Comprehensive analysis of the correlation between base-excision repair gene SNPs and esophageal squamous cell carcinoma risk in a Chinese Han population

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Abstract. This study sought to assess the relationship between single nucleotide polymorphisms (SNPs) affecting DNA base-excision repair (BER) genes and esophageal squamous cell carcinoma (ESCC) risk in a Han Chinese population. Genes screened for such SNPs included 8-oxoguanine DNA glycosylase (OGG1), apurinic/apyrimidinic endonuclease 1 (APE1) and X-ray repair cross-complementing group 1 protein (XRCC1). Blood samples that had been collected in a prospective manner were used for DNA extraction, with all DNA samples then being subjected to PCR-restriction fragment length polymorphism genotyping for BER gene SNPs, including APE1 Asp148Glu and -141T/G, OGG1 Ser326Cys, and XRCC1 Arg399Gln. The relationship between these SNPs and ESCC risk was then assessed, with the comparability of the case and control groups being enhanced via propensity score matching (PSM). This study initially included 642 healthy controls and 321 ESCC patients, with PSM optimization leading to a final analyzed total of 311 matched subjects per group (311 total). Factors associated with elevated ESCC risk in this analysis included advanced age, being male and smoking. We further identified that the XRCC1 399 Gln/Gln genotype was associated with a significant reduction in ESCC risk prior to propensity matching (odds ratio=0.48; 95% CI: 0.23-1.00; P<0.05), although this did not remain true following matching. For the remaining analyzed SNPs, no significant associations between genotype and ESCC risk were detected prior to or following propensity matching. A multivariate analysis incorporating patient age, sex, smoking status and drinking status failed to detect any relationship between the four tested genotypes and ESCC risk. In conclusion, being male, a smoker or of advanced age was associated with an elevated ESCC risk. However, we did not detect any significant relationship between ESCC risk and BER polymorphisms in XRCC1, OGG1, APE1 or the APE1 promoter region in a Han Chinese population.

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Introduction

Esophageal cancer (EC) is a common and often fatal cancer which has two main histological subtypes: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). More than 90% of EC cases in China are of the ESCC subtype (1). The development of ESCC is influenced by myriad genetic and environmental factors, with the latter being known to include alcohol and tobacco use, malnutrition, and exposure to nitrosamine carcinogens (2-5). Prior studies (6-8) have identified a large number of single nucleotide polymorphisms (SNPs) that are related to ESCC incidence. Mutations related to DNA damage repair pathway in particular have been found to be closely related to this form of cancer. The DNA damage repair system plays an important role in maintaining the stability of genomic DNA and preventing oncogenesis. Base excision repair (BER) is one of the primary pathways used to repair DNA damage caused by reactive oxygen species and other electrophiles, and as such, BER genes are good candidate susceptibility genes for ESCC.

The key BER pathway genes include 8-oxoguanine glycosylase-1 (OGG1), AP endonuclease-1 (APE1), and X-ray repair cross-complementing-1 (XRCC1), and as a result, several studies have assessed the relationship between SNPs in these genes, cancer development, and patient chemotherapeutic resistance (2,3,9-17). Whether the XRCC1 Arg399Gln and OGG1 Ser326Cys polymorphisms are associated with risk of ESCC development, however, remains a matter of controversy (2,3,9-15). In some reports, these two mutations were found to be linked with such risk (2,3,9,18,19), whereas other studies detected no such relationship for these genes (11-15,20,21). Furthermore, how the APE1-141T/G polymorphism or how these four SNPs (APE1 Asp148Glu and -141T/G, OGG1 Ser326Cys, and XRCC1 Arg399Gln) synergistically impact ESCC risk remains uncertain.

As no studies to date have firmly established the relationship between these BER gene SNPs and ESCC risk in a

Table I. Distribution of demographic characteristics of esophageal squamous cell carcinoma case and control participants.

	Before propensity matching			After propensity matching		
Variables	Controls, n (%) n=642	Cases, n (%) n=321	P-value	Controls, n (%) n=311	Cases, n (%) n=311	P-value
Age, years			<0.001			0.895
Mean age	51.7±17.6	61.9±10.2		61.59±14.33	61.99±10.23	
≥60	240 (37.4)	190 (59.2)		186 (59.8)	188 (60.5)	
<60	402 (62.6)	131 (40.8)		125 (40.2)	123 (39.5)	
Sex			<0.001			0.651
Male	346 (53.9)	270 (84.1)		267 (85.85)	263 (84.57)	
Female	296 (46.1)	51 (15.9)		44 (14.15)	48 (15.43)	
Smoking			<0.001			0.398
Never	372 (57.9)	116 (36.6)		117 (37.62)	114 (36.66)	
Former	40 (6.2)	19 (6.0)		26 (8.36)	18 (5.79)	
Current	230 (35.8)	182 (57.4)		168 (54.02%)	179 (57.56%)	
Drinking			0.884			0.91
Never	348 (54.2)	167 (52.5)		166 (53.38)	165 (53.05)	
Former	25 (3.9)	13 (4.1)		10 (3.22)	12 (3.86)	
Current	269 (41.9)	138 (43.4)		135 (43.41)	134 (43.09)	
Family history of cancer			0.343			0.303
Yes	620 (96.6)	306 (95.3)		290 (93.25)	296 (95.18)	
No	22 (3.4)	15 (4.7)		21 (6.75)	15 (4.82)	

Han Chinese population, the present study was designed to comprehensively analyze this topic of research.

Patients and methods

Patients and control group. This was a case-control study, approved by The Daping Hospital Ethics Committee with all participants providing informed consent. In total, we consecutively recruited 642 cancer-free control patients (296 females, 346 males; mean age: 51.7 years) and 321 patients with newly-diagnosed ESCC (51 females, 270 males; mean age: 61.9 years) at Daping Hospital, Third Military Medical University (Chongqing, China) from January 2008 to December 2012, with all participants declaring themselves as being of Han Chinese ethnicity, and with no sex or age restrictions being imposed during recruitment. Table I summarizes the general characteristics of these two populations. All ESCC patients were newly diagnosed with the disease based on pathological findings and were undergoing outpatient treatment at this hospital. The control group were those that had undergone health examinations at the Health Examination Center of this hospital during the same period. Patients were excluded from the present study if they met any of the following criteria: i) Non-Han ethnicity; ii) history of previous cancers and iii) history of treatment via radio - or chemotherapy.

In a questionnaire administered to all study participants, a family history of cancer was defined as any reports of cancer affecting first-degree relatives (children, siblings, or parents). With respect to alcohol consumption, anyone consuming 10 gr alcohol/day for >1 year was considered to be exposed to alcohol, while all other participants were considered to be non-drinkers or to be formerly exposed to alcohol if they had abstained from alcohol consumption for at least 1 year. With respect to smoking status, current smokers were those who reported partaking of a minimum of one cigarette per day for >1 year. Former smokers were those reporting to have deliberately abstained from smoking for at least 1 year, while all other participants were non-smokers.

Blood sample processing. EDTAK2 anticoagulant tubes were used to collect samples of venous blood from the antecubital vein of each study participant. These samples were immediately centrifuged for 10 minutes at 670.8xg at 4oC in order to facilitate serum removal. The peripheral blood leukocytes were then collected, and gDNA extraction was performed using an EZNASE Blood DNA kit (Omega Bio-Tek Inc.), with samples being stored at -80˚C.

SNPs selection and genotyping. The four non-synonymous BER gene SNPs selected for genotyping in the present study included: rs1130409 (APE1 exon 5; Asp148Glu; T/G), rs1760944 (APE1 promoter polymorphism; -141T/G), rs1052133 (OGG1 exon 7; Ser326Cys; C/G) and rs25487 (XRCC1 exon 10; Arg399Gln; G/A). BER gene SNP genotyping was conducted via the use of PCR-RFLP for these patient and non-patient samples, as previously described (22). For each allele, primer pairs and product lengths were specifically selected such that alleles could be identified according to product length. GenBank reference sequences were used to

Table II. Primer sequences used in the present study.

Target gene	Position	Sequence of primers	Allele and size of PCR products (bp)
APE1-141T/G	T-141G	F1: 5'-CTAACTGCCAGGGACGCCGA-3'	For T allele (136)
		R1: 5'-ACACTGACTTAAGATTCTAACTA-3'	
		F2: 5'-ACTGTTTTTTTCCCTCTTGCACAG-3'	For G allele (335)
		R2: 5'-TGAGCAAAAGAGCAACCCCG-3'	
APE1 Asp148Glu	T2197G	F1: 5'-CCTACGGCATAGGTGAGACC-3'	For G allele (167)
		R1: 5'-TCCTGATCATGCTCCTCC-3'	
		F2: 5'-TCTGTTTCATTTCTATAGGCGAT-3'	For T allele (236)
		R2: 5'-GTCAATTTCTTCATGTGCCA-3'	
OGG1 Ser326Cys	C1245G	F1: 5'-CAGCCCAGACCCAGTGGACTC-3'	For C allele (252)
		R1: 5'-TGGCTCCTGAGCATGGCGGG-3'	
		F2: 5'-CAGTGCCGACCTGCGCCAATG-3'	For G allele (194)
		R2: 5'-GGTAGTCACAGGGAGGCCCC-3'	
XRCC1 Arg399Gln	G28152A	F1: 5'-TCCCTGCGCCGCTGCAGTTTCT-3'	For G allele (447)
		R1: 5'-TGGCGTGTGAGGCCTTACCTCC-3'	
		F2: 5'-TCGGCGGCTGCCCTCCCA-3'	For A allele (222)
		R2: 5'-AGCCCTCTGTGACCTCCCAGGC-3'	

OCG1, 8-oxoguanine DNA glycosylase; APE1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing group 1 protein; F, forward; R, reverse.

Table III. Observed and expected genotypic frequencies of each single nucleotide polymorphism in the control group.

Genes	Observed, n (%)	Expected, n (%)	P-value (HWE)
OGG1Ser326Cys			0.71
Ser/Ser(CC)	100 (15.6)	98 (15.3)	
Ser/Cys(CG)	301 (46.9)	305 (47.5)	
Cys/Cys(GG)	241 (37.5)	239 (37.2)	
APE1 Asp148Glu			0.19
Asp/ Asp(TT)	230 (35.8)	222 (34.6)	
Asp/ Glu(TG)	295 (46.0)	311 (48.4)	
Glu/ Glu(GG)	117 (18.2)	109 (17.0)	
APE1 -141T/G			
TT	201 (31.31)	211 (32.9)	0.11
TG	334 (52.02)	314 (48.9)	
GG	107 (16.67)	107 (16.7)	
XRCC1 Arg399Gln			0.1
Arg/Arg(GG)	345 (53.74)	353 (55.0)	
Arg/Gln(GA)	262 (40.81)	246 (38.3)	
Gln/Gln(AA)	35 (5.45)	43 (6.7)	

OCG1, 8-oxoguanine DNA glycosylase; APE1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing group 1 protein; HWE, Hardy-Weinberg equilibrium.

guide primer design, with the resultant primers being shown in Table II. Replication of genotyping results was not performed.

Each PCR reaction was conducted in a 25 μl total volume that contained 2 μl gDNA, 1 μl primers, 12.5 μl Go Taq MIX (2x) for each of the four primers, and 6.5 μl dH_2O. Thermocycler settings were: 95˚C for 10 min; 30 cycles of 95˚C for 1 min, 60˚C (APE1 Asp148Glu), 58˚C (APE1-141T/G), 66˚C (XRCC1 Arg399Gln), or 64˚C (OGG1Ser326Cys) for 1 min, and 72˚C for 1 min. Agarose gel electrophoresis was then used to analyze the resultant PCR products.

Statistical analysis. SPSS 19.0 (IBM, Corp.) was used for all statistical testing. Only participants with complete demographic information pertaining to age, sex, and alcohol intake/smoking status were included in the present analysis. Ultimately, 642 non-affected participants and 321 ESCC patients were analyzed. We then further utilized a propensity score matching (PSM) analysis in order to balance out baseline differences between these two participant groups. This PSM analytical approach employed a 1:1 matching strategy, with 311 cases being successfully matched. This propensity model included age, sex, smoking status, alcohol intake, and family history of cancer when matching participants. Differences in these demographic variables and in SNP frequencies between groups were compared via Pearson χ^2 tests, and Hardy-Weinberg equilibrium for each SNP was additionally tested. Unconditional logistic regression was undertaken to estimate odds ratios (OR) and 95% CIs were estimated following PSM via unconditional logistic regression analysis. A two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

General information. For the present study, we recruited 963 total participants of Han Chinese ethnicity, including 642 cancer-free individuals and 321 ESCC patients, with study population characteristics being shown in Table I. There were

Table IV. Distribution of genotypes and OR determined for esophageal squamous cell carcinoma cases and controls before propensity matching.

A, OGG1Ser326Cys

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value
Genotype				
Cys/Cys	125 (38.9)	241 (37.5)		
Ser/Cys	143 (44.5)	301 (46.9)	0.92 (0.68-1.23)	0.56
Ser/Ser	53 (16.5)	100 (15.6)	1.02 (0.69-1.52)	0.92
Allele				
Cys	393 (61.2)	783 (61.0)		
Ser	249 (38.8)	501 (39.0)	0.99 (0.82-1.20)	0.92

B, APE1 Asp148Glu

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value
Genotype				
Asp/Asp	117 (36.4)	230 (35.8)		
Asp/Glu	148 (46.1)	295 (46.0)	0.97 (0.73-1.33)	0.93
Glu/Glu	56 (17.4)	117 (18.2)	0.94 (0.64-1.39)	0.76
Allele				
Asp	382 (59.5)	755 (58.9)		
Glu	260 (40.5)	529 (41.1)	0.97 (0.80-1.18)	0.77

C, APE1 -141T/G

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value
Genotype				
TT	98 (30.5)	214 (33.3)		
TG	138 (43.0)	287 (44.7)	1.05 (0.77-1.44)	0.76
GG	85 (26.5)	141 (22.0)	1.32 (0.92-1.89)	0.13
Allele				
T	334 (52.0)	715 (55.7)		
G	308 (48.0)	569 (44.3)	1.16 (0.96-1.60)	0.13

D, XRCC1 Arg399Gln

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value
Genotype				
Arg/Arg	153 (47.7)	331 (51.5)		
Arg/Gln	159 (49.5)	270 (42.1)	1.27 (0.97-1.68)	0.08
Gln/Gln	9 (2.8)	41 (6.4)	0.48 (0.23-1.00)	0.04
Allele				
Arg	465 (72.4)	932 (72.6)		
Gln	177 (27.6)	352 (27.4)	1.01 (0.82-1.25)	0.94

OCG1, 8-oxoguanine DNA glycosylase; APE1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing group 1 protein; OR, odds ratio.

significant differences between the control and cancer patient populations with respect to participant age, sex, and smoking status prior to PSM. There were significantly more participants that were male (59.2 vs. 37.4%), 60+ years old (84.1 vs. 53.9%),

Table V. Distribution of genotypes and OR determined for esophageal squamous cell carcinoma cases and controls after propensity matching.

A, OGG1Ser326Cys

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value	OR (95% CI)[a]	P-value[a]
Genotype						
Cys/Cys	120 (38.59)	110 (35.37)				
Ser/Cys	140 (45.02)	156 (50.16)	0.82 (0.58-1.16)	0.32	0.82 (0.58-1.17)	0.33
Ser/Ser	51 (16.40)	45 (14.47)	1.04 (0.65-1.67)	0.88	1.05 (0.63-1.57)	0.84
Allele						
Cys	380 (61.1)	376 (60.5)				
Ser	242 (38.9)	246 (39.5)	0.97 (0.78-1.22)	0.82	0.98 (0.80-1.23)	0.81

B, APE1 Asp148Glu

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value	OR (95% CI)[a]	P-value[a]
Genotype						
Asp/Asp	113 (36.33)	111 (35.69)				
Asp/Glu	142 (45.66)	149 (47.91)	0.94 (0.66-1.33)	0.71	0.93 (0.65-1.32)	0.69
Glu/Glu	56 (18.01)	51 (16.40)	1.08 (0.68-1.71)	0.75	1.10 (0.69-1.74)	0.70
Allele						
Asp	368 (59.2)	371 (59.6)				
Glu	254 (40.8)	251 (40.4)	1.02 (0.81-1.28)	0.86	1.03 (0.82-1.29)	0.88

C, APE1 -141T/G

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value	OR (95% CI)[a]	P-value[a]
Genotype						
TT	97 (31.19)	87 (27.97)				
TG	130 (41.80)	153 (49.20)	0.76 (0.53-1.11)	0.15	0.75 (0.52-1.10)	0.14
GG	84 (27.01)	71 (22.83)	1.06 (0.69-1.63)	0.79	1.07 (0.69-1.65)	0.77
Allele						
T	324 (52.1)	327 (52.6)				
G	298 (47.9)	295 (47.4)	1.02 (0.82-1.27)	0.87	1.01 (0.81-1.26)	0.86

D, XRCC1 Arg399Gln

Comparisons	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value	OR (95% CI)[a]	P-value[a]
Genotype						
Arg/Arg	147 (47.27)	165 (53.05)				
Arg/Gln	155 (49.84)	129 (41.48)	1.33 (0.98-1.86)	0.07	1.35 (0.98-1.87)	0.07
Gln/Gln	9 (2.89)	17 (5.47)	0.59 (0.26-1.38)	0.22	0.60 (0.26-1.40)	0.24
Allele						
Arg	449 (72.2)	459 (73.8)				
Gln	173 (27.8)	163 (26.2)	1.09 (0.85-1.39)	0.52	1.10 (0.85-1.40)	0.53

[a]Multivariate analysis. OCG1, 8-oxoguanine DNA glycosylase; APE1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing group 1 protein; OR, odds ratio.

or smokers (57.4 vs. 35.8%) in the ESCC group relative to the control group. After the PSM analysis, 622 matched subjects were included in the following analyses (n=311/group). Following PSM, there were no significant differences between

Table VI. Association between esophageal squamous cell carcinoma risk and the single nucleotide polymorphism variant of the base-excision repair gene in the recessive model.

Genes	Cases, n (%)	Controls, n (%)	Association OR (95% CI)	P-value
OGG1Ser326Cys				
Cys/Cys+Ser/Cys	260 (83.60)	266 (85.53)		
Ser/Ser	51 (16.40)	45 (14.47)	1.15 (0.75-1.79)	0.51
APE1 Asp148Glu				
Asp/Asp+Asp/Glu	255 (81.99)	260 (83.60)		
Glu/Glu	56 (18.01)	51 (16.40)	1.12 (0.74-1.70)	0.60
APE1 -141T/G				
TT+TG	227 (72.99)	240 (77.17)		
GG	84 (27.01)	71 (22.83)	1.25 (0.87-1.80)	0.23
XRCC1 Arg399Gln				
Arg/Arg+Arg/Gln	302 (97.11)	294 (94.53)		
Gln/Gln	9 (2.89)	17 (5.47)	0.52 (0.23-1.18)	0.11

OCG1, 8-oxoguanine DNA glycosylase; APE1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing group 1 protein; OR, odds ratio.

Table VII. Association between esophageal squamous cell carcinoma risk and the single nucleotide polymorphism variant of the base-excision repair gene in the dominant model.

Genes P-value	Cases, n (%)	Controls, n (%)	Association OR (95% CI)	
OGG1Ser326Cys				
Cys/Cys	120 (38.59)	110 (35.37)		
Ser/Cys+Ser/Ser	191 (61.41)	201 (64.63)	0.87 (0.63-1.21)	0.41
APE1 Asp148Glu				
Asp/Asp	113 (36.33)	111 (35.69)		
Glu/Glu+Asp/Glu	198 (63.67)	200 (64.31)	0.97 (0.70-1.35)	0.87
APE1 -141T/G				
TT	97 (31.19)	87 (27.97)		
GG+TG	214 (68.81)	224 (72.03)	0.86 (0.61-1.21)	0.38
XRCC1 Arg399Gln				
Arg/Arg	147 (47.27)	165 (53.05)		
Gln/Gln+Arg/Gln	164 (52.73)	146 (46.95)	1.26 (0.92-1.73)	0.15

OCG1, 8-oxoguanine DNA glycosylase; APE1, apurinic/apyrimidinic endonuclease 1; XRCC1, X-ray repair cross-complementing group 1 protein; OR, odds ratio.

case and control groups with respect to participant age, sex, smoking status, alcohol intake, or family history of cancer, thus confirming the comparability of these groups.

Association between BER polymorphisms in XRCC1, OGG1, APE1 and ESCC risk. APE1 (141T/G; Asp148Glu), OGG1 (Ser326Cys), and XRCC1 (Arg399Gln) genotypes and allele frequency distributions in the control group were all consistent with those predicted according to Hardy-Weinberg equilibrium (Table III; P>0.05).

Prior to PSM, no significant relationship between APE1 Asp148Glu, APE1 -141T/G, or OGG1 Ser326Cys and ESCC risk was detected, while a significant relationship was detected between XRCC1 Arg399Gln and ESCC risk (Table IV). However, following PSM there was no significant relationship between these four BER SNPs and ESCC risk (Table V), with this same lack of significance being observed in a recessive model (Table VI) and a dominant model (Table VII).

Associations between gene-gene interactions for four SNPs and ESCC risk. We additionally sought to test whether there were any associations between gene-gene interactions for these four SNPs and ESCC risk (Table VIII). As very few individuals contained all 6 of these risk alleles in a recessive

Table VIII. Joint pathway analysis of base-excision repair polymorphisms in esophageal squamous cell carcinoma risk using a dominant genetic model and recessive model.

Total number of risk genotypes	Cases, n (%)	Controls, n (%)	OR (95% CI)	P-value[a]
Dominant genetic model				
0	9 (2.9)	15 (4.8)	Ref.	
1	77 (24.8)	64 (20.6)	2.01 (0.82-4.89)	0.12
2	132 (42.4)	147 (47.3)	1.50 (0.63-3.53)	0.35
3	93 (29.9)	85 (27.3)	1.82 (0.76-4.39)	0.18
Recessive genetic model				
0	9 (2.9)	15 (4.8)	Ref.	
1	45 (14.5)	36 (11.6)	2.08 (0.82-5.31)	0.12
2	90 (28.9)	106 (34.1)	1.42 (0.59-3.39)	0.43
3	101 (32.5)	90 (28.9)	1.87 (0.78-4.48)	0.16
4	52 (16.7)	48 (15.4)	1.81 (0.72-4.51)	0.20
5-6	14 (4.5)	16 (5.1)	1.46 (0.49-4.36)	0.50

[a]Adjusted for age, sex, smoking, drinking and family history of cancer. A total of 622 patients were included for unconditional logistic regression analysis. OR, odds ratio.

model, individuals with 5 or 6 of these genotypes were pooled for analysis. Finally, no significant correlation was found between SNP-SNP interactions and individual susceptibility to ESCC in either a recessive or a dominant model.

Discussion

In China, esophageal cancer is the fourth most common cancer-associated cause of death, with 477,900 newly diagnosed cases in 2015 alone, including 157,200 cases in females and 320,800 in males (23). Indeed, males are more likely to be affected by this disease than are females, consistent with the results of the present study in which a significantly higher number of males than females were affected by ESCC in the study population. Several environmental factors have been associated with esophageal cancer risk, including malnutrition, Barrett's esophagus, exposure to nitrosamine carcinogens, smoking, and alcohol consumption (4,5). However, exposure to these factors alone is not sufficient to determine whether or not a given individual develops ESCC, and genetic factors thus also play a role in the etiology of this disease. As such, in the present study we assessed whether four BER gene SNPs (APE1 Asp148Glu, APE1-141T/G, OGG1 Ser326Cys, and XRCC1 Arg399Gln) were related with ESCC risk in a Han Chinese population.

XRCC1 is a key BER gene encoded on chromosome 19q13.2, q13.3 with 17 exons. XRCC1 plays a key role in mediating the repair of single-stranded DNA breaks as part of the BER pathway, with SNPs in this gene having the potential to alter or compromise protein functionality (3,19,24,25). Mutations in XRCC1 have been linked with many different cancer types, including hepatocellular carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, and lung, bladder, gastric, and cervical cancers (16,26-32). Previous studies have focused largely on three different XRCC1 polymorphisms when assessing their relationship with esophageal cancer risk, including Arg280His, Arg194Trp, and Arg399Gln (3,11,13,33). These studies have, however, yielded inconsistent results regarding whether the XRCC1 Arg399Gln SNP was associated with esophageal cancer risk (2,3,9-14). In a meta-analysis, the XRCC1 Arg399Gln SNP was found to be linked with elevated EC risk in a Chinese population, with this association being strongest for the ESCC subtype (2,3). However, other studies failed to detect any significant association between this SNP and EC risk using a variety of genetic models (11,13,20,21). These differing results may stem from differences in sample size, lifestyle, environmental factors, or geographic distributions between studies. In addition, PSM was not conducted in all of these prior studies as a means of controlling for potential confounding. In the present study, we did detect a significant relationship between XRCC1 Arg399Gln and ESCC risk prior to but not after PSM, suggesting that the impact of this XRCC1 SNP on ESCC risk may not only be related to its defective role in BER, but also to the hampering other intracellular processes (34,35).

OGG1 is an additional BER gene encoded on chromosome 3p26, and it has also been proposed to play a role in the transcriptional regulation of genes associated with inflammation and DNA repair, suggesting that OGG1 may contribute to carcinogenesis (36-38).Given this role, it is perhaps unsurprising that the OGG1 Ser326Cys SNP has been studied in the context of cancer risk in many different studies, although the conclusions of these studies were somewhat variable (39-41). A more recent meta-analysis that included 152 case-control studies suggested that these inconsistent results may have arisen due to differences in cancer type, sample size, and control participant sources (40). This meta-analysis ultimately failed to detect any significant relationship between the OGG1 Ser326Cys SNP and cancer risk, which was consistent with the lack of such an association detected in our present study.

APE1 functions as an important mediator of DNA repair and other cellular homeostatic processes, defects in which

are linked to the development and progression of cancer (42). Several APE1 SNPs have been detected to date (43), including two functional SNPs (rs1760944: -656 T>G in the promoter region; and rs1130409 1349 T>G in exon 5) (44). APE1 SNPs have been suggested to be associated with cancer susceptibility in previous epidemiological studies. For example, when patients were stratified according to cancer type in a meta-analysis the Asp148Glu APE1 SNP was linked with prostate cancer risk (45). However, a separate meta-analysis detected no significant relationship between APE1 Asp148Glu and digestive cancer (46). A further meta-analysis that included 6136 controls and 4856 cancer patients failed to detect any significant relationship between Asp148Glu and the risk of esophageal and colorectal cancer risk in any genetic model. Other studies have similarly detected no such relationship between Asp148Glu and EC risk (10,15). This was consistent with the results of our present study, which similarly found APE1 Asp148Glu to be unrelated to ESCC risk in any genetic model.

Overall, the findings from the present study suggest that being male, being 60 years of age or older, and being a smoker are each associated with elevated ESCC risk. However, we did not detect any significant relationship between the four tested BER SNPs (APE1 Asp148Glu, APE1-141T/G, OGG1 Ser326Cys, and XRCC1 Arg399Gln) and ESCC risk in this Chinese Han population. The results of this analysis will require further confirmation in an independent and larger cohort in order to better understand the genetic basis for ESCC risk.

In light of the important role that smoking and drinking status play in the development of ESCC, the absence of any gene-environment interaction or stratified analyses represent potential limitations of our study. In addition, f haplotype analysis for the two APE1 SNPs is required. Moreover, the limited sample size and potential resulting lack of statistical power in this study may have limited our ability to resolve meaningful phenotypes.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YP and LZ designed the research and analyzed the patient data, and drafted the manuscript. ND interpreted the results. MX was involved in study conception and design, analysis and interpretation of the results, and critical revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study conformed to the Clinical Research Guidelines and was approved by the Ethics Committee of Daping Hospital (Chongqing, China). Informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Liu B, Cheng B, Wang C, Chen P and Cheng Y: The prognostic significance of metabolic syndrome and weight loss in esophageal squamous cell carcinoma. Sci Rep 8: 10101, 2018.
2. Zhang ZY, Xuan Y, Jin XY, Tian X and Wu R: Meta-analysis demonstrates association of XRCC1 genetic polymorphism Arg399Gln with esophageal cancer risk in the Chinese population. Genet Mol Res 12: 2567-2577, 2013.
3. Yin M, Tan D and Wei Q: Genetic variants of the XRCC1 gene and susceptibility to esophageal cancer: A meta-analysis. Int J Clin Exp Med 2: 26-35, 2009.
4. Bosetti C, La Vecchia C, Talamini R, Simonato L, Zambon P, Negri E, Trichopoulos D, Lagiou P, Bardini R and Franceschi S: Food groups and risk of squamous cell esophageal cancer in northern Italy. Int J Cancer 87: 289-294, 2000.
5. Talamini G, Capelli P, Zamboni G, Mastromauro M, Pasetto M, Castagnini A, Angelini G, Bassi C and Scarpa A: Alcohol, smoking and papillomavirus infection as risk factors for esophageal squamous-cell papilloma and esophageal squamous-cell carcinoma in Italy. Int J Cancer 86: 874-878, 2000.
6. Hao B, Wang H, Zhou K, Li Y, Chen X, Zhou G, Zhu Y, Miao X, Tan W, Wei Q, *et al*: Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res 64: 4378-4384, 2004.
7. Li WQ, Hu N, Hyland PL, Gao Y, Wang ZM, Yu K, Su H, Wang CY, Wang LM, Chanock SJ, *et al*: Genetic variants in DNA repair pathway genes and risk of esophageal squamous cell carcinoma and gastric adenocarcinoma in a Chinese population. Carcinogenesis 34: 1536-1542, 2013.
8. Yang X, Zhu H, Qin Q, Yang Y, Yang Y, Cheng H and Sun X: Genetic variants and risk of esophageal squamous cell carcinoma: A GWAS-based pathway analysis. Gene 556: 149-152, 2015.
9. Wang Z, Gan L, Nie W and Geng Y: The OGG1 Ser326Cys polymorphism and the risk of esophageal cancer: A meta-analysis. Genet Test Mol Biomarkers 17: 780-785, 2013.
10. Dai ZJ, Shao YP, Kang HF, Tang W, Xu D, Zhao Y, Liu D, Wang M, Yang PT and Wang XJ: Relationship between apurinic endonuclease 1 Asp148Glu polymorphism and gastrointestinal cancer risk: An updated meta-analysis. World J Gastroenterol 21: 5081-5089, 2015.
11. Li S, Deng Y, You JP, Chen ZP, Peng QL, Huang XM, Lu QH, Huang XL, Zhao JM and Qin X: XRCC1 Arg399Gln, Arg194Trp, and Arg280His polymorphisms in esophageal cancer risk: A meta-analysis. Dig Dis Sci 58: 1880-1890, 2013.
12. Dai L, Wang K, Zhang J, Lv Q, Wu X and Wang Y: XRCC1 gene polymorphisms and esophageal squamous cell carcinoma risk in Chinese population: A meta-analysis of case-control studies. Int J Cancer 125: 1102-1109, 2009.
13. Yun YX, Dai LP, Wang P, Wang KJ, Zhang JY and Xie W: Association of polymorphisms in X-ray repair cross complementing 1 gene and risk of esophageal squamous cell carcinoma in a Chinese population. Biomed Res Int 2015: 509215, 2015.
14. Upadhyay R, Malik MA, Zargar SA and Mittal B: OGG1 Ser326Cys polymorphism and susceptibility to esophageal cancer in low and high at-risk populations of Northern India. J Gastrointest Cancer 41: 110-115, 2010.
15. Tse D, Zhai R, Zhou W, Heist RS, Asomaning K, Su L, Lynch TJ, Wain JC, Christiani DC and Liu G: Polymorphisms of the NER pathway genes, ERCC1 and XPD are associated with esophageal adenocarcinoma risk. Cancer Causes Control 19: 1077-1083, 2008.

16. Liu GC, Zhou YF, Su XC and Zhang J: Interaction between TP53 and XRCC1 increases susceptibility to cervical cancer development: A case control study. BMC Cancer 19: 24, 2019.
17. Nanda SS, Gandhi AK, Rastogi M, Khurana R, Hadi R, Sahni K, Mishra SP, Srivastava AK, Bhatt MLB and Parmar D: Evaluation of XRCC1 gene polymorphism as a biomarker in head and neck cancer patients undergoing chemoradiation therapy. Int J Radiat Oncol Biol Phys 101: 593-601, 2018.
18. Liu R, Yin LH and Pu YP: Reduced expression of human DNA repair genes in esophageal squamous-cell carcinoma in china. J Toxicol Environ Health A 70: 956-963, 2007.
19. Cai L, You NC, Lu H, Mu LN, Lu QY, Yu SZ, Le AD, Marshall J, Heber D and Zhang ZF: Dietary selenium intake, aldehyde dehydrogenase-2 and X-ray repair cross-complementing 1 genetic polymorphisms, and the risk of esophageal squamous cell carcinoma. Cancer 106: 2345-2354, 2006.
20. Li M, Yu X, Zhang ZY, Wu CL and Xu HL: Interaction of XRCC1 Arg399Gln polymorphism and alcohol consumption influences susceptibility of esophageal cancer. Gastroenterol Res Pract 2016: 9495417, 2016.
21. Djansugurova LB, Perfilyeva AV, Zhunusova GS, Djantaeva KB, Iksan OA and Khussainova EM: The determination of genetic markers of age-related cancer pathologies in populations from Kazakhstan. Front Genet 4: 70, 2013.
22. Hamajima N, Saito T, Matsuo K and Tajima K: Competitive amplification and unspecific amplification in polymerase chain reaction with confronting two-pair primers. J Mol Diagn 4: 103-107, 2002.
23. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J: Cancer statistics in China, 2015. CA Cancer J Clin 66: 115-132, 2016.
24. Yin J, Vogel U, Ma Y, Qi R and Wang H: Haplotypes of nine single nucleotide polymorphisms on chromosome 19q13.2-3 associated with susceptibility of lung cancer in a Chinese population. Mutat Res 641: 12-18, 2008.
25. Xing D, Qi J, Miao X, Lu W, Tan W and Lin D: Polymorphisms of DNA repair genes XRCC1 and XPD and their associations with risk of esophageal squamous cell carcinoma in a Chinese population. Int J Cancer 100: 600-605, 2002.
26. Xiong Y, Zhang Q, Ye J, Pan S and Ge L: Associations between three XRCC1 polymorphisms and hepatocellular carcinoma risk: A meta-analysis of case-control studies. PLoS One 13: e0206853, 2018.
27. Pan JL, Gao J, Hou JH, Hu DZ and Li L: Interaction between environmental risk factors and catechol-O-methyltransferase (COMT) and X-Ray repair cross-complementing protein 1 (XRCC1) gene polymorphisms in risk of lung cancer among non-smoking Chinese women: A case-control study. Med Sci Monit 24: 5689-5697, 2018.
28. Lin J, Ye Q, Wang Y, Wang Y and Zeng Y: Association between XRCC1 single-nucleotide polymorphisms and susceptibility to nasopharyngeal carcinoma: An update meta-analysis. Medicine (Baltimore) 97: e11852, 2018.
29. Bashir K, Sarwar R, Fatima S, Saeed S, Mahjabeen I and Akhtar Kayani M: Haplotype analysis of XRCC1 gene polymorphisms and the risk of thyroid carcinoma. J BUON 23: 234-243, 2018.
30. Feki-Tounsi M, Khlifi R, Louati I, Fourati M, Mhiri MN, Hamza-Chaffai A and Rebai A: Polymorphisms in XRCC1, ERCC2, and ERCC3 DNA repair genes, CYP1A1 xenobiotic metabolism gene, and tobacco are associated with bladder cancer susceptibility in Tunisian population. Environ Sci Pollut Res Int 24: 22476-22484, 2017.
31. Fouad H, Sabry D, Morsi H, Shehab H and Abuzaid NF: XRCC1 Gene polymorphisms and miR-21 expression in patients with colorectal carcinoma. Eurasian J Med 49: 132-136, 2017.
32. Chen S, Zhu XC, Liu YL, Wang C and Zhang KG: Investigating the association between XRCC1 gene polymorphisms and susceptibility to gastric cancer. Genet Mol Res 15, 2016.
33. Zhai XD, Mo YN, Xue XQ, Zhao GS, Gao LB, Ai HW and Ye Y: XRCC1 codon 280 and ERCC2 codon 751 polymorphisms and risk of esophageal squamous cell carcinoma in a Chinese population. Bull Cancer 96: E61-E65, 2009.
34. Moser J, Kool H, Giakzidis I, Caldecott K, Mullenders LH and Fousteri MI: Sealing of chromosomal DNA nicks during nucleotide excision repair requires XRCC1 and DNA ligase III alpha in a cell-cycle-specific manner. Mol Cell 27: 311-323, 2007.
35. Tomkinson AE, Naila T and Khattri Bhandari S: Altered DNA ligase activity in human disease. Mutagenesis 35: 51-60, 2020.
36. Wang R, ,Hao W, Pan L, Boldogh I and Ba X: The roles of base excision repair enzyme OGG1 in gene expression. Cell Mol Life Sci 75: 3741-3750, 2018.
37. Ba X and Boldogh I: 8-Oxoguanine DNA glycosylase 1: Beyond repair of the oxidatively modified base lesions. Redox Biol 14: 669-678, 2018.
38. Fleming AM and Burrows CJ: 8-Oxo-7,8-dihydroguanine, friend and foe: Epigenetic-like regulator versus initiator of mutagenesis. DNA Repair (Amst) 56: 75-83, 2017.
39. Wei B, Zhou Y, Xu Z, Xi B, Cheng H, Ruan J, Zhu M, Hu Q, Wang Q, Wang Z, *et al*: The effect of hOGG1 Ser326Cys polymorphism on cancer risk: Evidence from a meta-analysis. PLoS One 6: e27545, 2011.
40. Zou H, Li Q, Xia W, Liu Y, Wei X and Wang D: Association between the OGG1 Ser326Cys polymorphism and cancer risk: Evidence from 152 case-control studies. J Cancer 7: 1273-1280, 2016.
41. Peng Q, Lu Y, Lao X, Chen Z, Li R, Sui J, Qin X and Li S: Association between OGG1 Ser326Cys and APEX1 Asp148Glu polymorphisms and breast cancer risk: A meta-analysis. Diagn Pathol 9: 108, 2014.
42. Li M and Wilson DM III: Human apurinic/apyrimidinic endonuclease 1. Antioxid Redox Signal 20: 678-707, 2014.
43. Dai ZJ, Wang XJ, Kang AJ, Ma XB, Min WL, Lin S, Zhao Y, Yang PT, Wang M and Kang HF: Association between APE1 single nucleotide polymorphism (rs1760944) and cancer risk: A meta-analysis based on 6,419 cancer cases and 6,781 case-free controls. J Cancer 5: 253-259, 2014.
44. Zhou B, Shan H, Su Y, Xia K, Shao X, Mao W and Shao Q: The association of APE1 -656T>G and 1349 T>G polymorphisms and cancer risk: A meta-analysis based on 37 case-control studies. BMC Cancer 11: 521, 2011.
45. Zhong JH, Zhao Z, Liu J, Yu HL, Zhou JY and Shi R: Association between APE1 Asp148Glu polymorphism and the risk of urinary cancers: A meta-analysis of 18 case-control studies. Onco Targets Ther 9: 1499-1510, 2016.
46. Li H, Zou J, Mi J, Wei X, Zhao D, Zhang S and Tian G: Association of APE1 Gene Asp148Glu variant with digestive cancer: A meta-analysis. Med Sci Monit 21: 2456-2466, 2015.