

APE1 polymorphisms are associated with colorectal cancer susceptibility in Chinese Hans

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Abstract

AIM: To study the association between four base excision repair gene polymorphisms and colorectal cancer risk in a Chinese population.

METHODS: Two hundred forty-seven colorectal cancer (CRC) patients and three hundred cancer-free controls were enrolled in this study. Four polymorphisms (OGG1 Ser326Cys, APE1 Asp148Glu, -141T/G in the promoter region, and XRCC1 Arg399Gln) in components of the base excision repair pathway were determined in patient blood samples using polymerase chain reaction with confronting two-pair primers. The baseline information included age, gender, family history of

cancer, and three behavioral factors [smoking status, alcohol consumption, and body mass index (BMI)]. χ^2 tests were used to assess the Hardy-Weinberg equilibrium, the distributions of baseline characteristics, and the four gene polymorphisms between the cases and controls. Multivariate logistic regression analyses were conducted to analyze the correlations between the four polymorphisms and CRC risk, adjusted by the baseline characteristics. Likelihood ratio tests were performed to analyze the gene-behavior interactions of smoking status, alcohol consumption, and BMI on polymorphisms and CRC susceptibility.

RESULTS: The APE1 148 Glu/Glu genotype was significantly associated with an increased risk of colorectal cancer (OR = 2.411, 95%CI: 1.497-3.886, $P < 0.001$ relative to Asp/Asp genotype). There were no associations between OGG1, XRCC1, or APE1 promoter polymorphisms and CRC risk. A multivariate analysis including three behavioral factors showed that the APE1 148 Glu/Glu genotype was associated with an increased risk for CRC among both smokers and non-smokers, non-drinkers and individuals with a BMI ≥ 25 kg/m² (ORs = 2.356, 3.299, 2.654, and 2.581, respectively). The XRCC1 399 Arg/Gln genotype was associated with a decreased risk of CRC among smokers and drinkers (OR = 0.289, 95%CI: 0.152-0.548, $P < 0.001$, and OR = 0.327, 95%CI: 0.158-0.673, $P < 0.05$, respectively). The APE1 promoter polymorphism -141 T/G genotype was associated with a reduced risk of colorectal cancer among subjects with a BMI < 25 kg/m² (OR = 0.214, 95%CI: 0.069-0.660, $P < 0.05$ relative to T/T genotype). There were significant gene-behavior interactions between smoking status and XRCC1 Arg399Gln, as well as BMI and APE1 -141T/G polymorphism (all $P < 0.05$).

CONCLUSION: APE1 Asp148Glu is associated with increased CRC risk and smoking alters the association between XRCC1 Arg399Gln and CRC risk in the Chinese

Han population.

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Key words: Apurinic endonuclease 1; Base excision repair; Single nucleotide polymorphisms; Colorectal cancer; X-ray repair cross-complementing groups

Core tip: There are discrepancies in reports concerning the association between polymorphisms in genes involved in the base excision DNA repair pathway (OGG1, APE1, and XRCC1) and colorectal cancer susceptibility. This study examines four of these polymorphisms in a Chinese Han population from the southwest region of China. Results show that the APE1 148 Glu/Glu genotype is associated with an increased risk of CRC. Moreover, analyses examining gene-behavior interactions revealed that smoking may influence the relationship between the XRCC1 Arg399Gln polymorphism and CRC risk.

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second most common cancer in females. Incidence rates of CRC are highest in Australia, New Zealand, Europe, and North America and lowest in Africa and South-Central Asia. However, CRC incidence rates are rapidly increasing in several areas historically at low risk, including Spain and a number of countries within Eastern Europe and Eastern Asia^[1]. Approximately 608000 deaths from CRC are estimated worldwide, accounting for 8% of all cancer deaths, making it the fourth most deadly cancer^[2].

Many cancers, including CRC, can be initiated by DNA damage induced by chemical agents, smoking, alcohol consumption, and fat metabolism^[3]. To avoid accumulation of such damage, cells have developed precise and effective DNA repair systems. Base excision repair (BER) is the major DNA repair pathway for most oxidative DNA lesions^[4] that recognizes and repairs base modifications and single strand breaks (SSB)^[5]. BER is initiated by a mono- or bifunctional DNA glycosylase and involves: (1) base lesion recognition, excision, and cleavage of an abasic site; (2) end-processing of SSB termini to generate 3' hydroxyl (OH)/5' phosphate (P) group ends; (3) gap-filling after lesion excision; and (4) nick sealing by DNA ligases^[6]. Three key human proteins involved in the BER and SSB pathways^[7] are X-ray repair cross-complementing protein 1 (XRCC1), which acts as

a scaffold to recruit BER proteins, 8-oxoguanine DNA-glycosylase 1 (OGG1), which participates in generating SSBs with 3' P $\alpha\beta$ unsaturated aldehyde and 5' P termini^[6], and apurinic endonuclease 1 (APE1), the key enzyme responsible for the incision of the apurinic/aprimidinic sites and the generation of 3'-OH termini^[8].

Polymorphisms in genes coding for these three key proteins could affect the accumulation of DNA lesions in colorectal mucosa, thus influencing CRC risk^[9]. Among all the polymorphisms in these proteins, OGG1 Ser326Cys, APE1 Asp148Glu, and XRCC1 Arg399Gln are the most common and well-studied^[4]. Although the associations of OGG1 Ser326Cys and XRCC1 Arg399Gln gene polymorphisms and CRC risk have been inconsistent^[3,10-12], the APE1 Asp148Glu polymorphism is associated with an increased risk of CRC in Turkish and Polish populations^[7,13]. Studies focused on the promoter polymorphism in APE1 (-141T/G) are rare, with only two articles reporting that the APE1 -141G/G genotype was a protective factor in lung cancer risk^[14,15], and one study showing that the variant allele G is associated with a significantly decreased risk for glioblastoma^[16]. A genome-wide association study investigating gene polymorphisms and CRC risk conducted in 2011 identified XRCC1 Arg399Gln among the 6216 single nucleotide polymorphisms within 100 kb of the 157 DNA repair loci, but revealed no relationship between this polymorphism and CRC risk^[17]. Another meta-analysis studied 455 polymorphisms in 110 different genes and showed a protective effect of homozygous variants of XRCC1^[18]. As the associations between these four key gene polymorphisms and CRC are still uncertain in the Chinese population, the aim of this study was to define the relationships between CRC risk and the OGG1 Ser326Cys, APE1 Asp148Glu and the promoter variation -141T/G, and XRCC1 Arg399Gln polymorphisms in the Chinese Han population.

MATERIALS AND METHODS

Study population

The study population included 247 cancer patients (60 with colon cancer and 187 with rectal cancer) and 300 cancer-free controls admitted to the Daping Hospital from January 2006 to December 2012. All subjects were Han Chinese from the southwest area of China between 20 and 90 years of age with complete demographic and behavioral information. Patients and controls were matched for age and gender. Pathological confirmation for all cancer patients was performed, and control subjects had no tumor history before or during the study. The study protocol was approved by the ethics committee of Daping Hospital and informed consent was obtained from each participant.

A uniform questionnaire was used for all subjects regarding sociodemographic characteristics, smoking status, alcohol consumption, body mass index (BMI), and other potential confounding factors. Subjects were considered smokers if they were a current or past smoker before the

Table 1 Primer sequences

Target gene	Sequence of primers	Allele and PCR product size (bp)
OGG1 Ser326Cys	F1: 5'-CAGCCCAGACCCAGTGGACTC-3' R1: 5'-TGGCTCCTGAGCATGGCGGG-3'	C allele (252 bp)
	F2: 5'-CAGTGCCGACCTGCGCCAATG-3' R2: 5'-GGTAGTCACAGGGAGGCCCC-3'	G allele (194 bp)
XRCC1 Arg399Gln	F1: 5'-TCCCTGCGCCGCTGCAGTTTCT-3' R1: 5'-TGGCGTGTGAGGCCCTACCTCC-3'	G allele (447 bp)
	F2: 5'-TCGGCGGCTGCCTCCCA-3' R2: 5'-AGCCCTCTGTGACCTCCCAGGC-3'	A allele (222 bp)
APE1 Asp148Glu	F1: 5'-CCTACGGCATAGGTGAGACC-3' R1: 5'-TCCTGATCATGCTCCTCC-3'	G allele (167 bp)
	F2: 5'-TCTGTTTCATTCTATAGCGAT-3' R2: 5'-GTCAATTCTTCATGTGCCA-3'	T allele (236 bp)
APE1 promoter -141T/G	F1: 5'-CTAACTGCCAGGGACGCCGA-3' R1: 5'-ACACTGACTTAAGATTCTAACTA-3'	T allele (136 bp)
	F2: 5'-ACTGTTTTTTCCCTCTGCACAG-3' R2: 5'-TGAGCAAAAGAGCAACCCCG-3'	G allele (335 bp)

PCR: Polymerase chain reaction; OGG1: 8-oxoguanine DNA-glycosylase 1; APE1: Apurinic endonuclease 1; XRCC1: X-ray repair cross-complementing protein 1.

date of enrollment, whereas non-smokers were defined as those who reported that they had never smoked before or during the study duration. For alcohol consumption, drinkers were described as having alcohol every day, whereas non-drinkers did not consume alcohol daily. Height and current body weight were recorded to analyze the BMI (kg/m^2), with a cut-off threshold of $25 \text{ kg}/\text{m}^2$.

DNA isolation and genotyping

Genomic DNA was extracted from peripheral whole blood obtained from all participants by using an EZNASE Blood DNA kit (Omega Bio-tek, Norcross, GA, United States) and stored at -80°C . The extracted samples were used for characterization of the following polymorphic DNA repair genes: OGG1 (rs1052133; Ser326Cys, C/G in Exon 7), APE1 (rs1130409; Asp148Glu, T/G in Exon 5 and rs1760944; -141T/G in the promoter region), and XRCC1 (rs25487; Arg399Gln, G/A in Exon 10). Polymerase chain reaction with confronting two-pair primers (PCR-CTPP) was used for genotyping, which is an inexpensive and time-saving method applicable for most single nucleotide polymorphisms^[19]. For detecting a single nucleotide polymorphism (base X or Y), one primer for the X allele is set to include X^{*} (antisense of X) at the 3' end, with the counterpart sense primer upstream. For the Y allele, a sense primer including Y at the 3' end is set, with the antisense primer downstream. One common band and one specific band for each allele are amplified, allowing for direct genotyping by electrophoresis^[20]. Primer pairs were designed using GenBank reference sequences to provide unique product lengths for each allele (Table 1).

PCR amplification was performed in glass capillaries in $25 \mu\text{L}$ reaction mixtures containing $2 \mu\text{L}$ genomic DNA, $12.5 \mu\text{L}$ Go Taq MIX (2x), $1 \mu\text{L}$ primer for each of the four primers, and $6.5 \mu\text{L}$ dH_2O . Reaction conditions included initial denaturation at 95°C for 10 min,

then 30 cycles of denaturation at 95°C for 1 min, annealing for 1 min at 60°C (APE1 Asp148Glu), 58°C (APE1 -141T/G), 66°C (XRCC1 Arg399Gln), or 64°C (OGG1 Ser326Cys), and elongation at 72°C for 1 min. PCR products were analyzed by agarose gel electrophoresis.

Statistical analysis

Statistical analyses were performed with SPSS version 19.0 (IBM, Armonk, NY, United States). A χ^2 test was conducted for assessing the differences in demographic variables, family history of cancer, behavioral risk factors, and distribution of the four gene polymorphisms between case and control subjects, as well as the Hardy-Weinberg equilibrium. Unconditional logistic regression was undertaken to estimate odds ratios (OR) and 95%CI after adjustment for age, gender, family history of cancer, smoking status, alcohol consumption, and BMI. As the distribution of the XRCC1 Gln/Gln genotype was relatively rare in both groups, the homozygous Arg/Arg and Gln/Gln genotype were combined as the adverse genotype in the subgroup analysis, but not the interaction test. Statistical significance for the interaction was tested by the likelihood ratio test, which compared logistic models with and without interaction terms. Linkage disequilibrium was assessed using Haploview (v.4.2, 2008, Daly Lab at the Broad Institute, Cambridge, MA, United States).

RESULTS

Geographic characteristics of subjects

The clinical and demographic characteristics of research subjects are summarized in Table 2. There were no statistically significant differences between cases and controls in terms of age, gender, family history of cancer, or the three behavior factors (smoking, alcohol consumption, and BMI).

Table 2 Demographic characteristics of colorectal cancer cases and control participants *n* (%)

Variables	Cases (<i>n</i> = 247)	Controls (<i>n</i> = 300)	<i>P</i> value
Age ¹			
Mean age ± SE	59.22 ± 14.54	56.96 ± 15.84	0.574
< 60 yr	120 (48.58)	153 (51.00)	
≥ 60 yr	127 (51.42)	147 (49.00)	
Gender			0.930
Male	145 (58.70)	175 (58.33)	
Female	102 (41.30)	125 (41.67)	
Family history of cancer			0.633
No	214 (86.64)	264 (88.00)	
Yes	33 (13.36)	36 (12.00)	
Smoking			0.801
Nonsmokers	159 (64.37)	190 (63.33)	
Smokers	88 (35.63)	110 (36.67)	
Alcohol consumption			0.749
Nondrinkers	176 (71.25)	210 (70.00)	
Drinkers	71 (28.75)	90 (30.00)	
Body mass index			0.968
< 18.5	9 (3.64)	12 (4.00)	
18.5-24.9	37 (14.98)	46 (15.33)	
≥ 25	201 (81.38)	242 (80.67)	

¹Age is a continuous variable in the regression model analysis.

Single gene distribution and CRC risk

Genotype distributions of the four polymorphisms in control subjects were consistent with the Hardy-Weinberg equilibrium. The distributions of OGG1 Ser326Cys, APE1 Asp148Glu, -141T/G in the promoter region, and XRCC1 Arg399Gln genotypes in CRC patients and controls are shown in Table 3. The APE1 148 Glu/Glu genotype was higher in CRC patients than in controls (28.34% *vs* 13.67%, *P* < 0.001). Compared with the APE1 148 Asp/Asp genotype, the Glu/Glu genotype showed a statistically significant increased risk of CRC (OR = 2.411, 95%CI: 1.497-3.886, *P* < 0.001). Frequency of the APE1 Glu allele was significantly higher in CRC patients than in controls (46.56% *vs* 36.50%, OR = 1.516, 95%CI: 1.189-1.932, *P* < 0.001). There were no statistically significant differences between cases and controls in APE1 -141T/G, XRCC1 Arg399Gln, or OGG1 Ser326Cys genotypes, or allelic frequencies. As the APE1 Asp148Glu and -141T/G polymorphisms are located on the same chromosome, the linkage disequilibrium test was conducted to determine if there was a chain expression between the two loci. The result showed weak linkage disequilibrium between APE1 Asp148Glu and -141T/G polymorphisms (*D'* = 0.28, *r*² = 0.065, data not shown), indicating no need for haplotype analysis.

Gene polymorphisms and smoking status

Table 4 summarizes the combined effects of smoking and the four gene polymorphisms, adjusted for age, gender, alcohol consumption, BMI, and family history of cancer. An increased OR of CRC associated with the APE1 148 Glu/Glu genotype was found in smokers and non-smokers (smoker: OR = 3.299, 95%CI: 1.428-7.623; non-smoker: OR = 2.336, 95%CI: 1.273-4.360, all *P* <

0.05). Compared with the XRCC1 399 homozygous combined genotype (Arg/Arg and Gln/Gln), the OR for the Arg/Gln genotype was significantly decreased in smokers (OR = 0.289, 95%CI: 0.152-0.548, *P* < 0.001), but not in non-smokers (OR = 1.120, 95%CI: 0.720-1.743), with an interaction observed between smoking status and XRCC1 Arg399Gln polymorphism (*P* < 0.05). Compared with the homozygous wild type, the adjusted ORs for APE1 -141 T/G and OGG1 Ser326Cys polymorphisms showed no statistically significant differences between smokers and non-smokers. There were no significant gene-behavior interactions observed between smoking status and OGG1 Ser326Cys, APE1 Asp148Glu, or -141T/G.

Gene polymorphisms and alcohol consumption

Table 5 shows the genotypes of subjects stratified by alcohol consumption, adjusted for age, gender, smoking status, BMI, and family history of cancer. Although there was an increased risk for CRC in those who were classified as non-drinkers with the APE1 Glu/Glu genotype (OR = 2.654, 95%CI: 1.489-4.730, *P* < 0.05) but not in drinkers (OR = 2.095, 95%CI: 0.819-5.360), there was no significant interaction between alcohol use and APE1. Compared with the combined XRCC1 Arg/Arg and Gln/Gln genotypes, the Arg/Gln genotype showed a decreased risk of CRC in drinkers (OR = 0.327, 95%CI: 0.158-0.673, *P* < 0.05). There was no significant risk for CRC observed among non-drinkers, and there was no gene-behavior interaction between alcohol use and XRCC1. There were no statistically significant differences in APE1 -141T/G or G/G genotypes compared with the T/T genotype, and no differences between the OGG1 326 Ser/Cys and Cys/Cys genotypes compared with the Ser/Ser genotype. No significant gene-behavior interactions between alcohol consumption and APE1 -141T/G and OGG1 Ser326Cys genotypes were observed.

Gene polymorphisms and BMI

The distributions of the four gene polymorphisms stratified by BMI are presented in Table 6. Subjects with a BMI ≥ 25 kg/m² and the APE1 Glu/Glu genotype showed a higher risk of CRC (OR = 2.581, 95%CI: 1.489-4.474, *P* < 0.05). In contrast, no clear interaction with regard to risk was found between the BMI and APE1 Asp148Glu polymorphism. The APE1 -141T/G genotype indicated a lower risk of CRC in subjects with BMI < 25 kg/m² (OR = 0.214, 95%CI: 0.069-0.660, *P* < 0.05). There was a significant interaction between BMI and APE1 -141T/G (*P* < 0.05), but not with OGG1 Ser326Cys or XRCC1 Arg399Gln gene polymorphisms.

DISCUSSION

This study is the first report showing the association between the Glu allele of the APE1 Asp148Glu gene variant and an increased risk of CRC in a Chinese Han population, consistent with the results of Jelonek *et al*^[13]

Table 3 Gene distributions *n* (%)

Genes			Cases (<i>n</i> = 247)	Controls (<i>n</i> = 300)	Crude OR (95%CI) ¹	<i>P</i> value ¹	Adjusted OR (95%CI) ²	<i>P</i> value ²
OGG1 Ser326Cys	Genotype	Ser/Ser	44 (17.81)	48 (16.00)	1.000		1.000	
		Ser/Cys	111 (44.94)	139 (46.33)	0.871 (0.540-1.407)	0.572	0.862 (0.532-1.395)	0.546
		Cys/Cys	92 (37.25)	113 (37.67)	0.888 (0.542-1.454)	0.637	0.914 (0.556-1.502)	0.723
XRCC1 Gln399Arg	Allele	Ser	199 (40.28)	235 (39.17)	1.000			
		Cys	295 (59.72)	365 (60.83)	0.954 (0.748-1.217)	0.707		
		Arg/Arg	131 (53.04)	142 (47.33)	1.000		1.000	
APE1 Asp148Glu	Genotype	Arg/Gln	91 (36.84)	132 (44.00)	0.747 (0.523-1.068)	0.110	0.744 (0.519-1.066)	0.107
		Gln/Gln	25 (10.12)	26 (8.67)	1.042 (0.573-1.896)	0.892	1.055 (0.577-1.930)	0.862
		Allele	353 (71.46)	416 (69.33)	1.000			
APE1 promoter -141T/G	Allele	Gln	141 (28.54)	184 (30.67)	0.903 (0.695-1.173)	0.444		
		Asp/Asp	87 (35.22)	122 (40.66)	1.000		1.000	
		Asp/Glu	90 (36.44)	137 (45.67)	0.921 (0.628-1.351)	0.674	0.939 (0.639-1.379)	0.747
APE1 promoter -141T/G	Allele	Glu/Glu	70 (28.34)	41 (13.67)	2.394 (1.491-3.844)	< 0.001	2.411 (1.497-3.886)	< 0.001
		Asp	264 (53.44)	381 (63.50)	1.000			
		Glu	230 (46.56)	219 (36.50)	1.516 (1.189-1.932)	0.001		
APE1 promoter -141T/G	Genotype	TT	93 (37.65)	93 (31.00)	1.000		1.000	
		TG	102 (41.30)	140 (46.67)	0.729 (0.496-1.070)	0.106	0.748 (0.508-1.104)	0.144
		GG	52 (21.05)	67 (22.33)	0.776 (0.489-1.232)	0.282	0.781 (0.490-1.247)	0.301
APE1 promoter -141T/G	Allele	T	288 (58.30)	326 (54.33)	1.000			
		G	206 (41.70)	274 (45.67)	0.851 (0.669-1.082)	0.188		

¹Obtained by χ^2 test, and the significance level was adjusted to 0.0125; ²Adjusted with age, gender, smoking status, alcohol consumption, body mass index, and family history of cancer. OGG1: 8-oxoguanine DNA-glycosylase 1; APE1: Apurinic endonuclease 1; XRCC1: X-ray repair cross-complementing protein 1.

Table 4 Distribution of genotypes and odds ratios for colorectal cancer stratified by smoking status

	Non-smokers			Smokers			<i>P</i> interaction
	Case/control	OR (95%CI) ¹	<i>P</i> value	Case/control	OR (95%CI) ¹	<i>P</i> value	
OGG1 Ser326Cys							0.432
Ser/Ser	30/32	1.000		14/16	1.000		
Ser/Cys	75/86	0.921 (0.505-1.679)	0.788	36/53	0.753 (0.315-1.798)	0.523	
Cys/Cys	54/72	0.850 (0.454-1.593)	0.613	38/41	1.087 (0.452-2.612)	0.853	
XRCC1 Arg399Gln							0.003
Arg/Arg + Gln/Gln	93/118	1.000		63/50	1.000		
Arg/Gln	66/72	1.120 (0.720-1.743)	0.614	25/60	0.289 (0.152-0.548)	< 0.001	
APE1 Asp148Glu							0.706
Asp/Asp	58/80	1.000		29/42	1.000		
Asp/Glu	60/84	1.089 (0.669-1.772)	0.733	30/53	0.867 (0.433-1.735)	0.687	
Glu/Glu	41/26	2.356 (1.273-4.360)	0.006	29/15	3.299 (1.428-7.623)	0.005	
APE1 -141T/G							0.858
TT	59/55	1.000		34/38	1.000		
TG	66/91	0.668 (0.404-1.107)	0.118	36/49	0.796 (0.406-1.562)	0.507	
GG	34/44	0.659 (0.361-1.201)	0.173	18/23	0.794 (0.352-1.791)	0.794	

¹Adjusted for age, gender, alcohol consumption, body mass index, and family history of cancer. OGG1: 8-oxoguanine DNA-glycosylase 1; APE1: Apurinic endonuclease 1; XRCC1: X-ray repair cross-complementing protein 1.

in a Polish population and Canbay *et al*^[7] in a Turkish population. Kasahara *et al*^[21] also reported that the Glu allele was associated with a 2-3 fold increased risk for CRC in a Japanese population. In the present study, no gene-behavior interactions were observed between the three behavioral factors and the APE1 Asp148Glu polymorphism, but the risk among smokers was slightly higher. Additionally, individuals with the APE1 Glu/Glu genotype that were non-drinkers or had a BMI \geq 25 kg/m² showed an increased risk of CRC.

The APE1 gene consists of five exons and four introns within a 2.21 kb span on chromosome 14 at q11.2-q12 and encodes a 317 amino acid protein^[14]. APE1 has 3'-phosphodiesterase activity and efficiently

removes 3' phosphoglycolate groups^[22]. It initiates repair of abasic sites in DNA by hydrolyzing the phosphodiester 5' backbone^[23]. Additionally, APE1/Ref-1 also functions as a redox agent, maintaining transcription factors such as AP-1, nuclear factor- κ B, Myb, hypoxia-inducible factor-1 α , HLF, PAX, and p53 that are involved in cancer promotion and progression in an active reduced state^[14,23-25]. However, biochemical characterization of this variant shows normal endonuclease and abasic-DNA binding activity^[4], though severe functional damage in the APE1 protein may cause early death or abortion, making it difficult to assess function in adults. A report in 2002 indicated that a prolonged cell-cycle delay observed in breast cancer samples was associated with the number

Table 5 Distribution of genotypes and odds ratios for colorectal cancer stratified by alcohol consumption

	Non-drinkers			Drinkers			<i>P</i> interaction
	Case/control	OR (95%CI) ¹	<i>P</i> value	Case/control	OR (95%CI) ¹	<i>P</i> value	
OGG1 Ser326Cys							0.068
Ser/Ser	33/32	1.000		11/16	1.000		
Ser/Cys	87/98	0.888 (0.500-1.576)	0.684	24/41	0.793 (0.296-2.119)	0.643	
Cys/Cys	56/80	0.728 (0.397-1.332)	0.303	36/33	1.806 (0.685-4.760)	0.232	
XRCC1 Arg399Gln							0.174
Arg/Arg + Gln/Gln	106/121	1.000		50/47	1.000		
Arg/Gln	70/89	0.909 (0.600-1.376)	0.651	21/43	0.327 (0.158-0.673)	0.002	
APE1 Asp148Glu							0.848
Asp/Asp	62/89	1.000		25/33	1.000		
Asp/Glu	64/92	1.043 (0.656-1.660)	0.857	26/45	0.816 (0.379-1.756)	0.603	
Glu/Glu	50/29	2.654 (1.489-4.730)	0.001	20/12	2.095 (0.819-5.360)	0.123	
APE1 -141T/G							0.618
TT	68/63	1.000		25/30	1.000		
TG	72/98	0.651 (0.405-1.045)	0.076	30/42	0.805 (0.374-1.734)	0.580	
GG	36/49	0.612 (0.346-1.082)	0.091	16/18	0.912 (0.366-2.270)	0.842	

¹Adjusted for age, gender, smoking status, body mass index, and family history of cancer. OGG1: 8-oxoguanine DNA-glycosylase 1; APE1: Apurinic endonuclease 1; XRCC1: X-ray repair cross-complementing protein 1.

Table 6 Distribution of genotypes and odds ratios for colorectal cancer stratified by body mass index

	< 25 kg/m ²			≥ 25 kg/m ²			<i>P</i> interaction
	Case/control	OR (95%CI) ¹	<i>P</i> value	Case/control	OR (95%CI) ¹	<i>P</i> value	
OGG1 Ser326Cys							0.706
Ser/Ser	9/8	1.000		35/40	1.000		
Ser/Cys	17/26	0.529 (0.149-1.880)	0.325	94/113	0.973 (0.567-1.668)	0.920	
Cys/Cys	20/24	0.936 (0.269-3.258)	0.917	72/89	0.938 (0.536-1.643)	0.823	
XRCC1 Arg399Gln							0.755
Arg/Arg + Gln/Gln	27/32	1.000		129/136	1.000		
Arg/Gln	19/26	0.928 (0.396-2.175)	0.863	72/106	0.754 (0.510-1.114)	0.156	
APE1 Asp148Glu							0.725
Asp/Asp	17/22	1.000		70/100	1.000		
Asp/Glu	13/25	0.609 (0.222-1.674)	0.337	77/112	1.023 (0.666-1.571)	0.919	
Glu/Glu	16/11	1.770 (0.594-5.274)	0.305	54/30	2.581 (1.489-4.474)	0.001	
APE1 -141T/G							0.044
TT	17/9	1.000		76/84	1.000		
TG	15/33	0.214 (0.069-0.660)	0.007	87/107	0.934 (0.608-1.434)	0.754	
GG	14/16	0.406 (0.122-1.352)	0.142	38/51	0.860 (0.506-1.462)	0.577	

¹Adjusted for age, gender, smoking status, body mass index, and family history of cancer. OGG1: 8-oxoguanine DNA-glycosylase 1; APE1: Apurinic endonuclease 1; XRCC1: X-ray repair cross-complementing protein 1.

of APE1 Asp148Glu and XRCC1 Arg399Gln variant alleles^[26]. Furthermore, increased APE1 transcription was observed in CRC patients with the OGG1 326 Ser allele^[27]. These findings suggest that the APE1 Asp148Glu polymorphism may act as a co-factor with other genes in tumorigenesis, though further research is needed to reveal the exact mechanism.

Promoter polymorphisms can affect transcription factor recognition, and thus impact gene expression. Although the APE1 -141T/G promoter polymorphism has not been thoroughly examined in CRC, Jing *et al.*^[28] reported that the G allele of this variant is associated with a decreased risk of prostate cancer. Lu *et al.*^[15] also found that the APE1 -141T/G polymorphism was associated with a decreased risk of lung cancer. Their study showed that the -141 G allele was associated with reduced promoter activity and lower *APE1* mRNA levels in human

peripheral blood mononuclear cells and normal lung tissues. However, Zhou *et al.*^[16] found no significant association between APE1 promoter -141T/G polymorphism and glioma risk, though the stratified histologic analysis revealed a decreased glioblastoma risk with the G allele variant. Results from the present study also indicate no association between the APE1 -141T/G variants and CRC susceptibility. However, subgroup analysis stratified by BMI revealed a protective effect of the T/G genotype on development of CRC among subjects with a BMI < 25 kg/m². As this analysis was limited by a small sample size, further in-depth studies are needed to confirm this effect.

The *XRCC1* gene is located at 19q13.2 and consists of 17 exons encoding a 633 amino acid non-enzymatic nuclear scaffold protein that interacts with enzymatic factors such as polyadenosine diphosphate-ribose poly-

merase, DNA ligase III, and DNA polymerase β to facilitate protein-protein responses^[4] and efficient repair of DNA SSBs^[29]. Although the XRCC1 Arg399Gln polymorphism has been shown to rescue sensitivity to the alkylating agent methyl methanesulfonate and the DNA repair defect in the XRCC1-deficient Chinese hamster ovary cell line EM9^[4], there are inconsistent reports concerning XRCC1 variants and CRC. Some reports have revealed an increased risk for CRC with the Gln/Gln genotype^[11,13,30,31], whereas results from studies in Turkey and the Czech Republic report no relationship between the gene variant and CRC risk^[7,32,33]. A meta-analysis published last year showed that XRCC1 Arg399Gln polymorphism is significantly associated with increased CRC risk^[34].

The results of this study show that the XRCC1 Arg399Gln polymorphism is not associated with CRC risk, though a protective effect against CRC was observed in smokers with the Asp/Gln genotype. The observed gene-behavior interaction suggests that tobacco use may modify the association of the XRCC1 Arg399Gln variant and CRC risk. It has been shown that the XRCC1 Gln399Gln genotype is linked with an increased risk of tobacco-related cancers among light smokers, but a decreased risk among heavy smokers^[35], which is consistent with these findings. The same protective effect was also seen among drinkers with the Arg/Gln genotype, though no significant interaction between alcohol consumption and XRCC1 polymorphism was observed. This protective effect did not correspondingly increase with the number of Gln alleles. It is possible that polymorphisms of other repair genes, such as ERCC1 or XRCC2, which are in linkage disequilibrium with XRCC1 Arg399Gln, may potentially modify the effect of this polymorphism on the risk of CRC. However, the Gln/Gln genotype was rare in the study cohort; large-scale investigations are needed to determine the exact interaction.

The OGG1 gene is located at 3p26.2 and encodes the major repair enzyme for the excision of 8-oxoguanine, a mutagenic base byproduct resulting from exposure to reactive oxygen. A well-characterized OGG1 polymorphism replacing C with G at nucleotide 1245 results in a substitution of serine for cysteine^[36]. The research of Yamane *et al.*^[37] reveals this cysteine reduces the ability of OGG1 to prevent mutagenesis by 8-hydroxyguanine in human cells *in vivo*. However, the clinical investigations between the OGG1 Ser326Cys polymorphism and the risk of CRC are inconsistent. Several studies suggest that the Cys/Cys genotype may increase the CRC risk in different ethnic populations^[7,32,38,39], yet results from a study by Hansen *et al.*^[40] suggest that carriers of the Cys allele have a lower risk of CRC. Furthermore, a meta-analysis conducted by Zhang *et al.*^[3] indicated no association between the OGG1 Ser326Cys gene variant and risk of CRC, which is consistent with the results of the present study.

In conclusion, the data presented here indicate that the homozygous APE1 148 Glu/Glu variant genotype

is significantly associated with an elevated risk of CRC, especially for smokers and overweight individuals. These results suggest that the APE1 gene polymorphism and BER pathway contribute to the possible harmful effects of smoking and obesity. Tobacco use may modify the association between CRC risk and the XRCC1 Arg399Gln polymorphism. However, these findings are limited by uncontrolled biases that were present in the selection of participants and the low penetrance of these variants in CRC susceptibility. Further large-population based studies are therefore needed to confirm the results of this study.

COMMENTS

Background

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide, and a leading cause of cancer-related death. DNA damage plays an important role in the development and occurrence of CRC. Precise and effective DNA repair systems, such as the base excision repair pathway, have evolved to maintain genomic stability and minimize accumulation of damage.

Research frontiers

Gene polymorphisms in DNA repair pathways could affect DNA repair capacity, and thus influence the risk of CRC. Several polymorphisms in genes encoding components of these repair pathways have been identified, including 8-oxoguanine DNA-glycosylase 1 (OGG1), apurinic endonuclease 1 (APE1), and X-ray repair cross-complementing protein 1 (XRCC1). Among these, OGG1 Ser326Cys, APE1 Asp148Glu, and XRCC1 Arg399Gln are the most studied polymorphisms. An additional polymorphism in the promoter region of APE1 has been identified, though less studied in cancer research.

Innovations and breakthroughs

This research is the first to study base excision repair gene polymorphisms in a Chinese Han population from the southwest part of China. Results from this study demonstrate an interaction between smoking and the XRCC1 Arg399Gln variant.

Applications

These results provide population characteristic data and corresponding gene polymorphisms associated with a risk for CRC, which will help to identify a potential high-risk population.

Terminology

Single nucleotide polymorphisms are DNA sequence variations occurring when a single nucleotide in the genome differs between members of a biological species or paired chromosomes. Gene-environment interaction is the association between genes and environmental factors. Some environmental factors could influence the association between genes and some certain diseases, and cause an increase or decrease in risk in a particular group of people.

Peer review

The authors analyzed an important aspect of risk factors for CRC. The number of patients included in this study is adequate and it is very interesting because it has been conducted in an Asian population that has different genetic characteristics with respect to a Western population. This study is of clinical relevance due to the potential in identifying a high-risk CRC population.

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