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

Christian Chandra¹; Desak Made Wihandani²*, I Gede Putu Supadmanaba²; Ni Nyoman Ayu Dewi²; Putu Anda Tusta Adiputra³.
¹Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia;
²Department of Biochemistry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia;
³Department 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 protease 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 EGF.R.

In colorectal cancer, a subtype of matrix metalloproteinase class enzyme, MMP-7, was found to have increased expression in cancer lesions. 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. 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. 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). 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. 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.

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.

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 Ngeorah 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 polytroph 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 Ngeorah 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’-TGGTACCATAATGCTCCTGAAT-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°C for 5 minutes, 35 cycles of 95°C for 15 seconds, 55°C for 1 minute, 72°C for 30 seconds, and single cycle at 95°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.
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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 control groups as follows: 69.2% vs 65.4%, respectively. The proportion of male patients in the study sample between the case and control groups was 57.15 years (SD±10.612), while the control group was 53.96 years (SD±12.600). The representation of obtained PCR amplification of the MMP-7-181A/G gene by gel electrophoresis, read under UV lamp illumination is shown in Figure 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case, (n=26)</th>
<th>Control, (n=26)</th>
<th>p-Value</th>
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<tr>
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</tr>
<tr>
<td>≥50</td>
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<td>17</td>
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</tr>
<tr>
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<td>9</td>
<td>0.346</td>
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<tr>
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<td>17</td>
<td>0.569</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>9</td>
<td>0.346</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>6</td>
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<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>17</td>
<td>65.4</td>
<td></td>
</tr>
<tr>
<td>Histologic</td>
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</tr>
<tr>
<td>Good</td>
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<td>19.2</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>18</td>
<td>69.2</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
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<td>3.8</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
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</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
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<td></td>
</tr>
<tr>
<td>Early</td>
<td>2</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>8</td>
<td>30.8</td>
<td></td>
</tr>
</tbody>
</table>
| SD, Standard Deviation; * Based on the value of the Pearson Chi-square analysis. * 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 1.3-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 were 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 4 Analysis of the MMP-7-181A>G among genotype variants to the risk of colorectal cancer.

<table>
<thead>
<tr>
<th></th>
<th>Cases, n (%)</th>
<th>Control, n (%)</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-7-181A&gt;G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>19 (73.1)</td>
<td>22 (84.6)</td>
<td>1.00 (References)</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>6 (23.1)</td>
<td>4 (15.4)</td>
<td>1.73 (0.42-7.08)</td>
<td>0.499$^{a}$</td>
</tr>
<tr>
<td>GG</td>
<td>1 (3.8)</td>
<td>0 (0)</td>
<td>3.46 (0.13-89.95)$^{b}$</td>
<td>0.476$^{a}$</td>
</tr>
<tr>
<td>AG+GG</td>
<td>7 (26.9)</td>
<td>14 (51.5)</td>
<td>2.02 (0.51-8.00)</td>
<td>0.308$^{b}$</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, Confidence Interval; $^{a}$ Odd Ratio with Haldane-Anscombe, $^{b}$ Based on Fisher-Exact test results. $^{a}$ 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). 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.

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.

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.

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. 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.

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. 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 cas...
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La asociación de este polimorfismo con estudios identificando excesivas correlaciones expresivas MMP-7 con supervivencia global, supervivencia libre de enfermedad, y supervivencia libre de 5 años.9 Promotores regiones en genes generalmente regulan la expresión de genes a través de sus actores cis. Polimorfismos en esta región pueden alterar la expresión proteica codificada y potencialmente afectar la susceptibilidad a diversas enfermedades, incluyendo cáncer. En el polimorfismo MMP-7 181A>G (rs11568818), el cambio de alelo A a G indica diferencias en afinidad para el factor de transcripción CREB (AMP respuesta elemento uniendo proteína). Además, este polimorfismo forma un nuevo sitio de unión para el factor de transcripción CREB (NGAAN).11

En el desarrollo de nuevo sitio de unión al factor de transcripción CREB. Aunque las células gastricas con la expresión de MMP-7 en casos de cáncer colorrectal, correlacionando con características como el tamaño del tumor, metástasis ganglionares, y supervivencia global, y la declinación de supervivencia 5 años.13

Un factor influenciando la expresión proteica es la presencia de polimorfismos que pueden ocurrir en los alelos o reducir la expresión de un gen, principalmente en los genos-proteínas del promotor región. El MMP-7 181-A>G (rs11568818) polimorfismo es el más estudiado promotor región polimorfismo concerniendo riesgo de cáncer colorrectal. En el genotipo homozygote AA, el alelo A es encontrado a un mayor nivel en varias poblaciones y razas. Seis propuestas de mecanismos que ayudan a entender la relación entre incremento de expresión y características del genetomato con infecciones en pacientes. Estos mecanismos incluyen E-Cadherin degradación, ECM modificación, sFASL formación, crecimiento Factor activación, y pro-MMP activación facilitado por 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.9 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 HSP24.

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 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 find 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.

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A study in China in 2006 only found MMP-7 G/G with a frequency of 0.5% in the entire healthy population. 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. 

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). 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). 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.

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


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ASSOCIATION OF MMP-7-181A>G GENE POLYMORPHISM AND COLORECTAL CANCER


