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Relationship Between Interleukin-10 Gene C-819T Polymorphism and Gastric Cancer Risk: Insights From a Meta-Analysis

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Background: As a pleiotropic cytokine, interleukin-10 (IL-10) plays a regulatory role in carcinogenesis and tumor growth. The aim of this meta-analysis was to assess the susceptibility of the *IL-10* gene C-819T polymorphism to gastric cancer.

Material/Methods: Study identification and data extraction were independently completed by 2 authors. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated and summarized.

Results: In total, 11 articles including 1960 gastric cancer patients and 3705 controls were qualified. Overall analyses revealed a 13% reduced risk of gastric cancer conferred by the –819T allele relative to the –819C allele (OR=0.87; 95% CI: 0.77–0.97; P=0.016), without heterogeneity (I^2=35.1%). In subgroup analyses, a significant difference was identified in East Asian populations (OR=0.85; 95% CI: 0.73–0.98; P=0.029, I^2=43.6%), for gastric adenocarcinoma (OR=0.80; 95% CI: 0.66–0.96; P=0.017, I^2=0.0%), and in population-based studies (OR=0.81; 95% CI: 0.70–0.93; P=0.003, I^2=0.0%). The visual funnel plots and Egger's tests suggested no evidence of publication bias.

Conclusions: Extending previous findings, we demonstrate a protective role of the *IL-10* gene –819T allele in susceptibility to gastric cancer, and this role was more evident for gastric adenocarcinoma.

MeSH Keywords: Interleukin-10 • Meta-Analysis • Polymorphism, Genetic • Stomach Neoplasms

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Background

Interleukin-10 (IL-10) is a pleiotropic cytokine, and a wealth of evidence supports its regulatory role in carcinogenesis and tumor growth [1,2]. Observational studies have shown that there were high levels of serum IL-10 in patients with a variety of solid tumors, including gastric cancer [3-5]. In addition, experimental studies indicated that *IL-10* expression at early tumor sites in mice could cause systemic suppression of antitumor immunity [6]. It is therefore rational to list the *IL-10* gene as a cancer-susceptibility candidate.

The *IL-10* gene (Gene ID: 3586) is mapped on chromosome 1q31-q32, and includes 5 exons. Several polymorphic *loci* have been identified and characterized in the *IL-10* gene, and one of the most widely evaluated is C-819T (rs1800871) in the promoter region. Many association studies have examined the association of the *IL-10* gene C-819T polymorphism with cancer risk, but no firm conclusions have yet been reached. It is well recognized that genetic heterogeneity in carcinogenesis is recognized as a major reason for this inconclusiveness [7]. Other possible reasons include insufficient statistical power and varied linkage patterns across ancestries. In this study, we summarize available published data to assess the susceptibility of the *IL-10* gene C-819T polymorphism to gastric cancer risk via a comprehensive meta-analysis.

Material and Methods

Guideline

The conduct of this meta-analysis is in agreement with the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Article identification

We searched Medline and Embase to retrieve potential articles that assessed the relationship between the *IL-10* gene C-819T polymorphism and gastric cancer as of 30 March 2015. The key terms included 'gastric or stomach or cancer or carcinoma or tumor' and 'interleukin 10 or interleukin-10 or IL 10 or IL-10', in combination with 'polymorphism or variant or SNP or genetic or genotype or allele'. To avoid missing relevant studies, the reference lists of some major articles and reviews were manually checked.

Inclusion criteria

Articles were included if they met the following criteria: (1) being published in English language; (2) following a retrospective or nested case-control study design; (3) involving gastric cancer as the clinical outcome; (4) using validated genotyping platforms; (5) providing detailed genotype data of C-819T polymorphism in gastric cancer patients and cancer-free controls. We excluded conference abstracts/proceedings or posters because they contained insufficient data to make a complete evaluation.

Data abstraction

Baseline characteristics and genotype distributions from each qualified article were abstracted independently by 2 authors (Qingxian Huang and Fang Liu) according to a predetermined protocol formulated by all authors (Table 1). We resolved all disagreements in data abstraction through discussion and consensus.

Abstracted data included the first author's last name, year of publication, ethnicity, gastric cancer subtype, case-control matched status, source of controls, sample size, the genotype numbers of the *IL-10* gene C-819T polymorphism between gastric cancer patients and controls, as well as age, sex, smoking, drinking, family history of cancer, and *Helicobacter pylori* infection status.

Statistics

Statistical calculations were done with STATA software v11.2 (StataCorp, Texas, USA) for Windows.

The magnitude of association between *IL-10* gene C-819T polymorphism and gastric cancer risk was expressed as odds ratio (OR) and its 95% confidence interval (95% CI), which were calculated in a random-effects model using the DerSimonian and Laird method [8].

Publication bias was examined using the Begg's funnel plot and Egger's test. The trim-and-fill method was also used to infer the existence of unpublished hidden articles from a filled funnel plot, and correct the analysis by imputing the presence of missing studies to yield an unbiased pooled estimate.

Heterogeneity between studies was weighted by inconsistency index (I^2) statistic (range: 0% to 100%), which is defined as the percentage of the observed between-study variability that is due to heterogeneity rather than chance. In this meta-analysis, I^2 exceeding 50% was selected as a threshold to indicate significant heterogeneity.

Two steps were taken to explore possible causes of heterogeneity: (a) for categorical covariates, subgroup analyses were performed according to the degree of Hardy-Weinberg equilibrium, ethnicity of study groups, specific site of gastric cancer, case-control matched status, source of cancer-free controls,

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Table 1. Baseline characteristics and genotype distributions of *IL-10* gene C-819T polymorphism of all eligible populations in this meta-analysis.

Author (year)	Ethnicity	Cancer type	Matched	Source of controls	Sample size		Age (yrs)		Males (%)	
					Patients	Controls	Patients	Controls	Patients	Controls
Wu (2003)	East Asian	Gastric cancer	Yes	Hospital	220	230	60.9	60.7	61.82	61.74
Alpizar-Alpizar (2005)	Latinos	Gastric cancer	Yes	Hospital	45	45	59.8	61.4	79.30	79.30
Zambon (2005)	Caucasian	Gastric noncardia adenocarcinoma	NA	Hospital	129	644	NA	NA	60.47	45.71
Kamangar (2006)	Caucasian	Gastric adenocarcinoma	Yes	Population	98	152	58.5	59.0	NA	NA
Sugimoto (2007)	East Asian	Gastric adenocarcinoma	No	Hospital	105	168	66.8	45.9	80.95	66.67
Crusius (2008)	Caucasian	Gastric adenocarcinoma	Yes	Population	229	1094	NA	NA	NA	NA
Ko (2009)	East Asian	Gastric cancer	Yes	Population	58	233	NA	NA	70.00	70.00
Liu (2011)	East Asian	Gastric cancer	Yes	Population	234	243	61.2	NA	69.23	NA
He (2012)	East Asian	Gastric cancer	Yes	Hospital	196	248	NA	NA	70.40	68.50
Kim (2012)	East Asian	Gastric noncardia adenocarcinoma	Yes	Hospital	495	495	54.9	54.3	68.10	68.10
Zeng (2012)	East Asian	Gastric cancer	Yes	Population	151	153	59.4	57.1	64.20	66.70

Author (year)	Smokers (%)		Drinkers (%)		Family cancer history (%)		HP infection (%)		Patients			Controls			P for HWE
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	CC	CT	TT	CC	CT	TT	
Wu (2003)	51.36	34.35	NA	NA	68.64	55.65	NA	NA	27	105	88	20	83	127	0.231
Alpizar-Alpizar (2005)	NA	NA	NA	NA	NA	NA	82.80	91.40	25	16	4	18	24	3	0.180
Zambon (2005)	NA	NA	NA	NA	NA	NA	NA	NA	70	42	17	353	245	46	0.696
Kamangar (2006)	NA	NA	NA	NA	NA	NA	NA	NA	58	35	5	80	62	10	0.663
Sugimoto (2007)	NA	NA	NA	NA	NA	NA	100.00	0.00	6	57	42	9	73	86	0.194
Crusius (2008)	NA	NA	NA	NA	NA	NA	NA	NA	145	72	12	636	378	80	0.024
Ko (2009)	69.00	58.00	55.00	57.00	NA	NA	86.00	86.00	0	33	25	0	111	122	0.000
Liu (2011)	NA	NA	NA	NA	NA	NA	NA	NA	39	96	99	28	106	109	0.773
He (2012)	31.60	35.90	22.50	27.90	NA	NA	63.78	47.58	18	96	82	28	128	92	0.095
Kim (2012)	63.00	58.00	66.20	70.30	44.40	45.50	89.90	66.60	50	214	231	56	191	248	0.042
Zeng (2012)	24.50	22.22	62.25	42.48	23.84	11.77	68.20	45.10	11	80	60	10	65	78	0.467

HP – *Helicobacter pylori*; HWE – Hardy-Weinberg equilibrium; NA – not available.

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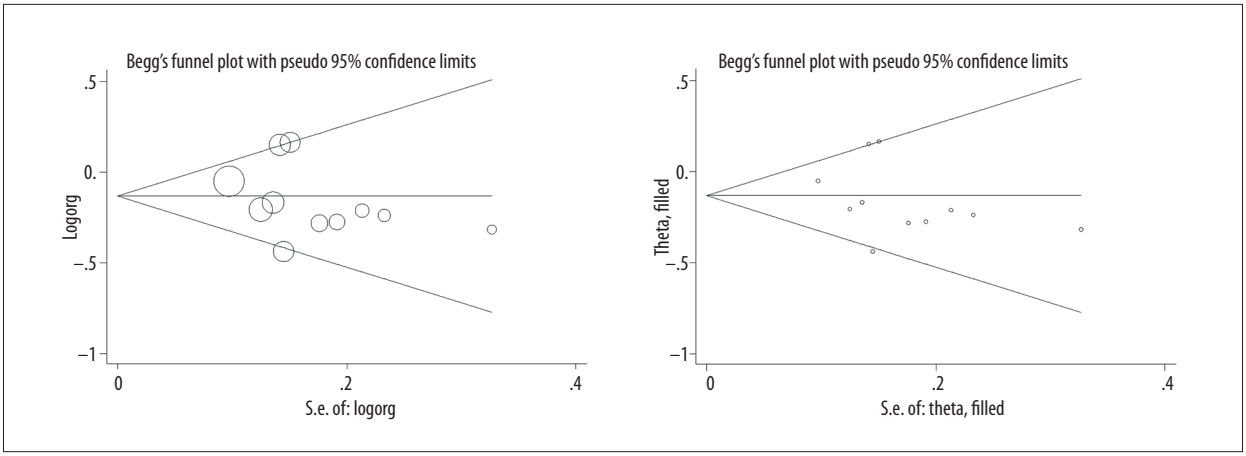

Figure 1. Begg's (the upper panel) and filled (the lower panel) funnel plots of *IL-10* gene C-819T polymorphism for gastric cancer risk.

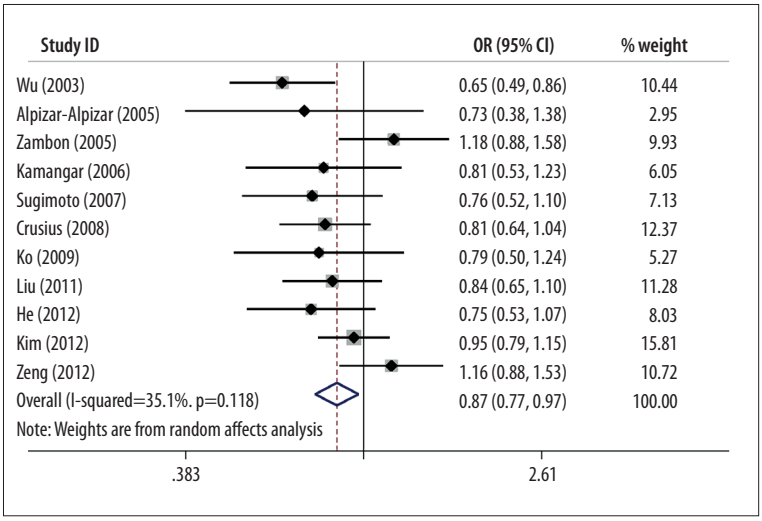

Figure 2. Forest plots of *IL-10* gene C-819T polymorphism for gastric cancer risk.

and sample size, respectively; and (b) for continuous covariates, meta-regression analyses were undertaken with restricted maximum likelihood estimates.

In addition, sensitivity analysis was conducted to evaluate the contribution of individual studies to pooled effect estimate by sequentially omitting each study one at a time and computing differential estimates for remaining studies.

Results

Eligibility

Out of 315 initially identified relevant articles, 11 articles were qualified for the final analysis according to the inclusion criteria [5,9–18] including 1960 gastric cancer patients and 3705 cancer-free controls in total.

Characteristics

The baseline characteristics of the 11 qualified articles are shown in Table 1. Seven articles enrolled study subjects of East Asian ancestry, 3 articles of Caucasian ancestry, and 1 article of Latino ancestry. Gastric adenocarcinoma was investigated in 3 articles and gastric noncardia adenocarcinoma in 2 articles. Controls were enrolled from hospitals in 6 articles and from populations in 5 articles. Three of 11 qualified articles had a total sample size of ≥500. The genotype distributions of *IL-10* gene C-819T polymorphism deviated from Hardy-Weinberg equilibrium in 3 articles.

Publication bias

From a visual inspection (Figure 1), the Begg's funnel plot was symmetrical, and no missing study was annotated in the filled funnel plot. As indicated by the Egger's test, there was no indication of publication bias (P=0.333).

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Table 2. Subgroup analyses of *IL-10* gene C-819T polymorphism for gastric cancer risk.

Subgroup	Number: Studies (patients/controls), n (n/n)		OR; 95% CI; P	I^2 (%)	P
Ethnicity					
East Asian	7	(1459/1770)	0.85; 0.73–0.98; 0.029	43.6	0.100
Caucasian	3	(456/1890)	0.93; 0.72–1.19; 0.548	50.7	0.132
Gastric cancer site					
Adenocarcinoma	3	(432/1414)	0.80; 0.66–0.96; 0.017	0.0	0.954
Noncardia adenocarcinoma	2	(624/1139)	1.03; 0.84–1.26; 0.805	31.2	0.228
Matched status					
Yes	9	(1726/2893)	0.85; 0.75–0.95; 0.006	25.7	0.216
Hardy-Weinberg equilibrium					
Satisfied	8	(1178/1883)	0.86; 0.73–1.02; 0.080	50.5	0.049
Unsatisfied	3	(782/1822)	0.88; 0.77–1.02; 0.092	0.0	0.538
Source of controls					
Hospital	6	(1190/1830)	0.91; 0.74–1.11; 0.338	61.7	0.023
Population	5	(770/1875)	0.81; 0.70–0.93; 0.003	0.0	0.991
Sample size					
<500	8	(1575/2226)	0.82; 0.71–0.94; 0.006	25.6	0.225
≥500	3	(385/1479)	0.96; 0.79–1.15; 0.625	44.3	0.166

OR – odds ratio; 95% CI – 95% confidence interval.

Pooled estimates

Pooling the results of 11 qualified articles together detected a 13% reduced risk of gastric cancer conferred by the –819T allele relative to the –819C allele (OR=0.87; 95% CI: 0.77–0.97; P=0.016), and evidence for heterogeneity was relatively week (I^2=35.1%) (Figure 2).

Stratified estimates

In spite of the nonsignificant heterogeneity for the overall estimate, an assessment of its diverse sources is still necessary. Subgroup analyses according to a panel of predetermined categorical variables are presented in Table 2.

According to the degree of Hardy-Weinberg equilibrium at a significance level of 5%, effect estimates were comparable between articles with C-819T genotypes in and not in Hardy-Weinberg equilibrium. By ethnicity, significance was only obtained in East Asians (OR=0.85; 95% CI: 0.73–0.98; P=0.029), without heterogeneity (I^2=43.6%). The effect estimate was potentiated (OR=0.80; 95% CI: 0.66–0.96; P=0.017) when gastric adenocarcinoma was specified, and there was no observable heterogeneity. After restricting analysis to articles with matched patients and controls on age or sex, effect estimate was slightly strengthened (OR=0.85; 95% CI: 0.75–0.95; P=0.006).

In subgroup analyses by source of controls, the effect estimate was significant only in population-based studies (OR=0.81; 95% CI: 0.70-0.93; P=0.003) relative to the hospital-based studies (OR=0.91; 95% CI: 0.74–1.11; P=0.338). By sample size, the magnitude of effect estimates was even stronger in small studies (total sample size <500) (OR=0.82; 95% CI: 0.71–0.94; P=0.006) than in large studies (total sample size ≥500) (OR=0.96; 95% CI: 0.79–1.15; P=0.625), with weak evidence of heterogeneity.

Meta-regression analysis

Other sources of heterogeneity were explored by meta-regression analyses. After regressing age, sex, smoking, drinking, family history of cancer, and *Helicobacter pylori* infection, none of the regression coefficients differed significantly from zero (data not shown).

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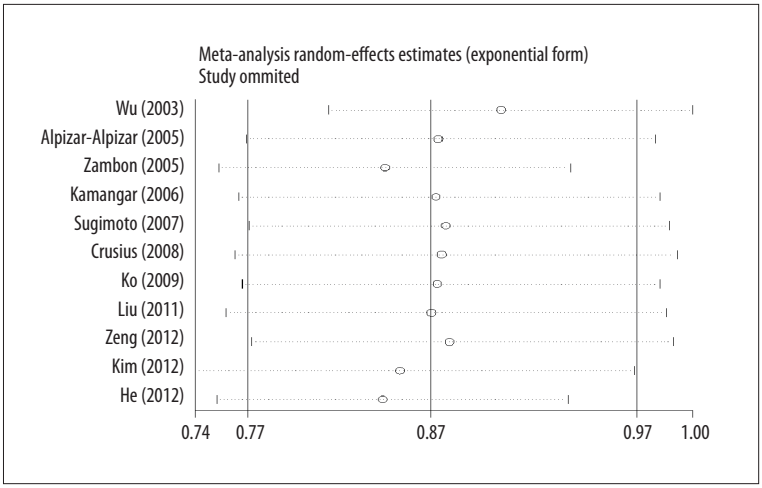

Figure 3. Sensitivity analysis of *IL-10* gene C-819T polymorphism for gastric cancer risk.

Sensitivity analysis

With regard to the comparison of –819T allele with –819C allele, pooled effect estimates of the other studies confirmed the overall difference in both direction and magnitude after removing each eligible study one at a time (Figure 3).

Discussion

Gathering data from 11 qualified studies in a meta-analysis, we demonstrate a protective role of *IL-10* gene –819T allele in susceptibility to gastric cancer, and this role was more evident for gastric adenocarcinoma. Moreover, the results of this meta-analysis were unlikely to have been biased by heterogeneity or publication bias.

The candidate gene approach is increasingly being used to tease out susceptible genes that may potentially trigger the initiation and progression of various types of cancer. One of these genes that might be associated with gastric cancer is the *IL-10* gene. However, such candidate gene studies are often criticized due to the repeated failure to validate results. As meta-analysis is a powerful tool to address the discrepancies in genetic association studies, we decided to evaluate the association of a promoter polymorphism C-819T in the *IL-10* gene with the development of gastric cancer by a comprehensive meta-analysis. Also, we conducted subgroup and meta-regression analyses to identify and control various sources of heterogeneity.

The promoter region of *IL-10* gene is polymorphic, and another 2 promoter polymorphisms, A-592C and A-1082G, also attract much interest and have been summarized by several meta-analyses on susceptibility to gastric cancer [19–21]. Extending previous findings and a recent meta-analysis by Xue et al. [20], the current meta-analysis demonstrated a significant association between the *IL-10* gene –819T allele and a reduced risk for gastric cancer, especially for gastric adenocarcinoma. There is functional evidence supporting a marked correlation between –819T allele and increased *IL-10* expression in both serum [19] and monocytic THP1 cells [22]. An understanding of how *IL-10* expression is regulated is therefore essential in unraveling the pathogenesis of gastric cancer. Thus far, the functional relevance of *IL-10* gene C-819T polymorphism has not been elucidated; it is reasonably expected that if involved, C-819T polymorphism might precipitate gastric cancer by altering the expression of the *IL-10* gene.

A note of caution should be sounded when interpreting our findings, especially in subgroup analyses, given the limited sample sizes involved. This is well exemplified in comparison of the small with the large studies, as significance was only attained in small studies. It has been suggested that to achieve satisfactory power, at least 1000 subgroups are required and in most cases depending on the prevalence of polymorphism examined in the general population [23]. We therefore must regard our findings as preliminary, which should be viewed as hypothesis-generating and call for further validation in large-scale and well-design studies.

There were several limitations to this meta-analysis. Firstly, this meta-analysis is based on the summary estimates of each qualified case-control study, which rarely establishes causal relationship, and it is encouraging to incorporate the concept of Mendelian randomization into observational association studies [24]. Secondly, only 1 promoter polymorphism, C-819T in the *IL-10* gene, was evaluated in this meta-analysis, which might not be sufficient to address the complex genetic architecture of gastric cancer. Thirdly, only published articles written in English language were retrieved for inclusion and some unpublished small and/or negative articles might be missing, leading to the potential existence of publication bias. Fourthly, it is essential to examine the gene-environment and gene-gene interactions at the levels of individual studies and

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meta-analysis. To achieve this goal, one usually needs to perform a meta-analysis of individual participant data, which is not always practical for the majority of available meta-analyses.

Conclusions

To sum up, this meta-analysis of 11 qualified studies and on 5665 subjects demonstrated a protective role of the *IL-10* gene –819T allele in susceptibility to gastric cancer, and this role was more evident for gastric adenocarcinoma. Further genetic and functional investigations are required to elucidate the mechanisms of *IL-10* gene and gastric cancer, and the relationship between the *IL-10* gene and other types of cancer.

Author disclosure

The authors declare they have no conflicts of interest.

References:

1. Holan V, Zajicova A, Javorkova E et al: Distinct cytokines balance the development of regulatory T cells and interleukin-10-producing regulatory B cells. Immunology, 2014; 141: 577–86
2. Tanikawa T, Wilke CM, Kryczek I et al: Interleukin-10 ablation promotes tumor development, growth, and metastasis. Cancer Res, 2012; 72: 420–29
3. Rad R, Dossumbekova A, Neu B et al: Cytokine gene polymorphisms influence mucosal cytokine expression, gastric inflammation, and host specific colonisation during *Helicobacter pylori* infection. Gut, 2004; 53: 1082–89
4. Szkaradkiewicz A, Karpinski TM, Drews M et al: Natural killer cell cytotoxicity and immunosuppressive cytokines (IL-10, TGF-beta1) in patients with gastric cancer. J Biomed Biotechnol, 2010; 2010: 901564
5. Kim J, Cho YA, Choi IJ et al: Effects of interleukin-10 polymorphisms, *Helicobacter pylori* infection, and smoking on the risk of noncardia gastric cancer. PLoS One, 2012; 7: e29643
6. Seo N, Hayakawa S, Takigawa M et al: Interleukin-10 expressed at early tumour sites induces subsequent generation of CD4(+) T-regulatory cells and systemic collapse of antitumour immunity. Immunology, 2001; 103: 449–57
7. Urbach D, Lupien M, Karagas MR et al: Cancer heterogeneity: origins and implications for genetic association studies. Trends Genet, 2012; 28: 538–43
8. Higgins JP, Thompson SG, Deeks JJ et al: Measuring inconsistency in meta-analyses. BMJ, 2003; 327: 557–60
9. Wu MS, Wu CY, Chen CJ et al: Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. Int J Cancer, 2003; 104: 617–23
10. Zambon CF, Basso D, Navaglia F et al: Pro- and anti-inflammatory cytokines gene polymorphisms and *Helicobacter pylori* infection: interactions influence outcome. Cytokine, 2005; 29: 141–52
11. Alpizar-Alpizar W, Perez-Perez GI, Une C et al: Association of interleukin-1B and interleukin-1RN polymorphisms with gastric cancer in a high-risk population of Costa Rica. Clin Exp Med, 2005; 5: 169–76
12. Kamangar F, Abnet CC, Hutchinson AA et al: Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). Cancer Causes Control, 2006; 17: 117–25
13. Sugimoto M, Furuta T, Shirai N et al: Effects of interleukin-10 gene polymorphism on the development of gastric cancer and peptic ulcer in Japanese subjects. J Gastroenterol Hepatol, 2007; 22: 1443–49
14. Crusius JB, Canzian F, Capella G et al: Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). Ann Oncol, 2008; 19: 1894–902
15. Ko KP, Park SK, Cho LY et al: Soybean product intake modifies the association between interleukin-10 genetic polymorphisms and gastric cancer risk. J Nutr, 2009; 139: 1008–12
16. Liu J, Song B, Wang JL et al: Polymorphisms of interleukin-10 promoter are not associated with prognosis of advanced gastric cancer. World J Gastroenterol, 2011; 17: 1362–67
17. He B, Pan Y, Xu Y et al: Increased risk for gastric cancer in carriers of the lymphotoxin-alpha+252G variant infected by *Helicobacter pylori*. Genet Test Mol Biomarkers, 2012; 16: 9–14
18. Zeng X, Li Y, Liu T et al: Diverse H. pylori strains, IL-10 promoter polymorphisms with high morbidity of gastric cancer in Hexi area of Gansu Province, China. Mol Cell Biochem, 2012; 362: 241–48
19. Jin L, Sturgis EM, Cao X et al: Interleukin-10 promoter variants predict HPV-positive tumors and survival of squamous cell carcinoma of the oropharynx. FASEB J, 2013; 27: 2496–503
20. Xue H, Lin B, An J et al: Interleukin-10-819 promoter polymorphism in association with gastric cancer risk. BMC Cancer, 2012; 12: 102
21. Yu Z, Liu Q, Huang C et al: The interleukin 10–819C/T polymorphism and cancer risk: A HuGE review and meta-analysis of 73 studies including 15,942 cases and 22,336 controls. OMICS, 2013; 17: 200–14
22. Reuss E, Fimmers R, Kruger A et al: Differential regulation of interleukin-10 production by genetic and environmental factors – a twin study. Genes Immun, 2002; 3: 407–13
23. Salanti G, Sanderson S, Higgins JP: Obstacles and opportunities in meta-analysis of genetic association studies. Genet Med, 2005; 7: 13–20
24. Sleiman PM, Grant SF: Mendelian randomization in the era of genomewide association studies. Clin Chem, 2010; 56: 723–28

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