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Association of *Adiponectin* Genotypes With Colorectal Cancer Susceptibility in Taiwan

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Abstract. *Aim: To investigate the association between adiponectin (ADIPOQ) genotypes and colorectal cancer (CRC) risk among Taiwanese. Materials and Methods: Polymerase chain reaction–restriction fragment length polymorphism was adopted to identify ADIPOQ rs266729, rs2241766 and rs1501299 genotypes among 362 CRC patients and 362 healthy controls. Results: ADIPOQ rs266729 GG genotype (p=0.0075) and G allele (p=0.0061) are associated with a significantly increased CRC risk. There is no differential distribution of rs2241766 and rs1501299 genotypes. As for the gene–lifestyle interaction, there are obvious joint effects of rs266729 genotype on the CRC risk among non-smoker, non-alcohol drinker, while not on smoker or non-drinker subgroups. No significant correlation was observed between rs266729 genotypic distributions and age, gender, tumor size, location or metastasis status. Interestingly, a correlation of rs266729 genotype and larger BMI on CRC risk was found. Conclusion: G allele at ADIPOQ rs266729 may serve as a determiner for CRC risk, especially for those with BMI ≥24.*

Colorectal cancer (CRC), the third most common cancer among men and the second among women, has been reported to be closely related to human morbidity and mortality worldwide (1-3). Interestingly, the incidence and mortality rates of CRC vary dramatically around the world with regional differences that can reach as high as ten-fold (2-4). Scientists in epidemiology attributed about 85% of CRC etiology to environmental factors, such as meat consumption, cigarette smoking, and exposure to carcinogens (5, 6). On the other hand, at least 15-20% of CRC cases, those with strong familial cancer history have attracted molecular epidemiologists to figure out the contributions of genomic susceptibility genotypes (7-9). In Taiwan, the incidence and mortality rates of CRC has been listed as the first and third cancer among the common types of cancer for decades and the extremely high incidence has been owed to the dietary alterations toward Western diet style and the decreasing consumption of fibers or grain-made foods. Although specific biomarkers for CRC prediction and detection have been reported within recent years (10-14), the interactions among the genomic, demographic and environmental risk factors remain largely unrevealed (15). Etiologically speaking, genomic, demographic and environmental factors team-up to play a significant role in the pathogenesis of CRC (16). CRC has been identified as

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an obesity-related malignancy (17). Certain epidemiological investigations have proposed that Western dietary styles and behavioral patterns, such as high-fat and low-fiber intake, low daily physical activity for more than half year, which leads to obesity, insulin resistance and hypertension, are the major determiners for the increasing CRC incidence, particularly in developing countries such as Taiwan (18, 19). In the post genomic era, the biomarker-guided personalized therapy for CRC shall play a more important role (20).

Adiponectin (ADIPOQ), which is exclusively secreted from adipocytes, is an anti-atherosclerosis, anti-inflammation and insulin-sensitizing adipokine (18, 19). In the literature, decreased levels of ADIPOQ in the circulation have been observed in a panel of cancers including gastric cancer (21), pancreatic cancer (22), breast cancer (23) endometrial cancer (24), and most of all, colorectal cancer (25). However, the results are controversial in the case of pancreatic cancer, since Dalamaga and colleagues found that serum ADIPOQ levels had a positive association with pancreatic cancer risk (26). This kind of inconclusiveness may also be found in CRC, which reminds us that the contribution of ADIPOQ to the elevated risk for cancer are cancer-specific and different among various ethnics.

As far as CRC is concerned, the associations between obesity, lectin, ADIPOQ with CRC risk have been revealed in several epidemiological investigations (17, 27, 28), however, no genomic marker is currently available for early diagnosis and prognosis. Although the function of about 600 polymorphic genotypes remains unrevealed, three of the commonly examined single nucleotide polymorphisms (SNPs) on *ADIPOQ*, rs2241766 (45T/G), rs266729 (-11377C/G) and rs1501299 (276G/T), are found to be determiners for the personal susceptibility for several human diseases including squamous cell esophageal cancer (29), non-alcoholic fatty liver disease (30), coronary heart disease (31) and type-2 diabetes mellitus (32). Supporting this idea, several groups have provided evidence that the people carrying the variant genotypes of these polymorphic sites have different levels of ADIPOQ in their blood (33), insulin resistance and obesity status (34), and CRC susceptibility compared to those carrying the wild-type genotype (18, 35). At the same time, several other groups present controversial findings (36, 37). To confirm the contributions of genotypes of *ADIPOQ* to CRC, we conducted a hospital-based case-control study to evaluate the three SNPs of *ADIPOQ*, rs2241766, rs266729 and rs1501299, regarding their possibility to serve as a predictor for CRC risk in Taiwan population.

Materials and Methods

Investigated CRC cases and controls. The investigated population included 362 CRC patients and 362 controls and the methodology has been described in our previous studies (10-13). Briefly, CRC patients who had visited our hospital were recruited at the outpatient clinics of general surgery. The pathological-clinical indexes of each patient were defined, graded and recorded by expert surgeons (38, 39). A 1:1 of non-cancer healthy people were selected as controls by matching for age, gender and some indulgences after initial random sampling from the Health Examination Cohort of the Hospital with the help of colleagues in the Department of Family Medicine. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin and any familial or genetic diseases. All participants have completed a self-administered questionnaire and provided a 5-ml sample of peripheral blood for genotyping. This study was approved by the Institutional Review Board of the China Medical University Hospital (IRB project identification coding number: DMR99-IRB-108) and written informed consent was obtained from all the participants with the help of Tissue Bank of China Medical University Hospital. The selective demographic information of the participants is summarized in Table I.

Procedures for ADIPOQ genotyping. Genomic DNA was extracted from the peripheral blood leukocytes of each subject within 24 h with a QIAamp Blood Mini Kit (Qiagen, Chatsworth, CA, USA), stored long-term at −80˚C, diluted and aliquoted for genotyping as a working stock at −20˚C as previously described (40-43). Consulting the NCBI database (www.ncbi.nlm.nih.gov/snp), we obtained three of the SNPs out of more than 600 of ADIPOQ, rs2241766, rs266729 and rs1501299, for the Han Chinese with the criteria of minor allele frequency ≥0.05 and r^2 ≥0.8. The typical polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technology was adopted to determine *ADIPOQ* rs2241766, rs266729 and rs1501299 genotypes. Concisely, the polymerase chain reaction (PCR) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 59˚C for 30 s and 72˚C for 30 s, and a final extension at 72˚C for 10 min. The genotyping PCR for *ADIPOQ* rs2241766 was conducted using the forward 5'-GAA GTA GAC TCT GCT GAG AT-3' and the reverse 5'-TAT CAG TGT AGG AGG TCTGT-3' primer pairs. The genotyping PCR for *ADIPOQ* rs266729 was conducted using the forward 5'-GCT CTG TGT GGA CTG TGG AG-3' and the reverse 5'-AGA AGC AGC CTG GAG AAC TG-3' primer pairs. The genotyping PCR for *ADIPOQ* rs1501299 was conducted using the forward 5'-TGG TCC TTT GGT GCT GAG TT-3' and the reverse 5'-TAC GCC AAG CTT TGC TTT CT-3' primer pairs. The obtained PCR products of *ADIPOQ* rs2241766, rs266729 and rs1501299 were then digested with *Sma*I, *Sap*I and *Bsm*I, respectively, and identified of individual genotype after 3% agarose gel electrophoresis. All the genotypic processing was repeated by two expert researchers independently and blindly, and their results were 100% concordant to each other. In addition, the success rate of PCR-restrictive fragment length polymorphism (RFLP) is 100%, and the genotypes of 5% of the participants in both the control and CRC patient groups were analyzed by PCR direct sequencing (Genomics BioSci & Tech Co). The concordance between direct sequencing and PCR-RFLP methods was 100%.

Statistical analysis. The Student's *t*-test was applied for the comparison of ages between the CRC cases and the control groups. The fitness of Hardy–Weinberg equilibrium for the control group were performed with the Chi-square test. Pearson's Chi-square or Fisher's exact test (when any cell analyzed was less than 5, such as that in Table V, right panel) was applied to compare the distribution of the *ADIPOQ* genotypes among the subgroups. The associations

Table I. *Summary of selected data from 362 patients with colorectal cancer and 362 matched non-cancer healthy controls.*

Characteristic	Controls (n=362)		Cases (n=362)		*p*-Value[a]
	n	%	n	%	
Age (years)					
≤60	93	25.7%	95	26.2%	0.8654
>60	269	74.3%	267	73.8%	
Gender					
Male	209	57.7%	203	56.1%	0.6525
Female	153	42.3%	159	43.9%	
BMI					
<24			193	53.3%	
≥24			169	46.7%	
Tumor size (cm)					
<5			195	53.9%	
≥5			167	46.1%	
Location					
Colon			257	71.0%	
Rectum			105	29.0%	
Lymph node involvement					
Negative			210	58.0%	
Positive			152	42.0%	

SD, Standard deviation; BMI, body mass index; [a]based on Chi-square test without Yates' correction.

between *ADIPOQ* genotypes and CRC risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. Statistically, any difference at $p<0.05$ was taken as significant between the two groups compared.

Results

The distributions of age, gender and BMI for the 362 CRC patients and 362 non-cancer healthy controls are presented in Table I (Table I, top panel). In addition, the tumor size, occurred location, and lymph node involvement are also summarized in Table I (Table I, bottom panel). Since we adopted the frequency matching methodology to include those non-cancer healthy citizens as controls, the statistical results showed that there was no difference in respect to the distribution of age and gender between the control and case groups (both $p>0.05$) (Table I, top panel). CRC patients with small (<5 cm) and large (≥5 cm) tumor sizes were 195 (53.9%) and 167 (46.1%), respectively. CRC patients with tumor location at colon and rectum were 257 (71.0%) and 105 (29.0%), respectively. CRC patients with and without lymph node involvement were 152 (42.0%) and 210 (58.0%), respectively (Table I, bottom panel).

The distribution of *ADIPOQ* rs2241766, rs266729 and rs1501299 genotypic frequencies among the 362 non-cancer healthy controls and the 362 CRC patients are presented in Table II. First, in the Hardy-Weinberg equilibrium examination, the results showed that all *ADIPOQ* rs2241766, rs266729 and rs1501299 genotypic frequencies in the control group complied well with the Hardy-Weinberg equilibrium (all $p>0.05$). Secondly, the results showed that the genotypes of *ADIPOQ* rs2241766 among Taiwanese were not differently distributed between the case and the control groups (p for trend=0.6148) (Table II, top panel). Thirdly, the genotypes of *ADIPOQ* rs266729 were differently distributed between the case and the control groups (p for trend=0.0233) (Table II, middle panel). In detail, the *ADIPOQ* rs266729 homozygous variant GG but not the heterozygous CG was associated with increased CRC risk, compared with the wild-type CC genotype (p=0.0075 and 0.1829, respectively; Table II middle panel). After being adjusted for confounding factors age, gender, smoking, alcohol and betel quid consumption, and BMI status, the ORs for homozygous variant GG and the heterozygous CG were 1.94 and 1.22, respectively (95%CI=1.23-1.98 and 0.91-1.64). In the dominant analyzing model, there was still an association between the combined CG+GG of *ADIPOQ* rs266729 and CRC risk, compared with CC wild-type genotype (adjusted OR=1.63, 95%CI=1.14-1.93, p=0.0001, Table II middle panel). Last, the genotypes of *ADIPOQ* rs1501299 were not differently distributed between the case and the control groups (p for trend=0.8921), either (Table II, bottom panel).

In order to validate the findings in Table II, the analysis of allelic frequency distribution for the *ADIPOQ* rs2241766, rs266729 and rs1501299 was further conducted and the

Table II. *Distribution of ADIPOQ rs2241766, rs266729 and rs1501299 genotypic frequencies among colorectal cancer patients and healthy controls*

	Cases, n (%)	Controls, n (%)	Adjusted OR (95% CI)[a]	*p*-Value[b]
rs2241766				
TT	195 (53.9)	189 (52.2)	1.00 (Reference)	
GT	137 (37.8)	148 (40.9)	0.91 (0.64-1.24)	0.4880
GG	30 (8.3)	25 (6.9)	1.14 (0.75-2.17)	0.6014
GT+GG	167 (46.1)	173 (47.8)	0.95 (0.72-1.26)	0.6550
p_{trend}				0.6148
rs266729				
CC	167 (46.1)	195 (53.9)	1.00 (Reference)	
CG	146 (40.3)	138 (38.1)	1.22 (0.91-1.64)	0.1829
GG	49 (13.6)	29 (8.0)	1.94 (1.23-2.98)	0.0075*
CG+GG	195 (53.9)	167 (46.1)	1.63 (1.14-1.93)	0.0001*
p_{trend}				0.0233*
rs1501299				
GG	183 (50.6)	185 (51.1)	1.00 (Reference)	
GT	146 (40.3)	141 (39.0)	1.08 (0.71-1.43)	0.7716
TT	33 (9.1)	36 (9.9)	1.03 (0.55-1.47)	0.7718
GT+TT	179 (49.4)	177 (48.9)	1.06 (0.78-1.49)	0.8818
p_{trend}				0.8921

OR, Odds ratio; CI, confidence interval. [a]Data have been adjusted for confounding factors age, gender, smoking, alcohol and betel quid consumption, and BMI status. [b]Based on Chi-square test without Yates' correction. *Statistically significant.

Table III. *Allelic frequencies for ADIPOQ rs2241766, rs266729 and rs1501299 polymorphisms among colorectal cancer patients and healthy controls.*

Allelic type	Cases, n (%) n=724	Controls, n (%) n=724	Adjusted OR (95% CI)[a]	*p*-Value[b]
rs2241766				
Allele T	527 (72.8)	526 (72.7)	1.00 (Reference)	
Allele G	197 (27.2)	198 (27.3)	0.96 (0.74-1.34)	0.9530
rs266729				
Allele C	480 (66.3)	528 (72.9)	1.00 (Reference)	
Allele G	244 (33.7)	196 (27.1)	1.41 (1.14-1.78)	0.0061*
rs1501299				
Allele G	512 (70.7)	511 (70.6)	1.00 (Reference)	
Allele T	212 (29.3)	213 (29.4)	0.97 (0.74-1.39)	0.9540

OR, Odds ratio; CI, confidence interval. [a]Data have been adjusted for confounding factors age, gender, smoking, alcohol and betel quid consumption, and BMI status. [b]Based on Chi-square test without Yates' correction. *Statistically significant.

results are shown in Table III. Consistent with the findings that genotype of *ADIPOQ* rs266729 was associated with CRC risk, the variant allele G was found at 33.7% in the case group, significantly higher than that of 27.1% in the control group (p=0.0061) (Table III, middle panel). At the same time, there was no such difference found in the analysis for *ADIPOQ* rs2241766 and rs1501299 (Table III, top and bottom panels).

Demographic variables, such as age, gender, familial CRC history, diets high in calories and animal fat, alcohol consumption, and obesity, in addition to other factors, such as tumor site, size, grade, histologic type, TNM stage, and carcinoembryonic antigen (CEA) level, have all been found to significantly affect survival in CRC (44-47). Since smoking and alcohol drinking habits are well-known risk factors for CRC in Taiwan, we were interested in investigating the interactions between the genotype of *ADIPOQ* rs266729 with personal cigarette smoking and alcohol drinking status. Firstly, among those non-smokers, people with *ADIPOQ* rs266729 CG and GG genotypes were at 1.16- and 1.87-fold odds of having CRC (95%CI=0.81-1.67 and 1.06-3.32, p=0.4017 and 0.0297, respectively)

Table IV. *Odds ratios for ADIPOQ rs266729 genotype and colorectal cancer after stratification by smoking status.*

Genotype	Non-smokers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value	Smokers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
CC	148	127	1.00 (ref)	1.00 (ref)		47	40	1.00 (ref)	1.00 (ref)	
CG	107	107	1.16 (0.81-1.67)	1.19 (0.79-1.72)	0.4017	31	39	1.48 (0.79-2.78)	1.34 (0.64-2.59)	0.2252
GG	23	37	1.87 (1.06-3.32)	1.74 (1.03-2.59)	0.0297*	6	12	2.35 (0.81-6.83)	1.98 (0.73-4.79)	0.1100
Total	278	271				84	91			

aBy multivariate logistic regression analysis; bby multivariate logistic regression analysis after adjusted for confounding factors age, gender, alcohol and betel quid consumption, and BMI status; *Statistically significant; CI, Confidence interval; aOR, adjusted odds ratio.

Table V. *Odds ratios for ADIPOQ rs266729 genotype and colorectal cancer after stratification by alcohol drinking status.*

Genotype	Non-drinker, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value	Drinkers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
CC	164	145	1.00 (ref)	1.00 (ref)		31	22	1.00 (ref)	1.00 (ref)	
CG	121	130	1.22 (0.87-1.70)	1.18 (0.76-1.69)	0.2519	17	16	1.33 (0.55-3.18)	1.24 (0.48-3.12)	0.5264
GG	26	43	1.87 (1.09-3.20)	1.74 (1.14-2.95)	0.0208*	3	6	2.81 (0.64-12.50)	2.42 (0.58-9.87)	0.2773
Total	311	318				51	44			

[a]By multivariate logistic regression analysis; [b]by multivariate logistic regression analysis after adjusted for confounding factors age, gender, smoking and betel quid consumption, and BMI status; *Statistically significant; CI, Confidence interval; aOR, adjusted odds ratio.

conferring risky effect, while a non-significant effect was observed in the case for those smokers (Table IV). After adjusting for age, gender, alcohol drinking, betel quid chewing and BMI status, the statistical significance still existed at a similar level (Table IV, left panel). Secondly, among non-drinkers, those with CG and GG genotypes at *ADIPOQ* rs266729 were at 1.22- and 1.87-fold odds of having CRC (95%CI=0.87-1.70 and 1.09-3.20, p=0.2519 and 0.0208, respectively) conferring a risk effect, while a non-significant effect was observed among those drinkers (Table V). After adjusting for age, gender, smoking, betel quid chewing and BMI status, the results were still the same for both non-drinker and drinker groups (Table V).

The correlations between genotypes of *ADIPOQ* rs266729 and clinicopathological features among the 362 CRC patients were analyzed and the results are shown in Table VI. No statistically significant correlation was observed between *ADIPOQ* rs266729 genotypic distributions and age, gender, tumor size, location or metastasis status (all p>0.05) (Table VI). Interesting, the percentages of CG and GG genotypes of *ADIPOQ* rs266729 were statistically higher among the patients with larger BMI (≥24) than those with smaller BMI (<24) (p=0.0162) (Table VI, middle panel).

Discussion

In the literature, mounting epidemiological evidence has demonstrated that obesity may increase the risk of several types of cancer, including CRC (48-50). Some reports have also shown that in obese subjects, serum levels of ADIPOQ are much lower than those in non-obese (51, 52). It is reasonable to hypothesize that decreased levels of ADIPOQ in the blood may be associated with the increased risk for CRC (53-56), and furthermore, the genotypes of *ADIPOQ* may contribute to the association. Supporting this notion, it is reported that ADIPOQ may suppress the cell growth in preneoplastic colonic lesions *via* several molecules such as leptin and NF-κB (57). In the literature, several investigations have shown that specific genotypes of *ADIPOQ* were associated with the levels of ADIPOQ in human blood, such as *ADIPOQ* rs266729, rs1501299 and rs2241766 (58-60). Noticeably, the G allele at *ADIPOQ* rs266729 was significantly associated with lower ADIPOQ levels (61), and the lower ADIPOQ levels was associated with elevated CRC risk (54, 55).

In the current study, we firstly examined the contribution of *ADIPOQ* rs266729, rs1501299 and rs2241766 genotypes to CRC susceptibility in Taiwan, where CRC is the highest

Table VI. *Correlation between ADIPOQ rs266729 genotypes and clinicopathological properties of 362 colorectal cancer patients.*

Characteristics	Case number	Genotypes			*p*-Value[a]
		CC (%)	CG (%)	GG (%)	
Age (years)					
≤60	95	46 (48.4)	39 (41.1)	10 (10.5)	
>60	267	121 (45.3)	107 (40.1)	39 (14.6)	0.5991
Gender					
Male	203	97 (47.8)	80 (39.4)	26 (12.8)	
Female	159	70 (44.0)	66 (41.5)	23 (14.5)	0.7590
BMI					
<24	193	101 (52.3)	73 (37.8)	19 (9.8)	
≥24	169	66 (39.1)	73 (43.2)	30 (17.7)	0.0162*
Tumor size					
<5 cm	195	91 (46.7)	79 (40.5)	25 (12.8)	
≥5 cm	167	76 (45.5)	67 (40.1)	24 (14.4)	0.9096
Location					
Colon	257	111 (43.2)	108 (42.0)	38 (14.8)	
Rectum	105	56 (53.3)	38 (36.2)	11 (10.5)	0.1907
Lymph node involvement					
Negative	210	99 (47.2)	82 (39.0)	29 (13.8)	
Positive	152	68 (44.7)	64 (42.1)	20 (13.2)	0.8425

[a]Based on Chi-square test without Yates's correction; *Statistically significant.

prevalent cancer in the country for many years. The results showed that the genotypes of *ADIPOQ* rs266729, which locates at the promoter region of the genes and is most likely to determine the expression level of it, are associated with risk of CRC in Taiwan (Table II). Noticeably, the GG genotype and the G allele of *ADIPOQ* rs266729 were significantly associated with elevated risk to CRC (Tables II and III). At the same time, there was no significant association as for the genotypes at *ADIPOQ* rs1501299 or rs2241766 with CRC for Taiwanese (Tables II and III). As far as we are aware of, the current study is the first to reveal the genotypic contribution of *ADIPOQ* promoter genotypes to CRC in Taiwan and this positive finding is consistent with previous investigations in American (37), Germany (62), and Japanese (63) populations.

As for the personal habits, we analyzed the interactions of *ADIPOQ* rs266729 genotype with smoking and alcohol drinking behaviors, finding that the genotypic contribution of *ADIPOQ* rs266729 genotype to CRC risk is more obvious among those non-smokers and non-alcohol drinkers, but not among those smokers or alcohol drinkers (Tables IV and V). The detailed mechanisms need further investigation. As for the clinical features, we did not find any correlation between the *ADIPOQ* rs266729 genotype with age, gender, tumor size, location or lymph node metastasis status, while there is synergistically an obvious interaction of *ADIPOQ* rs266729 and BMI (Table VI). It seems that those with BMI ≥24 and carrying G allele at *ADIPOQ* rs266729 in their genome may have higher risk of CRC. The detail mechanisms and the prognosis of these people are of our interest in further investigations in the near future.

In the future, there are several directions for us to conduct further studies investigating the contribution of ADIPOQ pathway in CRC. First, there are several other SNPs that may regulate the expression of activity of ADIPOQ, worthy of figuring out their roles in CRC (36). Secondly, we have to pay more attention to the receptors of ADIPOQ. ADIPOQ has been proposed as a biological link between obesity and various types of malignancies, such as CRC, through its actions mediated by binding and activating specific ADIPOQ receptors, ADIPOQ receptor 1 (AdipoR1) and ADIPOQ receptor 2 (AdipoR2) (64). These two types of ADIPOQ receptors have been identified to link ADIPOQ to the activation of adenosine monophosphate (AMP)-activated protein kinases, which help ADIPOQ to inhibit the proliferation of cancer cells (65). According to their differential distribution in the human body to conduct their individual functions, AdipoR1 and AdipoR2 are predominantly abundant in skeletal muscle cells and liver cells, respectively (66). AdipoR2 is a protein encoded by the AdipoR2 gene (67), in charge of mediating lots of metabolic processes such as oxidation of fatty acid and cell intake of glucose by ADIPOQ (68). Notably, the two types of ADIPOQ receptors are both reported to be expressed in human cancer cells, such as CRC, breast and prostate cancer, and mediate the anti-proliferative behaviors of ADIPOQ in these cancer cells (69). Supporting the idea that the ADIPOQ pathway indeed plays a critical role in CRC etiology, several single nucleotide polymorphisms

(SNPs) on the *ADIPOQ* or its receptor genes, such as rs1342387 and rs1063538, were reported to associate with CRC risk (18, 35, 62, 69). From the genomic viewpoint, two polymorphic sites on the *AdipoR2* gene, rs10773989 and rs1044471, have been reported to be associated with type-2 diabetes, prostate and gastric cancer (70-72). However, such associations between the polymorphic genotypes on *AdipoR2* and CRC remain inconclusive (37, 73). In the future, we are going to examine the contribution of the genotypes of ADIPOQ receptors to CRC, and analyze the interactions of genotypes for ADIPOQ and ADIPOQ receptors on CRC.

In conclusion, this study investigated the contribution of *ADIPOQ* genotypes and their interaction with demographic and behavioral status to determine personal susceptibility to CRC. The GG genotypes of *ADIPOQ* rs266729 may cause a relatively low level of ADIPOQ in the blood, defect its suppressive influence on CRC cell growth and proliferation, and increase the personal risk of CRC, especially for those with BMI ≥24.

Conflicts of Interest

All the Authors have declared no conflicts of interest regarding this study.

Authors' Contributions

Research design: Hung YC, Pei JS, Chou AK; patient and questionnaire summaries: Yang MD, Yang HR; experimental work: Wang YC, Chang WS, Hsiau YC; statistical analysis: Yang TM, Chen CP, Chen CC, Yu CC; manuscript writing: Yu CC, Tsai CW, Bau DT; review & revision: Chang WS, Tsai CW, Yu CC, Bau DT.

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