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# Association of Clinicopathological Factors With MMP13 (rs2252070) Gene Polymorphism in Swedish Patients With Colorectal Cancer

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**Abstract.** *Background/Aim: Matrix metalloproteinase 13 (MMP13) has been reported to be involved in tumor development and progression, including of colorectal cancer (CRC). This study aimed at evaluating whether the MMP13 rs2252070 gene polymorphism is associated with clinicopathological factors and its influence on long-term survival in Swedish patients with CRC. Patients and Methods: A total of 723 patients with CRC were genotyped using TaqMan single nucleotide polymorphism assays based on polymerase chain reaction. Results: Assessing clinicopathological factors, we demonstrated that having the G/G genotype for MMP13 rs2252070 was significantly associated with poor differentiation, higher serum level of carcinoembryonic antigen and higher lymph node status. Moreover, the presence of a G allele was significantly related to larger tumor size in rectal cancer but had a significantly protective role against mucinous cancer, perineural invasion and lymphovascular invasion. Kaplan-Meier analysis showed no difference between genotypes regarding cancer-specific survival. Conclusion: Our findings highlight the potential of MMP13 rs2252070 polymorphism as a useful predictor of poor differentiation, serum level of carcinoembryonic antigen, lymph node status, tumor size, mucinous cancer, perineural invasion and lymphovascular invasion in patients with CRC.*

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*Key Words:* MMP13, SNP, colorectal cancer, clinical parameters.



Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies worldwide (1). The initiation and progression of CRC are not completely known but accumulated insights have increased our understanding of diverse genetic and epigenetic changes (2, 3). Moreover, inflammatory processes and interactions between various cell types, in the tumor microenvironment (TME), such as lymphocytes, macrophages and fibroblasts have been linked to the initiation, progression and metastasis of CRC (4, 5). Through its interpatient and intratumor heterogeneity, CRC can have a pronounced effect on both treatment and prognosis (6). Therefore, it is important to improve patient diagnosis and prognosis through the selection of personalized therapy for patients with CRC by identification of new molecular biomarkers (7).

The composition of the TME is complex and, in addition to varying cell types, includes extracellular matrix (ECM) which, among other things, consists of proteins that can undergo remodeling and degradation (4, 8). These processes play an essential role not only in a wide range of physiological events such as tissue morphogenesis and wound healing but also during pathophysiological events such as tumor progression, including angiogenesis, invasion, and metastasis (8).

One specific group of proteolytic enzymes, matrix metalloproteinases (MMPs), has a dominant role during degradation of ECM, resulting in numerous biological

activities including signaling pathway modification, cell migration, proliferation, tumor promotion and inflammatory responses (8, 9). According to their substrate specificities, MMPs are divided into different subtypes (9). MMP13 (also known as collagenase-3) as a member of the collagenase subfamily can degrade a variety of collagens but also non-collagenous compounds such as fibronectin and laminin (10). Several studies have investigated the relationship between MMP13 and cancer, proposing that MMP13 is involved in tumor progression in head and neck, oral, renal, bladder, breast, and colorectal cancer (9-11).

Genetic variations, such as single nucleotide polymorphisms (SNPs), have been shown to be associated with gastrointestinal cancer, including CRC, and play a role in susceptibility as well as survival of patients with CRC (11-13). Several MMP-encoding SNPs have been discovered that affect gene and protein expression, as well as the enzymatic activity of MMP, and some of them constitute a risk factor (12-14).

The polymorphism rs2252070 (-70A/G) in *MMP13* gene on the human chromosome 11q22 is located in the promotor region and is known to influence *MMP13* transcription (14). The A allele is associated with two-fold higher transcriptional activity of the gene compared with that of the G allele (14). Overall, the expression and activation of MMP13 in cancer is regulated at multiple levels and by many factors including genetic components, cytokines, and proteases.

In the present study, we analyzed the *MMP13* rs2252070 polymorphism and its link with various clinical features and long-term survival in Swedish patients with CRC.

Table I. *Clinicopathological characteristics of patients with colorectal cancer (n=723).*

| Characteristic | | Value |
|---|---|---|
| Age, years | Median (range) | 73 (25-94) |
| Sex, n (%) | Female | 325 (45.0) |
| | Male | 398 (55.0) |
| Depth of tumor, n (%) | T1+T2 | 155 (21.4) |
| | T3 | 488 (67.5) |
| | T4 | 80 (11.1) |
| Tumor differentiation, n (%) | High/Medium | 567 (78.4) |
| | Poor | 156 (21.6) |
| TNM stage, n (%) | I | 121 (16.8) |
| | II | 267 (36.9) |
| | III | 248 (34.3) |
| | IV | 87 (12.0) |
| Tumor location, n (%) | Colon | 405 (56.0) |
| | Rectum | 318 (44.0) |
| Histological type, n (%) | Non-mucinous | 631 (87.3) |
| | Mucinous | 92 (12.7) |
| Recurrence, n (%) | No | 540 (78.8) |
| | Yes | 145 (21.2) |
| Tumor size, n (%) | <4 cm | 274 (42.0) |
| | ≥4 cm | 378 (58.0) |
| Lymph vascular invasion (LVI), n (%) | No | 413 (91.0) |
| | Yes | 41 (9.0) |
| Perineural invasion (PNI), n (%) | No | 405 (80.5) |
| | Yes | 98 (19.5) |
| Preoperative serum CEA, n (%) | <5 ng/ml | 325 (69.1) |
| | ≥5 ng/ml | 145 (30.9) |
| Lymph node status, n (%) | N0 | 396 (57.9) |
| | N1 | 169 (24.7) |
| | N2 | 119 (17.4) |

CEA: Carcinoembryonic antigen.

## Patients and Methods

*Patients and controls.* The study utilized blood samples from 723 patients with primary colorectal adenocarcinomas collected between 1996 and 2021 at the Department of Surgery, Ryhov County Hospital, Jönköping, Sweden. The samples were collected according to availability in strict chronological order and the patient data were prospectively recorded in a database. Follow-up for the estimation of cancer-specific survival ended on the date of death or in February 2022. Clinicopathological characteristics of the patients are shown in Table I and the tumors were classified according to The American Joint Committee on Cancer (AJCC) classification system (15).

Blood samples were collected at the start of surgery and were centrifuged to separate plasma and blood cells and then stored at –70˚C until analysis.

The investigation was approved by the Regional Ethical Review Board in Linköping, Linköping, Sweden (Dnr. 2013/271-31) and informed consent was obtained from each of the participants.

*Genotyping of MMP13 gene polymorphism.* Genomic DNA was isolated from all blood samples using QiaAmp DNA Blood Kit (Qiagen, Hilden, Germany). Genotyping was analyzed using TaqMan SNP genotype assays for *MMP13* rs2252070 (ID C-254740883_10; Applied Biosystems, Foster City, CA, USA). Ten nanograms of DNA was mixed with TaqMan Genotyping Master Mix (Applied Biosystems) and was analyzed with the 7500 Fast Real-Time PCR System (Applied Biosystems). The polymerase chain reaction was performed using an initial cycle at 50˚C for 2 min followed by one cycle at 95˚C for 10 min and finally 40 cycles at 95˚C for 15 s and at 60˚C for 1 min. The manual calling option in the allelic discrimination application ABI PRISM 7500 SDS software version 1.3.1 (Applied Biosystems) was used to assign the genotypes.

*Statistical analysis.* The genotype associations according to clinicopathological characteristics within the CRC subgroups were analyzed using the chi-squared test. The strength of association was assessed by calculation of the odds ratio (OR) with 95% confidence interval using logistic regression. The ORs were adjusted for potential covariates in accordance with Table I by multiple logistic regression models. Survival analysis was performed by Kaplan-Meier analysis with log-rank test and Cox´s regression. Statistical analysis was performed using Stata Statistical Software Release 15 (Stata Corp. College Station, TX, USA) and SPSS software for Windows, version 14.0 for (SPSS Inc., Chicago, IL, USA). Associations with values of $p<0.05$ were considered significant.

Table II. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and tumor differentiation in 723 patients with colorectal cancer.*

| Genotype | High/medium (N=567) | Poor (N=156) | OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| A/A | 276 (48.7) | 75 (48.1) | 1.00 (reference) | | | |
| G/A | 244 (43.0) | 57 (36.5) | 0.86 (0.58-1.26) | 0.441 | | |
| G/G | 47 (8.3) | 24 (15.4) | 1.88 (1.08-3.27) | **0.026** | 1.50 (1.09-1.94) | **0.010** |
| G/A+G/G | 291 (51.3) | 81 (51.9) | 1.02 (0.72-1.46) | 0.894 | | |

AOR: Adjusted odds ratio; CI: confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

Table III. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and the serum level of carcinoembryonic (CEA) in 470 patients with colorectal cancer.*

| Genotype | <5 ng/ml CEA (N=325) | ≥5 ng/ml CEA (N=145) | OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| A/A | 156 (48.0) | 69 (47.6) | 1.00 (reference) | | | |
| G/A | 147 (42.2) | 55 (37.9) | 0.84 (0.55-1.28) | 0.434 | | |
| G/G | 22 (6.8) | 21 (14.5) | 2.16 (1.11-4.18) | **0.023** | 2.20 (1.09-4.42) | **0.027** |
| G/A+G/G | 169 (49.0) | 76 (52.4) | 1.02 (0.68-1.50) | 0.933 | | |

AOR: Adjusted odds ratio; CI: Confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

Table IV. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and mucinous cancer in 723 patients with colorectal cancer.*

| Genotype | Non-mucinous (N=631) | Mucinous (N=92) | OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| A/A | 297 (47.1) | 54 (58.7) | 1.00 (reference) | | | |
| G/A | 270 (42.8) | 31 (33.7) | 0.63 (0.39-1.01) | **0.054** | 0.67 (0.40-1.03) | 0.055 |
| G/G | 64 (10.1) | 7 (7.6) | 0.60 (0.26-1.38) | 0.231 | | |
| G/A+G/G | 334 (52.9) | 38 (41.3) | 0.62 (0.40-0.97) | **0.038** | 0.78 (0.62-0.98) | **0.037** |

AOR: Adjusted odds ratio; CI: Confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

## Results

*Correlation between MMP13 rs2252070 polymorphism and clinicopathological characteristics of patients with CRC.* *MMP13* genotypes were evaluated in the CRC cohort to clarify the role of *MMP13* polymorphism in clinicopathological characteristics. We found several statistically significant associations with the genotypic variants of *MMP13* rs2252070 including tumor differentiation (Table II), carcinoembryonic antigen (CEA) (Table III), mucinous cancer (Table IV), perineural invasion (PNI) (Table V), lymphovascular invasion (LVI) (Table VI), tumor size (Table VII) and lymph node status (Table VIII). No association was found between *MMP13* rs2252070 and patent age, sex, depth of tumor, TNM stage, tumor location or recurrence (data not shown).

When we evaluated all the associations between *MMP13* rs2252070 and clinicopathological features, we compared patients carrying the G/A or G/G genotype with those carrying the A/A genotype.

Individuals carrying the G/G genotype were significantly more likely to have poorly differentiated cancer (OR=1.50, $p$=0.010) and a higher level of preoperative serum CEA (OR=2.20, $p$=0.027) (Table II and Table III). Moreover, we noted that carrying a G allele had a protective role against developing mucinous cancer (G/A+G/G: OR=0.78, $p$=0.037), PNI (G/A: OR=0.75, $p$=0.032; G/A+G/G: OR=0.77, $p$=0.039) and LVI (G/A: OR=0.53, $p$=0.004; G/A+G/G: OR=0.64, $p$=0.016) (Table IV, Table V and Table VI, respectively). Further, our study established that tumor size ≥4 cm in rectal cancer was more common in patients

Table V. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and perineural invasion (PNI) in 503 patients with colorectal cancer.*

| Genotype | No PNI (N=405) | PNI (N=98) | OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| A/A | 180 (44.4) | 55 (56.1) | 1.00 (reference) | | | |
| G/A | 187 (46.2) | 34 (34.7) | 0.59 (0.37-0.95) | **0.032** | 0.75 (0.60-0.97) | **0.032** |
| G/G | 38 (9.4) | 9 (9.2) | 0.77 (0.35-1.70) | 0.525 | | |
| G/A+G/G | 225 (55.6) | 43 (43.9) | 0.62 (0.40-0.97) | **0.038** | 0.77 (0.63-0.98) | **0.039** |

AOR: Adjusted odds ratio; CI: Confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

Table VI. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and lymphovascular invasion (LVI) in 454 patients with colorectal cancer.*

| Genotype | No LVI (N=413) | LVI (N=41) | OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| A/A | 198 (47.8) | 27 (65.9) | 1.00 (reference) | | | |
| G/A | 180 (43.7) | 8 (19.5) | 0.32 (0.14-0.73) | **0.007** | 0.53 (0.35-0.82) | **0.004** |
| G/G | 35 (8.5) | 6 (14.6) | 1.25 (0.48-3.26) | 0.638 | | |
| G/A+G/G | 215 (52.2) | 14 (34.1) | 0.48 (0.24-0.94) | **0.031** | 0.64 (0.44-0.92) | **0.016** |

AOR: Adjusted odds ratio; CI: Confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

Table VII. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and tumor size in 289 patients with colorectal cancer.*

| Genotype | Tumor size <4 cm (N=140) | Tumor size ≥4 cm (N=149) | OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| A/A | 80 (57.1) | 62 (41.6) | 1.00 (reference) | | | |
| G/A | 49 (35.0) | 73 (49.0) | 1.92 (1.17-3.14) | **0.009** | 1.91 (1.15-3.16) | **0.012** |
| G/G | 11 (7.9) | 14 (9.4) | 1.64 (0.69-3.86) | 0.256 | | |
| G/A+G/G | 60 (42.9) | 87 (58.4) | 1.87 (1.17-2.98) | **0.009** | 1.79 (1.11-2.90) | **0.017** |

AOR: Adjusted odds ratio; CI: Confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

Table VIII. *Association between matrix metalloproteinase 13 gene polymorphism rs2252070 and lymph node status in 684 patients with colorectal cancer.*

| Genotype | N0 (N=396) | N1 (N=169) | N2 (N=119) | *p*-Value | N1 *vs*. N2 OR (95% CI) | *p*-Value | AOR (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|---|---|
| A/A | 196 (49.5) | 82 (48.5) | 55 (46.2) | **0.027** | 1 (reference) | | | |
| G/A | 162 (40.9) | 79 (46.8) | 45 (37.8) | | 0.85 (0.51-1.40) | 0.522 | | |
| G/G | 38 (9.6) | 8 (4.7) | 19 (16.0) | | 3.54 (1.45-8.65) | **0.006** | 3.82 (1.39-10.40) | **0.009** |

AOR: Adjusted odds ratio; CI: Confidence interval; OR: odds ratio. Statistically significant *p*-values are shown in bold.

carrying a G allele (G/A: OR=1.91, $p$=0.012; G/A+G/G: OR=1.79, $p$=0.017; Table VII).

Regarding the presence of metastatic lymph nodes, we found that the genotype distribution between the different lymph node status was statistically different ($p$=0.027) and that G/G was markedly more common in patients with a higher lymph node status (N2) (OR=3.82, $p$=0.009; Table VII).

*MMP13 gene polymorphism and cancer-specific survival*. Follow-up data were available for 684 patients and Kaplan-Meier analysis showed that cancer-specific survival did not significantly differ according to genotype (Figure 1). Moreover, stratification analysis with regard to clinical parameters showed no significant survival difference controlled by the genotypes for *MMP13* rs2252070 (data not shown).

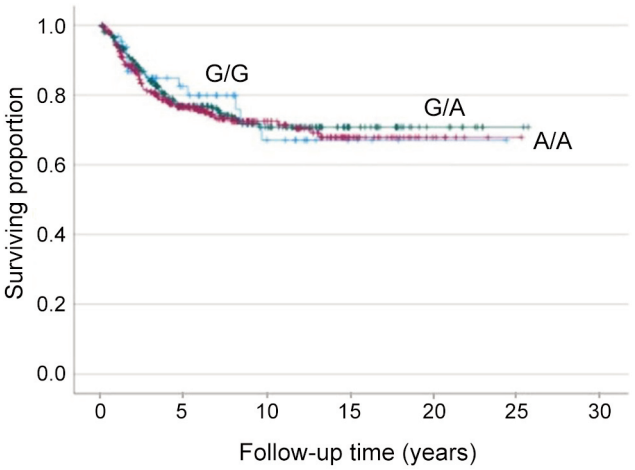


Figure 1. *Kaplan–Meier analysis of the effect of matrix metalloproteinase 13 rs2252070 polymorphism on cancer-specific survival among patients with colorectal cancer. Follow-up data for 684 patients were available; the numbers of carriers of genotype A/A, G/A and G/G were 333, 286 and 65, respectively. Log-rank test, p>0.05.*

## Discussion

Mucinous cancer is an aggressive subtype of CRC and the factors involved in the development of mucinous CRC are not yet known (16).

PNI is defined as tumor growth in, around and through nerves, and has been identified as an important pathological feature of a number of malignancies, including tumors of the pancreas, colon, rectum, prostate and stomach (17). PNI has been shown to be a marker of poor prognosis and reduced survival, including in CRC (18). The molecular mechanisms of PNI have not been successfully identified but the migration of tumors into the nerve sheath requires degradation of the ECM, which can be facilitated by MMPs (17).

The lymphatic system is an important metastatic pathway for CRC. LVI is defined as the presence of tumor cells in the lymphatic system and vascular structures and has gained acceptance as a predictor of poor outcome in patients affected by CRC (19, 20).

Accumulating evidence has established that SNPs of MMPs are associated with gastrointestinal cancer, including CRC (11, 13). Several SNPs in genes encoding MMPs influence MMP gene expression, protein production and thereby the enzymatic activity (11).

In the present study, we examined the association of *MMP13* rs2252070 gene polymorphism with various clinical features and long-term survival in Swedish patients with CRC. Our data showed an association with mucinous cancer, PNI and LVI, where we found that carrying a G allele has a protective role against these clinical features. Yoon *et al*. (14) concluded that the A allele in *MMP13* rs2252070 is associated with two-fold higher transcriptional activity of the gene compared with that of the G allele. One could speculate that our data regarding mucinous cancer, PNI and LVI reflect the transcriptional activity and therefore the level and activity of MMP13. In that case, however, our data contradict a study by Foda *et al*. (21) in which the protein expression of MMP13 was found to be significantly higher in non-mucinous carcinomas compared to mucinous carcinomas.

The promoter of *MMP13* contains several binding sites for transcription factors *e.g.,* activating protein-1 (*AP1*), inhibitor of growth family member 2 (*ING2*) and polyomavirus enhancer activator 3 *(PEA3)* (10). Besides the regulation of expression by transcription, the activity of *MMP13* is controlled by presence of tissue inhibitor of metalloproteinases in the TME (8). Moreover, intrinsic mechanisms, such as changes of expression of oncogenes and tumor suppressors, seem to directly activate *MMP13* expression (10, 22). Thus, the activity of MMP13 can be modulated in different ways.

According to the AJCC classification system (15), T stage, *i.e.,* the depth of tumor invasion, is used rather than tumor size defined as the maximum diameter of the horizontal tumor extension. One study suggests that in patients with tumors at the same T stage, the prognosis of those with a larger tumor size is worse than that of patients with a smaller tumor size, which may be due to the larger tumor burden and higher possibility of invading vascular and lymphatic channels by larger tumors (23). The tumor size has been reported to be prognostic in CRC and has an impact on survival (23-25), but it remains controversial.

Previous studies have investigated the relationship between *MMP13* and CRC and proposed that *MMP13* is involved in tumor progression [reviewed in (10)] and indicate that the *MMP13* expression in tumor tissue is significantly higher than in the corresponding normal mucosa (26). However, no association with tumor size has been found (26). In our study, in terms of genotypes of *MMP13* rs2252070, we established that the tumor size ≥4 cm was more common in both G allele carriers regarding rectal cancer. To the best of our knowledge, this study is the first to show an association between *MMP13* gene polymorphism and tumor size in rectal cancer. The resulting difference here between the colon and rectum may be the obvious difference

in molecular carcinogenesis, pathology, and expression of distinguishable genes for these locations (27). The underlying molecular mechanism involved in this process is unclear and requires detailed analyses. Regardless of the mechanism, our findings suggest a role for *MMP13* gene polymorphism in modulating tumor size.

CEA is a large glycoprotein involved in cell adhesion and is secreted by a variety of tumors, including CRC (28). Both preoperative and postoperative serum levels of CEA are used in clinical practice as a prognostic factor and to monitor recurrence for patients with CRC. However, controversy exists, and previous studies have noted different effectiveness regarding its associations with stage and prognosis (28-30). In this study, we found that individuals carrying the G/G genotype in *MMP13* rs2252070 had a higher preoperative level (≥5 ng/ml) of CEA in serum. Furthermore, we noted that the carriers of the G/G genotype were more likely to have poorly differentiated cancer. One research group demonstrated that preoperative serum levels of CEA did not correlate with tumor differentiation, but multivariate analysis revealed that the preoperative serum level of CEA was a significant independent prognostic factor (31). It remains to be clarified whether our results regarding the G/G genotype are related to the preoperative serum level of CEA and poorly differentiated cancer.

Lymph node involvement is an important variable of the AJCC system (15). The classification of lymph node status, N0-N2, represents tumor aggressiveness and progression of CRC, and is a predictor of worse outcome (32). In a previous report, a positive correlation between *MMP13* expression and lymph node status was found (33). In our study, the genotypes of *MMP13* rs2252070 were evaluated in a CRC cohort to clarify their role in lymph node status. We observed that the lymph node status by genotype distribution was statistically different, and that the G/G genotype was markedly more common in patients with N2 tumors. The underlying mechanisms should be further investigated.

In the present study, we examined the relationship between *MMP13* rs2252070 polymorphism and clinicopathological factors in patients with CRC and demonstrated that the presence of G/G was significantly associated with poor differentiation, higher serum level of CEA and increased lymph node status. Moreover, the presence of a G allele was significantly related to larger tumor size in rectal cancer but had a protective role against mucinous cancer, PNI and LVI. For other parameters, such as age, sex, depth of tumor, TNM stage, tumor location and recurrence, no relation to *MMP13* rs2252070 gene polymorphism were identified.

*MMP13* rs2252070 (-70A/G) is associated with altered transcriptional activity, with twice as much transcriptional activity with the A allele compared to the G allele in the same position (14). It is possible that the gene expression of *MMP13* is concomitant with other gene–gene or gene–environmental interactions. The effects of the G/G genotype may not be attributed to a reduced level of MMP13 *per se*, but a possible change in the balance between different MMPs. *MMP13* has as a central role in the MMP activation cascade by the activation of other MMPs, such as MMP2 and MMP9, which has been suggested to be a pivotal event in the development of CRC (8, 10). However, much remains unknown about the possible coordination of MMP13 action with other MMP family members during cancer pathogenesis. Tumor necrosis factor-α is an inflammatory mediator, one of several present at high levels in solid tumors and the serum of patients with CRC and is implicated in the progression and metastatic development of CRC (8, 10). A previous study has reported the regulation of *MMP13* through the activation of extracellular signal-regulated kinase–nuclear factor κB–*MMP13* pathway promotes by the chemokine receptor CCR4 resulting in up-regulation of tumor necrosis factor-α in CRC (34).

In CRC development, intrinsic mechanisms include changes of expression of oncogenes and tumor-suppressor genes (2, 3). Suppression of tumor-suppressor gene *p53* increases MMP13 expression in squamous cell carcinomas of the head and neck (22). Recently, a study indicated that MMP13 plays a key role in the context of the TWIST family bHLH transcription factor 1–CD44–MMP13 axis in tumor aggressiveness in esophageal squamous cell carcinoma and in epithelial–mesenchymal transition driven tumor progression (35). Further studies may confirm whether the results can be translated to CRC.

Some limitations of this study are worth noting. This study was of an exploratory nature. Factors influencing carcinogenesis such as environmental and lifestyle factors were not considered. The patients were selected from one hospital and therefore the generalizability of our results is limited, and they should be validated in another cohort. Moreover, further studies are required in which a larger number of samples must be examined.

In conclusion, as described in previous studies, there is an involvement of *MMP13* in CRC progression and metastasis. The exact mechanisms of its regulation and actions are still not fully understood. The current study is, to our knowledge the first to investigate the relationship between *MMP13* rs2252070 and a large number of clinicopathological factors in Swedish patients with CRC.

We noted that *MMP13* rs2252070 is a useful predictor of differentiation, serum level of CEA, lymph node status and tumor size in rectal cancer, and the presence of a G allele has a protective role against mucinous cancer, PNI and LVI in CRC. Considering the multifaceted role of *MMP13* in CRC, more in-depth research is needed for further understanding of the significance of *MMP13* rs2252070 in CRC.

## Conflicts of Interest

The Authors declare no conflicts of interest.

## Authors' Contributions

Research design and prepared the manuscript: SVN, DW and JD. Statistical analysis: SVN and JD. Performed the laboratory work: LS and SVN. Responsible for patient data and follow-up: KL and LS. Review and revision: SVN, LS, KL, DW and JD.

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