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Association between the omentin-1 gene rs2274907 A>T polymorphism and colorectal cancer in the Chinese Han population: a case-control study

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Abstract

Objective: To explore the relationship between the omentin-1 gene rs2274907 A>T polymorphism and colorectal cancer (CRC) in the Chinese Han population.

Methods: rs2274907 A>T was assessed by PCR–restriction fragment length polymorphism analysis. Plasma omentin-1 expression from 358 patients with CRC and 286 healthy controls was analyzed by enzyme-linked immunosorbent assay. CRC and control groups were divided into subgroups according to the body mass index (BMI) threshold of 25 kg/m^2.

Results: No significant differences were observed between CRC and control groups in terms of genotype or allele frequencies of rs2274907 A>T. Compared with individuals with BMI $<25\ kg/m^2$ and the rs2274907 TT genotype, those with AA+AT genotypes and BMI $\geq 25\ kg/m^2$ had a 3.027-fold increased risk of CRC. A significant tendency toward a higher stage of colorectal adenocarcinomas and depth of invasion was observed in individuals with the rs2274907 AA genotype compared with other genotypes.

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Conclusions: The omentin-1 gene rs2274907 A>T polymorphism does not seem to play a critical role in the development of CRC in the Chinese Han population, but an interaction between the rs2274907 A allele and BMI may increase the CRC risk. The rs2274907 AA genotype is a potential biomarker for CRC stage progression.

Keywords
Omentin-1, rs2274907, colorectal cancer, biomarker, Chinese Han, body mass index, genotype

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Introduction

Colorectal cancer (CRC) is one of the most frequent malignancies worldwide, ranking third in terms of incidence for malignant tumors and second in terms of mortality.[1] Epidemiological studies have shown that CRC is closely associated with obesity,[2,3] which mainly manifests as an increase in the size and number of fat cells and adipose tissues. Because it influences the metabolism of other organs and systems, adipose tissue is considered to be an active endocrine organ that produces proteins known as adipokines.[4] Various adipokines, such as visfatin, adiponectin, leptin, and resistin, were shown to play an important role in the pathogenesis of CRC and to provide a biomarker for disease severity.[5–7]

Omentin, a newly identified adipokine that is preferentially produced and secreted by visceral adipose tissue (predominantly expressed in stromal vascular cells), is associated with vascular, metabolic, and various chronic inflammatory diseases.[8] Omentin has two highly homologous isoforms: omentin-1 and omentin-2. Omentin-1 is the main circulating form identified in human plasma that increases insulin sensitivity by stimulating insulin-mediated glucose uptake in human adipocytes, and might be involved in the pathogenesis of obesity and related diseases.[9] Recently, several studies have found that plasma omentin-1 is elevated in patients with CRC, and that high prediagnostic omentin-1 concentrations are independently associated with a higher colorectal cancer risk.[10–12]

Genetic polymorphisms influence gene expression and activity.[13–15] The human omentin-1 gene is located on chromosome 1q21.39 and consists of eight exons and seven introns. The rs2274907 A>T polymorphism in exon 4 of the omentin-1 gene has been investigated in relation to type 2 diabetes, chronic inflammatory bowel disease, psoriasis, nonalcoholic fatty liver, coronary artery disease, rheumatoid arthritis, and the regulation of nutritional behaviors.[16–22] It is also thought to affect circulating omentin-1 levels.[22]

Thus far, no data are available on the possible relationships between variability in the omentin-1 gene and CRC. Therefore, this study aimed to evaluate the association between the omentin-1 rs2274907 A>T polymorphism and the risk of CRC and to investigate the clinicopathological characteristics and circulating omentin-1 levels of patients with CRC with different omentin-1 rs2274907 genotypes.

Materials and methods

Study subjects

We enrolled 358 Chinese Han patients aged ≥35 years with pathologically diagnosed

colorectal adenocarcinoma confirmed by a hospital pathologist. Patients underwent total colonoscopy by experienced gastrointestinal physicians using video endoscopy between September 2015 and September 2018 at the First Affiliated Hospital of Anhui Medical University. Patients with familial adenomatous polyposis, hereditary nonpolyposis CRC, previous gastrointestinal tract surgery, inflammatory bowel disease, serious liver and renal dysfunction, acute and chronic infectious disease, and those undergoing dietary or drug treatment for diabetes mellitus were excluded from this study. Two hundred seventy-one of the 358 patients were diagnosed with colon cancer, and the others were diagnosed with rectal cancer. A total of 286 Chinese Han individuals aged $\geq$35 years, without colorectal adenocarcinoma, colorectal polyp or inflammatory bowel disease, who accepted a total colonoscopy because of a voluntary health check-up or occult fecal blood loss during the same time period and at the same hospital were enrolled as controls, with the same exclusion criteria. For every eligible case, an attempt was made to randomly identify a control who was matched as closely as possible in terms of age ($\pm$ 5 years) and case admission time ($\pm$1 month). This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

Cancer lesions were treated appropriately by open surgical colectomy. For each case, the localization and size of the tumor, the histological grade, and the clinical and pathological stage were recorded. Histological typing, grading, and tumor staging were based on World Health Organisation criteria and the tumor–node–metastasis (TNM) system. According to tumor localization, samples were classified as "right-sided" (localized in the cecum or in the ascending or transverse colon) and "left-sided" (set in the descendant or sigmoid colon or in the rectum). Tumors were classified into two groups according to size: $\leq$4 cm and >4 cm. Local invasion was also classified into two groups: pT1–T2 and pT3–T4. Patients were subdivided into two groups based on their histological grade: grade 1 and grade 2, and grade 3 adenocarcinomas.

All participants were encouraged to complete a questionnaire concerning lifestyle and personal and family medical history, as described previously.[23] In brief, this inquired about smoking habits, alcohol intake, physical activity, vegetable intake, medications (such as antihypertension drugs and aspirin), and family history of CRC. The body weight, height, waist circumference, hip circumference, and blood pressure of participants were recorded, and the body mass index (BMI) and waist/hip ratio (WHR) were calculated.

Laboratory measurements

Blood samples were collected after overnight fasting when the endoscopic check was done and stored at –80°C until analysis. Glucose, insulin, and omentin-1 levels were measured in plasma samples, and total cholesterol (TCH) and triglycerides (TG) were measured in serum samples. Insulin resistance was calculated by the homeostatic model assessment of insulin resistance (HOMA-IR) method as follows: HOMA-IR = fasting glucose $\times$ fasting insulin / 22.5 (expressed in μU/L and glucose in mmol/L).

Plasma concentrations of omentin-1 were analyzed by enzyme-linked immunosorbent assay in one run using a human ELISA kit (BioVision Inc., Milpitas, CA, USA) which has reported intra-assay and inter-assay coefficients of variation for omentin-1 of 5.1% to 7.6% and 5.6% to 7.1%, respectively. Fasting plasma glucose (FPG) was measured using the glucose oxidase method,[7] and fasting plasma insulin

(FIST) was measured by radioimmunoassay (Wuhan Gene Beauty Technology, Wuhan, China) with an intra-assay coefficient of variation of 5.7% to 9.6% and an inter-assay coefficient of variation of 7.2% to 11.8%. TCH was measured by the cholesterol oxidase method, and TG was measured by the triglyceride oxidase method.[7]

Genotyping

Genomic DNA was extracted from 5 mL of whole blood samples, which were collected from all participants in ethylenediaminetetraacetic acid tubes, using a DNA isolation kit (Bioteke Corporation, Beijing, China) according to the manufacturer's instructions. Samples were stored at –80°C until analysis by the PCR–restriction fragment length polymorphism method (PCR–RFLP).

The omentin-1 gene rs2274907 A>T polymorphism genotype was determined by amplification using the following primers:[21] Forward, 5′-GAGCCTTTAGG CCATGTCTCT-3′; and reverse, 5′-CTC TCCTTCTTCTCCAGCCCAT-3′ (DNA-Technology A/S, Takara Biotechnology Co., Ltd., Dalian, China). PCR assays were performed on an ABI 9600 device (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. The reaction mix contained 0.25 μL of each primer, 0.125 μL of probe, 2 μL of PCR mixture reagent, and 25 ng of DNA in a total volume of 25 μL. Cycling conditions were an initial denaturing step at 95°C for 4 minutes followed by 40 cycles of 94°C for 1 minute, 62°C for 1 minute, and 72°C for 1 minute, with a final extension at 72°C for 5 minutes. PCR products were digested overnight with 10 U of *Xmi I* (*Acc* I) restriction endonuclease (Fermentas, Baden-Wurttemberg, Germany), and then run on 2% agarose gel electrophoresis. Approximately 5% of the samples were randomly chosen for a second run to validate the genotyping accuracy. All duplicate samples showed a concordance rate of 100%.

Statistical analysis

A goodness-of-fit chi-squared (χ^2) test was used to assess the Hardy–Weinberg equilibrium in this study. The significance of differences in genotype and allelic frequencies between patients with CRC and healthy controls was determined using 2×2 tables and a standard χ^2 test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used in calculating the corresponding χ^2 distribution test. Multivariate logistic regression analysis was used for association analyses with adjustments for age, BMI, WHR, TCH, TG, HOMA-IR, lifestyle characteristics, medications, and family history of CRC. The association of the rs2274907 A>T polymorphism genotype and CRC was estimated using the dominant model (defined as TT (reference) *vs* AT+AA) and recessive model (defined as AA *vs* TT+AT (reference)). Comparisons of clinical parameters of different genotypes among patients with CRC and healthy controls were assessed by one-way analysis of variance and the least significant difference test. The χ^2 test was used to assess the association of clinicopathologic characteristics and omentin genotypes in patients with CRC. All P-values were two-sided and $P < 0.05$ was considered statistically significant. The SPSS statistical software package for Windows version 17.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

Comparing patient and control characteristics

Patients with CRC were matched with control participants by age (within 5 years) and

date of diagnosis (within 1 month). Table 1 summarizes selected characteristics of patients and controls. There were no significant differences in mean age, sex, or the numbers of current smokers, ex-smokers, habitual alcohol drinkers, habitual non-steroidal anti-inflammatory drug (NSAID) users, habitual exercisers, and habitual vegetable consumers between the two groups. Moreover, there was no significant difference with respect to systolic blood pressure, diastolic blood pressure, BMI, WHR, HOMA-IR, insulin, glucose, TCH, or TG between the two groups. However, plasma omentin-1 concentrations were significantly higher in patients with CRC than in controls ($P = 0.005$).

Comparing rs2274907 A>T genotype and allele frequencies between patients and controls

Genotypic and allelic distributions of the omentin-1 gene rs2274907 A>T polymorphism in patients with CRC and controls are summarized in Table 2. Compared with the TT genotype, the AT and AA genotypes demonstrated no significant association with the risk of CRC. This non-significant association was maintained after adjusting for well-known CRC risk factors including age, BMI, WHR, TCH, TG, HOMA-IR, lifestyle characteristics, medications, and family history of CRC. There was also no significant correlation

Table 1. Selected characteristics of patients with CRC and controls [($\bar{x} \pm s$), n (%)].

Variable	Patients with CRC (n = 358)	Controls (n = 286)	P-value
Age (years), mean ± SD	60.9 ± 11.8	58.8 ± 12.9	0.715[a]
Sex			
Male	202	169	0.496
Female	156	117	
Smoking			
Current	123 (34.36)	82 (28.67)	0.124[b]
Previous	31 (8.66)	17 (5.94)	0.192[b]
Habitual alcohol use	86 (24.02)	65 (22.72)	0.761[b]
Habitual NSAID use	9 (2.51)	4 (1.40)	0.327[b]
Habitual exercise	95 (26.54)	77 (26.92)	0.933[b]
Habitual vegetable consumer	120 (33.52)	82 (28.67)	0.340[b]
Family history of CRC	93 (25.98)	29 (10.14)	0.001
SBP, mmHg	134 ± 12	128 ± 10	0.287
DBP, mmHg	83 ± 10	80 ± 7	0.301
BMI, kg/m^2	24.34 ± 3.44	24.11 ± 3.28	0.726
WHR	0.87 ± 0.08	0.86 ± 0.06	0.612
FPG, mmol/L	5.55 ± 0.31	4.97 ± 0.21	0.078
FINS, mIU/mL	11.21 ± 7.01	8.21 ± 4.57	0.193
HOMA-IR	2.77 ± 1.49	1.72 ± 1.02	0.108
TCH, mmol/L	4.59 ± 0.69	4.83 ± 0.81	0.421
TG, mmol/L	1.45 ± 0.65	1.46 ± 0.72	0.732
Omentin-1 (ng/mL)	67.28 ± 32.25	33.16 ± 19.93	0.005

[a]P-value evaluated by analysis of variance.

[b]P-values evaluated by χ^2 test.

CRC, colorectal cancer; NSAID, non-steroid anti-inflammatory drug; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist: hip ratio; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; TCH, total cholesterol; TG, triglyceride.

Table 2. Multivariable linear regression analysis of association between rs2274907 A>T and risk of CRC [n(%)].

Variable	Patients with CRC (n = 358)	Controls (n = 286)	Unadjusted odds ratios (95% CI)	P value	Adjusted odds ratios (95% CI)	P[a] value
Genotype						
TT	214 (59.8)	176 (61.5)	1.000 (Reference)	–	1.000 (Reference)	–
AT	101 (28.2)	86 (30.1)	1.116 (0.853–3.614)	0.398	1.121 (0.796–3.485)	0.306
AA	43 (12.0)	24 (8.4)	1.523 (0.891–4.792)	0.113	1.584 (0.808–4.673)	0.104
Dominant						
TT	214 (59.8)	176 (61.5)	1.000 (Reference)	–	1.000 (Reference)	–
AA+AT	144 (40.2)	110 (38.5)	1.381 (0.742–6.481)	0.201	1.295 (0.658–5.914)	0.297
Recessive						
TT+AT	315 (88.0)	262 (91.6)	1.000 (Reference)	–	1.000 (Reference)	–
AA	43 (12.0)	24 (8.4)	1.601 (0.798–7.261)	0.098	1.509 (0.773–6.075)	0.112
Allele						
T	529 (73.9)	438 (76.6)	1.000 (Reference)	–	–	–
A	187 (26.1)	134 (23.4)	1.127 (0.721–6.264)	–	–	–

[a]Adjusted for age, body mass index, waist: hip ratio, total cholesterol, triglyceride, homeostatic model assessment of insulin resistance, lifestyle characteristics, medications, and family history of CRC.
CRC, colorectal cancer; CI, confidence interval.

Table 3. Multivariable linear regression analysis of association between rs2274907 A>T and risk of CRC stratified by BMI.

Genotype	BMI (kg/m^2)	CRC (n = 358)	Controls (n = 286)	Unadjusted odds ratios (95% CI)	P value	Adjusted odds ratios (95% CI)	P[a] value
TT	<25	84	81	1.000 (Reference)	–	1.000 (Reference)	–
AT+AA	<25	71	65	1.013 (0.497–3.852)	0.731	1.008 (0.415–4.261)	0.806
TT	≥25	130	95	2.175 (1.176–7.283)	0.027	1.986 (1.059–6.272)	0.041
AT+AA	≥25	73	45	3.264 (1.276–9.735)	0.012	3.027 (1.165–8.253)	0.022

[a]Adjusted for age, body mass index, waist: hip ratio, total cholesterol, triglyceride, homeostatic model assessment of insulin resistance, lifestyle characteristics, medications, family history of CRC.
CRC, colorectal cancer; BMI, body mass index; CI, confidence interval.

between rs2274907 A>T and the risk of CRC in either dominant or recessive models. The frequency of the polymorphic T allele was 73.9% in patients with CRC and 76.6% in controls, which was not significantly different.

When focusing on individuals with BMI <25 kg/m^2 and TT genotypes, obesity (BMI ≥25 kg/m^2) was found to significantly increase the risk of CRC development in individuals with TT genotypes (adjusted OR = 1.986, 95% CI 1.059–6.272, P = 0.041), whereas individuals with AA+AT genotypes and BMI ≥25 kg/m^2 had a 3.027-fold increased risk of CRC (adjusted OR = 3.027, 95% CI 1.165–8.253, P = 0.022) (Table 3).

Comparing clinical parameters of different genotypes between patients and controls

There were no significant differences in mean age, sex, family history of CRC, SBP, DBP, BMI, WHR, HOMA-IR, FINS, FPG, TCH, or TG among individuals with different genotypes in either the CRC group or the control group. Additionally, there was no significant genotype effect on omentin-1 plasma levels (Table 4).

Relationship between the rs2274907 A>T polymorphism and CRC clinicopathologic features

We observed a significant tendency toward higher stage colorectal adenocarcinomas and depth of invasion, based on the T factor of the TNM system, in patients with CRC with the rs2274907 A>T AA genotype (Table 5). To investigate whether this effect was attributable to the T or A allele, we pooled T allele carriers into one group and compared them with AA homozygotes (Table 6); the same tendency toward higher stage colorectal adenocarcinomas and depth of invasion was observed ($P = 0.019$, $P < 0.001$, respectively), suggesting it was caused by the A allele.

Discussion

Although several studies have reported significant associations between circulating omentin-1 levels and the risk of CRC,[10–12] the distribution of omentin-1 gene rs2274907 A>T polymorphism genotypes in CRC cases and controls has not received much attention. The present study showed that mean omentin-1 levels were significantly higher in patients with CRC compared with controls, similar to previous findings,[10–12] and that this was independent of measures of obesity. However, there was no significant difference regarding rs2274907 A>T between patients and controls. Nevertheless, when patients with BMI $<25\,kg/m^2$ and TT genotypes were used as a reference, those with AA+AT genotypes and BMI $\geq 25\,kg/m^2$ had a 3.027-fold increased risk of CRC. These results suggest that an increased level of omentin-1 might be a risk factor for CRC, but that rs2274907 A>T does not play a critical role in the development of CRC in the Chinese Han population, although an interaction between AA+AT genotypes and BMI may increase the CRC risk. The present study is the first to find no significant effect of rs2274907 A>T genotypes on plasma omentin-1 levels in patients with CRC. However, a significant tendency toward higher stage colorectal adenocarcinomas and depth of invasion was seen in AA homozygotes, indicating that the AA genotype could be a CRC biomarker correlating with stage progression.

Recently, increasing evidence has suggested that abnormal omentin-1 expression in CRC may be associated with cancer development and progression.[10–12,24–26] Moreover, several studies have explored the prognostic effect of omentin-1 in CRC. A prospective cohort study by Splichal et al.[11] showed that a higher omentin-1 concentration was associated with an increased CRC risk, while Kim et al.[24] reported that the downregulation of omentin-1 was associated with poor prognosis in patients with advanced CRC. Maeda et al.[25] and Kawashima et al.[26] demonstrated that a lack of TMEM207, which participates in the processing of omentin-1, causes insufficient omentin-1 production, thus promoting colorectal carcinogenesis, and that the omentin-1/TMEM207 axis could be used as a prognostic biomarker of colorectal carcinomas.

Several single nucleotide polymorphisms (SNPs) in different genes were previously reported to be related to cancer

Table 4. Comparison of clinical parameters of different genotypes in patients with CRC and controls [($\bar{x}\pm s$), n (%)].

Variable/Group	Genotype			P value
	TT	AT	AA	
Age (years)				
Patients with CRC	59.7 ± 9.8	61.1 ± 12.3	60.3 ± 10.6	NS
Controls	58.9 ± 10.2	60.8 ± 12.3	59.6 ± 9.9	NS
Sex (Male/Female), n (%)				
Patients with CRC	123/91	53/48	26/17	NS
Controls	105/71	50/36	14/10	NS
Family history of CRC, n (%)				
Patients with CRC	60 (26.20)	25 (25.00)	8 (27.59)	NS
Controls	15 (9.04)	10 (11.63)	4 (11.76)	NS
SBP, mmHg				
Patients with CRC	135 ± 13	133 ± 12	132 ± 12	NS
Controls	129 ± 11	128 ± 9	127 ± 10	NS
DBP, mmHg				
Patients with CRC	83 ± 11	82 ± 12	83 ± 9	NS
Controls	81 ± 9	80 ± 9	80 ± 8	NS
BMI, kg/m^2				
Patients with CRC	23.85 ± 4.01	24.18 ± 3.42	24.69 ± 3.35	NS
Controls	24.16 ± 3.52	23.97 ± 3.37	24.25 ± 3.29	NS
WHR				
Patients with CRC	0.87 ± 0.08	0.87 ± 0.09	0.88 ± 0.08	NS
Controls	0.87 ± 0.06	0.86 ± 0.07	0.87 ± 0.07	NS
FPG, mmol/L				
Patients with CRC	5.59 ± 0.33	5.54 ± 0.34	5.56 ± 0.29	NS
Controls	4.98 ± 0.22	5.11 ± 0.26	4.97 ± 0.20	NS
FINS, mIU/mL				
Patients with CRC	12.32 ± 8.11	10.24 ± 6.89	11.23 ± 7.12	NS
Controls	10.11 ± 5.38	8.03 ± 4.11	8.11 ± 5.44	NS
HOMA-IR				
Patients with CRC	2.81 ± 1.56	2.68 ± 1.37	2.71 ± 1.48	NS
Controls	1.81 ± 1.17	1.71 ± 0.99	1.75 ± 1.08	NS
TCH, mmol/L				
Patients with CRC	4.58 ± 0.58	4.61 ± 0.72	4.57 ± 0.67	NS
Controls	4.82 ± 0.84	4.86 ± 0.76	4.81 ± 0.78	NS
TG, mmol/L				
Patients with CRC	1.46 ± 0.61	1.44 ± 0.73	1.46 ± 0.65	NS
Controls	1.47 ± 0.68	1.46 ± 0.74	1.45 ± 0.71	NS
Omentin-1 (ng/mL)				
Patients with CRC	70.35 ± 35.14	65.82 ± 31.57	60.82 ± 30.26	NS
Controls	35.88 ± 18.85	31.73 ± 22.17	27.69 ± 20.54	NS

CRC, colorectal cancer; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist: hip ratio; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; TCH, total cholesterol; TG, triglyceride; NS: non-significant.

Table 5. Relationship between rs2274907 A>T variants and clinicopathologic features in patients with CRC.

Variable/category	n	Genotype			P value
		AA	AT	TT	
Tumor size, cm					
≤4	194	19	56	119	0.750
>4	164	24	45	95	
Tumor site					
Right	186	23	52	111	0.793
Left	172	20	49	103	
Histological grade					
1–2	194	21	48	125	0.677
3	164	22	53	89	
T					
T1–T2	197	11	57	129	0.035
T3–T4	161	32	44	85	
N					
N0	169	18	48	103	0.356
N1–N2	189	25	53	111	
M					
M0	196	24	58	114	0.466
M1	162	19	43	100	
Tumor stage					
1–2	218	9	69	140	0.002
3–4	150	34	42	74	

CRC, colorectal cancer; T, tumor; N, node; M, metastasis.

development and are regarded as useful cancer biomarkers.[27,28] The omentin-1 gene is located at chromosomal region 1q22-q23, where many studies have reported linkage to insulin resistance-related diseases such as type 2 diabetes and metabolic syndrome in various populations,[29] which closely correlate with the development of CRC. Kohan et al.[21] and Splichal et al.[22] reported that rs2274907 A>T was associated with susceptibility to nonalcoholic fatty liver and daily energy intake, respectively. However, several studies[16–20] found no relationship between the rs2274907 A>T genotype and diseases such as chronic inflammatory bowel diseases, type 2 diabetes mellitus, psoriasis, and coronary artery disease. Similarly, we also failed to demonstrate significant differences in genotype and allele frequencies of rs2274907 A>T between patients with CRC and healthy controls. However, stratified analysis by BMI after adjustment for common CRC risk factors found that obese individuals carrying at least one A allele had a 3.027-fold increased risk of CRC. These results suggest that an interaction between AA+AT genotypes and BMI may increase the risk of CRC in the Chinese Han population, similar to findings by Splichal et al.[22] who reported that interactions between AA+AT genotypes and BMI may reduce insulin sensitivity, which is negatively correlated with the development of CRC.

Polymorphisms influence the expression of hundreds of genes and can affect gene function. However, no experimental data

Table 6. Relationship between rs2274907 A>T pooled variants and clinicopathologic features in patients with CRC.

		Genotype		
Variable/category	n	AA	AT+ TT	P value
Tumor size, cm				
≤4	194	19	175	0.529
>4	164	24	140	
Tumor site				
Right	186	23	163	0.499
Left	172	20	152	
Histological grade				
1–2	194	21	173	0.709
3	164	22	140	
T				
T1–T2	197	11	186	0.019
T3–T4	161	32	129	
N				
N0	169	18	151	0.553
N1–N2	189	25	164	
M				
M0	196	24	172	0.635
M1	162	19	143	
Tumor stage				
1–2	218	9	209	<0.001
3–4	150	34	116	

CRC, colorectal cancer; T, tumor; N, node; M, metastasis.

are currently available on the effect of rs2274907 A>T on protein function. In the present study, there was a tendency in both patients and controls toward lowest omentin levels in AA carriers and highest levels in TT carriers, similar to previous findings by Splichal et al.,[22] although there was no significant relationship between rs2274907 A>T and circulating levels of omentin. Additionally, the A allele frequency did not differ significantly between patients and controls. It therefore appears that high omentin levels in the patient group might not be associated with rs2274907 A>T but may result from the effects of another polymorphism in the gene or other as yet undetermined factors. This should be further investigated in larger population-based cohort studies.

Several studies reported that genetic variants affect gene expression and function, and play an important role in CRC development and progression.[30–32] For example, Ling et al.[33] found that the novel long noncoding RNA CCAT2 was highly overexpressed in CRC, that the rs6983267 SNP status affected its expression, and that individuals with the rs6983267 risk allele G produced more CCAT2 transcript than those with other alleles. Moreover, Jiang et al.[34] showed that rs2470151 C>T CT/TT genotype carriers had a significantly decreased risk of CRC compared with those with the CC genotype. Our current findings suggest that individuals with the rs2274907 A>T AA genotype had similar tumor localizations, tumor sizes, histological grades, and N and M stages to T allele carriers, but

presented with significantly higher T stages and TNM stages, which may be indicative of a more serious disease phenotype. Thus, our data indicate that rs2274907 A>T is a promising biomarker for CRC prognosis. Recently, it was reported that omentin-1 has autocrine actions in colon cancer cells, which may serve as a carcinogenetic role in CRC.[35] It is not clear whether rs2274907 A>T affects the autocrine function of omentin-1 in colon cancer cells, and then participates in the pathogenesis of CRC. Therefore, future work should use site-directed mutagenesis to investigate the functional consequences of rs2274907 A>T.

In conclusion, we herein suggest that rs2274907 A>T does not play a critical role in the development of CRC in the Chinese Han population, but that an interaction between AA+AT genotypes and BMI may increase the risk of CRC. rs2274907 A>T is a potential biomarker for CRC prognosis. We also confirmed that there is no significant link between rs2274907 A>T polymorphism and circulating omentin-1 levels. This study has several limitations, including the relatively small number of patients and performance at a single institution. Additionally, we did not investigate other omentin-1 sequence variations, or determine the relationship of causality between rs2274907 A>T and CRC. Our findings should be confirmed and expanded in further studies in other ethnic groups.

Data availability

The data sets used to support the findings of this study are available from the corresponding author upon request.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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