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ORIGINAL ARTICLE

Case Control Study

Association of colorectal cancer susceptibility variants with esophageal cancer in a Chinese population

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Abstract

AIM: To investigate the association between colorectal cancer (CRC) genetic susceptibility variants and esophageal cancer in a Chinese Han population.

METHODS: A case-control study was conducted including 360 esophageal cancer patients and 310 healthy controls. Thirty-one single-nucleotide polymorphisms (SNPs) associated with CRC risk from previous genome-wide association studies were analyzed. SNPs were genotyped using Sequenom Mass-ARRAY technology, and genotypic frequencies in controls were tested for departure from Hardy-Weinberg equilibrium using a Fisher's exact test. The allelic frequencies were compared between cases and controls using a χ^2 test. Associations between the SNPs and the risk of esophageal cancer were tested using various genetic models (codominant, dominant, recessive, overdominant, and additive). ORs and 95%CIs were calculated by unconditional logistic regression with adjustments for age and sex.

RESULTS: The minor alleles of rs1321311 and rs4444235 were associated with a 1.53-fold (95%CI:

1.15-2.06; *P* = 0.004) and 1.28-fold (95%CI: 1.03-1.60; *P* = 0.028) increased risk of esophageal cancer in the allelic model analysis, respectively. In the genetic model analysis, the C/C genotype of rs3802842 was associated with a reduced risk of esophageal cancer in the codominant model (OR = 0.52, 95%CI: 0.31-0.88; *P* = 0.033) and recessive model (OR = 0.55, 95%CI: 0.34-0.87; *P* = 0.010). The rs4939827 C/T-T/T genotype was associated with a 0.67-fold (95%CI: 0.46-0.98; *P* = 0.038) decreased esophageal cancer risk under the dominant model. In addition, rs6687758, rs1321311, and rs4444235 were associated with an increased risk. In particular, the T/T genotype of rs1321311 was associated with an 8.06-fold (95%CI: 1.96-33.07; *P* = 0.004) increased risk in the codominant model.

CONCLUSION: These results provide evidence that known genetic variants associated with CRC risk confer risk for esophageal cancer, and may bring risk for other digestive system tumors.

Key words: Colorectal cancer; Esophageal cancer; Single-nucleotide polymorphism; Susceptibility

Core tip: This case-control study investigates the association between colorectal cancer susceptibility variants (single-nucleotide polymorphisms) and esophageal cancer in a Chinese Han population. The minor alleles of rs1321311 and rs4444235 were associated with a 1.53-fold and 1.28-fold increased risk of esophageal cancer in allelic model analysis, respectively. In the genetic model analysis, rs3802842 and rs4939827 were associated with a decreased esophageal cancer risk, whereas rs6687758 was associated with an increased risk. These results provide evidence that known genetic variants associated with colorectal cancer risk may also confer risk for esophageal cancer.

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INTRODUCTION

Esophageal cancer, classified as adenocarcinoma or squamous cell carcinoma, is one of the top ten most malignant and deadly cancers worldwide, for which China has among the highest rates of incidence and mortality[1]. Highly advanced cancers of the esophagus have poor prognostic outcomes[2,3]. Of the two forms of esophageal cancer, squamous cell carcinoma is the most common, and prognosis highly correlates with disease stage and advancement.

Epidemiologic studies indicate that tobacco smoking, alcohol intake, nutritional deficiencies, and dietary carcinogen exposure contribute to the etiology of esophageal cancer[4,5]. However, only a small proportion of individuals exposed to these factors actually develop esophageal cancer, suggesting that genetic factors also play a vital role in susceptibility. It has been reported that susceptibility to esophageal cancer is not dependent on a single gene and is affected by population differences[6,7].

Colorectal cancer (CRC) is the most common malignant tumor of the digestive tract, and the second most common of all gastrointestinal tumors[8]. Recent studies have identified haplotype-tagging single-nucleotide polymorphisms (SNPs) that are associated with an increased colorectal cancer risk in the general population[9-12].

Previous genetic polymorphism studies in the Chinese population were focused solely on SNPs associated with esophageal cancer risk in genome-wide association studies (GWAS)[13-15]. The purpose of the present study was to identify digestive system tumor common susceptibility loci. To achieve this, 31 high-frequency SNPs associated with CRC risk in the Chinese population were evaluated with respect to esophageal cancer risk.

MATERIALS AND METHODS

Study participants

All participants were Chinese Han that were seen between January 2011 and February 2014 at the First Affiliated Hospital of the Medical College of Xi'an Jiaotong University. None of the study participants received neoadjuvant therapy or had previous histories of other cancers, chemotherapy, or radiotherapy. Participants were chosen without restrictions of age, sex, or disease stage. None of the healthy control subjects had any chronic or severe endocrine, metabolic or nutritional diseases. A total of 360 esophageal cancer cases and 310 controls were included in the study. Esophageal cancer was newly diagnosed according to the criteria established by the International Union Against Cancer tumor-node-metastasis classification system (7th ed)[16].

Clinical data and demographic information

We used a standard epidemiologic questionnaire and in-person interviews to collect personal data, including residential region, age, sex, education status, and family history of cancer. The case information was collected through consultation with treating physicians or from medical chart review. All of the participants signed an informed consent agreement. The Human Research Committee for Approval of Research Involving

Table 1 Characteristics of cases and controls in this study *n* (%)

Variable	Cases (*n* = 360)	Controls (*n* = 310)	*P* value
Sex			< 0.001
Male	288 (62.0)	197 (36.5)	
Female	72 (20.0)	113 (36.5)	
Age, yr (mean ± SD)	60.7 ± 8.9	49.4 ± 7.9	< 0.001

Human Subjects, The First Affiliated Hospital of the Medical College of Xi'an Jiaotong University approved the use of human tissue in this study.

Selection of SNPs and methods of genotyping

Thirty-one SNPs from 17 genes were chosen for analysis in this study. These SNPs were chosen from CRC GWAS[9-12]. Minor allele frequencies of all SNPs were > 5% in the HapMap of the Chinese Han Beijing population.

DNA was extracted from whole-blood samples using GoldMag-Mini Whole Blood Genomic DNA Purification Kits (GoldMag Co., Ltd., Hainan City, China), and quantified with a spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, United States). The multiplexed SNP MassEXTENDED assay was designed using Sequenom MassARRAY Assay Design 3.0 Software[17] (Sequenom Inc., San Diego, CA, United States). Genotyping was performed with the MassARRAY RS1000 system (Sequenom) using the standard protocol recommended by the manufacturer. Data management and analysis were performed using Sequenom Typer 4.0 Software[17,18].

Statistical analysis

Data were analyzed using SPSS version 18.0 statistical software (SPSS Inc., Chicago, IL, United States) and Excel (Microsoft Corp., Redmond, WA, United States). The lower frequency alleles were coded as the minor allele. A Fisher's exact test was used to assess the variation in each SNP frequency from the Hardy-Weinberg equilibrium in the control subjects. Differences in SNP genotype distribution between cases and controls were compared by the χ^2 test. ORs[19] and 95%CIs were determined using unconditional logistic regression analysis with adjustments for age and sex. All two-sided *P* values < 0.05 were considered statistically significant.

Associations between SNPs and risk of esophageal cancer were tested in genetic models using SNP Stats software (http://bioinfo.iconcologia.net). For the additive model, individuals were assigned a 0, 1, or 2, representing the number of risk alleles they possessed for that SNP. For the dominant model, individuals were coded as 1 if they carried at least one risk allele and 0 otherwise; for the recessive model, individuals were coded as 1 if they were homozygous for the risk allele, and 0 otherwise. Akaike's Information Criterion and Bayesian Information Criterion were applied to estimate the best-fit model for each SNP.

The statistical methods of this study were reviewed by Tianfeng from the National Engineering Research Center for Miniaturized Detection Systems.

RESULTS

There were significant differences in age and sex distribution between the case and control groups (*P* < 0.01) (Table 1).

Table 2 summarizes the major allelic frequencies of the SNPs among the individuals in the case and control groups. Three SNPs (rs10774214, rs2423279, and rs4925386) were excluded for significant deviation from Hardy-Weinberg equilibrium (*P* < 0.05); the other SNPs in the control group were similar to those of the HapMap Asian population (http://hapmap.ncbi.nlm.nih.gov/). A χ^2 analysis revealed that rs1321311 and rs4444235 were significantly associated with a 1.53-fold and 1.28-fold increased esophageal cancer risk, respectively (*P* < 0.05 for both).

In the genetic model analyses, the minor T allele of rs1321311 was associated with an increased risk of esophageal cancer based on analysis using the codominant and recessive models (*P* < 0.01 for both; Table 3). The minor C allele of rs4444235 was also significantly associated with an increased cancer risk in codominant and dominant models (*P* < 0.05 for both). The G/G genotype of rs6687758 was associated with a 2.54-fold increased risk in the recessive model (*P* < 0.05). In contrast, the minor C allele of rs3802842 was associated with a 0.52-fold and 0.55-fold reduced risk of esophageal cancer as revealed by the codominant and recessive models, respectively (*P* < 0.05 for both). Additionally, the dominant model showed that the rs4939827 SNP was significantly associated with an 0.67-fold decreased esophageal cancer risk (*P* < 0.05).

DISCUSSION

This study identifies three SNPs (rs1321311, rs4444235, and rs6687758) associated with an increased risk of esophageal cancer. The SNP rs1321311, located near *CDKN1A* at 6p21, has previously been associated with an increased risk of CRC[20,21]. This association was not strongly modified by sex, body mass index, alcohol, smoking, aspirin or various dietary factors[20]. The SNP rs4444235, which is located 9.4 kb upstream of the gene encoding bone morphogenetic protein 4 (*BMP4*), was previously associated with CRC and gastric cancer risk[22,23]. Although the CT genotype showed a protective effect against gastric cancer[23], it was also associated with an increased CRC risk[24]. This SNP has been proposed to act as a cis-regulator of *BMP4* and thus confer a risk for CRC[25,26]. Based on the results of the present study, the CT genotype is also associated with an increased risk of esophageal cancer. The rs6687758 SNP, which has been shown

Table 2 Allele frequencies in cases and controls and odds ratio estimates for esophageal cancer

SNP	Gene(s)	Locus	Alleles (A[1]/B)	Major allelic frequency		HWE *P* value	OR	95%CI	*P* value
				Case	Control				
rs1912453	*C1orf110*	1q23.3	C/T	0.404	0.392	0.812	1.054	0.846-1.314	0.639
rs10911251	*LAMC1*	1q25.3	C/A	0.487	0.494	0.256	0.976	0.787-1.211	0.826
rs6687758		1q41	G/A	0.243	0.222	0.191	1.127	0.873-1.455	0.358
rs11903757		2q32.3	C/T	0.039	0.044	1.000	0.889	0.518-1.525	0.668
rs10936599	*ARPM1*	3q26.2	C/T	0.480	0.453	0.909	1.116	0.899-1.384	0.320
rs13130787		4q22.2	C/T	0.307	0.315	0.239	0.965	0.765-1.217	0.765
rs367615		5q21.3	T/C	0.447	0.431	0.908	1.070	0.861-1.328	0.542
rs647161		5q31.1	A/C	0.296	0.274	0.198	1.113	0.877-1.413	0.377
rs1321311		6p21.2	T/G	0.200	0.140	0.234	1.534	1.145-2.055	0.004
rs2057314	*DCBLD1*	6q22.1	C/T	0.483	0.455	0.302	1.120	0.901-1.391	0.308
rs9365723	*SYNJ2*	6q25.3	G/A	0.411	0.373	0.224	1.169	0.935-1.462	0.171
rs7758229	*SLC22A3*	6q25.3	T/G	0.229	0.268	1.000	0.811	0.632-1.042	0.101
rs39453		7p15.3	C/T	0.304	0.339	0.528	0.851	0.676-1.073	0.172
rs10505477	*POU5F1B*	8q24.21	T/C	0.431	0.435	0.205	0.983	0.791-1.221	0.874
rs6983267			G/T	0.425	0.437	0.490	0.950	0.765-1.181	0.645
rs7014346			A/G	0.288	0.323	0.438	0.848	0.672-1.071	0.167
rs10114408		9q22.32	T/A	0.160	0.177	0.175	0.881	0.662-1.174	0.388
rs1665650	*HSPA12A*	10q25.3	A/G	0.304	0.306	0.595	0.991	0.784-1.251	0.937
rs3824999	*POLD3*	11q13.4	C/A	0.370	0.379	0.542	0.961	0.768-1.202	0.726
rs3802842	*C11orf93*	11q23.1	C/A	0.421	0.451	0.065	0.885	0.712-1.100	0.272
rs10774214	*CCND2*	12p13.32	T/C	0.320	0.318	0.026[2]	1.011	0.803-1.274	0.923
rs3217901			G/A	0.482	0.498	0.113	0.936	0.755-1.161	0.548
rs59336	*TBX3*	12q24.21	T/A	0.417	0.379	1.000	1.171	0.939-1.461	0.160
rs7315438			T/C	0.361	0.342	0.528	1.085	0.866-1.360	0.478
rs4444235	*BMP4*	14q22.2	C/T	0.497	0.435	0.730	1.281	1.027-1.599	0.028
rs4779584	*SCG5*	15q13.3	C/T	0.216	0.190	0.716	1.175	0.899-1.537	0.237
rs9929218	*CDH1*	16q22.1	A/G	0.163	0.163	1.000	0.997	0.745-1.334	0.984
rs4939827	*SMAD7*	18q21.1	T/C	0.204	0.248	0.227	0.776	0.600-1.004	0.053
rs961253		20p12.3	A/C	0.107	0.102	0.537	1.062	0.747-1.510	0.737
rs2423279			C/T	0.359	0.344	0.033[2]	1.069	0.853-1.340	0.563
rs4925386	*LAMA5*	20q13.33	T/C	0.251	0.253	0.010[2]	0.987	0.770-1.265	0.916

[1]Minor allele; [2]Site with HWE $P \leq 0.05$ excluded. HWE: Hardy-Weinberg equilibrium; SNP: Single-nucleotide polymorphism.

Table 3 Logistic regression analysis of the association between the single-nucleotide polymorphisms and esophageal cancer risk *n* (%)

SNP	Model	Genotype	Cases	Controls	OR[1] (95%CI)	*P* value	AIC	BIC
rs1321311	Codominant	G/G	226 (64.2)	226 (72.9)	1	0.004	670.6	693.0
		G/T	111 (31.5)	81 (26.1)	1.27 (0.84-1.93)			
		T/T	15 (4.3)	3 (1.0)	8.06 (1.96-33.07)			
	Dominant	G/G	226 (64.2)	226 (72.9)	1	0.066	676.1	694.1
		G/T-T/T	126 (35.8)	84 (27.1)	1.46 (0.97-2.19)			
	Recessive	G/G-G/T	337 (95.7)	307 (99.0)	1	0.002	669.9	687.8
		T/T	15 (4.3)	3 (1.0)	7.51 (1.84-30.66)			
rs4444235	Codominant	T/T	76 (23.5)	100 (32.4)	1	0.046	651.8	674.0
		C/T	174 (53.7)	149 (48.2)	1.69 (1.08-2.65)			
		C/C	74 (22.8)	60 (19.4)	1.75 (1.01-3.02)			
	Dominant	T/T	76 (23.5)	100 (32.4)	1	0.013	649.8	667.6
		C/T-C/C	248 (76.5)	209 (67.6)	1.71 (1.12-2.62)			
	Recessive	T/T-C/T	250 (77.2)	249 (80.6)	1	0.350	655.0	672.8
		C/C	74 (22.8)	60 (19.4)	1.25 (0.79-1.98)			
rs6687758	Codominant	A/A	212 (59.2)	183 (59.2)	1	0.066	679.0	701.5
		G/A	118 (33.0)	115 (37.2)	0.86 (0.58-1.28)			
		G/G	28 (7.8)	11 (3.6)	2.40 (1.01-5.74)			
	Dominant	A/A	212 (59.2)	183 (59.2)	1	0.950	682.4	700.4
		G/A-G/G	146 (40.8)	126 (40.8)	0.99 (0.68-1.44)			
	Recessive	A/A-G/A	330 (92.2)	298 (96.4)	1	0.027	677.5	695.5
		G/G	28 (7.8)	11 (3.6)	2.54 (1.08-6.00)			

rs3802842	Codominant	A/A	119 (33.4)	101 (32.8)	1	0.033	681.0	703.5
		C/A	174 (48.9)	136 (44.2)	0.91 (0.60-1.40)			
		C/C	63 (17.7)	71 (23.1)	0.52 (0.31-0.88)			
	Dominant	A/A	119 (33.4)	101 (32.8)	1	0.190	684.1	702.1
		C/A-C/C	237 (66.6)	207 (67.2)	0.77 (0.52-1.14)			
	Recessive	A/A-C/A	293 (82.3)	237 (77.0)	1	0.010	679.2	697.1
		C/C	63 (17.7)	71 (23.1)	0.55 (0.34-0.87)			
rs4939827	Codominant	C/C	228 (63.3)	179 (57.7)	1	0.110	687.0	709.5
		C/T	117 (32.5)	108 (34.8)	0.68 (0.46-1.02)			
		T/T	15 (4.2)	23 (7.4)	0.58 (0.26-1.33)			
	Dominant	C/C	228 (63.3)	179 (57.7)	1	0.038	685.1	703.2
		C/T-T/T	132 (36.7)	131 (42.3)	0.67 (0.46-0.98)			
	Recessive	C/C-C/T	345 (95.8)	287 (92.6)	1	0.330	688.5	706.5
		T/T	15 (4.2)	23 (7.4)	0.67 (0.30-1.50)			

[1]Adjusted by sex and age. AIC: Akaike's information criterion; BIC: Bayesian information criterion; SNP: Single-nucleotide polymorphism.

to be associated with an increased CRC risk[20], also increased the risk for esophageal cancer. However, the functional consequence of this polymorphism remains unknown.

This study also indentifies two SNPs, rs3802842 and rs4939827, associated with a decreased risk for esophageal cancer. Although these SNPs have been associated with CRC risk, the results are inconsistent[27,28]. It is possible that these results reflect different variant alleles in the populations studied, given that the minor allele frequency was different. The rs4939827 SNP likely influences cancer *via* inhibition of SMAD7[28,29], a component of the transforming growth factor-β signalling pathway that regulates growth and apoptosis and plays an important role in cancer initiation and progression[30-33].

Despite the adequate statistical power of the current study, some limitations should be considered. First, the sample size of our study was relatively small. Second, the association between genetic polymorphism and clinicopathologic type (adenocarcinoma or squamous cell carcinoma) was not evaluated. This could be an important factor, as rs4444235 and rs4939827 were shown to be over-represented in CRC-free patients with adenomas[32,33].

In conclusion, this association study investigated 31 SNPs identified from CRC GWAS as genetic susceptibility factors for esophageal cancer in a Chinese population. The replication of genetic associations from CRC to esophageal cancer highlights the utility of case-control studies to confirm novel associations characterized in large GWAS of digestive system diseases. Our study provides the first reported data of a possible association between the SNPs rs1321311, rs4444235, rs6687758, rs3802842, and rs4939827 and esophageal cancer risk. However, further investigations are needed to confirm these associations in other populations.

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COMMENTS

Background

Esophageal cancer and colorectal cancer (CRC) are the most common malignant tumors of the digestive tract, and are among the top ten most malignant and deadly cancers worldwide. China is among the countries with the highest incidence and mortality of esophageal cancer. Previous studies implicate the role of genetic factors in the susceptibility to these cancers. However, previous genome-wide association studies (GWAS) in the Chinese population have focused solely on single-nucleotide polymorphisms (SNPs) in esophageal cancer.

Research frontiers

Epidemiologic studies have revealed that tobacco smoking, alcohol intake, nutritional deficiencies, and dietary carcinogen exposure may contribute to the etiology of esophageal cancer. However, only a small proportion of exposed individuals actually develop esophageal cancer, suggesting that genetic factors also play a vital role in susceptibility.

Innovations and breakthroughs

This study aimed to identify common digestive system tumor susceptibility loci in a Chinese population. Thirty-one SNPs previously identified from CRC GWAS were selected to assess their association with risk for esophageal cancer. Five of these SNPs were identified as associated with both CRC and esophageal cancer risk, highlighting the utility of case-control studies to confirm novel associations characterized in large GWAS. This study provides the first reported data of a possible association between the SNPs rs1321311, rs4444235, rs6687758, rs3802842, and rs4939827 and esophageal cancer risk.

Applications

This study sheds new light on the study of susceptibility variants in digestive system tumors. The results suggest that genetic variation (rs1321311, rs4444235, rs6687758, rs3802842, and rs4939827) influences susceptibility to esophageal cancer, and may have a clinical impact in the future.

Peer-review

The article provides a novel result for esophageal cancer genetic risk factors, which has significance for clinical application.

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