PPARG rs3856806 C>T Polymorphism Increased the Risk of Colorectal Cancer: A Case-Control Study in Eastern Chinese Han Population

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Purpose: Functional variants in the peroxisome proliferator-activated receptor gamma (PPARG) and PPARG co-activator 1 (PPARGC1) family (e.g., PPARGC1A and PPARGC1B) genes were predicted to confer susceptibility to colorectal cancer (CRC). The aim of the present study was to explore the relationship between PPARG, PPARGC1A, PPARGC1B polymorphism and the risk of CRC.

Patients and methods: We conducted a case-control study with 1,003 CRC cases and 1,303 controls. We selected the PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A and PPARGC1B rs7732671 G>C and rs17572019 G>A SNPs to assess the relationship between PPARG, PPARGC1A, PPARGC1B polymorphism and the risk of CRC.

Results: We found that the PPARG rs3856806 C>T polymorphism increased the risk of CRC (TT vs. CC: adjusted OR, 1.59, 95% CI 1.08–2.35, P = 0.020; TT/CT vs. CC: adjusted OR, 1.26, 95% CI 1.06–1.49, P = 0.009 and TT vs. CC/CT: adjusted OR, 1.54, 95% CI 1.05–2.26, P = 0.028), even after a Bonferroni correction test. The stratified analysis revealed that the PPARG rs3856806 C>T polymorphism also increased the risk of CRC, especially in male, ≥61 years old, never smoking, never drinking, BMI ≥ 24 kg/m², colon cancer and rectum cancer subgroups.

Conclusion: Our findings highlight that the PPARG rs3856806 C>T polymorphism may increase the risk of CRC. In the future larger sample size case-control studies with a detailed functional assessment are needed to further determine the relationship of the PPARG rs3856806 C>T polymorphism with CRC risk.

Keywords: PPARG, PPARGC1A, PPARGC1B, polymorphism, colorectal cancer, risk
INTRODUCTION

Colorectal cancer (CRC) is one of the most common type of malignancies, accounting for 1.8 million cases in GLOBOCAN 2018 (1). The incidence of CRC is increasing in China, where it ranks as the fifth most common carcinoma in male and the fourth in female, with a total of 215,700 patients diagnosed in 2015 (2). Epidemiologic investigations have attributed most of CRC to some important environmental factors (3). The increase of the incidence of CRC is proposed to correlate with an unhealthy lifestyle, including drinking, smoking, low intake of dietary fiber, high intake of dietary fat, decreased consumption of vegetables, and fruits and being physically inactive (4–7). Accumulating evidence highlighted that besides these unhealthy lifestyles and environmental factors, some additional inherited susceptibility factors may be associated with the development of CRC. As CRC is associated with obesity and Waist-to-Hip Ratio (WHR) (8–10), the peroxisome proliferator-activated receptor gamma (PPARG), PPARG co-activator 1 (PPARGC1) family (e.g., PPARGC1A and PPARGC1B) may be strong candidate genes predisposing to CRC (11).

PPARG is located in 3p25. PPARG is also known as NR1C3 (nuclear receptor subfamily 1, group C, member 3) which shares some common conservative domains with other steroid receptors (e.g., estrogen, progesterone, retinoid, vitamin D and thyroid receptors). It was reported that PPARG is a regulator of adipocyte differentiation, energy homeostasis and obesity (12–14). PPARG decreases the inflammatory response of cells (15) and increases synthesis and release of peroxonase 1 (16). Wang et al. reported that PPARG gene might be one of the targets of miRNA-34a and a conceivable therapeutic targets for CRC (17): PPARGC1A and PPARGC1B, transcriptional co-activators of PPARG, may control transcription in adipogenesis, oxidative metabolism genes (18). Thus, PPARG, PPARGC1A, and PPARGC1B might be implicated in the development of cancer.

Pro12Ala and His499His (rs3856806 C>T) polymorphisms in the PPARG gene are two of the most common variants in the PPARG gene. Recently, a meta-analysis confirmed that the PPARG Pro12Ala polymorphism might decreased the risk of CRC (19). Several case-control studies focused on the potential role of PPARG variants in determining CRC susceptibility. The PPARG rs3856806 C>T is a common single-nucleotide polymorphism (SNP) in the coding region. Recently, a meta-analysis indicated that the PPARG rs3856806 C>T polymorphism may increase the susceptibility of overall cancer (20). In this pooled study, there were seven independent case-control studies with 1,720 cases and 3,458 controls focusing on the association of the PPARG rs3856806 C>T polymorphism with CRC risk (21–24). As well, a tendency to increased CRC susceptibility was noted. Because of the lack of sufficient sample sizes, the evidence may be limited. Additionally, (25) reported that the PPARGC1B rs7732671 G>C polymorphism may decrease the susceptibility of breast cancer. However, the association between PPARGC1A and PPARGC1B SNPs and the risk of CRC was unknown. The aim of this case-control study was to assess the association of PPARG, PPARGC1A, and PPARGC1B polymorphisms with CRC risk. We selected PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A SNPs to determine the relationship between their variants and CRC risk in an Eastern Chinese Han population.

MATERIALS AND METHODS

Study Subjects

This cohort was in part previously studied (19, 26). The CRC cases were recruited from Fujian Medical University Union Hospital (Fuzhou city, China) and the Affiliated People’s Hospital of Jiangsu University (Zhenjiang city, China) between October 2014 and August 2017. The major inclusion criteria of CRC cases were: (1) sporadic CRC cases; (2) newly diagnosed CRC patients via pathology; and (3) Han population who living in Eastern China. And the exclusion criteria were: (1) hereditary non-polyposis CRC; (2) CRC cases who have been treated with chemoradiotherapy and (3) with another malignancy history. During the period, a total of 1,186 CRC patients were diagnosed in those local hospitals. Our study includes 1,003 (84.57%) patients, who agree to attend this study and provided blood samples for SNP analysis. The mean age of CRC patients was 61.10 ± 12.17 years. From 1,521 selected controls, 1,303 (85.67%) agreed to participate and donated a biological sample in this study. The controls included 1,303 healthy volunteers who participated in a routine examination in these hospitals, with a mean age of 61.40 ± 9.61 years. For selecting controls, the inclusion criteria were: (1) without a carcinoma history subjects; (2) similar age matched to CRC group; and (3) Han population who is a resident of Eastern China. Additionally, subjects who had a cancer history were excluded. The controls were matched with CRC patients by age and sex. The information on risk factor was obtained from the CRC cases and controls during a medical interview. And weight and height were measured. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and BMI ≥ 24 kg/m^2 was considered as overweight and obesity for Chinese (27, 28). All participants enrolled in the present study signed the informed consent and were of Chinese origin. The study protocol was approved by the Ethics Committee of Fujian Medical University and Jiangsu University.

DNA Extraction and Genotyping

Two milliliters of Ethylenediamine tetra acetic acid (EDTA)-anticoagulated blood was collected from each participant. Blood samples were stored in a −80° C freezer. Using a Promega DNA Blood Mini Kit (Promega, Madison, USA), genomic DNA was isolated from lymphocytes. We placed the cryopreserved specimen at room temperature for an hour. After red blood cell removal, nuclear releasing and protein precipitation, we obtained genomic DNA. We add 300 µl of DNA solution (pH 8.0) and placed the sample in a refrigerator at 4°C for 1–2 weeks. A NanoDrop ND-1000 micro spectrophotometer was used to determine DNA concentration and purity. As described in previous studies, the genotypes of the PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C for the examined SNPs were determined by PCR-SSCP.
G>C and rs17572019 G>A SNPs was determined by a custom-design 48-Plex SNPscan Kit (Genesky Biotechnologies Inc., Shanghai, China) (29, 30). This genotyping method was designed as a multiplex fluorescence PCR (31). Ninety-two DNA samples (4%) were randomly selected and tested by another technician for quality control. The genotypes of these SNPs were not changed.

**Statistical Analysis**

We used an online Chi-square software (http://ihg.gsfc.de/cgi-bin/hw/hwa1.pl) to test deviation from the Hardy-Weinberg equilibrium (HWE) by using Pearson’s goodness-of-fit chi-square. The genotype frequencies of the PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A variants among CRC cases were compared to those of controls using a χ² test or Fisher’s exact test. Multivariate logistic regression analysis was harnessed to obtain crude and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) to predict the relationship of the PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A polymorphisms with susceptibility to CRC. Dominant, recessive, heterozygote and homozygote models were used to evaluate the association of these SNPs with CRC risk. The χ² test or Fisher’s exact test was first applied to compare the distribution of age, sex, alcohol consumption, smoking status, and BMI between CRC patients and controls. A Fisher’s exact test was first applied to compare the distribution of age, sex, alcohol consumption, smoking status, and BMI between CRC patients and controls. A Bonferroni tailed) was defined as a significant association. All data were analyzed by SAS software for Windows (9.4 version, SAS Institute, Cary, USA). In this case-control study, a Bonferroni correction test was applied for multiple testing (32, 33). An internal validation through bootstrap method was applied to PPARG rs3856806 C>T. We used 0.623 bootstrap method to resample 1,003 cases from the CRC patient group and 1,303 cases from the control group to validate our results.

**RESULTS**

**Study Characteristics**

Selected demographic variables and risk factors in the enrolled population and the correlation with CRC are summarized in Table 1. There was no significant difference between CRC patients and controls regarding sex (P = 0.867), age (61.10 ± 12.17 years for cases and 61.40 ± 9.61 years for controls, P = 0.496), suggesting that these variables were well-matched. Alcohol consumption, BMI and smoking status were statistically different (P < 0.001, P < 0.001, and P = 0.002, respectively) between two groups. The primary information of PPARG, PPARGC1A, and PPARGC1B SNPs is displayed in Table 2. The genotype distributions of PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A are in accordance with HWE in controls (P = 0.143, 0.925, 0.800, 0.059, 0.970, and 0.372, respectively).

**Association of PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A Polymorphisms With CRC Risk**

Table 3 summarizes the genotype distributions of PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A SNPs in CRC cases and controls. The genotype frequencies of PPARG rs3856806 C>T were 55.51% (CC), 38.16% (CT), and 6.33% (TT) in CRC cases and 60.69% (CC), 35.31% (CT), and 4.00% (TT) in controls. When the frequency of PPARG rs3856806 CC genotype was used as a reference, individuals carrying the PPARG rs3856806 TT genotype had an increased risk to CRC (crude OR = 1.67, 95% CI 1.13–2.45 for TT vs. CC, P = 0.009). When compared with the frequency of PPARG rs3856806 CC genotype, individuals carrying the PPARG rs3856806 TT/CT genotype also had an increased the risk of CRC (crude OR = 1.24, 95% CI 1.05–1.46 for TT/CT vs. CC, P = 0.009). When compared with the frequency of PPARG rs3856806 TT genotype, an increased risk of CRC (crude OR = 1.62, 95% CI 1.11–2.37 for TT vs. CC/CT, P = 0.012). After adjustments for age, sex, smoking, BMI, and drinking, the observed increased susceptibility of CRC was not essentially altered (TT vs. CC: adjusted OR,
1.59, 95% CI 1.08–2.35, \( P = 0.020 \); TT/CT vs. CC; adjusted OR, 1.26; 95% CI 95% CI 1.06–1.49; \( P = 0.009 \) and TT vs. CC/CT; adjusted OR, 1.54; 95% CI 95% CI 1.05–2.26; \( P = 0.028 \), Table 3.

Table S1 shows the internal validation results through the bootstrap method. When compared with the \( \text{PPARG} \) rs3856806 CC genotype, the \( \text{PPARG} \) rs3856806 TT, and TT/CT genotypes also indicate an increased CRC risk (crude OR = 1.56, 95% CI 1.09–2.23 for TT vs. CC, \( P = 0.015 \); crude OR = 1.20, 95% CI 1.02–1.42 for TT/CT vs. CC, \( P = 0.033 \)). When compared with the \( \text{PPARG} \) rs3856806 CC/CT genotype, \( \text{PPARG} \) rs3856806 TT genotype also suggest an increased CRC risk (crude OR = 1.53, 95% CI 1.08–2.18 for TT vs. CC/CT, \( P = 0.017 \)). After being adjusted by age, sex, smoking BMI, and drinking, the increased susceptibility of CRC was not essentially altered.

The genotype frequencies of \( \text{PPARGC1A} \) rs8192678 C>T were 35.10% (CC), 46.33% (CT), and 18.57% (TT) in CRC patients and 31.38% (CC), 49.62% (CT), and 19.00% (TT) in healthy controls. When the frequency of the \( \text{PPARGC1A} \) rs8192678 CC genotype was used as a reference, individuals carrying the \( \text{PPARGC1A} \) rs8192678 CT genotype had a decreased susceptibility to CRC (crude OR = 0.79, 95% CI 0.66–0.95 for CT vs. CC, \( P = 0.012 \)). After adjustments for age, sex, smoking, BMI and drinking, this association was also found (CT vs. CC; adjusted OR, 0.82; 95% CI 95% CI 0.68–0.989; \( P = 0.033 \)), Table 3.

We found no significant difference in the genotype distribution of the \( \text{PPARGC1A} \) rs3736265 G>A, rs2970847 C>T and \( \text{PPARGC1B} \) rs7732671 G>C, rs17572019 G>A polymorphisms among CRC cases and controls, Table 3. The Bonferroni correction test was applied to determine whether the association of the \( \text{PPARG} \) rs3856806 C>T and rs8192678 C>T polymorphisms with the risk of CRC was reliable. We defined the statistical significance level at 0.0125 (0.05/4 genetic models). We found the genotype distribution of that the \( \text{PPARG} \) rs3856806 C>T polymorphism was still significantly different between CRC patients and controls (TT/CT vs. CC: adjusted OR, 1.26; 95% CI 95% CI 1.06–1.49; \( P = 0.009 \)).

### Association of \( \text{PPARG} \) rs3856806 C>T Polymorphism With CRC Risk in a Stratified Analysis

To further assess the association of the \( \text{PPARG} \) rs3856806 C>T polymorphism with CRC risk, we conducted a stratified analysis by BMI, gender, age, tobacco using and alcohol consumption. Table 4 presents the different genotype frequencies of the \( \text{PPARG} \) rs3856806 C>T polymorphism in a subgroup analysis. After an adjustment by logistic regression analysis with gender, age, BMI, tobacco using and drinking status, we found that the \( \text{PPARG} \) rs3856806 C>T polymorphism significantly increased the risk of CRC in several subgroups: 1) male subgroup, TT vs. CC, adjusted OR = 1.88, 95% CI 1.14–3.10, \( P = 0.014 \) and TT vs. CT/CC, adjusted OR = 1.84, 95% CI 1.12–3.02, \( P = 0.016; 2) \geq 61 years subgroup, CT/TT vs. CC, adjusted OR = 1.36, 95% CI 1.08–1.71, \( P = 0.010; 3) \) never smoking subgroup, CT/TT vs. CC, adjusted OR = 1.27, 95% CI 1.05–1.55, \( P = 0.015; 4) \) never drinking subgroup, CT/TT vs. CC, adjusted OR = 2.65, 95% CI 1.36–5.17, \( P = 0.004; 5) \) BMI \( \geq 24 \text{kg/m}^2 \) subgroup, TT vs. CC: adjusted OR = 2.45, 95% CI 1.50–3.95, \( P = 0.001; 6) \) smoking subgroup, CT/TT vs. CC, adjusted OR = 1.38, 95% CI 1.05–1.81, \( P = 0.022, \) and TT vs. CT/CC, adjusted OR = 2.51, 95% CI 1.03–4.86, \( P = 0.006 \) (Table 4).
### TABLE 3 | Logistic regression analyses of associations between PPARG rs3856806 C>T, PPARGC1A rs2970847 C>T, rs8192678 C>T, rs3736265 G>A, and PPARGC1B rs7732671 G>C and rs17572019 G>A polymorphisms and risk of CRC.

| Genotype          | Cases (n = 1,003) | Controls (n = 1,303) | Crude OR (95%CI) | P     | Adjusted OR a (95%CI) | P     |
|-------------------|-------------------|----------------------|------------------|-------|-----------------------|-------|
| **PPARG rs3856806 C>T** |                   |                      |                  |       |                       |       |
| CC                | 544               | 789                  | 60.69            | 1.00  | 1.00                  | 1.00  |
| CT                | 374               | 459                  | 35.31            | 1.14(0.96–1.35) | 0.145 | 1.16(0.97–1.39) | 0.095 |
| TT                | 62                | 52                   | 4.00             | 1.67(1.13–2.45) | 0.009 | 1.59(1.08–2.35) | 0.020 |
| CT+TT             | 436               | 511                  | 39.31            | 1.24(1.05–1.46) | 0.013 | 1.26(1.06–1.49) | 0.009 |
| CC+CT             | 918               | 1,248                | 96.00            | 1.00  | 1.00                  | 1.00  |
| TT                | 62                | 52                   | 4.00             | 1.62(1.11–2.37) | 0.012 | 1.54(1.05–2.26) | 0.028 |
| T allele          | 498               | 563                  | 21.65            |       |                       |       |
| **PPARGC1A rs2970847 C>T** |                   |                      |                  |       |                       |       |
| CC                | 593               | 788                  | 60.62            | 1.00  | 1.00                  | 1.00  |
| CT                | 344               | 449                  | 34.54            | 0.98(0.83–1.17) | 0.855 | 0.97(0.81–1.16) | 0.743 |
| TT                | 43                | 63                   | 4.85             | 0.88(0.59–1.31) | 0.520 | 0.92(0.61–1.38) | 0.673 |
| CT+TT             | 387               | 512                  | 39.38            | 1.00(0.85–1.19) | 0.959 | 1.00(0.84–1.19) | 0.985 |
| CC+CT             | 937               | 1,237                | 95.15            | 1.00  | 1.00                  | 1.00  |
| TT                | 43                | 63                   | 4.85             | 0.90(0.61–1.34) | 0.610 | 0.95(0.63–1.42) | 0.787 |
| T allele          | 430               | 575                  | 22.12            |       |                       |       |
| **PPARGC1A rs3736265 G>A** |                   |                      |                  |       |                       |       |
| GG                | 685               | 936                  | 72.11            | 1.00  | 1.00                  | 1.00  |
| GA                | 260               | 322                  | 24.81            | 1.07(0.88–1.29) | 0.493 | 1.06(0.87–1.29) | 0.550 |
| AA                | 32                | 40                   | 3.08             | 1.06(0.66–1.70) | 0.813 | 1.04(0.64–1.68) | 0.885 |
| GA + AA           | 292               | 362                  | 27.89            | 1.10(0.92–1.32) | 0.297 | 1.09(0.91–1.31) | 0.357 |
| GG + GA           | 945               | 1,258                | 96.92            | 1.00  | 1.00                  | 1.00  |
| AA                | 32                | 40                   | 3.08             | 1.07(0.66–1.71) | 0.793 | 1.05(0.65–1.69) | 0.854 |
| A allele          | 324               | 402                  | 15.49            |       |                       |       |
| **PPARGC1A rs8192678 C>T** |                   |                      |                  |       |                       |       |
| CC                | 344               | 408                  | 31.38            | 1.00  | 1.00                  | 1.00  |
| CT                | 454               | 645                  | 49.62            | 0.79(0.66–0.95) | 0.012 | 0.82(0.68–0.98) | 0.033 |
| TT                | 182               | 247                  | 19.00            | 0.83(0.65–1.05) | 0.113 | 0.85(0.66–1.08) | 0.171 |
| CT+TT             | 636               | 892                  | 68.62            | 0.85(0.71–1.01) | 0.062 | 0.87(0.73–1.05) | 0.139 |
| CC+CT             | 798               | 1,053                | 81.00            | 1.00  | 1.00                  | 1.00  |
| TT                | 182               | 247                  | 19.00            | 0.97(0.79–1.20) | 0.796 | 0.98(0.79–1.21) | 0.832 |
| T allele          | 818               | 1,139                | 43.81            |       |                       |       |
| **PPARGC1B rs7732671 G>C** |                   |                      |                  |       |                       |       |
| GG                | 863               | 1,145                | 88.08            | 1.00  | 1.00                  | 1.00  |
| GC                | 113               | 150                  | 11.54            | 0.98(0.79–1.27) | 0.855 | 0.99(0.76–1.29) | 0.924 |
| CC                | 4                 | 5                    | 0.38             | 1.04(0.28–3.87) | 0.957 | 1.03(0.27–3.88) | 0.967 |
| GC+CC             | 117               | 155                  | 11.92            | 1.00(0.78–1.29) | 0.991 | 1.01(0.78–1.31) | 0.927 |
| GG + GC           | 976               | 1,295                | 99.62            | 1.00  | 1.00                  | 1.00  |
| CC                | 4                 | 5                    | 0.38             | 1.06(0.28–3.96) | 0.929 | 1.05(0.28–3.96) | 0.946 |
| C allele          | 121               | 160                  | 6.15             |       |                       |       |
| **PPARGC1B rs17572019 G>A** |                   |                      |                  |       |                       |       |
| GG                | 862               | 1,144                | 88.00            | 1.00  | 1.00                  | 1.00  |
| GA                | 115               | 149                  | 11.46            | 1.00(0.77–1.30) | 0.998 | 1.02(0.79–1.33) | 0.877 |
| AA                | 3                 | 7                    | 0.54             | 0.56(0.14–2.15) | 0.395 | 0.47(0.12–1.84) | 0.276 |
| GA + AA           | 118               | 156                  | 12.00            | 1.00(0.78–1.30) | 0.976 | 1.02(0.78–1.32) | 0.900 |
| GG + GA           | 977               | 1,293                | 99.46            | 1.00  | 1.00                  | 1.00  |
| AA                | 3                 | 7                    | 0.54             | 0.57(0.15–2.20) | 0.412 | 0.48(0.12–1.86) | 0.286 |
| A allele          | 121               | 163                  | 6.27             |       |                       |       |

*aAdjusted for age, sex, smoking status, alcohol use and BMI status. Bold values are statistically significant (P < 0.05).*
TABLE 4 | Stratified analyses between PPARG rs3856806 C>T polymorphism and CRC risk by sex, age, BMI, smoking status, and alcohol consumption.

| Variable          | PPARG rs3856806 C>T (case/control) | Adjusted OR (95% CI); P     |
|-------------------|-----------------------------------|-----------------------------|
|                   | CC       | CT       | TT       | CC       | CT       | TT       | CT/TT    | TT vs. (CT/CC) |
| **SEX**           |          |          |          |          |          |          |          |               |
| Male              | 188/382  | 84/183   | 15/22    | 1.00     | 1.13(0.90–1.41); P: 0.296 | 1.88(1.14–3.10); P: 0.014 | 1.25(1.01–1.56); P: 0.042 | 1.84(1.12–3.02); P: 0.016 |
| Female            | 146/288  | 79/135   | 9/19     | 1.00     | 1.23(0.92–1.64); P: 0.167 | 1.25(0.66–2.37); P: 0.487 | 1.26(0.96–1.67); P: 0.101 | 1.18(0.63–2.21); P: 0.603 |
| **AGE**           |          |          |          |          |          |          |          |               |
| <61               | 155/309  | 71/152   | 12/14    | 1.00     | 1.06(0.81–1.38); P: 0.692 | 1.77(0.98–3.21); P: 0.060 | 1.15(0.89–1.49); P: 0.285 | 1.76(0.98–3.16); P: 0.060 |
| ≥61               | 179/361  | 92/166   | 12/27    | 1.00     | 1.27(1.00–1.61); P: 0.053 | 1.49(0.88–2.50); P: 0.135 | 1.36 (1.08–1.71); P: 0.010 | 1.40(0.84–2.33); P: 0.202 |
| **SMOKING STATUS**|          |          |          |          |          |          |          |               |
| Never             | 201/541  | 103/252  | 13/34    | 1.00     | 1.20(0.98–1.47); P: 0.078 | 1.48(0.95–2.30); P: 0.082 | 1.27(1.05–1.55); P: 0.015 | 1.41(0.91–2.17); P: 0.123 |
| Ever              | 133/129  | 60/66    | 11/7     | 1.00     | 1.03(0.71–1.48); P: 0.892 | 2.09(0.87–5.05); P: 0.100 | 1.17(0.82–1.67); P: 0.391 | 2.13(0.89–5.09); P: 0.088 |
| **ALCOHOL CONSUMPTION**|          |          |          |          |          |          |          |               |
| Never             | 283/823  | 139/287  | 22/38    | 1.00     | 1.20(0.99–1.45); P: 0.067 | 1.48(0.97–2.26); P: 0.072 | 1.27(1.06–1.53); P: 0.011 | 1.41(0.93–2.15); P: 0.108 |
| Ever              | 51/47    | 24/31    | 2/3      | 1.00     | 1.01(0.62–1.65); P: 0.969 | 2.59(0.89–7.54); P: 0.082 | 1.20(0.75–1.92); P: 0.445 | 2.62(0.91–7.52); P: 0.073 |
| **BMI (kg/m²)**   |          |          |          |          |          |          |          |               |
| <24               | 210/353  | 107/171  | 20/22    | 1.00     | 1.13(0.90–1.42); P: 0.296 | 1.26(0.78–2.03); P: 0.343 | 1.18(0.95–1.47); P: 0.131 | 1.23(0.77–1.96); P: 0.391 |
| ≥24               | 124/317  | 56/147   | 4/19     | 1.00     | 1.21(0.92–1.61); P: 0.177 | 2.65(1.36–5.17); P: 0.004 | 1.39 (1.05–1.81); P: 0.022 | 2.51(1.03–4.86); P: 0.006 |

Bold values are statistically significant (P < 0.05).

For PPARG rs3856806 C>T, the genotyping was successful in 980 (97.71%) CRC cases, and 1300 (99.77%) controls.

Adjusted for multiple comparisons in a logistic regression model (age stratified analysis; sex, BMI, smoking status and alcohol consumption adjusted; sex stratified analysis: age, BMI, smoking status and alcohol consumption adjusted; BMI stratified analysis: age, sex, smoking status and alcohol consumption adjusted; smoking stratified analysis: age, sex, BMI and alcohol consumption adjusted and drinking stratified analysis: age, sex, BMI and smoking status adjusted).

**Association of PPARG rs3856806 C>T Polymorphism With CRC in a Stratification Group by Site of Tumor**

To determine whether the association between the PPARG rs3856806 C>T polymorphism and CRC risk was modified by the site of CRC, we conducted stratified analyses. The results of the stratified analyses suggested this SNP increased the risk of colon cancer (CT vs. CC: adjusted OR = 1.27, 95% CI 1.01–1.60, P = 0.044 and TT/CT vs. CC: adjusted OR = 1.34, 95% CI 1.07–1.68, P = 0.011) and rectum cancer (TT vs. CC: adjusted OR = 1.58, 95% CI 1.01–2.49, P = 0.045 and TT vs. CC/CT: adjusted OR = 1.58, 95% CI 1.01–2.46, P = 0.043), Table 5.

**DISCUSSION**

Accumulating evidence has highlighted that CRC is associated with obesity and Waist-to-Hip Ratio (WHR) (8–10). Some important metabolism-related genes may be strong candidates for predisposing to CRC (11). PPARG may be implicated in metabolism, inflammatory response, adipose cell differentiation, and cellular apoptosis (34–37). The PPARG family (e.g., PPARGC1A, PPARGC1B) also regulate fatty acid oxidation, gluconeogenesis and adaptive thermogenesis (38). These proteins may be involved in the development of obesity. Several studies have focused on the association between the PPARG rs3856806 C>T polymorphism and the risk of CRC (21–24). However, the results were inconsistent. In addition, the potential relationships of the PPARGC1A, PPARGC1B SNPs with the development of CRC are unknown. To shed some light on this issue, we carried out a case-control study in Eastern Chinese Han population. Our findings suggested that the PPARG rs3856806 C>T polymorphism is associated with an increased risk of CRC, especially in male, ≥ 61 years old, never smoking, never drinking, BMI ≥ 24 kg/m², colon cancer, and rectum cancer subgroups.

PPARG is one of the three subtypes of peroxisome proliferator-activated receptors (PPARs). The PPARG gene encodes a member of the PPAR subfamily of nuclear receptors, which form heterodimers with retinoid X receptors (RXRs) and then influence the transcription of many target genes. A previous...
A common functional polymorphism (His449His; rs3856806) in PPARG is a C → T coding-synonymous substitution in codon 449 of exon 6. Grygiel-Górniak and colleagues reported that higher BMI and visceral fat deposition were promoted by the presence of the PPARG rs3856806 T allele (40). Previous studies suggested a potential correlation of this SNP with atherosclerosis, type 2 diabetes and cancer (20, 41–44). Although rs3856806 is a coding-synonymous SNP, it is proposed that a C → T substitution could alter the expression of PPARG protein by altering mRNA processing or translation. Doecke et al. reported that the PPARG rs3856806 CT genotype may increase the susceptibility of adenocarcinoma of the esophagus in an obesity subgroup (BMI ≥ 30 kg/m²) (45). The PPARG rs3856806 C>T polymorphism was also found to be significantly over-represented in sporadic glioblastoma multiforme in American populations (46). Jiang et al. reported that the PPARG rs3856806 C>T polymorphism was associated with an increased risk of CRC in India (21). However, other case-control studies suggested that PPARG rs3856806 C>T might not influence the development of CRC (22–24). Thus, the results were inconsistent and ambiguous. Considering a common SNP having low penetrance susceptibility to cancer, we performed a case-control study with large sample sizes to obtain a more precise assessment. As demonstrated in the results, we found that the PPARG rs3856806 C>T polymorphism was associated with an increased risk of CRC, even after a Bonferroni correction test. Thus, our findings were reliable. Recently, a meta-analysis reported that the PPARG rs3856806 C>T polymorphism increased the risk of overall cancer (20). Our findings were very similar to this pooled-analysis. Additionally, it is worth noting that we found the that the PPARG rs3856806 C>T polymorphism was associated with an increased risk of CRC in the BMI ≥ 24 kg/m² subgroup. It suggested that this SNP might be implicated in the development of obesity and overweight, and subsequently lead to an increased risk to CRC.

There are, however, several limitations in this case-control study. First, the CRC patients and non-cancer controls were from two local hospitals. The potential selection bias might have occurred. Second, a replicated study focusing on the association of these SNPs with CRC risk was not carried out. Third, although we took some risk factors into consideration such as BMI, gender, age, drinking, and smoking status, many other environmental and lifestyle factors, possibly related to the development of CRC, were not collected in this study. Fourth, due to the moderate sample size in some subgroups, the power might be limited. Fifth, a functional study for the PPARG rs3856806 C>T polymorphism has not been conducted. Finally, in the future, it is necessary to carry out a functional study to identify the mechanism of the PPARG rs3856806 C>T polymorphism.

In conclusion, our findings suggest that the PPARG rs3856806 C>T polymorphism may increase the risk of CRC. In the future, larger sample size case-control studies with a detailed functional assessment are needed to further evaluate the relationship of PPARG rs3856806 C>T polymorphism with CRC risk.

### Table 5

| Genotype    | Colon cancer cases (n = 431) | Rectum cancer cases (n = 572) |
|-------------|-----------------------------|-------------------------------|
|             | Crude OR (95%CI)            | Adjusted OR (95%CI)           |
|             | P                           | Adjusted OR (95%CI)           |
|             | P                           | P                            |
|             | n                           | Crude OR (95%CI)             |
|             | %                           | Adjusted OR (95%CI)          |
| CC          |                             |                              |
| CT          |                             |                              |
| TT          |                             |                              |
| CT+TT       |                             |                              |
| CT+CC       |                             |                              |
| TT          |                             |                              |
| T allele    |                             |                              |

*Adjusted for age, sex, smoking status, alcohol use and BMI status.*

| Genotype | Crude OR (95%CI) | Adjusted OR (95%CI) |
|----------|------------------|---------------------|
|          |                  |                     |
|          |                  |                     |

Bold values are statistically significant (P < 0.05).
AUTHOR CONTRIBUTIONS
JL, YC, GC, and XZ conceived and designed the experiments. YC, WT, CL, and GC performed the experiments. JL, YC, SZ, and ZG analyzed the data. JL, YC, and WT wrote the paper.

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SUPPLEMENTARY MATERIAL
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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