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Original Article

Association of TNF-α, TNFRSF1A and TNFRSF1B gene polymorphisms with the risk of gastric cancer in Chinese population

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Abstract: Background: Gastric cancer (GC) is one of the most common malignancies worldwide. To date, the polymorphisms in the promoter region of tumour-necrosis factor-α (TNF-α) gene have been extensively studied in relation to different kinds of cancer, including GC. Methods and materials: In this case-control study, the case population consisted of 240 GC cases and 510 healthy controls. Genotyping of TNF-α, TNFRSF1A and TNFRSF1B polymorphism was determined by polymerase chain reaction restriction fragment length polymorphisms (PCRRFLP) analysis. Deviation of Hardy-Weinberg equilibrium was tested by using the χ^2 test for goodness of fit. Results: A total of 240 GC patients and 510 healthy controls were enrolled in our study. In the present study, we evaluated the associations between the functional polymorphisms in TNF-α, TNFRSF1A and TNFRSF1B (rs1800629 and rs361525 in TNF-α sequences; rs767455, rs4149577 and rs1800693 in TNFRSF1A sequences and rs1061622 and rs1061624 in TNFRSF1B) and risk of GC. With respect to GC susceptibility, our data suggest that the TNFRSF1A rs767455 CT, TNFRSF1A rs4149577 CT and TNFRSF1A rs1800693 AG are risk factors of GC risk. However, the results of allele distribution of TNF-α, TNFRSF1A and TNFRSF1B SNP in cases and controls showed that no single allele was associated with the risk of GC. Conclusion: In conclusion, we found that the variant genotypes of rs4149577and rs1800693 may contribute to an increased risk of GC. Moreover, no allele was associated with the incidence of GC in Chinese Han population patients.

Keywords: Gastric cancer, risk factor, polymorphism, case-control study, tumour-necrosis factor-α

Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide, with more than 930, 000 new cases every year. Mortality data was obtained from Iran show that, GC is the first cause of death due to cancer in both sexes. The incidence and mortality rates of GC are different throughout the world, with rates much higher in parts of Asian (such as China, Japan and Korea), Eastern Europe and South America than those in the United States, where GC incidence rates have fallen substantially since the mid-1980s. GC are classified as gastric noncardia cancer (GNCC) and gastric cardia cancer (GCC) according to anatomical location of the lesion. In contrast to a significant decrease in the incidence of the GNCC, a significant increase in the incidence rate of GCC has been observed in Western countries, which may suggest different etiology related to the two subtypes. Recently, progress has been made through epidemiological studies investigating environmental risk factors for GC. While GCCs may be related to gastroesophageal reflux (GER), white race, male gender, and tobacco smoking, the majority of GNCCs are attributable to chronic helicobacter pylori (HP) infection, tobacco smoking, consumption of salt and salt-preserved foods, and alcohol abuse.

Tumor necrosis factor (TNF), a pluripotent proinflammatory cytokine, plays a pivotal role in inflammation, proliferation, and apoptosis [1]. TNF-α and TNF-β (also known as lymphotoxin-α) are two members of the TNF super family. Many studies have demonstrated that TNF-α has an important role in the development of different

kind of cancer. For example, the levels of TNF-α are different in kinds of cancer [2, 3]. Moreover, TNF-α has been shown to stimulate the proliferation of several kinds of cancer cells in in vitro studies. Since its discovery, TNF has been the center of study for its roles in normal physiology, acute inflammation, chronic inflammation, autoimmune disease and cancer-related inflammation. The biological effects of TNF-α are elicited by binding to its two cognate cell surface receptors, TNFRSF1A/TNFR1 (p55/60) and TNFRSF1B/TNFR2 (p75/80), both of which are involved in increasing expression of other cytokines and immuno-regulatory molecules through the activation of nuclear factor κB [4, 5]. Through extensive examinations of expression and function, some genetic variations have been shown to explain inter-individual variation.

To date, the polymorphisms in the promoter region of tumour-necrosis factor-A (TNF-α) gene have been extensively studied in relation to different kinds of cancer, including GC [6]. Two functional polymorphisms (rs1800629 and rs361525) in TNF-A genes have been studied more than the other polymorphisms [7-9]. However, no accordant conclusion was got in different population and data sources. Besides, the polymorphisms in TNFRSF1A and TNFRSF1B gene might be potential biomarkers of GC and no previous studies were conducted. This study was conducted to explore the association between TNF-α, TNFRSF1A and TNFRSF1B polymorphisms and the risk of GC, and provide information regarding the molecular basis of GC risk in Chinese mainland population.

Materials and methods

Study population

In this case-control study, the case population consisted of 240 GC cases and 510 healthy controls in Department of General Surgery, Eastern Hospital of Medical College of Qingdao University, Qingdao Municipal Hospital from January 2013 to December 2013. All subjects were ethnic Chinese Han and came from China mainland. Enrollment criteria including histologically identified diagnosis, no previous surgical or medical treatment of gastric disease, no history of familial GC, and no other kinds of cancers. The control population consisted of 510 cancer-free healthy subjects recruited from the Department of Clinic Service. Each eligible subject was interviewed to gather demographic data (such as age, sex and ethnicity) and environmental exposure history, including smoking, alcohol consumption, meat and vegetable intake status. All the control subjects were frequency matched to GC cases on age and gender. This study was approved by the Ethical Committee of Medical College of Qingdao University and all patients provided written informed consent.

DNA extraction

In both the case and control groups, 1.5 ml of whole blood was extracted from each participant and stored at -80°C in our university laboratory as described previously [10]. DNA from each whole blood sample was extracted with the QIAamp DNA mini Kit (Qiagen, Hilden, Germany), as directed following the manufacturer's instructions. The concentration of DNA and the purity of each sample were measured by an ultraviolet spectrophotometer (GE Healthcare, USA). DNA samples were routinely stored at -80°C until DNA extraction.

Genotyping

Genotyping of TNF-α, TNFRSF1A and TNFRSF1B polymorphism was determined by polymerase chain reaction restriction fragment length polymorphisms (PCRRFLP) analysis. The primers are as the following: rs1800629 (forward 5'-AGGCAATAGGTTTTGAGGGCCAT-3' and reverse 5'-TGCACCTTCTGTCTCGGTTTCTT-3'); rs361525 (forward 5'-AGAAGACCCCCCTCGGAACC-3' and reverse 5'-AGAGGAGGGCGGGGAAAGAA-3'); rs767455 (forward: 5'-AGTGGCTGAGGTTAGGAC-3' and reverse 5'-CTATGCCCGAGTCTCAAC-3'); rs4149577 (forward 5'-GCAAGTTAAAGCCTGAATGAAG-3' and reverse 5'-ATGACCATTTCCCTGACCC-3'); rs1800693 (forward 5'-ACTGTGTTTCATTCTTCTGC-3' and reverse 5'-TAAACCAATGAAGAGGAGG-3'); rs1061622 (forward 5'-GCACACATCGTCACTCTC-3' and reverse 5'-AAGGAGTGAATGAATGAGAC-3') and rs1061624 (forward: 5'-CTGTGTCGTAGCCAAGGTG-3' and reverse 5'-GGCAGGTCACAGAGAGTCAG-3') which were designed based on the related gene were used for PCR. PCR amplification was carried out in a 20 μL reaction volume containing 2.0 μL of 1 × PCR buffer, 0.4 μL of each primer 10 pmol), 2.0 μL of each dNTP (2.0

Table 1. Clinicalpathologic features of gastric carcinoma patients and healthy controls

Variables	Cases (n = 240)	Percentage (%)	Control (n = 510)	Pecentage (%)	*P* value
Age (years, year ± SD)	57.9 ± 11.2		56.4 ± 10.1		0.367
< 60	122	50.83	245	32.67	0.475
≥ 60	118	49.17	265	35.33	
Gender					
Male	184	76.67	392	52.27	0.545
Female	56	23.33	118	15.73	
BMI	21.3 ± 4.2		21.9 ± 3.9		0.624
H. pylori infection					
Yes	220	91.67	223	43.73	P < 0.001
No	20	8.33	287	5.27	
Smoking status					
Never	67	27.92	212	28.27	< 0.0001
Ever	173	72.08	298	39.73	
Alcohol consumption					
Never	102	42.50	229	30.53	0.094
Ever	138	57.50	281	37.47	
Vegetable intake					
< 3 times/w	86	35.83	192	25.60	0.631
≥ 3 times/w	154	64.17	318	42.40	
Meat intake					
< 3 times/w	112	46.67	231	30.80	0.886
≥ 3 times/w	128	53.33	270	36.00	
Family history					
Yes	54	22.50	23	4.51	< 0.0001
No	186	77.50	481	95.49	
Location					
Cardia	90	37.50			
Non-cardia	150	62.50			
Histology					
Diffrenetiated	112	46.67			
Undiffrenetiated	128	53.33			
Family history					
Yes					
No					
TNM stage					
I	19	7.92			
II	23	9.58			
III	167	69.58			
IV	31	12.92			

BMI: body mass index; H. pylori: Helicobacer pylori.

mmol/L), 9.3 μL of sterilized water, 0.6 μL of $MgCl_2$, 0.3 μL of Taqenzyme (2.5 U/μL), and 5 μL of template DNA. The PCR reaction conditions consisted of an initial denaturation at 95°C for 15 min, followed by 35 cycles of 94°C for 30 s, 53°C for 1 min and 65°C for 1 min, and a final extension cycle at 72°C for 7 min. The PCR products were separated by 3% agarose gel electrophoresis.

Statistical analysis

Deviation of Hardy-Weinberg equilibrium was tested by using the χ^2 test for goodness of fit.

The significance of the differences of genotypes and allelic frequencies in the case and control groups was determined using 2 × 2 tables and a standard χ^2 test. Association was expressed as odds ratios (OR) as risk estimates with 95% confidence intervals (95% CI). χ^2 test was used to perform for the association of clinicopathologic characteristics and miR-196a2 genotypes and allelic frequencies among CRC patients. All statistical tests were two-sided, and a probability level of $P < 0.05$ was considered to be statistically significant. Data analysis was done using SPSS 11.0 software (SPSS, Inc.).

Results

General characteristics of the subjects

A total of 240 GC patients and 510 healthy controls were enrolled in our study. All of the subjects were ethnic Han Chinese. Demographic and other selected characteristics of cases and controls were presented in **Table 1**. Cases and controls did not show statistically significant differences with regard to sex, age, body mass index, smoking status, meat and vegetable intake status. Besides, the TNM stages of all the GC cases are reported as well. In general, 19 cases are in stage I, 23 cases in stage II, 167 in stage III and 31 cases in stage IV.

TNF-α polymorphism in the subjects

Genotype frequencies of TNF-α polymorphism rs1800629 and rs361525 in the subjects are presented in **Table 2**. The genotype distributions were in Hardy-Weinberg equilibrium in each group studied. As shown in **Table 2**, compared with the GG genotype in rs1800629, the frequencies of AG and AA are not significantly changed (AG vs GG, OR = 1.25, 95% CI = 0.87 to 1.80; AA vs GG, OR = 1.49, 95% CI = 0.33 to 6.72). In neither dominant nor recessive, there are significant associations were detected. However, compared with the GG genotype in rs361525, the frequencies of AG and AA are not significantly changed (AG vs GG, OR = 0.86, 95% CI = 0.51 to 1.43; AA vs GG, OR = 1.03, 95% CI = 0.09 to 11.37). As well as the rs1800629, in neither dominant nor recessive, there are significant associations were detected for the genotype rs361525.

TNFRSF1A and TNFRSF1B polymorphism in the subjects

Genotype frequencies of TNFRSF1A (rs767455, rs4149577 and rs1800693) and TNFRSF1B (rs1061622 and rs1061624) polymorphism in the subjects are presented in **Table 2**. As shown in **Table 2**, compared with the TT genotype in rs767455, the frequencies of AG and AA are not significantly associated with the incidence of GC. Besides, in neither dominant nor recessive, there are significant associations were detected. However, for the rs4149577 polymorphism, CT genotype is associated with the incidence of GC (CT vs CC, OR = 1.51, 95% CI = 1.07 to 2.12). However, no association was detected for the association of TT genotype in rs4149577 (TT vs CC, OR = 0.55, 95% CI = 0.18 to 1.67). Advanced analyses showed that it is dominant model (OR = 1.39, 95% CI = 1.00 to 1.93) rather than recessive model (OR = 1.12, 95% CI = 0.88 to 1.43) be associated with the GC incidence. For the rs1800693 polymorphism, compared with the TT genotype, the frequencies of AG genotype is significantly associated with the incidence of GC (AG vs AA, OR = 1.43, 95% CI = 1.01 to 2.02). Besides, the advanced analyses showed that dominant model in rs1800693 are associated with the increased incidence rate of GC.

Besides, the genotype frequencies of TNFRSF1B, including rs1061622 and rs1061624, are reported in **Table 2**. As shown in **Table 2**, compared with the TT genotype in rs1061622, the frequencies of GT and GG are not significantly changed (GT vs TT, OR = 0.85, 95% CI = 0.61 to 1.19; GG vs TT, OR = 0.87, 95% CI = 0.41 to 1.88). The advanced analyses showed that neither dominant model nor recessive model could show a significant association. Compared with the AA genotype in rs1061624, the frequencies of AG and GG are not significantly changed (AG vs AA, OR = 0.98, 95% CI = 0.70 to 1.38; GG vs AA, OR = 1.02, 95% CI = 0.62 to 1.68). The advanced analyses showed that neither dominant model (OR = 0.99, 95% CI = 0.72 to 1.37) nor recessive model (OR = 1.03, 95% CI = 0.66 to 1.63) could show a significant association.

Allele distribution of TNF-α, TNFRSF1A and TNFRSF1B SNP in subjects

The allele distributions of TNF-α single nucleotide polymorphisms (rs1800629 and rs361-

Table 2. Genotype distribution of TNF-α, TNFRSF1A and TNFRSF1B gene polymorphisms in gastric carcinoma patients and healthy controls

SNP	Genotype	Cases	Percentage (%)	Control	Pecentage (%)	*P* value	OR (95% CI)
TNF-α							
rs1800629	GG	207	86.25	411	80.59	-	Reference
	AG	30	12.50	95	18.63	0.222	1.25 (0.87 to 1.80)
	AA	3	1.25	4	0.78	0.785	1.49 (0.33 to 6.72)
	Dominant					0.643	0.79 (0.36 to 7.21)
	Recessive					0.592	0.66 (0.43 to 1.02)
rs361525	GG	216	90.00	443	86.86	-	Reference
	AG	23	9.58	55	10.78	0.231	0.86 (0.51 to 1.43)
	AA	1	0.42	2	0.39	0.061	1.03 (0.09 to 11.37)
	Dominant					0.298	0.86 (0.52 to 1.43)
	Recessive					0.853	1.04 (0.09 to 11.55)
TNFRSF1A							
rs767455	TT	169	70.42	383	75.10	-	Reference
	CT	66	27.50	116	22.75	0.086	1.29 (0.91 to 1.83)
	CC	5	2.08	13	2.55	0.872	0.87 (0.31 to 2.48)
	Dominant					0.129	1.25 (0.89 to 1.76)
	Recessive					0.326	1.07 (0.84 to 1.35)
rs4149577	CC	159	66.25	373	73.14	-	Reference
	CT	77	32.08	120	23.53	0.031	1.51 (1.07 to 2.12)
	TT	4	1.67	17	3.33	0.532	0.55 (0.18 to 1.67)
	Dominant					0.048	1.39 (1.00 to 1.93)
	Recessive					0.092	1.12 (0.88 to 1.43)
rs1800693	AA	164	68.33	384	75.29	-	Reference
	AG	70	29.17	115	22.55	0.032	1.43 (1.01 to 2.02)
	GG	6	2.50	11	2.16	0.532	1.28 (0.46 to 3.51)
	Dominant					0.045	1.41 (1.01 to 1.98)
	Recessive					0.523	1.16 (0.43 to 3.18)
TNFRSF1B							
rs1061622	TT	158	65.83	317	62.16	-	Reference
	GT	72	30.00	170	33.33	0.091	0.85 (0.61 to 1.19)
	GG	10	4.17	23	4.51	0.236	0.87 (0.41 to 1.88)
	Dominant					0.341	0.85 (0.62 to 1.18)
	Recessive					0.562	0.92 (0.43 to 1.97)
rs1061624	AA	81	33.75	171	33.53	-	Reference
	AG	127	52.92	273	53.53	0.319	0.98 (0.70 to 1.38)
	GG	32	13.33	66	12.94	0.198	1.02 (0.62 to 1.68)
	Dominant					0.328	0.99 (0.72 to 1.37)
	Recessive					0.327	1.03 (0.66 to 1.63)

525) are reported in **Table 3**. In the rs1800629, a allele was not associated with the risk of GC compared with the G allele (OR = 0.72, 95% CI = 0.49 to 1.07). While for the rs361525 location, allele was not associated with the risk of GC (OR = 0.65; 95% CI = 0.41 to 1.04).

For the TNFRSF1A location, three different single nucleotide polymorphisms (rs767455, rs-4149577 and rs1800693) are reported. In the rs767455, C allele is not associated with the risk of GC (OR = 1.20; 95% CI = 0.89 to 1.63). Compared with C allele in rs4149577, T allele is not associated with GC risk (OR = 1.21, 95% CI = 0.91 to 1.62). Advanced analyses showed that G allele in rs1800693 showed a significant risk of GC (OR = 1.33; 95% CI = 1.01 to 1.79). For the TNFRSF1A gene, neither G allele in

Table 3. Allele distribution of TNF-α, TNFRSF1A and TNFRSF1B single nucleotide polymorphism in gastric carcinoma patients and healthy controls

SNP	Allele	Cases	Percentage (%)	Controls	Pecentage (%)	*P* value	OR (95% CI)
TNF-α							
rs1800629	G	444	92.50	917	89.90	Reference	Reference
	A	36	7.50	103	10.10	0.263	0.72 (0.49 to 1.07)
rs361525	G	455	94.79	941	92.25	Reference	Reference
	A	25	5.21	79	7.75	0.127	0.65 (0.41 to 1.04)
TNFRSF1A							
rs767455	T	404	84.17	882	86.47	Reference	Reference
	C	76	15.83	138	13.53	0.384	1.20 (0.89 to 1.63)
rs4149577	C	395	82.29	866	84.90	Reference	Reference
	T	85	17.71	154	15.10	0.187	1.21 (0.91 to 1.62)
rs1800693	A	398	82.92	883	86.57	Reference	Reference
	G	82	17.08	137	13.43	0.042	1.33 (1.01 to 1.79)
TNFRSF1B							
rs1061622	T	388	80.83	804	78.82	Reference	Reference
	G	92	19.17	216	21.18	0.293	0.88 (0.67 to 1.16)
rs1061624	G	289	60.21	615	60.29	Reference	Reference
	A	191	39.79	405	39.71	0.584	1.00 (0.80 to 1.25)

rs1061622 (OR = 0.88; 95% CI = 0.67 to 1.16) nor A allele in rs1061624 (OR = 1.00, 95% CI = 0.80 to 1.25) are associated with GC risk (in **Table 3**).

Discussion

In the present study, we evaluated the associations between the functional polymorphisms in TNF-α, TNFRSF1A and TNFRSF1B (rs1800629 and rs361525 in TNF-α sequences; rs767455, rs4149577 and rs1800693 in TNFRSF1A sequences and rs1061622 and rs1061624 in TNFRSF1B) and risk of GC. With respect to GC susceptibility, our data suggest that the TNFRSF1A rs767455 CT, TNFRSF1A rs4149577 CT and TNFRSF1A rs1800693 AG are risk factors of GC risk. However, the results of allele distribution of TNF-α, TNFRSF1A and TNFRSF1B SNP in cases and controls showed that no single allele was associated with the risk of GC.

The TNF gene polymorphism and the risk of digestive system cancers have been long discussed and a pretty of previous studies have been reported. Helicobacter pylori (*Hp*) infection is the strongest risk factor for non-cardia GC and chronic gastritis [11]. Only < 1% of Hp carriers will ever develop GC. *Hp* is responsible for triggering a pathological progression in the gastric mucosa that begins with chronic gastritis and progresses to atrophic gastritis, intestinal metaplasia, dysplasia, and eventually GC [6]. TNF-α is a cytokine induced by Hp and inhibits gastric acid secretion. The TNF-A gene on chromosome 6p21.3 encoding. TNF and epidermal growth factor (EGF) are well-known stimuli of cyclooxygenase (COX)-2 expression, and TNF stimulates transactivation of EGF receptor (EGFR) signaling to promote survival in colon epithelial cells. We hypothesized that COX-2 induction and cell survival signaling downstream of TNF are mediated by EGFR transactivation [6, 12-15]. The TNF-α 308 promoter polymorphism is a biallelic G to A polymorphism, and the TNF-α. A allele is associated with increased levels of TNF in plasma. Although studies have reported TNF can modify the risk of GC, the exact role of TNF as a gastric carcinogen is still controversial. In the present study, we investigated the association between the TNF polymorphism and susceptibility to GC in Chinese Han population. In our study, there are no association between TNF-α polymorphisms and GC risk. Some case-control studies have been conducted to elucidate the correlation between TNF-α polymorphisms and the risk of gastric carcinoma [16-18]. Machado, et al, in a case-control study on an *Hp*-infected population including found that carriers of TNF-α A

allele are at increased risk for developing GC [6]. Some other case-control studies, which were conducted in the Asia did not find any significant association between TNF-α polymorphism and the risk of GC [19]. In a meta-analysis with fifty-eight studies from fifty-five publications with a total of 9986 cancer patients and 15511 healthy controls were included. The results showed that TNF-α polymorphisms are significantly associated with the risk of GC [6]. The differences in there studies may because of the heterogeneity of locality differences and genetic variance among the differences in all the studies [20].

Genetic polymorphisms of TNF-alpha and TNF receptor superfamily member, TNFRSF1A and TNFRSF1B have been examined in terms of susceptibility to various cancers. In a previous study, genetic polymorphisms of TNFRSF1B gene were evaluated Japanese esophageal squamous cell carcinoma (ESCC) patients treated with the definitive 5-FU/CDDP-based chemoradiotherapy and their predictive values of prognosis or severe acute toxicities were assessed. Genetic polymorphism of TNFRSF1B A1466G was found to be predictive response in Japanese ESCC patients with a definitive 5-FU/CDDP-based chemoradiotherapy. Further clinical investigation with a large number of patients or experiments in vitro should be performed to assess the predictive value of TNFRSF1B A1466G genotype after chemoradiotherapy [6, 21, 22]. A study was conducted to investigate the roles of 2 polymorphisms of the TNFRSF1A and TNFRSF1B (a coding polymorphism that results in an amino acid substitution-R92Q), as genetic modifiers of multiple sclerosis (MS), and to evaluate their potential functional implications in the disease. These findings suggest that both TNFRSF1A polymorphisms have functional consequences in the TNF-R1 [6]. In a case-only analysis in 335 Caucasian esophageal adenocarcinoma patients that were genotyped for 242 SNPs in 43 apoptotic genes and the results showed that TNFRSF1A rs4149579 had significant interaction with gastroesophageal reflux disease [6]. The effect of TNF-α/TNFR1 signaling pathway on the development of GC was studied by Oshima H et al. The results showed that TNF-α expressed by BM-derived cells (BMDCs) stimulates the TNFR1 on BMDCs by an autocrine or paracrine manner, which is important for gastric tumor promotion [23-28]. Moreover, the microarray analysis and colony formation assay indicated that NADPH oxidase organizer 1 (Noxo1) and Gna14 are induced in tumor epithelial cells in a TNF-α-dependent manner, and have an important role in tumorigenicity and tumor-initiating cell property of GC cells [7-9, 29, 30]. Accordingly, it is possible that the activation of TNF-α/TNFR1 signaling in the tumor microenvironment promotes gastric tumor development through induction of Noxo1 and Gna14, which contribute to maintaining the tumor cells in an undifferentiated state. The present results indicate that targeting the TNF-α/TNFR1 pathway may be an effective preventive or therapeutic strategy for GC [6].

In conclusion, we found that the variant genotypes of rs4149577 and rs1800693 may contribute to an increased risk of GC. Moreover, no allele was associated with the incidence of GC in Chinese Han population patients. Association studies with diverse populations and further functional analysis of the variants are needed to verify our findings. Advanced studies on this point would provide better understanding of GC pathophysiology and offer potential therapeutics.

Disclosure of conflict of interest

None.

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