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Association of Methylenetetrahydrofolate Reductase Gene rs1801133 Polymorphism and Controlling Nutritional Status (CONUT) Score with Colorectal Cancer Susceptibility

Zhuoxin Zhang[1], Zuguang Wu[1], Yuwen Zeng[1], Yunlin Li[1], Yingchuan Feng[1], Zhen Gao[1], Yijin Chen[2]

[1]Department of Gastrointestinal Surgery, Meizhou People's Hospital, Meizhou, People's Republic of China; [2]Department of Gastroenterology, Meizhou People's Hospital, Meizhou, People's Republic of China

Correspondence: Yijin Chen, Department of Gastroenterology, Meizhou People's Hospital, Meizhou, People's Republic of China, Email yijinchenmz@163.com

Background: Susceptibility to some cancers is linked to methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms and the Controlling Nutritional Status (CONUT) score in some populations. However, their relationship with susceptibility to colorectal cancer (CRC) susceptibility in the Hakka Chinese population remains unclear.

Methods: In total, 620 CRC patients and 734 controls were enrolled. *MTHFR* rs1801133 was genotyped, medical records (age, sex, smoking history, alcohol consumption, hypertension, diabetes mellitus, and family history of cancer, and blood cell parameters) were collected, and the relationship between this information and CRC susceptibility was analyzed.

Results: There were significant differences in the distribution of CONUT classification (p=0.002), and proportions of history of smoking (p<0.001), hypertension (p<0.001), diabetes mellitus (p<0.001), and family history of cancer (p=0.002) between patients and controls. There were statistically significant differences in *MTHFR* rs1801133 genotypes distribution (58.7% C/C, 35.5% C/T, and 5.8% T/T in patients vs 65.5%, 31.2%, and 3.3% in controls, p=0.010) and allele distribution (76.5% C, and 23.5% T allele in patients vs 81.1%, and 18.9% in controls, p=0.003) between patients and controls. Logistic regression analysis indicated that non-normal CONUT range (non-normal vs normal, odds ratio (OR): 1.451, 95% confidence interval (CI): 1.119–1.882, p=0.005), and *MTHFR* rs1801133 variant (C/T + T/T vs C/C, OR: 1.373, 95% CI: 1.091–1.728, p=0.007), older age (≥65 vs <65 years, OR: 1.298, 95% CI: 1.023–1.646, p=0.032), male sex (OR: 1.354, 95% CI: 1.067–1.718, p=0.013), and history of alcohol drinking (OR: 2.232, 95% CI: 1.164–4.282, p=0.016) were independently associated with CRC risk.

Conclusion: Individuals carried *MTHFR* rs1801133 variant and with non-normal CONUT range, advanced age, history of alcohol consumption may be at increased CRC risk in the Hakka population.

Keywords: colorectal cancer, susceptibility, *MTHFR*, controlling nutritional status, Hakka

Introduction

Colorectal cancer (CRC) is the most common cancer that occur in the digestive tract.[1] The mortality rate of CRC is second only to that of lung cancer among malignant tumors, and its incidence rate ranks third and is on the rise.[2] In China, CRC has a high incidence and mortality.[3] The occurrence of CRC is a long-term, slow, and dynamic process, usually under the joint action of environmental risk factors and genetic factors, which gradually develops into precancerous lesions, and then transforms into cancer.[4,5] Cancer can be prevented by changing the key risk factors; therefore, it is important to explore the risk factors for CRC and guide the early prevention.

Folic acid is an essential element in nucleic acid synthesis and plays an important role in cell growth, tissue repair, and protein metabolism.[6,7] Folic acid is involved in methylation, DNA synthesis and repair in the body by providing methyl groups.[8] Folic acid deficiency and impaired folate metabolism can lead to the changes in DNA methylation,

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which may lead to the inactivation of tumor suppressor genes and the activation of proto-oncogenes, thus causing tumors.[9] 5–10-Methylenetetrahydrofolate reductase (MTHFR) is a rate-limiting enzyme in the entire metabolism of the folic acid cycle, that can effectively regulate folate levels in the body.[10] MTHFR activity is directly related to the polymorphisms in the encoding gene *MTHFR*.[11] Rs1801133 (C677T) is the most common *MTHFR* polymorphism, and the conformation of the binding site of the flavin adenine dinucleotide (FAD) of MTHFR encoded by the *MTHFR* gene with this variant is altered, thus affecting its function.[12]

Moreover, the occurrence and progression of tumors are not only affected by the changes in cell properties, but are also related to the short- and long-term nutritional status of patients. Several studies support the idea that nutritional abnormalities are risk factor for CRC.[13–15] Goodarzi G et al found that individuals with abnormal metabolic and nutritional status have an increased risk of CRC.[16] The Controlling Nutritional Status (CONUT) score is a comprehensive index that combines, serum albumin concentration, total lymphocyte count, and total cholesterol concentration, and can effectively evaluate the nutritional status of individuals.[17] The CONUT score is composed of three factors related to protein synthesis capacity, immune capacity, and lipid metabolism, which reflect the immune defense function, calorie consumption capacity, and protein reserve capacity, respectively, to accurately and objectively evaluate the nutritional status of individuals.[18] The CONUT score has been shown to have potential value in the assessment of prognosis and survival in some solid tumors and hematological malignancies, such as gastric cancer, CRC, and multiple myeloma.[19–21] At present, the study of CONUT score in CRC is mainly aimed at evaluating the prognosis of CRC, and there is no study of CONUT score in CRC risk.

Differences in the risk of CRC in different regions and different populations may be related to differences in lifestyle and genetic backgrounds. The Hakka population is a Chinese Han populations with a unique genetic background formed by the Hakka ancestors from the Han nationality in central China, who migrated southward for many times and fused with the ancient Yue residents in the region of southern China.[22] To date, there have been no reports on the association *MTHFR* polymorphisms, CONUT score, and CRC susceptibility in the Hakka population. The purpose of this retrospective study was to explore the relationship between *MTHFR* gene polymorphism, CONUT score and CRC susceptibility, to clarify their clinical values as CRC risk assessment, and to provide variety of selective and individualized assessment indicators for CRC risk prediction.

Materials and Methods

Study Cohort

This study retrospectively analyzed 620 CRC patients and 734 controls from the Meizhou People's Hospital, between January 2019 and December 2023 by retrospectively analyzed. The inclusion criteria of patients were as follows: (1) diagnosis of histologically confirmed CRC; (2) absence of other tumors and severe organ dysfunction; and (3) had complete clinical records. The inclusion criteria for controls were as follows: (1) individuals who underwent physical examination at Meizhou People's Hospital during the same period; and (2) without tumor. Exclusion criteria of patients were excluded from the study for the following reasons: (1) with autoimmune disease or severe organ dysfunction; (2) patients with other malignant tumors; (3) CRC patients who have received radiation, chemotherapy, or immunotherapy; and (4) absence of complete clinical records. This study was approved by the Human Ethics Committees of the Meizhou People's Hospital.

Data Collection and MTHFR rs1801133 Genotyping

The collected clinical data included age, sex, body mass index (BMI), history of smoking, history of alcohol consumption, hypertension, diabetes mellitus, and family history of cancer. According to the Chinese standards, BMI was divided into three grades: <18.5 kg/m^2, 18.5–23.9 kg/m^2, and ≥24.0 kg/m.^{2} [23,24] Blood test data were collected during the first hospital examination.

Genomic DNA was extracted from whole blood, and *MTHFR* rs1801133 polymorphism was genotyped using an *MTHFR* genotyping kit (BaiO Technology Co, Ltd, Shanghai, China) as previously described by our colleagues.[25,26]

Data Processing and Statistical Analysis

CONUT score was calculated according to the serum albumin concentration (35–45g/L (1 point), 30–34.9g/L (2 points), 25–29.9g/L (4 points), and <25g/L (6 points)), peripheral lymphocyte count (≥1.6 × 10^9 count/L (0 point), 1.2–1.59×10^9 count/L (1 point), 0.8–1.19×10^9 count/L (2 points), and <0.8 × 10^9 count/L (3 points)), and total cholesterol level (>180mg/dL (0 point), 140–180mg/dL (1 point), ≥100 and <140mg/dL (2 points), and <100mg/dL (3 points)). CONUT score was assessed as normal on a score of 0–1, light on a score of 2–4, moderate on a score of 5–8, and severe on a score of 9−12.[27]

Data analysis was performed using SPSS statistical software version 26.0 (IBM Inc., USA). Continuous data were compared using Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables are expressed as the number of cases (%), and compared between groups using the χ^2 test or Fisher's exact test. Logistic regression analysis was applied to assess the effects of *MTHFR* rs1801133 polymorphism and CONUT score on CRC risk, adjusting for other major influencing factors, such as age, sex, smoking history, alcohol consumption, hypertension, diabetes mellitus, and family history of cancer.

Results

Characteristics of Subjects

There were 848 (62.6%) patients aged <65 years old, and 506 (37.4%) patients aged ≥65 years old. The proportion of male and female was 62.8% and 37.2%, respectively. There were 152 (11.2%) subjects with BMI <18.5 kg/m^2, and 329 (24.3%) with BMI ≥24 kg/m^2, and others with normal range (18.5–23.9 kg/m^2). The proportions of patients with a history of smoking, history of alcohol consumption, hypertension, diabetes mellitus, and a family history of cancer were 11.2% (151/1354), 4.4% (59/1354), 33.7% (456/1354), 16.8% (228/1354), and 0.6% (8/1354), respectively. There were 387 (28.6%), 858 (63.4%), 98 (7.2%), and 11 (0.8%) individuals with CONUT normal, light, moderate, and severe classification (Table 1).

There were significant differences in the distribution of CONUT classification (p=0.002), and proportions of patients with a history of smoking (p<0.001), hypertension (p<0.001), diabetes mellitus (p<0.001), and family history of cancer

Table 1 Clinical Characteristics of CRC Patients and Controls

Clinical Characteristics	Total (n=1354)	Controls (n=734)	CRC Patients (n=620)	*p* values
Age (years)				
<65, n(%)	848 (62.6%)	470 (64.0%)	378 (61.0%)	0.260
≥65, n(%)	506 (37.4%)	264 (36.0%)	242 (39.0%)	
Gender				
Male, n(%)	850 (62.8%)	445 (60.6%)	405 (65.3%)	0.080
Female, n(%)	504 (37.2%)	289 (39.4%)	215 (34.7%)	
BMI (kg/m^2)				
<18.5, n (%)	152 (11.2%)	84 (11.4%)	68 (11.0%)	0.958
18.5–23.9, n (%)	873 (64.5%)	473 (64.4%)	400 (64.5%)	
≥24.0, n (%)	329 (24.3%)	177 (24.1%)	152 (24.5%)	
History of smoking				
No, n(%)	1203 (88.8%)	627 (85.4%)	576 (92.9%)	<0.001
Yes, n(%)	151 (11.2%)	107 (14.6%)	44 (7.1%)	
History of alcohol drinking				
No, n(%)	1295 (95.6%)	704 (95.9%)	591 (95.3%)	0.689
Yes, n(%)	59 (4.4%)	30 (4.1%)	29 (4.7%)	
Hypertension				
No, n(%)	898 (66.3%)	449 (61.2%)	449 (72.4%)	<0.001
Yes, n(%)	456 (33.7%)	285 (38.8%)	171 (27.6%)	

(*Continued*)

Table 1 (Continued).

Clinical Characteristics	Total (n=1354)	Controls (n=734)	CRC Patients (n=620)	*p* values
Diabetes mellitus				
No, n(%)	1126 (83.2%)	588 (80.1%)	538 (86.8%)	0.001
Yes, n(%)	228 (16.8%)	146 (19.9%)	82 (13.2%)	
Family history of cancer				
No, n (%)	1346 (99.4%)	734 (100.0%)	612 (98.7%)	0.002
Yes, n (%)	8 (0.6%)	0 (0)	8 (1.3%)	
CONUT				
Normal, n(%)	387 (28.6%)	236 (32.2%)	151 (24.4%)	0.002
Light, n(%)	858 (63.4%)	433 (59.0%)	425 (68.5%)	
Moderate, n(%)	98 (7.2%)	57 (7.8%)	41 (6.6%)	
Severe, n(%)	11 (0.8%)	8 (1.1%)	3 (0.5%)	

Abbreviations: CRC, colorectal cancer; BMI, body mass index; CONUT, controlling nutritional status.

(p=0.002) between patients and controls. There was no significant difference in the distribution of age, sex, BMI, or proportion of history of alcohol consumption between the two groups (all p>0.05) (Table 1).

Distribution Frequencies of MTHFR rs1801133 Genotypes and Alleles

The distribution of *MTHFR* rs1801133 genotypes in CRC patients (χ^2= 0.130, p=0.718) and controls (χ^2=0.265, p=0.607) was consistent with Hardy-Weinberg equilibrium, respectively. There were statistically significant differences in the genotypes distribution (58.7% C/C, 35.5% C/T, and 5.8% T/T genotype in patients vs 65.5%, 31.2%, and 3.3% in controls, p=0.010) and allele distribution (76.5% C, and 23.5% T allele in patients vs 81.1%, and 18.9% in controls, p=0.003) between patients and controls (Table 2).

Comparison of Characteristics of Subjects in Different MTHFR rs1801133 Genotypes and CONUT Stages

There was a statistically significant difference in the age distribution (p=0.024) between the *MTHFR* rs1801133 C/C, and C/T+T/T genotypes. There was a statistically significant difference in the distribution of BMI (p=0.034) between subjects with a CONUT normal range and non-normal range. No statistically significant differences were observed in sex, smoking history, history of alcohol consumption, hypertension, diabetes mellitus, and family history of cancer in the different *MTHFR* rs1801133 genotypes and CONUT ranges (Table 3).

Table 2 The Prevalence of MTHFR rs1801133 Variants in Cases and Controls

	Total (n, %)	Controls (n, %)	CRC Patients (n, %)	*p* values
Genotypes				
C/C	845 (62.4%)	481 (65.5%)	364 (58.7%)	0.010
C/T	449 (33.2%)	229 (31.2%)	220 (35.5%)	
T/T	60 (4.4%)	24 (3.3%)	36 (5.8%)	
C/T + T/T	509 (37.6%)	253 (34.5%)	256 (41.3%)	
Alleles				
C	2139 (79.0%)	1191 (81.1%)	948 (76.5%)	0.003
T	569 (21.0%)	277 (18.9%)	292 (23.5%)	
HWE (χ^2, p)	χ^2=0.001, p=0.971	χ^2=0.265, p=0.607	χ^2=0.130, p=0.718	

Abbreviations: CRC, colorectal cancer; *MTHFR*, methylenetetrahydrofolate reductase; HWE, Hardy-Weinberg equilibrium.

Table 3 Clinical Characteristics of CRC Patients Stratified by MTHFR rs1801133 Genotypes and CONUT Ranges

Clinical Characteristics	*MTHFR* C/C Genotype (n=364)	*MTHFR* C/T + T/T Genotypes (n=256)	*p* values	CONUT Normal Range (n=151)	CONUT Non-normal Range (n=469)	*p* values
Age (years)						
<65, n(%)	208 (57.1%)	170 (66.4%)	0.024	93 (61.6%)	285 (60.8%)	0.924
≥65, n(%)	156 (42.9%)	86 (33.6%)		58 (38.4%)	184 (39.2%)	
Gender						
Male, n(%)	234 (64.3%)	171 (66.8%)	0.549	94 (62.3%)	311 (66.3%)	0.377
Female, n(%)	130 (35.7%)	85 (33.2%)		57 (37.7%)	158 (33.7%)	
BMI (kg/m^2)						
<18.5, n (%)	40 (11.0%)	28 (10.9%)	0.370	9 (6.0%)	59 (12.6%)	0.034
18.5–23.9, n (%)	242 (66.5%)	158 (61.7%)		97 (64.2%)	303 (64.6%)	
≥24.0, n (%)	82 (22.5%)	70 (27.3%)		45 (29.8%)	107 (22.8%)	
History of smoking						
No, n(%)	338 (92.9%)	238 (93.0%)	1.000	141 (93.4%)	435 (92.8%)	0.858
Yes, n(%)	26 (7.1%)	18 (7.0%)		10 (6.6%)	34 (7.2%)	
History of alcohol drinking						
No, n(%)	350 (96.2%)	241 (94.1%)	0.252	147 (97.4%)	444 (94.7%)	0.193
Yes, n(%)	14 (3.8%)	15 (5.9%)		4 (2.6%)	25 (5.3%)	
Hypertension						
No, n(%)	267 (73.4%)	182 (71.1%)	0.584	112 (74.2%)	337 (71.9%)	0.602
Yes, n(%)	97 (26.6%)	74 (28.9%)		39 (25.8%)	132 (28.1%)	
Diabetes mellitus						
No, n(%)	320 (87.9%)	218 (85.2%)	0.337	136 (90.1%)	402 (85.7%)	0.213
Yes, n(%)	44 (12.1%)	38 (14.8%)		15 (9.9%)	67 (14.3%)	
Family history of cancer						
No, n (%)	357 (98.1%)	255 (99.6%)	0.149	150 (99.3%)	462 (98.5%)	0.687
Yes, n (%)	7 (1.9%)	1 (0.4%)		1 (0.7%)	7 (1.5%)	
CONUT						
Normal, n(%)	89 (24.5%)	62 (24.2%)	0.979	-	-	-
Light, n(%)	248 (68.1%)	177 (69.1%)		-	-	
Moderate, n(%)	25 (6.9%)	16 (6.3%)		-	-	
Severe, n(%)	2 (0.5%)	1 (0.4%)		-	-	

Abbreviations: CRC, colorectal cancer; *MTHFR*, methylenetetrahydrofolate reductase; CONUT, controlling nutritional status; BMI, body mass index.

Impact of MTHFR rs1801133 and CONUT on CRC Risk

The results of univariate logistic regression analysis indicated that non-normal CONUT range (non-normal vs normal, odds ratio (OR): 1.472, 95% confidence interval (CI): 1.158–1.871, p=0.002), and *MTHFR* rs1801133 variant (C/T + T/T vs C/C, OR: 1.337, 95% CI: 1.072–1.667, p=0.010) were significantly associated with CRC. In multivariate logistic regression analysis, non-normal CONUT range (non-normal vs normal, OR: 1.451, 95% CI: 1.119–1.882, p=0.005), and *MTHFR* rs1801133 variant (C/T + T/T vs C/C, OR: 1.373, 95% CI: 1.091–1.728, p=0.007), advanced age (≥65 vs <65 years, OR: 1.298, 95% CI: 1.023–1.646, p=0.032), male sex (OR: 1.354, 95% CI: 1.067–1.718, p=0.013), and history of alcohol consumption (OR: 2.232, 95% CI: 1.164–4.282, p=0.016) were independently associated with CRC (Table 4).

Table 4 Logistic Regression Analysis of Risk Factors Associated with CRC

Variables	Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
CONUT (non-normal vs normal)	1.472(1.158–1.871)	0.002	1.451(1.119–1.882)	0.005
MTHFR rs1801133 variants (C/T + T/T vs C/C)	1.337(1.072–1.667)	0.010	1.373(1.091–1.728)	0.007
Age (≥65 vs <65, years)	1.140(0.914–1.421)	0.246	1.298(1.023–1.646)	0.032
Gender (Male vs Female)	1.223(0.980–1.527)	0.075	1.354(1.067–1.718)	0.013
BMI (kg/m^2)				
18.5–23.9	1.000 (reference)	-	1.000 (reference)	-
<18.5	0.957(0.677–1.353)	0.805	0.765(0.532–1.099)	0.147
≥24.0	1.015(0.787–1.310)	0.906	1.232(0.934–1.624)	0.139
History of smoking (Yes vs No)	0.448(0.310–0.647)	<0.001	0.300(0.187–0.480)	<0.001
History of alcohol drinking (Yes vs No)	1.151(0.683–1.941)	0.596	2.232(1.164–4.282)	0.016
Hypertension (Yes vs No)	0.600(0.477–0.755)	<0.001	0.591(0.458–0.761)	<0.001
Diabetes mellitus (Yes vs No)	0.614(0.457–0.824)	0.001	0.615(0.450–0.840)	0.002
Family history of cancer (Yes vs No)	-	0.999	-	0.999

Abbreviations: CRC, colorectal cancer; *MTHFR*, methylenetetrahydrofolate reductase; CONUT, controlling nutritional status; BMI, body mass index; OR, odds ratio; CI, confidence interval.

Discussion

CRC is the most common malignant tumors of the digestive tract, and is caused by a combination of genetic and environmental factors.[28] CRC is one of the most common malignant tumors in China, and its significant regional distribution is a prominent epidemiological feature, suggesting that environmental factors may play a major role in the occurrence of CRC.[29] However, only a few people in the same environment eventually develop CRC, suggesting that genetic factors also play an important role in the development of it.[30] The study of the risk factors for CRC susceptibility is helpful for understanding the pathogenesis of CRC and the screening of high-risk individuals, and provides a basis for targeted individual prevention.

When exposed to the same environmental factors, not all people will develop tumors, and there will always be some people who show a tendency to develop cancer, especially in patients with sporadic tumors. It suggests that there are certain genes with high visibility that may play an important role, and that the widespread polymorphism of these genes between different individuals may contribute to susceptibility to tumors. MTHFR is a rate-limiting enzyme that regulates the metabolism of folate and methionine, and the metabolic cycle of folate and methionine is related to DNA methylation, DNA synthesis and repair. Several studies have reported an association between the *MTHFR* rs1801133 variant and the risk of CRC in the Chinese population,[31] Taiwanese population,[32] Thai population,[33] Korean population,[34] Kashmiri population,[35] Turkish population,[36] and French population.[37] However, some studies have suggested that *MTHFR* rs1801133 variant is associated with a reduced risk of CRC.[38–42] Moreover, other studies have shown that *MTHFR* rs1801133 polymorphism is not associated with CRC risk in Asian populations,[43] Africans,[44] and Iranian population.[45] In this study, *MTHFR* rs1801133 variant (C/T + T/T) was independently associated with CRC susceptibility in Hakka population. Therefore, more researches are needed to reveal the relationship between *MTHFR* gene and CRC risk.

At present, studies on the relationship between the CONUT score and CRC are mainly used as indicators of preoperative risk assessment,[20,46,47] and prognosis of patients.[48–51] Cancer prevention has always been a focus of clinical studies. With the increasing research on cancer-related malnutrition, it is of great significance to analyze the relationship between nutritional status and the occurrence of CRC.[13,52] The relationship between CONUT score and CRC susceptibility has not yet been reported. Nutrient levels can increase gut susceptibility to carcinogens by altering the gut microbiome.[53] A study showed that food-derived cholesterol compounds modified by intestinal bacteria play a regulatory role in CRC lesions in animal experiments.[54] Cholesterol and its metabolism were involved in the pathogenesis of some cancers.[55,56] The gut microbiota is the origin of CRC, and T-lymphocyte mediated immune function plays an important role in CRC.[57,58] The CONUT score is a comprehensive index reflecting the nutritional and immune status, combining serum albumin levels, lymphocyte counts, and

total cholesterol. In this study, non-normal CONUT range (2–12 points) were independently associated with CRC. It provides valuable reference data for the role of nutritional status level in tumor risk assessment.

Moreover, some studies have found that CONUT scores in patients with CRC are correlated with some biochemical indicators of patients.[59] However, it was not studied in this study. Most studies have found that alcohol consumption is associated with an increased risk of CRC.[60–63] In addition, the relationship between alcohol consumption and CRC varies according to race, lifestyle factors, and tumor site.[64] A study has shown that long-term ethanol feeding can increase the total number of colon tumors in AOM/DSS treated mice by nearly 4 times.[65] Moreover, ethanol significantly increased the expression of colon mucosal proinflammatory cytokines and chemokines during the precancerous stage.[66] Alcohol itself is not a carcinogen, but the metabolites generated by alcohol metabolism can spread into the intestinal cavity through systemic circulation to causing mucosal damage and cell proliferation, inducing DNA damage and promoting the occurrence of CRC.[67] Therefore, bad lifestyle habits also play an important role in the development of CRC, such as alcohol consumption.

This research had some limitations. First, this study only analyzed the relationship between *MTHFR* gene status, CONUT score and CRC risk, but did not analyze their relationship with the clinicopathological features of CRC patients. Second, this study did not examine the relationship between other factors (diet, lifestyle, and living environment, and so on) and CRC risk. Third, in the absence of nutrition-related physical examinations, such as fat, muscle, and fluid status in this study, CONUT may not be able to comprehensively assess the nutritional status of the study subjects. Therefore, future studies with larger sample sizes, inclusion of more indicators, and comprehensive analyses are needed to investigate this relationship.

Conclusion

Individuals carried *MTHFR* rs1801133 variant and with non-normal CONUT range, advanced age, history of alcohol consumption may be at increased CRC risk among Hakka population. It provides variety of selective and individualized assessment indicators for CRC risk prediction. Of course, the relationship between *MTHFR* polymorphisms, CONUT and CRC susceptibility still needs to be confirmed by more in-depth researches.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the study obtained written informed consent from all the participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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