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

Yaqin Zhang¹,*, Xiaotong Zhao¹,*, Yongxiang Li², Youmin Wang¹ and Mingwei Chen¹,³

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/m².
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/m² and the rs2274907 TT genotype, those with AA+AT genotypes and BMI ≥25 kg/m² 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.

¹Department of Endocrinology, The First Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China
²Division of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China
³Institute of Traditional Chinese Medicine Diabetes Prevention, Anhui Academy of Traditional Chinese Medicine, Hefei, People's Republic of China

*These authors contributed equally to this work.

Corresponding author:
Mingwei Chen, Department of Endocrinology, The First Affiliated Hospital of Anhui Medical University, Shushan District, JiXi Road, No 218, Hefei 230032, People's Republic of China.
Email: chmw1@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
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

Date received: 28 January 2021; accepted: 3 March 2021

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.\(^25\)

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 ≥35 years, without colorectal adenocarcinoma, colorectal poly 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 (± 5 years) and case admission time (±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: ≤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. 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:

\[
\text{HOMA-IR} = \frac{\text{fasting glucose}}{22.5} \times \frac{\text{fasting insulin}}{\text{expressed in } \mu\text{U/L and glucose in mmol/L}}.
\]

Plasma concentrations of omentin-1 were analyzed by enzyme-linked immunoassay 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, 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 (Biotek 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 (χ²) 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 χ² test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used in calculating the corresponding χ² 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 χ² 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 [(x ± 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/m²                      | 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 $\chi^2$ 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.
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/m² and TT genotypes, obesity (BMI ≥25 kg/m²) 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/m² 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, 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 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/m² and TT genotypes were used as a reference, those with AA+AT genotypes and BMI ≥25 kg/m² 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. Moreover, several studies have explored the prognostic effect of omentin-1 in CRC. A prospective cohort study by Splichal et al. showed that a higher omentin-1 concentration was associated with an increased CRC risk, while Kim et al. reported that the downregulation of omentin-1 was associated with poor prognosis in patients with advanced CRC. Maeda et al. and Kawashima et al. 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/m²                 |            |   |   |         |
| 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.
development and are regarded as useful cancer biomarkers.\textsuperscript{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,\textsuperscript{29} which closely correlate with the development of CRC. Kohan et al.\textsuperscript{21} and Splichal et al.\textsuperscript{22} reported that rs2274907 A>T was associated with susceptibility to nonalcoholic fatty liver and daily energy intake, respectively. However, several studies\textsuperscript{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.\textsuperscript{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

\begin{table}
\centering
\caption{Relationship between rs2274907 A>T variants and clinicopathologic features in patients with CRC.}
\begin{tabular}{lcccc}
\hline
Variable/category & n & AA & AT & TT & P value \\
\hline
Tumor size, cm & & & & & \\
\leq 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 & \\
\hline
\end{tabular}
\end{table}

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., 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. For example, Ling et al. found that the novel long non-coding 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. 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

| Variable/category | n | Genotype | P value |
|-------------------|---|----------|---------|
| Tumor size, cm    |   |          |         |
| ≤4                | 194 | AA 19 | AT+ TT 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       |   |          | <0.001 |
| 1–2               | 218 | 9 | 209 | |
| 3–4               | 150 | 34 | 116 | |

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

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

Acknowledgments
We thank the participants of this study, including the doctors, nurses, administrative staff, and researchers from the Department of Endocrinology, the Division of General Surgery, and Division of Endoscopy in the First Affiliated Hospital of Anhui Medical University.

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.

Funding
Funding for this project was provided by the Natural Science Foundation of Anhui Province in China (1508085MH150) and the National Natural Science Foundation Youth Science Fund Cultivation Project of The First Affiliated Hospital of Anhui Medical University in China (2018kj19).

ORCID iD
Mingwei Chen https://orcid.org/0000-0002-8439-0469

References
1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424.
2. Cirillo F, Catellani C, Sartori C, et al. Obesity, insulin resistance, and colorectal cancer: could miRNA dysregulation play a role? Int J Mol Sci 2019; 20: 2922.
3. Goh LY and Goh KL. Obesity: an epidemiological perspective from Asia and its relationship to gastrointestinal and liver cancers. J Gastroenterol Hepatol 2013; 28: 54–58.
4. Jaganathan R, Ravindran R and Dhanasekaran S. Emerging role of...
adipocytokines in type 2 diabetes as mediators of insulin resistance and cardiovascular disease. Can J Diabetes 2018; 42: 446–456.e1.
5. Booth A, Magnuson A, Fouts J, et al. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig 2015; 21: 57–74.
6. Riondino S, Roselli M, Palmirotta R, et al. Obesity and colorectal cancer: role of adipokines in tumor initiation and progression. World J Gastroenterol 2014; 20: 5177–5190.
7. Zhang Y, Zhao X, Deng L, et al. High expression of FABP4 and FABP6 in patients with colorectal cancer. World J Surg Oncol 2019; 17: 171.
8. Khoshi A, Bajestani MK, Shakeri H, et al. Association of omentin rs2274907 and FTO rs9939609 gene polymorphisms with insulin resistance in Iranian individuals with newly diagnosed type 2 diabetes. Lipids Health Dis 2019; 18: 142.
9. Escoté X, Gómez-Zorita S, López-Yoldi M, et al. Role of omentin, vaspin, cardiotrophin-1, TWEAK and NOV/CCN3 in obesity and diabetes development. Int J Mol Sci 2017; 18: 1770.
10. Otani K, Ishihara S, Yamaguchi H, et al. Adiponectin and colorectal cancer. Surg Today 2017; 47: 151–158.
11. Aleksandrova K, Di Giuseppe R, Isermann B, et al. Circulating omentin as a novel biomarker for colorectal cancer risk: data from the EPIC-Potsdam cohort study. Cancer Res 2016; 76: 3862–3871.
12. Zhao X, Zhang Y, Deng L, et al. The association between Chinese patients’ elevated omentin-1 levels, their clinicopathological features, and the risk of colorectal cancer. Int J Clin Exp Pathol 2019; 12: 2264–2274.
13. Helfand BT, Catalona WJ and Xu J. A genetic-based approach to personalized prostate cancer screening and treatment. Curr Opin Urol 2015; 25: 53–58.
14. Wei Z, Han G and Bai X. Effect of proliferator-activated receptor-gamma Pro12Ala polymorphism on colorectal cancer risk: A meta-analysis. Med Sci Monit 2015; 21: 1611–1616.
15. Yang X, Li J, Cai W, et al. Adiponectin gene polymorphisms are associated with increased risk of colorectal cancer. Med Sci Monit 2015; 21: 2595–2606.
16. Schäfler A, Zeitouni M, Wobser H, et al. Frequency and significance of the novel single nucleotide missense polymorphism Val109Asp in the human gene encoding omentin in Caucasian patients with type 2 diabetes mellitus or chronic inflammatory bowel diseases. Cardiovasc Diabetol 2007; 6: 3.
17. Turan H, Yaykasli KO, Soğuktas H et al. Omenin serum levels and omentin-1 gene Val109Asp polymorphism in patients with psoriasis. Int J Dermatol 2014; 53: 601–605.
18. Yörük U, Yaykasli KO, Özhan H, et al. Association of omentin Val109Asp polymorphism with coronary artery disease. Anadolu Kardiylol Derg 2014; 14: 511–514.
19. Nazar S, Zehra S and Azhar A. Association of single nucleotide missence polymorphism Val109Asp of omentin-1 gene and coronary artery disease in Pakistani population: Multicenter study. Pak J Med Sci 2017; 33: 1128–1133.
20. Zhang C, Zhu KJ, Liu JL, et al. Omentin-1 plasma levels and omentin-1 expression are decreased in psoriatic lesions of psoriasis patients. Arch Dermatol Res 2015; 307: 455–459.
21. Kohan L, Safarpur M and Abdollahi H. Omentin-1 rs2274907 and resistin rs1862513 polymorphisms influence genetic susceptibility to nonalcoholic fatty liver disease. Mol Biol Res Commun 2016; 5: 11–17.
22. Splichal Z, Bienertova-Vasku J, Novak J, et al. The common polymorphism Val109Asp in the omentin gene is associated with daily energy intake in the Central-European population. Nutr Neurosci 2015; 18: 41–48.
23. Chen MW, Ye S, Zhao LL, et al. Association of plasma total and high-molecular-weight adiponectin with risk of colorectal cancer: an observational study in Chinese male. Med Oncol 2012; 29: 3129–3135.
24. Kim HJ, Kang UB, Lee H, et al. Profiling of differentially expressed proteins in stage IV colorectal cancers with good and poor outcomes. J Proteomics 2012; 75: 2983–2997.
25. Maeda K, Saigo C, Kito Y, et al. Expression of TMEM207 in colorectal cancer: Relation between TMEM207 and intelectin-1. *J Cancer* 2016; 7: 207–213.

26. Kawashima K, Maeda K, Saigo C, et al. Adiponectin and intelectin-1: Important adipokine players in obesity-related colorectal carcinogenesis. *Int J Mol Sci* 2017; 18: 866.

27. Chen PH, Huang B, Shieh TY, et al. The influence of monoamine oxidase variants on the risk of betel quid-associated oral and pharyngeal cancer. *Scientific World Journal* 2014; 2014: 183548.

28. Huang CY, Huang SP, Lin VC, et al. Genetic variants in the Hippo pathway predict biochemical recurrence after radical prostatectomy for localized prostate cancer. *Sci Rep* 2015; 5: 8556.

29. Pan X, Kaminga AC, Wen SW, et al. Omentin-1 in diabetes mellitus: A systematic review and meta-analysis. *PLoS One* 2019; 14: 0226292.

30. Li L, Sun R, Liang Y, et al. Association between polymorphisms in long non-coding RNA PRNCR1 in 8q24 and risk of colorectal cancer. *J Exp Clin Cancer Res* 2013; 32: 104.

31. Zhu X, Liu Y, Xu J, et al. miR-608 rs4919510 Polymorphism May Affect Susceptibility to Colorectal Cancer by Upregulating MRPL43 Expression. *DNA Cell Biol* 2020; 39: 2017–2027.

32. Zou D, Lou J, Ke J, et al. Integrative expression quantitative trait locus-based analysis of colorectal cancer identified a functional polymorphism regulating SLC22A5 expression. *Eur J Cancer* 2018; 93: 1–9.

33. LiLing H, Spizzo R, Atlasi Y, et al. CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. *Genome Res* 2013; 23: 1446–1461.

34. Jiang D, Jin M, Ye D, et al. Polymorphisms of a novel long non-coding RNA RP11-108K3.2 with colorectal cancer susceptibility and their effects on its expression. *Int J Biol Markers* 2020; 35: 3–9.

35. Zhang Y, Zhao X and Chen M. Autocrine action of adipokine omentin-1 in the SW480 colon cancer cell line. *Oncol Lett* 2020; 19: 892–898.