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Original Article

Epiregulin rs1460008 A>G polymorphism is associated with decreased risk of esophageal squamous cell carcinoma in a Chinese population

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Abstract: Objective: This study is to investigate the associations of *epiregulin* (*EREG*) and *DEC1* polymorphisms with risk of esophageal squamous cell carcinoma (ESCC) in a Chinese population. Methods: A total of 629 ESCC patients and 686 normal control subjects were recruited. Genotypes were determined using the ligation detection reaction method. Associations of single nucleotide polymorphisms (SNPs) with ESCC risk were analyzed with the logistic regression analysis. Results: ESCC and control groups were adequately matched regarding age and sex, while significant differences were noted for the smoking and drinking status. Based on SNP genotyping, compared with the *EREG* rs1460008 AA homozygote genotype, the GG genotype was not associated with ESCC risk, while the AG genotype was associated with decreased ESCC risk. In the dominant model, the *EREG* rs1460008 AG/GG variants were associated with the decreased risk of ESCC. In the recessive model, when the *EREG* rs1460008 AA/AG genotypes were used as reference, the GG homozygote genotype was not significantly associated with ESCC risk. Moreover, our results revealed no association of the *DEC1* rs4978620 T>C, rs2269700 T>C, and rs3750505 G>A polymorphisms with ESCC risk. Stratification analysis showed that, significantly decreased risk of ESCC was associated with the *EREG* rs1460008 A>G polymorphism, especially for older female subjects with no smoking and drinking habits. Conclusion: *EREG* rs1460008 A>G genotype is associated with decreased ESCC risk in the studied Chinese population, which might contribute to the understanding of the role of SNP in the disease pathogenesis.

Keywords: Esophageal squamous cell carcinoma (ESCC), epiregulin (EREG), polymorphism, molecular epidemiology

Introduction

Esophageal cancer (EC) is the fourth leading cause of cancer-related death and the fifth most commonly diagnosed cancer in China [1-4]. Esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of EC cases, with poor treatment outcomes [5]. It has been found that, besides the environmental risk factors, genetic risk factors play important roles in the carcinogenesis of ESCC, such as single nucleotide polymorphisms (SNPs) [6].

Epiregulin (EREG) is a member of the epidermal growth factor (EGF) family, which mediates the biological functions of epithelial and mesenchymal cells through the interaction with EGF receptors [7]. EREG could act as an autocrine growth factor in vitro [8], and the EREG SNPs have been shown to be associated with the susceptibility of some diseases [9]. On the other hand, deletion of esophageal cancer 1 (DEC1) is proposed to serve as an effective biomarker for ESCC [10]. It has been shown that DEC1 is down-regulated in both ESCC cell lines and tissue specimens [10, 11]. Moreover, both in vitro and in vivo assays reveal that DEC1 suppresses the growth of esophageal cancer cells [11]. Importantly, DEC1 SNPs have been shown to be associated with the reduced risk of other types

Table 1. Demographic characteristics of ESCC patients and normal control subjects

	ESCC (n = 629) n (%)	Controls (n = 686) n (%)	*P*
Age (years)	62.85±8.13	62.58±7.89	0.541
Age (years)			0.155
<63	310 (49.28%)	365 (53.21%)	
≥63	319 (50.72%)	321 (46.79%)	
Sex			0.185
Male	444 (70.59%)	461 (67.20%)	
Female	185 (29.41%)	225 (32.80%)	
Smoking status			<0.001
Never	355 (56.44%)	499 (72.74%)	
Ever	274 (43.56%)	187 (27.26%)	
Drinking status			<0.001
Never	428 (68.04%)	526 (76.68%)	
Ever	201 (31.96%)	160 (23.32%)	

of carcinomas, including the squamous cell carcinoma of the head and neck (SCCHN) [12]. However, the roles of EREG and DEC1 SNPs in the pathogenesis and development of ESCC have not yet been fully established [13].

In this study, the genotyping analysis of four EREG and DEC1 functional SNPs, i.e., EREG rs1460008 A>G, DEC1 rs4978620 T>C, rs2269700 T>C, and rs3750505 G>A, was performed in a Chinese population, including 629 ESCC patients and 686 normal control subjects. Associations between the SNPs and the risk of ESCC was also analyzed and discussed.

Materials and methods

Study subjects

Totally 629 patients with ESCC were included in this study, who were admitted to the Affiliated People's Hospital of Jiangsu University and the Affiliated Hospital of Jiangsu University from October 2008 to December 2010. Exclusion criteria included (1) previous diagnosis of cancer and (2) exposure to radiotherapy or chemotherapy. On the other hand, 686 trauma patients with matched age and sex were recruited as control, during the same time period. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of the Jiangsu University.

Using a pre-tested questionnaire, demographic data (e.g., age and sex) and related risk factors (e.g., smoking and drinking status) were obtained. Venous blood sample (2 mL) was collected from each subject. Individuals smoking one cigarette per day for more than one year were classified into the smoker category. Alcohol drinker was defined with the consumption of no less than three alcoholic drinks a week for over six months.

DNA isolation and genotyping

Genomic DNA was isolated from whole blood according to a previously published protocol [14]. Genotyping was performed by the Shanghai Biowing Applied Biotechnology Company (Shanghai, China), using the ligation detection reaction (LDR) method [15].

Statistical analysis

Data were expressed as mean ± SD. SAS 9.1.3 software (SAS Institute, Cary, NC, USA) was used for statistical analysis. After the Hardy-Weinberg equilibrium test, group comparison was performed using the X^2 test. With the logistic regression analysis, associations between the SNPs and the ESCC risk were estimated for crude and adjusted odds ratios (OR) considering age, sex, and smoking and drinking status. $P<0.05$ was considered statistically significant.

Results

Demographic characteristics of study population

The demographic characteristics of the ESCC patients and normal control subjects were summarized in **Table 1**. According to the X^2 test, the ESCC and control groups were adequately matched regarding age and sex. Moreover, significant differences were detected in the smoking and drinking status between these two groups. On the other hand, the information for the four genotyped SNPs was presented in **Table 2**. For the control group, the genotype frequencies for all these four polymorphisms were in the Hardy-Weinberg equilibrium, and the minor allele frequencies (MAF) of the SNPs were similar to that for the Chinese populations in database [16]. These results suggest that these ESCC patients and normal control subjects were suitable for the following investigation.

Table 2. *EREG* and *DEC1* SNP analysis in ESCC patients and normal control subjects

	EREG rs1460008 A>G	*DEC1* rs4978620 T>C	*DEC1* rs2269700 T>C	*DEC1* rs3750505 G>A
Chromosome	4	9	9	9
Function	UTR-3	Near Gene-5	Missense	UTR-3
Chr Pos (Genome Build 36.3)	75473146	116943312	117203384	117204395
Regulome DB score[a]	No data	No data	6	5
TFBS[b]	-	Y	-	-
Splicing (ESE or ESS)	-	-	Y	-
miRNA (miRanda)	Y	-	-	Y
miRNA (Sanger)	-	-	-	-
nsSNP	-	-	Y	-
MAF[c] for Chinese in database	0.329	0.458	0.221	0.293
MAF in control subjects	0.316	0.496	0.184	0.295
P value for HWE test[d] in control subjects	0.222	0.562	0.314	0.474
% Genotyping value	98.63%	96.81%	98.48%	98.02%

Note: a, http://www.regulomedb.org/; b, TFBS: Transcription Factor Binding Site (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm); c, MAF: minor allele frequency (DEC1 rs4978620 T>C MAF is in CHB+JPT population); d, HWE: Hardy-Weinberg equilibrium.

Associations of EREG rs1460008 A>G, DEC1 rs4978620 T>C, rs2269700 T>C, and rs3750505 G>A polymorphisms with ESCC risk

Associations of the SNPs (i.e., *EREG* rs1460008 A>G, *DEC1* rs4978620 T>C, rs2269700 T>C, and rs3750505 G>A) and the risk of ESCC were then investigated. As shown in **Table 3**, when the *EREG* rs1460008 AA homozygote genotype was used as reference, the GG genotype was not associated with the risk of ESCC, while the AG genotype was significantly associated with the decreased risk of ESCC (AG vs. AA: adjusted OR, 0.76; 95% CI, 0.60-0.96; $P = 0.020$). In the dominant model, the *EREG* rs1460008 AG/GG variants were associated with decreased risk of ESCC, compared with the *EREG* rs1460008 AA genotype (AG/GG vs. AA: adjusted OR, 0.77; 95% CI, 0.62-0.97; $P = 0.024$). In the recessive model, when the EREG rs1460008 AA/AG genotypes were used as reference, the GG homozygote genotype was not significantly associated with the altered risk of ESCC. On the other hand, our results revealed no association of the DEC1 rs4978620 T>C, rs2269700 T>C, and rs3750505 G>A polymorphisms with the risk of ESCC in all the comparison models (**Table 3**). These results suggest that the *EREG* rs1460008 A>G SNP is associated with the decreased risk of ESCC.

Stratification analysis of EREG rs1460008 A>G polymorphism and ESCC risk

To evaluate the effects of *EREG* rs1460008 A>G genotype on the ESCC risk based on age, sex, and smoking and drinking status, stratification analysis was performed. Our results showed that, significantly decreased risk of ESCC was associated with the *EREG* rs1460008 A>G polymorphism, especially for older female subjects with no smoking and drinking habits (**Table 4**). These results suggested that aging and living habits represent potential risk factors for ESCC with *EREG* rs1460008 A>G polymorphism.

Discussion

In the present study, our results showed that the *EREG* rs1460008 A>G SNP was associated with the decreased risk of ESCC. To our knowledge, this is the first study to show an association of *EREG* rs1460008 A>G polymorphism with ESCC risk. EREG is a member of the EGF family and a ligand for the EGF receptor. EREG mediates the biological functions in the epithelial and mesenchymal cells, through the interactions with EGF receptors [7]. In cancer pathogenesis, EREG and EGF receptors could regulate the cell differentiation, growth, and homeostasis [17]. It has also been shown that, EREG is a target gene of hsa-miR-181a [18]. In a pre-

Table 3. Logistic regression analysis of association between *EREG* and *DEC1* SNPs with ESCC risk

	ESCC (n = 629) n (%)	Controls (n = 686) n (%)	Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
EREG rs1460008 A>G						
AA	324 (52.6%)	312 (45.8%)	1.00		1.00	
AG	239 (38.8%)	308 (45.2%)	0.75 (0.59-0.94)	0.013	0.76 (0.60-0.96)	0.020
GG	53 (8.6%)	61 (9.0%)	0.84 (0.56-1.25)	0.382	0.85 (0.57-1.28)	0.433
GG v.s. AG v.s. AA				0.044		
AG+GG	292 (47.4%)	369 (54.2%)	0.76 (0.61-0.95)	0.015	0.77 (0.62-0.97)	0.024
AA+AG	563 (91.4%)	620 (91.0%)	1.00		1.00	
GG	53 (8.6%)	61 (9.0%)	0.96 (0.65-1.41)	0.823	0.97 (0.65-1.43)	0.861
A allele	887 (72.0%)	932 (68.4%)	1.00			
G allele	345 (28.0%)	430 (31.6%)	0.84 (0.71-1.00)	0.048		
DEC1 rs4978620 T>C						
TT	174 (29.0%)	167 (24.8%)	1.00		1.00	
TC	279 (46.5%)	344 (51.1%)	0.89 (0.68-1.18)	0.421	0.90 (0.68-1.19)	0.469
CC	147 (24.5%)	162 (24.1%)	1.15 (0.84-1.56)	0.379	1.19 (0.87-1.63)	0.283
CC v.s. TC v.s. TT				0.176		
TC+CC	426 (71.0%)	506 (75.2%)	0.98 (0.76-1.26)	0.859	0.99 (0.77-1.29)	0.966
TT+TC	453 (75.5%)	511 (75.9%)	1.00		1.00	
CC	147 (24.5%)	162 (24.1%)	1.24 (0.97-1.59)	0.093	1.27 (0.99-1.64)	0.062
T allele	627 (52.3%)	678 (50.4%)	1.00			
C allele	573 (47.8%)	668 (49.6%)	0.93 (0.79-1.08)	0.344		
DEC1 rs2269700 T>C						
TT	405 (65.4%)	446 (66.0%)	1.00		1.00	
TC	187 (30.2%)	211 (31.2%)	0.98 (0.77-1.24)	0.842	1.00 (0.78-1.27)	0.976
CC	27 (4.4%)	19 (2.8%)	1.57 (0.86-2.86)	0.145	1.61 (0.87-2.98)	0.131
CC v.s. TC v.s. TT				0.315		
TC+CC	214 (34.6%)	230 (34.0%)	1.03 (0.81-1.29)	0.836	1.05 (0.83-1.32)	0.710
TT+TC	592 (95.6%)	657 (97.2%)	1.00		1.00	
CC	27 (4.4%)	19 (2.8%)	1.58 (0.87-2.87)	0.135	1.61 (0.87-2.96)	0.127
T allele	997 (80.5%)	1103 (81.6%)	1.00			
C allele	241 (19.5%)	249 (18.4%)	1.07 (0.88-1.30)	0.495		
DEC1 rs3750505 G>A						
GG	312 (51.2%)	342 (50.3%)	1.00		1.00	
GA	239 (39.2%)	275 (40.4%)	0.95 (0.76-1.20)	0.681	0.95 (0.75-1.21)	0.693
AA	58 (9.5%)	63 (9.3%)	1.01 (0.68-1.49)	0.963	0.92 (0.62-1.37)	0.694
AA v.s. GA v.s. GG				0.908		
GA+AA	297 (48.8%)	338 (49.7%)	0.96 (0.77-1.20)	0.737	0.95 (0.76-1.18)	0.637
GG+GA	551 (90.5%)	617 (90.7%)	1.00		1.00	
AA	58 (9.5%)	63 (9.3%)	1.03 (0.71-1.50)	0.873	0.94 (0.64-1.38)	0.763
G allele	863 (70.9%)	959 (70.5%)	1.00			
A allele	355 (29.1%)	401 (29.5%)	0.98 (0.83-1.17)	0.850		

Note: a, OR adjusted for age, sex, and smoking and drinking status.

vious research with a moderate-sized cohort (500 cases and 502 controls), the *EREG* rs1460008 A>G SNP is not associated with the altered risk of gastric cancer [18]. However, our results indicated a protective effect of *EREG* rs1460008 A>G SNP in ESCC. Although *EREG* rs1460008 A>G is functional, and might act as an miR-binding site according to the SNP func-

Table 4. Stratification analysis of *EREG* rs1460008 A>G SNP in relation to ESCC risk with age, sex, and smoking and drinking status

	EREG rs1460008 A>G (ESCC/control)[a]				Adjusted OR[b] (95% CI); *P*				
	AA	AG	GG	AG+GG	AA	AG	GG	AG+GG	GG vs. (AG+AA)
Age (years)									
<63	144/168	131/163	24/33	155/196	1.00	0.92 (0.66-1.28); *P*: 0.629	0.86 (0.48-1.56); *P*: 0.620	0.91 (0.66-1.25); *P*: 0.567	0.90 (0.51-1.58); *P*: 0.705
≥63	180/144	108/145	29/28	137/173	1.00	0.61 (0.44-0.86); *P*: 0.004	0.87 (0.49-1.53); *P*: 0.623	0.65 (0.48-0.90); *P*: 0.008	1.08 (0.62-1.86); *P*: 0.792
Sex									
Male	222/211	174/205	39/41	213/246	1.00	0.83 (0.62-1.10); *P*: 0.193	0.93 (0.57-1.51); *P*: 0.765	0.85 (0.65-1.11); *P*: 0.222	1.01 (0.63-1.62); *P*: 0.957
Female	102/101	65/103	14/20	79/123	1.00	0.62 (0.41-0.94); *P*: 0.024	0.70 (0.33-1.47); *P*: 0.347	0.63 (0.42-0.94); *P*: 0.024	0.87 (0.42-1.78); *P*: 0.699
Smoking status									
Never	184/224	128/230	34/41	162/271	1.00	0.67 (0.50-0.90); *P*: 0.008	1.01 (0.61-1.67); *P*: 0.977	0.72 (0.55-0.96); *P*: 0.023	1.21 (0.74-1.97); *P*: 0.445
Ever	140/88	111/78	19/20	130/98	1.00	0.88 (0.59-1.32); *P*: 0.530	0.58 (0.29-1.18); *P*: 0.133	0.82 (0.56-1.20); *P*: 0.305	0.62 (0.32-1.22); *P*: 0.165
Drinking status									
Never	222/238	156/240	39/44	195/284	1.00	0.71 (0.53-0.94); *P*: 0.016	0.98 (0.61-1.59); *P*: 0.942	0.75 (0.57-0.98); *P*: 0.034	1.15 (0.72-1.84); *P*: 0.552
Ever	102/74	83/68	14/17	97/85	1.00	0.82 (0.53-1.29); *P*: 0.397	0.57 (0.26-1.27); *P*: 0.170	0.77 (0.51-1.19); *P*: 0.242	0.63 (0.29-1.35); *P*: 0.233

Note: a, genotyping was performed in 616 (97.9%) ESCC patients and 681 (99.3%) normal control subjects for *EREG* rs1460008 A>G; b, OR adjusted for age, sex, and smoking and drinking status in a logistic regression model.

tion prediction (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm), the mechanism has not yet been fully established and further in-depth studies are still needed. According to the Power and Sample Size Calculation (PS, version 3.0, 2009, http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize), the power of our analysis ($\alpha = 0.05$) based on 616 ESCC patients and 681 normal control subjects was 0.605, with an adjusted OR of 0.76.

There are several limitations for this study. Firstly, all the ESCC patients and normal control subjects were enrolled from the hospital; therefore the inherent bias may result in spurious findings. Secondly, the polymorphism analysis herein may not provide a comprehensive overview of the *EREG* and *DEC1* genetic variability, and further fine-mapping studies are required. Thirdly, owing to the moderate sample size and the absence of a validation cohort, the power of statistical analysis was limited. Finally, the information on the viral infections and immune parameters was not available in this study, which might restrict the power of our analysis.

In conclusion, our results showed that the *EREG* rs1460008 A>G polymorphism was associated with the decreased risk of ESCC in the Chinese population. Moreover, aging and living habits (such as smoking and drinking) represent potential risk factors for ESCC with *EREG* rs1460008 A>G. These findings might contribute to the understanding of the role of *EREG* polymorphism in the pathogenesis of ESCC.

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Disclosure of conflict of interest

None.

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