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Associations between Atopic Dermatitis and Risk of Gastric Cancer: A Nationwide Population-based Study

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Background/Aims: Epidemiologic and clinical data indicate that allergies may be associated with reduced risks for several cancers; however, to date, only a few studies have examined the associations between allergies and gastric cancer. This study aimed to examine the associations between allergies and gastric cancer using a large population-based dataset.

Methods: This cross-sectional study obtained data from the Korea National Health and Nutrition Examination Survey between 2010 and 2014, involving a total of 24,089 participants. The associations between allergies and gastric cancer were analyzed using univariable and multivariable logistic regression analyses with complex sampling, while adjusting for confounding factors that included age, sex, body mass index, smoking status, alcohol intake, and level of education.

Results: Multivariable logistic regression analyses that were adjusted for the potential confounders determined that a history of allergic diseases tended to be associated with reduced risk of gastric cancer; however, this relationship was not statistically significant (any allergy: odds ratio [OR], 0.62; 95% confidence interval [CI], 0.34-1.12; atopic dermatitis: OR, 0.34; 95% CI, 0.50-1.72; allergic rhinitis: OR, 0.71; 95% CI, 0.34-1.46; asthma: OR, 0.44; 95% CI, 0.15-1.29). Multivariable analysis showed that a history of atopic dermatitis was associated with reduced risk of gastric cancer in men (OR, 0.16; 95% CI, 0.03-0.75).

Conclusions: This findings of this study suggest that individuals with allergies tend to have a reduced risk of gastric cancer, without a statistically significant association. Furthermore, atopic dermatitis was associated with reduced risk of gastric cancer, particularly in men. (Korean J Gastroenterol 2018;71:38-44)

Key Words: Gastric cancer; Atopic dermatitis; Allergies

INTRODUCTION

Gastric cancer accounts for 6.8% of all cancers. Globally, it is the fifth most common malignancy worldwide and the third leading cause of cancer-related mortality.¹ Gastric can-

cer is a multifactorial disease, and a variety of factors are involved in its development. Although *Helicobacter pylori* (*H. pylori*) infection is a well-known risk factor for gastric cancer, only a small proportion of infected individuals develop gastric cancer.² Therefore, it is likely that other factors influence the

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development of gastric cancer.

In the context of the participation of the immune system in oncogenesis,^{3,4} the findings from several studies have suggested that the dysregulation of immune function in patients with histories of allergies may be associated with modified risks for cancer.⁵⁻⁹ Over the past few decades, substantial amounts of epidemiologic and clinical data have described the associations between allergic diseases and cancer.⁵⁻¹² However, to the best of our knowledge, only a few epidemiologic studies have examined the associations between allergic diseases and gastric cancer. One cohort study that analyzed subjects selected from a hospital discharge registry, reported that asthma was associated with reduced gastric cancer risk;¹³ however, this study included patients with only severe asthma, and the number of gastric cancer cases was small. Another study's findings showed that the risk of gastric cancer was reduced in patients who were hospitalized with severe asthma, and that patients with asthma who were treated as outpatients showed conflicting results.¹⁴ Inconsistent findings generated by these studies may be explained by the differences in the studies' methodologies, i.e. different study populations, limited sample sizes, and/or inadequate consideration of potential confounders.

To further elucidate the associations between allergic diseases and risk of gastric cancer, we investigated gastric cancer risk in Korean patients with allergic diseases using a large nationwide population-based dataset.

SUBJECTS AND METHODS

1. Study population and data source

We performed a cross-sectional study that utilized the data from the Korea National Health and Nutrition Examination Survey (KNHANES), which represents the entire South Korean population. KNHANES is a national surveillance system that enables the Korea Centers for Disease Control and Prevention to evaluate the health and nutritional statuses of the Korean people. This national cross-sectional survey's target population comprises institutionalized Korean civilians, including approximately 10,000 participants each year. KNHANES collects a range of information from three components, namely, health interviews, health examinations, and nutrition surveys. Health interviews and health examinations are performed by trained medical staff and interviewers; nu-

trition surveys are performed by experienced dietitians. These surveys collect detailed information regarding the participants' demographics, anthropometric measures, socioeconomic status, health behaviors, medical histories, health-care utilization, biochemical laboratory test results, radiography test results, food intakes, and dietary behaviors.¹⁵ A stratified multistage clustered probability sampling design was used for this study, and the data were selected from sampling units based on age, sex, and geographic area. Statisticians performed post-stratification weighting and accounted for the non-response rates and the extreme values.

Data from the KNHANES that were conducted in 2010, 2011, 2012, 2013, and 2014 were analyzed in this study. A total of 41,102 participants were identified between 2010 and 2014. We excluded participants who were <30 years of age ($n=13,214$), those who did not respond to the questionnaire regarding their history of gastric cancer ($n=2,964$), participants with incomplete data relating to their height, weight, smoking status, alcohol intake, and educational level, as well as histories of allergic diseases, including atopic dermatitis, allergic rhinitis, and asthma ($n=834$). Finally, 24,089 participants (10,178 men and 13,911 women) were included in this study. This study was approved by the Korea Centers for Disease Control and Prevention's Institutional Review Board (2010-02CON-21-C, 2011-02CON-06-C, 2012-01-EXP-01-2C, 2013-07CON-03-4C, and 2013-12EXP-03-5C). Before the commencement of the surveys, written informed consent was obtained from all of participants.

2. Data collection

Health interviews and health examinations were conducted at mobile examination centers by trained staff members, including physicians, medical technicians, and health interviewers. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meters. Educational levels were stratified as low (elementary school or lower), medium (middle or high school), and high (college or higher). Income levels were stratified into lower, middle, and higher tertiles. Smoking was defined as an individual who had smoked five or more packs in a lifetime, and a participant's smoking status was categorized as never smoker, past smoker, or current smoker. Alcohol consumption was categorized as less than one drink a month,

one-to-four drinks a month, or two or more drinks a week.

Participants were asked about their histories of allergic diseases, including atopic dermatitis, allergic rhinitis, and asthma, in the following manner: “Have you ever been diagnosed as having atopic dermatitis, allergic rhinitis, or asthma by a doctor?”, and the participants were recorded as having a positive history if they answered “yes” to this question. Participants were then asked about their age at diagnosis and their treatment histories with respect to the allergic diseases. Participants were also asked about their histories of gastric cancer, in the following manner: “Have you ever been diagnosed as having gastric cancer by a doctor?”, and the participants were recorded as having a positive history if they answered “yes” to this question. Participants were then asked about their age at diagnosis and their treatment histories in relation to gastric cancer. We divided the participants into two groups: the gastric cancer group and the control group, which comprised those with no history of gastric cancer.

3. Statistical analysis

Continuous variables were reported as the means (standard deviations), and categorical variables were presented as percentages. The groups were compared with respect to continuous variables using t-tests, and they were compared with

respect to categorical variables using chi-squared tests. We used logistic regression models to estimate the adjusted odds ratios (ORs) and to determine the 95% confidence intervals (CIs) for the associations between allergic diseases and gastric cancer. The multivariable models were adjusted for age, sex, BMI, smoking status (never vs. past vs. current smoker), alcohol intake (mild vs. modest vs. heavy intake), and the educational level (elementary school or less vs. middle or high school vs. college or higher). All results from univariable and multivariable logistic regression analyses are presented as weighted values. p-values of less than 0.05 were considered statistically significant; statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

1. Clinical and demographic characteristics

Of the 24,089 participants, 10,178 (48.4%) were men and 13,911 (51.6%) were women; the mean age was 50.6 years. The overall prevalence of gastric cancer was 0.9% (n=212). The characteristics of participants with gastric cancer and control individuals are shown in Table 1. The proportion of men was significantly higher in the gastric cancer group compared with that in the control group. The control group con-

Table 1. Baseline Characteristics of Participants according to the Presence of Gastric Cancer

Variables	All (n=24,089)	Gastric cancer cases (n=212)	Controls (n=23,877)	p-value
Age (years)	50.6±0.2	63.9±1.0	50.5±0.2	<0.001
Sex				0.008
Male	10,178 (48.4)	127 (59.0)	10,051 (48.3)	
Female	13,911 (51.6)	85 (41.0)	13,826 (51.7)	
Smoking status				<0.001
Never	14,289 (54.1)	92 (44.3)	14,197 (54.1)	
Former	5,046 (21.0)	95 (43.2)	4,951 (20.9)	
Current	4,754 (24.9)	25 (12.5)	4,729 (25.0)	
Alcohol consumption				<0.001
Less than once a month	7,526 (26.7)	114 (47.7)	7,412 (26.5)	
One to four times a month	12,155 (51.4)	71 (35.8)	12,084 (51.5)	
Two or more times a week	4,408 (21.9)	27 (16.5)	4,381 (21.9)	
Education level				<0.001
Low	6,824 (22.2)	100 (43.4)	6,724 (22.1)	
Medium	10,313 (45.8)	81 (39.5)	10,232 (45.8)	
High	6,952 (32.0)	31 (17.1)	6,921 (32.1)	
Income level				0.361
1Q	5,822 (24.0)	50 (23.3)	5,772 (24.0)	
2Q	6,084 (24.6)	49 (21.7)	6,035 (24.6)	
3Q	6,083 (25.7)	62 (30.8)	6,021 (25.7)	
4Q	6,100 (25.7)	51 (24.2)	6,049 (25.7)	
BMI (kg/m ²)	23.93±0.03	21.90±0.22	23.95±0.03	<0.001

Values are expressed as n (%) or mean±standard deviation.

1Q, first quartile; 2Q, second quartile; 3Q, third quartile; 4Q, fourth quartile; BMI, body mass index.

tained significantly higher proportions of individuals who were current smokers, had high alcohol consumptions, and had high levels of education compared with those in the gastric cancer group. The mean age in the gastric cancer group was higher than that in the control group. Mean BMI was higher in the control group than that in the gastric cancer group. We compared the participants' characteristics in relation to their histories of atopic disease (Table 2). Of the 24,089 participants, 371 (1.5%) participants had histories of atopic dermatitis, 777 (3.2%) had histories of asthma, 2,809 (11.7%) had histories of allergic rhinitis, and 3,656 (15.2%) had histories of any allergic disease. The mean age of participants in the atopic dermatitis group was lower than that in the control group. The proportion of participants with a high level of education was higher in the atopic dermatitis group compared with that in the control group. The smoking status, alcohol intakes, mean BMI, and income levels did not differ between the atopic dermatitis and the control groups.

2. Associations between atopic diseases and gastric cancer

The multivariable logistic regression analyses showed that old age (OR, 1.05; 95% CI, 1.04-1.07; $p<0.001$) and being male (OR, 1.71; 95% CI, 1.10-2.66; $p=0.017$) were asso-

ciated with increased risk of gastric cancer. A lower BMI was associated with a protective effect with respect to the risk of gastric cancer (OR, 0.80; 95% CI, 0.76-0.85; $p<0.001$) (Table 3). A history of allergic diseases showed a tendency to be associated with reduced risk of gastric cancer, which was an association without statistical significance.

We conducted subgroup analyses that were based on sex. Univariable regression analysis showed that history of atopic dermatitis (OR, 0.12; 95% CI, 0.02-0.55) and history of any allergic disease (OR, 0.46; 95% CI, 0.22-0.97) were associated with reduced risks of gastric cancer in men (Table 4). According to multivariable analysis, history of any allergic disease was not associated with reduced risk of gastric cancer (OR, 0.52; 95% CI, 0.25-1.07) and atopic dermatitis was significantly associated with reduced risk of gastric cancer (OR, 0.16; 95% CI, 0.03-0.75) in men. None of the specific allergic diseases analyzed nor any allergic disease were associated with reduced risk of gastric cancer in women (atopic dermatitis: OR, 0.89; 95% CI, 0.12-6.55; allergic rhinitis: OR, 0.93; 95% CI, 0.32-2.70; asthma: OR, 0.43; 95% CI, 0.06-3.21; any allergic disease: OR, 0.79; 95% CI, 0.32-1.99) (Table 5). Furthermore, we conducted subgroup analyses based on treatment history of allergic disease. There was no difference

Table 2. Baseline Characteristics of Participants according to History of Atopic Dermatitis

	All (n=24,089)	Atopic dermatitis cases (n=371)	Controls (n=23,718)	p-value
Age (years)	50.6±0.2	44.5±0.7	50.7±0.2	<0.001
Sex				0.667
Male	10,178 (48.4)	149 (49.7)	10,029 (48.3)	
Female	13,911 (51.6)	222 (50.3)	13,689 (51.7)	
Smoking status				0.229
Never	14,289 (54.1)	214 (52.7)	14,075 (54.1)	
Former	5,046 (21.0)	68 (18.2)	4,978 (21.1)	
Current	4,754 (24.9)	89 (29.1)	4,665 (24.8)	
Alcohol consumption				0.788
Less than once a month,	7,526 (26.7)	114 (47.7)	7,412 (26.5)	
One to four times a month	12,155 (51.4)	188 (35.8)	12,084 (51.5)	
Two or more times a week	4,408 (21.9)	69 (20.9)	4,381 (21.9)	
Education level				<0.001
Low	6,824 (22.2)	69 (14.7)	6,755 (22.4)	
Medium	10,313 (45.8)	138 (36.7)	10,175 (45.9)	
High	6,952 (32.0)	164 (48.6)	6,788 (31.7)	
Income level				0.976
1Q	5,822 (24.0)	92 (24.3)	5,730 (24.0)	
2Q	6,084 (24.6)	89 (24.5)	5,995 (24.6)	
3Q	6,083 (25.7)	89 (24.5)	5,994 (25.7)	
4Q	6,100 (25.7)	101 (26.7)	5,999 (25.7)	
BMI (kg/m ²)	23.93±0.03	23.86±0.21	23.93±0.03	0.733

Values are expressed as n (%) or mean±standard deviation.

1Q, first quartile; 2Q, second quartile; 3Q, third quartile; 4Q, fourth quartile; BMI, body mass index.

Table 3. Risk of Gastric Cancer in Univariable and Multivariable Analyses

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.07 (1.06-1.08)	<0.001	1.05 (1.04-1.07)	<0.001
Male sex	1.54 (1.11-2.13)	0.009	1.71 (1.10-2.66)	0.017
BMI	0.80 (0.76-0.85)	<0.001	0.80 (0.76-0.85)	<0.001
Current smoking	0.61 (0.34-1.10)	0.103	0.61 (0.30-1.23)	0.166
Modest alcohol intake	0.42 (0.25-0.71)	0.003	0.62 (0.35-1.10)	0.1
High education level	0.27 (0.17-0.44)	<0.001	0.93 (0.50-1.72)	0.813
History of atopic dermatitis	0.26 (0.06-1.14)	0.074	0.34 (0.08-1.63)	0.184
History of allergic rhinitis	0.46 (0.22-0.93)	0.031	0.71 (0.34-1.46)	0.348
History of asthma	0.62 (0.22-1.81)	0.384	0.44 (0.15-1.29)	0.134
History of any allergies	0.49 (0.27-0.87)	0.015	0.62 (0.34-1.12)	0.114

OR±95% CI were assessed by logistic regression model.

OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 4. Association between Atopic Diseases and Gastric Cancer in Men

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
History of atopic dermatitis	0.12 (0.02-0.55)	0.007	0.16 (0.03-0.75)	0.02
History of allergic rhinitis	0.44 (0.17-1.09)	0.077	0.57 (0.23-1.42)	0.227
History of asthma	0.74 (0.26-2.14)	0.581	0.45 (0.15-1.34)	0.153
History of any allergies	0.46 (0.22-0.97)	0.04	0.52 (0.25-1.07)	0.076

OR±95% CI were assessed by logistic regression model. Multivariable analysis adjusted for age, body mass index, smoking status, alcohol intake, and education level.

OR, odds ratio; CI, confidence interval.

Table 5. Association between Atopic Diseases and Gastric Cancer in Women

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
History of atopic dermatitis	0.47 (0.06-3.39)	0.449	0.89 (0.12-6.55)	0.909
History of allergic rhinitis	0.51 (0.18-1.48)	0.215	0.93 (0.32-2.70)	0.887
History of asthma	0.58 (0.08-4.19)	0.585	0.43 (0.06-3.21)	0.411
History of any allergies	0.55 (0.22-1.34)	0.187	0.79 (0.32-1.99)	0.628

OR±95% CI were assessed by logistic regression model. Multivariable analysis adjusted for age, body mass index, smoking status, alcohol intake, and education level.

OR, odd ratio; CI, confidence interval.

of the risk for gastric cancer according to the treatment history of allergic diseases (p-value: overall 0.831, men 0.712, women 0.414).

DISCUSSION

In this large cross-sectional study, which used the data from KNHANES, we investigated the associations between risk of gastric cancer and allergic diseases, including atopic dermatitis, asthma, and allergic rhinitis, as well as any allergic disease. Specific allergic diseases and any allergic disease had tendencies to be associated with reduced risks of gastric cancer, but without statistically significant association. Our findings suggest that atopic dermatitis was asso-

ciated with reduced risk of gastric cancer, at least in men.

The effect of allergies on malignancy remains controversial. Previous epidemiologic studies have examined the associations between allergies and different types of cancers, and their findings have demonstrated that allergies either protect against certain types of cancer or that they are risk factors for several other types of cancer. With a few exceptions, the findings from previous studies have indicated an increased risk of lung cancer in patients with asthma.¹⁶⁻¹⁹ Chronic inflammation may explain the association between increased risk of lung cancer and asthma. Previous studies that examined the associations between allergies and pancreatic cancer have generated varying results. The findings from one meta-analysis showed that there was no associa-

tion between asthma and risk of pancreatic cancer,²⁰ while the results from another, more recent, meta-analysis showed consistent inverse associations between asthma and risk of pancreatic cancer as well as between nasal allergies and risk of pancreatic cancer.⁶ The findings from a recent cohort study, which used a nationwide database, revealed that the associations between allergies and cancer are site specific, and that patients with more than one allergic disease had lower cancer risks compared with those with only one allergic disease.⁸

Moreover, conflicting results were found between several studies examining the associations between allergies and gastric cancer risk. The results from a Swedish study showed that a history of asthma was protective against gastric cancer.¹³ The findings from a Finnish study also demonstrated that a history of asthma was associated with reduced risk of gastric cancer.²¹ However, the results from a large cohort study, which used a national inpatient register, showed that there was no relationship between atopic dermatitis and incidence of gastric cancer.²² The inconsistency of these results can be attributed to the following: limited sample sizes, differences in the study populations, and heterogeneous and often incomplete control of confounders. The findings from studies demonstrating positive associations involved patients who were hospitalized with severe asthma, and the number of gastric cancer cases was relatively small. The results from studies that failed to show any relationship between atopic dermatitis and incidence of gastric cancer were strengthened by the large sample size, which was derived from a nationwide population-based dataset; however, these studies did not control for confounding factors, i.e. smoking status, alcohol intakes, body mass index, and socioeconomic factors.

In this study, risk of gastric cancer was reduced in men with atopic disease, but not in women. The overall prevalence of gastric cancer was low at 0.9% in this study population. The proportion of men was significantly higher in the gastric cancer group (men 59.0% vs. women 41.0%). The difference in the risk of gastric cancer between men and women is probably due to the small sample size of gastric cancer in women; hence, illustrating a lack of statistical power. However, sex-specified subgroup analysis showed no heterogeneity of risk of gastric cancer from atopic disease, with no significant interactions by sex (p for interaction, 0.103).

The mechanisms underlying the associations between al-

lergies and gastric cancer risk remain largely unknown. Allergy signifies an enhanced immune system, which increases tumor surveillance, leading to the identification and subsequent elimination of tumor cells.²³⁻²⁶ Allergic diseases have been associated with elevated eosinophil and immunoglobulin E levels.²⁷ There is mounting evidence that suggests that eosinophils and immunoglobulin E may play important roles in the protection against cancer development through activities associated with tumor cell cytotoxicity and tumor suppression.²⁸⁻³⁰ Conversely, chronic inflammation increases the susceptibility of the affected organs to cancer, which may explain higher risks of lung cancer among patients with asthma and nasal cavity cancer among patients with allergic rhinitis.^{8,17,31} Another explanation for the association between allergic disease and gastric cancer could be the inverse relationship between allergic disease and *H. pylori* infection, which is the most important risk factor for gastric cancer.³²

The results from this study should be interpreted in the context of the study's limitations. First, *H. pylori* infection is a strong and the most important risk factor associated with gastric cancer. Since data describing *H. pylori* infections were lacking, it was not possible to evaluate an association between allergic disease and gastric cancer risk that was independent of *H. pylori* infection. Second, although we considered several important confounding factors in the multivariable analysis, the possibility of the existence of residual confounding factors that were not considered in this study cannot be excluded. Third, the diagnoses of allergic disease and gastric cancer were based on a self-reported questionnaire. To reduce misclassification, the health survey was conducted by trained staff members. Finally, the study's cross-sectional design caused difficulties with respect to inferring causations based on the observed associations; therefore, our results should be interpreted with caution.

Our findings suggest that certain allergies are associated with reduced risk of gastric cancer. The findings from this study showed that while atopic dermatitis in men was associated with reduced risk of gastric cancer compared with the general population, other allergic diseases, including asthma and allergic rhinitis, were not associated with reduced risks of gastric cancer. Conducting longitudinal cohort study that evaluate certain allergic diseases in the context of the *H. pylori* status and subsequent gastric cancer risk will help

to better elucidate the associations between allergic diseases and gastric cancer.

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