JMU
Jurnal Medika Udayana

ISSN: 2597-8012 JURNAL MEDIKA UDAYANA, VOL. 13 NO.05, MEI, 2024

Received: 2023-12-22 Revision: 2024-02-24 Accepted: 02-04-2024

ASSOCIATION OF MMP-7-181A>G GENE POLYMORPHISM AND COLORECTAL CANCER RISK AT PROF.DR.I.G.N.G.NGOERAH GENERAL HOSPITAL BALI

Christian Chandra[1]; Desak Made Wihandani[2,*]; I Gede Putu Supadmanaba[2]; Ni Nyoman Ayu Dewi[2]; Putu Anda Tusta Adiputra[3].

[1]Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia;
[2]Department of Biochemistry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia;
[3]Department of Surgical, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia;
[*]Corresponding Author.
e-mail: dmwihandani@unud.ac.id

ABSTRACT

Background: Colorectal cancer is the third most diagnosed cancer worldwide and ranks second as the cause of cancer-related mortality. Matrix Metalloproteinase (MMP) enzymes are known to be closely associated with the carcinogenesis of colorectal cancer. The MMP-7-181A>G polymorphism has been previously linked to the risk of various types of cancer. However, the association of the MMP-7-181A>G polymorphism with the risk of colorectal cancer has not been investigated in Indonesia. *Objective:* This study aims to determine the relationship between the MMP-7-181A>G polymorphism and the risk of colorectal cancer. *Methods:* Polymerase chain reaction (PCR) followed by Sanger sequencing was employed to obtain genotype data from 26 cases and 26 controls. Univariate and bivariate statistical analyses were conducted to determine the association of MMP-7-181A>G polymorphism to the risk of colorectal cancer by evaluating obtained Odds Ratio (OR) and p-values. *Results:* The distribution of the AG and GG variants in the case group was 23.1% and 3.8%, respectively. Meanwhile, the distribution of the AG and GG variants in the control group was 15.4% and 0%. Data analysis shows an insignificant increase in colorectal cancer risk in genotypes with the G allele (OR=2.02, 95% CI: 0.51-8.00, p=0.308). *Conclusion:* The study suggests that the MMP-7-181A>G polymorphism cannot be directly associated with colorectal cancer risk, emphasizing the need to consider multiple interactions with other MMP gene polymorphisms. Further investigations into direct associations of this polymorphism with MMP-7 expression levels in colorectal cancer lesions could help give a clearer understanding of genetic risk factors in colorectal cancer.

Keywords : Colorectal Cancer., Colorectal Cancer Risk Factors., MMP-7-181A>G Polymorphism

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world, accounting for 10% of all cancer cases. CRC also ranks second as the cause of cancer-related deaths worldwide.[1] In 2035, it is projected that the incidence of colorectal cancer will increase to reach up to 2-5 million new cases, with a prominently higher rise in incidence among individuals under 50 years of age.[2] In the Asia-Pacific region, CRC is among the top five cancers, with the highest prevalence in high-income countries such as Japan, Korea, and Singapore. Due to an initially higher prevalence outside of Asia, studies targeting colorectal cancer in the Asian population have not been as extensively investigated compared to studies focusing on Western populations.[3] In Indonesia, the number of new colorectal cancer cases by 2020 ranked fourth overall and second among men, with a total of 34,189 new cases (8.6%) and 17,786 deaths (7.6%) in both genders.[4] In Bali province, specifically at Prof. Dr. I.G.N.G Ngoerah Bali General Hospital, 133 cases of colorectal cancer were identified between 2009 and 2014, and showing a continuous trend of increasing case numbers.[5]

In the progression and carcinogenesis of cancer, the process of remodeling the microenvironment by specific proteinase enzymes, particularly the Matrix Metalloproteinases (MMP) group, becomes the main mediator of changes in the microenvironment observed in cancer progression.[6] These changes in the microenvironment are an important part of cancer progression because they contribute to the hallmarks of cancer. MMPs are known to interact with growth factors such as epidermal growth factor receptor (EGFR), insulin-

like growth factors (IGFs), transforming growth factor (TGF)-α, and heparin-binding EGF (HB-EGF). MMPs also can help cancer cells avoid apoptosis, for example, by cleaving ligand-FAS by MMP-7, cleaving laminin that affects integrin signaling, and indirectly interacting with serine/threonine kinase Akt/protein kinase B through IGFR and EGFR.[7]

In colorectal cancer, a subtype of matrix metalloproteinase class enzyme, MMP-7, was found to have increased expression in cancer lesions.[8] The significant change in expression when compared to normal tissue is known to be influenced by the mechanism of regulation of its expression. MMP-7 itself, in its expression, goes through various stages of regulation, one of which is the transcriptional regulation process. In transcriptional regulation, the promoter part, which is a non-coding DNA region located upstream of the main coding gene, plays an important role as a docking site for RNA polymerase, the binding site for various transcription factors, and influences epigenetic mechanisms such as DNA methylation and histone modification.[9] The presence of polymorphism promoter region, one of which is the Single Nucleotide Polymorphism (SNP), will affect the expression of the MMP-7 gene. The presence of polymorphism has been frequently linked with the risk of colorectal cancer.[10] In vitro research findings have also discovered a significant increase in MMP-7 expression in the homozygous model of the MMP-7-181A>G polymorphism (rs11568818).[11] This polymorphism is one of the polymorphisms in the MMP-7 gene promoter region that has been widely studied because it shows potential association with the risk of colorectal cancer through mechanism of increased MMP-7 expression. The MMP-7-181A>G polymorphism is a transition from A to G at the non-coding region on position -181 behind the transcription start site of the MMP-7 gene.[12] This SNP occurs in its promoter region, whereas the coding gene for MMP-7 protein itself is located in position 11q21-q22, consisting of 13 exons.[13]

Several studies have been conducted in various populations with different ethnicities, including Caucasian, Asian, and Latin in multiple different countries. It is found that there is a general increase in the risk of cancer associated with the MMP-7-181A>G polymorphism. However, specific to colorectal cancer, the findings from both meta-analyses and individual studies remain inconsistent. The latest meta-analysis, in particular, identified a significant association of this polymorphism to colorectal cancer risk only in Asian populations, with no significant association observed in populations outside Asia.[14]

In Southeast Asia, especially in Indonesia, there is currently a lack of research investigating MMP-7-181A>G polymorphism and its association with the risk of colorectal cancer. Based on this gap, we conducted a study on this polymorphism to gather distribution data of this polymorphism variant among the Balinese population. Whereas, through the case-control study design, we aimed to assess the association between this polymorphism and the risk of colorectal cancer in Bali.

METHODS

In this *case-control* study, samples were collected from patients admitted to Prof. dr. I.G.N.G Ngoerah General Hospital Bali in the years 2019 – 2022. The total number of research samples used in this study which have been selected based on inclusion and exclusion criteria was 52 samples. These samples were grouped into a case group consisting of 26 samples and a control group of colorectal polyp cases consisting of 26 samples. The inclusion criteria in the case group include all patient who has been diagnosed with colorectal cancer by the excellent medical team from the Department of Digestive Surgery at Prof. dr. I.G.N.G Ngoerah General Hospital Bali, and its sample has been stored as a biological material in the form of DNA isolates at the Biochemistry Laboratory, Faculty of Medicine, Udayana University. Exclusion criteria applied for control group included all form of previous malignancy or metastasized cancer from either known or unknown origin. This study has been ethically reviewed and approved by the Local Research Ethics Committee Unit of Udayana University (Ethical clearance identification number: 776/UN14.2.2. VII.14/LT/2023).

To determine the distribution of MMP-7-181A>G polymorphism variants among samples, *Polymerase Chain Reaction* (PCR) amplification of DNA isolates obtained from peripheral blood was done using the following primers: Forward : F-5'-TGGTACCATAATGTCCTGAAT-3' and Reverse : R-5'-TTTATATAGCTTCTCAGCCTCG-3'. These primers were specifically designed to include rs11568818 polymorphism in its fragment by amplifying sequence fragments of 277 bp long. The condition used for PCR cycle were as follow : single initial denaturation cycle at 95^0 C for 5 minutes, 35 cycles of 95^0 C for 15 seconds, 55.9^0 C for 1 minutes, 72^0 C for 30 seconds, and single cycle at 72^0 C for 5 minutes.

The obtained PCR products were then run on a 1% agarose gel through electrophoresis at 50V for 40 minutes, to visually confirm the length of the DNA fragments produced by PCR and ensure their readiness for DNA sequencing. The electrophoresis results indicated that the length of the PCR-generated DNA fragments matched the expected amplification target length (Figure 1).

DNA sequencing was carried out by our research partner Apical Scientific through the Sanger sequencing by capillary electrophoresis procedure. The sequencing results produced DNA sequence data in chromatographic form (Figure 2), allowing visualization of the three MMP-7-181A>G polymorphism variants, namely AA, AG, and GG. To determine the location of the MMP-7-181A>G gene in the sequencing results, a matching process was performed by aligning the flanking reference sequences with the sequencing results of each sample using the NCBI BLAST tool.

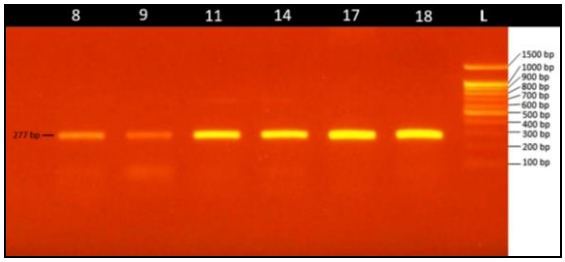

Figure 1. The representation of obtained PCR amplification of the MMP-7-181A/G gene by gel electrophoresis, read under UV lamp illumination

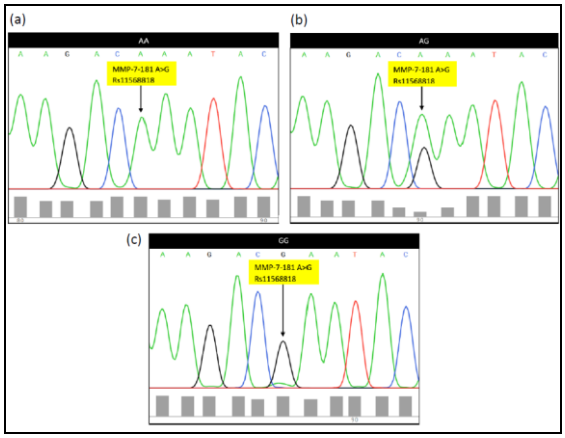

Figure 2. Chromatogram of DNA sequencing results. (a) Homozygous variant AA. (b) Heterozygous variant AG. (c) Homozygous variant GG.

RESULTS

The mean age of patients in the control group was 57.15 years (SD±10.612), while the mean age of patients in the case group was 53.96 years (SD±12.600). The comparison of the mean age between the control and case groups did not show a significant difference (p=0.328). The distribution of patient ages in the study sample was dominated by patients over 50 years old, with proportions in the case and control groups as follows: 69.2% and 65.4%, respectively. The proportion of male patients in the study sample between the case and control groups was 57.7% and 65.4%, respectively. Meanwhile, the proportion of female patients in the study sample between the case and control groups was 42.3% and 34.6%, respectively. Data analysis did not show a significant disparity in the proportion of both age and gender among the case and control groups (p=0.768 and p=0.569, respectively).

The characteristics of colorectal cancer in the case group were mainly located in the rectum, with 65% of cases having poor differentiation, 19.2% having good differentiation, and 3.8% having poor differentiation. Metastatic lymph node disease was found in 30.8% of cases, with the disease progressing to early and advanced stages in a stepwise manner, accounting for 7.7% and 30.8% of cases, respectively. The overall characteristics of the study sample can be seen in Table 1.

Table 1 Summary of patient characteristics in cases and control groups

Characteristic	Cases, (n=26)		Control, (n=26)		*p*-Value[a]
	n	%	n	%	
Mean Age	57.15 ± 10.612		53.96 ± 12.600		0.328[b]
Age (Years)					
≥50	18	69.2	17	65.4	0.768
<50	8	30.8	9	34.6	
Genders					
Male	15	57.7	17	65.4	0.569
Female	11	42.3	9	34.6	
Location					
Colon	6	23.1			
Rectum	17	65.4			
Histologic Differentiation					
Good	5	19.2			
Moderate	18	69.2			
Poor	1	3.8			
Lymph Node Metastasis					
Positive	8	30.8			
Negative	2	7.7			
Stage					
Early	2	7.7			
Late	8	30.8			

SD, Standard Deviation; [a] Based on the value of the Pearson Chi-square analysis. [b] Based on Independent T-Test analysis.

The distribution of genotype found in 52 research samples (Table 2) is as follows: genotype AA in 41 samples (78.8%), heterozygous genotype AG in 10 samples (19.2%), genotype GG in 1 sample (1.9%). The frequency of variant G allele in the total samples is 11.5%, while the common variant A allele is found with a frequency of 88.5% (*not shown in table*). The results of our analysis indicate that the MMP-7 rs11568818 AG+GG polymorphism is not significantly correlated with colorectal cancer risk despite showing a tendency towards a 2.02-fold higher risk of colorectal cancer compared to their dominant variant AA (OR=2.02, 95% CI: 0.51–8.00, *p*=0.308, Table 4). The comparison between the genotypes AG and AA also shows a non-significant tendency towards a 1.73-fold increased risk of colorectal cancer (OR=1.73, 95% CI: 0.42-7.08, *p*=0.499, Table 4). Analysis between the two homozygotes also reveals a non-significant tendency towards a 3.46-fold higher risk of colorectal cancer in the GG genotype compared to the AA genotype (OR=3.46, 95% CI: 0.13-89.95, *p*=0.476, Table 4). The analysis to compare the risk between GG and AA to colorectal cancer risk was conducted by applying the Haldane-Anscombe correction, which involves adding 0.5 to all cells to correct the value of 0 in the control group with the GG genotype.

Fisher-exact tests was performed for AG vs AA and GG vs AA due to the presence of cells with expected count values below five consecutively being 25% and 50%. Fisher-exact tests were conducted on the two comparisons that did not meet the criteria, namely having expected

values less than five, with a maximum of 20% cells. The Fisher-exact analysis did not find any statistically significant correlation between the polymorphism of genotypes AG or GG and the risk of colorectal cancer (p=0.499 and p=0.476, respectively)(Table 4).

Allelic comparison, as presented in Table 3, shows an absence of statistically significant distribution difference between the cases and control groups. The following results consistently align with the analysis among genotype variants. The G allele polymorphism variant was found to have an equal occurrence in both groups.

Table 2 Genotype distribution of the MMP-7-181A>G variants among samples.

MMP-7-181A>G	n	n (%)
Genotype		
AA	41	78.8
AG	10	19.2
GG	1	1.9

Table 3 Allele distribution of the MMP-7-181A>G variants among samples.

MMP-7-181A>G	Case[a], n=52 (%)	Control[a], n=52 (%)	p-value[b]
Allele			
A	44 (84.6)	48 (92.3)	0.227
G	8 (15.4)	4 (7.7)	

[a]Allele count from Hardy-Weinberg equation of n=26 cases and n=26 control.[b] Based on Pearson Chi-square analysis.

Table 4 Analysis of the MMP-7-181A>G among genotype variants to the risk of colorectal cancer.

	Cases, n (%)	Control, n (%)	OR (95% CI)	p-Value
MMP-7-181A>G				
AA	19 (73.1)	22 (84.6)	1.00 (References)	
AG	6 (23.1)	4 (15.4)	1.73 (0.42-7.08)	0.499 [a]
GG	1 (3.8)	0 (0)	3.46 (0.13-89.95)[#]	0.476 [a]
AG+GG	7 (26.9)	4 (15.4)	2.02 (0.51-8.00)	0.308 [b]

OR, Odds ratio; CI, Confidence Interval, [#] Odd Ratio with *Haldane-Anscombe*, [a] Based on *Fisher-Exact* test results, [b] Based on Pearson Chi-square analysis.

DISCUSSION

The characteristics described among the case group in this study include age, gender, location, grading, lymph node metastasis, and stage. Meanwhile, in the control group, the described characteristics are the age and gender of the patients. The age characteristic in the control group is dominated by patients aged over 50 years with a mean age of 57.15 years. This is consistent with previous research findings that examined the characteristics of colorectal cancer patients. In that study, it was found that the majority of colorectal cancer cases were in the age group of 46-65 years (66.7% of cases).[15] Furthermore, a study examining the characteristics of colorectal cancer patients in Bali in 2016 found similar results, where the majority of diagnosed colorectal cancer patients (92.3% of cases) were aged 50 years and above.[5]

Globally, colorectal cancer predominantly occurs in patients aged 50 and above. The risk of colorectal cancer is three times higher in individuals aged over 65 compared to those aged 50-64, and it is 30 times more likely than in the 25–49 age group. However, recently, an increase in the incidence of early-onset colorectal cancer has been observed in younger patients, associated with exposure to more predominant risk factors in the younger age group such as imbalanced diet, smoking, and alcohol consumption.[16]

Colorectal cancer characteristics in patients under 50 are significantly more dominant in the rectum compared to the colon, with histopathological features being more aggressive than cases in older patients. Colorectal cancer found in younger population is associated with a greater incidence of signet-ring cell carcinoma and mucinous adenocarcinoma, which are histological subtypes that tend to be rarely found in colorectal cancer.[17,18]

Gender in colorectal cancer is recognized as one of the risk factors, with a 30% increased risk in men compared to women. Additionally, there is a difference in the location of lesions between both genders, where lesions are more frequently found on the right side of the colon in women than in men.[16] The difference in location between genders is suspected to be caused by a decrease in estrogen levels in older women, which has a protective effect against the carcinogenesis pathway of microsatellite instability, leading to a higher incidence of MSI-high colorectal cancer predominantly found on the right side of the colon [19]

Furthermore, differences in the risk and characteristics of colorectal cancer between genders are also associated with disparities in mutation frequencies (for example, higher STK11 mutations in men), epigenetics (for example, higher tumor suppressor gene p16INKa methylation in women), differences in dietary patterns, and variations in exposure to tobacco and alcohol.[20] In this study, in the case group, males dominated, accounting for 57.7% of the total cases. However, no significant difference in proportion was found between genders in both the case and control groups in this study.

In this study, the case group is predominantly composed of patients in advanced stages, with 8 out of a total of 10 patients having data on the cancer stage. This is consistent with previous research that found the majority of

colorectal cancer cases diagnosed at advanced stages (64.1%).[15] The occurrence of lymph node metastasis in this study was also found in 8 out of the total 10 patients in the case group. This contrasts with the characteristics in previous research, which found a more dominant presence of negative lymph node metastasis (58.9%).[21]

The histological differentiation status found in this study is mostly dominated by moderately differentiated lesions, with a frequency in the sample of 18 (69.2%) patients. Generally, previous research has found similar histological characteristics. Colorectal cancer is mostly diagnosed with moderately differentiated histological differentiation (70%). Meanwhile, well-differentiated and poorly differentiated histological differentiations are found in only 10% and 20% of cases, respectively.[22]

Numerous studies have investigated the role of matrix metalloproteinase enzymes in the degradation of the extracellular matrix, a process found to be elevated in apoptosis, tumor cell invasion, and metastasis of various cancer cell types.[23] MMP-7 has been extensively studied in various cancer cases, such as esophageal, renal, breast, gastric, and colorectal tumors. These studies have revealed increased MMP-7 expression in cancer cases, correlating with characteristics such as tumor size, lymph node involvement, and overall survival rate decline.[13]

One factor influencing protein expression is the presence of polymorphisms that can enhance or reduce the expression of a protein, primarily in the protein-coding promoter region. The MMP-7 181-A>G (rs115688) polymorphism is the most studied promoter region polymorphism concerning colorectal cancer risk. In the homozygote AA wild type of MMP-7-181-A>G polymorphism, allele A is found at a higher frequency in various populations and races. Several proposed mechanisms aim to understand the relationship between increased expression and cancer characteristics found in patients. These mechanisms include E-Cadherin degradation, ECM modification, sFASL formation, Growth Factor activation, and pro-MMP activation facilitated by MMP-7.[23]

Research on this polymorphism's association with colorectal cancer was conducted by Ghilardi in the European population in 2003 as a prospective study following the initial identification of the MMP-7-181-A>G polymorphism by Jormsjo et al in 2001, who also found differences in promoter activity among polymorphism variants.[24,25] Ghilardi's study revealed a significant association, where the GG genotype had a 2.41 times higher risk than the AA genotype. This significant result prompted further research in other populations with larger and more diverse samples. A study in the Kashmir population (Asia) in 2015 found similar significant results, indicating a 1.31 times increased risk for the GG genotype. Additionally, a study conducted in Poland (Caucasian) in 2006 by Dziki supported this with 2.12 times increased risk for the GG homozygote.[26,27]

The increased risk associated with this polymorphism aligns with studies identifying excessive MMP-7 expression correlations with overall survival, disease-free survival, and 5-year survival rate.[8] Promoter regions in genes generally regulate gene transcription through their cis-acting elements. Polymorphisms in this region can alter the encoded protein's expression and potentially affect susceptibility to various diseases, including cancer. In the MMP-7 181-A>G (rs11568818) polymorphism, the change from allele A to G indicates differences in affinity for the transcription factor CREB (cAMP response element-binding protein). Furthermore, this polymorphism forms a new binding site for the heat shock transcription factor (NGAAN).[11]

In vitro research by Kesh et al. found higher basal activity in gastric adenocarcinoma cell cultures with the G allele. Through Chromatin immunoprecipitation (ChIP) assays, stronger interaction with CREB was found in the A allele promoter compared to G.[28] Initial identification by Jormsjo et al found increased protein core binding to the DNA strand with the G allele. Computer analysis using the TRANSFAC database found the formation of a new NGGAN site capable of binding to HSTF. However, the increased binding affinity due to the formation of a binding site for HSTF is still unclear, as no supershift was found in EMSA using antibodies targeting HSFP.[24]

According to our findings, the MMP-7-181-A>G polymorphism, specifically the AG+GG genotypes, did not exhibit a statistically significant correlation with the risk of colorectal cancer when compared to the wild-type AA genotype. However, the AG+GG genotype is found to have a slight, though non-significant, tendency towards an increased risk of colorectal cancer. This aligns with some previous studies and theories supporting increased affinity for various transcription factors in this polymorphism variant. Although, in our studies, the increased risk found to have an insignificant p-value of 0.308. Several limitations of our study that may potentially influence the analysis results include: a relatively small sample size, risk analysis using only a single polymorphism that could be related to polymorphisms in other positions or other interacting MMP polymorphisms, the interaction of other proteins with MMP-7, and the low frequency of the G allele found in the study sample. Additionally, this study did not adjust for some confounding factors known to be a colorectal cancer risk factors, such as smoking history, alcohol consumption, and dietary patterns, due to data limitations.

Although several studies have shown promising results supporting the significance of this polymorphism in colorectal cancer risk and increased promoter activity and MMP-7 gene expression, some studies conducted in Asian populations, specifically in East Asia (Korea, Japan, and China), couldn’t found any samples with GG homozygote polymorphisms. This is partly due to the very low allele frequency in East Asian populations and, leading to a biased distribution of MMP-7 polymorphism in these populations.

A study in China in 2006 only found MMP-7 G/G with a frequency of 0.5% in the entire healthy population.[29] In contrast to East Asia, studies conducted in Caucasian, Latin, and Kashmiri populations found a much higher G allele frequency, reaching up to 50% in the study samples.[14]

Contrary to early study results, a study conducted by Lievre et al in the year 2006 in France (Caucasian) with a relatively large sample size found that the MMP-7 -181A>G polymorphism did not have a significant impact on colorectal cancer risk (OR=1.14, 95% CI: 0.76–1.71, p=0.746).[30] A meta-analysis in 2019 by Zare et al concluded the significance for this polymorphism exclusively on the Asian population but not in other populations. However, Zare's meta-analysis concluded that this polymorphism is protective in Asia (GG vs. AA; OR=0.490, 95% CI: 0.286-0.838, p=0.009).[14] This contradicts the initial theory associating GG homozygotes in the MMP-7 -181A>G polymorphism with excessive MMP-7 expression and colorectal cancer risk, as well as a significantly increased risk in some other cancers with this polymorphism variant.[25]

CONCLUSION

In conclusion, no statistically significant correlation was found between MMP-7-181A>G polymorphism variants and the risk of colorectal cancer at Prof. dr. I.G.N.G. Ngoerah General Hospital Bali. Distribution of MMP-7-181A>G variants found among the Balinese population, was dominated by the AA variant, followed by the AG and GG variants. The allelic frequencies observed in the research samples closely resemble those commonly identified in the Asian population.

Further investigation is needed to evaluate the relationship between the occurrence of these polymorphisms and the expression levels of MMP-7 in colorectal cancer lesion tissues. Additionally, research examining the interaction of MMP-7 with enzymes of the metalloproteinase group and their inhibitors, as well as several other proteins, is necessary as they may act as cofactors influencing the risk of colorectal cancer. Further studies are required to assess the relationship between the occurrence of these polymorphisms while considering other risk factors such as dietary patterns, family history, smoking history, and alcohol consumption.

Furthermore, a combined analysis of several polymorphisms in related enzymes can provide a clearer picture of their association with the risk of colorectal cancer. Research using larger sample sizes is also needed to ensure that the results obtained more accurately reflect the occurrence of these polymorphisms and their relationship to colorectal cancer.

CONFLICT OF INTEREST

The Author declares no conflicts of interest regarding this study.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2021 Feb 4 [cited 2021 Apr 18];caac.21660. Available from: https://onlinelibrary.wiley.com/doi/10.3322/caac.21660
2. Siegel RL, Jakubowski CD, Fedewa SA, Davis A. Colorectal Cancer in the Young : Epidemiology , Prevention , Management. 2021;75–88.
3. Pourhoseingholi MA. Epidemiology and burden of colorectal cancer in Asia-Pacific region: what shall we do now? Transl Gastrointest Cancer [Internet]. 2014;3(4):169–73. Available from: http://www.amepc.org/tgc/article/view/4445/5581
4. World Health Organization. Global Cancer Obeservatory 2020. 2020.
5. Dwijayanthi NKA, Dewi NNA, Mahayasa IM, Surudarma IW. Karakteristik Pasien Kanker Kolorektal di Rumah Sakit Umum Pusat (RSUP) Sanglah Berdasarkan Data Demografis, Temuan Klinis dan Gaya Hidup. OJS UNUD [Internet]. 2020;9(12). Available from: https://ojs.unud.ac.id/index.php/eum70
6. Niland S, Riscanevo AX, Eble JA. Matrix Metalloproteinases Shape the Tumor Microenvironment in Cancer Progression. Int J Mol Sci [Internet]. 2022 Jan 1 [cited 2023 Dec 14];23(1). Available from: /pmc/articles/PMC8745566/
7. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J. 2011;278(1):16–27.
8. Sun D wei, Zhang Y yi, Qi Y, Zhou X tong, Lv G yue. Prognostic significance of MMP-7 expression in colorectal cancer : A meta-analysis. Cancer Epidemiol [Internet]. 2015;1–8. Available from: http://dx.doi.org/10.1016/j.canep.2015.01.009
9. Hubner RA, Houlston RS. Single nucleotide polymorphisms and cancer susceptibility. Oncotarget. 2017;8(66):231–9.
10. National Institute of Health. Promoter [Internet]. National Human Genome Research Institution. 2022 [cited 2022 Oct 26]. Available from: https://www.genome.gov/genetics-glossary/Promoter
11. Subramanian L, Maghajothi S, Singh M, Kesh K, Kalyani A, Sharma S, et al. A common tag nucleotide variant in MMP7 promoter increases risk for hypertension via enhanced interactions with CREB (Cyclic AMP Response Element-Binding Protein) transcription factor. Hypertension. 2019 Dec 1;74(6):1448–59.

12. Hegde MR, Crowley MR. Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics. 2019. 53–77 p.
13. Ke P, Wu Z De, Wen HS, Ying MX, Long HC, Qing LG. Current evidence on associations between the MMP-7 (-181A>G) polymorphism and digestive system cancer risk. Asian Pacific J Cancer Prev [Internet]. 2013 [cited 2021 Apr 17];14(4):2269–72. Available from: https://pubmed.ncbi.nlm.nih.gov/23725125/
14. Zare M, Jafari-Nedooshan J, Aghili K, Ahrar H, Jarahzadeh MH, Seifi-Shalamzari N, et al. Association of mmp-7-181a>g polymorphism with colorectal cancer and gastric cancer susceptibility: A systematic review and meta-analysis [Internet]. Vol. 32, Arquivos Brasileiros de Cirurgia Digestiva. Colegio Brasileiro de Cirurgia Digestiva; 2019 [cited 2021 Apr 17]. Available from: /pmc/articles/PMC6812146/
15. Widya A G, Siswandi A, Wulandari M. Karakteristik Pasien Kanker Kolorektal Stadium I-IV di Rumah Sakit Umum Daerah DR. H. Abdul Moeloek. J Ilmu Kedokt dan Kesehat. 2023;10(7):2360–74.
16. Sawicki T, Ruszkowska M, Danielewicz A, Niedźwiedzka E, Arłukowicz T, Przybyłowicz KE. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers (Basel). 2021;13(9):1–23.
17. Patel SG, Boland CR. Colorectal Cancer in Persons Under Age 50: Seeking Causes and Solutions. Gastrointest Endosc Clin N Am. 2020;30(3):441–55.
18. Nitsche U, Zimmermann A, Späth C, Müller T, Maak M, Schuster T, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg. 2013;258(5):775–83.
19. Baraibar I, Ros J, Saoudi N, Salvà F, García A, Castells MR, et al. Sex and gender perspectives in colorectal cancer. ESMO Open [Internet]. 2023;8(2):101204. Available from: https://doi.org/10.1016/j.esmoop.2023.101204
20. Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21(17):5167–75.
21. Yueh TC, Wu CN, Hung YW, Chang WS, Fu CK, Pei JS, et al. The contribution of MMP-7 genotypes to colorectal cancer susceptibility in Taiwan. Cancer Genomics and Proteomics. 2018;15(3):207–12.
22. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. J Gastrointest Oncol. 2012;3(3):153–73.
23. Ii M, Yamamoto H, Adachi Y, Maruyama Y, Shinomura Y. Experimental Biology and Medicine Role of Matrix Metalloproteinase-7 (Matrilysin) in Human Cancer Invasion ,. 2006;7:20–7.
24. Jormsjö S, Whatling C, Walter DH, Zeiher AM, Hamsten A, Eriksson P. Allele-specific regulation of matrix metalloproteinase-7 promoter activity is associated with coronary artery luminal dimensions among hypercholesterolemic patients. Arterioscler Thromb Vasc Biol. 2001;21(11):1834–9.
25. Ghilardi G, Biondi ML, Erario M, Guagnellini E, Scorza R. Colorectal Carcinoma Susceptibility and Metastases Are Associated with Matrix Metalloproteinase-7 Promoter Polymorphisms. Clin Chem. 2003;49(11):1937–40.
26. Banday MZ, Sameer AS, Mir AH, Mokhdomi TA, Chowdri NA, Haq E. Matrix metalloproteinase (MMP) -2, -7 and -9 promoter polymorphisms in colorectal cancer in ethnic Kashmiri population — A case–control study and a mini review. Gene [Internet]. 2016;589(1):81–9. Available from: http://dx.doi.org/10.1016/j.gene.2016.05.028
27. Dziki Ł, Przybyłowska K, Majsterek I, Trzciński R, Sygut M. A/G Polymorphism of the MMP-7 gene promoter region in colorectal cancer. Pol Prz Chir Polish J Surg. 2011;83(11):622–6.
28. Kesh K, Subramanian L, Ghosh N, Gupta V, Gupta A, Bhattacharya S, et al. Association of MMP7 - 181A → G promoter polymorphism with gastric cancer risk: Influence of nicotine in differential allele-specific transcription via increased phosphorylation of cAMP-response element-binding protein (CREB). J Biol Chem. 2015;290(23):14391–406.
29. Ohtani H, Maeda N, Murawaki Y. Functional polymorphisms in the promoter regions of matrix metalloproteinase-2,-3,-7,-9 and TNF-alpha Genes, and the risk of colorectal neoplasm in Japanese. Yonago Acta Med. 2009;52(1):47–56.
30. Lièvre A, Milet J, Carayol J, Le Corre D, Milan C, Pariente A, et al. Genetic polymorphisms of MMP1, MMP3 and MMP7 gene promoter and risk of colorectal adenoma. BMC Cancer. 2006;6:2–9.