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Effects of Interleukin-10 Polymorphisms and Smoking on the Risk of Gastric Cancer in Taiwan

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Abstract. *Gastric cancer is the second cause of death from cancer worldwide and its prevalence and mortality rates are still very high in developed countries. Interleukin-10 (IL10) is a pleiotropic cytokine produced by macrophages which can suppress and stimulate the immune response in tumorigenesis signaling. However, the contribution of IL10 genomic variants to gastric cancer is still largely unknown. In the present study, we aimed at investigating the role of IL10 genotypes in gastric cancer risk. The promoter single nucleotide polymorphisms on IL10, A-1082G (rs1800896), T-819C (rs3021097) and A-592C (rs1800872), were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method among 716 Taiwanese people (358 patients gastric cancer and 358 cancer-free controls). The results showed that there was a significant difference between the patient and control groups in the genotypic frequency distribution of IL10 A-1082G genotypes ($p=0.0004$). In addition, those carrying the G allele were found to have a higher risk for gastric cancer compared with those with the A allele ($p=3.19\times10^{-5}$). Furthermore, personal cigarrete smoking habits enhanced the gastric cancer risk for those IL10 A-1082G AG and GG carriers. In conclusion, AG and GG genotype at IL10 A-1082G, together with smoking, synergistically contribute to individual susceptibility for gastric cancer in Taiwan.*

Gastric cancer is reported to be more common in males and in those aged 50 years or older (1-3). In literature, smoking, obesity, salt intake and *Helicobacter pylori* infection are well-known factors for gastric cancer progression (4, 5). Geographically speaking, gastric cancer is prevalent in developing countries in East Asia, East Europe and South America, while the incidence is low in North America and Africa (2). Clinically the prognosis of gastric cancer is usual poor, with a 5-year survival of less than 20% for those with advanced disease (3). There are some beneficial developments which have reduced the incidence of gastric cancer in the past two decades, such as the increasing use of refrigerators, the lowering dependence on salts for preserving food, the increasing availability and intake of fresh fruits and vegetables, and the effective control of chronic infection with *H. pylori*. However, it remains a critical cancer threat, accounting for 8% of the total cancer incidence and 10% of the total cancer death worldwide (2).

The *IL10* gene located on human chromosome 1q31-32 is composed of five exons and four introns. IL10 is a pleiotropic cytokine with the dual anticancer properties of immune-suppression and immune-stimulation (6). The three promoter SNPs, A-1082G (rs1800896), T-819C (rs3021097), and A-592C (rs1800872), have been reported to regulate the transcription of *IL10* messenger RNA and the expression of

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Table I. *Distributions of selected characteristics among patients with gastric cancer and controls.*

Characteristic	Controls (n=358)			Patients (n=358)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			62.1 (9.5)			63.8 (11.4)	0.5811
Gender							0.2219
Male	242	67.6%		258	72.1%		
Female	116	32.4%		100	27.9%		
Personal smoking status							
Cigarette smokers	234	65.4%		256	71.5%		0.0912
Non-smokers	124	34.6%		102	28.5%		

[a]Based on two-sided Chi-square test without Yate's correction.

IL10 *in vitro* (7, 8). Recently, the three promoter polymorphisms of *IL10* have been examined for their contribution to some types of cancer, for instance, hepatocellular carcinoma (9), breast cancer (10) and renal cell carcinoma (11). For gastric cancer, the contribution of *IL10* to gastric cancer has been investigated, but the findings remain conflicting and inconclusive (12-18). The inconsistency may possibly be due to differences in study design such as sample collection, or ethnic differences in the populations recruited. Mechanically, increased levels of serum IL10 have been found in patients with solid and hematopoietic tumors in addition to gastric cancer (19). Since the three promoter polymorphisms *IL10* A-1082G, T-819C and A-592C were reported to influence the transcription of *IL10* messenger RNA and the expression of IL10 *in vitro* (7, 8), it is very possible that the genotypes determine the personal susceptibility to gastric cancer and could serve as a biomarker for early detection. Thus, the specific aim of the present study was to determine the genotypic frequency of the three promoter polymorphisms of *IL10* gene in a Taiwan gastric cancer population and their feasibility to serve as potential gastric cancer biomarkers.

Materials and Methods

Study population and sample collection. Three hundred and fifty-eight patients diagnosed with gastric cancer were recruited at the outpatient clinics of general surgery between 2001-2009 at the China Medical University Hospital, Taichung, Taiwan, Republic of China. The equal number of non-cancer healthy people were selected by matching for age and gender after initial random sampling from the Health Examination Cohort of the hospital as controls. The mean age of the patients and the controls was 63.8 (range=38-81, SD=11.4) and 62.1 (range=39-79, SD=9.5) years, respectively (see Table I). All patients and controls voluntarily participated, completed a self-administered questionnaire and provided their peripheral blood samples. Our study was approved by the Institutional Review Board of the China Medical University Hospital and written informed consent was obtained from all participants.

Genotyping conditions. Genomic DNA of each participant was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed according to our previous articles (20-22). The polymerase chain reaction (PCR) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min. The sequences of primers for PCR and the specific restriction enzymes for each DNA product are listed in Table II.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *IL10* single nucleotide polymorphisms in the controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's Chi-square test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *IL10* genotypes between cases and controls. The associations between the *IL10* polymorphisms and gastric cancer risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for possible confounders. A value of $p<0.05$ was considered statistically significant, and all statistical tests were two-sided.

Results

The characteristics of age, gender and personal cigarette smoking habits of all the investigated subjects are summarized in Table I. The results showed that there was no difference in the distribution of these characteristics among patients and controls (Table I).

The frequencies for *IL10* A-1082G, T-819C and A-592C promoter genotypes among the controls and gastric cancer patients are summarized and their differential distributions analyzed in Table III. Among the three polymorphic sites analyzed, the distribution of genotypic frequencies at *IL10* A-1082G was significantly different among the patients with gastric cancer and non-cancer controls ($p=0.0004$). In detail, the percentages of AA, AG and GG genotypes at *IL10* A-1082G were 78.5%, 18.7% and 2.8% among the controls and 65.6%, 28.2% and 6.2% among the patients, respectively

Table II. *The primer sequences, polymerase chain reaction and restriction fragment length polymorphism conditions for interleukin-10 A-1082G, T-819C and A-592C genotyping work.*

Polymorphism (location)	Primer sequences	Restriction enzyme	SNP sequence	DNA fragment size (bp)
A-1082G (rs1800896)	F: 5'-CTCGCTGCAACCCAACTGGC-3'	*Mnl* I	A	139 bp
	R: 5'-TCTTACCTATCCCTACTTCC-3'		G	106+33 bp
T-819C (rs3021097)	F: 5'-TCATTCTATGTGCTGGAGAT-3'	*Mae* III	T	209 bp
	R: 5'-TGGGGGAAGTGGGTAAGAGT-3'		C	125+84 bp
A-592C (rs1800872)	F: 5'-GGTGAGCACTACCTGACTAG-3'	*Rsa* I	C	412 bp
	R: 5'-CCTAGGTCACAGTGACGTGG-3'		A	236+176 bp

*F and R indicate forward and reverse primers, respectively; SNP: single nucleotide polymorphism.

(Table III). The AG and GG genotypes were more frequent among the patients than in the controls (Table III). As for the other two polymorphic sites, *IL10* T-819C and A-592C, there was no difference among patients with gastric cancer and controls in the distribution of their genotypic frequencies (p=0.8811 and 0.8651, respectively) (Table III).

The analysis of allelic distributions at *IL10* A-1082G, T-819C and A-592C among the non-cancer controls and patients with gastric cancer are summarized and presented in Table IV. For the three promoter sites genotyped, only the distribution of *IL10* A-1082G was significantly different among controls and patients with gastric cancer ($p=3.19\times10^{-5}$). In detail, the percentage of patients with gastric cancer with variant G allele (20.3%) was much higher than that in the controls (12.2%) (Table IV). As for *IL10* T-819C and A-592C, there was no difference between patient and control groups in the distribution of their allelic frequencies (p=0.6837 and 0.8170, respectively) (Table III). From the results of Tables III and IV we can conclude that Taiwanese individuals carrying a G allele on *IL10* A-1082G were at higher risk of gastric cancer.

The genetic–lifestyle interaction was of interest and thereby the interaction between *IL10* A-1082G and personal smoking status on gastric cancer risk was analyzed. The results showed that the genotypic distribution of *IL10* A-1082G was significantly different between cancer and control groups only among those who had a smoking habit (OR=2.29, 95% CI=1.52-3.46, p=0.0001), but not among those who were non-smokers (OR=1.31, 95% CI=0.73-2.35, p=0.3735) (Table V). Consistent with the findings in Table III and IV, the percentages of AG and GG carriers (35.9%) were significantly higher in patients with gastric cancer who smoked than in the controls (19.7%). There was no such difference observed in the non-smoker groups (30.4% *vs*. 25.0%).

Table III. *Distribution of interleukin-10 A-1082G, T-819C and A-592C genotypes among patients with gastric cancer and controls.*

Genotype	Controls (n=358)	%	Patients (n=358)	%	p-Value[a]
A-1082G (rs1800896)					0.0004*
AA	281	78.5%	235	65.6%	
AG	67	18.7%	101	28.2%	
GG	10	2.8%	22	6.2%	
T-819C (rs3021097)					0.8811
TT	186	52.0%	190	53.1%	
CT	132	36.8%	132	36.9%	
CC	40	11.2%	36	10.0%	
A-592C (rs1800872)					0.8651
AA	180	50.3%	186	52.0%	
AC	141	39.4%	134	37.4%	
CC	37	10.3%	38	10.6%	

[a]Based on Chi-square test; *statistically significant.

Table IV. *Distribution of allelic frequencies at A-1082G, T-819C and A-592C of interleukin-10 gene among patients with gastric cancer and controls.*

Allele	Controls	%	Patients	%	p-Value[a]
A-1082G (rs1800896)					3.19×10^{-5}*
Allele A	629	87.8%	571	79.7%	
Allele G	87	12.2%	145	20.3%	
T-819C (rs3021097)					0.6837
Allele T	504	70.4%	512	71.5%	
Allele C	212	29.6%	204	28.5%	
A-592C (rs1800872)					0.8170
Allele A	501	67.0%	506	70.7%	
Allele C	215	33.0%	210	29.3%	

[a]Based on Chi-square test; *statistically significant.

Discussion

Previously, our group found several potential genetic markers for early detection and prediction of gastric cancer in Taiwan (23-26). In the current study, we aimed at investigating the association of *IL10* genotypes and gastric cancer risk in Taiwan. We selected and genotyped three promoter polymorphic sites IL10 A-1082G, T-819C and A-592C among the 358 gastric

Table V. *Distribution of interleukin-10 A-1082G genotypes in patients with gastric cancer after stratification by personal smoking status.*

Genotypes	Non-smokers		*p*-Value	OR (95% CI)[a]	Smokers		*p*-Value	OR (95% CI)
	Controls	Patients			Controls	Patients		
AA	93	71	0.3735	1.000 (Reference)	188	164	0.0001*	1.000 (Reference)
AG+GG	31	31		1.31 (0.73-2.35)	46	92		2.29 (1.52-3.46)*
Total	124	102			234	256		

OR: Odds ratio, CI: confidence interval; ORs were estimated with multivariate logistic regression analysis. *Statistically significant.

cancer cases and 358 non-cancer controls. It was found that individuals carrying the AG and GG genotypes were at higher risk of gastric cancer compared with those carrying AA genotype on *IL10* A-1082G (Table III). As for *IL10* T-819C and A-592C, there was no similar differentially genotypic distribution found (Table III). In addition, the results of allelic frequency distribution analysis support the idea that those individuals carrying the variant G allele were at higher risk of gastric cancer compared with those carrying wild-type A allele (Table IV). Furthermore, there is a synergistic genetic–lifestyle interaction for *IL10* A-1082G and personal smoking habit (Table V), however, whether *IL10* A-1082G genotype has interaction with other factors, such as *H. pylori* infection, or fruit and vegetable intake, needs further investigations.

In literature, the contribution of *IL10* promoter genotypes to gastric cancer risk has been investigated by several groups but the findings remain conflicting and inconclusive (12-18). Recently, Asian meta-analyses reported that *IL10* promoter genotypes may be associated with increased gastric cancer risk (18, 27, 28), meanwhile, Western population studies have shown a reverse association (14, 29). It is reasonable that ethnic differences in the distribution of the genotypes may affect the findings and conclusions of genotyping work. In addition, any difference in criteria in the inclusion and exclusion of sampling, study design, recording of patient age at diagnosis, genotyping methodologies, and lifestyle background may also influence the overall findings.

IL10 promoter genotypes were reported to control the production of *IL10* (30, 31), and it was reported that IL10 levels were elevated in gastric mucosa after *H. pylori* infection, and were higher in patients that have severe chronic inflammation (32). In advanced stages of gastric carcinogenesis, *IL10* mRNA expression and serum levels were also elevated (33, 34). As mentioned in the introduction, *IL10* plays a role in carcinogenesis acting not only as an anti-inflammatory cytokine but also as an immunosuppressant (35). Thus, *H. pylori*-induced IL10 production may have beneficial effects *via* limiting inflammation-induced tissue damage, but at the same time adding risk *via* rendering the mucosal immune cells unable to adequately defend against malignant cells (32). The current study revealed the association of *IL10* genotypes and their interaction with smoking status, but did not provide answers for interactions of other factors such as *H. pylori* infection or obesity with *IL10* genotypes to gastric carcinogenesis. The roles of *IL10* and its contribution to the pathogenesis of gastric cancer require further investigations from DNA, mRNA, protein and functional angles.

In conclusion, our study found that *IL10* A-1082G genotypes may play a role in gastric carcinogenesis in Taiwan *via* interaction with cigarette smoking status. The results provided evidence supporting that gastric carcinogenesis is multiple step process that involves both genetic and environmental/lifestyle factors. The G allele of *IL10* A-1082G may be a useful marker in gastric oncology for early cancer detection and prediction.

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