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IL1RN Polymorphisms Are Associated with a Decreased Risk of Esophageal Cancer Susceptibility in a Chinese Population

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Keywords
Case-control study · Esophageal cancer · *IL1RN* · Single nucleotide polymorphism · MassARRAY technology

Abstract
Background: Recent evidence suggested that *IL1RN* (interleukin-1 receptor antagonist) polymorphisms increased the susceptibility to cancers. The present study aimed to evaluate whether *IL1RN* was related to esophageal cancer susceptibility in a Northwest Han Chinese population. ***Methods:*** The case-control study was conducted on 384 esophageal cancer patients and 499 healthy controls. We successfully genotyped four SNPs distributed in *IL1RN*. The Gene Expression Profiling Interactive Analysis (GEPIA) database was used to observe the expression of *IL1RN* in esophageal cancer tissues and normal tissues. RegulomeDB and HaploReg v4.1 were used to calculate possible functional effects of the polymorphisms. We also used genetic models to detect any potential association between *IL1RN* variants and esophageal cancer risk. ***Results:*** In our study, rs3181052 was associated with a reduced risk of esophageal cancer in the codominant (odds ratio [OR] = 0.70, 95% confidence interval [CI] 0.52–0.93, $p = 0.040$), the dominant (OR = 0.75, 95% CI 0.57–0.99, $p = 0.041$), and the overdominant (OR = 0.71, 95% CI 0.54–0.93, $p = 0.012$) model. The rs452204 was associated with a 0.76-fold (OR = 0.76, 95% CI 0.58–0.99; $p = 0.043$) decreased esophageal cancer risk under the overdominant model without adjustment. We also found that rs3181052 had a negative effect on esophageal cancer under the overdominant model (OR = 0.72, 95% CI 0.53–0.97, $p = 0.033$) adjusted for age and gender. In stratified analyses by age >55 years, rs3181052 reduced the risk of esophageal cancer in the dominant and overdominant models. In addition, rs315919 had a remarkable influence on esophageal cancer risk in females, while the association was not significant between rs3181052 and esophageal cancer risk in males. ***Con-***

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clusions: Our study provided the first evidence that *IL1RN* rs3181052, rs452204, and rs315919 are correlated with a decreased risk of esophageal cancer in a Northwest Han Chinese population. These findings may be useful for the development of early prognostics for esophageal cancer. However, further larger studies on different ethnic populations are warranted to verify these findings.

Introduction

Esophageal cancer is the seventh most commonly diagnosed cancer and the sixth most common cause of cancer-related death worldwide [1]. Despite advances in diagnosis and treatment, the overall 5-year survival rate still ranges from 15 to 25%, and the better outcomes are associated with diagnoses made at the early stages compared to those made at later stages [2]. It has been estimated that there are around 400,000 newly diagnosed cases worldwide every year, and the incidence rates vary greatly from region to region [3]. In China, esophageal cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death, with an estimated 479,000 new cases and 375,000 deaths in 2015 [4, 5]. However, the etiology of esophageal cancer has not been poorly determined.

Recently, numerous epidemiologic studies have shown that alcohol consumption, cigarette smoking, drinking hot tea, poor oral health, and low socioeconomic status are contributing risk factors for esophageal cancer [6, 7]. However, only a small proportion of individuals exposed to these factors actually develop esophageal cancer, suggesting that genetic factors may play an important role in the development of esophageal cancer. Current reports suggest that associations between some gene polymorphisms and risk of esophageal cancer exist [8–11].

It is generally accepted that inflammation plays a pivotal role in cancers [12]. Interleukin-1 (IL-1) is a major proinflammatory cytokine produced by monocytes, macrophages, and epithelial cells which plays a central role in the regulation of immune and inflammatory responses to various acute and chronic inflammatory conditions. Evidence has demonstrated that IL-1 may be a strong risk factor for tumor growth, vascular endothelial cell proliferation, angiogenesis, and metastasis in various human malignancies [13, 14]. IL1RN is a natural antagonist of IL-1 and modulates a variety of IL-1-related immune and inflammatory responses. So far, studies of variants in *IL1RN* in individuals have shown that *IL1RN* polymorphisms are involved in an increased risk of pulmonary tuberculosis [15], oral malignancy [16], and gastric cancer [14]. Researchers also reported that *IL1RN* variants are associated with the risk of breast cancer in the female population of South Korea, India, and China [17–19].

However, there are few data regarding the possible role of *IL1RN* polymorphisms in esophageal cancer; thus, the aim of this study was to investigate the possible association between *IL1RN* polymorphisms and esophageal cancer risk in a Chinese population.

Methods

Study Population

This case-control study was carried out to assess the association between *IL1RN* variants and esophageal cancer risk in a Chinese population. A total of 384 esophageal cancer patients and 499 healthy controls were recruited from the Shaanxi Provincial Cancer Hospital Affiliated to Medical College, and all those who had a cancer history or metastasized cancers were excluded.

SNP Selection, DNA Extraction, and Genotyping

We selected four candidate SNPs in the *IL1RN* gene from the database of SNPs and previously published polymorphisms associated with cancers [16, 19]. Each SNP had a minor allele frequency >5% in the global population from the 1000 Genomes Project (http://www.internationalgenome.org/). Peripheral blood samples of the participants were collected using Vacutainer tubes containing EDTA and stored at −80 °C after centrifugation. Then, we extracted genomic DNA from blood samples with the Whole Blood Genomic DNA Extraction Kit (GoldMag Co. Ltd., Xi'an, China) according to the instructions of the manufacturer. Quantification of the extracted DNA was checked using NanoDrop2000 (Thermo Fisher Scientific, Waltham, MA, USA). Assay Design Suite v2.0 (https://agenacx.com/online-tools/) was used to design a Multiplexed SNP MassEXTEND assay (Table 1) and the MassARRAY iPLEX platform (Agena Bioscience, San Diego, CA, USA) was utilized to perform genotyping of the four SNPs. Data analyses and management were conducted with Agena Bioscience Typer software v4.0.

Statistical Analyses

All statistical analyses were performed with SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The Hardy-Weinberg equilibrium was assessed using the χ^2 test for each genotyped SNP in controls. The associations between *IL1RN* variants and esophageal cancer risk were evaluated by ORs and 95% CIs under different genetic models with adjustment for age and sex. Statistical differences were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Basic Characteristics of the Subjects

The distribution of sex and age among the cases and controls is shown in Table 1. A total of 384 cases (76 females and 308 males) and 499 controls (198 females and

Table 1. PCR primers of the loci used in this study

SNP ID	Alleles	1st-PCR primer sequences	2nd-PCR primer sequences	UEP sequences
rs17042888	A/G	ACGTTGGATGTGGAGTTGGAGTCTTGTTGG	ACGTTGGATGCTACTTGCTCAGCACCATAC	agcGGTGTTGAAATCCCAAAA
rs315919	C/A	ACGTTGGATGCCAGACAATAAAGCAAGCAG	ACGTTGGATGCACACAAATCCTAACCGGAG	tTTGCAAACTGGCAGCTTATA
rs3181052	G/A	ACGTTGGATGCTTTATGTTTGTCTGGGCCG	ACGTTGGATGACAGTCCCCATATCTGGAAG	cttaACTCATACACCCACAGAGCC
rs452204	G/A	ACGTTGGATGAAAAGAGCCTCAACATGCAG	ACGTTGGATGTAGACTTAGCCACGTGACTG	gcccATAGGATGATGCAAGCAGAAGT

PCR, polymerase chain reaction; UEP, unextended mini-sequencing primer.

Table 2. Association of SNPs in *IL1RN* with esophageal cancer risk

SNP ID	Gene	Chr	Position	Alleles A/B	MAF		HWE *p* value	OR (95% CI)	p^1
					case	control			
rs17042888	*IL1RN*	2q13	113862173	A/G	0.249	0.261	0.728	0.94 (0.65–1.17)	0.594
rs315919	*IL1RN*	2q13	113876213	C/A	0.379	0.410	0.642	0.88 (0.72–1.07)	0.195
rs3181052	*IL1RN*	2q13	113886049	G/A	0.380	0.405	0.228	0.90 (0.74–1.10)	0.297
rs452204	*IL1RN*	2q13	113889061	G/A	0.343	0.347	0.921	0.98 (0.80–1.20)	0.855

SNP, single nucleotide polymorphism; A, minor alleles; B, major alleles; CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; HWE, Hardy-Weinberg equilibrium. [1] *p* values were calculated using Pearson's χ^2 test.

301 males) were recruited for our study. The mean age of the patients was 51.47 ± 11.84 years, and that of the controls was 60.81 ± 8.84 years.

Association between IL1RN *SNPs and Esophageal Cancer Risk*

The basic information about all the SNPs, including gene, position, alleles, minor allele frequency, and OR (95% CI) results, are presented in Table 2. Overall, four SNPs were analyzed in the study. The differences in frequency distribution of the alleles between cases and controls were compared by Pearson's χ^2 test. However, no statistically significant association was found between *IL1RN* polymorphisms and esophageal cancer risk.

Five genetic models (codominant, dominant, recessive, overdominant, and additive) were used to further identify associations between the SNPs and risk of esophageal cancer (Table 3). The results showed that rs3181052 significantly decreased the risk of esophageal cancer in the codominant (OR = 0.70, 95% CI 0.52–0.93, $p = 0.040$), the dominant (OR = 0.75, 95% CI 0.57–0.99, $p = 0.041$), and the overdominant (OR = 0.71, 95% CI 0.54–0.93, $p = 0.012$) model. Furthermore, the results showed that rs452204 decreased the risk of esophageal cancer under the overdominant model (OR = 0.76, 95% CI 0.58–0.99, $p = 0.043$). We also found that rs3181052 had a negative effect on esophageal cancer under the overdominant model (OR = 0.72, 95% CI 0.53–0.97, $p = 0.033$) adjusted for age and gender.

In addition, we performed a stratification analysis by age and gender. When stratified by age >55 years, we observed that the genotype "G/A-G/G" of rs3181052 conferred a lower risk of esophageal cancer than the wild type "A/A" in the dominant model (OR = 0.61, 95% CI 0.40–0.94, $p = 0.025$). In the overdominant model, the SNP was still associated with a decreased esophageal cancer risk (OR = 0.66, 95%CI 0.43–0.99, $p = 0.043$) (Table 4). However, after stratification by age ≤55 years, there were no significant correlations between either of the two variants and esophageal cancer risk. In addition, the results of gender stratification (Table 5) showed that rs315919 had a potential association with esophageal cancer risk (OR = 0.54, 95% CI 0.31–0.96, $p = 0.037$) in the female population in the dominant model, while the association was not significant in the male population. The effect of rs3181052 on the genetic predisposition to esophageal cancer indicated the opposite result: rs3181052 had a negative effect on the risk of esophageal

Table 3. Genetic model analyses of SNPs in the *IL1RN* and esophageal cancer risk

SNP ID	Model	Genotype	Controls, *n* (%)	Cases, *n* (%)	Crude analysis		After adjustment for age and gender	
					OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs17042888	Codominant	G/G	271 (54.3)	220 (57.7)	1.00	0.340	1.00	0.830
		G/A	196 (39.3)	132 (34.6)	0.83 (0.62–1.10)		0.93 (0.67–1.27)	
		A/A	32 (6.4)	29 (7.6)	1.12 (0.66–1.90)		0.86 (0.47–1.59)	
	Dominant	G/G	271 (54.3)	220 (57.7)	1.00	0.310	1.00	0.570
		G/A-A/A	228 (45.7)	161 (42.3)	0.87 (0.66–1.14)		0.92 (0.68–1.24)	
	Recessive	G/G-G/A	467 (93.6)	352 (92.4)	1.00	0.490	1.00	0.700
		A/A	32 (6.4)	29 (7.6)	1.20 (0.71–2.02)		0.89 (0.49–1.61)	
	Overdominant	G/G-A/A	303 (60.7)	249 (65.3)	1.00	0.160	1.00	0.700
		G/A	196 (39.3)	132 (34.6)	0.82 (0.62–1.08)		0.94 (0.69–1.29)	
	log-additive	–	–	–	0.94 (0.76–1.17)	0.600	0.93 (0.73–1.18)	0.540
rs315919	Codominant	T/T	175 (35.4)	154 (41.3)	1.00	0.170	1.00	0.150
		G/T	234 (47.3)	155 (41.5)	0.75 (0.56–1.01)		0.73 (0.52–1.02)	
		G/G	86 (17.4)	64 (17.2)	0.85 (0.57–1.25)		0.76 (0.49–1.17)	
	Dominant	T/T	175 (35.4)	154 (41.3)	1.00	0.075	1.00	0.054
		G/T-G/G	320 (64.7)	219 (58.7)	0.78 (0.59–1.03)		0.74 (0.54–1.01)	
	Recessive	T/T-G/T	409 (82.6)	309 (82.8)	1.00	0.930	1.00	0.590
		G/G	86 (17.4)	64 (17.2)	0.99 (0.69–1.41)		0.90 (0.60–1.34)	
	Overdominant	T/T-G/G	261 (52.7)	218 (58.5)	1.00	0.093	1.00	0.140
		G/T	234 (47.3)	155 (41.5)	0.79 (0.60–1.04)		0.79 (0.59–1.08)	
	log-additive	–	–	–	0.89 (0.73–1.07)	0.210	0.84 (0.68–1.04)	0.110
rs3181052	Codominant	A/A	170 (34.1)	155 (40.8)	1.00	0.040*	1.00	0.098
		G/A	254 (50.9)	161 (42.4)	0.70 (0.52–0.93)		0.71 (0.51–0.98)	
		G/G	75 (15)	64 (16.8)	0.94 (0.63–1.39)		0.94 (0.60–1.47)	
	Dominant	A/A	170 (34.1)	155 (40.8)	1.00	0.041*	1.00	0.085
		G/A-G/G	329 (65.9)	225 (59.2)	0.75 (0.57–0.99)		0.76 (0.56–1.04)	
	Recessive	A/A-G/A	424 (85)	316 (83.2)	1.00	0.470	1.00	0.530
		G/G	75 (15)	64 (16.8)	1.14 (0.80–1.65)		1.14 (0.76–1.71)	
	Overdominant	A/A-G/G	245 (49.1)	219 (57.6)	1.00	0.012*	1.00	0.033*
		G/A	254 (50.9)	161 (42.4)	0.71 (0.54–0.93)		0.72 (0.53–0.97)	
	log-additive	–	–	–	0.90 (0.74–1.09)	0.300	0.91 (0.73–1.13)	0.390
rs452204	Codominant	A/A	212 (42.7)	176 (46.6)	1.00	0.110	1.00	0.240
		G/A	224 (45.2)	145 (38.4)	0.78 (0.58–1.04)		0.79 (0.57–1.10)	
		G/G	60 (12.1)	57 (15.1)	1.14 (0.76–1.73)		1.11 (0.70–1.76)	
	Dominant	A/A	212 (42.7)	176 (46.6)	1.00	0.260	1.00	0.340
		G/A-G/G	284 (57.3)	202 (53.4)	0.86 (0.65–1.12)		0.86 (0.64–1.17)	
	Recessive	A/A-G/A	436 (87.9)	321 (84.9)	1.00	0.200	1.00	0.340
		G/G	60 (12.1)	57 (15.1)	1.29 (0.87–1.91)		1.24 (0.80–1.91)	
	Overdominant	A/A-G/G	272 (54.8)	233 (61.6)	1.00	0.043*	1.00	0.100
		G/A	224 (45.2)	145 (38.4)	0.76 (0.58–0.99)		0.77 (0.57–1.05)	
	log-additive	–	–	–	0.98 (0.81–1.19)	0.860	0.98 (0.79–1.21)	0.840

p values were calculated by Wald test under logistic regression. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. * $p < 0.05$ indicates statistical significance.

cancer in males based on the overdominant model (OR = 0.64, 95% CI 0.43–0.94, $p = 0.023$), whereas in females the variant had no significant relationship to the risk of esophageal cancer.

Discussion

In this case-control study, we calculated the association of *IL1RN* polymorphisms with the risk of esophageal

Table 4. Significant variants in *IL1RN* associated with esophageal cancer susceptibility after stratification by age

Gene	SNP	Model	Genotype	Controls, *n* (%)	Cases, *n* (%)	Stratification by age >55 years		Controls, *n* (%)	Cases, *n* (%)	Stratification by age ≤55 years	
						OR (95% CI)	*p* value			OR (95% CI)	*p* value
IL1RN	rs3181052	Codominant	A/A	57 (30)	117 (41.8)	1.00	0.070	100 (36.6)	38 (38)	1.00	0.670
			G/A	104 (54.7)	121 (43.2)	0.59 (0.37–0.93)		132 (48.4)	40 (40)	0.88 (0.50–1.55)	
			G/G	29 (15.3)	42 (15)	0.70 (0.37–1.32)		41 (15)	22 (22)	1.21 (0.59–2.46)	
		Dominant	A/A	57 (30)	117 (41.8)	1.00	0.025*	100 (36.6)	38 (38)	1.00	0.900
			G/A-G/G	133 (70)	163 (58.2)	0.61 (0.40–0.94)		173 (63.4)	62 (62)	0.97 (0.57–1.64)	
		Recessive	A/A-G/A	161 (84.7)	238 (85)	1.00	0.870	232 (85)	78 (78)	1.00	0.440
			G/G	29 (15.3)	42 (15)	0.95 (0.54–1.69)		41 (15)	22 (22)	1.30 (0.68–2.47)	
		Overdominant	A/A-G/G	86 (45.3)	159 (56.8)	1.00	0.043*	141 (51.6)	60 (60)	1.00	0.460
			G/A	104 (54.7)	121 (43.2)	0.66 (0.43–0.99)		132 (48.4)	40 (40)	0.82 (0.49–1.38)	
		log-additive	–	–	–	0.78 (0.58–1.05)	0.099	–	–	1.06 (0.75–1.51)	0.740

p values were calculated by Wald test under logistic regression with adjustment for gender and age. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
* $p < 0.05$ indicates statistical significance.

cancer in a Chinese population. Our results indicated that rs3181052 and rs452204 in *IL1RN* were correlated with a significantly decreased risk of esophageal cancer in this Han Chinese population.

IL1RN is a member of the IL-1 cytokine family that modulates a variety of IL-1-related immune and inflammatory responses. Numerous lines of evidence have shown that IL1RN plays a key role in the regulation of cancer pathogenesis and chronic inflammation [20–22]. We obtained the expression data for *IL1RN* from the GEPIA online database (http://gepia.cancer-pku.cn/) (Fig. 1), whose results indicated that the *IL1RN* gene is significantly downregulated in esophageal cancer tissues compared to normal tissues. Thus, we inferred that IL1RN may play an important role in the development of esophageal cancer.

Also, it was well described as a candidate cancer susceptibility gene [23, 24]. In a previous report, we observed that *IL1RN* gene polymorphisms (rs928940, rs315919, rs3181052, and rs452204) were associated with a decreased risk of breast cancer in a Han Chinese population [19]. Furthermore, rs3181052 has been associated with progression of knee osteoarthritis [25]. In addition, the previous literature has illustrated that the inflammatory response after *Helicobacter pylori* infection has been linked to the *IL-1* gene cluster (*IL-1A*, *IL-1B*, and *IL1RN*). A meta-analysis of *H. pylori* infection performed by Zhang et al. [21] demonstrated that *IL1RN* polymorphisms may increase the risk of *H. pylori* infection, especially in Asians. Therefore, we can infer that *IL1RN* polymorphisms may be associated with the risk of esophageal

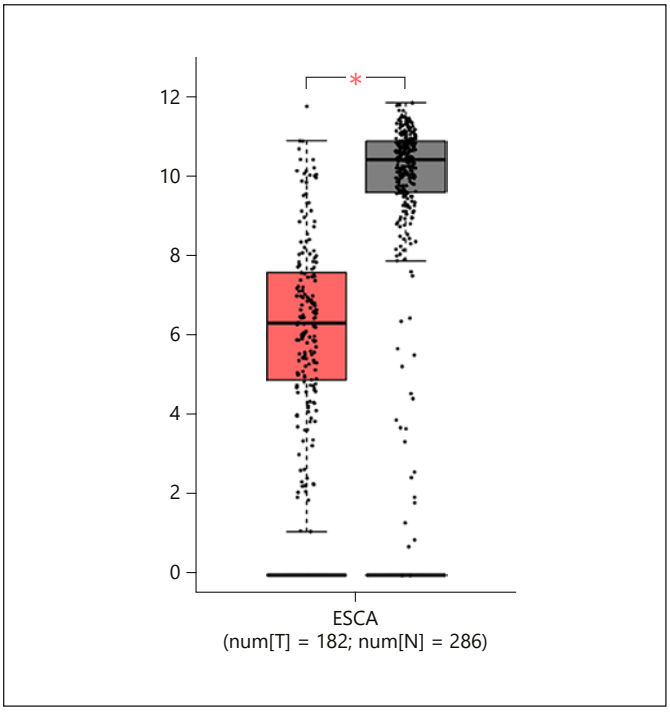

Fig. 1. On the basis of the GEPIA database, the *IL1RN* gene was significantly downregulated in esophageal cancer tissues compared with matched normal tissues.

cancer with *H. pylori* infection. Also, the present study is the first to demonstrate a significant association between *IL1RN* polymorphisms (rs3181052, rs452204, and rs315919) and susceptibility to esophageal cancer, in so

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Table 5. Significant variants in *IL1RN* associated with esophageal cancer susceptibility after stratified by gender

Gene	SNP	Model	Genotype	Controls, *n* (%)	Cases, *n* (%)	Females		Controls, *n* (%)	Cases, *n* (%)	Males	
						OR (95% CI)	*p* value			OR (95% CI)	*p* value
IL1RN	rs315919	Codominant	T/T	66 (33.7)	35 (48)	1.00	0.110	96 (36.5)	119 (39.7)	1.00	0.650
			G/T	96 (49)	28 (38.4)	0.55 (0.30–1.03)		121 (46)	127 (42.3)	0.82 (0.54–1.27)	
			G/G	34 (17.4)	10 (13.7)	0.51 (0.22–1.20)		46 (17.5)	54 (18)	0.84 (0.48–1.46)	
		Dominant	T/T	66 (33.7)	35 (48)	1.00	0.037*	96 (36.5)	119 (39.7)	1.00	0.350
			G/T-G/G	130 (66.3)	38 (52)	0.54 (0.31–0.96)		167 (63.5)	181 (60.3)	0.83 (0.55–1.23)	
		Recessive	T/T-G/T	162 (82.7)	63 (86.3)	1.00	0.360	217 (82.5)	246 (82)	1.00	0.770
			G/G	34 (17.4)	10 (13.7)	0.70 (0.32–1.54)		46 (17.5)	54 (18)	0.93 (0.56–1.54)	
		Overdominant	T/T-G/G	100 (51)	45 (61.6)	1.00	0.170	142 (54)	173 (57.7)	1.00	0.500
			G/T	96 (49)	28 (38.4)	0.67 (0.38–1.19)		121 (46)	127 (42.3)	0.87 (0.59–1.29)	
		log-additive	–	–	–	0.67 (0.45–1.01)	0.054	–	–	0.90 (0.69–1.18)	0.440
	rs3181052	Codominant	A/A	64 (32.3)	29 (38.2)	1.00	0.480	93 (35.1)	126 (41.5)	1.00	0.072
			G/A	105 (53)	39 (51.3)	0.80 (0.44–1.46)		131 (49.4)	122 (40.1)	0.65 (0.42–1.00)	
			G/G	29 (14.7)	8 (10.5)	0.58 (0.23–1.46)		41 (15.5)	56 (18.4)	1.07 (0.61–1.88)	
		Dominant	A/A	64 (32.3)	29 (38.2)	1.00	0.330	93 (35.1)	126 (41.5)	1.00	0.150
			G/A-G/G	134 (67.7)	47 (61.8)	0.75 (0.42–1.34)		172 (64.9)	178 (58.5)	0.75 (0.50–1.12)	
		Recessive	A/A-G/A	169 (85.3)	68 (89.5)	1.00	0.330	224 (84.5)	248 (81.6)	1.00	0.240
			G/G	29 (14.7)	8 (10.5)	0.66 (0.28–1.56)		41 (15.5)	56 (18.4)	1.35 (0.81–2.26)	
		Overdominant	A/A-G/G	93 (47)	37 (48.7)	1.00	0.790	134 (50.6)	182 (59.9)	1.00	0.023*
			G/A	105 (53)	39 (51.3)	0.93 (0.53–1.61)		131 (49.4)	122 (40.1)	0.64 (0.43–0.94)	
		log-additive	–	–	–	0.77 (0.50–1.18)	0.230	–	–	0.95 (0.73–1.25)	0.730

p values were calculated by Wald test under logistic regression with adjustment for age. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. * $p < 0.05$ indicates statistical significance.

far as the polymorphisms of *IL1RN* showed a decreased association with esophageal cancer risk. Thus, we hypothesized that these variants had a protective effect on susceptibility to esophageal cancer.

However, some limitations of this study may have affected the objectivity of the conclusions and should be taken into account when interpreting the results. For example, esophageal cancer is the result of diverse gene-environment interactions. However, we did not get to explore any interactions between polymorphisms and environmental factors. Therefore, further studies are needed to identify any interactions to understand the biological mechanisms of the effect of *IL1RN* gene polymorphisms on esophageal cancer.

Conclusions

This study is the first to demonstrate that the *IL1RN* polymorphisms rs3181052, rs452204, and rs315919 were associated with a decreased risk of esophageal cancer in a Northwest Han Chinese population. Further studies with larger-sized samples and different ethnicities should be conducted to ascertain the current findings.

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Statement of Ethics

We have obtained written informed consent from all the participants. All procedures of this study were reviewed and approved by the Ethics Committee of the Shaanxi Provincial Cancer Hospital Affiliated to Medical College and complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Disclosure Statement

The authors have no conflicts of interest to declare.

Availability of Data and Materials

All data generated or analyzed during this study were included in this paper.

Author Contributions

Tianchang Wang, Yan Feng, and Qiufang Liu are responsible for the design of the study. Zheng Zhao, Hao Wang, Yanbing Zhang, and Yongtong Zhang contributed to the organization of participant enrollment. Tianchang Wang, Yan Feng, Huijuan Liu, Tianbo Jin, and Qiufang Liu acquired the data used in the study. All authors were involved in the analysis and interpretation of the data. Tianchang Wang, Yan Feng, and Qiufang Liu drafted the manuscript. All the authors commented critically on the revision of the manuscript. Qiufang Liu supervised the study.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.

2 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec;127(12):2893–917.

3 Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006 May;24(14):2137–50.

4 Li G, Jin T, Liang H, Tu Y, Zhang W, Gong L, et al. Skewed X-chromosome inactivation in patients with esophageal carcinoma. Diagn Pathol. 2013 Apr;8(1):55.

5 Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016 Mar-Apr;66(2):115–32.

6 Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013 Sep;19(34):5598–606.

7 An J, Zhao J, Zhang X, Ding R, Geng T, Feng T, et al. Impact of multiple Alcohol Dehydrogenase gene polymorphisms on risk of laryngeal, esophageal, gastric and colorectal cancers in Chinese Han population. Am J Cancer Res. 2015 Jul;5(8):2508–15.

8 Sadot E, Kraus S, Stein M, Naboishchikov I, Toledano O, Kazanov D, et al. CD24 gene polymorphism – a novel prognostic factor in esophageal cancer. Int J Biol Markers. 2014 Mar;29(1):e49–54.

9 Guo LY, Yang N, Hu D, Zhao X, Feng B, Zhang Y, et al. PLCE1 rs2274223 polymorphism and susceptibility to esophageal cancer: a meta-analysis. Asian Pac J Cancer Prev. 2014;15(21):9107–12.

10 Yang X, Zhu H, Qin Q, Yang Y, Yang Y, Cheng H, et al. Genetic variants and risk of esophageal squamous cell carcinoma: a GWAS-based pathway analysis. Gene. 2015 Feb;556(2):149–52.

11 Geng TT, Xun XJ, Li S, Feng T, Wang LP, Jin TB, et al. Association of colorectal cancer susceptibility variants with esophageal cancer in a Chinese population. World J Gastroenterol. 2015 Jun;21(22):6898–904.

12 Sethi G, Shanmugam MK, Ramachandran L, Kumar AP, Tergaonkar V. Multifaceted link between cancer and inflammation. Biosci Rep. 2012 Feb;32(1):1–15.

13 Ma J, Sawai H, Matsuo Y, Ochi N, Yasuda A, Takahashi H, et al. Interleukin-1α enhances angiogenesis and is associated with liver metastatic potential in human gastric cancer cell lines. J Surg Res. 2008 Aug;148(2):197–204.
14 El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature. 2000 Mar;404(6776):398–402.
15 Hashemi M, Naderi M, Ebrahimi M, Aminia S, Bahari G, Taheri M, et al. Association between Interleukin-1 Receptor Antagonist (IL1RN) Variable Number of Tandem Repeats (VNTR) Polymorphism and Pulmonary Tuberculosis. Iran J Allergy Asthma Immunol. 2015 Feb;14(1):55–9.
16 Shiiba M, Saito K, Yamagami H, Nakashima D, Higo M, Kasamatsu A, et al. Interleukin-1 receptor antagonist (IL1RN) is associated with suppression of early carcinogenic events in human oral malignancies. Int J Oncol. 2015 May;46(5):1978–84.
17 Lee KM, Park SK, Hamajima N, Tajima K, Choi JY, Noh DY, et al. Genetic polymorphisms of interleukin-1 beta (IL-1B) and IL-1 receptor antagonist (IL-1RN) and breast cancer risk in Korean women. Breast Cancer Res Treat. 2006 Mar;96(2):197–202.
18 Konwar R, Chaudhary P, Kumar S, Mishra D, Chattopadhyay N, Bid HK. Breast cancer risk associated with polymorphisms of IL-1RN and IL-4 gene in Indian women. Oncol Res. 2009;17(8):367–72.
19 Jin T, Cao W, Zuo X, Li M, Yang Y, Liang T, et al. IL-1RN gene polymorphisms are associated with breast cancer risk in a Chinese Han population. J Gene Med. 2017 Dec;19(12):e2996.
20 Drici AM, Moulessehoul S, Tifrit A, Diaf M, Turki DK, Bachir M, et al. Effect of IL-1β and IL-1RN polymorphisms in carcinogenesis of the gastric mucosa in patients infected with Helicobacter pylori in Algeria. Libyan J Med. 2016 Jun;11(1):31576.
21 Zhang J, Sun X, Wang J, Zhang F, Li X, Han J. Association of the IL-1RN variable number of tandem repeat polymorphism and Helicobacter pylori infection: A meta-analysis. PLoS One. 2017 Apr;12(4):e0175052.
22 Bozdoğan ST, Erol B, Dursun A, Bozdoğan G, Dönmez I, Mungan NA, et al. The IL-1RN and IL-4 gene polymorphisms are potential genetic markers of susceptibility to bladder cancer: a case-control study. World J Urol. 2015 Mar;33(3):389–95.
23 Kanterman J, Sade-Feldman M, Baniyash M. New insights into chronic inflammation-induced immunosuppression. Semin Cancer Biol. 2012 Aug;22(4):307–18.
24 Khatami M. Chronic Inflammation: Synergistic Interactions of Recruiting Macrophages (TAMs) and Eosinophils (Eos) with Host Mast Cells (MCs) and Tumorigenesis in CALTs. M-CSF, Suitable Biomarker for Cancer Diagnosis! Cancers (Basel). 2014 Jan;6(1):297–322.
25 Wu X, Kondragunta V, Kornman KS, Wang HY, Duff GW, Renner JB, et al. IL-1 receptor antagonist gene as a predictive biomarker of progression of knee osteoarthritis in a population cohort. Osteoarthritis Cartilage. 2013 Jul;21(7):930–8.