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Association of *hTERT* Gene Polymorphism and Colorectal Cancer (CRC) Risk in the Chinese Han Population

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The catalytic subunit telomerase reverse transcriptase (hTERT) is a prerequisite for malignant transformation of human cells. Colorectal cancer (CRC) is a common malignant tumor. The genetic association of *hTERT* gene rs2853669 and rs2736098 polymorphisms with CRC was surveyed in the Chinese population. Two hundreds patients with CRC and 200 healthy controls were taken for blood sample collection. Sanger sequencing was applied for genotyping. Multiple logistic regression analysis was performed, and odds ratio (OR) together with confidence interval (CI) were calculated to obtain the corresponding association power. Among CRC cases (49.50%), *hTERT* gene rs2736098 GA genotype carriers were more prevalent compared with the control group (41.00%, $P = 0.035$), which increased the risk of CRC by 1.576 times (95% CI, 1.031-2.409). Distribution of the rs2736098 genotypes was significantly associated with TNM stage, tumor differentiation, tumor size and lymph node metastasis ($P < 0.05$). The frequencies of *hTERT* gene rs2853669 polymorphism were not significantly different between CRC patients and healthy controls. Logistic regression analysis indicated that both body mass index (BMI) and *hTERT* gene rs2736098 polymorphism remained significantly correlated with CRC susceptibility. The frequencies of *hTERT* gene rs2853669 polymorphism did not differ significantly between CRC patients and control group ($P > 0.05$). The *hTERT* gene rs2736098 polymorphism was correlated with CRC risk in the Chinese Han population, and the GA genotype was a risk element for the onset of CRC.

Keywords: colorectal cancer; genetic predisposition; *hTERT* gene; logistic regression; SNP
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Introduction

Colorectal cancer (CRC) is a common malignant tumor of digestive tract, with high morbidity and mortality in the world (Dekker et al. 2019). By 2020, the number of CRC cases diagnosed worldwide will reach 1.93 million (Benmokhtar et al. 2022). Epidemiological studies show that CRC has become the third most dominant cancer and the fifth leading cause of death related to cancer in China (Liu et al. 2018a; Wu et al. 2023). Dietary habits, obesity, lack of physical exercise, and large amounts of alcohol are important causes of CRC, such as long-term high-fat and low-fiber diets, and love to eat barbecue, pickled and processed foods (Baidoun et al. 2021). The incidence of CRC increases rapidly after the age of 40 and is higher in men than in women (Mobley and Kuo 2015). CRC generally takes 5-10 years to progress from precancerous lesions to cancer, which offers a vital time window for early diagnosis

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and timely therapeutic intervention of the disease (Mahmoud 2022). A large number of studies and practices have shown that CRC screening and early diagnosis and treatment can effectively reduce the mortality of CRC (Heinimann 2018). Currently, colonoscopy is the cheapest and most accurate "gold standard" for detecting early colorectal cancer (Gupta 2022). However, because colonoscopy is an invasive procedure, its acceptance is low.

Genetic factors are one of the important causes of CRC (Picard et al. 2020). Studies have shown that about 5% to 10% of CRC are caused by genetic factors (Faghani et al. 2012). Some specific genetic variants can increase an individual's risk of colorectal cancer, such as *MLH1*, *MSH2*, *MSH6* and *PMS2*, which play a key role in DNA repair and apoptosis (Schafmayer et al. 2007; Wang et al. 2012; Mik et al. 2017). Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic variation and constitute a major part of phenotypic diversity between individuals. SNP refers to DNA sequence polymorphisms caused by single base variation at the nucleotide level of the genome. The catalytic subunit telomerase reverse transcriptase (hTERT) is one of the components of the core telomerase complex, and its expression is a prerequisite for the malignant transformation of human cells (Assani et al. 2018). Further studies have found that hTERT is a key factor in tumor invasion and metastasis of various cancer, including gastric cancer, liver cancer and esophageal cancer (Lamy et al. 2013). For CRC, hTERT is determined to promote cancer progression via stimulating epithelial-to-mesenchymal transition (EMT) (Qin et al. 2016). *hTERT* gene is located on human chromosome 5p15.33, and its gene polymorphisms have been determined to be related to chromosomal instability and increased cancer risk (Iizuka et al. 2013). Rs2853669 (−245T > C) and rs2736098 are two common functional SNPs in the promoter region of *hTERT* gene, and can influence the telomerase activity and telomere length (Oztas et al. 2016). In previous studies, *hTERT* gene rs2853669 and rs2736098 polymorphisms are detected in multiple tumors, such as gastric cancer, melanoma, hepatocellular carcinoma and so on (Bayram et al. 2016; Li et al. 2016; Yalinbas Kaya and Ulger 2022). In terms of CRC, the genetic association of *hTERT* gene rs2853669 with CRC has been studied in the Turkish population, but the results are conflicting (Yalinbas Kaya and Ulger 2022). Another study in the Turkish population reported by Jannuzzi et al. (2015) has determined the positive association of *hTERT* gene rs2736098 polymorphism with an increased risk of CRC. In light of these findings, the association between *hTERT* gene polymorphic loci and susceptibility to cancers is strongly race-specific. However, there are no enough researches illustrating the relaionship of the *hTERT* gene polymorphisms with CRC, and this correlation has not been examined in the Chinese population. It was hypothesized that *hTERT* gene rs2853669 and rs2736098 polymorphisms may be influence factors related to the development of CRC in the Chinese population.

Therefore, the genetic association of *hTERT* gene rs2853669 and rs2736098 polymorphisms with CRC was surveyed by taking 200 patients with CRC and 200 healthy controls in the Chinese Han population.

Materials and Methods

Study participants

In this study, a case-control study was performed to assess the genetic association between 200 patients with CRC and 200 healthy controls. A total of 200 patients who were diagnosed with CRC in West China Hospital of Sichuan University were enrolled as the case group. The CRC was diagnosed based on the colonoscopy and pathological examination results. Patients with histologically confirmed CRC newly diagnosed were enrolled in this

Table 1. The detailed information of two study groups.

Characteristics	Healthy controls	CRC group	*P* values
Age, years	55.36 ± 7.78	54.25 ± 8.24	0.213
Sex, n (%)			0.762
Female	114 (57.00)	111 (55.50)	
Male	86 (43.00)	89 (44.50)	
BMI, n (%)			0.034*
< 25 kg/m^2	98 (49.00)	77 (38.50)	
≥ 25 kg/m^2	102 (51.00)	123 (61.50)	
Risky drinking, n (%)			0.432
No	149 (74.50)	142 (71.00)	
Yes	51 (25.50)	58 (29.00)	
Smoking, n (%)			0.156
No	123 (61.50)	109 (54.50)	
Yes	77 (38.50)	91 (45.50)	
Tumor location, n (%)			
Left		68 (34.00)	
Rectum		102 (51.00)	
Right		30 (15.00)	
TNM stage, n (%)			
I		37 (18.50)	
II		63 (31.50)	
III		81 (40.50)	
IV		19 (9.50)	
Differentiation, n (%)			
Low		103 (51.50)	
High		97 (48.50)	
Tumor size, n (%)			
< 5 cm		111 (55.50)	
≥ 5 cm		89 (44.50)	
Lymph node metastasis, n (%)			
N0		103 (51.50)	
N1		57 (28.50)	
N2		40 (20.00)	

Data are shown as mean ± SD, or n (%).
* means a significant difference.
BMI, body mass index; CRC, colorectal cancer.

study. Exclusion criteria were: (1) patients with neuroendocrine carcinoma; (2) with malignant melanoma, (3) gastrointestinal stromal tumor, (4) with metastatic colorectal carcinoma. Other 200 healthy controls who underwent physical examination during the same period were recruited as the control group. Controls were excluded if they had history of gastrointestinal disease or any chronic diseases. The basic information including age, sex, body mass index (BMI), history of drinking and smoking was recorded in detail. In addition, the pathological features of tumors were also recorded, including tumor location, TNM stage, tumor differentiation, tumor size and lymph node metastasis. The study was designed with the approval of the ethics committee of West China Hospital of Sichuan University.

DNA extraction

Blood sample was taken from each participant at diagnosis before treatment initiation. Genomic DNA extraction was processed in the TaKaRa Genome DNA Extraction Kit (Dalian Biological Engineering CO., LTD., Dalian, Liaoning, China) according to the manufacturer's instructions. Extracted DNAs were dissolved in sterile distilled water, then frozen at −20°C for standby application after the quantity and quality evaluation using the Qubit® fluorometer (Invitrogen, Carlsbad, CA, USA).

Genotyping

The genotyping of *hTERT* gene rs2853669 and rs2736098 polymorphism was processed via direct sequencing. Firstly, the target DNA fragments were amplified via polymerase chain reaction (PCR) using StepOnePlus real-time PCR system (Applied Biosystems, Foster City, CA, USA). And primers used for the amplification were designed in Primer Premier 5.0 software and synthesized by Sangon Biotech (Shanghai, China). Primer sequences were: rs2853669, forward 5′-CAGCGCTGCCT GAAACTC-3′ and reverse 5′-GTCCTGCCCCTTCAC CTT-3′; rs2736098, forward 5′-GCCAGACCCGCCGA AGAAG-3′ and reverse 5′-GCGCGTGGTTCCCAAG CAG-3′. The PCR cycling conditions were as follows: initial degeneration at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at 60°C for 1 min, and a final extension at 72°C for 7 min. Then the PCR products with a 260-/280-nm purity absorbance ratio of 1.8-21 were employed as templates for Sanger sequencing by the Sangon Biotech Company.

Statistical analysis

All statistical analyses were processed in SPSS 21.0 software and the figure was drawn in GraphPad 7.0 software. The age of each group was summarized as the mean and standard deviation (SD), and the student's *t* test was used to compare the difference between two groups. Chi-square test was applied to compare enumeration data, including sex, BMI, drinking and smoking, which was expressed as number and percentage (%). Odds ratio (OR) together with confidence interval (CI) were calculated to obtain the corresponding association power. Multiple logistic regression analysis was done to evaluate the relationship of age (< 55 years old = 0; 1: ≥ 55 years old = 1), sex (female = 0; male = 1), BMI (< 25 kg/m^2 = 0; ≥ 25 kg/m^2 = 1), drinking (No = 0; Yes = 1), smoking (No = 0; Yes = 1) and rs2736098 polymorphism (GG = 0; GA/AA = 1) with the onset of CRC, and the results were shown in forest map. $P < 0.05$ was accepted as the criterion of significant difference. The Hardy Weinberg equilibrium (HWE) test was applied for each polymorphism in both case and control groups, and $P < 0.05$ indicates deviation from HWE.

Table 2. The genotype and allele frequencies of *hTERT* gene polymorphisms.

Genotype/Allele	Healthy controls (n = 200)	CRC (n = 200)	χ^2	OR (95% CI)	*P* values
Rs2853669					
CC	70 (35.00)	59 (29.50)	-	1	-
CT	104 (52.00)	109 (54.50)	0.950	1.243 (0.802-1.928)	0.330
TT	26 (13.00)	32 (16.00)	1.426	1.460 (0.783-2.722)	0.232
C	244 (61.00)	227 (56.75)	-	1	-
T	156 (39.00)	173 (43.25)	1.492	1.192 (0.899-1.580)	0.222
P^{HWE}	0.189	0.119			
Rs2736098					
GG	94 (47.00)	72 (36.00)		1	-
GA	82 (41.00)	99 (49.50)	4.441	1.576 (1.031-2.409)	0.035*
AA	24 (12.00)	29 (14.50)	2.080	1.578 (0.847-2.938)	0.149
G	270 (67.50)	243 (60.75)		1	-
A	130 (32.50)	157 (39.25)	3.961	1.342 (1.004-1.793)	0.047*
P^{HWE}	0.354	0.591			

* means a significant difference.
CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

Results

General characteristics of the study groups

The general characteristics of the two study groups are displayed in Table 1. In both the case and control groups, more than half of cases aged more than 50 years old, which showed no significant difference between the two groups ($P > 0.05$). One hundred fourteen females and 86 males constituted the control group, while 111 females and 89 males made up the CRC group. The sex distribution had no statistical difference between the two groups ($P > 0.05$). In addition, number of the risky drinking and smoking participants also did not differ from the case and the control groups ($P > 0.05$). Notably, a large proportion of CRC participants had high values of BMI compared with the control group, and a significant difference was detected ($P < 0.05$). Besides, the pathological features of tumors were also recorded, including tumor location, TNM stage, tumor differentiation, tumor size and lymph node metastasis.

The genotype and allele frequencies of hTERT gene polymorphisms in the two study groups

To analyze the association of *hTERT* gene polymorphisms and CRC risk, Chi-square test was performed for the genotype and allele distribution comparison between the case and control groups. Deviation from HWE was cal-

Table 3. Association of *hTERT* gene rs2736098 polymorphism with colorectal cancer (CRC) patients' characteristics.

Characteristics	GG (n = 72)	GA/AA (n = 128)	*P* values
Age, n (%)			0.213
< 50	21 (29.17)	35 (27.34)	
≥ 50	51 (70.83)	93 (72.66)	
Sex, n (%)			0.991
Female	40 (55.56)	71 (55.47)	
Male	32 (44.44)	57 (44.53)	
BMI, n (%)			0.698
< 25 kg/m^2	29 (40.28)	48 (37.50)	
≥ 25 kg/m^2	43 (59.72)	80 (62.50)	
Risky drinking, n (%)			0.542
No	53 (73.61)	89 (69.53)	
Yes	19 (26.39)	39 (30.47)	
Smoking, n (%)			0.508
No	37 (51.39)	72 (56.25)	
Yes	35 (48.61)	56 (43.75)	
Tumor location, n (%)			0.988
Left	24 (33.33)	44 (34.38)	
Rectum	37 (51.39)	65 (50.78)	
Right	11 (15.28)	19 (14.84)	
TNM stage, n (%)			0.010*
I	18 (25.00)	19 (14.84)	
II	29 (40.28)	34 (26.56)	
III	22 (30.56)	59 (46.09)	
IV	3 (4.16)	16 (12.50)	
Differentiation, n (%)			0.001**
Low	26 (36.00)	77 (60.16)	
High	46 (63.89)	51 (39.84)	
Tumor size, n (%)			0.001**
< 5 cm	51 (70.83)	60 (46.88)	
≥ 5 cm	21 (29.17)	68 (53.12)	
Lymph node metastasis, n (%)			0.009**
N0	46 (63.89)	57 (44.53)	
N1	19 (26.39)	38 (29.69)	
N2	7 (9.72)	33 (25.78)	

BMI, body mass index.
*$P < 0.05$; **$P < 0.01$.

culated, and $P > 0.05$ indicated that the two variants were in accordance with HWE in the population. As shown in Table 2, the frequencies of *hTERT* gene rs2853669 polymorphism were not significantly different between CRC patients and healthy controls ($P > 0.05$). For allelic analysis, individuals carrying the T allele had a tendency to increased risk of CRC (OR = 1.192, 95% CI = 0.899-1.580), but it was not significant ($P = 0.222$).

The genotype and allele frequencies of *hTERT* gene rs2736098 polymorphism differed statistically significantly between the CRC group and healthy controls. Among CRC cases (49.50%), the GA genotype carriers were more prevalent compared with the control group (41.00%, $P = 0.035$), which increased the risk of CRC by 1.576 times (95% CI = 1.031-2.409). In addition, individuals carrying A allele had 1.342 times more risk (95% CI = 1.004-1.793, $P = 0.047$) of developing CRC than the G allele carriers.

Correlation of hTERT gene rs2736098 genotype frequencies with clinicopathological characteristics of the CRC participants

Table 3 presented the correlation of *hTERT* gene rs2736098 genotype frequencies with clinicopathological characteristics of the CRC participants. Distribution of the rs2736098 genotypes was significantly associated with TNM stage, tumor differentiation, tumor size and lymph node metastasis ($P < 0.05$). In detail, there was a higher trend that the GA/AA carriers had a larger proportion of high TNM stage ($P = 0.010$), low tumor differentiation ($P = 0.001$), large tumor size ($P = 0.001$), and larger lymph node metastasis ($P = 0.009$) compared with the GG genotype carriers, and the differences reached significant levels.

Independent relationship of hTERT gene rs2736098 polymorphism with CRC risk

The demographic indicators and general clinical indicators shown in Table 1 were set as the confound factors, which were included in the multivariate logistic regression model to identify factors independently related to CRC risk. OR values were adjusted by age, sex, BMI, risky drinking, smoking and *hTERT* gene rs2736098 polymorphism (Fig. 1). In this model, both BMI and *hTERT* gene rs2736098 polymorphism remained significantly correlated with CRC susceptibility. BMI has an OR value of 1.55 (95% CI = 1.04-2.32), while rs2736098 had the OR value of 1.61 (95% CI = 1.07-2.42). Compared with GG genotype, GA/AA genotypes conferred a significantly increased risk for CRC (adjusted OR = 1.61; 95% CI = 1.07-2.42).

Discussion

CRC is a deadly disease around the world, and familial predisposition and genetic factors are important elements in the occurrence of CRC. hTERT is a key element in telomerase activity, which serves as the core of the core telomerase complex (Pang et al. 2017). The association of hTERT with tumor cell proliferation, migration and invasion has been reported in some malignant tumors (Leao et al. 2018). Studies have presented that SNPs in *hTERT* gene are closely related to an increased risk of cancers (Leao et al. 2018). In studies conducted in the Turkish population, *hTERT* gene rs2853669 and rs2736098 polymorphisms are investigated in CRC, and negative correlations are detected between rs2853669 and rs2736098 polymorphisms and CRC susceptibility (Jannuzzi et al. 2015; Yalinbas Kaya and Ulger 2022). Currently, our study is the first to investigate the association of *hTERT* gene rs2853669 and rs2736098 polymorphisms with CRC susceptibility in the Chinese Han population. It was found that *hTERT* gene rs2736098 GA genotype was a risk factor for CRC, and cases carrying rs2736098 GA genotype may be at a higher risk of CRC than GG genotype carriers, which was consistent with the results reported in the Turkish population. However, no genetic association was identified between *hTERT* gene rs2853669 polymorphism and CRC risk.

Rs2853669 is located on the upstream of *hTERT* gene promoter region, and its genetic association with various human cancers has been reported in multiple ethnicities,

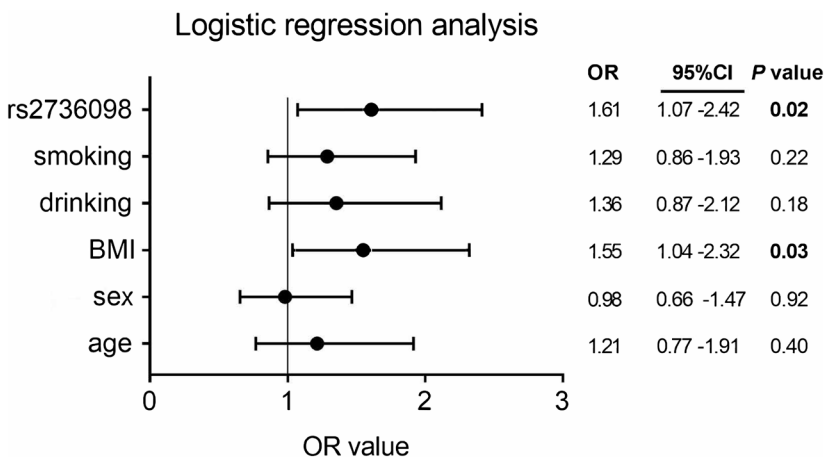

Fig. 1. Forest map of multiple logistic regression analysis results.
Identification of factors related to colorectal cancer (CRC) risk based on multiple logistic regression analysis.

although the results are inclusive (Liu et al. 2018b). A previous study has reported the inhibitory role of rs2853669 in Ets/TCF binding, further affecting the telomere length and telomerase activity (Hosen et al. 2015; Yoo et al. 2015). That might be the participation mechanism of rs2853669 in human cancers. In Asians, an increased risk of lung cancer is detected in CC genotype and C allele carriers in three independent studies (Zhong et al. 2013; Yoo et al. 2015; Xing et al. 2016). Based on the current results, *hTERT* gene rs2853669 polymorphism showed no genetic association reaching statistical significance with CRC susceptibility in the Chinese Han population, which was consistent with the findings reported by Jannuzzi et al. (2015) in the Turkish population. But in another study, Yalinbas Kaya and Ulger (2022) have determined the intimate relationship between rs2853669 and CRC occurrence, which was conflicting with our present findings. It may probably be due to the disparity in sample size and ethnic difference. The findings indicated that different populations might have different tumorigenesis mechanisms of CRC.

In addition, an explosion of the genetic relationship between *hTERT* gene rs2736098 polymorphism and cancer susceptibility has been witnessed in recent years (Zhang et al. 2013). *hTERT* gene rs2736098 polymorphism impacts the telomerase action and curtails telomere length owing to its propensity in the gene regulatory elements (Wang et al. 2017). It has been substantiated from recent studies that the association of variant rs2736098 with cancer risk is in coherence (Qi et al. 2012). According to the current results, individuals carrying rs2736098 GA genotype had an increased probability to suffer from CRC compared with GG genotype carriers. Notably, a number of studies have determined the association between rs2736098 polymorphism and cancer susceptibility which is consistent with the present findings (Wang and Sun 2020). As a recent meta-analysis reported, rs2736098 GA/AA genotypes are identified to be risk factors for the increased risk of overall cancer, and the association is more obvious in Asians (Li et al. 2016). The subsequent analyses stratified by cancer type indicate that rs2736098 is related to susceptibility for lung cancer (OR = 1.18; 95% CI = 1.07-1.29) and hepatocellular carcinoma risk (OR = 1.38; 95% CI = 1.20-1.59) (Li et al. 2016). Moreover, the close association between rs2736098 polymorphism and CRC risk was further determined by multiple logistic regression analysis after adjusting for other clinical indicators. In regard to BMI and CRC risk, previous epidemiological studies have concluded clear associations (Shaukat et al. 2017). Consistently, the current case-control study suggested elevated risk for CRC among individuals with high values of BMI. It was concluded that rs2736098 GA/AA genotypes conferred a significantly increased risk for CRC compared with GG genotype. Similar to our results, the positive association of *hTERT* gene rs2736098 polymorphism with an increased risk of CRC has also been reported by Jannuzzi et al. (2015) in the Turkish population. As a previous study determined, the rs2736098 G allele may enhance hTERT expression and subsequently telomerase activity, which ultimately leads to an increased telomere length and subsequently to a decreased risk of cancer (de Martino et al. 2016). In addition, a close association was also detected between BMI and CRC risk based on the logistic regression model, and high BMI individuals had 1.55 times greater risk of CRC than those who had BMI less than 25.0 kg/m^2. In regard to BMI and CRC risk, previous epidemiological studies have concluded clear associations (Zheng et al. 2018). Consistently, the current case-control study suggested elevated risk for CRC among individuals with high values of BMI.

In conclusion, the current study is the first to determine the relationship between *hTERT* gene rs2736098 polymorphism and CRC risk in the Chinese Han population. Our findings indicated that *hTERT* gene rs2736098 GA genotype was a risk element for the onset of CRC. Of course, since the sample size of this study was relatively small, another study with a larger population is required to verify the present findings in the Chinese population. In addition, due to ethnic differences, the results of this study need to be further verified in other ethnic groups.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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