		Hinoda[91]	Japanese	101/127	Cancer risk	Increased cancer risk in 2G/2G	2G/2G *vs* 1G/1G + 1G/2G	2.08	1.22-3.53	0.007
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Biondi[93]	Caucasian	63/164	Cancer risk	More 2G allele in cancer patients				< 0.08
		de Lima[95]	Brasilian	130/130	Cancer risk	No difference in cancer risk				
					Distant metastases	Increased risk of metastases in 1G allele (trend)				
					LN metastases	No difference in LN metastases				
		Elander[90]	Caucasian	127/208	Cancer risk	Increased cancer risk in 2G allele carriers	2G allele *vs* 1G allele	1.41	1.02-1.96	0.037
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Kouhkan[88]	Iranian	150/100	Cancer risk	Increased cancer risk in 2G/2G and G-allele				
					Distant metastases	Earlier metastases in 2G/2G				
MMP-2	-1306 C/T	Xu[102]	Chinese	126/126	Cancer risk	Increased cancer risk in CC	CC *vs* CT+TT	1.96	1.06-3.64	< 0.05
					Infiltration depth	More serosa/ adventitia involvement in CC	CC *vs* CT+TT			0.042
		Hettiaratchi[96]	Australian	503/471	Cancer risk	No difference in cancer risk				
					Survival	No difference in survival				
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Langers[105]	Caucasian	215/0	Survival	10 year survival worse in TT	CC/CT *vs* TT	1.4	1.02-1.91	0.038

		Ohtani[103]	Japanese	47/67	Cancer risk	No difference in cancer risk				
		Elander[90]	Caucasian	127/208	Cancer risk	No difference in cancer risk				
					Clinicopath. par.	No correlation with any clinicopath. par.				
MMP-2	-790 T/G	Xu[104]	Chinese	126/126	Cancer risk	No difference in cancer risk				
					Infiltration depth	No difference in infiltration depth				
MMP-2	-955 A/C	Xu[104]	Chinese	126/126	Cancer risk	No difference in cancer risk				
					Infiltration depth	No difference in infiltration depth				
MMP-2	-1575 G/A	Xu[104]	Chinese	126/126	Cancer risk	Increased cancer risk in GG and G allele	GG *vs* GA+AA	1.96	1.06-3.64	0.04
					Infiltration depth	More serosa/ adventitia infiltration in GG	GG *vs* GA+AA			< 0.05
MMP-3	-1171 5A/6A	Hinoda[91]	Japanese	101/127	Cancer risk	Increased cancer risk in 6A/6A	6A/6A *vs* 5A/5A + 5A/6A	2.11	1.17-3.82	0.01
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Biondi[93]	Caucasian	63/164	Cancer risk	No difference in cancer risk				
		Ghilardi[92]	Caucasian	60/164	Cancer risk	No difference in cancer risk				
					Distant metastases	No difference in metastases				
		Woo[89]	Korean	185/304	Cancer risk	No difference in cancer risk				
					LN metastases	No difference in LN metastases				
		Ohtani[103]	Japanese	47/67	Cancer risk	No difference in cancer risk				
		Elander[90]	Caucasian	127/208	Cancer risk	No difference in cancer risk				
					Clinicopath var.	No correlation with any clinicopath. par.				
		Zinzindohoue[99]	Caucasian	201/0	Survival	No difference in overall survival				
		Hettiaratchi[96]	Australian	503/471	Cancer risk	No difference in cancer risk				
					Survival	No difference in survival				
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Xu[97]	Chinese	126/126	Cancer risk	No difference in cancer risk				
					Clinicopath. par.	No correlation with any clinicopath. par.				
MMP-7	-153 C/T	Ghilardi[111]	Caucasian	58/111	Cancer risk	Increased cancer risk in T allele carriers	T allele in patients *vs* controls	2.2	0.89-5.48	0.05
					Clinicopath. par.	No correlation with any clinicopath. par.				
		Langers[110]	Caucasian	174/0	Survival	Better survival in CC patients	CC *vs* CT+TT (LR)	14		0.001
MMP-7	-181 A/G	Woo[89]	Korean	185/304	Cancer risk	No difference in cancer risk				
					LN metastases	No difference in LN metastases				
		Fang[94]	Chinese	237/252	Cancer risk	No difference in cancer risk				

		Ghilardi[111]	Caucasian	58/111	Cancer risk	Increased cancer risk in GG	GG in patients *vs* controls	2.41	0.98-5.89	0.03
					Distant metastases	GG more often distant metastases	G in M+ *vs* M-	7.5	2.07-27.19	0.001
					LN metastases	GG more frequent LN metastases				
		Ohtani[103]	Japanese	47/67	Cancer risk	No difference in cancer risk				
		Langers[110]	Caucasian	174/0	Survival	No difference in survival				
		de Lima[95]	Brasilian	130/130	Cancer risk	No difference in cancer risk				
					Distant metastases	No difference in metastases				
					LN metastases	No difference in LN metastases				
MMP-9	R279Q	Woo[89]	Korean	185/304	Cancer risk	No difference in cancer risk				
					LN metastases	No difference in LN metastases				
		Xing[106]	Chinese	137/199	Cancer risk	No difference in cancer risk				
					LN metastases	No difference in LN metastases				
		Fang[94]	Chinese	237/252	Cancer incidence	Increased cancer risk in RR	RR *vs* QQ	2.21	1.25-3.93	0.006
MMP-9	-90(CA)n	Woo[89]	Korean	185/304	Cancer risk	No difference in cancer risk				
					LN metastases	No difference in LN metastases				
MMP-9	-1562 C/T	Xu[107]	Chinese	126/126	Cancer risk	No difference in cancer risk				
					Infiltration depth	No difference in infiltration depth				
		Woo[89]	Korean	185/304	Cancer risk	Increased cancer risk in CC patients	GG in patients *vs* controls	1.7	1.04-2.66	0.03
					LN metastases	No difference in LN metastases				
		Xing[106]	Chinese	137/199	Cancer risk	No difference in cancer risk				
					LN metastases	Increased risk of LN metastases in CT+TT	CT+TT *vs* CC			0.02
		Langers[105]	Caucasian	215/0	Survival	No difference in survival				
		Ohtani[103]	Japanese	47/67	Cancer risk	No difference in cancer risk				
		Elander[90]	Caucasian	127/208	Cancer risk	No difference in cancer risk				
					Clinicopath. par.	No relationschip with clinicopath. par.				
MMP-12	-82A/G	Woo[89]	Korean	185/304	Cancer risk	No difference in cancer risk				
					LN metastases	No difference in LN metastases				

SNP: Single nucleotide polymorphism; LN: Lymph node; Clinicopath. par.: Clinicopathological parameters; OR: Odds ratio; aOR: Adjusted odds ratio; 95% CI: 95% confidence interval.

ond meta-analysis[87]. Xing *et al*[106] reported a decrease of lymph node metastases in 137 Chinese CRC patients with the CC genotype of the MMP-9 -1562 SNP, whereas the other studies did not find an association with lymph node metastases, survival, infiltration depth or any other clinicopathological variable. The mechanism of action of MMP-9 in cancer is intriguing and not as straightforward as some of the other MMPs. In colorectal cancer, both very high and very low levels of MMP-9 in tumor tissue seem to be associated with poor prognosis compared to intermediate MMP-levels[105]. Similarly, in ovarian cancer, the presence of MMP-9 within the ovarian cells is associated with better survival, whereas higher stromal expression is a marker of worse prognosis[108]. The -90(CA)$_{14\text{-}27}$

polymorphism, in which the number of CA repeats influences expression of MMP-9, is not associated with cancer risk or the risk of lymph node metastases[89]. Thus, no consistent relation emerges between MMP-9 genotypes and CRC expression. In a single study of 185 Taiwanese colorectal cancer patients, no association of the MMP-12 -82A/G polymorphism and colorectal cancer risk of development or lymph node metastases was found[89].

Insertion of an extra Adenosine (A) at position -1171 of the MMP-3 promoter generates a 6A allele with lower promoter activity compared to the 5A allele[19]. This polymorphism has been studied quite extensively in colorectal cancer, and in all but one paper, no contribution to cancer risk, clinicopathological parameters or survival was demonstrated[89-93,96,97,99,103]. Only Hinoda *et al* found a two-fold increase in CRC risk in the 6A/6A homozygotes (OR = 2.11, 95% CI: 1.16-3.82, $P = 0.013$) in the previously mentioned study of a Japanese cohort of 101 CRC patients and 127 controls. In 302 patients with small adenomas and 568 polyp-free controls, the 6A/6A genotype of the -1171 MMP-3 polymorphism was associated with a significant risk of small adenomas (OR = 1.50, 95%CI: 0.99-2.28, $P = 0.008$) and this association was even stronger in individuals with the combined genotype MMP-3 -1171 6A/6A + MMP-1 -1607 2G/2G (OR =1.88, 95%CI: 1.08-3.28, $P = 0.001$)[101]. When the MMP-3 genotype of 295 patients of that study with large adenomas was compared to either the patients with small adenomas or the polyp-free controls, no difference in genotype distribution was found. These findings suggest that this MMP-3 5A/6A polymorphism (and the -1607 1G/2G polymorphism) might be of importance early in the process of adenoma formation. The 6A/6A genotype of the MMP-3 -1171 5A/6A polymorphism has a lower transcriptional activity and higher plasma levels of MMP-3 were measured in 5A/5A homozygote patients with acute coronary syndrome compared to 6A/6A homozygotes[109]. Apparently, the association between this polymorphism and increased susceptibility for developing early colorectal adenomas does not provide an insight into the functional activity of the protein.

No clear association between MMP-7 -181 A/G polymorphism and colorectal cancer incidence, lymph node metastases or survival was found in most of the publications[89,94,95,103,110]. The only exception is by Ghilardi *et al*[111] who showed that the GG genotype increases the colorectal cancer risk. Furthermore, in the 58 patients with colorectal cancer included in this study, the CC genotype predisposed for lymph node metastases and distant metastases at the time of diagnosis[111]. Ghilardi *et al*[111] also studied the C/T polymorphism at position -153 of the MMP-7 promoter and found an increase in colorectal cancer risk in T allele carriers, but no association with any of the clinicopathological variables. In a study of 174 colorectal cancer patients, Langers *et al*[110] reported that patients with the CC genotype had a better 10-year survival than the patients with the CT or TT genotype (CC *vs* CT+TT: Log Rank 14.0, $P = 0.0009$). The study of Ghilardi *et al*[111] included 58 patients, a relatively small number for studying the influence of gene polymorphisms on cancer susceptibility and prognosis. This may explain the discordant results between the different studies and illustrates the need for larger sample sizes. Peng *et al* tried to solve this problem by performing meta-analyses of case control studies investigating the role of gene polymorphisms of MMP-1, -2, -3, -7 and -9 on cancer susceptibility in lung, head and neck, esophageal, gastric, colorectal, hepatocellular, breast, renal, bladder, cervical, ovarian, endometrial, prostate and skin cancer[38,87]. In these meta-analyses, a consistent positive association with colorectal cancer risk was observed for the MMP-1 -1607 1G/2G polymorphism, but not for MMP-2 -735C/T, MMP-2 -1306 C/T, MMP-7 -181A/G and MMP-9 -1562 C/T.

In summary, although data are still emerging there appears to be evidence for associations between the MMP-1 -1607 1G/2G, MMP-2 -1306 C/T, MMP-7 -181 A/G and MMP-9 -1562 C/T polymorphisms and CRC susceptibility. In affected individuals, an association of the MMP polymorphism with the course of the disease or prognostic parameters was reported in some studies, as shown in Table 3, although these results await further confirmation.

DISCUSSION

The three major regulatory mechanisms that eventually determine the function of MMPs are transcription, activation of latent MMPs and inhibition by specific inhibitors. Along with local activation and inhibition, regulation of transcription seems to be of major importance for the function of MMPs[112]. Most of the promoter polymorphisms that are described in this review have been shown to influence promoter activity and to increase or decrease transcription *in vitro*, as shown in Table 1. Some SNPs are associated with gastrointestinal cancer susceptibility and in some cases, a correlation with clinicopathological parameters and outcome of the disease was observed. Surprisingly, only a few studies have actually looked at the correlation between the promoter polymorphism of MMPs and the corresponding tumor protein levels. Two studies reported no association between the different genotypes and MMP protein expression in the tumor[56,105]. It would be interesting to correlate the values in normal tissues from these patients with their genotypes to further elucidate their contribution to the phenotypic expression of the MMPs in cancer patients. Besides the regulation of expression by transcription, the presence of MMPs in the (tumor) microenvironment depends on the inactivation/clearing, which is regulated by the inhibitors. High clearance could lead to low protein levels despite high levels of expression. Furthermore, a specific genotype can have different (and even opposite) effects in different cell types. Wang *et al* showed that the -799T/-381G/+17G haplotype of MMP-8 increased promoter activity in cells resembling chorion cytotrophoblasts, but the same haplotype decreased promoter activity in a leukocyte cell line and had no effect on promoter activity in a macrophage cell

line[23]. Cell-specific functional effects of SNPs have been described for several cancer-associated proteins[113,114]. This phenomenon makes the translation of the effect of a promoter polymorphism on gene transcription to the *in vivo* situation even more complex, especially as many different stromal cell types as well as tumor cells are involved in the production of MMPs (Figure 1). A correlation between a particular polymorphism and cancer susceptibility does not necessarily demonstrate the implication of the corresponding gene in the process of cancer development or progression. It could also be the result of a linkage (dis)equilibrium between the examined (potentially functionally neutral) SNP and another (potentially functionally important) SNP[85].

Although for some MMP-polymorphisms the results between different studies are unanimous, there is often a discrepancy between the results of different studies on the same polymorphism. However, some trends can be observed. An increased incidence of esophageal cancer in CC carriers of the MMP-2 -1306 C/T polymorphism was reported in 2 studies[15,39] and this association was corroborated in a meta-analysis[38]. In the Asian population, G-allele carriers of the MMP-7 -181 A/G polymorphism have an increased risk of developing both esophageal cancer and gastric cancer[45,63,64]. In hepatocellular cancer, no association was found between any of the MMP SNPs and cancer risk, although 5A-allele carriers of the MMP-3 5A/6A polymorphism might have a worse prognosis. Although some studies concerning CRC report a correlation between cancer incidence and the MMP-1 1G/2G, MMP-2 -1306 C/T, MMP-7 -181A/G and MMP-9 -1562 C/T polymorphism, the only association that was found to be significant in a meta-analysis was a higher cancer risk in 2G allele carriers of the MMP-1 1G/2G polymorphism[87]. Sometimes, as for the MMP-7 -181 A/G polymorphism in gastric cancer, the variability in results between the different studies is likely to be explained by ethnic differences between the study groups. Different genotype distributions of MMP-2 and MMP-9 SNPs have been reported in Caucasians and African-Americans, which seem to be associated with differences in prevalence of cancer and cardiovascular disease[115]. The diverse results in the publications described in this review emphasize the need for studies on larger numbers of patients before definite associations between genetic polymorphism and susceptibility to cancer or with the course of the disease in affected individuals can be established. There is a need for large cohorts of patients who are genotyped, and information about disease progression, lymph node metastases, distant metastases and prognosis needs gathered. In the meantime meta-analyses rather than single studies are the best indicators of the practical value of single SNPs. The recent meta-analysis of Zhou *et al*[116] including almost 3000 breast carcinoma patients, suggested MMP-2 -1306 C/T as a potential indicator, whereas the SNPs of MMP-1, MMP-3 and MMP-9 were not indicative.

Genome-wide association studies (GWAS) may further highlight the genes that are important in identifying people at high risk for the development of cancer or patients who are likely to have an unfavorable outcome of their disease.To date, fourteen loci identified by GWAS analysis have been shown to influence the risk of developing colorectal cancer[117]. None of them is located in any of the MMP genes. However, in an extensive mutation analysis of the human genome in which 13.023 genes were involved, Sjöblom *et al*[118] identified MMP-2, ADAM29 and three ADAMTS family members among the 69 CAN genes that are often mutated in colorectal cancer.

CONCLUSION

To predict the cancer risk in a population and the outcome of the disease in affected individuals, a genomic profile including functional SNPs of several genes would probably be a better tool than the use of a single SNP. Being key players in the process of cancer development and progression, SNPs of selected MMPs or TIMPs could be included in such a profile to predict disease susceptibility and/or the course of a disease. Because of the heterogeneity of previous studies that have included a relatively small number of patients, further research on large cohorts of cancer patients and healthy controls is needed before a definite conclusion can be drawn about the impact of these genes on gastro-intestinal cancer risk and prognosis.

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