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Original Article

Dietary Intake of Soy Products, Vegetables, and Dairy Products and Gastric Cancer Survival according to Histological Subtype: a Long-term Prospective Cohort Study

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ABSTRACT

Purpose: Owing to differences in the general characteristics of gastric cancer (GC) according to histological type, the association of GC risk factors, such as diet, may also differ depending on the histological type. We investigated the associations between individual and combined intake of soy products, vegetables, and dairy products and GC mortality by following up cases of death among Korean GC cases and whether these associations differ according to the histological type.
Materials and Methods: A total of 508 GC cases were enrolled from two hospitals between 2002 and 2006. Their survival or death was prospectively followed up until December 31, 2016, through a review of medical records and telephonic surveys. Finally, 300 GC cases classified as intestinal- or diffuse-type GC cases were included. The median follow-up period was 7.1 years.
Results: In the fully adjusted model, a high intake of soy products (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.19–0.96) and the combination of soy products and vegetables (HR, 0.34; 95% CI, 0.12–0.96) or soy products and dairy products (HR, 0.37; 95% CI, 0.14–0.98) decreased the mortality from intestinal-type GC. In particular, patients consuming various potentially protective foods (HR, 0.23; 95% CI, 0.06–0.83) showed a highly significant association with a lower mortality from intestinal-type GC. However, no significant association was found with diffuse-type GC.
Conclusions: High intake of potentially protective foods, including soy products, vegetables, and dairy products, may help increase survival in intestinal-type GC.

Keywords: Stomach neoplasms; Mortality; Cohort study; Diet; Histological type

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

INTRODUCTION

According to the World Health Organization, cancer is the leading cause of death before the age of 70 years in 59 (including South Korea) of 183 countries [1]. The mortality rate of gastric cancer (GC) has been reported to be the 4th highest globally [2] and in South Korea, with an estimated rate of 14.9/100,000 persons in 2019 [3]. However, the 5-year survival rate of GC in South Korea was 76.5% in 2013–2017 [4], which was higher than that in other countries [5]; this may be attributed to population-based endoscopic screening programs for the early detection of GC and advances in medical technology and pharmaceuticals in South Korea [5,6]. To increase the survival rate of GC, it is very important to not only diagnose it early but also to identify and control modifiable factors (such as smoking, drinking, and dietary habits) that affect the survival rate.

According to the World Cancer Research Fund International, the evidence for diet protective against GC, including vegetables, soy products, and dairy products, is limited and inconclusive [7]. However, several studies have suggested that nutrients or phytochemicals in these food products or items may help prevent GC [8-10]. Soy products contain isoflavones, such as genistein, daidzein, and glycitein, which are well-known cancer-preventive phytochemicals [11]. In addition, vegetables and dairy products are considered potentially protective factors against cancer because vegetables contain numerous beneficial bioactive compounds such as minerals, vitamins, and phytochemicals [12], and dairy products contain nutrients such as calcium, potassium, magnesium, riboflavin, and vitamin B12 [13]. Therefore, in this study, we reviewed potential dietary factors through a recent meta-analysis [10,14-15] and selected soy products, vegetables, and dairy products as dietary factors that showed potential protection. Individual intake of foods such as soy products, vegetables, and dairy products may have a beneficial effect on reducing GC mortality [16-18]. However, rather than focusing on individual food items, assessment of combined food items or dietary patterns may be a more suitable approach for clarifying the associations between dietary factors and cancer because each food item could have complementary effects that enhance or block the overall uptake of nutrients [19]. In a meta-analysis, the Mediterranean diet, which mainly consists of fruits, vegetables, legumes, dairy products, and oils, significantly reduced overall cancer mortality and GC mortality [20].

In addition, GC mortality varies according to the histological type of GC. According to the Lauren classification, GC can be classified into intestinal, diffuse, and mixed types; this classification is widely used clinically [21,22]. In our previous study, the 5-year survival rate of diffuse-type GC was significantly lower than that of intestinal-type GC in South Korea [23]. In addition, diffuse-type GC occurs in younger female patients, with poorer clinical outcomes due to a high metastatic rate and rapid progression compared to intestinal-type GC [24-26]. On the other hand, intestinal-type GC is more affected by environmental factors than diffuse-type GC [27]. Since there are differences in the characteristics of patients (i.e., age, sex, and mortality rate) according to GC type, the influence of dietary factors according to the histological type of GC may also be different. However, cohort studies on the association between individual and combined food intake and mortality from GC according to histological type are scarce.

Therefore, this cohort study investigated the associations between individual and combined intake of soy products, vegetables, and dairy products and mortality from GC by following up cases of death among Korean GC cases and whether these associations differ according to the histological type of GC.

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MATERIALS AND METHODS

Subject

We included 508 patients aged ≥20 years who were diagnosed with GC at Chungnam National University Hospital or Hanyang University Guri Hospital between March 2002 and September 2006. Because of the slight change in the questionnaire items during the study period, patients were classified into the following stages: March 2002 to August 2003 and October 2003 to September 2006. The histological types of GC were classified by a pathologist as intestinal, diffuse, mixed, or unclassified [21]. Intestinal-type GC cases were defined based on the adherence of the tumor cells and the formation of glands and tubular structures. In contrast, diffuse-type GC cases were defined as cases in which the tumor cells lacked adhesion, did not form glands, and had the characteristics of single cells infiltrating the gastric wall. Mixed-type GC cases were considered to have both intestinal and diffuse characteristics. In addition, unclassified cases were defined as cases in which only tissue biopsy was performed by gastroscopy without surgery or cases in which the histological type could not be identified by microscopy. Among the 508 patients, 18 without epidemiological data and 13 with abnormal energy intake (<500 or >5,000 kcal) were excluded. Furthermore, because our study aimed to identify the associations between the potentially protective dietary factors and mortality from intestinal- and diffuse-type GC according to Lauren's classification, mixed type (n=20) and unclassified (no surgery, n=56; not identified, n=101) cases were excluded. Therefore, 300 patients (178 with intestinal-type and 122 with diffuse-type) were analyzed. All patients provided written informed consent to voluntarily participate in the study, which was approved by the Institutional Review Board (IRB) of Hanyang University Guri Hospital (IRB No. 2003-4). Additional approval was obtained from the IRBs of Chungnam National University Hospital (IRB No. CNHU 2017-12-039) and Hanyang University Guri Hospital (IRB No. 2018-01-021-001).

Follow-up

Cases were followed up from diagnosis until the date of death from GC and censored at the date of death from other causes or at the end of follow-up. A total of seven follow-up investigations (2003, 2004, 2005, 2008, 2011, 2012, and 2017) were performed to confirm the death of patients in this study, and the last follow-up was conducted on December 31, 2016. The overall follow-up rate was 77.8%, and the date and cause of death were confirmed through the examination of medical records. However, if they could not be confirmed in the medical records, we investigated the survival status after GC surgery through telephone surveys. Furthermore, if the exact date of death was not investigated by the number of days, the median value of month (15) was substituted. The final status of the cases was investigated in five categories (GC death, non-GC death, GC recurrence, survival, and follow-up failure). The survival period was calculated from the date of surgery to the date of last follow-up. For patients who had not undergone surgery, the survival period was calculated from the date of diagnosis to the date of last follow-up.

Data collection

The questionnaire included questions on sociodemographic characteristics (such as age, sex, and education level), anthropometric factors (such as height and weight), behavioral factors (such as smoking status, alcohol consumption, and dietary habits), and clinicopathological factors (such as surgery, adjuvant chemotherapy, and GC stage). Pathological data of all cases were reviewed in March 2018, and the tumors were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification

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for GC. We grouped the participants into 3 categories based on their body mass index (BMI): obese, ≥25 kg/m^2; overweight, 23.0–24.9 kg/m^2; and underweight and normal weight, <22.9 kg/m^2. The presence of *Helicobacter pylori* (*H. pylori*) infection was assessed using the Campylobacter-like organism test kit (Product No: 60480; Kimberly-Clark/Ballard Medical Products, Draper, UT, USA), a rapid urea degradation test. Family history of GC included first degree relatives.

Dietary data

Data on dietary factors were collected using a quantitative food frequency questionnaire (FFQ). We used a slightly modified version of the validated FFQ used in our previous study [28]. All questionnaires were administered by a well-trained interviewer, and the frequency and amount of food consumed during the 12 months of the past 3 years before the date of the interview were determined to assess past dietary intake. The reason to recall their usual dietary intake from 3 years earlier is that the patient may have changed their dietary habits owing to signs of poor health status before GC diagnosis. Also, in nutrition-related cancer studies, remote dietary intake may be more important than recent diet because of the long latency of cancer. During the first stage (March 2002 to August 2003), the FFQ assessed 102 food or dish items; intake period (1–12 months) during 1 year; frequency of food consumption per month, week, or day; and one serving size. For the second stage (October 2003 to September 2006), the FFQ comprised 115 food or dish items, frequency of food consumption in 9 categories ("never or less than once a month," "1–3 times a month," "1 time a week," "2–4 times a week," "5–6 times a week," "once a day," "2–3 times a day," "4–5 times a day," and "≥6 times a day"), and one serving size. There was a slight difference in the number of FFQ items included in the first and second stages, because the food or dish items that patients eat more frequently are subdivided in the second stage. We classified the protective food groups as follows: First, soy products were comprised of three foods: 1. soybeans boiled in soy sauce, 2. tofu, and 3. soymilk. Second, vegetables were comprised of 10 foods (1. lettuce, cabbage, and Chinese cabbage, 2. cucumber, 3. chili pepper, 4. carrot, 5. perilla, 6. celery and broccoli, 7. cooked soybean sprouts and mung bean sprouts, 8. spinach, 9. Korean zucchini, and 10. bracken, platycodon, etc.). Third, dairy products were comprised of three foods: 1. milk, 2. fermented milk products (yogurt), and 3. cheese. We selected common food groups or items for the first stage based on the second stage. Daily food intake was calculated by considering the intake frequency and the amount of each food group according to each stage. In each food group, intake above the median value was classified as high intake, while those below the median value were classified as low intake. The combined score for each food group was calculated as follows: 1 point was given for intake above the median value, 0 points were given for intake below the median value, and the sum of each food group was calculated. Thus, the total potentially protective food scores ranged from 0 to 3, with higher scores indicating more potentially protective food intake. The total energy intake for each food item was estimated using the Korean Foods and Nutrients Database [29].

Statistical analyses

The general characteristics of the patients are presented as numbers with proportions. Categorical variables were compared using the χ^2 test. Survival analysis was performed using the Kaplan–Meier method with a log-rank test. The proportional hazards assumption was tested using the goodness of fit. The P-value was not statistically significant; thus, we concluded that the proportional hazards assumption was met. Cox proportional hazard regression analysis was performed to assess the risk of GC mortality. We analyzed factors influencing the prognosis of GC mortality, and selected age, sex, alcohol consumption, GC

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stage, and adjuvant chemotherapy as covariates that showed significant results. In addition, additional adjusted covariates (i.e., smoking, education level, BMI, registered hospital, family history of GC, *H. pylori* infection, and surgery) that are known to affect the prognosis of GC mortality through a literature review study were selected. Model I was adjusted for age (as continuous), sex, adjuvant chemotherapy (no or yes), and stage (I, II, III, IV, and unknown). Model II was further adjusted for BMI (≤22.99 kg/m^2, 23.0–24.99 kg/m^2, ≥25 kg/m^2, or missing), education level (lower than or equal to elementary school or none, middle or high school, college or higher, or unknown), smoking status (never, past, or current smokers), alcohol consumption (never, past, <20 g/day for women or <40 g/day for men, or ≥20 g/day for women or ≥40 g/day for men), energy intake (as continuous), hospital visits (Chungnam National University Hospital or Hanyang University Guri Hospital), family history of GC (no or yes), *H. pylori* infection (negative, positive, and not evaluated), and surgery (no or yes). The event was defined as GC death, and the other cases were coded as censored cases. The risk of death was presented as hazard ratio (HR) with a 95% confidence interval (CI). Statistical significance was set at P<0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

In the 300 GC cases, the total person-years was 25,683, and the median follow-up period was 7.1 years. Among 178 intestinal-type GC cases, 51 GC deaths were observed during a median follow-up period of 7.3 years. Additionally, among 122 diffuse-type GC cases, 48 GC deaths were observed during a median follow-up period of 6.8 years.

Fig. 1 shows the Kaplan–Meier plots for GC-specific survival according to age group. In intestinal-type GC, the 5-year GC-specific survival rates of patients aged <50, 50–59, 60–69, and ≥70 years were 85.2%, 91.7%, 80.8%, and 52.4%, respectively. In diffuse-type GC, the 5-year GC-specific survival rates of patients aged <50, 50–59, 60–69, and ≥70 years were 65.1%, 68.1%, 55.8%, and 53.3%, respectively. The 10-year GC-specific survival rates did not differ from the 5-year survival rates.

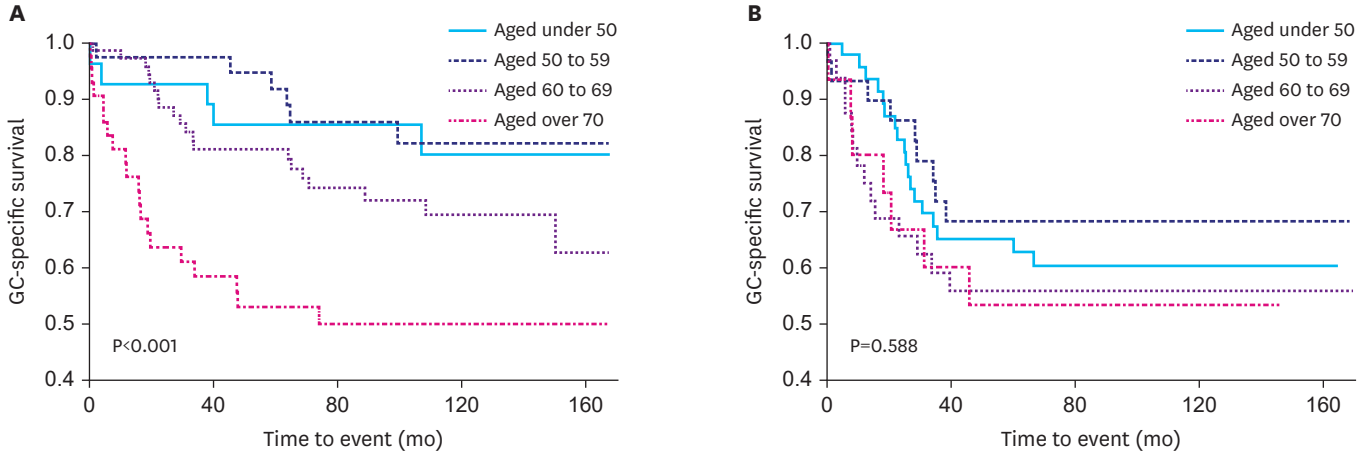

Fig. 1. Kaplan-Meier plots for GC-specific survival according to age group. (A) Intestinal type, (B) Diffuse type.
GC = gastric cancer.

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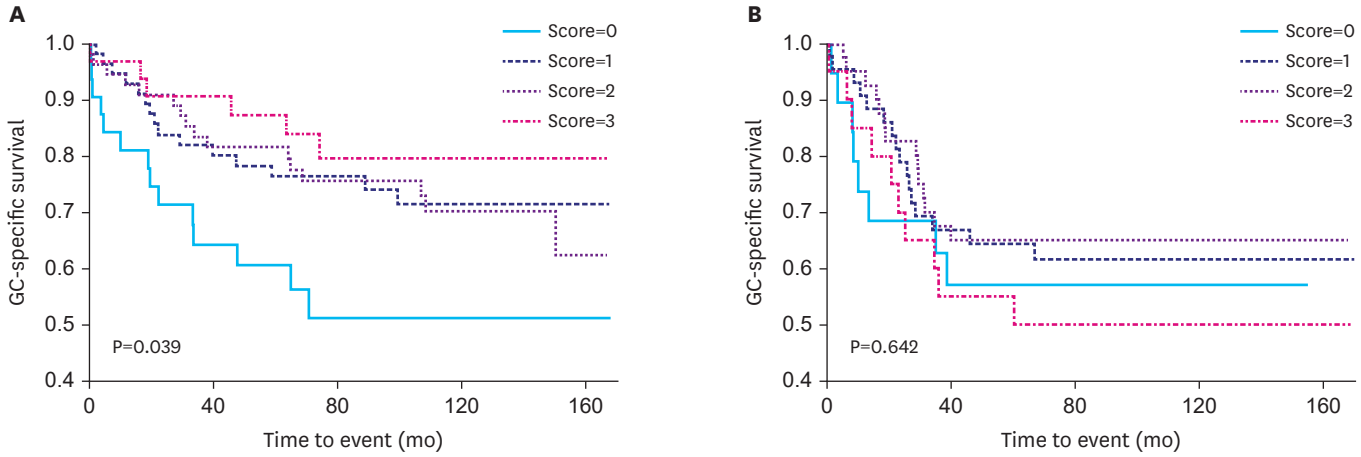

Fig. 2. Kaplan-Meier plots for GC-specific survival according to the intake score of protective food groups. (A) Intestinal type, (B) Diffuse type. Score=0: Low intake for all food groups, Score=1: High intake for 1 food group, Score=2: High intake for 2 food groups, Score=3: High intake for 3 food groups. In each food group of soy products, fruits, vegetables, and dairy products, 1 point was given for intakes of above the median value, 0 points were given for intakes below the median value, and the sum of each food group was calculated.
GC = gastric cancer.

Fig. 2 shows the Kaplan–Meier plots for GC-specific survival according to the intake score of protective food groups. In intestinal-type GC, the 5-year GC-specific survival rates of patients with score 0, 1, 2, and 3 were 60.7%, 76.4%, 81.6%, and 87.4%, respectively. Also, the 10-year GC-specific survival rates of patients with score 0, 1, 2, and 3 were 51.2%, 71.5%, 70.3%, and 79.8%, respectively. In diffuse-type GC, the 5-year GC-specific survival rates of patients with score 0, 1, 2, and 3 were 57.0%, 64.3%, 65.0%, and 55.0%, respectively. The 10-year GC-specific survival rates did not differ from the 5-year survival rates.

General characteristics

Table 1 shows the general characteristics of GC cases in the baseline survey according to the histological types of GC. The proportion of male patients was higher in intestinal-type GC than in diffuse-type GC (82.0% vs. 54.1%; P<0.001). In intestinal-type GC, the proportion of patients aged 60–69 years was high (39.9%), whereas in the diffuse-type GC, the proportion of patients aged <50 years was high (37.7%) (P<0.001). Regarding smoking status, the proportion of patients who were past smokers was high (39.9%) in intestinal-type GC, while that of never smokers was high (45.9%) in diffuse-type GC (P<0.001). For the registered hospitals, intestinal-type GC had a high rate (55.1%) at Hanyang University Guri Hospital, and the diffuse-type GC had a high rate (63.1%) at Chungnam National University Hospital (P=0.002). The rate of *H. pylori* infection was higher in intestinal-type GC than in diffuse-type GC (34.3% vs. 24.6%; P=0.035). For adjuvant chemotherapy, the proportion of untreated patients was higher in intestinal-type GC than in diffuse-type GC (P=0.002). Regarding the GC stage, the proportion of patients with stage I was higher in intestinal-type GC than in diffuse-type GC (P=0.032).

Adjusted HR for GC mortality according to major prognostic factors

Table 2 presents the HRs for GC mortality according to major prognostic factors. The GC mortality rate increased with age in both groups. Regarding alcohol consumption, the GC mortality rate decreased in both groups when men drank less than 40 g and women less than 20 g. Meanwhile, the GC mortality rate increased with increasing GC stage in both groups. In terms of sex, the GC mortality rate was higher in men than in women only in patients with intestinal-type GC. Regarding surgery status, the GC mortality rate was higher in those who underwent surgery than in those who did not undergo surgery only in patients with diffuse-type GC.

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Table 1. Baseline characteristics of GC cases according to histological type

Characteristics	Intestinal type (n=178)	Diffuse type (n=122)	P-value
Sex			<0.001
Male	146 (82.0)	66 (54.1)	
Female	32 (18.0)	56 (45.9)	
Ages groups (yr)			<0.001
<50	27 (15.2)	46 (37.7)	
50–59	38 (21.4)	29 (23.8)	
60–69	71 (39.9)	32 (26.2)	
≥70	42 (23.6)	15 (12.3)	
Education level			0.162
Elementary school or none	65 (36.5)	34 (27.9)	
Middle or high school	27 (15.2)	20 (16.4)	
College or higher	69 (38.8)	61 (50.0)	
Unknown	17 (9.6)	7 (5.7)	
Smoking status			<0.001
Never	40 (22.5)	56 (45.9)	
Past	71 (39.9)	28 (22.9)	
Current	67 (37.6)	38 (31.2)	
Alcohol consumption*			0.068
Never	45 (25.3)	48 (39.3)	
Past	40 (22.5)	19 (15.6)	
<20 for women or <40 for men	51 (28.7)	30 (24.6)	
≥20 for women or ≥40 for men	42 (23.6)	25 (20.5)	
Body mass index			0.078
Underweight or normal weight	79 (44.4)	63 (51.6)	
Overweight	49 (27.5)	18 (14.8)	
Obese	39 (21.9)	32 (26.2)	
Unknown	11 (6.2)	9 (7.4)	
Registered Hospital			0.002
Chungnam National University	80 (44.9)	77 (63.1)	
Hanyang University Guri	98 (55.1)	45 (36.9)	
Family history of GC†			0.567
No	152 (85.4)	107 (87.7)	
Yes	26 (14.6)	15 (12.3)	
Helicobacter pylori infection			0.035
Negative	66 (37.1)	40 (32.8)	
Positive	61 (34.3)	30 (24.6)	
Not performed‡	51 (28.7)	52 (42.6)	
Surgery			0.151
No	6 (3.4)	1 (0.8)	
Yes	172 (96.6)	121 (99.2)	
Adjuvant chemotherapy			0.002
No	138 (77.5)	74 (60.7)	
Yes	40 (22.5)	48 (39.3)	
Stage§			0.032
I	113 (63.5)	57 (46.7)	
II	25 (14.0)	22 (18.0)	
III	32 (18.0)	39 (32.0)	
IV	6 (3.4)	3 (2.5)	
Unknown	2 (1.1)	1 (0.8)	

GC = gastric cancer.
*This category was divided according to the WHO recommendation. †Family history of GC included first degree relatives. ‡It was impossible to collect tissue. §Classification by 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system for GC.

Association between individual or combined protective food intake and GC mortality

Table 3 shows the HR of GC mortality according to individual or combined protective foods in histological types of GC. In intestinal-type GC, high intake of soy products showed a

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Table 2. Adjusted hazard ratios and 95% confidence intervals for GC-specific death by major prognostic factors

Characteristics	Intestinal-type GC	Diffuse-type GC
	HR (95% CI)‡	HR (95% CI)‡
Sex		
Male	1.00	1.00
Female	3.69 (1.12–12.18)	0.71 (0.22–2.32)
Ages (yr) (as continuous)		
1 years increased	1.06 (1.02–1.11)	1.03 (1.00–1.07)
Education level		
Elementary school or none	1.00	1.00
Middle or high school	1.17 (0.41–3.33)	1.59 (0.59–4.28)
College or higher	1.01 (0.44–2.33)	1.17 (0.44–3.10)
Smoking status		
Never	1.00	1.00
Past	0.42 (0.12–1.43)	1.22 (0.36–4.11)
Current	0.44 (0.13–1.44)	1.29 (0.34–4.86)
Alcohol consumption*		
Never	1.00	1.00
Past	1.45 (0.55–3.81)	0.89 (0.27–2.91)
<20 for women or <40 for men	0.33 (0.11–0.95)	0.27 (0.09–0.83)
≥20 for women or ≥40 for men	1.15 (0.46–2.86)	0.91 (0.33–2.58)
Body mass index		
Underweight or normal weight	1.00	1.00
Overweight	1.27 (0.54–3.01)	1.89 (0.70–5.12)
Obese	1.83 (0.60–5.57)	1.02 (0.43–2.45)
Registered Hospital		
Chungnam National University	1.00	1.00
Hanyang University Guri	0.70 (0.28–1.75)	0.48 (0.21–1.09)
Family history of GC†		
No	1.00	1.00
Yes	0.90 (0.30–2.70)	1.19 (0.43–3.34)
Helicobacter pylori infection		
Negative	1.00	1.00
Positive	1.70 (0.77–3.77)	0.95 (0.35–2.56)
Surgery		
No	1.00	1.00
Yes	2.51 (0.21–30.66)	28.56 (2.36–345.07)
Adjuvant chemotherapy		
No	1.00	1.00
Yes	1.08 (0.48–2.44)	0.77 (0.31–1.90)
Stage§		
I	1.00	1.00
II	5.05 (1.89–13.47)	13.25 (3.87–45.36)
III	11.82 (4.19–33.35)	18.51 (5.75–59.58)
IV	42.67 (5.24–347.20)	263.01 (40.66–1,701.20)

GC = gastric cancer, HR = hazard ratio, CI = confidence interval.
*This category was divided according to the WHO recommendation. †Family history of GC included first degree relatives. ‡Fully adjusted model: adjusted for age, sex, adjuvant chemotherapy (no or yes), stage (I, II, III, IV, and unknown), body mass index (≤22.99, 23.0–24.99, ≥25, or missing), education level (≤elementary school or none, middle or high school, ≥college or higher, or unknown), smoking status (never, past, or current smokers), alcohol consumption (never, past, <20 g/day for women or <40 g/day for men, or ≥20 g/day for women or ≥40 g/day for men), energy intake, hospital (Chungnam National University Hospital or Hanyang University Guri Hospital), family history of GC (no or yes), *Helicobacter pylori* infection (negative, positive, and not performed), and surgery (no or yes). §Classification by 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system for GC.

significantly lower GC mortality than low intake (HR, 0.43; 95% CI, 0.19–0.96) in model II. However, daily individual intake of vegetables and dairy products was not associated with GC mortality. The results of the combined association analysis showed that patients with a high intake of both soy products and vegetables had a significantly lower GC mortality than those with a low intake (HR, 0.34; 95% CI, 0.12–0.96) in model II. In addition, patients with a high

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Table 3. Adjusted hazard ratios and 95% confidence intervals for GC-specific death by histological type of GC

Variables	Intestinal-type GC				Diffuse-type GC			
	No. of GC death	Person-years	GC-specific death		No. of GC death	Person-years	GC-specific death	
			Model I*	Mode1 II†			Mode1 I*	Model II†
Individual association								
Soy products								
Low	35/89	564.3	1.00	1.00	26/61	371.4	1.00	1.00
High	16/89	767.2	0.47 (0.25–0.88)	0.43 (0.19–0.96)	22/61	437.4	1.22 (0.66–2.26)	1.08 (0.55–2.14)
Vegetables								
Low	29/88	598.7	1.00	1.00	22/61	415.4	1.00	1.00
High	22/90	732.7	0.85 (0.48–1.53)	0.73 (0.38–1.40)	26/61	393.4	2.30 (1.19–4.43)	1.67 (0.77–3.65)
Dairy products								
Low	24/89	652.9	1.00	1.00	22/61	398.1	1.00	1.00
High	27/89	678.6	0.72 (0.40–1.29)	0.67 (0.33–1.35)	26/61	410.7	1.05 (0.58–1.93)	0.89 (0.45–1.77)
Combined association‡								
Soy products & Vegetables								
Low/Low	22/56	324.1	1.00	1.00	15/36	227.7	1.00	1.00
Low/High	13/33	240.2	1.00 (0.45–2.02)	0.79 (0.36–1.74)	11/25	143.7	2.21 (0.90–5.40)	1.17 (0.40–3.41)
High/Low	7/32	274.6	0.49 (0.20–1.22)	0.46 (0.16–1.36)	7/25	187.7	1.04 (0.39–2.84)	0.63 (0.20–1.99)
High/High	9/57	492.6	0.46 (0.20–1.03)	0.34 (0.12–0.96)	15/36	249.7	2.45 (1.08–5.58)	1.68 (0.68–4.12)
Soy products & Dairy products								
Low/Low	18/47	257.9	1.00	1.00	12/31	193.7	1.00	1.00
Low/High	17/42	306.4	0.60 (0.30–1.22)	0.69 (0.30–1.55)	14/30	177.6	0.83 (0.35–1.99)	0.77 (0.29–2.05)
High/Low	6/42	395.0	0.32 (0.11–0.89)	0.35 (0.10–1.18)	10/30	204.3	0.94 (0.37–2.35)	0.89 (0.30–2.62)
High/High	10/47	372.2	0.37 (0.17–0.85)	0.37 (0.14–0.98)	12/31	233.0	1.28 (0.56–2.94)	0.96 (0.36–2.59)

GC = gastric cancer.
*Model I: adjusted for age, sex, adjuvant chemotherapy (no or yes), and stage (I, II, III, IV, and unknown).
†Model II: model I + further adjusted for body mass index (≤22.99, 23.0–24.99, ≥25, or missing), education level (≤ elementary school or none, middle or high school, ≥ college or higher, or unknown), smoking status (never, past, or current smoker), alcohol consumption (never, past, <20 g/day for women or <40 g/day for men, or ≥20 g/day for women or ≥40 g/day for men), energy intake, hospital (Chungnam National University Hospital or Hanyang University Guri Hospital), family history of GC (no or yes), *Helicobacter pylori* infection (negative, positive, and not performed), and surgery (no or yes).
‡The P-value for interaction was not significant (P >0.05).

intake of both soy and dairy products had a significantly lower GC mortality than those with a low intake (HR, 0.37; 95% CI, 0.14–0.98) in model II.

Contrary to the results for intestinal-type GC, the HR of GC mortality according to the individual or combined protective foods in diffuse-type GC was not statistically significant in model II.

Association between the intake score of potentially protective food groups and GC mortality

Table 4 shows the association between the intake score of potentially protective food groups and GC mortality. For intestinal-type GC, patients with the highest score (score=3, high intake for three protective foods) showed a significantly lower GC mortality than those with the lowest score (score=0, low intake for all food groups) (HR, 0.23; 95% CI, 0.06–0.83) in model II. However, there were no statistically significant differences in diffuse-type GC.

DISCUSSION

In this study, we found that high daily intake of soy products and the combination of soy products, vegetables, and dairy products was associated with lower GC mortality in intestinal-type GC. In particular, patients consuming various potentially protective foods showed a highly significant association with lower GC mortality in intestinal-type GC. However, no significant results were found for diffuse-type GC.

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Table 4. Adjusted hazard ratios and 95% confidence intervals for GC-specific death by the intake score of protective food groups

Variables	No. of GC deaths	Person-years	GC-specific death	
			Model I*	Model II†
Intestinal-type GC				
Intake Score of protective food groups‡				
0: Low intake for all food groups	14/32	156.0	1.00	1.00
1: High intake for 1 food group	15/57	449.3	0.49 (0.22–1.07)	0.48 (0.19–1.20)
2: High intake for 2 food groups	16/56	449.3	0.53 (0.25–1.14)	0.51 (0.21–1.24)
3: High intake for 3 food groups	6/33	276.9	0.33 (0.12–0.89)	0.23 (0.06–0.83)
P for trend			0.043	0.041
Diffuse-type GC				
Intake Score of protective food groups‡				
0: Low intake for all food groups	8/19	115.3	1.00	1.00
1: High intake for 1 food group	16/43	278.8	0.78 (0.31–1.98)	0.76 (0.22–2.56)
2: High intake for 2 food groups	14/40	281.3	1.21 (0.49–3.01)	0.48 (0.15–1.49)
3: High intake for 3 food groups	10/20	133.4	2.18 (0.75–6.34)	2.33 (0.62–8.74)
P for trend			0.080	0.546

GC = gastric cancer.
*Model I: adjusted for age, sex, adjuvant chemotherapy (no or yes), and stage (I, II, III, IV, and unknown).
†Model II: model I + further adjusted for body mass index (≤22.99, 23.0–24.99, ≥25, or missing), education level (≤ elementary school or none, middle or high school, ≥ college or higher, or unknown), smoking status (never, past, or current smoker), alcohol consumption (never, past, <20 g/day for women or <40 g/day for men, or ≥20 g/day for women or ≥40 g/day for men), energy intake, hospital (Chungnam National University Hospital or Hanyang University Guri Hospital), family history of GC (no or yes), *Helicobacter pylori* infection (negative, positive, and not performed), and surgery (no or yes).
‡In each food group of soy products, fruits, vegetables, and dairy products, 1 point was given for intakes of above the median value, and 0 points were given for intakes below the median value, and the sum of each food group was calculated.

Soy products contain cancer-preventive phytochemicals, including isoflavones such as genistein, daidzein, and glycitein [11]. Huang et al. reported an experimental basis for using genistein to improve the treatment of patients with GC [30]. They found that genistein inhibited GC stem cell properties, reduced GC cell tumorigenicity, and enhanced the chemosensitivity of GC cells. In animal models of *H. pylori*-induced gastropathy, Siriviriyakul et al. [31] reported that genistein has gastroprotective effects through the reduction of pro-inflammatory mediators and gastric mucosal apoptosis. In addition, a meta-analysis of cohort studies reported that higher soy intake was inversely associated with GC mortality (pooled effect size=0.49; 95% CI, 0.35–0.68) [14]. However, controversies exist regarding these beneficial associations according to sex [32], genetic background [33], and fermentation status of soy products [34]. In addition, the difference in these results may differ depending on the histological type of GC, but this has not been identified in previous studies. In our study, we found that a higher intake of soy products significantly reduced GC mortality in intestinal-type GC.

Vegetables, including minerals, vitamins, fiber, and phytochemicals, are likely to protect against cancer [12]. A meta-analysis of prospective studies reported that a high intake of vegetables was associated with a reduced risk of total cancer (risk ratio [RR]=0.95; 95% CI, 0.90–0.99) [15]. In addition, in a meta-analysis of Korean and Japanese individuals, fresh vegetable consumption significantly lowered the GC risk (overall summary odds ratio, 0.63; 95% CI, 0.46–0.85) [35]. A recent review suggested that phytochemicals such as carotenoids, proanthocyanidins, and organosulfur compounds help improve gastrointestinal cancer prognosis by regulating various mechanisms (such as downregulation of β-catenin phosphorylation or upregulation of the adenosine monophosphate-activated protein kinase pathway) [36]. However, despite this mechanistic support, another meta-analysis [37] and an ecological study [38] reported no association between vegetable intake and GC mortality. The difference in these results is thought to be because vegetables are rich in antioxidant nutrients, but they also contain nitrate [39], which is associated with an increased risk of

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GC. In our study, the association between vegetables and GC mortality was not significant. The association of vegetables with GC risk may differ depending on the type of vegetable consumed (fresh or cooked).

Dairy products, similar to vegetables, contain both positive (e.g., calcium, potassium, magnesium, riboflavin, and vitamin B12) [13] and negative factors (e.g., insulin-like growth factor I) [40]. A meta-analysis of epidemiological studies found that increased consumption of total dairy food was associated with a reduced GC risk (RR=0.76; 95% CI, 0.64–0.91) in cohort studies [10]. A review study also reported an inverse association between dairy consumption and GC [41]. However, a prospective study among Koreans found that consumption of dairy products increased the risk of atrophic gastritis and intestinal metaplasia, a pre-stage of GC [42]. According to a recent meta-analysis, dairy products are positively associated with GC risk because the consumption of more dairy products could possibly alleviate symptoms such as indigestion [43].

In our study, there was no statistical significance in GC mortality between consumption of vegetables and dairy products, but a high intake of a combination of soy products/vegetables, or soy products/ dairy products significantly reduced GC mortality. However, these results were only observed in intestinal-type GC. According to previous studies, positive or negative associations with diet are prominent in intestinal-type GC [44,45]. Harrison et al. [44] suggested that protective dietary factors such as vitamin B6, folate, niacin, and fruits play a more important role in preventing intestinal-type GC. In a case-control study of Koreans, the association between dietary inflammatory index (DII) and GC risk was investigated and stratified according to histological type [45]. In this study, the risk of GC significantly increased with a high DII in intestinal-type GC.

The reason for the association between GC mortality and dietary factors only in intestinal-type GC may be explained as follows. As mentioned earlier, diffuse-type GC has poorer clinical outcomes due to its high metastatic rate and rapid progression compared to intestinal-type GC [24-26]. Since there is a difference in the rate of progression after the onset of cancer, it is thought that the association with diet is more pronounced in intestinal-type GC, which progresses more slowly than diffuse-type GC. Second, intestinal-type GC is more closely related to environmental factors such as diet, whereas diffuse-type GC is more closely related to genetic susceptibility and family history [27]. Therefore, intestinal-type GC has a higher incidence rate in older people exposed to environmental factors such as diet for a long time, and diffuse-type GC has a higher incidence rate in younger people. Differences in the characteristics of these types of GC are thought to cause differences in the incidence and survival rates according to dietary intake.

A Portuguese study of patients with GC reported that a high intake of various food groups may affect survival rates [46]. In this study, high consumption of most food groups and low consumption of vegetable soup were significantly associated with a better prognosis among patients with GC. In addition, a meta-analysis reported that the Mediterranean diet, which mainly consists of fruits, vegetables, legumes, dairy products, and oils, significantly reduced mortality in overall cancer and GC [20]. A high intake of various food groups may have synergistic effects in increasing GC survival rates, as each food has a complementary effect that either enhances or blocks the overall intake of nutrients. In addition, a review study has suggested that administration of cancer treatments combined with phytochemicals may improve disease prognosis, as they are more effective in modulating different signaling

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pathways associated with tumor cell growth [47]. In our study, the GC mortality rate was significantly lower in patients with a high intake of potentially protective foods than in those with low intake. We also analyzed the association of soy products, vegetables, and dairy products with all-cause mortality. The results of all-cause mortality were similar to the results of GC mortality presented in **Tables 2** and **3**, because our study was a cohort study of GC patients (**Supplementary Table 1**).

Vahid et al. [48] reported that the intake of nutrients (such as vitamin A, thiamine, vitamin B6, and vitamin B12) or food (such as low-fat milk and raw vegetables) decreased after receiving chemotherapy in patients diagnosed with GC. Therefore, to increase the survival rate of patients with GC, continuous nutrition education for a balanced intake of various foods such as soy products, dairy products, and vegetables is required, and it is thought that healthy dietary habits may help reduce the mortality rate of intestinal-type GC.

This study has both strengths and limitations. The strengths of our study include that the temporal relationship between dietary factors and mortality is clear because we prospectively followed up mortality after collecting lifestyle and dietary factors before GC diagnosis. Second, our study subdivided GC and analyzed it according to histological classification. To the best of our knowledge, this is the first study to confirm that the association between potentially protective foods and GC mortality differed according to the histological type of GC. Third, we adjusted for cancer stage, which is the strongest prognostic factor of death, and used the Union for International Cancer Control (UICC)/AJCC 8th edition staging system, which is the latest staging method with improved prognostic power. However, this study has some limitations. First, some deaths could not be confirmed because follow-up could not be conducted if contact information was changed among patients who were transferred to another hospital or those who did not visit the hospital. Second, since dietary information was obtained by recall, the possibility of recall bias could not be excluded. However, despite this limitation, a study reported that the FFQ results, which recalled the diet 10 years ago, are reliable [49]. The study of the validity of the FFQ reported that the reproducibility and validity of the FFQ performed at 3-year intervals were acceptable [50]. Third, this study did not consider changes in dietary habits and lifestyle after GC diagnosis, which is related to patient survival. However, as the GC stage worsens, the nutritional status is more likely to deteriorate [51]. Thus, we adjusted the GC stage to reflect the nutritional status after GC surgery. Fourth, among the recruited cases, 157 were not classified according to Lauren's classification. Among them, 56 cases could not be classified because only tissue biopsy was performed by gastroscopy without surgery, and 101 cases could not be classified by microscopy.

In conclusion, we found that a high intake of soy products, a high intake of the combination of soy products and vegetables or soy products and dairy products, and high intake of three protective foods may help improve the survival rate only in intestinal-type GC.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Adjusted hazard ratios and 95% confidence intervals for overall death by the intake score of protective food groups

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