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Soybean Product Intake Modifies the Association between Interleukin-10 Genetic Polymorphisms and Gastric Cancer Risk[1–3]

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Abstract

In this study, our aim was to investigate the association of inflammation-related genetic polymorphisms and gastric cancer risk and to examine whether the combined effect of soybean product intake modified cancer risk. Eighty-four incident gastric cancer cases and 336 matched controls were selected from the Korean Multi-Center Cancer Cohort. We selected 14 single nucleotide polymorphisms (SNP) from 5 genes [*interleukin* (*IL*)*-1β, IL-2, IL-4, IL-8,* and *IL-10*] and used unconditional logistic regression model to calculate the odds ratios (OR) and 95% CI adjusting for *H. pylori* seropositivity, smoking, age, sex, enrollment year, and residential area. The risk for gastric cancer in relation to genetic polymorphisms and haplotypes were assessed according to soybean product intake levels. Although no single SNP effect was found, the combined effect between *IL-10* gene variants of *−592 GG/GA*, *−819 TC/CC*, or *−1082 AG/GG* and low intake of soybean products had an increased risk for gastric cancer compared with the group with no risk gene variants and a high intake of soybean products (OR [95% CI] = 2.82 [1.04–7.62], 2.75 [1.02–7.44], and 4.34 [1.51–12.5], respectively). Among the low-soybean product intake group, *IL-10 CCG* haplotype had an increased risk of gastric cancer (OR = 3.38 [1.40–8.13]) relative to the *ATA* haplotype. Our results suggest that the association between IL-10 genetic polymorphisms and gastric cancer risk was modified by soybean product intake. J. Nutr. 139: 1008–1012, 2009.

Introduction

Gastric cancer is the fourth most common cancer and second leading cause of cancer deaths in the world (1). Numerous epidemiologic studies that evaluated gastric cancer risk factors have reported *Helicobacter pylori* infection as a significant risk factor (2–4) and the International Agency for Research on Cancer classified *H. pylori* as a gastric carcinogen (*5*).

Although *H. pylori* infection is a known risk factor of gastric cancer, <3% of *H. pylori* carriers develop gastric cancer (6). Thus, *H. pylori* virulence factors (7,8) and environmental factors such as smoking (9), dietary factors, and several biological markers, including plasma glucose concentration (10), have been proposed in the etiology of gastric carcinogenesis (11,12). Genetic susceptibility may also underlie the association of gastric cancer risk (13).

Chronic *H. pylori* infection of the gastric epithelium can induce chronic inflammation, which is a critical step in gastric carcinogenesis (14). In chronic gastric inflammation, activated neutrophils and mononuclear cells produce different types of cytokines that are proinflammatory cytokines, including interleukin (IL)[9]-1β, IL-6, IL-8, and antiinflammatory cytokines, including IL-10 (15,16). Although many studies have assessed the association between genetic polymorphisms of inflammation-related cytokine and gastric cancer, the results have been inconsistent. Also in terms of environmental factors, previous epidemiologic studies indicated that high consumption of soy food may lower the risk of gastric cancer (17,18).

In this study, we investigated the association between inflammation-related genetic polymorphisms of the IL genes -1β, -2, -4, -8, and -10 and gastric cancer risk. Additionally, we examined whether the combined effect of intake of soybean product that is abundant in the Korean diet and IL genetic polymorphisms modify the risk of gastric cancer.

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[3] Supplemental Table 1 is available with the online posting of this paper at jn.nutrition.org.
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[9] Abbreviations used: IL, interleukin; OR, odds ratio; SNP, single nucleotide polymorphism.

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Materials and Methods

Study population and data collection. Participants were selected from the Korean Multi-center Cancer Cohort, a community-based prospective cohort of male and female volunteers over 30 y of age in Korea who were recruited from 1993 to 2004. The Korean Multi-center Cancer Cohort is described in detail elsewhere (19). Information on general lifestyle, physical activity, diet, reproductive factors, and pesticide exposures were obtained by structured questionnaire interviews. Information on soybean product intake was collected using a self-administered FFQ beginning in 1995. The FFQ included 33 food items that were reported to have a possible relation to cancer risk, particularly among Asian groups, and soybean product intake was one of the selected food items. Participants were asked to report their consumption frequency of soybean products according to 4 categories (almost never, 3–4 times/mo, 3–4 times/wk, more than once/d). Anthropometric measurements, blood samples, and spot urine samples were also collected. Serum, plasma, and buffy coat samples were stored at −70°C. The study protocol was approved by the institutional review boards of Seoul National University Hospital and the National Cancer Center of Korea.

Selection of cases and controls. In December 2002, among 14,440 cohort participants, we identified 136 gastric cancer cases through computerized record linkages to the Korean National Cancer Registry and National Death Certificate databases. We excluded cases who were diagnosed before recruitment ($n = 36$) and cases with insufficient DNA for genotyping ($n = 16$). The median interval from initial blood collection to diagnosis of gastric cancer was 2.4 y. We matched 4 controls to 1 cancer case by incidence density sampling based on age within 5 y, gender, residence area, and the year of recruitment. Finally, 84 cases and 336 controls were included in our analysis.

Genotyping. We genotyped 14 single nucleotide polymorphisms (SNP) in 5 *IL* genes that were IL-1β (−31 T/C, −511 C/T, −1473 G/C, and −3954 C/T), IL-2 (−114 T/G and −384 T/G), IL-4 (−33 T/C and −590 T/C), IL-8 (−251 T/A, +396 T/G, and −781 C/T), and IL-10 (−592 A/C, −819 T/C, and −1082 A/G).

Genotyping was performed using Taqman (IL-1β, IL-2–384 T/G, and IL-8–781 C/T) or Snapshot (IL-2–114 T/G, IL-4, IL-8–251 T/A, +396 T/G, and IL-10). The call rates ranged from 92.9 to 98.8%. Ten samples that were randomly selected to assess reliability of the laboratory test were concordant for all SNP.

H. pylori *antibody assays.* Sera were assayed using immunoblot kits (Helico Blot 2.1, MP Biomedicals Asia Pacific) that identified IgG antibodies specific for *H. pylori* according to the manufacturer's instruction. Sensitivity for *H. pylori* IgG antibody was 99% and specificity was 98% in the Korean population (20).

Statistical analysis. We compared baseline characteristics of cases and controls and assessed the Hardy-Weinberg equilibrium of allele frequencies using the chi-square test. Unconditional logistic regression models were used to calculate the odds ratios (OR) and 95% CI. OR were adjusted for age, gender, residence area, the year of recruitment, smoking history (never smoker, ex-smoker, and current smoker), and *H. pylori* infection status (yes or no). Subgroup analyses were stratified by soybean product intake level. Consumption of soybean products was divided into 2 groups: low (almost never and 3–4 times/mo) and high (3–4 times/wk and more than once/d) intake. Haplotypes for each gene were constructed with haploview. The most common haplotype was used as the referent category in the analysis on the association between haplotypes and gastric cancer risk. Statistical analyses were performed using SAS v9.1.

Results

Demographic, lifestyle, and medical characteristics are presented in **Table 1**. Gastric cancer risk was higher in the smoking group than in the nonsmoking group (OR = 2.74; 95% CI = 1.23–6.08). Cases and controls did not differ in education level, alcohol drinking history, gastric ulcer history, and *H. pylori* IgG antibody positivity. Low soybean intake tended to increase ($P = 0.10$) the risk of gastric cancer (OR = 1.84; 95% CI = 0.89–3.81).

Table 2 presents a summary of the 5 genes and 14 SNP in our analysis. Individual SNP effects (OR and corresponding 95% CI) for gastric cancer risk adjusted for age, sex, year enrolled, cigarette smoking history, and *H. pylori* IgG antibody positivity are shown in **Supplemental Table 1**. The selected SNP for IL-1β, IL-2, IL-4, IL-8, and IL-10 were not associated with gastric cancer risk.

The combined effect of *IL-10* polymorphisms and soybean intake on gastric cancer risk is presented (**Table 3**). Because the FFQ were conducted starting in 1995 and information was missing on soybean product intake level among participants enrolled between 1993 and 1994, only 58 cases and 233 controls were included in this analysis. Compared with participants with the *IL-10–592 AA* genotype and high intake of soybean products, participants with *AC* or *CC* genotype and low intake of soybean products increased the risk of gastric cancer ($P = 0.04$; OR = 2.8; 95% CI = 1.0–7.6). Similarly, participants with the *IL-10–819 TC* or *CC* genotype and low intake of soybean products increased the risk of gastric cancer compared with participants with the *TT* genotype and high intake of soybean products (OR = 2.8; 95% CI = 1.0–7.4). Participants with the risk variant for the *IL-10–1082 AG* or *GG* genotype and low

TABLE 1 Baseline characteristics of gastric cancer cases and controls and their association with gastric cancer risk

	Cases, $n = 84$	Controls, $n = 336$	OR[1] (95% CI)
Sex	*n (%)*		
Male	59 (70)	236 (70)	
Female	25 (30)	100 (30)	
Age			
<65 y	45 (54)	196 (58)	
≥65 y	39 (46)	140 (42)	
Residential area			
Chungju	38 (45)	152 (45)	
Haman	46 (55)	184 (55)	
Formal education			
No	22 (26)	98 (29)	1.0
Yes	62 (73)	237 (71)	1.4 (0.8–2.6)
Smoker			
No	26 (31)	141 (42)	1.0
Yes	58 (69)	193 (58)	2.7 (1.2–6.1)
Alcohol drinker			
No	38 (45)	144 (43)	1.0
Yes	46 (55)	188 (57)	0.8 (0.4–1.4)
Peptic ulcer history			
No	72 (87)	303 (90)	1.0
Yes	11 (13)	32 (10)	1.7 (0.7–4.2)
Soybean intake[2]			
High	13 (22)	85 (35)	1.0
Low	45 (76)	156 (65)	1.8 (0.9–3.8)
H. Pylori IgG positivity			
(−)	12 (14)	48 (14)	1.0
(+)	72 (86)	288 (86)	1.0 (0.5–2.1)

[1] Adjusted for age, sex, area, and the year enrolled.
[2] High: 3–4 times/wk, more than once/d; low: almost never, 3–4 times/mo.

TABLE 2 Summary of the 5 genes and 14 SNP analyzed in the study

Chromosome	Gene	db SNP ID	Position	MAF, %
2	*IL-1β*	rs1143627	−31 T > C	49
		rs16944	−511 C > T	49
		rs1143623	−1473 G > C	42
		rs1143634	−3954 C > T	3
4	*IL-2*	rs2069763	−114 T > G	48
		rs2069762	−384 T > G	33
5	*IL-4*	rs2070874	−33 T > C	22
		rs2243250	−590 T > C	21
4	*IL-8*	rs4073	−251 T > A	33
		rs2227307	+396 T > G	33
		rs2227306	−781 C > T	23
1	*IL-10*	rs1800872	−592 A > C	30
		rs1800871	−819 T > C	30
		rs1800896	−1082 A > G	6

TABLE 3 Combined effect of *IL-10* genetic polymorphisms and soybean intake on gastric cancer risk

	Cases, *n*	Controls, *n*	OR[1] (95% CI)
−592 A/C, soybean intake[2]			
Risk variants[3] (−) high intake	6	42	1.0
Risk variants (+) high intake	7	39	1.3 (0.4–4.2)
Risk variants (−) low intake	19	79	1.9 (0.7–5.5)
Risk variants (+) low intake	26	71	2.8 (1.04–7.6)*
−819 T/C, soybean intake			
Risk variants[3] (−) high intake	6	42	1.0
Risk variants (+) high intake	7	39	1.3 (0.4–4.2)
Risk variants (−) low intake	19	80	1.9 (0.7–5.4)
Risk variants (+) low intake	26	72	2.8 (1.02–7.4)*
−1082 A/G, soybean intake			
Risk variants[3] (−) high intake	12	66	1.0
Risk variants (+) high intake	0	9	0.3 (0.1–5.1)[4]
Risk variants (−) low intake	34	126	1.7 (0.8–3.6)
Risk variants (+) low intake	10	14	4.3 (1.5–12.5)*

[1] Adjusted for age, sex, area, enrolled year, smoking history, and *H. pylori* infection. Asterisks indicate *Helicobacter pylori*.
[2] Low intake: almost never, 3–4 times/mo; high intake: 3–4 times/wk, more than once/d.
[3] Gene variant: C allele for −592A/C, C allele for −819 T/C, and G allele for −1082A/G.
[4] Logit estimates.

soybean product intake had an increased risk for gastric cancer (OR = 4.3; 95% CI = 1.5–12.5) compared with their counterparts with the *AA* genotype and high soybean product intake. However, none of the interaction effects was significant in the multiplicative interaction level.

Table 4 shows *IL-10* gene haplotype frequencies and their association with gastric cancer risk stratified by soybean intake levels. In the low soybean intake group, individuals with the *GCC* haplotype had an increased risk of developing gastric cancer compared with those with the *ATA* haplotype (OR = 3.4; 95% CI = 1.4–8.1). However, among participants in the high soybean intake group, the *GCC* haplotype was not associated with risk of gastric cancer (OR = 0.4; 95% CI = 0.1–6.8).

Discussion

Our findings show that *IL-10* genetic variants and low intake of soybean products are associated with increased gastric cancer risk compared with participants without IL-10 variants and high intake of soybean products.

IL-10 is an antiinflammatory cytokine by downregulating cell–mediated immune response and cytotoxic inflammatory response in animal models (21–23). *IL-10* is increased in chronic gastritis associated with *H. pylori* infection (24). A study conducted in a Japanese population (25) showed that the *C* allele of *IL-10–592* (OR = 1.85l; 95% CI = 1.02–3.38) and of *IL-10–819* (OR = 1.87; 95% CI = 1.02–3.41) was associated with an increased risk for gastric cancer, whereas the *IL-10–1082* polymorphism was not associated with development of gastric cancer. A recent meta-analysis reported that the *IL-10–1082* polymorphism may be associated with gastric cancer among Asians (26). In the case of IL-10 haplotypes, the *GCC* haplotype of the *IL-10*-1082/-819/-592 polymorphism was associated with a significantly increased risk for gastric cancer relative to the *ATA* haplotype in the Japanese and Scottish populations (25,27). In contrast, another study showed that the *GCC* haplotype had a decreased risk for gastric cancer in the Taiwanese population (28). In our study, the GCC haplotype had a significantly increased risk for gastric cancer in the low soybean intake group.

The low-soy diet had the strongest factor in contributing to the elevated risk of gastric cancer through an interaction with IL genetic variants. Studies have reported the beneficial effects of soy factors on gastric cancer. A high consumption of soybean products was associated with a reduced risk of gastric cancer among Koreans and Japanese participants (18,29–33). The benefits of soybeans may be induced by isoflavones such as genistein and daidzein (34) that have antiinflammatory and antioxidative effects (35). Soy factors can potentiate immunologic functions such as lymphocyte proliferation, cellular and humoral immune responses, thymocyte differentiation, and tumor immunity (36,37). Therefore, a low-soy diet may act as a risk factor through blockage of antiinflammatory and antioxidative effects and increasing the effects on immune function.

Our study showed that the interactive effect between soybean product intake and *IL-10* genetic variants modifies gastric cancer risk. Although there are few epidemiologic studies that examine this interactive effect, there are several experimental studies that provide indirect evidence. The studies showed that soybean-derived isoflavone genistein inhibits growth of *H. pylori* (38). Previous studies on B cell malignancies demonstrated that genistein decreased IL-10 secretion, followed by upregulation of interferon-γ and inhibition of cell proliferation (34,39). This suggests a possible interactive role between IL-10 and soybean products, although it is unclear why antiinflammatory properties of IL-10 are effective among the high soybean intake group but ineffective among the low soybean intake group.

We hypothesize that with high intakes of soybeans, genistein functions to decrease secretion of IL-10 that promotes antiinflammation effects of both genistein and IL-10 and inhibition of *H. pylori* and consequently reduces gastric cancer risk. In contrast, under low levels of soybean intake, the inhibitory function of genistein is weak and, thus, *H. pylori*-related inflammation may increase, leading to gastric carcinogenesis. Nevertheless, this does not explain the antiinflammatory effect of IL-10. A study reported that the IL-10 (−1082/−819/−592) GCC haplotype had higher IL-10 mRNA levels than the ATA haplotype (40), which suggests the IL-10 GCC haplotype can be related to a lower risk of gastric cancer through an increased IL-10 antiinflammation effect. In contrast, Rad et el (40). also reported that the IL-10 GCC haplotype was associated with colonization

TABLE 4 Haplotype distribution of *IL-10* gene in gastric cancer cases and controls and their associations with gastric cancer risk according to soybean intake level

	Low soybean intake[2]			High soybean intake[2]		
Haplotypes[1]	Cases, *n*	Controls, *n*	OR (95% CI)[3]	Cases, *n*	Controls, *n*	OR (95% CI)[3]
ATA	56	205	1.0	16	105	1.0
ACC	21	61	1.2 (0.7–2.2)	8	35	1.5 (0.5–4.1)
GCC	11	16	3.4 (1.4–8.1)*	0	8	0.4 (0.1–6.8)[4]

[1] Composed of 3 polymorphic sites: −1082A/G, −819T/C, and −592A/C.
[2] Low intake: almost never, 3–4 times/mo; high intake: 3–4 times/wk, more than once/d.
[3] Adjusted for age, sex, area, enrolled year, smoking history, and *H. pylori* infection. Asterisk indicates *Helicobacter pylori*.
[4] Logit estimates.

of virulent cagA+, VacAs1+, and babA2+ *H. pylori* stains and significant gastric inflammation responses compared with the ATA haplotype. This apparent paradox may partly explain why in our study, the GCC haplotype that is related to higher IL-10 expression had an increased risk for gastric cancer among the lower soybean intake group. Among the lower soybean intake group that had a decreased antiinflammatory effect, IL-10 GCC genetic variants may allow infection with more virulent *H. pylori* strains and exaggerate gastric inflammation of the bacterium. In contrast, among participants with higher soy product intakes, IL-10 GCC genetic variants may not have been associated with gastric cancer risk due to the antiinflammatory effects of soy. The IL-10 GCC haplotype was not associated with gastric cancer risk among in these participants (Table 4).

IL-8 is a proinflammatory cytokine that can stimulate the division of endothelial cells as well as induce angiogenesis (41). Japanese studies (42,43) showed that the *IL-8–251 AA* type increased the risk of gastric cancer compared with the *TT* type and Chinese studies (44,45) have suggested similar results. However, European studies (46,47) reported a null association between IL-8 and gastric cancer. In our study, the *IL-8–251 AA* genotype tended to be associated with an increased risk of gastric cancer ($P = 0.18$).

IL-1β plays an important role in controlling inflammatory processes and inhibits gastric acid secretion (48). Although studies have investigated the association between *IL-1β -31 T/C* and *−511 C/T* genetic polymorphisms and the risk of gastric cancer, it was not associated with gastric cancer in meta-analysis (49). For *IL-1β −1473 G/C*, there are only a small number of studies (50), so further research is needed.

IL-2 and -4 play roles in inducing *H. pylori*-associated gastric atrophy by regulating T helper type 1 immune responses (51,52) and inhibiting gastric acid secretions (52). However, it is unclear whether *IL-2* and -4 polymorphisms are associated with gastric cancer risk due to inconsistencies across studies (27,53–55).

Our study had several limitations. First, we did not have information on the anatomical location and histological subtype of gastric cancer. Gastric cancer is heterogenous neoplastic disease according to anatomical and histological subtype and each category causes cancer in different pathways (56), so the genetic polymorphism of IL may affect carcinogenesis in different pathways according to the subtype of gastric cancer. Second, the number of cases was small and information on soybean products was partially missing, because information on diet was collected starting in 1995. However, we think that this would not have affected our results, because we matched for recruitment year and thus comparability was maintained. Additionally, participants with missing variables were not significant for gastric cancer risk, and so there might be no selection bias caused from excluding the participants with missing variables.

Nevertheless, our study had several strengths. The nested case-control study design allowed us to prospectively investigate the association between IL genetic polymorphisms and gastric cancer in the Korean population. To minimize the confounding effect, we adjusted for gastric cancer risk factors, including *H. pylori* infection, cigarette smoking, age, and sex. In addition, we examined whether genetic polymorphisms of gastric cancer risk were modified by other factors, including *H. pylori* virulence factor and intake of soybean products.

Our results suggest that the interaction between *IL-10* gene variants and soy factor can modify individual susceptibility in gastric cancer development by affecting immunologic and inflammatory functions.

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