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miR-499 rs3746444 polymorphism is associated with colorectal cancer susceptibility: A case-control study in a Chinese population.

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Abstract

Background: Previous study suggested that miR-499 rs3746444 may contribute to the risk and prognosis of Colorectal Cancer (CRC). However, other studies did not support association between rs3746444 and CRC risk. Therefore, we did this study to assess whether miR-499 rs3746444 affect the risk of CRC.
Method: A total of 913 subjects were included in this case-control study, including 434 patients with CRC and 479 healthy controls. The miR-499 rs3746444 was genotyped using the TaqMan methodology in 96-well plates and read with the Sequence Detection Software (SDS, version 1.4) on an Applied Biosystems (ABI) 7500 Real-Time PCR System.
Results: The miR-499 rs3746444 polymorphism showed significant difference between CRC patients and healthy controls in genotype comparison (TC *vs.* TT: OR=1.37, 95% CI 1.01-1.88, P=0.04; CC *vs.* TT: OR=3.18, 95% CI 1.83-5.55, P<0.01; CC+TC *vs.* TT: OR=1.64, 95% CI 1.22-2.24, P<0.01). Additionally, the miR-499 rs3746444 T allele was significantly associated with CRC risk (OR=2.89, 95% CI 1.69-5.09, P<0.01).
Conclusion: The results of our study suggested that miR-499 rs3746444 was significantly associated with CRC risk.

Keywords: Colorectal cancer, miR-499, Risk.

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Introduction

Colorectal cancer is the second leading cause of cancer-related deaths in the United States [1]. At current rates, approximately 5%-6% of individuals will develop a cancer of the colon or rectum within their lifetime [2]. Approximately 20-25% of Colorectal Cancer (CRC) patients present with metastatic disease, and another 25% will develop metastases in the follow-up period [3].

MicroRNAs (miRNAs) are a group of non-coding small RNAs (approximately 21-23 nucleotides in length) that can target multiple distinct transcripts, thus playing an important role in regulation of mRNA expression [4]. MiR-499 is a miRNA that is abundantly found in cardiac cells and is essentially undetectable in human cardiac stem cells (hCSCs). Previous study indicated that miR-499-5p promoted invasion and metastasis of colorectal cancer and might be a new potential therapeutic target for colorectal cancer [5]. Li et al. suggested that miR-499 rs3746444 may contribute to the risk of CRC [6]. However, Du et al. did not support association between rs3746444 and CRC risk [7]. Therefore, we did this study to assess whether miR-499 rs3746444 affect the risk of CRC.

Methods

Study population

The present study was performed on 434 unrelated patients with histologically confirmed CRC treated between 2009 and 2016. The control group consisted of 479 healthy persons without a history of cancers. All recruited subjects were local residents of Han Chinese population, and all CRC subjects were diagnosed by surgical resection and pathologic examination. The CRC subjects who had a history of personal malignant tumor or autoimmune disorder, or had undergone radiotherapy or chemotherapy were excluded. All participants were given an explanation of the study, and written informed consent was obtained from each participant. This study was conducted under the approval of the Ethics Committees.

Genotyping method

Blood samples were collected from all participants at the time of recruitment. Genomic DNA was extracted from peripheral blood obtained from each participant using the DNA Extraction Kit (Tiangen Biotech (Beijing) Co., Ltd.) according to the manufacturer's protocol. The miR-499 rs3746444 was genotyped using the TaqMan methodology in 96-well plates and read with the Sequence Detection Software (SDS, version

1.4) on an Applied Biosystems (ABI) 7500 Real-Time PCR System.

Statistical analysis

The associations between miR-499 rs3746444 and the risk of CRC were analysed by unconditional logistic regression for Odds Ratio (OR) and 95% Confidence Interval (CI). Statistical analyses were implemented in SAS 9.1.3 software (SAS Institute, Cary, NC). A P<0.05 (two-tailed) was defined as the criterion of statistical significance.

Results

A total of 913 subjects were included in this case-control study, including 434 patients with CRC and 479 healthy controls. The baseline characteristics were listed in Table 1. There were no significant differences between the groups in their gender and age.

The genotype and allele frequency distributions for miR-499 rs3746444 polymorphism among the cases and controls and their associations with risk for CRC are shown in Table 2. The genotype distribution was in the Hardy-Weinberg equilibrium in control group (P>0.05). The miR-499 rs3746444 polymorphism showed significant difference between CRC patients and healthy controls in genotype comparison (TC *vs.* TT: OR=1.37, 95% CI 1.01-1.88, P=0.04; CC *vs.* TT: OR=3.18, 95% CI 1.83-5.55, P<0.01; CC+TC *vs.* TT: OR=1.64, 95% CI 1.22-2.24, P<0.01; Table 2). Additionally, the miR-499 rs3746444 T allele was significantly associated with CRC risk (OR=2.89, 95% CI 1.69-5.09, P<0.01; Table 2).

Table 1. *Clinical characteristics of the patients and controls.*

Characteristics	No. of patients (n=434)	No. of controls (n=479)
Age (y)		
Median	59.5	60
Range	45-82	43-81
Gender		
Male	303	338
Female	131	141
Smoking habit		
Yes	281	287
No	153	192
Alcohol consumption		
Yes	238	181
No	196	298
Staging		
I+II	173	
III+IV	261	

Table 2. *Alleles and genotypes frequencies of mir-499 rs3746444 polymorphism among patients and controls.*

Frequency	Case	Control	OR (95% CI)	P value
TT	263	342	1 (Reference)	
TC	110	102	1.37 (1.01-1.88)	0.04
CC	47	19	3.18 (1.83-5.55)	<0.01
CC+TC	157	121	1.64 (1.22-2.24)	<0.01
T allele	636	786	1 (Reference)	
C allele	204	140	2.89 (1.69-5.09)	<0.01

Discussion

In the present case-control study, the miR-499 rs3746444 polymorphism showed significant difference between CRC patients and healthy controls in genotype comparison. Additionally, the miR-499 rs3746444 T allele was significantly associated with CRC risk.

Cancer is a multistep process in which genetic and environmental factors interact in the development of cancer. Mu et al. found that miR-499 rs3746444 polymorphism was associated with a risk of breast cancer [8]. Zhang et al. suggested that miR-499 rs3746444 polymorphism may contribute to genetic susceptibility to oral squamous cell cancer [9]. Shi et al. identified rs3746444 was a potential biomarker to predict the recurrence of early gastric cancer [10]. Hashemi et al. indicated that miR-499 rs3746444 polymorphism increased the risk of PCa in an Iranian population [11].

Several potential limitations of the present meta-analysis should be acknowledged. First, the sample size was not large enough. Second, this was a hospital based case-control study, and the subjects were not fully representative of the general population; thus, selection bias was unavoidable. Third, biospecimens were not collected from controls at the inception of the study.

The results of our study suggest that miR-499 rs3746444 was significantly associated with CRC risk.

Conflicts of Interest

None

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