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Original Article

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Association of Soy Foods With Gastric Cancer Considering *Helicobacter pylori*: A Multi-Center Case-Control Study

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ABSTRACT

Purpose: This study aims to explore the relationship between soy food consumption and gastric cancer (GC) risk, accounting for *Helicobacter pylori* infection status.
Materials and Methods: We analyzed data from patients with GC and healthy individuals prospectively enrolled by 6 hospitals between 2016 and 2018. Dietary intake was evaluated using questionnaires that categorized seven dietary habits and 19 food groups. Multivariate logistic regression models were applied to examine associations. Model I adjusted for various epidemiological factors, while Model II included further adjustments for *H. pylori* infection. Primary exposures examined were consumption frequencies of nonfermented, unsalted soy foods (soybean/tofu) and fermented, salty soy foods (soybean paste stew).
Results: A total of 5,535 participants were included, with 1,629 diagnosed with GC. In Model I, the frequency of soybean/tofu consumption was inversely related to GC risk; adjusted odd ratios (aORs) were 0.62 (95% confidence interval [CI], 0.48–0.8), 0.38 (95% CI, 0.3–0.49), 0.42 (95% CI, 0.33–0.53), and 0.33 (95% CI, 0.27–0.42) for 1 time/week, 2 times/week, 3 times/week, and ≥4 times/week. Consumption of 2 servings/week of soybean paste stew showed the lowest GC association, forming a V-shaped curve. Both low (aOR, 4.03; 95% CI, 3.09–5.26) and high serving frequencies of soybean paste stew (aOR, 2.23; 95% CI, 1.76–2.82) were associated with GC. The association between soy foods and GC in Model II was similar to that in Model I. The soy food-GC associations were consistent across sexes in Model I. Nonetheless, the positive correlation between frequent consumption of soybean paste stew (≥5 times/week) and GC was more pronounced in women (aOR, 7.58; 95% CI, 3.20–17.99) compared to men (aOR, 3.03; 95% CI, 1.61–5.88) in Model II. Subgroup analyses by *H. pylori* status and salty diet revealed a consistent inverse relationship between soybean/tofu and GC risk. In contrast, soybean paste stew showed a V-shaped relationship in *H. pylori*-positive or salty diet groups and no significant association in the *H. pylori*-negative group.
Conclusions: Soybean/tofu intake is consistently associated with a decreased risk of GC. However, the relationship between soybean paste stew consumption and GC risk varies, depending on *H. pylori* infection status and dietary salt intake.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Conceptualization: P.J.H., N.B.H., K.S.H., P.D.J., Y.H.K., L.H.J.; Data curation: P.J.H., K.J., C.Y.S., L.S., P.S., C.H., K.Y., S.E.; Formal analysis: P.J.H., N.B.H.; Funding acquisition: Y.H.K.; Investigation: P.J.H., L.S., P.S., C.H., K.Y., S.E.; Methodology: P.J.H., N.B.H., L.S., P.S., C.H., K.Y., S.E., K.S.H., P.D.J., Y.H.K., L.H.J.; Project administration: K.S.H., P.D.J., Y.H.K., L.H.J.; Resources: N.B.H., K.S.H., P.D.J., Y.H.K., L.H.J.; Software: N.B.H.; Supervision: K.S.H., P.D.J., Y.H.K., L.H.J.; Validation: P.J.H., N.B.H., K.S.H., P.D.J., Y.H.K., L.H.J.; Visualization: P.J.H., Y.H.K., L.H.J.; Writing - original draft: P.J.H.,; Writing - review & editing: P.J.H., N.B.H., K.J., C.Y.S., L.S., P.S., C.H., K.Y., S.E., K.S.H., P.D.J., Y.H.K., L.H.J.

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Keywords: Gastric cancer; Soy beans; *Helicobacter pylori*

INTRODUCTION

Although the incidence and mortality rates of gastric cancer (GC) have declined over several decades, GC remains the most prevalent cancer in Korea and the third leading cause of cancer-related deaths worldwide [1]. Various environmental factors, including lifestyle choices, dietary habits, and *Helicobacter pylori* infection, influence the risk of developing GC. The declining prevalence of *H. pylori* infection is primarily responsible for the reduced incidence of GC, with improvements in dietary habits also contributing. A recent umbrella review suggests that GC is associated with the consumption of salted fish and is weakly linked to salted foods, salt, processed meats, and pickled vegetables [2]. Additionally, high fruit and vegetable intakes are protective [3], while consumption of soybean and tofu may offer further protective benefits against GC. In contrast, soybean paste stew may increase GC risk [4]. The beneficial effects of soy on cancer risk are believed to be due to its antioxidant and anti-inflammatory properties. Soy and soy isoflavones may reduce oxidative stress by activating nuclear factor erythroid 2-related factor 2 (Nrf2) [5,6] and by modulating the expression of genes involved in cell proliferation and apoptosis [7]. Moreover, soy isoflavones are thought to inhibit the expression of inflammatory mediators [8]. However, most previous studies exploring the diet-GC relationship have not adjusted for *H. pylori* status [9-12], and those that have typically involved only a limited number of participants [13,14]. Unlike earlier studies that relied on threshold-based dietary patterns and food groups, recent research indicates a nonlinear association between contributing factors and cancer risk, exemplified by the nonlinear relationship reported between body mass index (BMI) and cancer risk [15].

In this study, we explored the relationship between soybean/tofu (non-fermented, unsalted soy foods) and soybean paste stew (fermented, salted soy foods) and GC, taking into account epidemiological factors and *H. pylori* status, using data from a large-scale, prospective multicenter registry.

MATERIALS AND METHODS

Study population

This study was a multicenter case-control study. Patients with GC and healthy controls were prospectively enrolled at five university hospitals and one general hospital from October 2016 through December 2018 (**Fig. 1A**). Patients with a prior diagnosis of GC were excluded. Both control subjects and patients with GC underwent endoscopy and serum *H. pylori* immunoglobulin G (IgG) testing. Additionally, all controls received basic laboratory tests. Individuals with active peptic ulcers or gastric neoplastic lesions, such as GC, lymphoma, or gastric adenoma, were excluded from the screening process.

The study adhered to the Declaration of Helsinki, received ethical approval from the Institutional Review Board of Kyungpook National University Chilgok Hospital (KNUMC 2016-07-014), and all participants provided written informed consent. The study is registered at ClinicalTrials.gov (NCT03046745).

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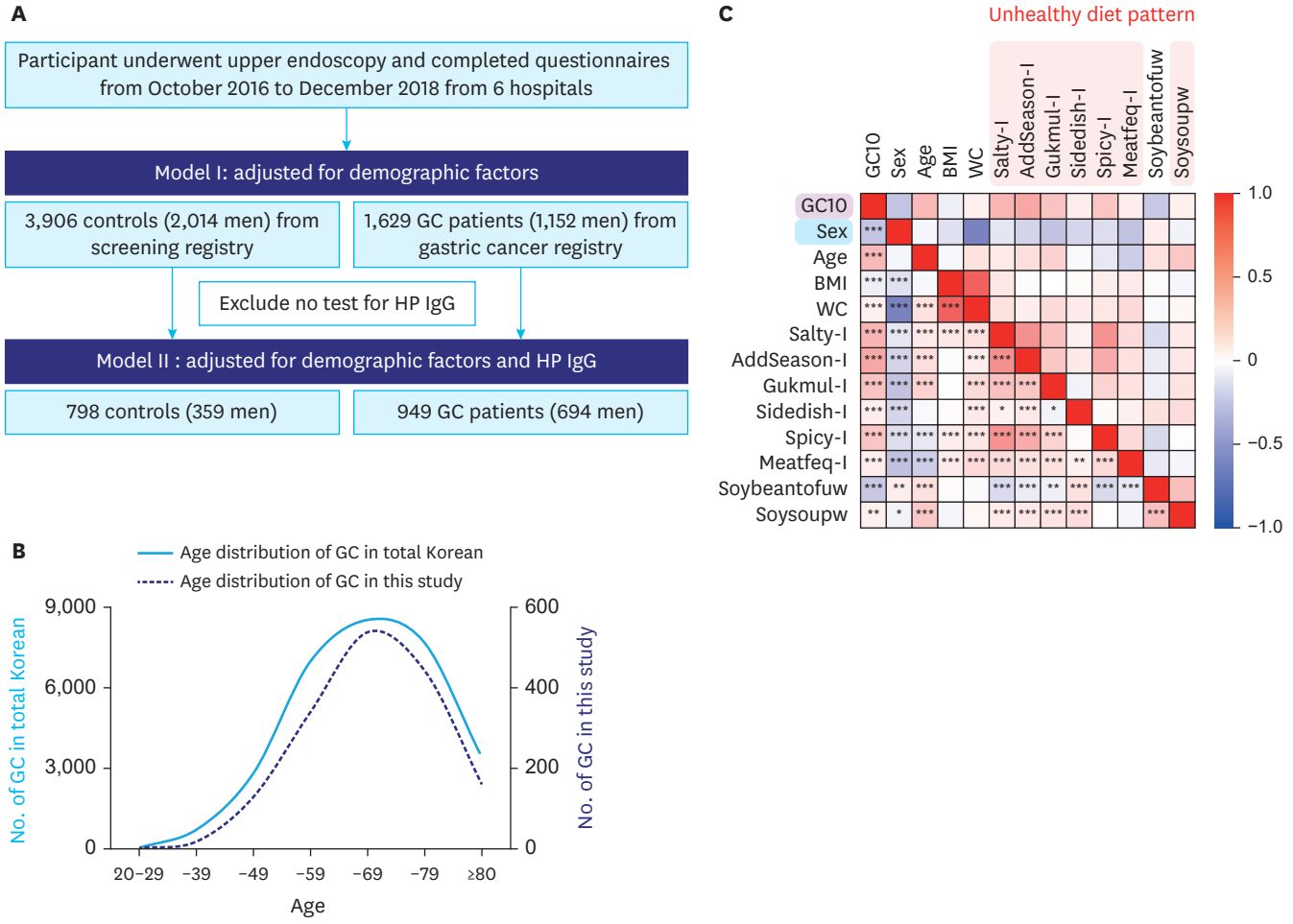

Fig. 1. Study overview and correlation matrix.
(A) Study Model: The gastric cancer registry comprises newly diagnosed patients with gastric cancer from 6 hospitals. The health screening registry includes subjects from the same hospitals who underwent upper endoscopy and were confirmed to be negative for gastric cancer. Analyses were adjusted for epidemiologic factors (Model I) and further adjusted for *H. pylori* status (Model II). (B) Age Distribution: Comparison of age distribution of patients with gastric cancer in the total Korean population versus this study's population. (C) Correlation Matrix: Illustrates the relationships between gastric cancer, dietary patterns, and soy food intake. Pearson correlation coefficients (R) and P-values are provided in **Supplementary Table 2**.
HP = *Helicobacter pylori*; IgG = immunoglobulin G; GC = gastric cancer; BMI = body mass index; WC = waist circumference; AddSeason-I = additional seasoning; Gukmul-I = drinking broth; Meatfreq-I = meat consumption; Salty-I = salty food intake; Spicy-I = spicy food intake; Soybeantofuw = soybean and tofu intake; Soysoupw = soy paste stew intake.
Significance levels are indicated by *P<0.05, **P<0.01, ***P<0.001.

Epidemiologic and dietary questionnaire

Participants were interviewed by well-trained clinical research coordinators for approximately 25–30 minutes and completed validated questionnaires addressing epidemiologic and dietary factors. BMI (kg/m^2) was calculated from weight (kg) and height (m).

The epidemiologic questionnaire gathered data on various factors including age, sex, obesity index, education level, occupation, income, chronic diseases, medication use, previous cancer history, surgical history, GC screening, smoking habits, alcohol consumption, *H. pylori* infection and eradication history, physical activity, general family information, family history of GC, and gynecological status for female participants (**Supplementary Table 1**). The dietary questionnaires evaluated seven dietary habits and nineteen food groups. Dietary habits assessed included the average daily frequency of eating out, salty food intake, use of additional seasonings, broth consumption, frequency of having more than three side dishes, preference

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for spicy food, and meat consumption (**Supplementary Table 1**). Participants also reported the average weekly consumption frequency of each food group over the past year, encompassing fruit, vegetables, red meat, fish, white meat, processed meat, soybean/tofu, seeds/nuts, eggs, noodles/bread, salt-preserved fish, salt-preserved crab, salt-preserved vegetables, instant foods, soybean paste stew, coffee, decaffeinated coffee, tea, and ginseng beverages.

Endoscopy and serologic test

Upper endoscopy was performed using flexible endoscopes after patients had fasted overnight and were sedated with midazolam and/or propofol. *H. pylori* IgG levels were determined through a chemiluminescent immunoassay (IMMULITE® 2000 *H. pylori* IgG; Siemens, Manchester, UK). Results were classified as negative if the IgG value was below 0.9, positive if above 1.10, and indeterminate if between 0.9 and 1.09. Approximately 5% of cases were equivocal for *H. pylori* IgG and were categorized as negative for analytical purposes.

Age and sex distribution of GC in the total Korean population

To assess the age and sex distribution patterns of our study cohort relative to the total Korean population, we used data on GC age and sex distribution from the Korean Statistical Information Service (http://kosis.kr/index/index.do). Males constituted 49.3% of the total Korean population according to 2016–2018 national statistics. The crude incidence of GC in males was about twice that of females, with 20,509 male cases compared to 9,995 female cases in 2016. The age distribution of newly diagnosed GC cases was similar between the total Korean population and our study cohort (**Fig. 1B**).

Statistical analysis

Analyses were conducted on the overall sample and an age- and sex-matched cohort (1:1 matching). Data are presented as mean ± standard deviation or number (percentage). Pearson's χ^2 test was used for categorical variables, while the independent t-test was applied to continuous variables to compare differences in epidemiologic factors and dietary patterns between control subjects and patients with GC. The correlations between GC and age, BMI, and dietary factors were examined using Pearson's correlation test.

Logistic regression models were utilized to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the association between soybean food intake and GC risk. Fractional polynomial regression was employed to quantify estimates of GC risk concerning dietary soy foods and evaluate linearity. Additionally, we calculated the ratio of GC by serving frequency of soybean/tofu and soybean paste stew, categorizing serving frequencies into five groups. The group with the lowest or highest GC rate served as the reference in each dietary category to examine the association. Unconditional logistic regression models were applied for the unmatched group and both unconditional and conditional logistic regression models for the matched group. In Model I, potential confounding variables—age, sex, BMI, smoking status, diabetes, hypertension, cerebrovascular disease, physical activity, family history of GC, and occupation—were adjusted for in the multivariable analysis. Model II included adjustments for *H. pylori* IgG in addition to the variables in Model I. All adjusted analyses simultaneously considered soybean/tofu, soybean paste stew, and overall dietary habits. Interaction analysis (joint test) was performed to examine the relationships between soy food intake and potential cofactors (*H. pylori* status and salty diet) in relation to GC risk, along with a subgroup analysis. Pearson correlation analysis and the construction of matrix figures were conducted using GraphPad Prism (version 10.0; GraphPad Software, Boston, MA, USA).

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All other statistical analyses were performed using Stata 15 (StataCorp, College Station, TX, USA). All tests were two-sided, with a P-value of <0.05 considered statistically significant.

RESULTS

Epidemiologic characteristics

We summarized the epidemiologic characteristics and overall dietary habits of 3,906 control subjects without gastric neoplasms and 1,629 patients with GC (**Table 1**). Patients with GC were older than those in the control group. *H. pylori* IgG positivity was significantly higher among patients with GC (90.1%) compared to controls (43.2%). Overall, seropositivity was higher in men (74.2% [781/1,053]) than in women (60.4% [419/694]), reflecting the higher incidence of GC among men. Among patients with GC, seropositivity rates were similar for men (90.6% [629/694]) and women (88.6% [226/255]). In the control group, seropositivity rates were also comparable between men (42.3% [152/359]) and women (44% [193/439]). The highest rate of GC was observed among primary industry workers, whereas the lowest rate was noted among unemployed individuals and housekeepers. Rates of diabetes, cerebrovascular disease, previous surgical history, current smoker status, former smoking status, and family history of GC were significantly higher in patients with GC than in controls. Overall dietary habits also varied significantly between the control and GC groups. A large proportion of the patients were diagnosed with early-stage GC (n=1,155, 70.9%), while 29.1% (n=474) had advanced GC. The majority of patients had non-cardiac cancer (n=1,567, 96.2%), with only 3.8% (n=62) having cardiac cancer.

Baseline characteristics and overall dietary habits in the age- and sex-matched group are detailed in **Table 1**. The associations between GC and most demographic factors in the matched sample were similar to those observed in the unmatched sample, except for chronic diseases.

Association between soybean/tofu and soybean paste stew and GC

GC was positively correlated with the consumption of soybean paste stew, salty foods, additional seasoning, spicy foods, and meat intake, collectively referred to as an unhealthy diet. Conversely, it was negatively correlated with soybean/tofu intake (**Fig. 1C**, **Supplementary Table 2**). Fractional polynomial regression revealed a non-linear association between soy foods and GC (**Fig. 2A and B**). Unadjusted analyses showed that frequent consumption of soybean/tofu was inversely associated with GC, whereas soybean paste stew displayed a V-shaped association with GC risk (**Table 2**). Adjusted analyses for epidemiologic factors (Model I) confirmed the inverse association of frequent soybean/tofu consumption with GC (**Fig. 2C**). Consuming more than two servings of soybean/tofu per week significantly reduced GC risk, with a plateau effect observed thereafter. This association persisted in the adjusted analysis for epidemiologic factors and *H. pylori* status (Model II). The distribution of soybean/tofu consumption among participants was left-skewed (**Fig. 2D**), with approximately 63% consuming more than 2 servings per week.

However, soybean paste stew demonstrated a V-shaped association with GC risk (**Fig. 2E**). The lowest risk of GC was observed at a consumption level of 2 servings per week. Both low (adjusted odds ratio [aOR], 4.03; 95% CI, 3.09–5.26 for 0 servings/week and aOR, 1.83; 95% CI, 1.48–2.26 for 1 serving/week, compared to 2 servings/week) and high consumption frequencies (aOR, 1.76; 95% CI, 1.46–2.12 for 3–4 servings/week and aOR, 2.23; 95% CI, 1.76–2.82 for ≥5 servings/week) were associated with an increased risk of GC in Model I. Model

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Table 1. Epidemiologic characteristics and overall dietary habits in control participants and patients with gastric cancer

Characteristics	Non-matched			Age- and sex-matched		
	Control (n=3,906)	Gastric cancer (n=1,629)	P-value*	Control (n=1,457)	Gastric cancer (n=1,457)	P-value*
Age (yr)	59.4±11.3	65.2±11.1	<0.001	63.6±10.4	63.6±10.4	1.000
Body mass index (kg/m^2)	23.8±3.1	23.5±3.2	0.003	23.8±3.1	23.6±3.2	0.003
Male sex	2,014 (51.6)	1,152 (70.7)	<0.001	1,016 (69.7)	1,016 (69.7)	1.000
H. pylori IgG	(n=798)	(n=949)	<0.001	(n=299)	(n=860)	<0.001
Negative	453 (56.8)	94 (9.9)		175 (58.5)	84 (9.8)	
Positive	345 (43.2)	855 (90.1)		124 (41.5)	776 (90.2)	
Job			<0.001			<0.001
Profession, office worker	631 (16.2)	293 (18.0)		227 (15.6)	272 (18.7)	
Service	188 (4.8)	114 (7.0)		56 (3.8)	111 (7.6)	
Primary industry, labor	282 (7.2)	324 (19.9)		133 (9.1)	285 (19.6)	
Jobless, housekeeper	2,343 (60.0)	527 (32.4)		873 (59.9)	434 (29.8)	
Others	391 (10.0)	356 (21.8)		148 (10.2)	341 (23.4)	
Missing	71 (1.8)	15 (0.9)		20 (1.4)	14 (1.0)	
Presence of chronic disease						
Any chronic disease	2,041 (53.2)	1,012 (62.7)	<0.001	873 (60.6)	875 (60.6)	0.994
Hypertension	1,002 (25.6)	565 (34.7)	<0.001	437 (30.0)	481 (33.0)	0.079
Diabetes	472 (62.6)	282 (37.4)	<0.001	217 (14.9)	250 (17.2)	0.095
Angina, myocardial infarction	195 (5.0)	73 (4.9)	0.420	104 (7.1)	62 (4.3)	0.001
Cerebrovascular disease	66 (1.7)	59 (3.6)	<0.001	34 (2.3)	48 (3.3)	0.117
Previous operation	1,059 (27.7)	708 (44.6)	<0.001	375 (26.2)	622 (43.8)	<0.001
Smoking status			<0.001			<0.001
Never	2,468 (63.2)	674 (41.4)		774 (53.1)	599 (41.1)	
Past	796 (20.4)	522 (32.0)		410 (28.1)	452 (31)	
Current	548 (14.0)	418 (25.7)		248 (17.0)	392 (26.9)	
Unknown	94 (2.4)	15 (0.9)		25 (1.7)	14 (1.0)	
Presence of family history†	459 (12.0)	334 (20.7)	<0.001	177 (12.3)	307 (21.3)	<0.001
Overall dietary habits						
Salty diet	(n=3,838)	(n=1,608)	<0.0001	(n=1,440)	(n=1,437)	<0.0001
Not salty	839 (21.9)	213 (13.2)		296 (20.6)	185 (12.9)	
Average	2,240 (58.4)	628 (39.1)		850 (59.0)	580 (40.4)	
Salty/very salty	759 (19.8)	767 (47.7)		294 (20.4)	672 (46.8)	
Additional seasoning	(n=3,825)	(n=1,594)	<0.0001	(n=1,432)	(n=1,423)	<0.0001
No	3,621 (94.7)	1,153 (72.3)		1,335 (93.2)	1,040 (73.1)	
Yes	204 (5.3)	441 (27.7)		97 (6.8)	383 (26.9)	
Drinking broth	(n=3,831)	(n=1,612)	<0.0001	(n=1,437)	(n=1,441)	<0.0001
Less than half/Rarely	1,901 (49.6)	526 (32.6)		650 (45.2)	475 (33.0)	
More half	1,165 (30.4)	459 (28.5)		463 (32.2)	411 (28.5)	
Almost	765 (20.0)	627 (38.9)		324 (22.5)	555 (38.5)	
Spicy diet	(n=3,833)	(n=1,612)	<0.0001	(n=1,439)	(n=1,441)	<0.0001
Not spicy	928 (24.2)	280 (17.4)		328 (22.8)	239 (16.6)	
Average	2,164 (56.5)	706 (43.8)		835 (58.0)	633 (43.9)	
Very spicy/spicy	741 (19.3)	626 (38.8)		276 (19.2)	569 (39.5)	
Meat diet	(n=3,833)	(n=1,607)	<0.0001	(n=1,434)	(n=1,436)	<0.0001
Rarely	787 (20.5)	384 (23.9)		279 (19.5)	332 (23.1)	
Average	2,454 (64.0)	813 (50.6)		923 (64.4)	730 (50.8)	
Always/Frequent	592 (15.4)	410 (25.5)		232 (16.2)	374 (26.0)	

Values are presented as mean ± standard deviation or number (%).
*P-values were derived from t-tests or χ^2 tests.
†Family history refers to the presence of a family history of gastric cancer in first-degree relatives.

II showed similar trends, with both low (aOR, 2.94; 95% CI, 1.67–5.26 for 0 servings/week and aOR, 1.85; 95% CI, 1.19–2.86 for 1 serving/week, compared to 2 servings/week) and high consumption frequencies (aOR, 2.22; 95% CI, 1.52–3.23 for 3–4 servings/week and aOR, 4.35; 95% CI, 2.56–7.14 for ≥5 servings/week) being associated with increased GC risk (**Table 2**). The distribution of participants according to soybean paste stew intake approximated a normal distribution, with about 36% of participants falling into the lowest risk category (**Fig. 2F**).

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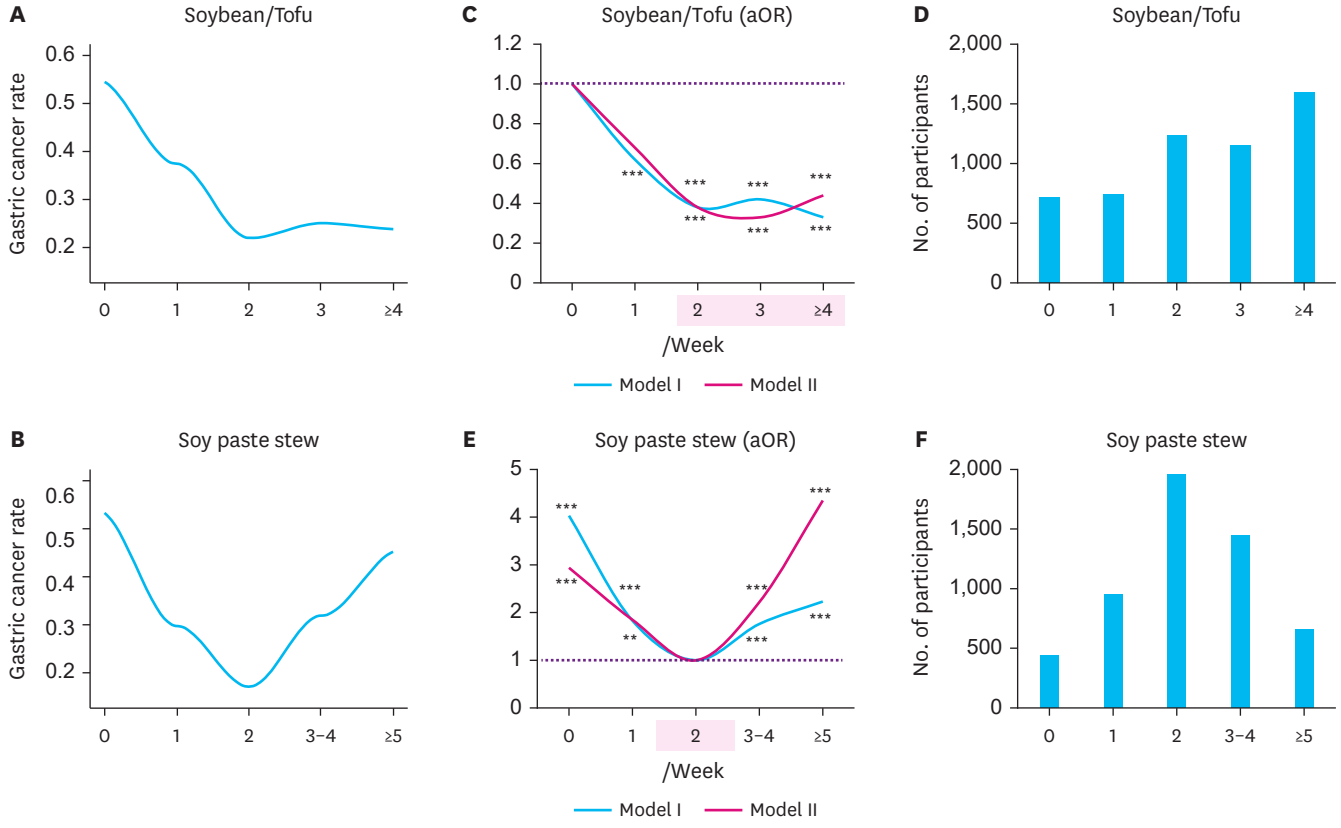

Fig. 2. aORs between dietary factors and gastric cancer.
(A) Fractional Polynomial Analysis: Relationship between soybean/tofu intake and gastric cancer risk. (B) Fractional Polynomial Analysis: Relationship between soybean paste stew intake and gastric cancer risk. (C) aORs: For soybean/tofu intake and gastric cancer risk. (D) Participant Distribution: According to soybean/tofu intake levels. (E) aORs: For soybean paste stew intake and gastric cancer risk. (F) Participant Distribution: According to soybean paste stew intake levels. Model I (blue line) is adjusted for age, sex, diabetes, hypertension, cerebrovascular disease, smoking status, occupation, BMI, family history of gastric cancer, and dietary factors. Model II (red line) includes adjustments for age, sex, *H. pylori* status, diabetes, hypertension, cerebrovascular disease, smoking status, occupation, family history of gastric cancer, and dietary factors. The purple dotted line represents the reference value, while the pink shade indicates a significantly reduced point.
aOR = adjusted odd ratio; BMI = body mass index.
Significance is denoted as **P<0.01, ***P<0.001.

The association patterns between dietary soybean foods and GC in the age- and sex-matched group using the unconditional logistic regression model were consistent with those observed in the overall population (**Supplementary Table 3**). However, the associations appeared stronger in the conditional logistic regression model compared to the unconditional model.

Association between dietary habits, other cofactors, and GC

A diet high in salty foods, additional seasoning, broth, spicy foods, and meat was associated with an increased risk of GC (**Supplementary Table 2**). Adjusted analyses (Model I) showed that a diet high in salt (OR, 1.86; 95% CI, 1.47–2.35), additional seasoning (OR, 2.77; 95% CI, 2.21–3.47), broth consumption (OR, 1.50; 95% CI, 1.26–1.78), and spicy foods (OR, 1.87; 95% CI, 1.50–2.34) were strongly associated with GC. Both frequent (OR, 1.42; 95% CI, 1.18–1.71) and infrequent meat intake (OR, 1.36; 95% CI, 1.14–1.62) correlated with increased GC risk (**Supplementary Table 4**). Factors such as male sex, older age, *H. pylori* IgG positivity, employment in primary industries, current smoking status, presence of cerebrovascular disease, and a family history of GC were also significantly linked to GC (**Supplementary Table 4**). Further adjusted analyses for epidemiologic factors and *H. pylori* IgG (Model II) echoed the results of Model I, but revealed a higher OR for additional seasoning (OR, 7.14;

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Table 2. Association between soybean food groups and gastric cancer

Variables	Control	Cancer	Univariate analysis		Multivariate analysis			
					Model I*		Model II†	
	No. (%)	No. (%)	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Soybean/tofu, serving/week								
0	327 (8.5)	391 (24.2)	1		1		1	
1	464 (12.1)	278 (17.2)	0.50 (0.41–0.62)	<0.001	0.62 (0.48–0.8)	<0.001	0.68 (0.4–1.16)	0.161
2	966 (25.2)	273 (16.9)	0.24 (0.19–0.29)	<0.001	0.38 (0.3–0.49)	<0.001	0.38 (0.23–0.63)	<0.001
3	865 (22.5)	290 (18.0)	0.28 (0.23–0.34)	<0.001	0.42 (0.33–0.53)	<0.001	0.33 (0.2–0.55)	<0.001
≥4	1,215 (31.7)	382 (23.7)	0.26 (0.22–0.32)	<0.001	0.33 (0.27–0.42)	<0.001	0.44 (0.27–0.71)	0.001
P for trend				<0.001				<0.001
Soybean paste stew, serving/week								
0	206 (5.4)	235 (14.6)	5.50 (4.41–6.86)	<0.001	4.03 (3.09–5.26)	<0.001	2.94 (1.67–5.26)	<0.001
1	667 (17.4)	283 (17.5)	2.04 (1.71–2.45)	<0.001	1.83 (1.48–2.26)	<0.001	1.85 (1.19–2.86)	0.006
2	1,620 (42.2)	336 (20.8)	1		1		1	
3–4	984 (25.6)	462 (28.6)	2.26 (1.92–2.66)	<0.001	1.76 (1.46–2.12)	<0.001	2.22 (1.52–3.23)	<0.001
≥5	360 (9.4)	298 (18.5)	3.99 (3.28–4.84)	<0.001	2.23 (1.76–2.82)	<0.001	4.35 (2.56–7.14)	<0.001
P for trend				0.564				0.425

The reference group was defined as the category with the highest or lowest risk.
CI = confidence interval; OR = odds ratio.
*Adjusted for age, sex, diabetes, hypertension, cerebrovascular disease, smoking status, occupation, body mass index, physical activity, family history of gastric cancer, and dietary factors (soybean/tofu, soybean paste stew, salty diet, additional seasoning, broth consumption, spicy diet, and meat intake).
†Additionally adjusted for *H. pylori* infection status in addition to adjustments made in Model I.

95% CI, 3.85–14.29). However, a preference for spicy foods was not associated with GC in Model II.

Subgroup analysis by sex

An unhealthy diet was inversely associated with female sex (**Fig. 1C**). Interaction analysis showed a borderline interaction between soybean/tofu intake and sex concerning GC risk (P=0.06), prompting a subgroup analysis by sex (**Table 3**). In Model I, the associations between soybean/tofu, soybean paste stew, and GC were consistent for both men and women. However, in Model II, the risk of GC associated with a high intake of soybean paste stew was more pronounced in women than in men, with the aOR for consuming ≥5 servings per week being 3.03 (95% CI, 1.61–5.88) in men and 7.58 (95% CI, 3.20–17.99) in women.

In the age- and sex-matched group, the association patterns between dietary soy foods and GC by sex were consistent with those observed in the overall population, except for soybean/tofu (**Supplementary Table 5**). While the inverse association between soybean/tofu and GC was similar in both men and women in Model I, it was notably stronger in men (aOR, 0.12–0.31) and not significant in women (aOR, 0.71–0.83).

Subgroup analysis by salty diet

A significant interaction was found between soybean paste stew intake and a salty diet in relation to GC risk (P-interaction=0.001), leading to a subgroup analysis by salty diet (**Table 3**). In both Models I and II, soybean/tofu consumption was consistently inversely associated with GC in a dose-dependent manner across all salty diet subgroups. However, the relationship between soybean paste stew and GC was more pronounced in the salty/very salty group compared to the not salty/average group. In Model II, the serving frequency of soybean paste stew had no significant association with GC in the not salty/average group.

Subgroup analysis by *H. pylori* status

A subgroup analysis was also conducted based on *H. pylori* status (**Table 4**). The frequency of soybean/tofu consumption showed an inverse association with GC in a dose-dependent

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Table 3. Subgroup analysis by sex and salty diet

Variables	By sex								By salty diet							
	Model I*				Model II†				Model I‡				Model II§			
	Men		Women		Men		Women		Not salty/average		Salty/very salty		Not salty/average		Salty/very salty	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Soybean/tofu, serving/week																
0	1		1		1		1		1		1		1		1	
1	0.64 (0.47–0.88)	0.006	0.56 (0.36–0.86)	0.008	0.51 (0.26–1.02)	0.059	0.99 (0.40–2.46)	0.993	0.45 (0.29–0.69)	0.0003	0.69 (0.5–0.96)	0.029	0.35 (0.12–0.98)	0.046	0.64 (0.32–1.29)	0.2142
2	0.41 (0.30–0.56)	<0.001	0.33 (0.22–0.49)	<0.001	0.31 (0.16–0.6)	0.001	0.44 (0.19–1.00)	0.053	0.33 (0.22–0.49)	<0.0001	0.41 (0.3–0.57)	<0.0001	0.2 (0.07–0.52)	0.0011	0.35 (0.18–0.68)	0.0022
3	0.48 (0.35–0.64)	<0.001	0.34 (0.22–0.51)	<0.001	0.32 (0.17–0.63)	0.001	0.35 (0.15–0.82)	0.015	0.31 (0.21–0.48)	<0.0001	0.5 (0.36–0.68)	<0.0001	0.18 (0.06–0.54)	0.0022	0.30 (0.15–0.57)	0.0003
≥4	0.34 (0.26–0.46)	<0.001	0.31 (0.21–0.45)	<0.001	0.41 (0.21–0.78)	0.007	0.46 (0.21–0.99)	0.049	0.26 (0.18–0.39)	<0.0001	0.34 (0.25–0.46)	<0.0001	0.25 (0.09–0.68)	0.0066	0.31 (0.17–0.58)	0.0002
P-interaction	0.060								0.758							
Soybean paste stew, serving/week																
0	4.12 (2.94–5.77)	<0.001	3.69 (2.36–5.78)	<0.001	3.33 (1.52–7.14)	0.003	2.93 (1.15–7.46)	0.024	2.01 (1.25–3.24)	0.0039	4.34 (3.08–6.12)	<0.0001	1.14 (0.32–4.05)	0.8428	3.99 (1.89–8.45)	0.0003
1	2.16 (1.65–2.83)	<0.001	1.51 (1.06–2.17)	0.024	2.86 (1.59–5.26)	0.001	1.21 (0.58–2.53)	0.615	1.27 (0.87–1.86)	0.2173	2.12 (1.61–2.8)	<0.0001	0.6 (0.22–1.59)	0.3016	2.81 (1.57–5)	0.0005
2	1		1		1		1		1		1		1		1	
3–4	1.57 (1.24–1.98)	<0.001	2.15 (1.55–2.98)	<0.001	2.08 (1.28–3.45)	0.004	2.53 (1.35–4.78)	0.004	1.34 (0.96–1.85)	0.0831	1.89 (1.47–2.42)	<0.0001	0.84 (0.38–1.88)	0.6746	3.2 (1.92–5.35)	<0.0001
≥5	2.01 (1.5–2.69)	<0.001	2.71 (1.82–4.05)	<0.001	3.03 (1.61–5.88)	0.001	7.58 (3.2–17.99)	<0.001	1.14 (0.78–1.66)	0.505	2.87 (2.09–3.92)	<0.0001	1.09 (0.41–2.94)	0.8585	7 (3.48–14.08)	<0.0001
P-interaction	0.283								0.001							

The reference group was defined as the category with the highest or lowest risk.
CI = confidence interval; OR = odds ratio.
*Adjusted for age, diabetes, hypertension, cerebrovascular disease, smoking status, occupation, body mass index, physical activity, family history of gastric cancer, and dietary factors (soybean/tofu, soybean paste stew, salty diet, additional seasoning, broth consumption, spicy diet, and meat intake).
†Additionally adjusted for *H. pylori* infection status in addition to adjustments made in Model I*.
‡Adjusted for age, sex, diabetes, hypertension, cerebrovascular disease, smoking status, occupation, body mass index, physical activity, family history of gastric cancer, and dietary factors (soybean/tofu, soybean paste stew, additional seasoning, broth consumption, spicy diet, and meat intake).
§Additionally adjusted for *H. pylori* infection status in addition to adjustments made in Model I‡.

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Table 4. Subgroup analysis by *H. pylori* status

Variables	*H. pylori* IgG			
	Positive		Negative	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Soybean/tofu, serving/week				
0	1		1	
1	0.38 (0.14–1.01)	0.0516	0.42 (0.11–1.63)	0.2069
2	0.21 (0.08–0.52)	0.0007	0.16 (0.04–0.66)	0.0116
3	0.38 (0.15–0.93)	0.0338	0.23 (0.06–0.89)	0.0325
≥4	0.45 (0.18–1.09)	0.0757	0.12 (0.03–0.44)	0.0016
P-interaction	0.886			
Soybean paste stew, serving/week				
0	7.61 (2.3–25.17)	0.0009	0.86 (0.18–4.00)	0.8418
1	3.21 (1.45–7.13)	0.0041	0.89 (0.26–3.06)	0.849
2	1		1	
3–4	3.5 (1.82–6.75)	0.0002	1.06 (0.35–3.26)	0.9131
≥5	3.26 (1.45–7.34)	0.0044	1.39 (0.36–5.38)	0.6364
P-interaction	0.237			

The reference group was defined as the category with the highest or lowest risk.
CI = confidence interval; OR = odds ratio.
*Adjusted for age, sex, diabetes, hypertension, cerebrovascular disease, smoking status, occupation, body mass index, physical activity, family history of gastric cancer, and dietary factors (soybean/tofu, soybean paste stew, salty diet, additional seasoning, broth consumption, spicy diet, and meat intake).

manner in both *H. pylori*-positive and *H. pylori*-negative groups. In contrast, soybean paste stew exhibited a V-shaped association with GC in the *H. pylori*-positive group but showed no significant association with GC in the *H. pylori*-negative group.

DISCUSSION

In this study, high consumption of soybean/tofu was inversely associated with GC, while soybean paste stew exhibited a nonlinear association. Consuming 2 servings per week of soybean paste stew was associated with the lowest risk of GC. Both lower (0 or 1 serving/week) and higher intake frequencies (≥3 servings/week) were associated with an increased risk of GC. Further adjustments for epidemiologic factors and *H. pylori* status demonstrated a similar pattern to the initial adjusted analyses. However, the adverse association of frequent soybean paste stew consumption with GC was more pronounced in the *H. pylori*-adjusted model (Model II). These associations between soy foods and GC were consistently observed in the age- and sex-matched population. Sex-specific analyses revealed a comparable impact of dietary factors on GC risk for both men and women in Model I; however, the adjusted odds ratio for higher intake of soybean paste stew was greater in women than in men in Model II. These findings were similarly observed in the age- and sex-matched population. Subgroup analyses by salty diet and *H. pylori* status consistently showed a negative association between soybean/tofu consumption and GC in a dose-dependent manner. However, the relationship between the frequency of soybean paste stew intake and GC varied according to *H. pylori* status and salty diet.

The association between soy food consumption and GC varied depending on the type of soy food preparation. We separately analyzed the associations of soybean/tofu (non-fermented, non-salty soy foods) and soybean paste stew (fermented, salty soy foods) with GC. The frequency of soybean/tofu consumption was inversely related to GC risk, showing a protective effect that increased up to two servings per week and plateaued thereafter. Therefore, a minimum of 2 servings per week of soybean/tofu is recommended. While previous studies

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have suggested a protective association between soybean/tofu and GC, studies that have adjusted for both diet and *H. pylori* are exceedingly rare. A meta-analysis reported a negative association for a high intake of non-fermented soy foods (OR, 0.64), whereas a high intake of fermented soy foods was associated with an increased GC risk (OR, 1.22) [16]. Notably, our study found that the lowest GC risk was associated with consuming two servings per week of soybean paste stew. The finding that high consumption of soybean paste stew (≥3 servings per week) was associated with GC aligns with results from a meta-analysis of Korean and Japanese populations [16] and another meta-analysis of 13 prospective studies [17]. A meta-analysis of Asian populations also found a positive association between high intake of fermented soy foods and GC (OR, 1.22; 95% CI, 1.02–1.44), whereas high intake of non-fermented soy foods was linked to a decreased risk of GC (OR, 0.64; 95% CI, 0.54–0.77) [16]. Another meta-analysis demonstrated that total soy food consumption (highest vs. lowest: risk ratio [RR], 0.78; 95% CI, 0.62–0.98) and non-fermented soy food consumption (RR, 0.63; 95% CI, 0.50–0.79) were inversely associated with GC, while high intake of miso soup was positively associated with GC in men (RR, 1.17; 95% CI, 1.02–1.36). In our study, a low intake of soybean paste stew (0–1 servings per week) was also associated with GC, a finding that, to our knowledge, has not been previously reported. The preparation of soybean paste stew often includes spicy and salty ingredients and seasonings, suggesting that the harmful effects of frequent consumption may be due to increased intake of salty and spicy foods. However, because salty and spicy foods encompass many different food groups, we adjusted for overall dietary habits and soy food intake in the present study.

Further adjusted analysis for epidemiologic factors and *H. pylori* IgG (Model II) showed results akin to those observed in Model I, with higher aORs for frequent consumption of soybean paste stew. In the subgroup analysis by sex, the association patterns of soy foods with GC were similar for men and women in Model I. However, in Model II, the association between frequent intake of soybean paste stew and GC was more pronounced in women than in men. The trends in the age- and sex-matched population mirrored those in the unmatched population in Model I, but soybean/tofu did not show statistical significance for GC in women in Model II. Previous subgroup analyses by sex have been reported, but these did not account for *H. pylori* status [18-20]. In men, consuming more than 2 servings of tofu per week was associated with a 37% lower risk of GC compared to less frequent consumption, while soybean paste showed no association with GC [18]. Among men with a BMI of less than 25 kg/m^2, increased consumption of both soybean paste (P for trend=0.02) and tofu (P for trend=0.01) was inversely associated with GC [18]. Japanese studies have indicated a similar direction of effect in both men and women [19,20]. Biological differences between men and women, such as variations in sex hormones, may contribute to the differing effect sizes of soy food consumption on GC risk.

Subgroup analyses by salty diet and *H. pylori* status revealed a consistent dose-dependent inverse association between the frequency of soybean/tofu consumption and GC. In contrast, the associations between soybean paste stew and GC varied according to salty diet and *H. pylori* status. These consistent negative associations between soybean/tofu and GC across various models and subgroup analyses reinforce the inverse associations found in numerous previous studies [13,18,21,22]. Although several studies did not reach statistical significance [19,23], many have demonstrated a negative association between non-fermented soy foods and GC [13,18,21,22]. While subgroup analyses by sex have been previously conducted on this topic [18-20], analyses by salty diet and *H. pylori* status have not been reported.

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In this study, the association between soybean paste stew and GC differed in subgroup analyses by salty diet and *H. pylori* status. Previous studies have reported variable associations: some found a positive association with fermented soy foods [21,22,24-26], others reported no association [27-29], and a few identified a negative association [30]. These inconsistent results may stem from differences in study populations, sample sizes, study designs, and concomitant cofactors. The association was more pronounced in the salty/very salty group compared to the not salty/average group in the epidemiologic factor-adjusted model (Model I). In contrast, in the *H. pylori*-adjusted model (Model II), the frequency of soybean paste stew consumption was not associated with GC in the not salty/average group. Soybean paste stew exhibited a V-shaped association with GC in the *H. pylori*-positive group but showed no significant association in the *H. pylori*-negative group. In summary, after adjusting for *H. pylori*, soybean paste stew consumption was not associated with GC in the *H. pylori*-negative and not salty groups. Given the distinct V-shaped association observed in the salty diet and *H. pylori*-positive groups, consuming soybean paste stew approximately twice a week may be appropriate for these populations.

Several biological mechanisms have been proposed to explain the cancer-preventive effects of soy foods, including their antioxidant and anti-inflammatory properties. Soy and soy isoflavones inhibit oxidative stress by activating Nrf2 [5,6] and modulate the expression of genes involved in cell proliferation and apoptosis [7]. Soy isoflavones also inhibit mitogen-activated protein kinase phosphatase 2 in human prostate cancer cells (LNCaP) [31] and are thought to suppress the expression of inflammatory mediators [8]. Isoflavones, recognized as key inhibitors of protein-tyrosine kinases, may exert anti-mitotic and anti-angiogenic effects by inhibiting endothelial cell proliferation and capillary formation in response to vascular endothelial growth factor [32].

In this study, a salty diet, spicy diet, broth consumption, and the use of additional seasoning were strongly associated with GC in Model I. It is well-established that a high-salt diet increases the risk of GC [33]. Many Korean broths contain high levels of salt; thus, consuming broth frequently results in significant salt intake. The association between a spicy diet and GC remains controversial. Small-scale studies have shown varied associations between GC and spicy food intake, reporting both positive associations [21,22] and no associations [34]. The use of additional seasoning was also strongly linked to GC, with GC (OR, 3.1 in Model I and 6.79 in Model II). Given that additional seasoning often includes salty or spicy ingredients such as salt, soy sauce, pepper paste, or pepper powder, its use reflects high consumption of these components. Both frequent and infrequent meat consumption were associated with GC. Associations between red and processed meat consumption and GC have been inconsistent, with some studies reporting positive associations [35] and others finding no link [36]. A recent meta-analysis suggested a positive relationship between GC and consumption of red (OR, 1.67) and processed meat (OR, 1.76) in case-control studies [37].

The study used high-quality data from a prospective registry, and the large sample size addressed the statistical insignificance seen in previous smaller studies. This allowed for more precise clarification of the association between soy foods and GC and enabled detailed subgroup analyses by sex, salty diet, and *H. pylori* status. The consistent inverse association between soybean/tofu consumption and GC across all analyses reinforces this relationship, while the variable associations between soybean paste stew and GC in subgroups defined by salty diet and *H. pylori* status suggest that the impact of soybean paste stew intake may depend on these cofactors. The study proposed a nonlinear relationship between soybean

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paste stew consumption and GC, with moderate intake associated with the lowest risk, a finding that is the first of its kind. Analyses conducted in both unmatched and age- and sex-matched groups showed similar associations across both groups. The similarity in age and sex distribution for GC between this study and the overall Korean population enhances the reliability of our findings. Finally, adjusting for *H. pylori* status is a notable strength, given that few studies have examined the association between GC and dietary soy food while considering *H. pylori* status.

This study had several limitations. First, it relied on qualitative food frequency questionnaires, which limited quantitative measurement. Second, as a multicenter case-control study, it identified associations between GC and dietary factors but could not establish causality. However, the large study population and the similarity in age and sex distribution between our study cohort and the total Korean population may partially mitigate this limitation. Furthermore, large prospective cohort studies that consider both diet and *H. pylori* status are scarce. Third, despite age and sex matching, there were differences in many covariates between the 2 groups, making it challenging to fully adjust for all biases influencing the association between soy/tofu intake and GC risk. For example, we did not perform subgroup analyses based on histologic types such as diffuse or intestinal types of GC. Fourth, the absence of validation analyses limits the generalizability of our findings. Fifth, the food frequency questionnaires were not internally validated. Finally, *H. pylori* status was determined using *H. pylori* IgG, which can be positive in cases of current or recent past infection [38]. Although rapid urease tests were conducted in most GC cases, they were performed in a limited number of individuals in the control group.

In conclusion, the frequency of soybean/tofu consumption consistently showed an inverse association with GC in a dose-dependent manner across various models and subgroup analyses by sex, salty diet, and *H. pylori* status. A moderate intake (2 servings per week) of soybean paste stew was associated with a reduced risk of GC, whereas both low and high dietary intakes were associated with an increased risk. These associations were also observed in the age- and sex-matched group. In the model adjusted for epidemiologic factors and *H. pylori* status, the adverse association between frequent soybean paste stew consumption and GC was more pronounced in women than in men, suggesting that women may be more susceptible to GC from this dietary habit. The associations between soybean paste stew and GC varied in subgroup analyses by salty diet and *H. pylori* status. Given the clear V-shaped association observed in the salty diet group and the *H. pylori*-positive group, consuming soybean paste stew about twice a week appears appropriate for these populations.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Questionnaires for gastric cancer registry

Supplementary Table 2
Pearson R and P-values

Supplementary Table 3
Association between Soybean food groups and gastric cancer (age, sex matched population)

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Supplementary Table 4

Other cofactors associated with gastric cancer

Supplementary Table 5

The association between soybean food groups and gastric cancer by sex in age, sex matched population

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