The association between IL-17 gene variants and risk of colorectal cancer in a Chinese population: a case–control study

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Interleukin (IL)-17 have been reported to be associated with the pathogenesis of colorectal cancer (CRC). Few studies investigated the association between IL-17 gene polymorphisms and risk of CRC with inconsistent findings. Thus, we recruited 352 CRC cases and 433 controls in a Chinese population and their genotyping was done using polymerase chain reaction-restriction fragment length polymorphism method. Our data showed that IL-17A rs2275913 polymorphism was associated with the increased risk of CRC, while no association was observed for IL-17F rs763780 polymorphism. Stratified analyses revealed that the significant association was also obtained in the females, smokers, drinkers and age ≥ 60 years groups for rs2275913 polymorphism. Moreover, the CC and/or GC genotype of rs2275913 polymorphism were correlated with TNM stage and lymph node metastasis. No association was shown between IL-17F rs763780 polymorphism and clinical characteristics of CRC. In conclusion, our data indicate that IL-17A rs2275913 polymorphism but not IL-17F rs763780 polymorphism contributes to increased risk for CRC patients in this Chinese population.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer death [1]. More than 1.2 million patients are diagnosed with CRC annually and more than 600,000 die from this disorder [2]. It is well known that environmental and inherited genetic factors made great contributions to susceptibility to CRC [3]. Genome-wide association studies (GWAS) and meta-analysis using 1000 Genomes for imputation have identified novel risk variants for CRC patients [4].

Two inflammatory cytokines, Interleukin (IL)-17A and IL-23, produced by myeloid cells and different lymphocyte subsets, have been implicated in the pathogenesis of inflammatory associated cancers such as CRC [5]. The up-regulation of IL-17 ad IL-23 was observed in a mouse model of colorectal tumorigenesis [6]. In CRC, elevated expression of IL-17A was associated with adverse prognostic outcome and rapid progression to metastatic disease [7]. Th17-type cytokines (IL-17A, IL-17F, IL-21, IL-22), IL-6 and tumour necrosis factor-α synergistically activate STAT3 and NF-κB to promote CRC growth [8]. Single-nucleotide polymorphism (SNP) in IL-17 gene may influence genomic stability and increase the production of IL-17, thereby conferring susceptibility to CRC [9].

Many studies have investigated the association between IL-17 gene polymorphisms and risk of CRC [9–15], mainly focusing on two polymorphisms (rs2275913, IL-17A; rs763780, IL-17F). However, their findings were conflicting. Furthermore, there is no study to investigate the association between IL-17A rs2275913 polymorphism and risk of CRC in a Chinese population. In addition, only one study [12]
has thrown lights on the rs763780 polymorphism for Chinese population. Therefore, we conducted this hospital-based case–control study to evaluate the effects of IL-17A rs2275913 and IL-17F rs763780 polymorphisms on the risk of CRC.

Patients and methods

Subjects
In the present study, 352 CRC patients with newly histopathologically diagnosed CRC and 433 sex- and age-matched controls were recruited from Zhejiang Cancer Hospital, Taizhou Cancer Hospital, Quzhou Kecheng People's Hospital and Lanxi People's Hospital from May 2012 to May 2018. No patients had received radiotherapy or chemotherapy prior to surgery. Approximately 58.2% of CRC patients were rectal cancer and were classified according to the American Joint Committee on cancer (AJCC) classification system. The control groups were selected from individuals receiving health examinations at the same period. The individuals with family history of cancer or digestive diseases were excluded.

Data on demographic and risk factor information for all subjects were obtained using a self-designed questionnaire, including body mass index (BMI), smoking status, alcohol consumption and family history of cancer. The individuals who smoked at least one cigarette per day at least one year was defined as "smoker". Individuals were defined as drinkers if they drank alcohol at least once a week for more than 1 year. Subjects with at least one first-degree relative or two second-degree relatives having CRC were defined as having family history of cancer. We obtained clinical information about C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); TNM stage, localization of tumor, tumor size, differentiation, lymph node metastasis and histopathological characteristics from the medical record. The study was approved by the Ethics Committee of the above four hospitals and met the standards of Declaration of Helsinki. Written informed consent was obtained from each subject.

Blood sampling and genotyping
Peripheral blood (2 ml) was taken from all subjects and genomic DNA was extracted from peripheral blood using the TIANamp Blood DNA kit (Tiangen Biotech, Beijing, China) according to manufacturer's instructions. The quality and concentration of extracted DNA was measured in two OD wavelength 260 and 280 nm using NanoDrop (Thermo Scientific, U.S.A.). SNP genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism method. The primers used for the nucleotide extension reaction were AACAAGTAAGAATGAAAAGAGGACATGGT (forward) and CCCCAATGAGGTCATAGAAGAATC (reverse) for rs2275913 and ACCAAGGCT-GCTCTGTTTCT (forward) and GGTAAGGAGTGCCATTCTA (reverse) for rs763780 polymorphism. For PCR, 25 μl reaction mixture contained as follows: 2.5 μl of 10× reaction buffer (with 1.5 mM MgCl₂), 2 μl of deoxynucleotide triphosphate (dNTP; 2.5 mM), 2 μl of each pair primer, 50 ng DNA template, 1 μl of 0.4U Taq polymerase (Applied Biosystems, Evry, France) and 14.5 μl ddH₂O. The cycling program involved preliminary denaturation at 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 57°C for 30 s, and 72°C for 30 s with a final extension at 72°C for 8 min. The digested PCR products were with XagI (Fermentas, Lithuania) for IL-17A rs2275913 polymorphism and NlaIII (BioLabs, England) for IL-17F rs763780 polymorphism overnight at 37°C. The PCR products were analyzed by horizontal electrophoresis on an ethidium bromide-stained agarose gel (2% w/v) and then photographed. About 4% of selected samples were reconfirmed with direct sequencing to ensure the genotyping accuracy.

Statistical analysis
The demographic variables were expressed as means ± standard deviation (continuous variables) and frequencies and percentages (categorical variables) respectively. Differences between means were compared by Student's t-test or Mann–Whitney U test (where the data were not distributed normally). The chi-square test was used to evaluate the differences in frequency distributions of categorical between cases and controls. The Hardy–Weinberg equilibrium (HWE) was applied to test for deviation between observed and expected frequencies among controls using a goodness-of-fit chi-square test. The SNP-associated disease risk was assessed with logistic regression analysis adjusted for age and sex. P < 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 22.0 software (SPSS Inc., Chicago, U.S.A.).

Results

Characteristics of the study population
The demographic and medical data of participants are shown in Table 1. The mean age of CRC patients was 62.27 years
Table 1  Patient demographics and risk factors in colorectal cancer.

| Characteristics                  | Case (N = 352) | Control (N = 433) | P     |
|----------------------------------|----------------|-------------------|-------|
| Age, years                       | 62.27 ± 8.10   | 62.38 ± 7.78      | 0.848 |
| Sex                              |                |                   | 0.629 |
| Male                             | 69 (19.6%)     | 79 (18.2%)        |       |
| Female                           | 283 (80.4%)    | 354 (81.8%)       |       |
| BMI, kg/m²                       | 25.12 ± 4.00   | 24.84 ± 3.80      | 0.306 |
| Smoking                          |                |                   | 0.361 |
| Yes                              | 192 (54.5%)    | 222 (51.3%)       |       |
| No                               | 160 (45.5%)    | 211 (48.7%)       |       |
| Alcohol                          |                |                   | 0.774 |
| Yes                              | 206 (58.5%)    | 249 (57.5%)       |       |
| No                               | 146 (41.5%)    | 184 (42.5%)       |       |
| CRP, mg/l                        | 7.73 ± 17.38   |                   |       |
| ESR, mm/h                        | 10.85 ± 12.00  |                   |       |
| Family history                   |                |                   |       |
| Yes                              | 47 (13.4%)     |                   |       |
| No                               | 305 (86.6%)    |                   |       |
| Histological grade               |                |                   |       |
| Well differentiated              | 34 (9.7%)      |                   |       |
| Moderately differentiated        | 275 (78.1%)    |                   |       |
| Poorly differentiated            | 43 (12.2%)     |                   |       |
| TNM stage                        |                |                   |       |
| I+II                             | 192 (54.5%)    |                   |       |
| III+IV                           | 160 (45.5%)    |                   |       |
| Tumor size                       |                |                   |       |
| >5 cm                            | 202 (57.4%)    |                   |       |
| ≤5 cm                            | 150 (42.6%)    |                   |       |
| Lymph node metastasis            |                |                   |       |
| No                               | 230 (65.3%)    |                   |       |
| Yes                              | 122 (34.7%)    |                   |       |
| Histology                        |                |                   |       |
| Adenocarcinoma                   | 338 (96.0%)    |                   |       |
| Squamous cell carcinoma          | 10 (2.8%)      |                   |       |
| Others                           | 4 (1.2%)       |                   |       |

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TNM, tumor node metastasis.

compared with 62.38 years of control groups, which revealed no statistically difference (P = 0.848). The distribution of sex, smoking, BMI and drinking did not differ significantly. Among the 352 cases, 215 (61.1%) were adenocarcinoma; 123 (34.9%) were squamous cell carcinoma; and 14 (4.0%) were other types of CRC. We have also investigated other clinical information of CRC patients, including histological grade, TNM stage, tumor size and lymph node metastasis.

**IL-17 gene polymorphisms analysis**

The product lengths (bp) of different genotypes were as following: AA: 102bp, AG: 102 bp + 68bp + 34bp, GG: 68bp + 34bp (IL-17A rs2275913 polymorphism); TT: 63bp + 80bp, CT: 143bp + 80bp + 63bp, CC: 143bp (IL-17F rs763780 polymorphism). Table 2 shows the genotype and allele distributions for IL-17 gene polymorphisms in the CRC patients and controls. The observed genotype frequencies for the two polymorphisms (rs2275913 and rs763780) in the controls did not departure from HWE. For rs2275913 polymorphism, A allele was related to increased risk for CRC (AA vs GG: OR, 1.31; 95% CI, 1.06–1.64; P = 0.014); the AA genotype (not GA genotype) had a significantly elevated risk for CRC compared to GG genotype (AA vs GG: OR, 1.72; 95% CI, 1.02–2.88; P = 0.041). Similarly, AA+GA genotype or A allele was associated with the increased risk for CRC. Further, rs2275913 polymorphism was significant in homozygous, dominant and allelic models after adjusting for sex and age. However, no significant associations with the CRC risk was demonstrated for rs763780 polymorphism before and after adjusting for sex and age.

Stratified analyses were conducted according to sex, age, smoking, alcohol and BMI (Table 3). For rs2275913, a significantly increased CRC risk with the AA genotype was found among smokers (AA vs. GG, OR 2.38; 95% CI,
Table 2 Genotype frequencies of IL-17 gene polymorphisms in cases and controls

| Models          | Genotype | Case (n, %) | Control (n, %) | OR (95% CI) | P-value | *OR (95% CI) * | P-value |
|-----------------|----------|------------|----------------|-------------|---------|----------------|---------|
| rs2275913       | GG       | 160 (45.6%) | 231 (53.6%)    | 1.00 (reference) |         | 1.32 (0.98–1.77) | 0.071   |
|                 | GA       | 154 (43.9%) | 169 (39.2%)    | 1.31 (0.98–1.76) | 0.075   | 1.38 (1.04–1.83) | 0.026   |
|                 | AA       | 37 (10.5%)  | 31 (7.2%)      | 1.72 (1.02–2.88) | 0.041   | 1.73 (1.03–2.91) | 0.039   |
| Dominant        | GG       | 160 (45.6%) | 231 (53.6%)    | 1.00 (reference) |         | 1.32 (0.98–1.77) | 0.071   |
|                 | AA+GA   | 191 (54.4%) | 200 (46.4%)    | 1.37 (1.04–1.82) | 0.028   | 1.38 (1.04–1.83) | 0.026   |
|                 | AA+GG   | 37 (10.5%)  | 31 (7.2%)      | 1.52 (0.92–2.50) | 0.102   | 1.53 (0.93–2.52) | 0.098   |
| Allele          | G        | 474 (67.5%) | 631 (73.2%)    | 1.00 (reference) |         | 1.31 (1.06–1.64) | 0.014   |
|                 | A        | 228 (32.5%) | 231 (26.8%)    |             |         | 1.31 (1.06–1.64) | 0.014   |
| rs763780        | TT       | 241 (68.7%) | 284 (65.7%)    | 1.00 (reference) |         | 0.89 (0.65–1.21) | 0.459   |
|                 | TC       | 100 (28.5%) | 132 (30.6%)    | 0.89 (0.65–1.22) | 0.462   | 0.87 (0.65–1.18) | 0.369   |
|                 | CC       | 10 (2.8%)   | 16 (3.7%)      | 0.73 (0.33–1.65) | 0.453   | 0.72 (0.32–1.63) | 0.434   |
| Dominant        | TT       | 241 (68.7%) | 284 (65.7%)    | 1.00 (reference) |         | 0.87 (0.65–1.18) | 0.369   |
|                 | CC+TC   | 110 (31.3%) | 148 (34.3%)    | 0.87 (0.65–1.18) | 0.375   | 0.75 (0.34–1.58) | 0.485   |
| Allele          | T        | 582 (82.9%) | 700 (81.0%)    | 1.00 (reference) |         | 0.88 (0.68–1.14) | 0.335   |
|                 | C        | 120 (17.1%) | 164 (19.0%)    |             |         | 0.88 (0.68–1.14) | 0.335   |

The genotyping was successful in 351 cases and 431 controls for rs2275913; The genotyping was successful in 351 cases and 432 controls for rs763780; Bold values are statistically significant (P < 0.05).

*Adjust for age and sex.

1.19–4.76; P = 0.014) and non-drinkers (AA vs. GG, OR 4.22; 95% CI, 1.72–9.82; P < 0.001). The increased effect also appeared stronger in the subgroup of age ≥ 60 years (AA vs. GG, OR 2.44; 95% CI, 1.29–4.60; P = 0.006) and females (GA vs. GG, OR 1.42; 95% CI, 1.02–1.98; P = 0.037). No significant findings were obtained in the analysis of rs2275913 polymorphism and BMI. However, stratified analyses by sex, age, smoking and drinking indicated that the allele or genotype frequencies of rs763780 polymorphism did not differ significantly between the cases and controls. Next, we investigated the association between these two SNPs and clinicopathologic features of CRC patients (Table 4). The AA genotype of rs2275913 polymorphism is more frequent in patients with TNM stage III+IV and in patients with lymph node metastasis. This indicated that IL-17 rs2275913 polymorphism was correlated with TNM stage and lymph node metastasis (P = 0.043 and 0.026, respectively). We observed no evidence of association between rs763780 polymorphism and other clinical characteristics such as CRP, ESR, histological grade, TNM stage, tumor size, lymph node metastasis, family history and histology.

Discussion

In the present study, we found that IL-17A rs2275913 polymorphism was associated with the increased risk for CRC in a Chinese population. However, no association was observed for the IL-17F rs763780 polymorphism. Additionally, rs2275913 polymorphism showed significant correlation with TNM stage and lymph node metastasis in CRC patients. Recently, several studies investigated the association between IL-17A rs2275913 polymorphism and risk of CRC [9,11,13–15]. Omrane et al. firstly conducted a population-based study to explore the association of rs2275913 polymorphism with CRC risk in a Tunisian population involving 102 CRC patients and 139 controls [11]. They found that IL-17A rs2275913 polymorphism conferred susceptibility to CRC and was associated with tumor location and tumor differentiation [11]. However, no significant association with CRC risk was observed for rs2275913 polymorphism in another Tunisian study conducted by Bedoui et al. [15]. Additionally, two Caucasian studies also investigated the effect of this SNP on the risk of CRC [9,13]. Nemati et al. revealed that AG genotype showed a significantly elevated risk for CRC compared to GG genotype in the Iranian population [13]. This significant association was also observed in the Saudi population [9]. However, no study has explored this SNP in the Chinese population. In this study, we observed that IL-17A rs2275913 polymorphism increased the risk of CRC under the additive, dominant and allelic models. The significant association observed in the whole population was also shown in the female, smoker, drinker and individuals with age ≥ 60 years groups. According to the dbSNP database, rs2275913 polymorphism was located...
in the promoter region of IL-17A gene. We hypothesized that IL-17A rs2275913 polymorphism conferred susceptibility to CRC by altering the IL-17 expression. In addition, IL-17A rs2275913 polymorphism was related to TNM stage III+IV and lymph node metastasis.

IL-17F rs763780 polymorphism was also investigated in several studies [9,10,12–14]. Three studies failed to find allele or genotype association with CRC susceptibility [9,10,14]. However, Ma et al. found that CC genotype or C allele was associated with the increased risk of CRC in a Chinese population [12]. Significant associations with the CRC risk were also demonstrated in an Iranian population [13]. In the present study, there was no significant association for this SNP in the overall analysis and in the stratified analyses of sex, age and smoking. Obviously, the findings of this study were consistent with most previous studies [9,10,14].

Several limitations of the present study need to be addressed. First, the sample size was not large, thus we could not rule out the possibility of false-positive results. Second, environmental factors might have affected the final results, including occupation and educational level. Third, we did not follow up on CRC patients, limiting our further analysis. Fourth, the controls from the hospital may not fully represent the entire population.
Table 4 The stratified analysis between rs2275913/rs763780 polymorphisms and clinical characteristics of CRC patients

| Characteristics               | rs2275913 |     |     |     |     |
|------------------------------|-----------|-----|-----|-----|-----|
|                              | GG        | GA  | AA  | GA+AA|     |
| Histological grade           |           |     |     |     |     |
| MD/WD                        | 130/16    | 117/15 | 27/3 | 144/18|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.96 (0.46–2.03); 0.915 | 1.11 (0.30–4.07); 0.877 | 0.99 (0.49-2.01); 0.966|     |
| Histological grade           |           |     |     |     |     |
| PD/WD                        | 14/16     | 22/15 | 7/3 | 29/16|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.68 (0.63–4.43); 0.296 | 2.67 (0.58–12.33); 0.201 | 1.84 (0.73–4.60); 0.195|     |
| TNM stage                    |           |     |     |     |     |
| III+IV/I+II                  | 70/90     | 86/68 | 23/14 | 109/82|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.63 (1.04–2.54); 0.032 | 2.11 (1.01–4.40); 0.043 | 1.71 (1.12–2.61); 0.013|     |
| Tumor size                   |           |     |     |     |     |
| >5 cm/≤5 cm                  | 99/61     | 82/72 | 21/16 | 103/88|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.70 (0.45–1.10); 0.122 | 0.81 (0.39–1.67); 0.565 | 0.72 (0.47-1.11); 0.133|     |
| Lymph node metastasis        |           |     |     |     |     |
| Yes/No                       | 62/97     | 80/74 | 22/15 | 102/89|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.67 (1.06–2.61); 0.025 | 2.26 (1.09–4.68); 0.026 | 1.77 (1.15–2.70); 0.009|     |
| Family history               |           |     |     |     |     |
| Yes/No                       | 24/136    | 17/137 | 6/31 | 23/168|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.70 (0.36–1.37); 0.296 | 1.10 (0.41–2.91); 0.853 | 0.78 (0.42–1.44); 0.418|     |
| Histology                    |           |     |     |     |     |
| Adenocarcinoma/Not           | 155/5     | 149/5 | 33/4 | 182/9|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.96 (0.27–3.39); 0.951 | 0.27 (0.07–1.05); 0.058 | 0.65 (0.21-1.99); 0.452|     |
| ESR                          |           |     |     |     |     |
| ≥10/<10                     | 63/97     | 68/86 | 17/20 | 85/106|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.22 (0.78–1.91); 0.391 | 1.31 (0.64–2.69); 0.464 | 1.24 (0.81–1.89); 0.333|     |
| CRP                          |           |     |     |     |     |
| ≥25/<25                     | 13/147    | 9/145 | 7/30 | 16/175|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.70 (0.29–1.69); 0.431 | 2.64 (0.97–7.17); 0.057 | 1.03 (0.49–2.22); 0.932|     |
| rs763780                     |           |     |     |     |     |
| Histological grade           |           |     |     |     |     |
| MD/WD                        | 187/23    | 77/11 | 9/1  | 87/11|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.86 (0.40–1.86); 0.701 | 0.49 (0.10–2.46); 0.378 | 0.97 (0.45-2.09); 0.943|     |
| Histological grade           |           |     |     |     |     |
| PD/WD                        | 31/23     | 12/11 | 0/0  | 12/11|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.61 (0.30–2.16); 0.672 | NA | 0.81 (0.30-2.16); 0.672|     |
| TNM stage                    |           |     |     |     |     |
| III+IV/I+II                  | 116/125   | 39/61 | 5/5  | 44/66|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.69 (0.43–1.11); 0.123 | 1.08 (0.30–3.82); 0.908 | 0.72 (0.46–1.14); 0.156|     |
| Tumor size                   |           |     |     |     |     |
| >5 cm/≤5 cm                  | 135/106   | 60/40 | 7/3  | 67/43|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.18 (0.73–1.89); 0.499 | 1.83 (0.46–7.26); 0.382 | 1.22 (0.77–1.94); 0.390|     |
| Lymph node metastasis        |           |     |     |     |     |
| Yes/No                       | 80/155    | 31/69 | 5/5  | 36/74|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.81 (0.49–1.33); 0.407 | 1.80 (0.51–6.40); 0.356 | 0.88 (0.54–1.41); 0.589|     |
| Family history               |           |     |     |     |     |
| Yes/No                       | 32/209    | 15/85 | 1/9  | 15/95|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.15 (0.59–2.24); 0.675 | 0.73 (0.09–5.92); 0.764 | 1.03 (0.53–1.99); 0.927|     |
| Histology                    |           |     |     |     |     |
| Adenocarcinoma/Not           | 231/10    | 96/4  | 9/1  | 105/5|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.04 (0.32–3.39); 0.950 | 0.39 (0.05–3.38); 0.393 | 0.91 (0.30-2.73); 0.865|     |
| ESR                          |           |     |     |     |     |
| ≥10/<10                     | 100/141   | 37/63 | 2/8  | 39/71|     |
| OR (95%CI); P-value          | 1.0 (reference) | 0.83 (0.51–1.34); 0.441 | 0.35 (0.07–1.70); 0.193 | 0.78 (0.49-1.24); 0.284|     |
| CRP                          |           |     |     |     |     |
| ≥25/<25                     | 12/229    | 6/94  | 1/9  | 7/103|     |
| OR (95%CI); P-value          | 1.0 (reference) | 1.22 (0.44–3.34); 0.802 | 2.12 (0.25–18.13); 0.492 | 1.30 (0.50–3.99); 0.596|     |

Bold values are statistically significant (P < 0.05). PD, poorly differentiation; MD, moderately differentiation; WD, well differentiation; TNM, tumor node metastasis.
In conclusion, \textit{IL-17A} rs2275913 polymorphism is associated with increased risk for CRC in a Chinese population. Furthermore, this SNP was associated with higher TNM stage and regional lymph node metastasis. However, no positive findings were obtained for \textit{IL-17F} rs763780 polymorphism. Further studies in other studies with larger sample sizes, as well as functional evaluation of studied SNPs, are warranted to further validate these findings.

**Author Contribution**

H.X.J. conceived the entire study; H.Y.F. and R.B.Y. analyzed the data; H.Y.F., T.J.C. and H.L.C. performed statistical analysis; H.Y.F. and H.X.J. wrote the paper. All authors read and agreed with the final version of this manuscript.

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**Competing Interests**

The authors declare that there are no competing interests associated with the manuscript.

**Abbreviations**

CRC, colorectal cancer; CRP, C-reactive protein; IL, interleukin; SNP, single-nucleotide polymorphism.

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