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ORIGINAL ARTICLE

Association of gastrointestinal gland cancer susceptibility loci with esophageal carcinoma among the Chinese Han population: a case–control study

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Abstract Esophageal carcinoma (EC) is a common malignancy worldwide. Previous studies indicated that gastrointestinal gland cancer and EC share some susceptibility loci. Our aim was to identify new single nucleotide polymorphisms (SNPs) associated with EC by investigating whether known gastrointestinal cancers susceptibility loci are found in EC patients. A Chinese Han population case–control study was conducted to assess SNP associations with EC risk. Twenty-six SNPs were selected from gastrointestinal cancer susceptibility loci, and 360 EC patients and 310 controls were genotyped for these SNPs using Sequenom MassARRAY technology. The association of SNP frequencies with EC was analyzed by chi-square tests, and genetic model analysis. After Hardy–Weinberg equilibrium (HWE) p value screening, we excluded two SNPs. Based on chi-square tests, the minor alleles of rs13294589 (p=0.046) and rs4924935 (p=0.046) were correlated with reduced EC risk and rs4269383 (p=0.010) and rs10953615 (p=0.036) were correlated with increased EC risk. In the genetic model analyses, we found that the minor alleles "T" of rs401681, "A" of rs10088262, and "C" of rs4924935 may reduce the risk of EC. rs401681 has previously been reported to be associated with EC. To the best of our knowledge, we are the first to report an association of the other five SNPs with EC. Our findings provide evidence for the genetic variants associated with susceptibility to EC in the Chinese Han population, which might be used as potential molecular markers for detecting susceptibility to EC in Chinese Han people.

Keywords Esophageal carcinoma (EC) · Single nucleotide polymorphism (SNP) · Case–control study · Susceptibility loci · Chinese Han population

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Introduction

Esophageal cancer (EC) is one of the most common causes of cancer-related mortality worldwide, and its incidence rate has significantly increased in recent years [1]. There are two different forms of EC, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). There were 223,306 patients diagnosed with EC and 197,472 patients died in China in 2012. The incidence rate (7.3 %) was ranked fifth, and the mortality rate (9.0 %) was ranked fourth for both sexes [2, 3]. For both incidence and mortality, the rate of EC is much higher in men than in women, in rural areas than in urban areas, and peaks at age 80–84 years [4]. The majority of EC cases occur in developing countries, such as China. Our study focused on China's main population, the Han Chinese.

More than half of the EC global cases were diagnosed in China, a high-incidence area for esophageal carcinoma [5]. The actual etiology of EC remains unclear, but extensive evidence collected in the past decades has demonstrated that tobacco smoking, hot beverage intake, and alcohol are prominent risk factors for this disease [6–9]. The risk gene variants may confer different magnitudes of increased risk in different populations for a variety of reasons, including differences in allele frequency and lifestyles and differences in genetic and environmental backgrounds that interact with the variants [10, 11]. Only a few of individuals that partake in risk factors such as smoking develop EC, indicating that an individual's genetic makeup plays an important role in esophageal carcinogenesis [12].

Because the function of the gastrointestinal gland is closely related to the esophagus and since a recent study indicates that gastrointestinal cancer and EC may share genetic risk factors [13], we used susceptibility loci associated with gastrointestinal gland cancer to identify new loci associated with EC. We selected 26 single nucleotide polymorphisms (SNPs) from gastrointestinal gland cancer susceptibility loci to analyze their association with EC in the Chinese Han population.

Materials and methods

Study population

This study was conducted as a population-based case–control study. All participants were Han Chinese, had histologically confirmed EC including ESCC or EA, were at least 18 years old, and were in good mental condition. Exclusion criteria included self-reported cancer history and previous radiotherapy and/or chemotherapy. A total of 360 patients newly diagnosed with histologically confirmed EC were consecutively recruited between March 2011 and July 2014 in the First Affiliated Hospital of Xi'an Jiaotong University and in Tangdu Hospital, Xi'an City, China. We also recruited a random sample of unrelated healthy individuals between March 2011 and July 2014 from the health centers of Tangdu Hospital, Xi'an City, China. The control population was matched with the EC population based on age and gender. This minimized factors could influence mutation rate, thus maximizing the study's power. None of the healthy control subjects had any chronic or severe endocrine, metabolic, or nutritional diseases. The study was comprised of 310 unrelated healthy subjects (113 females and 197 males with a mean age of 49.4 years) and 360 EC patients (72 females and 288 males with a mean age of 60.7 years). Basic population information is shown in Table 1.

Table 1 Characteristics of EC cases and controls in this study

Characteristic	Case (N=360)	Control (N=310)	Total	p value
Sex, No. (%)				<0.001
Male	288 (80)	197 (63.5)	485	
Female	72 (20)	113 (36.5)	185	
Age				<0.001
Min	35	28		
Max	86	75		
Mean age±SD	60.74±8.9	49.43±7.9		

$p<0.05$ indicates statistical significance

EC esophageal carcinoma

Demographic and clinical data

For each participant, a standard questionnaire was used to collect demographic information, including age, sex, smoking status, alcohol use, education, and family history of cancer. Detailed clinical information was collected from treating physicians or medical chart reviews. Blood samples (5 ml) and signed informed consent forms were obtained from every participant enrolled. This protocol was approved by the Clinical Research Ethics Committee of Baoji Central Hospital. In addition, alpha-fetoprotein and plasma carcinoembryonic antigen levels were analyzed to ensure that no participants in the control group suffered from cancer.

SNP selection and genotyping

We selected 26 SNPs from previously published polymorphisms associated with gastrointestinal cancer susceptibility loci. Two SNPs (rs17401966 and rs455804) were selected from previous research of hepatocellular carcinoma [14]. Twenty SNPs (rs6736997, rs401681, rs6879627, rs9502893, rs9363918, rs4269383, rs3016539, rs7832232, rs10088262, rs10788473, rs12413624, rs10500715, rs1000589, rs1585440, rs9573163, rs9543325, rs4924935, rs225190, rs372883, and rs1547374) were selected from previous research of pancreatic cancer [15–20]. Four SNPs (rs975334, rs10953615, rs13294589, and rs7504990) were selected from previous research of gallbladder cancer [21]. All of the SNPs in this study had minor allele frequencies (MAFs) of >5 % in the Asian Population HapMap and had previously been reported to be associated with gastrointestinal cancer. Basic information about the 26 SNPs is listed in Table 2. Genomic DNA was extracted from the peripheral blood using phenol–chloroform, and its concentration was measured using a DU 530 UV/VIS spectrophotometer (Beckman Instruments, Fullerton, CA, USA) according to the manufacturer's protocol. MassARRAY Assay Design 3.0 Software (Sequenom, San Diego, CA, USA) was used to design Multiplex SNP MassEXTEND assays [22]. Genotyping was performed using

Table 2 Basic information of the 26 SNPs

SNP ID	Chr	Position	Mapped gene region	Source	A/B	O-HET	E-HET	HWE–p[a]
rs17401966	1p36.22	10385471	*KIF1B*	Hepatocellular carcinoma	G/A	0.4129	0.4121	1
rs6736997	2q37.2	235615197	*ARL4C–HSPA8P10*	Pancreatic cancer	A/C	0.4161	0.3295	5.53E−08*
rs975334	3p26.2	2846316	*CNTN4*	Gallbladder cancer	C/T	0.3065	0.3022	1
rs401681	5p15.33	1322087	*CLPTM1L*	Pancreatic cancer	T/C	0.4419	0.449	0.801
rs6879627	5p15.33	2109901	*IRX4–IRX2*	Pancreatic cancer	T/C	0.4774	0.4917	0.644
rs9502893	6p25.3	1340189	*FOXQ1–FOXF2*	Pancreatic cancer	C/T	0.4355	0.4675	0.226
rs9363918	6q12	69142008	*NUFIP1P–BAI3*	Pancreatic cancer	T/G	0.2751	0.2821	0.686
rs4269383	6q25.3	156197502	*NOX3–MIR1202*	Pancreatic cancer	A/G	0.2935	0.2813	0.548
rs3016539	6q26	162236075	*PARK2*	Pancreatic cancer	G/A	0.2032	0.2127	0.421
rs10953615	7q31.1	109152711	*DNAJB9–EIF3IP1*	Gallbladder cancer	G/A	0.1968	0.1928	1
rs7832232	8p11.22	38469303	*RNF5P1–TACC1*	Pancreatic cancer	G/A	0.4839	0.4953	0.731
rs10088262	8q24.13	124765702	*ANXA13–FAM91A1*	Pancreatic cancer	A/G	0.4452	0.448	0.899
rs13294589	9p21.2	26694888	*TUSC1–CAAP1*	Gallbladder cancer	G/A	0.2129	0.2003	0.397
rs10788473	10q23.1	87740753	*GRID1*	Pancreatic cancer	C/T	0.309	0.2703	0.010*
rs12413624	10q26.11	120278944	*FAM204A–PRLHR*	Pancreatic cancer	A/T	0.4742	0.4921	0.564
rs10500715	11p15.4	9973062	*SBF2*	Pancreatic cancer	G/T	0.2968	0.3314	0.084
rs1000589	13q21.31	64141913	*RPL32P28–OR7E156P*	Pancreatic cancer	G/T	0.4419	0.4359	0.896
rs1585440	13q21.32	66481815	*HNRNPA3P5–MIR548X2*	Pancreatic cancer	A/C	0.4498	0.4169	0.219
rs9573163	13q22.1	73908846	*RNY1P8–MARK2P12*	Pancreatic cancer	C/G	0.4774	0.489	0.727
rs9543325	13q22.1	73916628	*RNY1P8–MARK2P12*	Pancreatic cancer	C/T	0.4871	0.4904	0.908
rs4924935	17p11.2	18753870	*TVP23B–PRPSAP2*	Pancreatic cancer	C/T	0.2387	0.2248	0.445
rs225190	17q11.2	30877658	*MYO1D*	Pancreatic cancer	G/A	0.3968	0.4134	0.493
rs7504990	18q21.2	50517776	*DCC*	Gallbladder cancer	T/C	0.3548	0.3701	0.446
rs372883	21q21.3	30717737	*BACH1*	Pancreatic cancer	G/A	0.4628	0.4847	0.414
rs455804	21q21.3	31146169	*GRIK1*	Hepatocellular carcinoma	T/G	0.4032	0.4288	0.291
rs1547374	21q22.3	43778895	*TFF2–TFF1*	Pancreatic cancer	G/A	0.4645	0.48	0.556

A/B minor/major alleles, *O-HET* observed heterozygosity, *E-HET* expected heterozygosity, *HWE* Hardy–Weinberg equilibrium

*$p<0.05$, statistical significance

[a] p value calculated using exact test

the Sequenom MassARRAY RS1000 following a standard protocol recommended by the manufacturer [23], and data were analyzed using Sequenom Typer 4.0 Software (Sequenom, San Diego, CA, USA) [23, 24].

Statistical analyses

The association of each of the SNPs with EC was evaluated using unconditional logistic regression models include dominant, co-dominant, recessive, and log-additive genetic models. In all analyses, the lower frequency allele was defined as the risk allele. For example, for the additive model, individuals were assigned with 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; and for the recessive model, individuals were coded as 1 if they were homozygous for the risk allele (two copies) and 0 otherwise.

We used Microsoft Excel and the SPSS 16.0 Statistical Package (SPSS, Chicago, IL, USA) to perform statistical analyses. In controls, each SNP was tested to determine whether it fit the Hardy–Weinberg equilibrium (HWE). Chi-square tests [25] and SNPStats Software from http://bioinfo.iconcologia.net/snpstats/start.htm [26] were used to test the association between genetic polymorphisms and EC. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using unconditional logistic regression analyses adjusted for age and gender [27], and the most common control homozygote was used as reference. Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to choose the best model for each SNP. All p values reported in this study were two-tailed, and p values less than 0.05 were considered statistically significant. Linkage disequilibrium (LD) of the candidate SNPs was analyzed using HaploView v4.2 [28]. Pairwise LD and haplotype constructions were performed using the SHEsis Software (http://analysis.bio–x.cn/myAnalysis.php) [29].

Results

In our initial analyses, we sought to determine whether the 26 selected SNPs fit the Hardy–Weinberg equilibrium. We found that all SNPs were in Hardy–Weinberg equilibrium in EC patients and controls ($p>0.05$ after Bonferroni correction) except for rs6736997 ($p=5.53E{-}08$) and rs10788473 ($p=0.010$) in the controls. These two SNPs were excluded, and only the remaining 24 SNPs were used for subsequent association analysis. Detailed information of the observed heterozygosity (O-HET) and expected heterozygosity (E-HET) of the SNPs is listed in Table 2. Chi-square tests suggested that we found rs4269383 (OR=1.429, 95 % CI=1.087–1.878, $p=0.010$), rs10953615 (OR=1.418, 95 % CI=1.022–1.968, $p=0.036$), rs13294589 (OR=0.690, 95 % CI=0.479–0.996, $p=0.046$), and rs4924935 (OR=0.706, 95 % CI=0.500–0.995, $p=0.046$) are correlated with EC risk (Table 3).

In the genetic model analyses (Table 4), the minor allele "T" of rs401681 was associated with reduced EC risk, based on the results from the co-dominant ($p=0.01$) and dominant (OR=0.60, 95 % CI=0.41–0.87, $p=0.0073$) models. The minor allele "A" of rs10088262 was associated with reduced risk of EC, based on the co-dominant model ($p=0.045$). The minor allele "C" of rs4924935 may reduce the risk of EC, based on the co-dominant ($p=0.023$) and dominant (OR=0.54, 95 % CI=0.34–0.85, $p=0.008$) model. In contrast, the minor allele A of rs4269383 was associated with increased risk of EC as revealed by the co-dominant model ($p=0.024$) and the genotype "AA" may significantly increase EC risk in the recessive model (OR=3.37, 95 % CI=1.28–8.89, $p=0.009$).

Finally, we looked for interactions of the SNPs in the same chromosome from patients adjusted by age and gender and found that none of the analyzed SNPs correlated with age or gender (data not shown).

Discussion

In this Chinese Han population-based case–control study, we found that six susceptibility loci were associated with EC and first found that five loci (rs4269383 located in 6q25.3,

Table 3 Pearson chi-square test of the 24 SNPs

SNP ID	A/B[a]	Case		Control		OR	95 % CI	Chi–p
		A count	B count	A count	B count			
rs17401966	G/A	206	490	180	440	1.028	0.810–1.304	0.822
rs975334	C/T	138	582	115	505	1.041	0.791–1.370	0.773
rs401681	T/C	209	509	211	409	0.796	0.632–1.003	0.053
rs6879627	T/C	301	399	270	350	0.978	0.786–1.216	0.841
rs9502893	C/T	244	414	231	389	0.992	0.791–1.245	0.948
rs9363918	T/G	105	613	105	513	0.837	0.623–1.124	0.236
rs4269383	A/G	162	556	105	515	1.429	1.087–1.878	0.010*
rs3016539	G/A	70	640	75	545	0.795	0.563–1.122	0.192
rs10953615	G/A	105	611	67	553	1.418	1.022–1.968	0.036*
rs7832232	G/A	321	389	280	340	1.002	0.807–1.244	0.985
rs10088262	A/G	255	457	210	410	1.089	0.869–1.366	0.458
rs13294589	G/A	58	660	70	550	0.690	0.479–0.996	0.046*
rs12413624	A/T	301	419	271	349	0.925	0.745–1.149	0.482
rs10500715	G/T	144	574	130	490	0.946	0.725–1.234	0.680
rs1000589	G/T	217	503	199	421	0.913	0.724–1.151	0.440
rs1585440	A/C	193	517	183	435	0.887	0.699–1.127	0.327
rs9573163	C/G	323	391	264	356	1.114	0.897–1.384	0.329
rs9543325	C/T	321	389	267	353	1.091	0.878–1.355	0.432
rs4924935	C/T	67	641	80	540	0.706	0.500–0.995	0.046*
rs225190	G/A	190	502	181	439	0.918	0.722–1.168	0.486
rs7504990	T/C	176	544	152	468	0.996	0.776–1.279	0.976
rs372883	G/A	295	361	255	363	1.163	0.932–1.453	0.182
rs455804	T/G	237	477	193	427	1.099	0.873–1.384	0.421
rs1547374	G/A	308	410	248	372	1.127	0.906–1.402	0.284

*$p<0.05$, statistical significance

[a] Minor/major (A/B) alleles on the control sample frequencies

rs10953615 located in 7q31.1, rs10088262 located in 8p11.22, rs13294589 located in 13q21.31, and rs4924935 located in 17p11.2) were associated with EC. We searched for these SNPs in electronic databases (PubMed, Medline, Web of Knowledge, CNKI, and Google Scholar) to identify eligible studies that were published before September 2014. We found that rs401681 was reported to be associated with EC, lung cancer, pancreatic cancer, and melanoma. rs4269383, rs10088262, and rs4924935 were reported to be associated with pancreatic cancer [18, 15], rs10953615 with gallbladder cancer [18], and rs455804 with hepatocellular carcinoma [14]. Previous research suggests that the minor allele "G" of rs49249935 is associated with increased risk of pancreatic cancer with OR=1.37 (95 % CI=1.19–1.58, p=8.15E−06) under the dominant model [18]. The minor allele A of rs10088262 is associated with increased risk of pancreatic cancer with OR=1.40 (95 % CI=1.21–1.61, p=4.30E−06) under the dominant model [18]. The minor allele T of

Table 4 SNP association with esophageal cancer (adjusted by sex and age)

SNP	Model	Genotype	Control, *n* (%)	Case, *n* (%)	OR (95 % CI)	*p* value
rs401681	Co-dominant	C/C	136 (43.9)	193 (53.8)	1	0.01*
		T/C	137 (44.2)	123 (34.3)	0.54 (0.36–0.81)	
		T/T	37 (11.9)	43 (12)	0.83 (0.46–1.52)	
	Dominant	C/C	136 (43.9)	193 (53.8)	1	0.007*
		T/C–T/T	174 (56.1)	166 (46.2)	0.60 (0.41–0.87)	
	Recessive	C/C–T/C	273 (88.1)	316 (88)	1	0.76
		T/T	37 (11.9)	43 (12)	1.09 (0.62–1.93)	
	Log-additive	–	–	–	0.78 (0.60–1.02)	0.072
rs4269383	Co-dominant	G/G	212 (68.4)	222 (61.8)	1	0.024*
		A/G	91 (29.4)	112 (31.2)	1.19 (0.79–1.78)	
		A/A	7 (2.3)	25 (7)	3.56 (1.34–9.47)	
	Dominant	G/G	212 (68.4)	222 (61.8)	1	0.12
		A/G–A/A	98 (31.6)	137 (38.2)	1.37 (0.93–2.01)	
	Recessive	G/G–A/G	303 (97.7)	334 (93)	1	0.009*
		A/A	7 (2.3)	25 (7)	3.37 (1.28–8.89)	
	Log-additive	–	–	–	1.44 (1.04–1.99)	0.025*
rs10088262	Co-dominant	G/G	136 (43.9)	155 (43.5)	1	0.045*
		G/A	138 (44.5)	147 (41.3)	0.68 (0.46–1.02)	
		A/A	36 (11.6)	54 (15.2)	1.31 (0.73–2.35)	
	Dominant	G/G	136 (43.9)	155 (43.5)	1	0.24
		G/A–A/A	174 (56.1)	201 (56.5)	0.80 (0.55–1.16)	
	Recessive	G/G–G/A	274 (88.4)	302 (84.8)	1	0.1
		A/A	36 (11.6)	54 (15.2)	1.57 (0.91–2.73)	
	Log-additive	–	–	–	1.00 (0.76–1.30)	0.97
rs4924935	Co-dominant	T/T	233 (75.2)	292 (82.5)	1	0.023*
		C/T	74 (23.9)	57 (16.1)	0.51 (0.32–0.83)	
		C/C	3 (1)	5 (1.4)	0.98 (0.19–5.02)	
	Dominant	T/T	233 (75.2)	292 (82.5)	1	0.008*
		C/T–C/C	77 (24.8)	62 (17.5)	0.54 (0.34–0.85)	
	Recessive	T/T–C/T	307 (99)	349 (98.6)	1	0.89
		C/C	3 (1)	5 (1.4)	1.12 (0.22–5.68)	
	Log-additive	–	–	–	0.61 (0.40–0.92)	0.019*
rs455804	Co-dominant	G/G	151 (48.7)	154 (43.1)	1	0.110
		G/T	125 (40.3)	169 (47.3)	1.49 (1.00–2.20)	
		T/T	34 (11)	34 (9.5)	0.96 (0.50–1.82)	
	Dominant	G/G	151 (48.7)	154 (43.1)	1	0.098
		G/T–T/T	159 (51.3)	203 (56.9)	1.37 (0.94–1.98)	
	Recessive	G/G–G/T	276 (89)	323 (90.5)	1	0.460
		T/T	34 (11)	34 (9.5)	0.79 (0.43–1.46)	
	Log-additive	–	–	–	1.14 (0.86–1.51)	0.36

OR odds ratio, *CI* confidence interval

*p<0.05, statistical significance

rs4269383 is associated with reduced risk of pancreatic cancer with OR=0.75 (95 % CI=0.66–0.87 p=8.5E−06) [18]. The rs401681 allele T is implicated in pancreatic cancer with the log-additive model; each additional copy of the minor allele T is associated with a 1.24-fold increased risk of pancreatic cancer (OR=1.24, 95 % CI=1.06–1.44, p=5.61E−03), The minor allele T of rs401681 is also associated with reduced risk of EC and increased lung cancer [15, 19, 30, 31]. The minor allele C of rs10953615 is associated with increased risk of gallbladder cancer, with OR=10.13 (95 % CI=3.33–30.78, p=4.43E−05) under the recessive model. The minor allele G of rs13294589 is associated with increased risk of gallbladder cancer with OR=20.98 (95 % CI=4.96–88.78, p=3.55E−05) under the recessive model [18].

Of the six EC susceptibility loci, we identified and found that only the minor allele of rs10953615 was a similar risk factor for gallbladder and esophageal carcinoma and this allele was associated with increased risk for both cancers [21]. The other five SNPs showed results that were inconsistent with previous studies. For example, we found that rs40681, which mapped to the *CLPTM1L* minor allele A, was associated with a reduced risk of EC but previous reports linked it to an increased risk of pancreatic cancer. The function of *CLPTM1L* and its role in tumorigenesis is largely unknown. However, a recent study reported that *CLPTM1L* is a commonly overexpressed anti-apoptotic factor in lung cancer [30, 32]. Our study and previous research suggest that one SNP can be associated with two or more cancers; for example, rs401681 is associated with many cancers including pancreatic cancer, lung cancer, bladder cancer, and hepatocellular carcinoma [33–35]. Further studies are needed to clarify the genetic mechanism of esophageal carcinogenesis by fine mapping the susceptibility region of the variants.

Our data demonstrate six loci that are associated with EC. Our assessment of the risk of the 24 investigated SNPs was based on the linear analysis model in the discovery set, not including further analysis of the differences between eating habits, family history, or age, making it neither prospective nor epidemiologically rigorous. Alternatively, our sample size (360 cases and 310 controls) could be too small to detect an association in the other SNPs. Moreover, we did not conduct a pathological classification of our EC patients. Due to the low incidence of salivary gland cancer, our loci were chosen based on their association with pancreatic cancer, hepatocellular carcinoma, and gallbladder cancer. Thus, we need to increase the sample size, investigate more SNP from the EC-associated loci, and further investigate whether these SNPs are involved in EC in the Han population.

In our intelligent research, initially, there was a link between these loci and EC but there was no more other evidence of a direct association between gastrointestinal cancer and EC. Gene expression analysis could be used to elucidate the pathogenesis of EC and the relationship between EC and digestive gland tumors. It is known that the contribution of risk alleles to EC risk may vary between populations; this phenomenon may be due to differences in allelic frequencies or specific LD structures or because of additional genetic factors or environmental backgrounds that may influence the effect of these genetic variants. Our research was limited to Han in Chinese population. Our conclusions may, thus, not extent to other populations. Our study did not distinguish between ESCC and EA, which may have different risk factors. Further analysis is required to elucidate the differences between these types of EC.

Conclusion

Our study provides strong evidence that the six SNPs described here may contribute to the risk of EC and other upper gastrointestinal cancers. rs401681 was previously reported to be associated with EC. The other five SNPs characterized here have not been previously shown to be associated with EC. We recommend that those who carry increased risk alleles should concentrate on developing healthy eating habits and receive regular physical examinations. Additionally, larger studies and in vitro or tissue-specific biological characterization are required to confirm our preliminary findings.

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Conflicts of interest None

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