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ORIGINAL ARTICLE

Case Control Study

Association between polymorphisms of *APE1* and *OGG1* and risk of colorectal cancer in Taiwan

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Abstract

AIM: To evaluate the effects of *OGG1* (Ser326Cys, 11657A/G, and Arg154His) and *APE1* (Asp148Glu, and T-656G) polymorphisms on colorectal cancer (CRC) risk.

METHODS: We enrolled 727 cases newly diagnosed with colorectal adenocarcinoma and 736 age- and sex-matched healthy controls from a medical center in Taiwan. Genomic DNA isolated from the buffy coat was used for genotyping through polymerase chain reaction. Unconditional logistic regressions were used for calculating ORs and 95%CIs to determine the association between the genetic polymorphisms and CRC risk. Haplotype frequencies were estimated using PHASE software. Moreover, stratification analyses on

the basis of sex, age at diagnosis, and tumor subsite and stage were performed.

RESULTS: The CRC risk was higher in patients with the *OGG1* 326Ser/Cys + Cys/Cys genotype (OR = 1.38, 95%CI: 1.03-1.85, *P* = 0.030), particularly high in patients with stage Ⅲ + Ⅳ cancer (OR = 1.48, 95%CI: 1.03-2.13) compared with patients with the Ser/Ser genotype. In addition, *OGG1* 11657G allele carriers had a 41% reduced CRC risk among stage 0-Ⅱ patients (OR = 0.59, 95%CI: 0.35-0.98). The CRC risk was significantly higher among females with the *APE1* Glu allele (OR = 1.41, 95%CI: 1.02-1.96). The *APE1* 148Glu/-656G haplotype was also associated with a significant CRC risk in females (OR = 1.36, 95%CI: 1.03-1.78).

CONCLUSION: *OGG1* and *APE1* polymorphisms are associated with stage- and sex-specific risk of CRC in the Taiwanese population.

Key words: *APE1*; *OGG1*; Taiwan; Colorectal cancer; Polymorphisms

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Core tip: The associations between base excision repair DNA polymorphisms and colorectal cancer (CRC) risk is controversial. The present study examined the effects of *OGG1* and *APE1* polymorphisms on the CRC risk by using a large-scale sample of 727 CRC cases and 736 healthy controls. Results demonstrated that *OGG1* 326Cys and *APE1* 148Glu alleles were significantly associated with an increased CRC risk in patients with stage Ⅲ + Ⅳ cancer (OR = 1.48) and females (OR = 1.41). Females carrying the *APE1* 148Glu/-656G haplotype also exhibited a 36% increased CRC risk. These findings suggest that OGG1 and APE1 polymorphisms are associated with stage- and sex-specific risk of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer and third leading cause of cancer-related deaths in Taiwan[1]. Studies have indicated that both endogenous and exogenous oxidative damage resulting from reactive oxygen species (ROS) generation participates in all stages of cancer[2,3]. Several ROS can cause oxidative DNA damage, including single- or double-strand breakages, base modifications, deoxyribose modifications, and DNA cross-links[4]. DNA repair enzymes are critical in preventing drug resistance and protecting the genome against ROS carcinogenesis[2]. More than 100 proteins are involved in the DNA repair system through different pathways, including base excision repair (BER), nucleotide excision repair, double-strand break repair, and mismatch repair[5].

The BER gene family is activated through internal oxidative stress and DNA damage and involves 8-oxoguanine glycosylase 1 (*OGG1*) and apurinic-apyrimidinic endonuclease 1 (*APE1*)[6]. *OGG1* is located at 3p26.2 and encodes the major repair enzyme for directly removing 8-oxo-guanine (8-oxoG) from the damaged DNA[7]. In addition to catalyzing 8-oxoG excision from DNA, *OGG1* can incise at abasic sites through an apurinic and apyrimidinic (AP) lyase activity[8]. Studies have suggested low in DNA repair efficiency in patients with cancer. Most studies focused on the common single nucleotide polymorphism (SNP) C1245G that results in the substitution of serine with cysteine at codon 326 (Ser326Cys, rs1052133)[5,9-12]. The 326Cys protein, whose enzyme activity is lower than that of Ser, might be associated with cancer risk[5,13]. Two other *OGG1* SNPs, 11657A/G and Arg154His (rs 56053615), located in the downstream region have also been associated with cancer risk[14-16].

Human *APE1* is located on chromosome 14q11.2-q12 and comprises five exons spanning 2.21 kb[17]. *APE1* is crucial in initiating the BER of basic sites in DNA hydrolyzing the phosphodiester backbone 5' to an AP site and recruiting DNA polymerase β and DNA ligase Ⅲ[18,19]. Known allelic variants of *APE1* include an amino acid change from aspartic acid to glutamic acid (Asp148Glu, rs 1130409) in exon 5, which may be associated with hypersensitivity to ionizing radiation and cancer risk[20-22]. Moreover, a T to G SNP observed in the promoter region (T-656G, rs1760944) was associated with a 57% reduced risk of lung cancer[18].

Numerous studies have examined the association of *OGG1* and *APE1* polymorphisms with the CRC risk, but the results are controversial[5,7,12,23-25]. Therefore, in this study, we evaluated the association of genetic polymorphisms of *OGG1* (Ser326Cys, 11657A/G, and Arg154His) and *APE1* (Asp148Glu, and T-656G) with the CRC risk in a hospital-based case-control study in Taiwan. In addition, because age at diagnosis, sex, and tumor site and stage may modify the aforementioned association[23,26-29], we used stratification analysis for investigating whether these factors affect the association between *OGG1* and *APE1* polymorphisms and CRC risk.

MATERIALS AND METHODS

Participants

Participant characteristics have been previously des-

cribed[26,30]. Briefly, cases newly diagnosed with colorectal adenocarcinoma were enrolled from Chang Gung Memorial Hospital between January 1995 and January 1999. Age- and sex-matched healthy controls were enrolled from the Physical Check-Up Department during the same period. After excluding patients diagnosed with hereditary colorectal diseases, other related malignancies, or a history of cancer, 727 cases (94%, 727/776) and 736 controls (98%, 736/747) were included in this study. The Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol, and all participants provided written informed consent.

Questionnaire

Trained nurses conducted standardized interviews of all participants in the hospital. Data on socio-demographic characteristics and risk factors for CRC, namely physical activity in the past year, cigarette smoking history, alcohol and coffee use, medical history, and food intake 5 years preceding the interview, were obtained from a structured questionnaire; simultaneously 10 mL of venous blood was collected.

Genotyping Assays

Genotyping assays for examining *OGG1* Ser326Cys and 11657A/G polymorphisms were performed on the genomic DNA extracted from the buffy coat by using the template-directed dye-terminator incorporation assay with fluorescence polarization detection[31]. DNA was amplified in a 10-μL final volume containing 2 pmol/L of each primer, 25 ng of genomic DNA, 10 mmol/L of $MgCl_2$, 2.5 mmol/L of dNTPs, and 0.5 U of Taq DNA polymerase (Roche, Mannheim, Germany) in the buffer provided by the manufacturer. PCR reactions were performed in a Mastercycler (Eppendorf, Hamburg, Germany). The Ser326Cys polymorphism was amplified using the following primers: Forward, 5′-TCCACCTCCCAACACTGTCACTA-3′ and Reverse, 5′-TCACCTGCTTCCCTACCACT-3′. The PCR program involved a 2-min denaturing step at 92 ℃, 10 cycles of 10 s at 92 ℃, 20 s at 62 ℃, and 30 s at 68 ℃, and followed by 30 cycles of 10 s at 92 ℃, 20 s at 60 ℃, and 30 s at 68 ℃. The 11657A/G polymorphism was amplified using the following primers: Forward, 5′-GGCAATCAGAGATGGTTAGA-3′, and Reverse, 5′-TGGCATTAAATCAAGCACTA-3′. The PCR program involved a 5-min denaturing step at 94 ℃ followed by 35 cycles of 30 s at 94 ℃, 45 s at 58 ℃, and 60 s at 72 ℃.

After amplification, the residual primers and dNTPs were degraded in a 10 μL final volume of 1 U of shrimp alkaline phosphatase (Roche) and 1 U of exonuclease I (USB, Cleveland, OH, United States) for 45 min at 37 ℃, followed by 15 min at 95 ℃ for enzymes inactivations.

The template-directed dye-terminator incorporation assay was performed using the AcycloPrime™-FP SNP detection kit (PerkinElmer Life Sciences, Boston, MA, United States). The AcycloPrime-FP reaction was conducted in a 10-μL mixture containing 2 μL of amplified and processed PCR product, 9 pmol/L of probe, 0.5 U of the appropriate AcycloTerminator kit, 0.025 μL of AcycloPol in the buffer provided by the manufacturer. The PCR program involved a 2-min denaturing step at 95 ℃ followed by 39 cycles of 15 s at 95 ℃ and 30 s at 55 ℃. The forward probes 5′-AGTGCCGACCTGCGCCAAT-3′ and 5′-CCAGGA-AGGACAAGGCTCA-3′ were used for Ser326Cys and 11657A/G polymorphisms, respectively. Fluorescence polarization was measured using the PerkinElmer Victor^2 reader (PerkinElmer) connected with data analysis and allele-calling software. All genotyping assays included three known genotypes and a negative control, and the laboratory analyser was blinded to the case-control status of the participants.

Genotyping for assessing the *OGG1* Arg154His polymorphism was modified from a previously reported method using primer extension and denaturing high-performance liquid chromatography (PE-DHPLC)[26]. Briefly, forward (5′-AGCAGGTACCTCTCCTACC-3′) and reverse (5′-AGGTCCAAAAGCCTGGCAC-3′) primers were used for PCR amplification. Reactions were run in 25 μL volumes using an amplification protocol involving an initial denaturation step at 95 ℃ for 5 min, followed by 34 cycles of 95 ℃ for 1 min and 60 ℃ for 30 s 72 ℃ for 30 s, and 72 ℃ for 5 min. After amplification, a 5 μL PCR product was degraded using 0.64 U of exonuclease I and 0.08 U of shrimp alkaline phosphatase for 40 min at 37 ℃. Furthermore, the product was amplified in a 25 μL final volume containing 1 mmol/L of dNTP and ddATP, 10 μmol/L of primer (5′-CCTCCAACAACAACATCGCCC-3′) and 0.5 U of Thermo Sequenase™ DNA polymerase (Amersham, Cleveland, OH, United States) in the buffer. Reactions were conducted as follows: an initial denaturation step of 95 ℃ for 75 s; 49 cycles of 95 ℃ for 15 s, 43 ℃ for 15 s, and 60 ℃ for 100 s, and an extension step of 96 ℃ for 30 s. The extended products were analyzed through DHPLC with a linear acetonitrile gradient in a triethylamine acetate buffer.

The *APE1* Asp148Glu polymorphism was determined using a 5′-nuclease assay with allele-specific TaqMan probes including 148Asp probe (5′-VIC-AATTCTGTTTCATTTCTATAGGCGAGGAG-GAGCATGATCAGGAAGGCCGGG-TAMRA-3′) and 148Glu probe (5′-FAM-AATTCTGTTTCATTTCTATAGGCGA-TGAGGAGCATGATCAGGAAGGCCGGG-TAMRA-3′). TaqMan SNP genotyping assay kits were purchased from Applied Biosystems (Foster City, CA, United States). Genotyping was performed using an allelic discrimination assay in the ABI 7500 FAST Real-Time PCR system (Applied Biosystems), and genotypes were distinguished using automated ABI 7500 software v2.0 (Applied Biosystems). Reactions were run in 10 μL volumes by using an amplification protocol with an

Table 1 Age, sex, and genotype frequencies of the cases and controls *n* (%)

Variable	Cases $n = 727$	Controls $n = 736$	*P* value[1]
Age (mean ± SD), yr	60.3 ± 12.8	60.7 ± 13.0	0.639
Gender			0.751
Male	410 (56.4)	409 (55.6)	
Female	317 (43.6)	327 (44.4)	
Colon/rectum, *n*	352/375		
OGG1 Ser326Cys			0.021
Ser/Ser	93 (13.0)	125 (17.1)	
Ser/Cys	363 (50.8)	324 (44.4)	
Cys/Cys	258 (36.1)	281 (38.5)	
Missing	13	6	
OGG1 11657A/G			0.318
A/A	648 (91.9)	654 (90.1)	
A/G	55 (7.8)	72 (9.9)	
G/G	2 (0.3)	0 (0.0)	
Missing	22	10	
OGG1 Arg154His			0.158
Arg/Arg	720 (100.0)	720 (99.7)	
Arg/His	0 (0.0)	2 (0.3)	
His/His	0 (0.0)	0 (0.0)	
Missing	7	14	
APE1 Asp148Glu			0.567
Asp/Asp	236 (33.0)	249 (34.3)	
Asp/Glu	349 (48.8)	361 (49.7)	
Glu/Glu	130 (18.2)	117 (16.1)	
Missing	12	9	
APE1 T-656G			0.876
T/T	217 (30.1)	211 (28.9)	
T/G	368 (51.0)	380 (52.0)	
G/G	136 (18.9)	140 (19.2)	
Missing	6	5	

[1]Continuous variables were tested by Student's *t*-test, and categorical variables were tested by χ^2 or Mantel-Haenszel χ^2 test.

initial denaturation step of 60 ℃ for 1 min and 95 ℃ for 10 min followed by 40 cycles of 95 ℃ for 15 s and 60 ℃ for 1 min.

The genotyping method for assessing the *APE1* T-656G polymorphism was modified from a previously reported method using a high resolution melting assay in the ABI 7500 FAST Real-Time PCR system (Applied Biosystems). Genotypes were distinguished using automated High Resolution Melting software v2.0. Forward (5'-CACAGCACATTGTGTGACACTGA-3') and reverse (5'-AGCCCTCTCCACTGTTTTTTTCC-3') primers used for the PCR reactions were run in 20 μL volumes by using an amplification protocol with a holding step of 95 ℃ for 10 min followed by 36 cycles of 95 ℃ for 15 s and 60 ℃ for 20 s. The melting curve stage was maintained at 95 ℃ for 15 s, 50 ℃ for 1 min, 95 ℃ for 15 s, and 60 ℃ for 15 s.

Statistical analysis

We compared the different distributions for each categorical variable measured using the chi-squared test, and continuous variables were measured using the Student's *t*-test. Allelic frequencies were examined using the χ^2 test for concordance with those expected in Hardy-Weinberg equilibrium. We used unconditional logistic regression for estimating the OR and 95%CI with the factors (age and sex) matched in the model[32]. Stratified analyses were conducted for evaluating the differences between sex, age at diagnosis (≤ 60 and > 60 years old), tumor subsites (colon and rectum), and tumor stages (stage 0 + Ⅰ + Ⅱ and Ⅲ + Ⅳ). Haplotype frequencies were estimated on the basis of a Bayesian algorithm by using PHASE 2.1. All analyses were performed using the SAS statistical package (Version 9.2 for Windows; SAS Institute, Inc., Cary, NC, United States) and all statistical tests were two-sided. The powers were estimated using Quanto.

RESULTS

Age, sex, and *OGG1* and *APE1* genotypes of all participants are summarized in Table 1. Patients with CRC had a mean age of 60.3 years, and 410 (56.4%) males and 352 (48.4%) experienced colon cancer. The mean age and sex distribution was comparable between the patients with CRC and controls. The variant allelic frequencies for *OGG1* Ser326Cys, *OGG1* 11657A/G, *OGG1* Arg154His, *APE1* Asp148Glu, and *APE1* T-656G among the controls were, 60.7%, 5.0%, 0.14%, 40.9%, and 45.1%, respectively. All genotype frequencies were in Hardy-Weinberg equilibrium. The distribution of the *OGG1* Ser326Cys genotype was significantly different between the patients and controls (*P* = 0.021). However, other genotypic distributions did not significantly differ among the patients and controls. Because of the low frequency of sequence variants of *OGG1* Arg154His (His allele, 0.14%), this polymorphism was excluded from further analyses.

Table 2 shows the CRC risks associated with *OGG1* and *APE1* polymorphisms. Compared with the Ser/Ser genotype, the *OGG1* Ser326Cys heterozygous genotype was significantly associated with the CRC risk (OR = 1.51; 95%CI: 1.11-2.05, *P* = 0.009). However, other *OGG1* Ser326Cys genotypes were not associated with the CRC risk. The CRC risks associated with the heterozygous or homozygous genotypes of all the studied polymorphisms were similar; therefore, we used dominant models for determining the effects of polymorphisms on the CRC risk. Carriers of the *OGG1* 326Cys allele exhibited a significantly increased CRC risk (OR = 1.38; 95%CI: 1.03-1.85, *P* = 0.030). No significant associations were observed between other variant alleles and the CRC risk. The dominant genetic models of the studied polymorphisms were used for further stratification analysis.

Stratified analyses by sex, age at diagnosis, tumor subsites, and stage for the CRC risk associated with the *OGG1* polymorphisms are shown in Table 3. Data stratified by the tumor stage demonstrated that compared with the Ser/Ser genotype, the *OGG1* Ser326Cys Ser/Cys + Cys/Cys genotype was associated with an increased

Table 2 Distribution of *OGG1* and *APE1* polymorphisms between cases and controls *n* (%)

Genotype	Cases	Controls	OR (95%CI)[1]	*P* value
OGG1 Ser326Cys				
Ser/Ser	93 (13.0)	125 (17.1)	1.00 (ref)	
Ser/Cys	363 (50.8)	324 (44.4)	1.51 (1.11-2.05)	0.009
Cys/Cys	258 (36.1)	281 (38.5)	1.23 (0.90-1.69)	0.198
Ser/Cys + Cys/Cys	621 (87.0)	605 (82.9)	1.38 (1.03-1.85)	0.030
OGG1 11657A/G				
A/A	648 (91.9)	654 (90.1)	1.00 (ref)	
A/G	55 (7.8)	72 (9.9)	0.77 (0.53-1.12)	0.168
G/G	2 (0.3)	0 (0.0)	-	
A/G + G/G	57 (8.1)	72 (9.9)	0.80 (0.56-1.15)	0.230
APE1 Asp148Glu				
Asp/Asp	236 (33.0)	249 (34.3)	1.00 (ref)	
Asp/Glu	349 (48.8)	361 (49.7)	1.02 (0.81-1.29)	0.864
Glu/Glu	130 (18.2)	117 (16.1)	1.17 (0.86-1.60)	0.308
Asp/Glu + Glu/Glu	479 (67.0)	478 (65.8)	1.06 (0.85-1.32)	0.615
APE1 T-656G				
T/T	217 (30.1)	211 (28.9)	1.00 (ref)	
T/G	368 (51.0)	380 (52.0)	0.94 (0.74-1.20)	0.630
G/G	136 (18.9)	140 (19.2)	0.95 (0.70-1.28)	0.731
T/G + G/G	504 (69.9)	520 (71.1)	0.95 (0.75-1.18)	0.621

[1]ORs and 95%CIs were estimated from unconditional logistic regressions after controlling for age and sex.

risk of CRC in patients with stage Ⅲ + Ⅳ tumors (OR = 1.48; 95%CI: 1.03-2.13). Conversely, the *OGG1* 11657A/G A/G + G/G genotype was associated with a decreased risk of CRC in patients with stage 0 + Ⅰ + Ⅱ tumors (OR = 0.59; 95%CI: 0.35-0.98). However, the *OGG1* polymorphisms associated with the CRC risk were not significantly modified by sex, age at diagnosis, and tumor subsite.

Table 4 presents the results of a similar stratification analysis for *APE1* polymorphisms. Among females, compared with genotypes containing the Asp/Asp genotype, those containing the *APE1* 148Glu allele (Asp/Glu + Glu/Glu) were associated with an increased CRC risk (OR = 1.41, 95%CI: 1.02-1.96). However, this sex-specific CRC risk was not observed for the *APE1* T-656G polymorphism. In addition, no *APE1* polymorphism was significantly associated with the CRC risk among subgroups of age at diagnosis, tumor subsite, and tumor stage.

To assess the combined influence of these polymorphisms, we conducted haplotype analysis for *OGG1* Ser326 and 111657A/G as well as for *APE1* Asp148Glu and T-656G (Table 5). Linkage analysis between each pairwise combination revealed significantly weak linkage disequilibrium (all $P < 0.001$). The r^2 values for the Ser326 and 111657A/G pair and Asp148Glu and T-656G pair were 0.06 and 0.04, respectively. Compared with the most common Asp/T haplotype in females, the *APE1* Glu/G haplotype was significantly associated with the CRC risk (OR = 1.36; 95%CI: 1.03-1.78). No significant associations were observed for the *OGG1* haplotypes and CRC risk (data not shown).

DISCUSSION

We observed a significant association between the *OGG1* Ser326Cys polymorphism and CRC risk. The Ser/Cys + Cys/Cys genotypes were associated with an increased CRC risk. Furthermore, this harmful effect of the 326Cys allele was more marked in patients with late-stage (Ⅲ + Ⅳ) CRC. Conversely, carrying the *OGG1* 111657G allele was beneficial for patients with early stage (0 + Ⅰ + Ⅱ) CRC. In addition, the CRC risk was high in females carrying the *APE1* 148Glu allele (Asp/Glu + Glu/Glu) or the 148Glu/-656G haplotype. No significant associations were observed between the *APE1* T-656G polymorphism and CRC risk.

OGG1 is a crucial DNA-repair gene involved in the BER pathway that can recognize and excise several lesions from the damaged DNA[5]. Mutations that alter the amino acid sequence affect the association of *OGG1* with other proteins, resulting in different DNA-repair activities[10,13,24]. Obtulowicz *et al*[10] reported that the *OGG1* repair capacity reduces with an increases in the Cys allele. Hill *et al*[13] observed that the 326Cys allele excised 8-oxoG from a duplex DNA and cleaved abasic sites 2- to 6-fold lower rates than did the 326Ser allele. Therefore, patients with the *OGG1* 326Cys allele have a lower DNA-repair activity and might be at a higher risk of cancer.

Our results are consistent with those of previous studies that reported a positive association between the *OGG1* 326Cys allele and CRC risk[12,33]. Moreno *et al*[12] observed that the *OGG1* 326Cys allele was associated with an increased risk of CRC (OR = 2.3; 95%CI: 1.1-5.0). Kim *et al*[33] demonstrated that the OR for colon cancer with frequent meat intake increased from 1.72 to 4.31 in carriers of the Cys/Cys genotype, whereas it was not increased in those of the Ser/Ser or Ser/Cys genotype. However, no significant association has been reported between the Ser326Cys polymorphism and CRC risk[5,34].

Functional studies have suggested that the *APE1* 148Glu allele altered endonuclease and DNA-binding activity, reduced the ability to communicate with other BER proteins, and increased mitotic delay after exposure to ionizing radiation[35,36]. Studies have also reported that the *APE1* -656G allele influenced the transcriptional activity, thus resulting in lung cancer risk[18,37]. Although we did not observe any significant independent associations between other DNA-repair genes and CRC risk, the risk slightly increased for the *APE1* 148Glu allele and decreased for the *OGG1* 11657G and *APE1* -656G alleles. Our findings were not completely consistent with those of some previous reports. Kasahara *et al*[25] reported that the *APE1* 148Glu allele significantly increased the CRC risk (OR = 2.33; 95%CI: 1.21-4.48). Zhou *et al*[20] evaluated 37 case-control studies and observed that the cancer risk was significantly low in participants with the *APE1* -656G allele. However, Li *et al*[23] and Moreno *et al*[12] have reported that the *APE1* Asp148Glu polymorphism

Table 3 Odds ratio and 95%CI of two *OGG1* single nucleotide polymorphisms for colorectal cancer stratified by sex, age at diagnosis, and tumor site and stage

	OGG1 Ser326Cys				OGG1 11657A/G			
	Ser/Ser		Ser/Cys + Cys/Cys		A/A		A/G + G/G	
	No.[1]	OR (95%CI)[2]	No.[1]	OR (95%CI)[2]	No.[1]	OR (95%CI)[2]	No.[1]	OR (95%CI)[2]
Gender								
Male	50/67	1.00 (ref)	350/340	1.38 (0.93-2.05)	364/358	1.00 (ref)	31/47	0.65 (0.40-1.05)
Female	43/58	1.00 (ref)	271/265	1.38 (0.90-2.12)	284/296	1.00 (ref)	26/25	1.09 (0.61-1.93)
Age at diagnosis (yr)								
≤ 60	44/54	1.00 (ref)	275/264	1.28 (0.83-1.97)	292/283	1.00 (ref)	23/32	0.70 (0.40-1.22)
> 60	49/71	1.00 (ref)	346/341	1.47 (0.99-2.17)	356/371	1.00 (ref)	34/40	0.89 (0.55-1.43)
Tumor site								
Colon	45/125	1.00 (ref)	299/605	1.39 (0.96-2.01)	316/654	1.00 (ref)	23/72	0.67 (0.41-1.09)
Rectum	48/125	1.00 (ref)	322/605	1.39 (0.97-1.99)	332/654	1.00 (ref)	34/72	0.93 (0.61-1.43)
Stage								
0, Ⅰ, Ⅱ	46/125	1.00 (ref)	283/605	1.28 (0.88-1.84)	307/654	1.00 (ref)	20/72	0.59 (0.35-0.98)[a]
Ⅲ, Ⅳ	47/125	1.00 (ref)	338/605	1.48 (1.03-2.13)[a]	341/654	1.00 (ref)	37/72	0.99 (0.65-1.51)

[1]Number of cases/number of controls; [2]Adjustment for age and sex (except in gender stratification, where only sex was adjusted for). The [a]P < 0.05 is the comparison between CRC patients in stage 0, Ⅰ, Ⅱ and controls in calculating OR for A/G + G/G genotype *vs* A/A genotype.

Table 4 Odds ratio and 95%CI of two *APE1* single nucleotide polymorphisms for colorectal cancer stratified by sex, age at diagnosis, and tumor site and stage

	APE1 Asp148Glu				APE1 T-656G			
	Asp/Asp		Asp/Glu + Glu/Glu		T/T		T/G + G/G	
	No.[1]	OR (95%CI)[2]	No.[1]	OR (95%CI)[2]	No.[1]	OR (95%CI)[2]	No.[1]	OR (95%CI)[2]
Gender								
Male	137/122	1.00 (ref)	264/283	0.83 (0.62-1.12)	128/111	1.00 (ref)	277/296	0.81 (0.60-1.10)
Female	99/127	1.00 (ref)	215/195	1.41 (1.02-1.96)[a]	89/100	1.00 (ref)	227/224	1.14 (0.81-1.60)
Age at diagnosis (yr)								
≤ 60	105/110	1.00 (ref)	213/205	1.09 (0.78-1.51)	108/99	1.00 (ref)	215/219	0.90 (0.65-1.26)
> 60	131/139	1.00 (ref)	266/273	1.03 (0.77-1.38)	109/112	1.00 (ref)	289/301	0.99 (0.73-1.35)
Tumor site								
Colon	114/249	1.00 (ref)	231/478	1.06 (0.81-1.40)	105/211	1.00 (ref)	244/520	0.94 (0.71-1.25)
Rectum	122/249	1.00 (ref)	248/478	1.05 (0.81-1.38)	112/211	1.00 (ref)	260/520	0.95 (0.72-1.24)
Stage								
0, Ⅰ, Ⅱ	106/249	1.00 (ref)	226/478	1.11 (0.84-1.47)	107/211	1.00 (ref)	226/520	0.85 (0.64-1.12)
Ⅲ, Ⅳ	130/249	1.00 (ref)	253/478	1.02 (0.79-1.33)	110/211	1.00 (ref)	278/520	1.03 (0.79-1.36)

[1]Number of cases/number of controls; [2]Adjustment for age and sex (except in gender stratification, where only sex was adjusted for). The [a]P < 0.05 is the comparison between CRC cases and controls among female in calculating OR for Asp/Glu + Glu/Glu genotype *vs* Asp/Asp genotype.

was unassociated with CRC.

We observed that the *OGG1* Ser326Cys polymorphism was significantly associated with an increased risk of CRC in patients with stage Ⅲ + Ⅳ tumors, whereas the *OGG1* 11657A/G polymorphism was associated with a decreased risk of CRC in patients with stage 0 + Ⅰ + Ⅱ tumors. This finding suggests that the *OGG1* 11657A/G polymorphism contributed to tumor initiation and that the *OGG1* Ser326Cys polymorphism may play a role in tumor progression. The exact mechanism underlying specific *OGG1* polymorphisms involved in different tumor stages remains unclear. Further studies are required to delineate the association.

Similar to the findings of earlier studies, our investigation demonstrated no association between the *OGG1* polymorphisms and CRC risk stratified by sex and tumor sites. Pardini *et al*[38] and Kasahara *et al*[25] have shown that the *OGG1* Ser326Cys polymorphism was not significantly associated with colon or rectal cancer, respectively. Our study was the first to evaluate the sex-specific risk of CRC associated with the *OGG1* polymorphisms, but no significant association was observed. Moreno *et al*[12] observed that the increased CRC risk associated with the 326Cys allele was marked among younger participants, but our study failed to find such an association.

We observed an elevated CRC risk associated with the *APE1* 148Glu allele in females, which was inconsistent with results of previous studies. Pardini *et al*[38] reported that compared with the Asp/Asp genotype, the Asp/Glu + Glu/Glu genotype was unassociated with the CRC risk. By contrast, they observed that the Asp/Asp genotype was associated with an increased risk of colon cancer (OR = 1.50; 95%CI: 1.01-2.22). In a study of a Japanese population, the *APE1* Glu allele

Table 5 Odds ratio and 95%CI of *APE1* haplotypes for colorectal cancer stratified by sex, age at diagnosis, and tumor site and stage

	APE1 Asp148Glu/T-656G							
	Asp/T		Asp/G		Glu/T		Glu/G	
	Ca/Co (%)[1]	OR (95%CI)[2]	Ca/Co (%)[1]	OR (95%CI)[2]	Ca/Co (%)[1]	OR (95%CI)[2]	Ca/Co (%)[1]	OR (95%CI)[2]
All	41.1/41.5	1.00 (ref)	16.3/17.7	0.93 (0.75-1.15)	14.5/13.4	1.09 (0.87-1.37)	28.1/27.5	1.03 (0.86-1.24)
Gender								
Male	42.5/40.0	1.00 (ref)	16.0/16.8	0.87 (0.66-1.16)	14.5/14.6	0.91 (0.67-1.22)	27.1/29.7	0.84 (0.66-1.06)
Female	39.3/44.6	1.00 (ref)	16.7/18.9	1.00 (0.73-1.36)	14.5/11.8	1.39 (0.98-1.97)	29.5/24.7	1.36 (1.03-1.78)[a]
Age at diagnosis (yr)								
≤ 60	42.1/42.7	1.00 (ref)	17.1/17.2	1.01 (0.74-1.38)	15.7/14.8	1.08 (0.77-1.50)	25.0/25.3	1.00 (0.76-1.32)
> 60	40.3/40.5	1.00 (ref)	15.6/18.1	0.87 (0.65-1.15)	13.5/12.3	1.10 (0.81-1.50)	30.6/29.1	1.06 (0.84-1.34)
Tumor site								
Colon	40.4/41.5	1.00 (ref)	16.7/17.7	0.96 (0.74-1.25)	15.5/13.4	1.20 (0.91-1.58)	27.4/27.5	1.03 (0.82-1.28)
Rectum	41.7/41.5	1.00 (ref)	16.0/17.7	0.90 (0.69-1.16)	13.5/13.4	0.99 (0.75-1.31)	28.8/27.5	1.04 (0.84-1.29)
Stage								
0, Ⅰ, Ⅱ	41.1/41.5	1.00 (ref)	15.8/17.7	0.90 (0.69-1.17)	14.9/13.4	1.14 (0.86-1.51)	28.2/27.5	1.02 (0.82-1.28)
Ⅲ, Ⅳ	41.1/41.5	1.00 (ref)	16.7/17.7	0.95 (0.74-1.23)	14.1/13.4	1.06 (0.81-1.39)	28.1/27.5	1.04 (0.84-1.29)

[1]Percentage of cases/percentage of controls; [2]Adjustment for age and sex (except in gender stratification, where only sex was adjusted for). The [a]$P < 0.05$ is the comparison between CRC cases and controls among female in calculating OR for Glu/G haplotype *vs* Asp/T haplotype.

carriers exhibited a significantly increased risk of colon cancer (OR = 3.04; 95%CI: 1.38-671)[25]. Li *et al*[23] observed that the *APE1* Asp148Glu polymorphism was unassociated with CRC even when stratified by sex, age at diagnosis, and tumor site. A meta-analysis of 27 case-control studies showed that the *APE1* Glu allele was associated with an increased CRC risk (OR = 1.23; 95%CI: 1.05-1.43) but not in the Asian population (OR = 1.03; 95%CI: 0.92-1.16)[39]. Furthermore, we also observed that the *APE1* 148Glu/-656G haplotype was associated with a significantly increased risk of CRC in females, which is inconsistent with a previous report. Pan *et al*[28] observed that carriers of the *APE1* 148Asp/-656T haplotype were at a higher risk of lung cancer than those of the 148Glu/-656G haplotype. The exact mechanism underlying this sex-specific risk of CRC associated with the *APE1* Asp148Glu polymorphism or Asp148Glu/T-656G haplotype remain unclear.

Our study has potential limitations. First, we did not examine OGG1 or APE1 mRNA expression levels nor did we measure the 8-oxoG levels for analyzing their correlations. Second, the case-control study design has inherent limitations. The controls are hospital based, but we consider that the genotype of DNA-repair genes do not affect the possibility of a participant being selected. The small sample size is another limitation. The power to detect a significant CRC risk for the *OGG1* 326Cys carriers (OR = 1.38) is approximately 60%. Therefore, an additional larger study is necessary to clarify the causality.

In conclusion, we reported a significant association between *OGG1* and *APE1* polymorphisms and the CRC risk in the Taiwanese population, particularly in patients with *OGG1* Ser326Cys in stage Ⅲ + Ⅳ tumors, *OGG1* 11657A/G in stage 0 + Ⅰ + Ⅱ tumors, and *APE1* Asp148Glu in females. Our results suggest that genetic variants in the DNA-repair pathway genes modulate the risk of sporadic CRC in this population; however, additional studies are required for verifying the findings.

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COMMENTS

Background

Colorectal cancer (CRC) is the second most commonly diagnosed cancers and third leading cause of cancer-related deaths in Taiwan. Oxidative damages resulting from reactive oxygen species (ROS) generation participate in the development and occurrence of CRC. DNA-repair enzymes are critical in maintaining genomic stability and minimizing damage accumulation from ROS. The expression of the base excision repair (*BER*) gene family is activated by internal oxidative stress and DNA damage. The BER pathway involves 8-oxoguanine glycosylase 1 (OGG1) and apurinic-apyrimidinic endonuclease 1 (APE1).

Research frontiers

Molecular epidemiological studies have suggested that polymorphisms in DNA repair pathways affect the DNA repair capacity to renovate the damaged DNA and may predispose participants to CRC risk. Studies have shown that polymorphisms of *OGG1* (Ser326Cys, 11657A/G, and Arg154His) and *APE1* (Asp148Glu, and T-656G) were associated with enzyme activities. However, the results are controversial.

Innovations and breakthroughs

This research recruited 727 cases with newly diagnosed colorectal adenocarcinoma and 736 age- and sex-matched healthy controls from a medical center in Taiwan. The authors not only confirmed the association of *OGG1* and *APE1* polymorphisms with the CRC risk but also suggest that genetic variants in DNA-repair pathway genes modulate the risk of sporadic CRC in the Taiwanese population.

Applications

These findings revealed a significant association between *OGG1* and *APE1*

polymorphisms and the CRC risk in Taiwanese Patients, particularly in *OGG1* Ser326Cys in stage Ⅲ + Ⅳ cases, *OGG1* 11657A/G in stage 0 + Ⅰ + Ⅱ cases, and *APE1* Asp148Glu in females. These results might facilitate identifying Taiwanese patients at a high risk of CRC.

Terminology

Single nucleotide polymorphism (SNP), also known as simple nucleotide polymorphism, is a DNA sequence variation prevalent in populations, in which a single nucleotide differs between members of a biological species or paired chromosomes. SNP in some genes may affect mRNA or protein expression resulting in an increase or decrease in the risk of certain diseases.

Peer-review

This manuscript is well established to investigate the association between *BER* gene polymorphisms and CRC susceptibility. The language and logic is well expressed, the structure and methods of this research were reasonable and completed.

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