Adiponectin Gene Polymorphisms are Associated with Increased Risk of Colorectal Cancer

Background: This meta-analysis investigates the associations of adiponectin (ADIPOQ) genetic polymorphisms with the susceptibility to colorectal cancer (CRC).

Material/Methods: 2 reviewers independently searched 6 databases – PubMed, Cochrane Library, Ovid, Embase, China National Knowledge Infrastructure (CNKI) and Wanfang databases – to identify published studies relevant to adiponectin gene polymorphisms and CRC. Studies retrieved from database searches were screened using our stringent inclusion and exclusion criteria. Full texts of the selected studies were accessed and related data was extracted using a standardized data extraction form. Comprehensive Meta-analysis 2.0 software was used for statistical analyses.

Results: A total of 188 studies were initially retrieved from database search, and 6 studies were eventually selected, through a rigorous screening process, for inclusion in this meta-analysis. The 6 studies contained a total of 1897 patients (Asians: 1190; white: 707) with CRC in case group and 2475 healthy controls (Asians: 1325; white: 1150) in the control group. Results of the current meta-analysis revealed that the rs2241766 T>G single-nucleotide polymorphisms (SNP) increase the risk of CRC; rs1501299 G>T under dominant model was associated with increased risk of CRC; and rs266729 C>G SNP under allele model conferred an increased risk of CRC.

Conclusions: Our meta-analysis strongly suggests that the ADIPOQ rs2241766 T>G, rs1501299 G>T, and rs266729 C>G SNPs correlate with an increased risk of CRC.

MeSH Keywords: Adiponectin • Colorectal Neoplasms • Polymorphism, Genetic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893472
Background

Colorectal cancer (CRC) ranks third among the most frequent malignancies in the Western world, and despite significantly improved treatment modalities, CRC remains a major cause of cancer mortality [1,2]. At an estimated 608 000 deaths worldwide each year, CRC is the fourth most common cause of deaths among all cancers, accounting for 8% of all cancer-related deaths [3]. Nearly 150 000 are newly diagnosed with CRC annually in the US and approximately one-third of CRC patients die from this disease [4]. CRC is characterized by late clinical presentation and a relatively rapid disease progression, which is the primary underlying reason for increased mortality and morbidity in patients with this malignancy [3,5]. However, advances in treatment modalities, including surgery, radiation therapy, and chemotherapy, have steadily improved the 5-year survival rate for CRC [6]. Etiologically, interactions of genetic and environmental factors play central roles in the pathogenesis of CRC [7]. The exact processes underlying pathogenesis of CRC are complex and only partially understood, but current research suggests body fat and its associated metabolic dysregulation play a central role [8]. A growing body of evidence suggests that adiponectin (ADIPOQ) may be the link between obesity and CRC [9,10].

**ADIPOQ** is an adipocyte-derived peptide hormone and insulin-sensitizing adipokine expressed as a single subunit and is abundantly secreted by adipocytes into circulation [11]. **ADIPOQ** and its receptors (ADIPOR1/2) are expressed in colonic tissues as well, and the expression of ADIPOR1 and ADIPOR2 is found at higher levels in colorectal carcinomas, compared to normal colonic epithelium [12]. **ADIPOQ** appears to exert its influence in preneoplastic colonic lesions to modulate cell growth through activating, altering, or interacting with some pathways including leptin and NF-κB pathway [13]. In human, **ADIPOQ** is encoded by the **ADIPOQ** gene located on chromosome 3q27 and is comprised of three exons with 2 introns [14]. In human plasma, the circulating **ADIPOQ** level ranges between 3 to 30 μg/ml [15] and is reduced in patients with insulin resistance, type II diabetes [16], obesity [17], cardiovascular disease [18], gastric cancer [19] and colorectal adenomas and carcinoma [20]. Low plasma **ADIPOQ** levels in these disease states are accompanied by reduced **ADIPOQ** gene expression in adipose tissue caused by single nucleotide polymorphisms (SNPs) in **ADIPOQ** gene [20,21]. Although the function of most of these SNPs remains unclear, three common SNPs, rs1501299 (276G/T), rs2241766 (45T/G) and rs266729 (-11377C/G), are suspected to play a direct role in the susceptibility to some diseases, including coronary heart disease, type 2 diabetes mellitus, squamous cell esophageal cancer and liver disease [22–25]. Consistent with this notion, previous studies linked these polymorphisms with altered serum levels of **ADIPOQ** [26], obesity [27], and CRC [28,29]. However, other studies failed to confirm such associations with these diseases, and the results remain controversial [30,31]. Considering the conflict results existed, we conducted this meta-analysis with the hypothesis that the **ADIPOQ** rs2241766 T>G, rs1501299 G>T and rs266729 C>G SNPs may correlate with an increased risk of CRC.

Material and Methods

Search strategy

A literature research was conducted using PubMed, Cochrane Library, Ovid, Embase, Wanfang and China National Knowledge Infrastructure (CNKI) databases, to identify studies published prior to October 2014. Relevant studies were identified using the terms: “adiponectin or ADIPOQ” and “polymorphisms or variant” and “colorectal tumor or cancer”. The search was confined to humans. A manual search of references of the original articles related with this topic was used to identify additional studies. If the data or data subsets were published in more than one paper, only the paper with the largest sample size was enrolled.

Study selection

Studies were selected for meta-analysis if they met the inclusion criteria as follows: (1) case-control study design; (2) studies that investigated the association between the **ADIPOQ** SNPs and CRC; (3) study subjects were CRC patients confirmed by histopathology in case group; (4) the enrolled studies provided loci information of **ADIPOQ** rs2241766 T>G, rs1501299 G>T and rs266729 C>G. The exclusion criteria were: (1) reviews and summaries; (2) repetitive publications; (3) no raw data of the **ADIPOQ** genotype.

Data extraction

Two investigators extracted data independently and reached agreements on all the items. If there were any disagreements between the 2 investigators, the data were re-examined and, following a thorough discussion and evaluation of each item, a consensus was reached. Data extracted from the enrolled papers included first author, publication year, country, ethnicity, number of cases, age, genotyping method and SNP of loci information. The methodological quality of enrolled studies was assessed by critical appraisal skill program (CASP) criteria by 2 of the independent investigators independently (http://www.casp-uk.net/). The following criteria were used to rate each item: the study addressed a clearly focused issue (CASP01); the research problem is appropriate and the research design answers the research problem (CASP02); the cases were recruited in an acceptable way (CASP03); the controls were selected in an acceptable way (CASP04); the
measurement for exposure factors is accurate to minimize bias (CASPO5); the study controls other important confounding factors (CASPO6); the research result is complete (CASPO7); the research result is precise (CASPO9); the research result is applicable to the local population (CASPO10); the research result is precise (CASPO11).

**Statistical methods**

Pooled odds risk (OR) and 95% confidence intervals (CI) were calculated with the usage of fixed-effects or random-effects model. Z test was employed to detect the significance of overall effect size [32], and forest plots were conducted to display values of OR at 95%CI between case and control groups. Heterogeneity of the combined studies was assessed with Cochran's Q-statistic test and $I^2$ test [33,34]. The P value of Cochran's Q-statistic of below 0.05 was considered statistically significant heterogeneity. The $I^2$ test provides a measure of the degree of heterogeneity in the results. Typically, values of 0~25% are considered to represent no heterogeneity, 25~50% to be modest heterogeneity, 50~75% to be large heterogeneity, and 75~100% to be extreme heterogeneity. A Monte Carlo simulation (MCS) was performed to correct and verify the results [33,36,37]. Sensitivity analysis was conducted by omitting individual studies sequentially to assess stability of the results. The Egger's test, funnel plots, and classic fail-safe N were used to identify publication bias [38–40].

**Table 1. Baseline characteristics of the studies included in this meta-analysis.**

| First author | Year | Country | Disease | Sample size | Total | Sample size | Gender (M/F) | Age (years) | Genotyping methods | Gene | SNP |
|--------------|------|---------|---------|-------------|-------|-------------|--------------|-------------|-------------------|------|-----|
| Liu WH-a     | 2014 | China   | CRC     | 800         | 400   | 400         | –            | 22~75       | 55.74             | PCR-RFLP | ADIPOQ | rs2241766 |
| Liu WH-b     | 2014 | China   | CRC     | 800         | 400   | 400         | –            | 22~75       | 55.74             | PCR-RFLP | ADIPOQ | rs1501299 |
| Zhang Y-b    | 2012 | China   | CRC     | 740         | 370   | 370         | 245/125      | 226/144     | 63.13±12.47       | PCR-RFLP | ADIPOQ | rs1501299 |
| Zhang Y-a    | 2012 | China   | CRC     | 740         | 370   | 370         | 245/125      | 226/144     | 63.13±12.47       | PCR-RFLP | ADIPOQ | rs1501299 |
| Zhang Y-c    | 2012 | China   | CRC     | 740         | 370   | 370         | 245/125      | 226/144     | 63.13±12.47       | PCR-RFLP | ADIPOQ | rs1501299 |
| He B-c       | 2011 | China   | CRC     | 975         | 420   | 555         | 280/140      | 339/216     | 62.88±12.32       | PCR-RFLP | ADIPOQ | rs266729  |
| He B-b       | 2011 | China   | CRC     | 975         | 420   | 555         | 280/140      | 339/216     | 62.88±12.32       | PCR-RFLP | ADIPOQ | rs1501299 |
| Partida-Perez| 2010 | Mexico  | CRC     | 170         | 68    | 102         | 36/32        | 78/24       | 58                | PCR-RFLP | ADIPOQ | rs1501299 |
| Partida-Perez| 2010 | Mexico  | CRC     | 170         | 68    | 102         | 36/32        | 78/24       | 58                | PCR-RFLP | ADIPOQ | rs266729  |
| Tsilidis K   | 2009 | USA     | CRC     | 589         | 208   | 381         | 96/112       | 173/208     | 62.8±11.4         | PCR-RFLP | ADIPOQ | rs2241766 |
| Kaklamani V  | 2008 | USA     | CRC     | 1099        | 441   | 658         | –            | –          | 255/186 211/447   | PCR-RFLP | ADIPOQ | rs2241766 |
| Kaklamani V  | 2008 | USA     | CRC     | 1099        | 441   | 658         | –            | –          | 255/186 211/447   | PCR-RFLP | ADIPOQ | rs266729  |
| Kaklamani V  | 2008 | USA     | CRC     | 1099        | 441   | 658         | –            | –          | 255/186 211/447   | PCR-RFLP | ADIPOQ | rs266729  |

M – male; F – female; CRC – colorectal cancer; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; ADIPOQ – adiponectin; SNP – single nucleotide polymorphisms; a – rs2241766; b – rs1501299; c – rs266729.
Results

Study characteristics

The database search strategy retrieved 188 potentially relevant studies. Based on the inclusion criteria, after excluded 20 duplicates, 17 animal studies, 54 studies unrelated to the research topics, and 8 letters, reviews, or meta-analyses, 8 cohort studies, 14 studies not relevant to ADIPOQ, 22 studies not relevant to ADIPOQ polymorphism, 34 studies unrelated to CRC, and 5 studies that had no enough information, a sum of 6 studies, published between 2008 and 2014, were included.
The 6 selected studies contained a total of 1897 CRC (Asians: 1190; White: 707) patients and 2475 healthy controls (Asians: 1325; white: 1150). Of the 6 studies, 3 studies were performed in Asians, in China; the other 3 studies were performed in whites, with 2 studies in the US and 1 trial in Mexico.

Table 2. Comparisons of genotype and allele frequencies between the case and the control groups.

| SNP         | rs2241766 T>G | rs1501299 G>T | rs266729 C>G |
|-------------|---------------|---------------|--------------|
|              | OR 95%CI      | P             | OR 95%CI     | P          | OR 95%CI     | P          |
| M allele vs. W allele (allele model) |               |               |              |            |              |            |
| Asians      | 1.198 0.833   | 0.030 0.738   | 0.003 0.720   | 0.026      |               |              |
| Caucasians  | 1.015 0.789   | 0.088 0.714   | 0.159 0.714   | 0.157      |               |              |
| Overall     | 1.147 0.796   | 0.01 0.675   | 0.163 0.754   | 0.009      |               |              |
| WM + MM vs. WW (dominant model) |               |               |              |            |              |            |
| Asians      | 0.833 0.738   | 0.003 0.720   | 0.003 1.091   | 0.149      |               |              |
| Caucasians  | 1.111 0.960   | 0.159 1.118   | 0.374 0.663   | 0.149      |               |              |
| Overall     | 1.229 0.796   | 0.002 0.787   | 0.047 0.816   | 0.065      |               |              |
| MM vs. WW (homozygous model) |               |               |              |            |              |            |
| Overall     | 1.17 0.896    | 0.248 0.858   | 0.172 1.037   | 0.821      |               |              |
| MM vs. WM (heterozygous model) |               |               |              |            |              |            |
| Overall     | 1.07 0.817    | 0.623 0.946   | 0.554 0.934   | 0.672      |               |              |
| MM vs. WW + WM (recessive model) |               |               |              |            |              |            |
| Overall     | 1.061 0.819   | 0.653 1.001   | 0.995 1.049   | 0.758      |               |              |

SNP – single nucleotide polymorphisms; OR – odds risk; 95% CI – 95% confidential intervals.

**Figure 3.** Forest plots of the correlations between adiponectin rs1501299 G>T polymorphisms and the susceptibility to colorectal cancer (A: allele model, B: dominant model).

in this meta-analysis [28,41–45]. The 6 selected studies contained a total of 1897 CRC (Asians: 1190; White: 707) patients and 2475 healthy controls (Asians: 1325; white: 1150). Of the 6 studies, 3 studies were performed in Asians, in China; the other 3 studies were performed in whites, with 2 studies in the US and 1 trial in Mexico. The sample sizes of the studies...
varied between 58 and 441. The uniform genotyping method in the studies was polymerase chain reaction with the restriction fragment length polymorphism (PCR-RFLP). In the controls, the distribution of genotypes was in accordance with Hardy-Weinberg equilibrium (HWE) for the all selected trials except for 1 study [42] for rs1501299 G>T, 1 study for rs266729 C>G [45], and 1 study [41] for rs1501299 G>T and rs2241766 T>G.

Baseline characteristics and quality scores of all included studies are displayed in Table 1 and Figure 1.

**Association between ADIPOQ rs2241766 T>G and susceptibility to CRC**

Five studies investigated the correlation between SNP of ADIPOQ rs2241766 T>G and the susceptibility to CRC. Heterogeneity test revealed that no heterogeneity existed under allele and dominant models, and thus a fixed-effect model was used (P>0.05). The results of this meta-analysis suggested that rs2241766 T>G SNP was associated with an increased risk of CRC (allele model: OR=1.147, 95% CI=1.033~1.272, P=0.010 (Figure 2A); dominant model: OR=1.229, 95% CI=1.077~1.401, P=0.002) (Figure 2B). Subgroup analysis based on ethnicity indicated that the rs2241766 T>G SNP increased the risk of CRC in Asian population (allele model: OR=1.198, 95% CI=1.062~1.353, P=0.003; dominant model: OR=1.282, 95% CI=1.095~1.500, P=0.002), while no significant association between rs2241766 T>G and CRC was found in whites (allele mode: OR=1.015, 95% CI=0.829~1.241, P=0.888; dominant model: OR=1.115, 95% CI=0.879~1.500, P=0.370) (Table 2).

**Association between ADIPOQ rs1501299 G>T and susceptibility to CRC**

Six studies investigated the correlation between SNP of ADIPOQ rs1501299 G>T and the susceptibility to CRC. Heterogeneity test revealed that no heterogeneity existed under allele and dominant models; therefore, a fixed-effects model was used (P>0.05). The results of this meta-analysis suggested rs1501299 G>T under allele model had no significant association with the susceptibility to CRC (OR=0.936, 95% CI=0.852~1.027, P=0.163) (Figure 3A), while rs1501299 G>T under dominant model increased the risk of CRC (OR=0.874, 95% CI=0.766~0.998, P=0.047) (Figure 3B). Subgroup analysis by ethnicity indicated that the rs1501299 G>T SNP was associated with increased risk of CRC in Asians (allele model: OR=0.833, 95% CI=0.738~0.940, P=0.003; dominant model: OR=0.790, 95% CI=0.675~0.925, P=0.003), while no significant association was found in whites (allele mode: OR=1.111, 95% CI=0.960~1.287, P=0.159; dominant model: OR=1.118, 95% CI=0.875~1.428, P=0.374) (Table 2).

![Figure 4. Forest plots of the correlations between adiponectin rs266729 C>G polymorphisms and the susceptibility to colorectal cancer](image-url)

(A: allele model, B: dominant model).
Association between ADIPOQ rs266729 C>G and susceptibility to CRC

Three studies investigated the correlation between SNP of ADIPOQ rs266729 C>G and the susceptibility to CRC. Heterogeneity test revealed that there was heterogeneity under allele model, and thus a random-effects model was used (P<0.05). However, no heterogeneity was detected under the dominant model, and thus a fixed-effects model was applied (P>0.05). The results of this meta-analysis suggested rs266729 C>G SNP under allele model was associated with increased risk of CRC (OR=0.850, 95% CI=0.754–0.960, P=0.009)
Subgroup analysis by ethnicity suggested that in Asians, rs266729 C>G SNP under allele model increased the risk of CRC (OR=0.839, 95% CI=0.720~0.979, P=0.026), while no significant correlation with CRC was found under the dominant model (OR=1.091, 95% CI=0.871~1.367, P=0.449). There was also no strong association between rs266729 C>G SNP and the risk of CRC in whites (allele model: OR=0.868, 95% CI=0.714~1.056, P=0.157; dominant model: OR=0.833, 95% CI=0.653~1.062, P=0.140) (Table 2).

Sensitivity analysis and publication bias

Univariate analysis suggested that publication year (Figure 5A), country (Figure 5B), ethnicity (Figure 5C), SNP (Figure 5D), language (Figure 5E) and sample size (Figure 5F) were all not the main source of heterogeneity or key factors influencing the overall effect size (P>0.05). Multivariate analysis further verified the result of univariate analysis (Table 3). The results of sensitivity analyses for rs2241766 T>G (allele: Figure 6A; dominant: Figure 6B) suggested that no single study had a marked effect on the pooled ORs. The funnel plots of the differences in gene frequencies of rs2241766 T>G, rs1501299 G>T and rs266729 C>G were symmetrical, suggesting no publication bias. Classic fail-safe N and Egger test further verified that no publication bias existed (Figure 9).

Discussion

Globally, CRC is known as one of the most frequent gastrointestinal tumors [46]. Over the past decade, the correlations between ADIPOQ SNPs and the risk of cancers, including CRC, have been extensively investigated, with conflicting results [47]. We conducted the present meta-analysis to explore the correlations between ADIPOQ rs2241766 T>G, rs1501299 G>T, and rs266729 C>G SNPs and the susceptibility to CRC. We found that rs2241766 T>G SNP, rs1501299 G>T under dominant model, and rs266729 C>G SNP under allele model were strongly correlated with an increased susceptibility to CRC, indicating that the ADIPOQ polymorphisms confer a marked risk of CRC. ADIPOQ is a 30-kDa adipocytokine hormone secreted by the adipose tissue, which mediates antineoplastic as
Figure 7. Sensitivity analysis of the correlations between adiponectin rs1501299 G>T and the susceptibility to colorectal cancer (A: allele model, B: dominant model).

Well as anti-angiogenic effects through binding its receptors, Adipo-R1 and Adipo-R2, which are also expressed in colorectal cancer tissues [11]. ADIPOQ is insulin-sensitizing, anti-inflammatory, anti-atherogenic, and anti-angiogenic [48,49]. In vitro, ADIPOQ directly controls the malignant behavior of tumor cells, including cell proliferation, adhesion, invasion, and colony formation [50]. ADIPOQ influences angiogenesis through inducing apoptosis of endothelial cells, thus functioning as an angiogenesis inhibitor [51,52]. The SNPs reduce the expression and function of ADIPOQ, and thus influence CRC susceptibility. Consistent with this, several epidemiology studies showed that low ADIPOQ levels are correlated with increased susceptibility to multiple obesity-associated malignancies, including breast, endometrial, prostate, and colorectal cancers in both cross-sectional and prospective studies [53,54]. Suggested mechanisms by which ADIPOQ might play a part in the CRC development include suppressing inflammation, improving insulin sensitivity, inhibiting cell growth and inducing apoptosis [30]. However, contrary to our results, Mingyang Song et al. reported findings that did not support any correlation between the known ADIPOQ SNPs and CRC [30]. This null result might be due to the fact that the plasma ADIPOQ data in that study was only from a subset of the 2 cohorts of the consortium, which precluded a simultaneous analysis of the genetic component and the circulating ADIPOQ levels in relation to CRC in the same set of subjects.

Subgroup analysis based on ethnicity indicated that the rs2241766 T>G, rs1501299 G>T and under allele model rs266729 C>G increased the risk of CRC in Asians, while no significant association between ADIPOQ SNPs and risk of CRC was observed in whites. We suspect genetic polymorphisms at other loci such as in protein disulfide isomerase (PDI) or in the other members of the multi-subunit ADIPOQ complex, geographical position, dietary habits, lifestyle or limitations in existing detection methods could account for these observations, and we plan to follow up with further studies to address ethnic differences about the association between ADIPOQ SNPs and the risk of CRC.

Some limitations in the present meta-analysis should be pointed out. First, due to the publication limitations or incomplete...
**Figure 8.** Sensitivity analysis of the correlations between adiponectin rs266729 C>G polymorphisms and the susceptibility to colorectal cancer (A: allele model, B: dominant model).

| Author          | Statistics with study removed | Odds ratio (95%CI) with study removed |
|-----------------|--------------------------------|--------------------------------------|
| rs266729 C>G    |                                |                                      |
| rs266729 C>G    |                                |                                      |
| Zhang Y (2012)  | Point: 0.971; Limit: 0.848-1.113 | Z-Value: -0.419; P-Value: 0.675       |
| He B (2011)     | Point: 0.723; Limit: 0.618-0.845 | Z-Value: -4.062; P-Value: 0.000       |
| Kaklamani VG (2008) | Point: 0.839; Limit: 0.720-0.979 | Z-Value: -2.234; P-Value: 0.026       |
| Overall         | Point: 0.850; Limit: 0.754-0.960 | Z-Value: -2.630; P-Value: 0.009       |

| rs266729 C>G    |                                |                                      |
| rs266729 C>G    |                                |                                      |
| Zhang Y (2012)  | Point: 0.955; Limit: 0.800-1.139 | Z-Value: -0.511; P-Value: 0.609       |
| He B (2011)     | Point: 0.870; Limit: 0.700-1.080 | Z-Value: -1.266; P-Value: 0.206       |
| Kaklamani VG (2008) | Point: 1.091; Limit: 0.871-1.367 | Z-Value: 0.757; P-Value: 0.449        |
| Overall         | Point: 0.963; Limit: 0.816-1.136 | Z-Value: -0.446; P-Value: 0.656       |

**Figure 9.** Publication bias of the correlations between adiponectin rs2241766 T>G, rs1501299 G>T and rs266729 C>G polymorphisms and the susceptibility to colorectal cancer (rs2241766 T>G: A: allele; B: dominant; rs1501299 G>T: C: allele; D: dominant; rs266729 C>G: E: allele; F: dominant).
data, several relevant studies were not able to be enrolled in this analysis. Second, the number of enrolled trials, especially for rs266729 C>G SNP was not large enough for a comprehensive analysis, and some trials with small size, such as the study by Partida-Perez M et al., might not have sufficiently statistical power to obtain the real correlation. Third, our results were based on unadjusted estimates, and insufficient information for data analysis might cause confounding bias. Despite these limitations, our analysis also had some advantages. First, substantial number of cases and controls were pooled from different trials, which significantly increased statistical power of the meta-analysis. Second, the quality of case-control studies included in current meta-analysis was relatively satisfactory and met our predefined inclusion criteria. Third, we did not find any publication bias, suggesting that the overall pooled result is unbiased.

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Conclusions

In summary, the rs2241766 T>G SNP, under dominant model rs1501299 G>T and under allele model rs266729 C>G SNP was associated with an increase the risk of CRC, suggesting that the rs2241766 T>G SNP, rs1501299 G>T, and rs266729 C>G SNPs might be correlated with the increased susceptibility to CRC and may be useful biomarkers for early diagnosis of CRC.

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