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Research Article

Correlation between miR-27 rs895819 and miR-423 rs6505162 Polymorphisms and Susceptibility to Colorectal Cancer in the Iranian Population: A Case-Control Study

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Abstract

Objectives: MicroRNAs play a vital role in biological processes, and their irregularities have been associated with colorectal cancer (CRC) development. This study utilized a case-control method to investigate the possible link between two particular miRNA variations, mir-27a rs895819 and mir-423 rs6505162, and CRC susceptibility in the Iranian population.

Methods: This case-control study included 120 CRC patients and 120 healthy individuals. Genotyping of the mir-27a rs895819 and mir-423 rs6505162 polymorphisms was performed using the PCR-RFLP method. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to evaluate the correlations.

Results: No significant disparities were detected between the cases and controls regarding age, gender, BMI, family history of CRC, and residency. The analysis indicated that the GG genotype of the mir-27a rs895819 polymorphism was notably linked to a higher CRC risk (OR=2.134, 95% CI 1.008-4.517, p=0.048). Nevertheless, no substantial connection was noted between the mir-423 rs6505162 polymorphism and CRC susceptibility.

Conclusion: The study results indicate that the mir-27a rs895819 polymorphism could serve as a potential biomarker for CRC progression. However, no correlation was found for the mir-423 rs6505162 polymorphism. Further research with diverse ethnic groups and larger sample sizes is necessary to confirm the link between these polymorphisms and CRC development

Keywords: Colorectal neoplasms, MicroRNAs, mir-27a, mir-423, polymorphism

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Cancer is a major cause of death in both economically underdeveloped and affluent nations, making it a global health issue that requires immediate attention and comprehensive solutions.[1–3] Colorectal cancer (CRC) is the third most common cancer, after lung and breast cancer, which are even more common in the general population.[4,5] It is important to note that in the United States alone, an estimated 50,000 individuals succumb to this disease annually, further emphasizing the significance of effectively combating this ailment through comprehensive prevention strategies, early detection methods, and advanced treatment modalities.[6,7] The lifetime risk of developing CRC in the United States is estimated to be around 5 to 6%, as per research findings.[8,9] The incidence of CRC may vary by geographical location, with Western Europe being recognized as having a high prevalence of this disease, as well as Australia, New Zealand, and North America.[9,10] The incidence of CRC is rising and is expected to surge by 60% by 2030, leading to over 2.2 million new cases and 1.1 million deaths worldwide.[10,11] Additionally, it is crucial to emphasize the significant rise in the prevalence of CRC in Iran in recent decades, which has raised concerns in the medical field.[12,13] Furthermore, the incidence of CRC in Iran is on the rise, especially among patients under 50 years old.[13] It is the fourth most prevalent cancer in Iranian men and the second most prevalent cancer in Iranian women.[6,14] The age-standardized incidence rate of CRC in the Iranian population was 11.6 for men and 10.5 for women per 100,000 person-years.[15] The increasing trend in the incidence of CRC globally and within specific regions highlights the urgent need for effective prevention and early detection strategies to reduce the burden of this disease on individuals and healthcare systems. Several risk factors, including age,[16,17] smoking,[18] alcohol consumption,[18] consumption of red and processed meat,[19,20] obesity,[18] body mass index (BMI),[21] and Diabetes Mellitus Type 1 and 2,[22,23] have been examined to establish a connection to the development of CRC. Genetic and environmental factors jointly contribute significantly to the etiology of CRC.[24,25] The vast majority of CRC cases are not inherited and occur randomly (sporadically), with only about a quarter of patients having a confirmed positive familial history.[26,27]

MicroRNAs, a type of non-coding RNA molecule, typically consist of 20 to 25 nucleotides. They play a crucial role in suppressing gene expression and have been found to be irregular in the context of cancer.[28–30] The function of MicroRNAs is predominantly in the cytoplasm as negative post-transcriptional gene expression regulators, and they seem to play a ubiquitous role, either as tumor suppressors or promoters.[31,32] Since their discovery in 1993, numerous studies have established a series of theories regarding the involvement of miRNA in cancer development.[31,33] Through genomic data analysis, differentially expressed genes and miRNAs have been identified in various stages of cancer, indicating their stage-specific nature.[31,34] Currently, MicroRNAs show promise as biomarkers for diagnosing and predicting the prognosis of CRC.[35,36] Among these MicroRNAs, mir-27a and mir-423 have been extensively investigated across multiple indications and disease states. Mir-27a specifically exhibits a strong correlation with metabolic processes, particularly cholesterol homeostasis and arteriosclerosis, as well as neurodegenerative disorders and the differentiation of benign cells such as myoblasts.[37,38] Furthermore, this miRNA has been found to play a clinical role in drug sensitivity, cancer treatment, and prognosis.[39] Additionally, various studies have reported that the expression of mir-423 is altered in several different types of cancers, suggesting that miR-423 may play a significant role in the development of cancer.[40] The miR-27a rs895819 polymorphism is linked to reduced dihydropyrimidine dehydrogenase (DPD) activity in CRC patients.[41] The miR-423 rs6505162 polymorphism is significantly linked to overall survival and recurrence-free survival in CRC.[42] It has also been identified as the most significant SNP in pre-miR-423 concerning CRC.[43] A meta-analysis found that the miR-27a rs895819 polymorphism is associated with an increased risk of digestive system cancers, including CRC.[44] However, a study in a Chinese population found no association between miR-27a rs895819 and CRC risk.[45] Conversely, another study reported an association between the miR-27a rs895819 polymorphism and increased atrophic gastritis risk, improved gastric cancer prognosis, and a negative interaction with Helicobacter pylori in gastric carcinogenesis.[46] These results highlight the possible significance of these genetic variations as predictors of outcomes and their effect on CRC susceptibility. However, the specific effects of the mir-27a rs895819 and mir-423 rs6505162 variations on susceptibility to CRC are still unclear, especially in the Iranian population. In this case-control study, we aimed to explore the potential connection between mir-27a rs895819 and mir-423 rs6505162 variations and the risk of developing CRC by conducting genotyping in a cohort of Iranian patients.

Methods

Study Population

In our case-control study, we examined a group of 240 people, consisting of 120 Iranian individuals diagnosed with CRC and an equal number of healthy volunteers.

These volunteers were carefully chosen to match the age and gender of the CRC patients. The CRC patients were randomly selected from Shahid Sadoughi Hospital and a General Hospital, Yazd, Iran, between August 2021 and March 2022. Initially, we conducted clinical interviews and reviewed medical records to gather a wide range of information, including age, gender, tumor stage and grade, family history of cancer, and marital status. Additionally, we confirmed the diagnosis of CRC in each patient by thoroughly reviewing their medical histories, which included data from clinical assessments and histopathological examinations, and ensuring that they had not received any treatment before blood sample collection. All recruited subjects were unrelated individuals with CRC, while the healthy controls had no family history of CRC and were selected to be similar to the cases in terms of age and sex. It is important to note that all participants in this study provided informed consent willingly, following the guidelines of the local Ethical Committee at Islamic Azad University in Ashkezar, Iran.

Genotyping

DNA was extracted from peripheral blood using the Blood Genome DNA Extraction Kit. The miR-27 rs895819 and miR-423 rs6505162 polymorphisms were analyzed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Primers were designed with Oligo software and the NCBI BLAST search engine, as detailed in Table 1, which also includes information on fragment sizes, restriction enzymes, and annealing temperature for each polymorphism. The PCR amplification was performed in a 25 mL reaction mixture containing 50 ng genomic DNA, 12.5 mL of 2 Taq DNA Polymerase Master Mix Red (Ampliqon), 1.5 mL of each primer, and 7.5 mL of sterilized water. For the mir-27a rs895819 polymorphism, the reaction mixtures underwent denaturation at 95°C for 5 min, followed by 35 cycles of 95°C for 25 s, 60°C for 30 s, and 72°C for 30 s, with a final elongation step at 72°C for 10 min. The PCR products were then digested with DraIII (Thermo Scientific) at 37°C overnight and subjected to 3% agarose gel electrophoresis. Genotypes were determined based on the presence of specific fragments: a single 182-bp fragment indicated the GG genotype, two fragments measuring 155 and 27 bp represented the AA genotype, and three fragments measuring 182, 155, and 27 bp represented the AG genotype. As for the mir-423 rs6505162 polymorphism, the initial denaturation step was performed at 95°C for 5 min, followed by 7 cycles at 94°C for 30 s, 66°C for 30 s, and 72°C for 30 s, with the annealing temperature decreasing by 1°C per cycle. This was followed by 28 cycles at 94°C for 30 s, 60°C for 30 s, and 72°C for 30 s, and a final extension at 72°C for 10 min. The PCR products were digested with the restriction endonuclease Csp6i (Thermo Scientific) and separated on a 2% agarose gel. Genotypes were determined based on the presence of specific fragments: a single 127-bp fragment indicated the AA genotype, two fragments measuring 108 and 19 bp represented the CC genotype, and three fragments measuring 127, 108, and 19 bp represented the AC genotype. The genotypes were determined by visualizing the resulting band patterns under UV light. Quality control samples and negative controls were included in each PCR run to ensure the accuracy and reliability of the genotyping results.

Statistical Analysis

The chi-square test was also applied to examine the distribution variations of genotype and allele frequencies between cases and controls. The Hardy-Weinberg equilibrium was assessed using the chi-squared test to evaluate the distribution of genotypes in the study population. The allelic and genotypic frequencies of the miR-27 rs895819 and miR-423 rs6505162 polymorphisms were compared between cases and controls using appropriate statistical tests. To compare the differences in average age and gender between CRC cases and controls, we used the chi-square test or Fisher's exact test. We calculated the odds ratio (OR) and 95% confidence interval (CI) to assess the correlation between the mir-27a rs895819 and mir-423 rs6505162 polymorphisms and CRC risk. Statistical analyses were conducted using SPSS 20.0 software, with a significance level set at $p<0.05$.

Table 1. Genotyping characteristics and PCR amplification primer sequences for polymorphism genotyping

SNP-ID	Polymorphism	Primers Sequence	Restriction Enzyme	Fragments Size
mir-27a rs895819	A>G	F: 5′-GAACTTAGCCACTGTGAACACCACTTGG-′3 R: 5′-TTGCTTCCTGTCACAAATCACATTG-3′	DraIII	G:182 A:155 and 27
mir-423 rs6505162	C>A	F: 5′-CCC CTCAGTCTTGCTTCGTA-3′ R: 5′-ACTTGAGCTTCTGCCAAG GA-3′	Csp6	C:108 and 19 A:127

Table 2. Characteristics of subjects in the control and colorectal cancer groups

Variables	CRC cases (n=120)	Healthy Controls (n=120)	p
Age (year)			
Mean±SD	66.3±9.4	65.3±9.8	0.812
Range, n (%)			
≤50	64 (53.3)	65 (54.2)	0.896
>50	56 (46.7)	55 (45.8)	
Gender, n (%)			
Male	87 (72.5)	90 (75.0)	0.659
Female	33 (27.5)	30 (25.0)	
BMI (kg/m^2)			
Mean±SD	25.5±3.2	25.3±2.1	0.701
Range, n (%)			
≤25	71 (59.2)	66 (55.0)	0.514
>25	49 (40.)	54 (45.0)	
Family History of CRC, n (%)			
Yes	11 (9.1)	4 (3.3)	0.069
No	112 (90.9)	116 (9.7)	
Residence, n (%)			
Urban	89 (74.2)	95 (79.2)	0.359
Rural	31 (25.8)	25 (20.8)	
Smoking Status, n (%)			
Ever	53 (44.2)	34 (28.3)	0.010
Never	67 (55.8)	86 (71.7)	
Tumor location, n (%)			
Colon	62 (51.7)		
Rectum	58 (48.3)		
Tumor grading, n (%)			
I-II	82 (68.3)		
III- IV	38 (31.7)		
Lymph node, n (%)			
Yes	69 (57.5)		
No	51 (42.5)		

Results

The characteristics of CRC cases and healthy subjects are summarized in Table 2. Upon analysis, no significant differences were found in age, gender, BMI, family history of CRC, and residency (p>0.05). However, a notable difference was observed in the smoking status of CRC cases compared to controls. The results of the genetic analysis revealed no significant deviations from the Hardy-Weinberg equilibrium for mir-27a rs895819 (p=0.511) and mir-423 rs6505162 (p=0.136) in the control subjects. This suggests that these genetic variations are distributed in the population as expected under the equilibrium. The genotypes and allele frequencies for these polymorphisms are detailed in Table 3, providing valuable insights into the genetic profiles of the study participants.

For miR-27 rs895819, the frequencies of genotypes AA, AG, and GG, as well as alleles A and G, were 46.7%, 34.2%, 19.1%, 63.8%, and 36.2% in CRC cases, and 50.0%, 40.0%, 10.0%, 70.0%, and 30.0% in healthy subjects. A significant difference in the distribution of the GG genotype of miR-27 rs895819 was observed between CRC cases and controls (p=0.048). Additionally, a significant correlation was found between the miR-27 rs895819 (GG) polymorphism and increased CRC risk, with an odds ratio of 2.134 and a 95% confidence interval of 1.008–4.517 (p=0.048). Regarding miR-423 rs6505162, the frequencies of genotypes AA, AG, and GG, as well as alleles A and G, were 55.8%, 37.5%, 6.7%, 75.6%, and 25.4% in CRC cases, and 60.0%, 31.7%, 8.3%, 75.8%, and 24.2% in healthy subjects. No significant differences were observed in the distribution of genotypes and alleles at miR-423 rs6505162 between CRC cases and controls. These findings suggest a lack of correlation between miR-423 rs6505162 and the risk of developing CRC.

Table 3. Genotypes and allele frequencies of miR-27 and miR-423 in CRC cases and controls

SNPs	Genotypes/Alleles	CRC (n=120)	Controls (n=120)	OR	95% CI	p
miR-27 rs895819						
Genotypes, n (%)	AA	56 (46.7)	61 (50.0)	Ref.		
	AG	41 (34.2)	47 (40.0)	0.806	(0.476-1.364)	0.350
	GG	23 (19.1)	12 (10.0)	2.134	(1.008-4.517)	0.048
Alleles, n (%)	A	153 (63.8)	169 (70.0)	Ref.		
	G	87 (36.2)	71 (30.0)	1.353	(0.924-1.984)	0.121
miR-423 rs6505162						
Genotypes, n (%)	CC	67 (55.8)	72 (60.0)	Ref.		
	CA	45 (37.5)	38 (31.7)	1.295	(0.759-2.207)	0.414
	AA	8 (6.7)	10 (8.3)	0.786	(0.299-2.065)	0.625
Alleles, n (%)	C	179 (74.6)	182 (75.8)	Ref.		
	A	61 (25.4)	58 (24.2)	1.069	(0.707-1.619)	0.751

Tables 4 and 5 compare genotype frequencies of miR-27 rs895819 and miR-423 rs6505162 polymorphisms between CRC case and control groups based on age, gender, BMI, residency, and smoking status. The association of miR-27 rs895819 persisted in male patients (OR=3.261, 95% CI 1.357–7.835, p=0.008) when stratified by gender. Significant differences were observed in urban residents (OR=2.358, 95% CI 1.064–5.230, p=0.034) when data were

Table 4. Comparison of genotype frequencies of the miR-27 rs895819 polymorphism in CRC patients and healthy controls

Variables	CRC (%)	Controls (%)	OR (95% CI)	p
Age				
≤50				
AA	29 (45.2)	34 (52.2)	Ref.	
AG	25 (39.1)	27 (41.6)	0.902 (0.446-1.824)	0.774
GG	10 (15.7)	4 (6.2)	2.824 (0.837-9.527)	0.094
>50				
AA	27 (48.2)	27 (49.1)	Ref.	
AG	16 (28.6)	20 (36.4)	0.700 (0.314-1.555)	0.381
GG	13 (23.2)	8 (14.5)	1.776 (0.671-4.699)	0.247
Gender				
Male				
AA	39 (44.8)	46 (51.1)	Ref.	
AG	27 (31.0)	36 (40.0)	0.675 (0.363-1.254)	0.0213
GG	21 (24.2)	8 (8.9)	3.261 (1.357-7.835)	0.008
Female				
AA	17 (51.5)	15 (50.0)	Ref.	
AG	14 (42.4)	11 (36.7)	1.272 (0.461-3.508)	0.641
GG	2 (6.1)	4 (13.3)	0.419 (0.071-2.475)	0.337
BMI				
≤25				
AA	35 (50.7)	33 (50.0)	Ref.	
AG	22 (31.9)	26 (39.4)	0.609 (0.302-1.228)	0.166
GG	12 (17.4)	7 (10.6)	1.685 (0.620-4.577)	0.305
>25				
AA	21 (33.33)	28 (51.8)	Ref.	
AG	19 (37.25)	21 (38.9)	0.933 (0.424-2.052)	0.863
GG	11 (21.57)	5 (9.3)	2.695 (0.864-8.398)	0.087
Residence				
Urban				
AA	38 (42.7)	45 (47.3)	Ref.	
AG	30 (33.7)	39 (41.1)	0.720 (0.355-1.460)	0.362
GG	21 (23.6)	11 (11.6)	2.358 (1.064-5.230)	0.034
Rural				
AA	18 (58.1)	16 (64.0)	Ref.	
AG	11 (35.5)	8 (32.0)	1.168 (0.382-3.571)	0.784
GG	2 (6.4)	1 (4.0)	1.655 (0.141-19.386)	0.688
Smoking Status				
Ever				
AA	20 (37.7)	11 (32.4)	Ref.	
AG	20 (37.7)	19 (55.9)	0.478 (0.199-1.148)	0.098
GG	13 (24.6)	4 (11.7)	3.250 (0.950-11.115)	0.060
Never				
AA	36 (53.8)	50 (58.1)	Ref.	
AG	21 (31.3)	28 (32.6)	0.945 (0.476-1.876)	0.873
GG	10 (14.9)	8 (9.3)	1.710 (0.635-4.605)	0.288

stratified by residency location. The association of miR-423 rs6505162 polymorphism with CRC risk was not significant in any of the stratified analyses (Table 5). These findings suggest a potential role of miR-27 rs895819 in the susceptibility to CRC, particularly in male patients and urban residents.

Table 5. Comparison of genotype frequencies of the miR-423 rs6505162 polymorphism in CRC patients and healthy controls

Variables	CRC (%)	Controls (%)	OR (95% CI)	p
Age				
≤50				
AA	36 (56.3)	38 (58.5)	Ref.	
AG	23 (35.9)	21 (32.3)	1.175 (0.567-2.435)	0.435
GG	5 (7.8)	6 (9.2)	0.833 (0.241-2.881)	0.773
>50				
AA	31 (55.3)	34 (61.8)	Ref.	
AG	22 (39.3)	17 (30.9)	1.446 (0.660-3.167)	0.923
GG	3 (5.4)	4 (7.3)	0.721 (0.153-3.385)	0.679
Gender				
Male				
AA	52 (59.7)	55 (61.1)	Ref.	
AG	29 (33.4)	25 (27.8)	1.300 (0.684-2.469)	0.802
GG	6 (6.9)	10 (11.1)	0.592 (0.205-1.707)	0.332
Female				
AA	15 (45.4)	17 (56.7)	Ref.	
AG	16 (48.5)	13 (43.3)	1.230 (0.455-3.324)	0.682
GG	2 (6.1)	0 (0.0)	0.079 (0.001-4.915)	0.228
BMI				
≤25				
AA	35 (50.7)	34 (51.5)	Ref.	
AG	29 (42.1)	26 (39.4)	1.115 (0.561-2.217)	0.755
GG	5 (7.2)	6 (9.1)	0.781 (0.226-2.694)	0.695
>25				
AA	32 (62.7)	38 (70.4)	Ref.	
AG	16 (31.4)	12 (22.2)	1.600 (0.668-3.829)	0.291
GG	3 (5.9)	4 (7.4)	0.781 (0.166-3.675)	0.754
Residence				
Urban				
AA	49 (55.0)	56 (58.9)	Ref.	
AG	34 (38.2)	30 (31.6)	1.339 (0.729-2.460)	0.346
GG	6 (6.8)	9 (9.5)	0.690 (0.235-2.026)	0.500
Rural				
AA	18 (58.1)	16 (64.0)	Ref.	
AG	11 (35.5)	8 (32.0)	1.168 (0.382-3.571)	0.784
GG	2 (6.4)	1 (4.0)	1.655 (0.141-19.386)	0.688
Smoking Status				
Ever				
AA	34 (64.1)	19 (55.9)	Ref.	
AG	16 (30.2)	13 (38.2)	0.698 (0.282-1.729)	0.438
GG	3 (5.7)	2 (5.9)	0.960 (0.151-6.065)	0.965
Never				
AA	33 (49.2)	53 (61.6)	Ref.	
AG	29 (43.3)	25 (29.1)	1.862 (0.951-3.642)	0.069
GG	5 (7.5)	8 (9.3)	0.937 (0.290-3.024)	0.914

Discussion

MicroRNAs play a crucial role in regulating important biological processes such as cell differentiation, proliferation, apoptosis, and metabolism.[47,48] Dysregulation of these processes can lead to diseases, including cancer. MicroRNAs have the potential to serve as tissue-specific biomarkers for identifying and characterizing different types of cancer.[49] The human genome contains a vast number of microRNAs, and it's estimated that over 30% of human genes are controlled by these molecules, highlighting their regulatory influence and significance in maintaining cellular homeostasis. Studies have shown an upregulation of microRNAs in tumor cells, indicating their involvement in cancer development and progression.[50–52] Research has focused on investigating the relationship between functional polymorphisms at specific microRNAs and cancer risk. The miR-27 and miR-423 polymorphisms have been extensively studied in different ethnic populations to determine their association with various types of cancer.[53–55] In this study, researchers aimed to evaluate the correlation between the mir-27a rs895819 and mir-423 rs6505162 polymorphisms and the risk of CRC in an Iranian population. Understanding the genetic factors contributing to CRC development is crucial, as CRC is one of the most common types of cancer worldwide. By examining these specific microRNA polymorphisms, the researchers sought insights into potential genetic predisposition to CRC in the Iranian population. Our study indicates that the mir-27a rs895819 polymorphism is notably linked to CRC risk in the Iranian population. Conversely, the mir-423 rs6505162 polymorphism does not exhibit a significant correlation. Moreover, upon stratification by gender, the correlation of miR-27 rs895819 remained noteworthy in male patients (OR=3.261, 95% CI 1.357–7.835, p=0.008). Notable variances were observed in urban dwellers (OR=2.358, 95% CI 1.064–5.230, p=0.034) when categorized by residency. Nevertheless, the correlation of the miR-423 rs6505162 polymorphism with CRC risk did not demonstrate significance in any of the stratified analyses.

The human miR-27a gene is located on chromosome 19p13.13 and consists of a single exon. Additionally, the variant rs895819 is found in the terminal loop of the pre-miR-27a molecule.[56] The role of miR-27a in the development of various malignancies, particularly those affecting the digestive system, is significant.[56,57] This microRNA promotes the proliferation of cancer cells by suppressing the expression of prohibitin, thereby hindering the functioning of the Protein kinase B (PKB) or tyrosine signaling pathway associated with the E2F family of transcription factors.[58] Moreover, miR-27a has recently been identified as a key regulator of cancer metabolism reprogramming, influencing the response of CRC to chemotherapy and exhibiting properties that are independent of specific microRNA targets.[58] Additionally, the diagnostic and therapeutic potential of this microRNA in CRC is worth exploring.[59] Our findings suggest a significant and noteworthy association between the miR-27a rs895819 polymorphism and the progression of CRC within our specific population, indicating a potential genetic susceptibility towards the development of this disease. In 2020, Zhang and colleagues conducted a case-control study in a Chinese population, genotyping the miR-27a rs895819 polymorphism using the TaqMan allelic discrimination assay. The study included 208 CRC cases and 312 healthy subjects. Similarly, their findings demonstrated the significant involvement of the miR-27a rs895819 polymorphism in the development of CRC within this particular population.[45] Furthermore, Yuan et al.[60] conducted a meta-analysis of twelve case-control studies involving a total of 2655 CRC patients and 3106 control individuals. The analysis showed a significant correlation between the miR-27a rs895819 polymorphism and an increased susceptibility to CRC within the Chinese population. Dai et al.[61] conducted a comprehensive meta-analysis to examine the correlation between mir-27a rs895819 and various forms of cancer susceptibility. Their analysis included gastric cancer, CRC, breast cancer, lung cancer, esophageal cancer, gallbladder cancer, renal cancer, cervical cancer, ovarian cancer, and prostate cancer. Results from 35 case-control studies showed a significant association between the mir-27a rs895819 polymorphism and increased risk of CRC and breast cancer. However, no significant correlation was found with other types of cancer.[61] A recent meta-analysis of 22 studies, involving 7419 cases and 8194 controls, has revealed a potential correlation between the miR-27a rs895819 polymorphism and an increased risk of digestive system cancers. This finding underscores the importance of understanding the implications of this polymorphism for public health and cancer prevention.[57] In a separate study, Kupcinskas et al. examined 193 CRC cases and 428 control subjects to explore the connection between specific polymorphisms (miR-27a rs895819, miR-146a rs2910164, miR-196a-2 rs11614913, miR-492 rs2289030, and miR-608 rs4919510) and susceptibility to CRC in the European population. Their results contradicted a previous meta-analysis, as they did not find a significant correlation between these polymorphisms and the risk of CRC in the European population.[62]

In humans, the miR-423 gene is mapped to chromosome 17q11.2 and can produce two mature miR-423-3p and miR-423-5p sequences.[63] The rs6505162 variant is located in 12 bp at the 3'-UTR of mature miR-423-3p.[40] To date, only two studies have evaluated the correlation between miR-423

rs6505162 polymorphism and CRC risk.[40,43] In 2018, Jia et al., in a study among 117 CRC cases and 84 controls recruited from Hunan Tumor Hospital, Changsha, evaluated the link between miR-423 rs6505162 polymorphism and CRC risk. Their findings showed that miR-423 rs6505162 polymorphism was correlated with the susceptibility and metastasis of CRC, indicating that this polymorphism might be a potential biomarker for CRC in the Chinese population.[40] Xing et al.[43] reported that the rs6505162 in pre-miR-423 had a significant correlation with the overall survival and the recurrence-free survival of the CRC patients in a Chinese population. However, two previous meta-analyses reported a negative link between miR-423 rs6505162 polymorphism and the risk of cancer.[53,64] Moazeni-Roodi et al.,[64] in a meta-analysis based on 27 case-control studies with 10,500 cases and 13,781 controls, evaluated the correlation of miR-423 rs6505162 polymorphism with the risk of cancer. They indicated that miR-423 rs6505162 polymorphism may play a role in protection against cancer. Moreover, their stratified analyses by type of cancer showed that the polymorphism was significantly correlated with decreased risk of gastrointestinal cancer, colorectal cancer, and lung cancer. Similarly, Zhang et al.,[53] in a meta-analysis based on 45 studies, reported that miR-423 rs6505162 polymorphism was not correlated with the risk of cancer overall.

Conclusion

In summary, our research indicates that the mir-27a rs895819 polymorphism is significantly linked to CRC risk in the Iranian population. Conversely, the mir-423 rs6505162 polymorphism exhibits no significant correlation with CRC risk. This study advances our comprehension of the intricate relationship between genetic variations and cancer susceptibility, paving the way for more precise prevention and treatment strategies. To confirm and broaden these observed associations, future research should encompass diverse ethnicities, larger sample sizes, and more rigorous methodological designs. These additional investigations will yield a more comprehensive understanding of the connection between these specific genetic polymorphisms and the risk of developing CRC.

Disclosures

Ethics Committee Approval: The institutional review board approved this study. The study was conducted following the ethical standards set by the board to safeguard the well-being of all participants.

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