ANTICANCER RESEARCH *43*: 3979-3985 (2023)
doi:10.21873/anticanres.16585

Impact of Matrix Metalloproteinase-8 Genotypes on Colorectal Cancer Risk in Taiwan

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Abstract. *Background/Aim: This study aimed to investigate the involvement of matrix metalloproteinase-8 (MMP-8) genotypes in the development of colorectal cancer (CRC). Materials and Methods: The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was used to analyze the genotypes of MMP-8 C-799T (rs11225395), Val436Ala (rs34009635), and Lys460Thr (rs35866072) in 362 patients with CRC and 362 controls. Additionally, the potential associations between these genotypes and factors such as age, sex, smoking, alcohol consumption, and body mass index (BMI) status in relation to CRC risk were also assessed. Results: No significant differences in the distribution of MMP-8 rs11225395 genotypes were found between the control and case groups (p for trend=0.3836). Logistic regression analysis demonstrated that individuals with the MMP-8 rs11225395 variant CT and TT genotypes had a 0.83 and 0.77-fold risk of CRC, respectively. Moreover, carriers of the rs11225395 CT+TT genotypes were not associated with CRC risk either (p=0.2063). Furthermore, individuals with the MMP-8 rs11225395 TT genotype exhibited significantly lower odds of CRC risk compared to those with the CC genotype among non-smokers (p=0.0379). No significant associations were observed with respect to MMP-8 rs34009635 or rs35866072. Conclusion: The analyzed genotypes of MMP-8 play a minor role in determining individual susceptibility to CRC risk.*

Colorectal cancer (CRC) accounts for approximately 11% of all newly diagnosed cancer cases and is the third most common cancer worldwide, causing the second highest number of cancer-related deaths (1, 2). The pathogenesis of CRC involves various factors that contribute to complex genetic and epigenetic processes, ultimately leading to the transformation of normal colonic mucosa into cancerous tissue (3). Numerous molecular signaling networks implicated in CRC initiation and progression have been reported in the literature, including the ERK/MAPK, TGF-β, PI3K/Akt, Src/FAK, and β-catenin related signal transduction pathways. These pathways are associated with the hallmarks of cancer, such as inflammation, angiogenesis, metastasis, and invasion. Notably, activation and over-expression of matrix metalloproteinases (MMPs) have been linked to these signal transduction pathways, making MMPs potential prognostic factors for CRC (4, 5). Thus, MMPs have been suggested to be potential prognostic factors for CRC.

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Key Words: Colorectal cancer, genotype, *MMP-8*, phenotype, polymorphism, Taiwan.

MMP-8 is an intriguing matrix metalloproteinase (MMP) that has been found to possess antitumor activity and immune-regulatory properties, although its role in CRC has not been extensively studied. MMP-8 is commonly expressed by neutrophils and is responsible for cleaving various substrates, including type I, II, and III collagen. A study conducted by Väyrynen and his colleagues in 2012 revealed that preoperative serum MMP-8 levels were higher in 148 patients with CRC compared to 83 controls. Furthermore, the levels of preoperative serum MMP-8 were positively correlated with disease stage, the extent of primary tumor necrosis, and blood neutrophil count (6). In 2018, Sirnio and his colleagues found that elevated serum MMP-8 levels were associated with decreased survival and systemic inflammation in patients with CRC (7). Additionally, in 2021, Reijonen *et al*. reported that high levels of MMP-8, both preoperatively and postoperatively, were associated with worse 10-year overall survival rates (8). However, the genetic role of *MMP-8* in CRC remains undisclosed.

In 2020, Tai *et al*. conducted a study to investigate the association between *MMP-8* rs11225395 polymorphism and CRC risk. The study included 551 CRC cases and 623 controls from a Han population (9). They found that individuals carrying the variant TT genotype had a 1.76-fold increased risk of CRC compared to those carrying the CC genotype. Furthermore, individuals carrying the rs11225395 TT genotype not only had a higher CRC risk but also exhibited poorer overall survival compared to those carrying the CC genotype (9). However, no other literature is available to validate their findings. Therefore, our aim was to examine the role of *MMP-8* rs11225395 in determining CRC risk in a Taiwanese population consisting of 362 patients with CRC and 362 controls.

Materials and Methods

Investigated CRC population. The recruitment of CRC cases and healthy controls followed the methodology outlined in our previous publications (10, 11). Briefly, CRC cases were recruited from patients visiting the Department of General Surgery at China Medical University Hospital (CMUH), and comprehensive pathological data were recorded for each case. The control subjects were carefully matched 1:1 to the cases based on age and sex. All participants provided informed consent and donated blood samples for the study. The study protocols were approved and overseen by the Institutional Review Board of CMUH (approval code: DMR99-IRB-108) and conducted in accordance with the principles of the Declaration of Helsinki.

Genotyping methodology of MMP-8 polymorphisms. Genomic DNA was extracted from the blood samples using a Qiagen kit (Qiagen, Chatsworth, CA, USA) according to the protocols described in our previous publication (12, 13). The genotyping of *MMP-8* rs11225395, rs34009635, and rs35866072 was carried out using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, as previously described (14, 15).

PCR amplification was conducted using a PCR Thermocycler (Bio-RAD, Hercules, CA, USA) with the following cycling conditions: initial denaturation at 94˚C for 5 min, followed by denaturation at 94˚C for 30 s, annealing at 64˚C for 40 s, and extension at 72˚C for 45 s. This was repeated for 35 cycles, followed by a final extension step at 72˚C for 10 min. The amplified PCR products for *MMP-8* rs11225395, rs34009635, and rs35866072 were visualized using 3% agarose gel electrophoresis to confirm the success of PCR amplification. Subsequently, the PCR products of *MMP-8* rs11225395, rs34009635, and rs35866072 were subjected to digestion using *Sfc* I, *Nla* III, and *Bbs* I, respectively. The resulting digestion fragments were then analyzed by 4% agarose gel electrophoresis to identify the specific genotypes.

Statistical analysis. To compare the ages between the case and control groups, we conducted an unpaired Student's *t*-test. The distributions of sex, personal habits, BMI, different *MMP-8* genotypes, and alleles among the subgroups were assessed using either Pearson's chi-square test (when n>5) or Fisher's exact test (when n≤5). The associations between different *MMP-8* genotypes and the risk of CRC were evaluated by calculating individual odds ratios (ORs) with their corresponding 95% confidence intervals (Cis). Statistical significance was indicated when *p*-value <0.05.

Results

Characteristics of study population. The demographic characteristics of the 362 patients with CRC and the matched 362 controls are shown in Table I. Since the controls were matched 1:1 to the cases based on age and sex, there were no significant differences in the distribution of these two variables between the case and control groups. Additionally, there were no significant differences in the distribution frequencies of smokers (p=0.543), alcohol drinkers (p=0.441), and individuals with lower (<24) or higher (≥24) BMI (p=0.181) between the case and control groups.

Association of MMP-8 rs11225395, rs34009635, and rs35866072 with CRC risk in Taiwan. The genotypes of *MMP-8* rs11225395 and rs34009635 in the control groups were consistent with the expected frequencies based on the Hardy-Weinberg equation (p=0.1401 and 0.7899, respectively). All individuals examined had the same TT genotype at the rs35866072 polymorphic site (Table II). There appeared to be no significant association between *MMP-8* rs11225395 genotypes and the risk of CRC (p for trend=0.3836). Specifically, compared to the wild-type CC genotype, individuals carrying the heterozygous variant genotype CT had an OR of 0.83 (95%CI=0.61-1.14, p=0.2963), whereas those carrying the homozygous variant TT genotype had a 0.77-fold increased risk of CRC (95%CI=0.48-1.23, p=0.3260). Individuals carrying the variant genotypes (CT+TT) had a 0.82-fold increased risk of CRC compared to those carrying the wild-type CC genotype (95%CI=0.61-1.10, p=0.2063) (Table II). Similarly, no significant association was found between *MMP-8*

Table I. *Selected characteristics of the 362 patients with colorectal cancer and 362 non-cancer controls.*

Characteristic	Controls, n=362		Cases, n=362		*p*-Value[a]
	n	%	n	%	
Age (years)					
≤60	95	26.2%	95	26.2%	1.0000
>60	267	73.8%	267	73.8%	
Sex					
Male	203	56.1%	203	56.1%	1.0000
Female	159	43.6%	159	43.9%	
Smoking					
Yes	84	23.2%	91	25.1%	0.5434
No	278	76.8%	271	74.9%	
Alcohol drinking					
Yes	51	14.1%	44	12.2%	0.4410
No	311	85.9%	318	87.8%	
BMI					
<24	175	48.3%	193	53.3%	0.1809
≥24	187	51.7%	169	46.7%	
Tumor size (cm)					
<5			195	53.9%	
≥5			167	46.1%	
Location					
Colon			257	71.0%	
Rectum			105	29.0%	
Lymph node involvement					
Negative			210	58.0%	
Positive			152	42.0%	

SD: Standard deviation; BMI: body mass index; [a]based on Chi-square test with Yates' correction.

rs34009635 genotypes and the risk of CRC. Specifically, compared to the wild-type AA genotype, individuals carrying the heterozygous variant genotype AC had an OR of 1.10 (95%CI=0.46-2.63, p=0.8247). No subjects were found to carry the *MMP-8* rs34009635 CC genotype (Table II).

Association of MMP-8 rs11225395, rs34009635, and rs35866072 allelic frequencies with CRC risk in Taiwan. The results of allelic frequency tests for *MMP-8* rs11225395, rs34009635, and rs35866072 polymorphic sites in relation to CRC risk are presented in Table III. Consistent with the findings in Table II, the frequency of the variant T allele in rs11225395 was slightly lower in the CRC patient group (29.7%) compared to the control group (33.1%) but did not reach statistical significance (p=0.1742). Individuals carrying the variant T allele had a 0.85-fold increased risk of CRC (95%CI=0.68-1.06). Similarly, there was no significant difference in the allelic frequency of *MMP-8* rs34009635 between the case and control groups (OR=1.10, 95%CI=0.46-2.61, p=0.8260) (Table III).

Stratified analyses of MMP-8 rs11225395 genotypes by age, sex, smoking, alcohol drinking, and BMI status. We conducted stratified analyses to examine the association between *MMP-8* rs11225395 genotype and CRC risk based on age, sex, smoking, alcohol drinking, and BMI status, and the results are presented in Table IV. Overall, significant associations between *MMP-8* rs11225395 genotype and CRC risk were observed in all the strata, except for the non-smoker subgroup. Notably, in the non-smoker subgroup, the risk associated with the homozygous variant TT genotype reached statistical significance (OR=0.53, 95%CI=0.30-0.93, p=0.0379). Even after adjusting for age, sex, BMI, and alcohol drinking behavior, the significance persisted (OR=0.57, 95%CI=0.28-0.88) (Table IV). However, no significant associations were found for *MMP-8* rs34009635 and rs35866072 polymorphic sites in any of the analyzed subgroups (data not shown).

Discussion

The precise role of MMP-8 in CRC carcinogenesis remains unclear. Previous studies have shown conflicting results regarding the correlation between MMP-8 protein levels and tumor malignancy in CRC. Verspaget and his colleagues reported a step-wise increase in MMP-8 levels correlating with tumor malignancy as early as 1999 (16). However, Koskensalo and Takeha did not observe a similar correlation

Table II. *Associations between MMP-8 genotypes and colorectal cancer risk in Taiwan.*

SNP	Genotype	Cases	Controls	*p*-Value	OR (95%CI)
rs11225395	CC	186 (51.4%)	168 (46.4%)		1.00 (Ref)
	CT	137 (37.8%)	148 (40.9%)	0.2963	0.83 (0.61-1.14)
	TT	39 (10.8%)	46 (12.7%)	0.3260	0.77 (0.48-1.23)
p_{trend}				0.3836	
p_{HWE}				0.1401	
	CT+TT	176 (48.6%)	194 (53.6%)	0.2063	0.82 (0.61-1.10)
rs34009635	AA	351 (97.0%)	352 (97.2%)		1.00 (Ref)
	AC	11 (3.0%)	10 (2.8%)	0.8247	1.10 (0.46-2.63)
	CC	0 (0.0%)	0 (0.0%)	---	---
ptrend				---	
pHWE				0.7899	
rs35866072	TT	362 (100.0%)	362 (100.0%)		1.00 (Ref)
	CT	0 (0.0%)	0 (0.0%)	---	---
	CC	0 (0.0%)	0 (0.0%)	---	---

OR: Odds ratio; CI: confidence interval; *p*-Values were calculated by Chi-square with Yates' correction; p_{HWE}: *p*-Value for Hardy-Weinberg Equilibrium; p_{trend}: *p*-Value for trend analysis.

Table III. *Associations of MMP-8 alleles with colorectal cancer risk.*

Allelic type	Cases	Controls	*p*-Value	OR (95%CI)
rs11225395				
C	509 (70.3%)	484 (66.9%)		1.00 (Ref)
T	215 (29.7%)	240 (33.1%)	0.1742	0.85 (0.68-1.06)
rs34009635				
A	713 (98.5%)	714 (98.6%)		1.00 (Ref)
C	11 (1.5%)	10 (1.4%)	0.8260	1.10 (0.46-2.61)
rs35866072				
T	724 (100.0%)	724 (100.0%)		1.00 (Ref)
C	0 (0.0%)	0 (0.0%)	1.0000	----

OR: Odds ratio; CI: confidence interval; *p*-Value was calculated by Chi-square with Yates' correction.

in their studies (17, 18). Furthermore, increased serum levels of MMP-8 have been reported in patients with CRC compared to healthy controls, and high levels of MMP-8 have been associated with increased malignancy, reduced survival rates, and systemic inflammation (6, 7, 19). In this current study, we investigated the potential contribution of *MMP-8* rs11225395, rs34009635, and rs35866072 genotypes to the risk of CRC in Taiwan. Our results indicate that none of these three SNPs, rs11225395, rs34009635, or rs35866072, were associated with an increased risk of CRC in the Taiwanese population (Table II and Table III).

Our findings are inconsistent with a previous study conducted by Tai and colleagues, which reported a significant association between the *MMP-8* rs11225395 TT genotype and increased CRC risk in a Chinese population (9). Their study had a representative sample size, including 551 CRC cases and 623 controls. However, they did not investigate other SNPs in their study.

In recent years, several studies have examined the association of *MMP-8* rs11225395 genotypes with various types of cancer in different populations. Kubben and colleagues found no association between *MMP-8* rs11225395 genotypes and gastric cancer risk or survival rate in the Dutch population (20). Qiu *et al*. reported no association between *MMP-8* rs11225395 genotypes and hepatocellular carcinoma risk in a subpopulation of Han Chinese consisting of 434 cases and 480 controls (21). Debniak *et al*. reported that *MMP-8* rs11225395 TT genotypes were associated with an increased risk of malignant melanoma in a Polish population (22). Nor Hashim and colleagues suggested that *MMP-8* rs11225395 polymorphism was a protective factor for nasopharyngeal carcinoma susceptibility in a Southeast

Table IV. *Associations between MMP-8 rs11225395 genotypes and colorectal cancer risk in stratified analyses.*

Genotype	Controls	Cases	OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value[c]
Age					
≤60 years old					
CC	47	49	1.00 (ref)	1.00 (ref)	
CT	37	36	0.93 (0.51-1.72)	0.96 (0.68-1.38)	0.9465
TT	11	10	0.87 (0.34-2.24)	0.91 (0.54-2.06)	0.9655
>60 years old					
CC	121	137	1.00 (ref)	1.00 (ref)	
CT	111	101	0.80 (0.56-1.16)	0.89 (0.63-1.14)	0.2778
TT	35	29	0.73 (0.42-1.27)	0.81 (0.52-1.46)	0.3289
Sex					
Males					
CC	96	102	1.00 (ref)	1.00 (ref)	
CT	82	77	0.88 (0.58-1.34)	0.89 (0.61-1.27)	0.6359
TT	25	24	0.90 (0.48-1.69)	0.86 (0.44-1.72)	0.8742
Females					
CC	72	84	1.00 (ref)	1.00 (ref)	
CT	66	60	0.78 (0.49-1.25)	0.76 (0.53-1.26)	0.3575
TT	21	15	0.61 (0.29-1.27)	0.69 (0.31-1.54)	0.2572
Smoking behavior					
Non-smokers					
CC	121	144	1.00 (ref)	1.00 (ref)	
CT	119	103	0.72 (0.51-1.04)	0.76 (0.44-1.10)	0.0979
TT	38	24	0.53 (0.30-0.93)	0.57 (0.28-0.88)	0.0379*
Smokers					
CC	47	42	1.00 (ref)	1.00 (ref)	
CT	29	34	1.31 (0.69-2.51)	1.28 (0.61-2.39)	0.5102
TT	8	15	2.10 (0.81-5.45)	1.67 (0.73-4.36)	0.1910
Alcohol drinking behavior					
Non-drinkers					
CC	139	165	1.00 (ref)	1.00 (ref)	
CT	130	123	0.80 (0.57-1.11)	0.77 (0.62-1.23)	0.2129
TT	42	30	0.60 (0.36-1.01)	0.57 (0.29-1.24)	0.0728
Drinkers					
CC	29	21	1.00 (ref)	1.00 (ref)	
CT	18	14	1.07 (0.44-2.63)	1.31 (0.51-2.87)	0.8758
TT	4	9	3.11 (0.84-11.46)	2.49 (0.69-7.93)	0.1196
BMI					
<24					
CC	84	100	1.00 (ref)	1.00 (ref)	
CT	69	71	0.86 (0.56-1.34)	0.88 (0.63-1.65)	0.5915
TT	22	22	0.84 (0.43-1.62)	0.87 (0.29-2.01)	0.7254
≥24					
CC	84	86	1.00 (ref)	1.00 (ref)	
CT	79	66	0.82 (0.52-1.27)	0.77 (0.70-1.78)	0.4327
TT	24	17	0.69 (0.35-1.38)	0.75 (0.29-2.14)	0.3815

[a]By multivariate logistic regression analysis; [b]by multivariate logistic regression analysis after the adjustments of confounding factors; [c]by Pearson's chi-square test (n>5) or Fisher's exact test (n≤5); *statistically significant; CI: confidence interval; aOR: adjusted odds ratio.

Asian population, including 24 Chinese, 24 Malaysians, and 48 controls (23). It is worth noting that although the sample size was small, this study was a genome-wide association study examining a panel of 768 SNPs. In an Indian study with 200 cases and 200 age-matched controls, *MMP-8* rs11225395 TT genotypes were found to decrease the risk of bladder cancer (24). Arechavaleta-Velasco *et al*. reported that *MMP-8* rs11225395 TT genotypes were associated with an increased risk of ovarian cancer in Mexican women (25). Their DNA samples were extracted from 35 malignant ovarian tumors, 51 benign tumors, and 37 normal ovary tissues, not from blood. Debniak and his colleagues also found no association between *MMP-8* rs11225395 genotypes and breast cancer risk (22). This is consistent with Hsiao's

study investigating 1,232 breast cancer cases and 1,232 age-matched non-cancer controls in Taiwanese women (26). On the contrary, Wang *et al*. reported that *MMP-8* rs11225395 TT genotypes increased the risk of breast cancer in a subpopulation of East Asians comprising 571 cases and 578 controls (27). In addition to the findings in breast cancer (26), other studies aimed at the Taiwanese population consistently showed no association between *MMP-8* rs11225395 genotypes and childhood leukemia (14), lung cancer (28), oral cancer (15), and bladder cancer risk (29). To date, there is only one study investigating the association of *MMP-8* rs34009635 and rs35866072 with cancer, which found no association with lung cancer risk (28).

In 2019, a meta-analysis was conducted by Feng *et al*. to address the inconsistent results from various studies investigating the association of *MMP-8* rs11225395 genotype with different types of cancer, including those mentioned previously. The meta-analysis revealed no association between *MMP-8* rs11225395 genotype and overall cancer risk worldwide (30). Based on the current available evidence, it is tentatively concluded that there may be an elevated cancer risk associated with *MMP-8* rs11225395 genotype in non-Asian populations, while no association has been found in Asian populations (30). This finding is consistent with the present study, which found no association between *MMP-8* rs11225395 genotype and CRC risk. Further studies are necessary to validate the role of *MMP-8* genotypes in determining individual susceptibility to different types of cancer, particularly CRC.

In the present study, we investigated the association between *MMP-8* genotypes, specifically *MMP-8* rs11225395 (C-799T at promoter region), rs34009635 (Val436Ala), and rs35866072 (Lys460Thr), and the risk of CRC in the Taiwanese population. Our findings, as summarized in Table II and Table III, indicate that none of these genotypes were significantly associated with CRC risk. Furthermore, when we performed stratified analyses based on age, sex, smoking status, drinking status, and BMI of patients with CRC, no significant joint effects between these subgroups and *MMP-8* rs11225395 genotype were observed, except in the case of non-smokers (Table IV). However, the underlying mechanisms by which the *MMP-8* rs11225395 TT genotype exerts a protective effect on non-smokers with respect to CRC risk remain unknown. Further investigations are warranted to provide a comprehensive understanding of these mechanisms. Interestingly, a previous study has suggested that the *MMP-8* rs11225395 TT genotype may be associated with higher expression levels of MMP-8 in the serum of CRC patients (9).

In conclusion, our study findings suggest that the genotypes of *MMP-8* rs11225395, rs34009635, and rs35866072 are not associated with a modified risk of CRC in the Taiwanese population. However, we observed a potential protective effect of the TT genotype of *MMP-8* rs11225395 in non-smokers. Further investigations are required to validate and elucidate the role of *MMP-8* genotypes in determining individual susceptibility to various types of cancer, particularly CRC.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Conceptualization: D.Y., D.T.B., C.W.T. and W.S.C.; Collection: T.W.K. and Y.C.H.; Data curation: M.C.M. and C.W.T.; Genotyping: Y.C.W., Y.T.C. and W.S.C.; Statistics: Y.C.Y. and C.W.T.; Phenotyping: D.T.B. and W.S.C.; Project administration: T.C.Y. and D.T.B.; Supervision: D.T.B., W.S.C. and C.W.T.; Validation: T.W.K. and W.S.C.; Writing – original draft: D.Y., and C.W.T.; Writing – review and editing, D.T.B., D,Y. and W.S.C.; All Authors have read and agreed to the published version of the manuscript.

Acknowledgements

The Authors would like to acknowledge the Tissue-Bank of China Medical University Hospital for their invaluable technical support. Furthermore, the Authors would like to extend their gratitude to all the study participants, as well as the doctors, nurses, and colleagues who contributed to the study. The technical assistances from Yu-Hsin Lin, Yi-Wen Hung, and Hou-Yu Shih are appreciated by all the Authors.

Funding

This study received significant support from China Medical University Hospital (DMR-112-022). The funders had no involvement in the study design, data collection, statistical analysis, decision to publish, or manuscript preparation.

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Received June 13, 2023
Revised July 13, 2023
Accepted July 14, 2023