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Interleukin-10 gene -592C>A polymorphism and susceptibility to gastric cancer

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ABSTRACT. Numerous studies have evaluated the association between the human interleukin-10 gene -592C>A polymorphism and gastric cancer risk. However, the results have been inconsistent. This meta-analysis was designed to resolve these controversies. Systematic searches of the electronic databases Embase, PubMed, and Google Scholar were performed to identify relevant studies. A meta-analysis was performed to examine the association between the interleukin-10 gene -592C>A polymorphism and gastric cancer risk. Odds ratios (OR) and its 95% confidence intervals (CI) were used for statistical analysis. Twelve studies were included in the meta-analysis, which included 2116 gastric cancer cases and 4077 controls. No significant association was found between the interleukin-10 gene -592C>A polymorphism and gastric cancer risk in total population analysis. In stratified analysis, a significant association was found in the Asian subgroup (AA *vs* AC: OR = 0.79, 95%CI = 0.64-0.98; dominant model: OR = 1.26, 95%CI = 1.04-1.57), and no significant association was observed among Caucasians. In addition, the corresponding pooled ORs were not substantially altered after excluding one study that deviated from Hardy-Weinberg equilibrium in the control group. This meta-analysis supports an association between the interleukin-10 gene -592C>A polymorphism and gastric cancer risk in Asians but not in Caucasians.

Further large and well-designed studies are needed to confirm these conclusions.

Key words: Gastric cancer; Gene polymorphism; Interleukin-10; Meta-analysis

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death worldwide, with nearly one million new cases diagnosed each year (Crew and Neugut, 2004). Although current practice that combines chemotherapy or radiation therapy with surgical resection has greatly increased the overall survival of gastric cancer patients, the overall 5-year survival rate remains low. Generally, the highest incidence rates are in Asia, particularly in East Asian countries such as Korea, Japan, and China (American Cancer Society, 2011). Extensive epidemiology studies have shown that a number of environmental factors are related to the development of gastric cancer. Low consumption of fresh fruits and vegetables, high consumption of salty food, smoking, and *Helicobacter pylori* infection are important risk factors (Zhang et al., 1997). In addition, the genetic factors of gastric cancer have received a great deal of attention (Bernini et al., 2006).

Interleukin-10 (IL-10) is a multifunctional anti-inflammatory cytokine that downregulates cell-mediated immune responses and cytotoxic inflammatory responses. IL-10 inhibits the production of pro-inflammatory cytokines by inhibiting T-helper 1 (Th1) lymphocytes and stimulating B lymphocytes and Th2 lymphocytes to downregulate the inflammatory response (de Waal Malefyt et al., 1991). The gene encoding IL-10 is located on chromosome1 (1q31-1q32). It has been reported to contain 3 polymorphisms in the 5'-flanking region of IL-10 at positions -1082 G>A, -819 C>T, and -592 C>A, which are related to high transcriptional promoter activity (Turner et al., 1997).

To date, the human IL-10 gene -592C>A polymorphism has been shown to be linked to susceptibility to renal cell cancer, colon cancer, lung cancer, and breast cancer; several case-control studies have investigated the association between the -592C>A polymorphism and gastric cancer risk. However, because they included relatively small sample sizes, limited information was provided by these studies. In the present study, we investigated whether the -592C>A polymorphism is associated with gastric cancer risk by performing meta-analysis.

MATERIAL AND METHODS

Literature review

All case-control studies assessing the association between the IL-10 gene -592C>A polymorphism and gastric cancer risk published through September 2013 were identified by searching the PubMed, EMBASE, and Google Scholar databases. There was no language limitation. The following search terms were used: “gastric cancer”, “interleukin-10 gene”, “-592C>A”, and “gene polymorphism” for relevant citations. If sequential or multiple publications from the same data were identified, the publication reporting data from the largest or most recent study was included.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they satisfied the inclusion criteria as follows: 1) case control studies; 2) studies that assessed the association between the -592C>A polymorphism and gastric cancer risk; 3) provided sufficient information to estimate odds ratios (OR) with its 95% confidence interval (95%CI); and 4) provided data regarding genotype frequency of the -592C>A polymorphism. Major exclusion criteria included: 1) no control population; 2) no available genotype frequency; and 3) duplicated studies.

Data extraction

Essential data were carefully extracted from all eligible studies independently by 2 investigators (M. Qi and D.M. Liu), and discrepancies were resolved by consensus between the 2 authors. For each study, the following data were collected: first author's surname, year of publication, country, ethnicity, total numbers of cases and controls, and the numbers of cases and controls with the AA, CA, and CC genotypes.

Statistical analysis

We pooled the unadjusted ORs with their 95%CIs to assess the strength of the association between the -592C>A polymorphism and gastric cancer risk for a homozygote comparison (AA *vs* CC), a heterozygote comparison (AA *vs* AC), a dominant model (CC+AC *vs* AA) and a recessive mode (AA+AC *vs* CC) between groups. Between-study heterogeneities were estimated using I^2 test. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively (Wang and Pan, 2012). If heterogeneity was found among the studies, the pooled OR was estimated using the fixed-effects model ($P > 0.10$ or $I^2 < 50\%$). Otherwise, the random-effects model was used to estimate the pooled OR. We tested whether genotype frequencies of controls were in Hardy-Weinberg equilibrium (HWE) using the χ^2 test. Subgroup analysis based on nationality was used to explore the diversity among the results of different studies. Sensitivity analysis was performed by removing the unreliable study that deviated from HWE in the control group. Publication bias was investigated using funnel plot and Begg's funnel plot. All analyses were performed using the STATA version 12.0 (Stata Corporation, College Station, TX, USA), and the significance level was set at 0.05.

RESULTS

Eligible studies

A total of 12 eligible including studies involving 2116 cases and 4077 controls met the inclusion criteria were included in the pooled analyses (El-Omar et al., 2003; Wu et al., 2003; Savage et al., 2004; Alpízar-Alpízar et al., 2005; Lee et al., 2005; Zambon et al., 2005; Kamangar et al., 2006; Sicinschi et al., 2006; Sugimoto et al., 2007; Crusius et al., 2008; Kang et al., 2009; Liu et al., 2011). Publication years of the included studies ranged from 2003-2011 (Figure 1). The characteristics of these 12 case-control studies are shown in Table 1, containing the population studies of 6 Caucasians (El-Omar et al., 2003; Alpízar-Alpízar et al., 2005; Zambon et al., 2005; Kamangar et al., 2006; Sicinschi et al., 2006; Crusius et al., 2008) and 6

Asians (Wu et al., 2003; Savage et al., 2004; Lee et al., 2005; Sugimoto et al., 2007; Kang et al., 2009; Liu et al., 2011). The genotype distributions are shown in Table 1. Studies including control that were not in HWE were also considered for the meta-analysis, but were excluded from sensitivity analysis (Crusius et al., 2008).

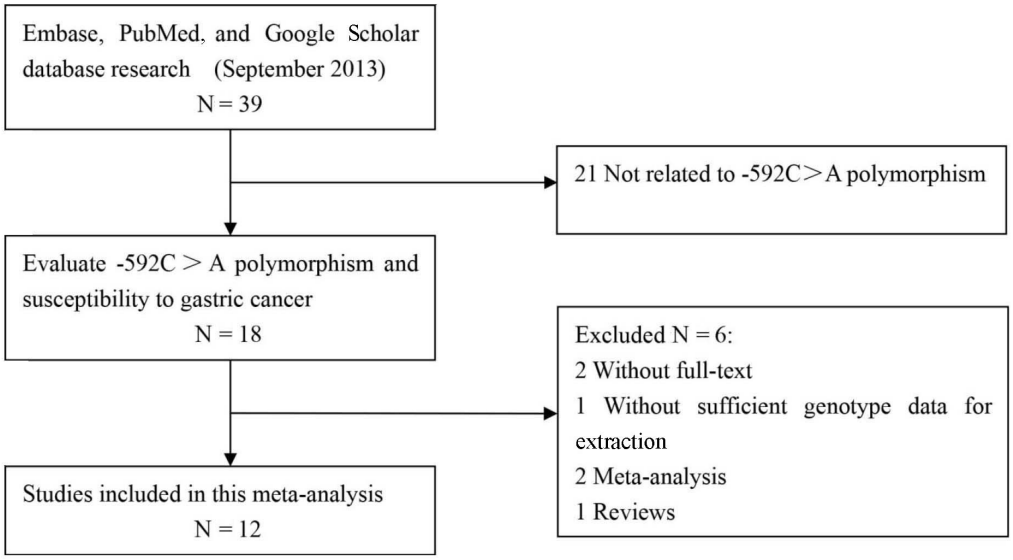

Figure 1. Flow diagram of study searching and selection process.

Table 1. Characteristics of studies included in the meta-analysis.

Study included	Year	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
					CC	CA	AA	CC	CA	AA	
El-Omar et al.	2003	USA	Caucasians	314/210	178	101	35	127	70	13	0.427
Wu et al.	2003	China	Asians	220/230	27	105	88	20	83	127	0.231
Savage et al.	2004	China	Asians	84/386	36	39	9	171	166	49	0.383
Alpízar-Alpízar et al.	2005	Costa Rica	Caucasians	45/45	21	20	3	18	21	5	0.761
Lee et al.	2005	Korea	Asians	122/120	8	62	52	7	60	53	0.059
Zambon et al.	2005	Italy	Caucasians	129/644	70	42	17	353	245	46	0.696
Kamangar et al.	2006	Finland	Caucasians	112/208	68	38	6	109	82	17	0.776
Sicinschi et al.	2006	Mexico	Caucasians	181/369	51	90	40	98	176	95	0.377
Sugimoto et al.	2007	Japan	Asians	105/168	8	54	43	10	70	88	0.419
Crusius et al.	2008	Netherlands	Caucasians	237/1122	148	78	11	642	397	83	0.049
Kang et al.	2009	Korea	Asians	333/332	34	157	142	41	145	146	0.592
Liu et al.	2011	China	Asians	234/243	39	96	99	28	106	109	0.772

Meta-analysis

A summary of the meta-analysis findings regarding the association between the -592C>A polymorphism and gastric cancer risk is provided in Table 2. Overall, we did not observe a significant association between the -592C>A polymorphism and gastric cancer risk (Figure 2). In the subgroup analysis based on ethnicity studies included were divided into Cau-

casian and Asian populations, and the same association was found in Asians (AA *vs* AC: OR = 0.79, 95%CI = 0.64-0.98; dominant model: OR = 1.26, 95%CI = 1.04-1.57). Sensitivity analysis was performed by omitting a non-HWE study (Crusius et al., 2008) and the results did not change, indicating that the results of the meta-analysis were statistically significant (Table 2).

Table 2. Summary ORs and 95%CI of Interleukin-10 gene -592C>A polymorphism with gastric cancer risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95%CI	z	P
Overall	AA *vs* CC	2116	4077	Fixed	43.4%	0.05	0.87	0.66-1.14	0.00	1.00
	AA *vs* AC			Fixed	46.1%	0.04	0.89	0.71-1.10	0.00	1.00
	Dominant model			Random	51.9%	0.02	1.15	0.92-1.44	0.00	1.00
	Recessive model			Fixed	0.0%	0.65	0.91	0.79-1.04	0.00	1.00
Asians	AA *vs* CC	1058	1479	Fixed	0.0%	0.44	0.78	0.59-1.03	0.00	1.00
	AA *vs* AC			Fixed	23.6%	0.26	0.79	0.64-0.98	0.00	1.00
	Dominant model			Fixed	29.1%	0.22	1.26	1.04-1.57	0.00	1.00
	Recessive model			Fixed	0.0%	0.48	0.90	0.71-1.14	0.00	1.00
Caucasians	AA *vs* CC	1058	2598	Random	61.6%	0.02	0.97	0.60-1.57	1.04	0.30
	AA *vs* AC			Random	54.2%	0.05	1.08	0.69-1.69	1.04	0.30
	Dominant model			Random	62.2%	0.02	0.99	0.62-1.57	1.04	0.30
	Recessive model			Fixed	0.0%	0.52	0.91	0.78-1.07	1.04	0.30
Consistent with HWE	AA *vs* CC	1879	2955	Fixed	43.2%	0.06	0.92	0.75-1.13	0.00	1.00
	AA *vs* AC			Fixed	49.6%	0.03	0.88	0.75-1.02	0.00	1.00
	Dominant model			Random	54.1%	0.92	1.12	0.89-1.41	0.00	1.00
	Recessive model			Fixed	0.0%	0.64	0.94	0.81-1.09	0.00	1.00

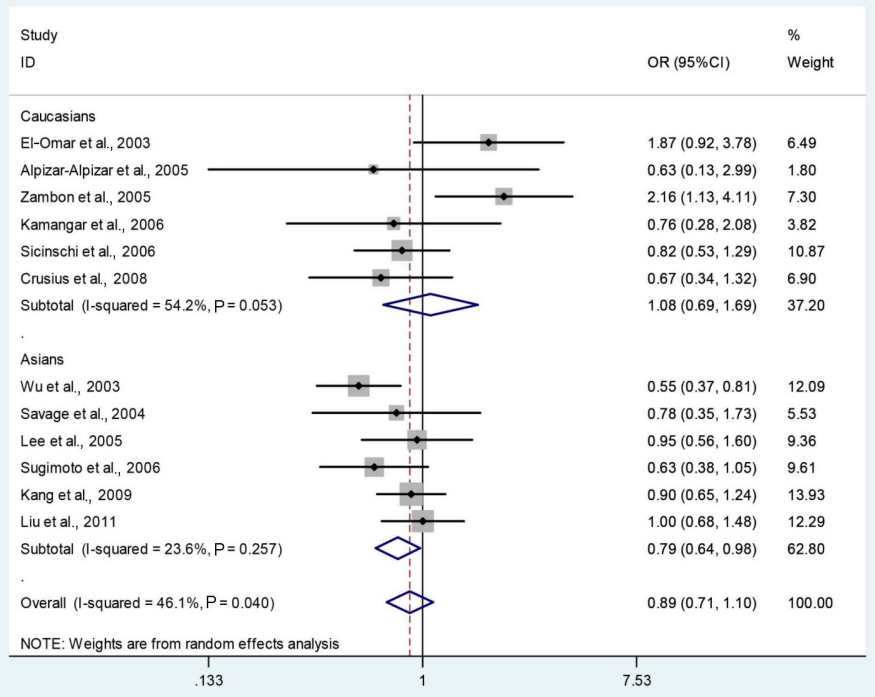

Figure 2. Meta-analysis of the relationship between the interleukin-10 gene -592C>A polymorphism and gastric cancer risk for AA *vs* AC in the race-related subgroup analysis.

Publication bias

The funnel plot and Begg's test were used to assess publication bias. There was no evidence of publication bias in our study (Figure 3). These results suggest there was no publication bias in our meta-analysis (all $P > 0.05$).

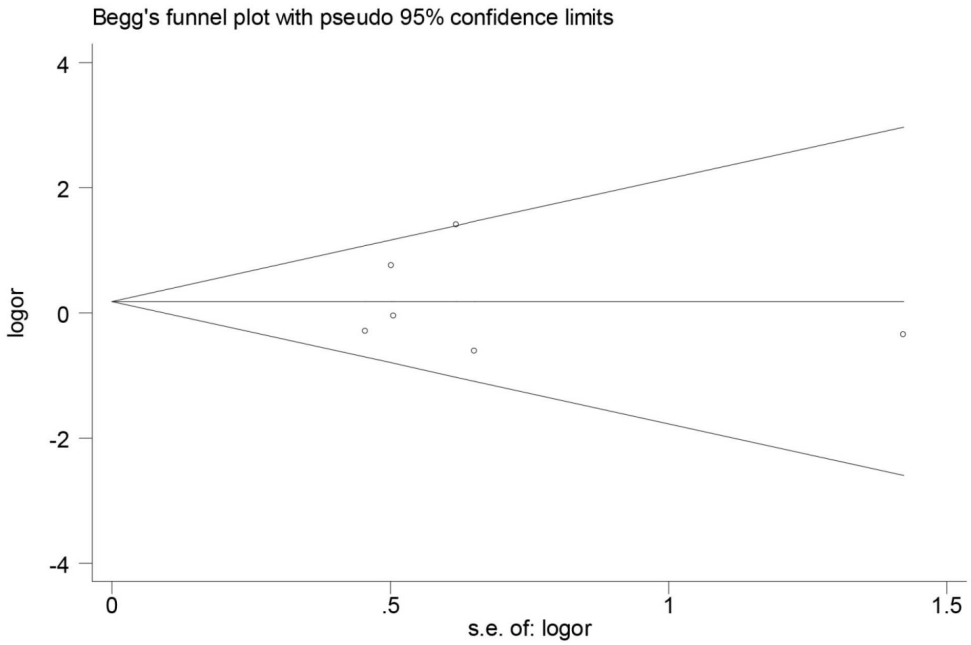

Figure 3. Begg's funnel plot test of publication bias for the association between the interleukin-10 gene -592C>A polymorphism and gastric cancer risk for AA *vs* AC.

DISCUSSION

Inflammation is an essential component of the carcinogenic process in gastric cancer (Coussens and Werb, 2001). IL-10 is an anti-inflammatory cytokine involved in down-regulating cell-mediated and cytotoxic inflammatory responses (Wu et al., 2002). It is well known that single-nucleotide polymorphisms are the most common sources of human genetic variation, which may contribute to an individual's susceptibility to cancer. Multiple studies have demonstrated an association between the IL-10 gene -592C>A polymorphism and gastric cancer. However, the results are inconsistent. Our meta-analysis quantitatively assessed the association between the -592C>A polymorphism and gastric cancer risk. A total of 12 case-control studies were included and assessed, encompassing a total of 2116 gastric cancer patients and 4077 healthy controls. The main meta-analysis results showed that there were significant associations between the -592C>A polymorphism and gastric cancer risk (AA *vs* AC: OR = 0.86, 95%CI = 0.74-1.00). Furthermore, we performed subgroup analysis based on ethnicity. Interestingly, the subgroup analysis results showed the same association in Asians

(AA *vs* AC: OR 0.80, 95%CI = 0.67-0.95; dominant model: OR 1.26, 95%CI = 1.07-1.50), but not in Caucasians. There are several explanations for the inconsistent results. First, gastric cancer is a complex multifactorial and multistage process in which both host genetic factors and environmental influences are involved. Environmental and lifestyles are very different for individuals of different races. Second, the difference in the linkage disequilibrium structure among different populations may be a more likely reason. Third, the -592C>A polymorphism site varied for different ethnicities. There was no evidence of publication bias in this meta-analysis (all $P > 0.05$). Because the number of studies included was small in this meta-analysis of the -592C>A polymorphism, further investigation is required.

The mechanism the interaction between the -592C>A polymorphism and gastric cancer risk remains unclear. Previous studies have found that IL-10 is highly expressed in patients with gastric cancer (De Vita et al., 1999; Ren et al., 2001). The haplotype alleles formed in the promoter region of the IL-10 gene at positions 1082, 819, and 592 (GCC) are related to the ability to produce high levels of IL-10 (Crawley et al., 1999; Edwards-Smith et al., 1999). The GCC haplotype stimulated peripheral blood mononuclear cells, increased expression of mRNA, and elevated serum levels of IL-10, which is linked to the susceptibility and severity of gastric cancer. In addition, tobacco use has been shown to affect the immune system and influence the production of IL-10 (Vassallo et al., 2005). Smokers have impaired T lymphocyte suppressor cell function and decreased natural killer cell activity compared with non-smokers. Furthermore, IL-10 may protect tumors by inhibiting cytotoxic T lymphocyte-mediated tumor-specific cell lysis. Further gene-environment relationships should be examined.

There were some limitations to our study. First, the sample size was relatively small and may not provide sufficient power to estimate an association between the -592C>A polymorphism and gastric cancer. Second, our meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs, and when they did, the ORs were not adjusted by the same potential confounders, such as age and gender. Third, the effects of gene-gene and gene-environment interactions were not addressed in this meta-analysis.

In conclusion, our results indicate that the -592C>A polymorphism is associated with an increased risk of gastric cancer in Asians. Because of the limitations of the present meta-analysis, further research using standardized unbiased methods, larger sample studies, and well-matched controls are necessary.

Conflicts of interest

The authors declare no conflict of interest.

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