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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

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Colorectal carcinogenesis involves environmental factors and genetic predispositions. Recent studies have suggested the associations between colorectal neoplasm and functional polymorphism of matrix metalloproteinases (MMPs) and cytokine genes. In this study, we analyzed polymorphisms of MMPs and tumor necrosis factor (TNF)-alpha genes, focusing on the susceptibility to colorectal neoplasm and the tumor progression. The subjects were 186 patients (95 men and 91 women) who underwent total colonoscopy, and were classified into cancer, adenoma and non-neoplasm (control) groups of 47, 72 and 67 patients, respectively. The polymorphisms at the MMP-2 –1306C/T, MMP-3 –1171 5A/6A, MMP-7 –181A/G, MMP-9 –1562C/T and TNF-alpha –308G/A loci were analyzed. Regarding background factors, significant differences were found in the age, sex ratio and alcohol-drinking and cigarette-smoking histories in the adenoma and cancer groups, compared to those in the control group. On these factors-adjusted logistic regression analysis of polymorphisms and disease susceptibility, no significant difference was noted in the frequency of any polymorphism in the adenoma and cancer groups, compared to those in the control group. The analysis of the involvement of polymorphisms in tumor progression in the adenoma and cancer groups revealed that the odds ratio for the MMP-3 5A allele was significantly higher in the cancer group (2.74; 95% confidence interval = 1.11–6.74, $P = 0.02$). The polymorphisms of MMP genes and TNF-alpha genes were not associated with the susceptibility to colorectal neoplasm, but the involvement of the MMP-3 5A allele in the progression of adenoma to cancer was suggested.

Key words: colorectal neoplasm; gene analysis; matrix metalloproteinase; polymorphism; tumor necrosis factor-alpha

Recently, the rate of colorectal cancer has been increasing rapidly in Japan, and it is now the main cause of death from malignant disease, as in many other countries (Yoshimi and Sobue, 2004). In fact, age-standardized rates are similar to those in Caucasian populations of the United States (Yiu et al., 2004). The reason has generally been ascribed to the Westernized diet, characterized by a high intake of fat and meat, popular after World War II (Kono, 2004), whereas the relevance of genetic predispositions has not been sufficiently analyzed in Japanese. Colorectal neoplasm is known to be a multifactorial disease, with dietary factors, lifestyle habits and genetic predispositions contributing to its development.

Abbreviations: MMP, matrix metalloproteinase; RFLP, restriction fragment length polymorphism; TNF, tumor necrosis factor

Matrix metalloproteinases (MMPs) are proteolytic enzymes that play key roles not only in extracellular matrix degradation but also in all stages of cancer initiation, invasion and metastasis (Curran and Murray, 1999; Zhu et al., 2001; Behrens et al., 2003). Furthermore, recent studies have suggested that MMPs are involved in tumor initiation and development, including the regulation of cell proliferation, apoptosis, angiogenesis, loss of cell adhesion and immune responses to cancer (Egeblad and Werb, 2002). In fact, the over-expression of MMPs has been demonstrated in various cancers (Adachi et al., 1999; Ohashi et al., 2000; Aglund et al., 2004; Jordan et al., 2004). Polymorphisms of MMPs in the promoter region, naturally occurring sequence variations, may result in the differential expression of MMPs in individuals (Ye, 2000). To date, the promoters of MMP-2, -3, -7 and -9 genes have been reported to contain polymorphisms, exhibit allele-specific effects on the regulation of MMP gene transcription, and have been associated with changes in the susceptibility to or development of some cancers (Liang et al., 2002; Ghilardi et al., 2002, 2003; Matsumura et al., 2005).

On the other hand, previous studies have shown that tumor necrosis factor (TNF)-alpha expression may act as a high-risk factor or a poor prognostic factor in some cancers (Warzocha et al., 1997; El-Omar et al., 2003; Machado et al., 2003; Sharma et al., 2008). However, a few previous reports have suggested that there is no significant association between the TNF-alpha –308A/G polymorphism allele and colorectal cancer development (Park et al., 1998; Landi et al., 2003).

To explore the possible association between these polymorphisms and the risk of colorectal neoplasms, we analyzed promoter genes in MMP-2, -3, -7 and -9 and TNF-alpha in a Japanese sample of colorectal neoplasm patients and controls who had no finding of colonoscopy.

Materials and Methods

Subjects

A total of 186 Japanese subjects (91 women and 95 men, with a mean age of 64 ± 13 years) were studied between August 2003 and March 2007. All subjects had undergone total colonoscopy just prior to enrollment. One hundred nineteen patients with histologically confirmed colorectal neoplasm (47 cancers and 72 adenomas) and 67 non-neoplasm subjects (controls) were interviewed regarding their medical history, family history of colorectal cancer, anamnesis of diabetes, and habits such as alcohol intake and cigarette smoking. Before enrollment and blood sampling, written informed consent was obtained from all recruited subjects. This study was approved by the Ethics Committee of Tottori University Faculty of Medicine.

Table 1. Sequences of PCR primers

Gene	Polymorphism	Forward primer and reverse primer (5´–3´)	Tm (°C)	Restriction enzyme
MMP-2	–1306 C/T	*CTT CCT AGG CTG GTC CTT ACT GA*	60	*Xsp* I
		CTG AGA CCT GAA GAG CTA AAG AGC T		
MMP-3	–1171 5A/6A	*CTT CCT GGA ATT CAC ATC ACT GCC ACC ACT*	65	*Tth111* I
		GGT TCT CCA TTC CTT TGA TGG GGG GAA AGA		
MMP-7	–181 A/G	*TGG TAC CAT AAT GTC CTG AAT GAT ACC TAT G*	65	*EcoR* I
		TCG TTA TTG GCA GGA AGC ACA CAA TGA ATT		
MMP-9	–1562 C/T	*GCC TGG CAC ATA GTA GGC CC*	60	*Sph* I
		CTT CCT AGC CAG CCG GCA TC		
TNF-alpha	–308 G/A	*GAG GCA ATA GGT TTT GAG GGC CAT*	55	*Nco* I
		GGG ACA CAC AAG CAT CAA G		

DNA extraction

Genomic DNA samples were extracted from peripheral white blood cells using a DNA extracting kit (DnaQuickII: Dainipponseiyaku, Osaka, Japan) according to the manufacturer's instructions.

Determination of genotypes

Using the extracted DNA as a template, the promoter region of each MMP was amplified by PCR using commercially available kits (HotStarTaq: QIAGEN, GmbH, Germany), following the manufacturer's instructions. The sequences of primers are summarized in Table 1. The methods used to type the MMP-2 –1306 C/T, MMP-3 –1171 5A/6A, MMP-7 –181A/G, MMP-9 –1562 C/T and TNF-alpha –308 G/A polymorphisms have been described previously (Jormsjö et al., 2001; Vasků et al., 2004; Zhang et al., 2004; Perri et al., 2005; Tuet al., 2007). Briefly, reactions were carried out under the following conditions: 5 min at 95˚C, and then amplification for 35 cycles consisting of 30 s at 95˚C, 30 s at an appropriate temperature and 30 s at 72˚C. A final extension step at 72˚C for 5 to 10 min was added to terminate the amplification. Subsequently, the PCR products were digested with appropriate restriction enzymes that cleave from 1 to 2 fragments. The digests were then electrophoresed on a 1 to 2% agarose gel using TBE buffer (45 mM Tris-borate, pH 8.3, and 2 mM EDTA) to confirm cleavage using molecular size marker IV (Nippon Gene, Tokyo, Japan). Gels were stained with ethidium bromide and visualized under UV light. As examples for gel documentation, the results of MMPs genotyping were shown in Fig. 1.

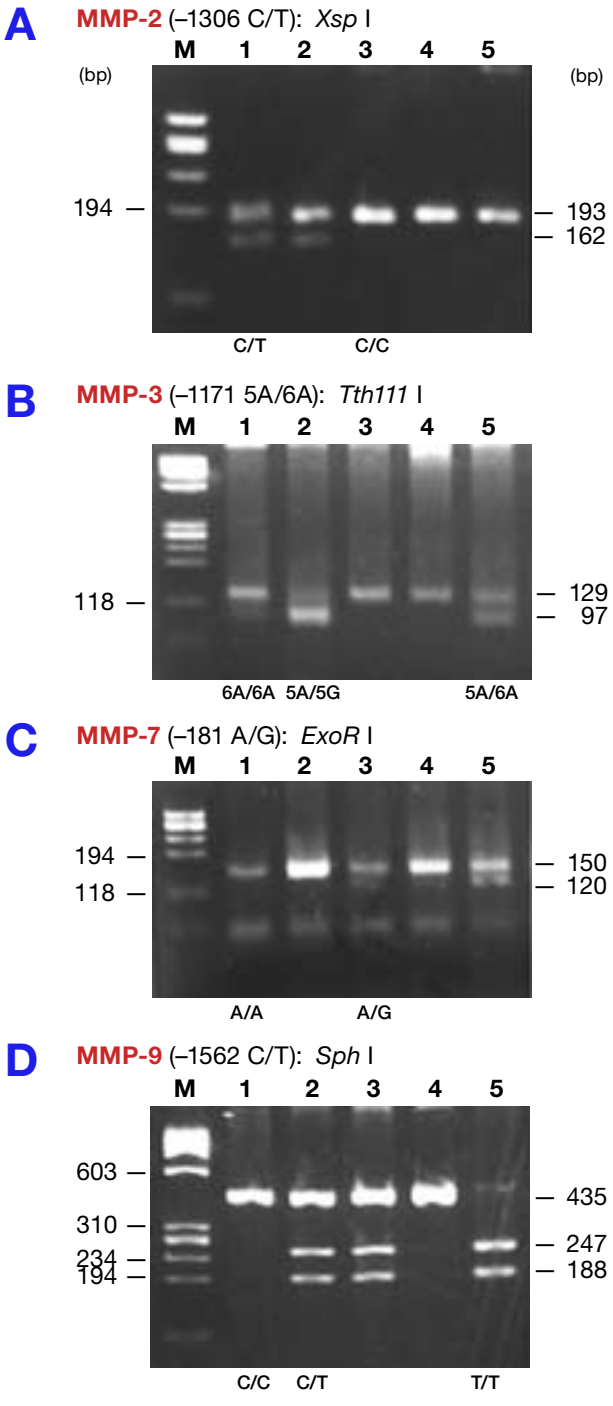

Fig. 1. Genotyping of MMP-2 C/T, MMP-3 5A/6A, MMP-7 A/G and MMP-9 C/T by PCR-restriction fragment length polymorphism.

A: MMP-2 C/T. The PCR products were digested with XspI restriction enzyme and subjected to electrophoresis on a 2.5% agarose gel. M, molecular marker; 1 and 2, C/T genotype; 3, 4 and 5, C/C genotype.

B: MMP-3 5A/6A. The PCR products were digested with Tth111I restriction enzyme and subjected to electrophoresis on a 2.5% agarose gel. M, molecular marker; 1, 3 and 4, 6A/6A genotype; 2, 5A/5A genotype; 5, 5A/6A genotype.

C: MMP-7 A/G. The PCR products were digested with EcoRI restriction enzyme and subjected to electrophoresis on a 2.5% agarose gel. M, molecular marker; 1, 2 and 4, A/A genotype; 3 and 5, A/G genotype.

D: MMP-9 C/T. The PCR products were digested with Sph I restriction enzyme and subjected to electrophoresis on a 2.5% agarose gel. M, molecular marker; 1 and 4, C/C genotype; 2 and 3, C/T genotype; 5, C/T genotype.

Table 2. Characteristics of subjects

		Control [67] Ratio	Patient with Adenoma [72] Ratio	*P*†	Patient with Cancer [47] Ratio	*P*†	*P*‡
Age (year)		61.3 ± 2.0	66.3 ± 1.1	0.04	67.3 ± 1.7	0.04	NS
Sex	Male/female	25/42	42/30	0.02	28/19	0.03	NS
Family history§	Yes/no	8/59	3/69	NS	10/37	NS	0.008
Smoking status	Smoker/non-smoker	19/48	31/41	NS	26/21	0.006	NS
Alcohol status	Drinker/non-drinker	21/46	36/36	0.03	25/22	0.03	NS
Diabetes	Yes/no	5/62	5/67	NS	9/38	NS	NS

[ ], number of subjects.
Ratio, except age (mean ± SD).
NS, not significant.
† Compared with the control subjects.
‡ Compared with patients with adenoma.
§ Patients with family history of colorectal cancer in the 1st degree relatives.

Statistical analysis

The significance of differences in means or proportions was measured using analysis of variance or the chi-square test. Comparison of the genotypes of MMP-2, -3, -7 and -9 and TNF-alpha and the allelotype distribution in the study groups was performed by means of a 2-sided contingency table using the chi-square test. Relationships between the genotypes and clinicopathological characteristics of the patients were evaluated by Fisher's exact test. To evaluate the increased risk of colorectal neoplasm associated with the presence of polymorphic alleles, odds ratios and 95% confidence intervals were computed, adjusted by logistic regression for several covariates potentially associated with the colorectal neoplastic risk such as age, sex, family history of colorectal cancer, alcohol intake, smoking status and diabetes mellitus. All statistical analyses were performed using the software package SPSS II for Windows (version 11.0 J, SPSS Japan, Tokyo)

Results

Characteristics of subjects

Subjects who had undergone colonoscopy were divided into a control group with no finding and patient groups with adenoma or cancer of the colon. The backgrounds of groups are shown in Table 2. The mean age was 67.3 ± 1.7 years (range: 27–90) in the colorectal cancer group and 66.3 ± 1.1 years (range: 36–88) in the adenoma group. Compared to the control group, significant differences were noted in the age, sex ratio and alcohol-drinking history in the adenoma and cancer groups. No significant difference was noted in the cigarette-smoking history between the adenoma and control groups ($P = 0.10$), but one was present between the cancer and control groups ($P = 0.01$). There were no significant differences in the familial medical history of colorectal cancer or anamnesis of diabetes, compared to the control group.

On comparison of the adenoma and cancer groups, no significant differences were present in the age, sex ratio, or alcohol-drinking or cigarette-smoking history, but the frequency of familial medical history of colorectal cancer was significantly higher in the cancer group ($P = 0.007$). The frequency of anamnesis of diabetes was slightly higher in the cancer group, but the difference was not significant ($P = 0.08$).

Genotype distributions and the susceptibility for adenoma and cancer

The frequencies and odds ratios of polymorphisms of the MMP-2, -3, -7 and -9 and TNF-

Table 3. Genotype and allele frequencies of polymorphisms of the MMP-2, -3, -7 and -9 and TNF-alpha gene in controls and patients

Genotype and allele	Control [67] Number (%)	Patient with adenoma [72] Number (%)	Odds ratio† (95% CI)	*P*	Patient with cancer [47] Number (%)	Odds ratio† (95% CI)	*P*
MMP-2 –1306 C/T							
CC	64 (95)	66 (92)	1		41 (87)	1	
CT	3 (5)	6 (8)			5 (11)		
TT	0 (0)	0 (0)			1 (2)		
CT + TT	3 (5)	6 (8)	2.39 (0.51–11.7)	0.26	6 (13)	2.98 (0.62–14.29)	0.17
T	0.02	0.04			0.07		
MMP-3 –1171 5A/6A							
6A6A	50 (75)	58 (81)	1		31 (66)	1	
6A5A	17 (25)	13 (18)			14 (30)		
5A5A	0 (0)	1 (1)			2 (4)		
6A5A + 5A5A	17 (25)	14 (19)	0.79 (0.34–1.84)	0.59	16 (34)	1.56 (0.64–3.81)	0.32
5A	0.13	0.1			0.19		
MMP-7 –181 A/G							
AA	55 (82)	65 (90)	1		45 (96)	1	
AG	12 (18)	7 (10)			2 (4)		
GG	0 (0)	0 (0)			0 (0)		
AG + GG	12 (18)	7 (10)	0.61 (0.21–1.75)	0.35	2 (4)	0.21 (0.40–1.11)	0.06
G	0.09	0.05			0.02		
MMP-9 –1562 C/T							
CC	47 (70)	54 (75)	1		30 (64)	1	
CT	19 (28)	17 (24)			16 (34)		
TT	1 (2)	1 (1)			1 (2)		
CT + TT	20 (30)	18 (25)	0.78 (0.35–1.71)	0.53	17 (36)	1.41 (0.61–3.28)	0.41
T	0.16	0.19			0.13		
TNF-alpha –308 G/A 1							
GG	65 (97)	71 (99)	1		46 (98)	1	
GA	2 (3)	1 (1)			1 (2)		
AA	0 (0)	0 (0)			0 (0)		
GA + AA	2 (3)	1 (1)	0.62 (0.04–8.02)	0.71	1 (2)	0.77 (0.06–9.31)	0.83
A	0.01	0.01			0.01		

[ ], number of subjects.
CI, confidence interval.
† Odds ratio adjusted on age, sex, smoking and alcohol status.

alpha gene are shown in Table 3. Regarding the distribution of alleles in our study, most patients had C/C alleles in MMP-2, 6A/6A in MMP-3, A/A in MMP-7, C/C in MMP-9 and G/G in TNF-alpha, and, in reverse, none had G/G alleles in MMP-7, nor A/A alleles in TNF-alpha.

Logistic regression analysis adjusted for age, sex ratio, and alcohol-drinking and cigarette-smoking histories, which were background factors with significant differences, was performed in the control, adenoma and cancer groups.

There were no significant differences of these genotypes between controls and adenoma patients, and between controls and cancer patients, suggesting that colorectal neoplasm susceptibility was not found in any polymorphism of the MMP-2, -3, -7 and -9 or TNF-alpha gene.

Association with tumor progression

To investigate the association with tumor progression from adenoma to cancer, the frequencies and odds ratios of polymorphisms of the MMP-2, -3, -7 and -9 and TNF-alpha gene in the adenoma and cancer groups were calculated (Table 4). Logistic regression analysis adjusted for a familial history of colorectal cancer and anamnesis of diabetes was performed. We found that patients with the MMP-3 5A allele had significantly higher odds ratio (2.74) of cancer (P = 0.02). However, other genotypes showed no significant difference between the adenoma and cancer groups.

Table 4. Genotype and allele frequencies of polymorphisms of the MMP-2, -3, -7 and -9 and TNF-alpha gene in patients with adenoma and cancer

Genotype and allele	Patient with			*P*
	Adenoma [72]	Cancer [47]		
	Number (%)	Number (%)	Odds ratio† (95% CI)	
MMP-2 –1306 C/T				
CC	66 (92)	41 (87)	1	
CT + TT	6 (8)	6 (13)	1.54 (0.43–5.488)	0.49
MMP-3 –1171 5A/6A				
6A6A	58 (81)	31 (66)	1	
6A5A + 5A5A	14 (19)	16 (34)	2.74 (1.11–6.74)	0.02
MMP-7 –181 A/G				
AA	65 (90)	45 (96)	1	
AG + GG	7 (10)	2 (4)	0.58 (0.11–3.00)	0.52
MMP-9 –1562 C/T				
CC	54 (75)	30 (64)	1	
CT + TT	18 (25)	17 (36)	1.43 (0.61–3.37)	0.41
TNF-alpha –308 G/A				
GG	71 (99)	46 (98)	1	
GA + AA	1 (1)	1 (2)	0.58 (0.13–36.13)	0.58

CI, confidence interval.
†Odds ratio adjusted on family history and diabetes.

Discussion

It has been reported that MMPs play an important role in various cancer metastases and invasion including colorectal cancer (Asano et al., 2007), but no consistent finding has been obtained with regard to the association of any MMP gene polymorphism with colorectal cancer progression. Similarly, no association between TNF-alpha and colorectal cancer has been identified. We investigated polymorphisms of the MMP-2, -3, -7 and -9 and TNF-alpha gene and the susceptibility to colorectal neoplasm. In addition, considering that most colorectal cancer cases develop via the adenoma-carcinoma sequence (Fearon and Vogelstein, 1990), we studied the association of tumor progression with each gene polymorphism.

MMP-2 expression in colorectal cancer tissue has been reported to be correlated with the disease stage and prognosis, and considered to play an important role in colorectal cancer invasion and metastasis (Turpeenniemi-Hujanen, 2005). In the MMP-2 gene, C/T polymorphism is present at –1306, and the transcription activity is higher in the C than in the T allele (Price et al., 2001). In studies reported by Heittaratchi et al. (2007) and Elander et al. (2006), –1306 C/T was not associated with the sensitivity of colorectal cancer, 5-year survival rate or tumor characteristics, whereas Xu et al. (2004) reported that the risk of colorectal cancer development was higher in CC than in CT and TT types, showing that no consistent findings have been obtained with regard to the association of MMP-2 gene polymorphisms with colorectal cancer. In our study, no association of MMP-2 gene polymorphisms with the susceptibility to colorectal neoplasm or tumor progression was noted.

In colorectal cancer tissues, MMP-3 is mainly expressed in stromal cells (Newell et al., 1994). In the MMP-3 gene, 5A/6A polymorphism is present at –1171, and the transcription activity is higher in the 5A than in the 6A allele (Ye et al., 1996). Hinoda et al. (2002) reported that the 6A allele with low transcription activity indirectly contributed to colorectal cancer development, but no other study has supported this finding (Biondi et al., 2000; Ghilardi et al., 2001; Xu et al., 2006;

Hettiaratchi et al., 2007). The clinicopathological significance of the MMP-3 expression in colorectal cancer remains unclear. No association with colorectal neoplasm susceptibility was noted in the present study, but the frequency of the 5A allele with high transcription activity during the progression of adenoma to cancer was high in the cancer group. Sternlicht et al. (1999) investegated the MMP-3 in the breast cancer, and reported that MMP-3 promoted spontaneous premalignant changes and malignant conversion in the mammary glands of transgenic mice. Furthermore, regarding breast cancer, Nelson et al. (2008) reported that the overproduction of MMP-3 in mammary gland tissue triggered surrounding cells to increasingly produce reactive oxygen species, and induced DNA injury and genetic instability, finally leading to malignant conversion. Colorectal cancer may develop via a similar course.

While MMP-7 has a broad substrate specificity, it also exhibits "sheddase" activity mediating cell surface protein release, and its influence on the growth and progression of colorectal, esophageal, stomach, and lung cancers has been investigated (Leeman et al., 2003; Zhang et al., 2005). A strong correlation of MMP-7 with colorectal cancer malignancy has been reported, in which the expression frequency of MMP-7 was particularly high in cancer tissues, and the MMP-7 expression level was higher in metastatic lesions than in the primary lesion (Yoshimoto et al., 1993). In the MMP-7 gene, A/G polymorphism is present at –181 of the promoter lesion, and the transcription activity is higher in the G than in the A allele (Ghilardi et al., 2003). Ghilardi et al. (2003) reported that the MMP-7 –181 G/G genotype was involved in colorectal cancer and tumor progression in Italians, but we detected no association of MMP-7 gene polymorphisms with colorectal neoplasm susceptibility or tumor progression. One reason may have been the biased distribution of MMP-7 polymorphisms. The frequency of MMP-7 G/G was about 0.5% in healthy subjects in a study performed in China (Lu et al., 2006), but about 20% in another Asian country, India (Singh et al., 2008), suggesting regional variation. Actually, none of the subjects analyzed showed MMP-7 G/G in our study.

Regarding MMP-9, Zucker and Varcrca (2004) reported that the MMP-9 level rose in an early stage after the progression of adenoma to colon cancer, and Roeb et al. (2001) reported that MMP-9 transcription activity was 5 times higher in colorectal cancer than in the normal mucosa. In the MMP-9 gene, T/C polymorphism is present at –1562, and the transcription activity is higher in the C than in the T allele (Zhang et al., 1999). Matsumura et al. (2005) reported a relationship between stomach cancer invasion and the MMP-9 T allele position, and Grieu et al. (2004) reported that C homo improved the prognosis of breast cancer. Regarding colorectal cancer, Elander et al. (2006) investigated the relationship between C/T polymorphism at –1562 and colorectal cancer, and found no correlation, as observed in our study.

In the TNF-alpha gene, G/A polymorphism is present at –308, and the transcription activity is higher in the A than in the G allele (Abraham and Kroeger, 1999). Previous reports, however, support that there is no significant association between the TNF-alpha –308 A/G allele and colorectal cancer susceptibility (Park et al., 1998; Landi et al., 2003). The findings of our study are similar to those reports.

The present study clarified that the susceptibility to colorectal cancer is more strongly affected by age, gender, and cigarette-smoking and alcohol-drinking histories in Japanese, as reported by Otani et al. (2003), than gene polymorphisms studied. Colorectal cancer is a multifactorial disease involving environmental factors as well as a genetic predisposition, and properly cannot be explained by genetic predisposition alone. However, detailed clarification of the involvement of a genetic predisposition may contribute to the prediction and early discovery of cancer development as well as elucidation of the molecular mechanism involved in the carcinogenic factors and early stage of carcinogenesis.

In conclusion, no association with the susceptibility to colorectal neoplasm was noted in any polymorphism of the MMP-2, -3, -7 and -9 and TNF-alpha genes, but the involvement of the MMP-3 5A allele in tumor progression was suggested.

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