


Associations of Japanese food intake with survival of stomach and colorectal cancer: A prospective patient cohort study

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Abstract

Dietary factors may affect the prognosis of digestive tract cancer, but evidence has been sparse. We investigated the association between pretreatment intake of 6 Japanese foods (including soy food, miso [soybean paste] soup and seaweed) and the risk of death among patients with histologically confirmed major digestive tract cancers (stomach, 1931; colon, 793; rectum, 510) diagnosed during 1997-2013 at a single institution in Japan. Pretreatment dietary intake was assessed using a food frequency questionnaire, and the patients were followed until December 2016. The Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Among the patients with stomach cancer, frequent intake of soy food was inversely associated with the risk of all-cause (P_{trend} for four frequency groups = 0.01; HR = 0.72, 95% CI: 0.50-1.04 for highest vs lowest group) and stomach cancer (P_{trend} = 0.03; HR = 0.63, 95% CI: 0.40-0.99) death. A similar inverse association was also found for intake of miso soup. In contrast, frequent seaweed intake was inversely associated with the risk of all-cause death among the patients with colon cancer (P_{trend} = 0.03). Rectal cancer patients who had frequently consumed seaweed tended to have a lower risk of rectal cancer death (P_{trend} = 0.02). These findings indicate that pretreatment intake of Japanese foods such as soybean products and seaweed may have favorable effects on patient survival of stomach and colorectal cancer, although this needs to be confirmed by further research.

KEYWORDS

colorectal cancer, seaweed, soybean products, stomach cancer, survival

1 | INTRODUCTION

The major digestive tract cancers include those of the stomach, colon and rectum. Over the past several decades, trends in the incidence and mortality rates of these cancers have changed in Japan: the rate of stomach cancer has been declining, whereas those of colon and

rectal cancer have been increasing.^{1,2} According to the most recent cancer statistics for both sexes combined,³ colorectal cancer is the leading cancer in incidence and ranks second in terms of mortality. Stomach cancer is the second leading cancer in incidence and the third in terms of mortality.

For these major digestive tract cancers, previous epidemiologic studies have clarified the associations between lifestyle factors,

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including smoking, alcohol consumption and diet, and their incidence.^{4,5} Among various dietary factors, intake of salty food has been positively associated with the risk of stomach cancer,⁴⁻⁶ whereas meat intake has been shown to be associated with an increased risk of colorectal cancer.^{4,5,7} In contrast, some studies have focused on the association between intake of traditional Japanese foods such as soy food and miso (soybean paste) soup and the risk of digestive tract cancer.^{6,8-12} It has been suggested that intake of soy food is inversely associated with the risk of stomach^{8,10} and colon cancer.^{11,12} It has been reported that intake of miso soup might be associated with an increased risk of stomach cancer.^{6,8}

Some of the above lifestyle factors may affect not only the risk of cancer but also survival after diagnosis. Our previous study showed that smoking and alcohol consumption had adverse effects on the survival of patients with stomach cancer.¹³ Some other studies have also demonstrated an impact of smoking and alcohol consumption on the survival of patients with stomach¹⁴⁻¹⁶ and colorectal cancer.^{17,18} However, evidence for the effects of dietary factors has been sparse.^{14,15,19-21} Although intake of Japanese foods such as soy food and miso soup may also affect the survival of patients with digestive tract cancers, to our knowledge, no previous studies have investigated this possibility, despite the fact that this would clearly be an important issue for Japanese patients. Clarification of the respective impacts of dietary factors on stomach and colorectal cancer survival would, therefore, provide useful information in this context.

The present hospital-based prospective patient cohort study was, therefore, conducted to clarify the relationship between intake of selected traditional Japanese foods and survival after diagnosis of stomach and colorectal cancer. Data on food intake and clinical information on cancer patients were obtained from a questionnaire survey at their first admission and from a hospital-based cancer registry, and a long-term follow-up survey was conducted. In this study, we evaluated the risk of all-cause and disease-specific death among patients with stomach, colon and rectal cancer, respectively.

2 | MATERIALS AND METHODS

2.1 | Study subjects and data collection

Study subjects were selected from among patients who were admitted to the Miyagi Cancer Center Hospital (MCCH), Japan between January 1997 and December 2013. All of the admitted patients were asked to complete a self-administered questionnaire at the time of their initial admission.²² Patients diagnosed as having malignant tumors were registered in the hospital-based cancer registry (the MCCH Cancer Registry) and followed up. This registry records clinical data for newly or previously diagnosed malignant tumors in each patient. Through this registry, we identified 2435 first-admitted patients aged 30 years and over with newly diagnosed malignant gastric tumors and 1684 with newly diagnosed malignant colorectal tumors, none of whom had any previous history of malignant tumors. Among these patients, 2261 with malignant gastric tumors (92.9%)

and 1570 with malignant colorectal tumors (93.2%) responded to the questionnaire survey. From among these respondents, patients with non-epithelial malignant tumors and those without pathological data were excluded. After further excluding patients with concurrent malignant tumors other than the index cancers, 2024 patients with stomach cancer (ICD-O-3, C16) and 1383 with colorectal cancer (C18-C20) were primarily identified as the original patient cohort. The selection procedure for subjects with stomach cancer has already been described elsewhere.^{13,23} In the present study, the patients with colorectal cancer were divided into two groups: 831 patients with colon cancer (C 18) and 529 with rectal cancer (C19-C20). Patients with concurrent colon and rectal cancer ($n = 23$) were excluded.

The questionnaire covered demographic characteristics and general lifestyle factors, from which we obtained data on dietary intake and other lifestyle factors. The questionnaire was distributed to patients on the day of reservation for initial admission, and collected on the day of actual admission by nurses.²² At the MCCH, in principle, detailed diagnostic tests and initial therapy are initiated after admission. Therefore, the questionnaire data were considered to be pretreatment or prediagnosis data. We considered the return of questionnaires signed by the patients to imply their consent to participate in the study. The study was approved by the ethical review board of the Miyagi Cancer Center.

2.2 | Ascertainment of exposures and follow up

Dietary intake including Japanese food was evaluated using a food frequency questionnaire (FFQ). The study subjects were asked to indicate the average frequency of intake of each food within the past 1 year. This FFQ has been validated in a general population whose residential area was roughly the same as that of our study subjects.²⁴

The FFQ covered 40 food items, including 35 foods, alcohol, coffee, and three types of tea. Among the 35 food items, 10 were considered to be part of the traditional Japanese diet. In the present study, 6 Japanese food items (fresh fish such as sashimi, dried fish, seaweed, Japanese pickles, soy food such as tofu and fermented soybeans, and miso soup) were selected as exposures. The remaining 4 food items were excluded from the analysis because 1 of them (boiled fish paste) is processed boiled food, and the others (wild plants, food boiled with soy, and boiled beans) were found to have been consumed only infrequently during the recent period. Among the 6 selected food items, dried fish, Japanese pickles and miso soup are regarded as salted foods. Some researchers have considered whether the effects of Japanese food intake on cancer risk might be confounded by salt intake.^{6,8,10} Therefore, in the present study, the association of sodium intake (as an indicator of salt intake) with patient survival was also evaluated.

For the six selected food items, the FFQ determined the frequency of intake in terms of five categories: never, 1-2 times per month, 1-2 times per week, 3-4 times per week, and every day. Individuals who stated that they consumed miso soup every day

were further requested to record the number of bowls consumed per day. The estimated average daily sodium and energy intakes were computed based on the frequency of intake of 40 food items from the FFQ, using the Japanese Standard Tables of Food Composition. For daily intakes of food items, sodium and energy, the ranges of the Spearman correlation coefficients between dietary records and the FFQ (validity) were -0.30 to 0.65 in men and 0.00 to 0.67 in women (Table S1).²⁴

Because the FFQ data were incomplete for some patients in our original cohort, we decided to exclude from subsequent analysis patients for whom frequency data were missing for more than half (ie, at least 3) of the 6 selected food items (stomach, 93; colon, 38; rectum, 19). Consequently, 1931, 793 and 510 patients with stomach, colon and rectal cancer, respectively, were identified as subjects for analysis.

Follow up of the patients was performed by reference to the MCCH cancer registry up to December 2016. As a general rule for this registry, each individual follow up ends in the 11th year after diagnosis.¹³ Therefore, information on vital status at 11 years was available for the patients diagnosed during 1997-2005. For the patients diagnosed after 2006, vital status as of December 2016 was obtained. All of the colon cancer patients were completely followed up. Six patients with stomach cancer (0.3%) and two patients with rectal cancer (0.4%) were lost to follow up, and these were treated as censored cases.

2.3 | Statistical analysis

The end point of our analysis was all-cause death and disease-specific death due to the index cancer (stomach, colon and rectum) according to the ICD-10. Survival time was calculated for each patient from the date of diagnosis until the date of death or the end of follow up.

In the analysis, five original categories for frequency of food intake (exposure) were reorganized into four groups (never or 1-2 times per month, 1-2 times per week, 3-4 times per week, and every day) because only a few patients chose "never" or "1-2 times per month" for some foods. For sodium intake, energy-adjusted intake was estimated according to cancer site. Based on the distribution of energy-adjusted intake, the patients with cancers at each site were categorized into quartile groups. With regard to miso soup intake, six groups including the number of bowls consumed per day were also considered (never or 1-2 times per month, 1-2 times per week, 3-4 times per week, ≤ 1 bowl per day (every day), 1-2 bowls per day, > 2 bowls per day).

The Cox proportional hazards regression model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for mortality due to all causes or each index cancer controlled by confounders. We considered the following variables to be potential confounders: age, sex, year of diagnosis, referral status (from screening, other), stage (0-I, II, III and IV), histological type (adenocarcinoma, other), occupation (professional or office work, other), comorbidities

(no, yes), pretreatment body mass index (BMI), curative resection (no, yes), chemotherapy (no, yes) and energy intake (tertile groups for each cancer site). Staging was performed using the UICC TNM classification. Curability was evaluated mainly on the basis of the Japanese Classification for Gastric and Colorectal Carcinoma.^{25,26} Comorbidities included hypertension, ischemic heart disease, stroke, diabetes mellitus and liver disease. In the analysis for stomach cancer, family history of stomach cancer (no, yes) was controlled for. Family history of colorectal cancer (no, yes) was considered as a confounder in the analyses for cancers of the colon and rectum. Histories of smoking and alcohol consumption (never, ever) were also considered as confounders. Missing values for confounders were treated as an additional variable category, and included in the Cox model.

In the analysis using the Cox model, we first evaluated HR according to exposure among the subjects overall. Second, stratification according to stage (0-I and II, III and IV) was performed, because tumor progression, which is an important determinant of patient survival, may affect the dietary habits of cancer patients. Third, based on the results of overall analysis, some stratified analyses were considered for examining whether the association of food intake with survival was modified by the selected confounders.

Results were regarded as significant if the two-sided *P* values were < 0.05 . All statistical analyses were performed using SAS software (version 9.4; SAS Institute).

3 | RESULTS

During a median follow-up period of 6.5 years, among 1931 patients with stomach cancer, 827 all-cause and 512 stomach cancer deaths were observed. Among 793 colon cancer patients, 291 all-cause and 187 colon cancer deaths were observed during a median follow up of 7.1 years. For rectal cancer, 188 all-cause and 135 disease-specific deaths were documented during a median follow-up period of 6.2 years among 510 patients. Table 1 shows the characteristics of patients at the baseline and the distribution of causes of death according to cancer site. The patients with rectal cancer tended to be younger in comparison with those with stomach or colon cancer. Stomach cancer tended to be diagnosed at an early stage. The proportion of female patients was high among colon cancer patients. A large number of stomach cancer patients had a family history of the index cancer (27.6%).

Table 2 shows the associations between intakes of foods, including fresh fish, dried fish, seaweed, Japanese pickles and soy food, and the risk of all-cause and disease-specific death among the patients overall for each cancer site. Table 3 shows the risks for intakes of miso soup and sodium. For stomach cancer, intake of soy food showed a significant inverse association with the risk of all-cause ($P_{\text{trend}} = 0.01$) and disease-specific ($P_{\text{trend}} = 0.03$) death. Stomach cancer patients who had consumed soy food every day had a significantly lower risk of stomach cancer death (HR = 0.63, 95% CI: 0.40-0.99 vs never or 1-2 times per month). In contrast, the

TABLE 1 Characteristics of study subjects according to cancer site

Factor	Stomach	Colon	Rectum
Number of subjects, n	1931	793	510
Person-years	12 284.8	5417.4	3309.3
All-cause death, n	827	291	188
Cause of death, n (%)			
Vascular diseases	86 (10.4)	17 (5.8)	19 (10.1)
Pneumonia	75 (9.1)	18 (6.2)	6 (3.2)
Other cancers	86 (10.4)	46 (15.8)	17 (9.0)
Others	68 (8.2)	23 (7.9)	11 (5.9)
Index cancer	512 (61.9)	187 (64.3)	135 (71.8)
Age group, n (%)			
<60 y	456 (23.6)	189 (23.8)	179 (35.1)
≥60 y	1475 (76.4)	604 (76.2)	331 (64.9)
Age (years), mean ± SD	67.1 ± 10.9	66.5 ± 10.9	64.0 ± 11.5
Year of diagnosis, n (%)			
1997-2005	1029 (53.3)	439 (55.4)	262 (51.4)
2006-2013	902 (46.7)	354 (44.6)	248 (48.6)
Sex, n (%)			
Male	1350 (69.9)	428 (54.0)	320 (62.7)
Female	581 (30.1)	365 (46.0)	190 (37.3)
Referral status, n (%)			
From screen	431 (22.3)	191 (24.1)	96 (18.8)
Other	1500 (77.7)	602 (75.9)	414 (81.2)
Occupation, n (%)			
Professional or office work	443 (22.9)	208 (26.2)	129 (25.3)
Industrial work	728 (37.7)	262 (33.0)	207 (40.6)
Agriculture, forestry, or fishery	311 (16.1)	96 (12.1)	64 (12.5)
Others ^a	193 (10.0)	92 (11.6)	49 (9.6)
Missing	256 (13.3)	135 (17.0)	61 (12.0)
Stage of cancer, n (%)			
0-I	1307 (67.7)	324 (40.9)	216 (42.4)
II	141 (7.3)	147 (18.5)	89 (17.5)
III	121 (6.3)	152 (19.2)	120 (23.5)
IV	342 (17.7)	147 (18.5)	70 (13.7)
Unknown	20 (1.0)	23 (2.9)	15 (2.9)
Histological type, n (%)			
Adenocarcinoma	1764 (91.4)	787 (99.2)	487 (95.5)
Other	167 (8.6)	6 (0.8)	23 (4.5)
Curative resection, n (%)			
No	513 (26.6)	237 (29.9)	150 (29.4)
Yes	1418 (73.4)	556 (70.1)	360 (70.6)
Chemotherapy, n (%)			
No	1566 (81.1)	609 (76.8)	401 (78.6)
Yes	365 (18.9)	184 (23.2)	109 (21.4)
Comorbidities, ^b n (%)			
No	1198 (62.0)	468 (59.0)	319 (62.6)

(Continues)

TABLE 1 (Continued)

Factor	Stomach	Colon	Rectum
Yes	733 (38.0)	325 (41.0)	191 (37.4)
Family history of index cancer in first-degree relatives, n (%)			
No	1399 (72.4)	689 (86.9)	447 (87.7)
Yes	532 (27.6) ^c	104 (13.1) ^d	63 (12.3) ^d
Body mass index (kg/m ²), ^e n (%)			
<18.5	133 (6.9)	53 (6.7)	25 (4.9)
18.5 ≤ to <23.0	824 (42.7)	311 (39.2)	221 (43.3)
23.0 ≤ to <25.0	453 (23.4)	207 (26.1)	129 (25.3)
≥25	487 (25.2)	221 (27.9)	134 (26.3)
Missing	34 (1.8)	1 (0.1)	1 (0.2)
Smoking, n (%)			
Never	775 (40.1)	423 (53.3)	206 (40.4)
Ever	1116 (57.8)	352 (44.4)	289 (56.7)
Missing	40 (2.1)	18 (2.3)	15 (2.9)
Alcohol consumption, n (%)			
Never	776 (40.2)	356 (44.9)	203 (39.8)
Ever	1089 (56.4)	409 (51.6)	289 (56.7)
Missing	66 (3.4)	28 (3.5)	18 (3.5)
Energy intake (Kcal/d), mean ± SD	1548.8 ± 450.1	1483.0 ± 430.5	1483.4 ± 448.7

^aHousehold wife/Domestic help/Student/Others.^bComorbidities include hypertension/ischemic heart disease/stroke/diabetes mellitus/liver disease.^cHistory of stomach cancer in parents and siblings.^dHistory of colorectal cancer in parents and siblings.^eBody mass index was calculated based on pretreatment weight and height.

association of soy food intake with patient survival was unity for both colon ($P_{\text{trend}} = 0.65$ for all-cause death) and rectal ($P_{\text{trend}} = 0.98$) cancer. Intake of seaweed tended to be inversely associated with the risk of disease-specific death among patients with rectal cancer ($P_{\text{trend}} = 0.02$). For colon cancer, an inverse association with seaweed intake was observed for the risk of all-cause death ($P_{\text{trend}} = 0.03$). Intake of salted foods, such as dried fish and Japanese pickles, and sodium intake were not associated with patient survival for any of the three cancer sites. Intake of miso soup, one of the salted foods, showed a significant inverse association with the risk of all-cause ($P_{\text{trend}} = 0.03$) and stomach cancer ($P_{\text{trend}} = 0.04$) death among patients with stomach cancer. Analysis that included the number of bowls consumed per day also demonstrated a significant inverse association between miso soup intake and the risk of stomach cancer death ($P_{\text{trend}} = 0.04$). Although data are not shown in tables, further adjustment for sodium intake showed similar inverse association between miso soup intake and the risk of stomach cancer death ($P_{\text{trend}} = 0.06$; HR = 0.59, 95% CI: 0.35-0.99 for intake of more than two bowls per day vs never or 1-2 times per month).

To address the association between soy food and miso soup intake and patient survival, we attempted additional analysis based on reorganized groups, because the distribution of subjects was skewed in the original data. In this additional analysis using never or less than 1-2 times per week as the reference group, inverse associations of

soy food intake with the risk of all-cause ($P_{\text{trend}} = 0.01$) and disease-specific ($P_{\text{trend}} = 0.04$) death were observed for stomach cancer (Table S2), which were comparable to the results in the original analysis. The direction in mortality risk associated with miso soup intake was also similar to that in the original analysis.

Table 4 shows the distribution of food intake frequency according to early-stage (stage 0-I and II) and advanced-stage (stages III and IV) cancer for three cancer sites. Table 5 shows the associations of food intake with the risk of death according to early-stage and advanced-stage cancer among patients with stomach cancer. The risks for colon and rectal cancer are shown in Tables S3 and S4. Among the stomach cancer patients, those with advanced-stage cancer tended to consume soy food and miso soup less frequently (Table 4). There was no apparent difference in the distribution of food intake for patients with either colon or rectal cancer (Table 4). With regard to stomach cancer, an inverse association between intake of soy food and the risk of death was observed for patients with advanced-stage cancer (all-cause death, $P_{\text{trend}} = 0.01$; stomach cancer death, $P_{\text{trend}} = 0.01$ in Table 5). In contrast, intake of miso soup was inversely associated with the risk of death among patients with early-stage stomach cancer (all-cause death, $P_{\text{trend}} = 0.07$; stomach cancer death, $P_{\text{trend}} = 0.01$). With regard to colon and rectal cancer, an inverse association between seaweed intake and the risk of disease-specific death was observed among patients with advanced-stage colon cancer ($P_{\text{trend}} = 0.01$;

TABLE 2 Hazard ratio of all-cause and disease-specific death according to intake of selected Japanese foods

	Stomach					Colon					Rectum				
	Number of subjects	Person-years	Number of deaths	HR ^a	95% CI	Number of subjects	Person-years	Number of deaths	HR ^b	95% CI	Number of subjects	Person-years	Number of deaths	HR ^b	95% CI
All cause of death															
Fresh fish															
Never or 1-2 times per month	167	986.3	78	1.00 (reference)		54	324.4	24	1.00 (reference)		52	300.7	22	1.00 (reference)	
1-2 times per week	663	4085.5	280	0.98	0.76 - 1.27	252	1671.1	87	0.62	0.38 - 1.00	177	1110.1	69	1.26	0.71 - 2.22
3-4 times per week	671	4359.5	277	0.84	0.65 - 1.09	303	2073.8	111	0.55	0.34 - 0.89	187	1285.4	58	0.96	0.53 - 1.75
Everyday	364	2418.7	165	0.84	0.63 - 1.11	162	1178.2	61	0.70	0.42 - 1.17	88	576.3	36	0.96	0.51 - 1.81
p for trend					0.07					0.45					0.38
Dried fish															
Never or 1-2 times per month	685	4285.6	297	1.00 (reference)		300	1962.9	117	1.00 (reference)		196	1269.8	65	1.00 (reference)	
1-2 times per week	725	4650.1	298	0.94	0.80 - 1.11	311	2259.2	94	0.77	0.58 - 1.03	194	1260.9	70	1.00	0.69 - 1.44
3-4 times per week	245	1565.2	110	1.00	0.80 - 1.25	87	585.4	33	0.86	0.57 - 1.30	57	376.6	23	1.14	0.68 - 1.92
Everyday	57	344.7	21	0.86	0.55 - 1.34	24	149.2	14	1.74	0.94 - 3.21	11	76.4	5	1.23	0.48 - 3.20
p for trend					0.60					0.97					0.60
Seaweeds															
Never or 1-2 times per month	222	1326.1	98	1.00 (reference)		90	545.0	40	1.00 (reference)		76	462.5	24	1.00 (reference)	
1-2 times per week	711	4443.2	309	0.91	0.72 - 1.15	261	1752.6	93	1.05	0.70 - 1.58	169	1015.6	71	1.01	0.61 - 1.69
3-4 times per week	629	4108.4	266	0.91	0.72 - 1.16	261	1819.5	92	0.98	0.64 - 1.51	175	1206.2	58	0.78	0.46 - 1.33
Everyday	324	2119.7	138	1.00	0.76 - 1.32	163	1177.4	58	0.65	0.41 - 1.03	75	540.1	25	0.70	0.37 - 1.34
p for trend					0.87					0.03					0.10
Japanese pickles															
Never or 1-2 times per month	365	2141.4	163	1.00 (reference)		143	904.4	51	1.00 (reference)		99	562.2	34	1.00 (reference)	
1-2 times per week	375	2426.5	138	0.74	0.59 - 0.94	148	1080.5	54	1.14	0.75 - 1.71	116	737.8	44	0.88	0.55 - 1.40
3-4 times per week	419	2686.9	176	0.80	0.64 - 1.00	176	1182.8	62	1.24	0.83 - 1.84	116	753.2	48	0.91	0.57 - 1.46
Everyday	706	4605.1	324	0.86	0.71 - 1.06	297	2056.7	112	1.13	0.78 - 1.64	163	1161.2	52	0.73	0.46 - 1.15
p for trend					0.46					0.30					0.20
Soy food															
Never or 1-2 times per month	89	564.6	34	1.00 (reference)		26	172.6	10	1.00 (reference)		21	113.3	10	1.00 (reference)	
1-2 times per week	346	1933.1	158	0.91	0.62 - 1.32	130	841.6	49	1.18	0.56 - 2.48	96	536.3	40	1.73	0.76 - 3.95
3-4 times per week	620	3908.9	266	0.81	0.57 - 1.17	235	1656.2	87	0.82	0.40 - 1.68	151	1015.3	49	1.23	0.54 - 2.80
Everyday	830	5572.6	355	0.72	0.50 - 1.04	389	2658.7	139	0.93	0.46 - 1.90	229	1579.9	83	1.44	0.63 - 3.28
p for trend					0.01					0.65					0.98
Disease-specific death															
Fresh fish															
Never or 1-2 times per month	167	986.3	50	1.00 (reference)		54	324.4	17	1.00 (reference)		52	300.7	15	1.00 (reference)	
1-2 times per week	663	4085.5	173	0.94	0.68 - 1.30	252	1671.1	58	0.97	0.48 - 1.96	177	1110.1	53	1.74	0.86 - 3.54
3-4 times per week	671	4359.5	172	0.90	0.65 - 1.25	303	2073.8	76	0.88	0.44 - 1.78	187	1285.4	37	1.15	0.54 - 2.43
Everyday	364	2418.7	106	0.92	0.64 - 1.32	162	1178.2	32	0.75	0.35 - 1.63	88	576.3	27	1.30	0.60 - 2.82
p for trend					0.63					0.20					0.69
Dried fish															
Never or 1-2 times per month	685	4285.6	191	1.00 (reference)		300	1962.9	86	1.00 (reference)		196	1269.8	44	1.00 (reference)	
1-2 times per week	725	4650.1	187	0.88	0.72 - 1.09	311	2259.2	56	0.67	0.46 - 0.97	194	1260.9	54	1.10	0.71 - 1.70
3-4 times per week	245	1565.2	62	0.93	0.69 - 1.25	87	585.4	21	0.95	0.58 - 1.56	57	376.6	16	1.08	0.57 - 2.05
Everyday	57	344.7	16	0.95	0.56 - 1.60	24	149.2	7	0.99	0.42 - 2.31	11	76.4	4	1.67	0.57 - 4.90
p for trend					0.50					0.31					0.47
Seaweeds															
Never or 1-2 times per month	222	1326.1	62	1.00 (reference)		90	545.0	30	1.00 (reference)		76	462.5	17	1.00 (reference)	
1-2 times per week	711	4443.2	202	1.00	0.75 - 1.35	261	1752.6	56	1.04	0.59 - 1.80	169	1015.6	52	1.12	0.60 - 2.08
3-4 times per week	629	4108.4	155	0.92	0.68 - 1.26	261	1819.5	61	1.10	0.63 - 1.92	175	1206.2	45	0.75	0.39 - 1.45
Everyday	324	2119.7	83	1.23	0.86 - 1.74	163	1177.4	36	0.80	0.44 - 1.46	75	540.1	13	0.48	0.20 - 1.11
p for trend					0.44					0.64					0.02
Japanese pickles															
Never or 1-2 times per month	365	2141.4	109	1.00 (reference)		143	904.4	37	1.00 (reference)		99	562.2	26	1.00 (reference)	
1-2 times per week	375	2426.5	104	0.82	0.62 - 1.09	148	1080.5	37	1.44	0.81 - 2.56	116	737.8	30	0.77	0.44 - 1.35
3-4 times per week	419	2686.9	106	0.84	0.64 - 1.11	176	1182.8	40	1.16	0.65 - 2.08	116	753.2	38	0.97	0.56 - 1.69
Everyday	706	4605.1	180	0.84	0.65 - 1.09	297	2056.7	65	1.23	0.71 - 2.13	163	1161.2	35	0.66	0.38 - 1.14
p for trend					0.29					0.91					0.23
Soy food															
Never or 1-2 times per month	89	564.6	23	1.00 (reference)		26	172.6	7	1.00 (reference)		21	113.3	6	1.00 (reference)	
1-2 times per week	346	1933.1	105	0.77	0.48 - 1.22	130	841.6	36	0.81	0.32 - 2.05	96	536.3	32	2.13	0.76 - 5.91
3-4 times per week	620	3908.9	177	0.75	0.48 - 1.17	235	1656.2	56	0.53	0.22 - 1.31	151	1015.3	35	1.41	0.50 - 3.97
Everyday	830	5572.6	197	0.63	0.40 - 0.99	389	2658.7	84	0.67	0.28 - 1.64	229	1579.9	58	1.61	0.57 - 4.51
p for trend					0.03					0.32					0.85

^aAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), family history of stomach cancer (no, yes), comorbidities (no, yes), BMI (<18.5, 18.5 ≤ <23.0, 23.0 ≤ <25.0, ≥25.0, missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^bAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), family history of colorectal cancer (no, yes), comorbidities (no, yes), BMI (<18.5, 18.5 ≤ <23.0, 23.0 ≤ <25.0, ≥25.0, missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

Table S3). Among patients with advanced-stage rectal cancer, seaweed intake tended to be inversely associated with the risk of all-cause death ($P_{\text{trend}} = 0.13$; Table S4).

To further investigate the associations between soy food and miso soup intake and stomach cancer survival, stratified analyses were performed based on selected confounders; that is, a family history of stomach cancer and histories of smoking and alcohol consumption (Table 6). These confounders had been identified as prognostic factors for stomach cancer in our previous studies.^{13,23} In addition, analysis stratified by age group was also performed, because these previous studies had shown that the prognostic factors

might be modified by aging. Regardless of whether or not patients had a family history of stomach cancer, intakes of soy food and miso soup tended to be inversely associated with the risk of all-cause and stomach cancer death. Among never-smokers, intake of soy food was associated with a decreased risk of all-cause ($P_{\text{trend}} = 0.01$) and stomach cancer ($P_{\text{trend}} = 0.01$) death. An inverse association between miso soup intake and stomach cancer death was also observed among never-smokers ($P_{\text{trend}} = 0.05$). Stratification according to history of alcohol consumption demonstrated inverse associations between soy food and miso soup intake and the risk of all-cause and stomach cancer death among never-drinkers. According

TABLE 3 Hazard ratio of all-cause and disease-specific death according to intake of miso soup and sodium

	Stomach					Colon					Rectum				
	Number of subjects	Person-years	Number of deaths	HR ^a	95% CI	Number of subjects	Person-years	Number of deaths	HR ^b	95% CI	Number of subjects	Person-years	Number of deaths	HR ^b	95% CI
All cause of death															
Miso soup															
Never or 1-2 times per month	67	319.9	34	1.00 (reference)		33	198.8	10	1.00 (reference)		17	96.8	7	1.00 (reference)	
1-2 times per week	110	596.8	42	1.02	0.64 - 1.63	42	265.7	16	0.98	0.43 - 2.23	41	240.5	15	0.87	0.34 - 2.23
3-4 times per week	222	1420.9	88	0.70	0.46 - 1.05	93	594.3	32	0.93	0.45 - 1.96	68	428.6	21	0.44	0.17 - 1.09
Everyday	1499	9738.8	649	0.72	0.50 - 1.03	615	4289.3	228	0.91	0.47 - 1.77	379	2507.9	143	0.77	0.34 - 1.74
p for trend					0.03					0.71					0.95
Miso soup (including data for intake per day)															
Never or 1-2 times per month	67	319.9	34	1.00 (reference)		33	198.8	10	1.00 (reference)		17	96.8	7	1.00 (reference)	
1-2 times per week	110	596.8	42	1.03	0.64 - 1.65	42	265.7	16	1.00	0.44 - 2.30	41	240.5	15	0.89	0.35 - 2.29
3-4 times per week	222	1420.9	88	0.70	0.46 - 1.06	93	594.3	32	0.93	0.44 - 1.95	68	428.6	21	0.48	0.19 - 1.20
Everyday (<1 bowl per day)	404	2428.6	178	0.73	0.50 - 1.07	161	997.9	71	1.17	0.58 - 2.33	110	736.6	38	0.78	0.33 - 1.85
Everyday (1-2 bowls per day)	514	3499.2	213	0.71	0.49 - 1.04	254	1865.8	83	0.85	0.42 - 1.69	134	903.5	45	0.72	0.31 - 1.68
Everyday (>2 bowls per day)	478	3151.2	214	0.72	0.49 - 1.06	163	1146.7	63	0.91	0.45 - 1.84	106	680.5	49	0.94	0.39 - 2.27
p for trend					0.09					0.49					0.48
Quartile of sodium intake per day															
1 (low)	416	2509.3	160	1.00 (reference)		171	1117.6	66	1.00 (reference)		111	658.0	36	1.00 (reference)	
2	414	2548.5	191	0.92	0.74 - 1.15	172	1242.1	52	0.84	0.57 - 1.24	110	723.6	36	0.83	0.50 - 1.40
3	416	2719.2	179	0.97	0.78 - 1.21	171	1110.2	73	1.06	0.74 - 1.53	111	789.8	32	0.87	0.51 - 1.47
4 (high)	415	2660.7	183	0.87	0.69 - 1.11	171	1247.6	54	0.89	0.59 - 1.34	110	722.0	48	1.45	0.84 - 2.52
p for trend					0.38					0.85					0.21
Disease-specific death															
Miso soup															
Never or 1-2 times per month	67	319.9	27	1.00 (reference)		33	198.8	7	1.00 (reference)		17	96.8	5	1.00 (reference)	
1-2 times per week	110	596.8	30	0.84	0.48 - 1.47	42	265.7	13	0.90	0.30 - 2.73	41	240.5	12	1.12	0.37 - 3.36
3-4 times per week	222	1420.9	63	0.66	0.41 - 1.06	93	594.3	24	1.34	0.52 - 3.47	68	428.6	16	0.62	0.21 - 1.80
Everyday	1499	9738.8	384	0.65	0.43 - 0.99	615	4289.3	139	0.92	0.38 - 2.23	379	2507.9	101	1.00	0.38 - 2.64
p for trend					0.04					0.76					0.83
Miso soup (including data for intake per day)															
Never or 1-2 times per month	67	319.9	27	1.00 (reference)		33	198.8	7	1.00 (reference)		17	96.8	5	1.00 (reference)	
1-2 times per week	110	596.8	30	0.84	0.48 - 1.46	42	265.7	13	0.92	0.29 - 2.96	41	240.5	12	1.07	0.35 - 3.24
3-4 times per week	222	1420.9	63	0.65	0.40 - 1.05	93	594.3	24	1.30	0.48 - 3.52	68	428.6	16	0.64	0.22 - 1.87
Everyday (<1 bowl per day)	404	2428.6	125	0.69	0.44 - 1.08	161	997.9	49	1.15	0.44 - 3.01	110	736.6	28	0.95	0.34 - 2.64
Everyday (1-2 bowls per day)	514	3499.2	121	0.64	0.41 - 0.99	254	1865.8	45	0.62	0.24 - 1.63	134	903.5	34	0.93	0.34 - 2.54
Everyday (>2 bowls per day)	478	3151.2	114	0.61	0.39 - 0.96	163	1146.7	37	1.46	0.55 - 3.89	106	680.5	32	1.17	0.41 - 3.39
p for trend					0.04					0.94					0.49
Quartile of sodium intake per day															
1 (low)	416	2509.3	114	1.00 (reference)		171	1117.6	49	1.00 (reference)		111	658.0	30	1.00 (reference)	
2	414	2548.5	127	0.85	0.65 - 1.11	172	1242.1	34	0.74	0.44 - 1.26	110	723.6	27	0.86	0.47 - 1.56
3	416	2719.2	105	0.94	0.71 - 1.24	171	1110.2	45	1.24	0.78 - 1.96	111	789.8	26	0.92	0.50 - 1.68
4 (high)	415	2660.7	106	0.86	0.63 - 1.18	171	1247.6	32	0.99	0.60 - 1.65	110	722.0	32	1.50	0.78 - 2.90
p for trend					0.53					0.76					0.27

^aAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), family history of index cancer (no, yes), comorbidities (no, yes), BMI (<18.5, 18.5 ≤ <23.0, 23.0 ≤ <25.0, ≥25.0, missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^bAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), family history of colorectal cancer (no, yes), comorbidities (no, yes), BMI (<18.5, 18.5 ≤ <23.0, 23.0 ≤ <25.0, ≥25.0, missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

to age group (<60 years, ≥60 years), inverse associations for intakes of soy food and miso soup were clear in older patients (Table S5). Although such inverse associations were also observed in younger patients, the trend test showed that this was not significant.

4 | DISCUSSION

In this hospital-based patient cohort study, we clarified the associations between pretreatment intake of traditional Japanese food and the risk of all-cause and disease-specific death among Japanese patients with digestive tract cancers. Although the food items analyzed were limited, our results showed that the magnitude of risk associated with each food item differed among cancers of the stomach, colon and rectum. Among patients with stomach cancer, intake of soy food and miso soup was inversely associated with the risk of all-cause and stomach cancer death. For colon and rectal cancer, no association was observed between intake of these foods and the risk of death. In contrast, intake of seaweed tended to be associated with a decreased risk of death among patients with colon and rectal cancer.

With regard to the effects of soy food and miso soup intake on the disease progression of digestive tract cancer, previous epidemiologic studies have reported a positive association for intake of miso soup^{6,8}

and an inverse association for soy food with the risk of stomach cancer.^{8,10} However, it has been pointed out that these associations might be confounded by intake of other foods such as salt and vegetables.^{8,10} Very few studies have investigated the associations of soy food and miso soup intake with cancer patient survival. In the present study, sodium intake had no significant effect on patient survival. Additional adjustment for sodium intake did not substantially change the risk of death for miso soup (one of the salted foods) intake among patients with stomach cancer, suggesting that miso soup intake may have favorable independent impacts on patient survival. One previous study has suggested that intake of tofu might be associated with improved survival in patients with stomach cancer.¹⁴ An early epidemiologic study that evaluated the mortality risk for stomach cancer demonstrated a decreased risk associated with miso soup intake.^{27,28} These previous studies appear to support our present results. In contrast, the effects of soy food and miso soup intake on survival of patients with colorectal cancer have never been investigated previously. The association of seaweed intake with survival of patients with colorectal cancer has also remained unclear, although some studies, mainly case-control studies, have demonstrated an inverse association between seaweed intake and the risk of colorectal cancer.^{29,30} Our present results indicate that seaweed intake may favorably impact not only colorectal cancer risk but also patient survival.

TABLE 4 Distribution of intake of selected Japanese foods, miso soup and sodium stratified by cancer site and stage

	Stomach			Colon			Rectum		
	Stage 0-II	Stage III-IV	P ^a	Stage 0-II	Stage III-IV	P	Stage 0-II	Stage III-IV	P
Fresh fish									
Never or 1-2 times per month	8.3	10.4	.44	8.3	5.5	.21	11.0	9.0	.40
1-2 times per week	36.2	34.1		31.7	33.8		34.5	35.1	
3-4 times per week	36.3	34.8		37.8	42.4		39.2	35.1	
Every day	19.1	20.6		22.3	18.3		15.3	20.7	
Dried fish									
Never or 1-2 times per month	39.6	41.0	.74	41.0	41.8	.60	42.5	42.7	.20
1-2 times per week	43.0	40.2		44.5	40.4		45.0	38.6	
3-4 times per week	14.2	14.9		11.5	13.8		9.9	16.4	
Every day	3.2	3.9		3.0	4.0		2.6	2.3	
Seaweeds									
Never or 1-2 times per month	11.4	13.1	.37	11.3	12.0	.70	15.5	15.7	.59
1-2 times per week	37.0	39.9		33.3	34.7		33.8	34.6	
3-4 times per week	33.8	31.5		35.1	30.9		33.8	37.3	
Every day	17.8	15.5		20.3	22.3		16.9	12.4	
Japanese pickles									
Never or 1-2 times per month	18.8	22.0	.34	20.2	16.0	.22	22.0	17.4	.57
1-2 times per week	19.9	21.3		17.6	21.2		22.4	25.0	
3-4 times per week	23.0	20.8		24.6	21.2		22.0	25.0	
Every day	38.3	35.9		37.6	41.5		33.6	32.6	
Soy food									
Never or 1-2 times per month	5.0	4.0	.01	4.3	1.7	.13	4.0	4.8	.92
1-2 times per week	17.0	22.7		15.1	18.6		18.6	20.4	
3-4 times per week	31.7	36.7		29.0	31.2		31.1	29.6	
Every day	46.2	36.7		51.5	48.5		46.3	45.2	
Miso soup (including data for intake per day)									
Never or 1-2 times per month	3.3	5.1	.04	5.1	3.6	.40	2.8	5.1	.30
1-2 times per week	5.9	7.1		5.4	6.5		8.5	8.4	
3-4 times per week	11.7	14.0		11.6	12.7		16.2	12.4	
Every day (≤ 1 bowl per day)	21.7	25.1		19.7	25.0		20.5	27.5	
Every day (1-2 bowls per day)	29.6	26.0		34.9	33.0		30.0	24.7	
Every day (> 2 bowls per day)	27.9	22.8		23.3	19.2		21.9	21.9	
Quartile of sodium intake per day									
1 (low)	24.7	25.8	.06	23.9	26.9	.06	25.9	25.1	.41
2	23.3	29.3		28.7	19.4		22.9	28.2	
3	26.1	22.7		23.4	26.5		27.8	21.5	
4 (high)	25.8	22.2		24.1	27.3		23.3	25.1	

^a χ^2 test for comparing frequencies between stages 0-II and III-IV.

Some differences in the association between intake of certain food items and both cancer stage and patient survival were observed. Although stomach cancer tended to be diagnosed at an earlier stage than cancers of the colon and rectum in the present study, as shown in Table 1, the stage distributions for cancers of the stomach, colon and rectum were similar to those in national reports such as "Survival

Statistics of Japanese Association of Clinical Cancer Centers."³¹ Our analysis for stomach cancer revealed some variations in the frequencies of soy food and miso soup intake (Table 4) and risk estimates (Table 5) across stages. Such frequency variations for cancers of the colon and rectum were unclear. We interpreted the results for stomach cancer as follows. First, patients with early-stage stomach cancer

TABLE 5 Hazard ratio of all-cause and disease-specific death for stomach cancer according to intake of selected Japanese foods, miso soup and sodium stratified by stage

	All-cause death						Stomach cancer death					
	Stage 0-II ^a			Stage III-IV ^b			Stage 0-II ^a			Stage III-IV ^b		
	Number of deaths	HR	95% CI	Number of deaths	HR	95% CI	Number of deaths	HR	95% CI	Number of deaths	HR	95% CI
Fresh fish												
Never or 1-2 times per month	34	1.00 (reference)		40	1.00 (reference)		9	1.00 (reference)		39	1.00 (reference)	
1-2 times per week	136	0.90	0.61 - 1.33	141	0.94	0.65 - 1.35	37	1.04	0.48 - 2.24	134	0.90	0.62 - 1.31
3-4 times per week	127	0.69	0.46 - 1.03	144	0.99	0.69 - 1.43	32	0.73	0.33 - 1.61	137	0.97	0.67 - 1.40
Everyday	76	0.80	0.52 - 1.23	85	0.82	0.55 - 1.23	24	1.19	0.51 - 2.78	80	0.81	0.53 - 1.22
p for trend			0.12			0.41			0.95			0.43
Dried fish												
Never or 1-2 times per month	136	1.00 (reference)		154	1.00 (reference)		42	1.00 (reference)		145	1.00 (reference)	
1-2 times per week	140	1.16	0.91 - 1.48	151	0.80	0.63 - 1.02	39	0.97	0.62 - 1.54	145	0.82	0.64 - 1.06
3-4 times per week	55	1.30	0.93 - 1.80	54	0.95	0.68 - 1.33	11	0.90	0.45 - 1.80	50	0.99	0.70 - 1.40
Everyday	7	0.82	0.38 - 1.78	14	0.88	0.50 - 1.54	2	0.84	0.20 - 3.57	14	0.92	0.52 - 1.63
p for trend			0.27			0.43			0.73			0.62
Seaweeds												
Never or 1-2 times per month	42	1.00 (reference)		55	1.00 (reference)		7	1.00 (reference)		55	1.00 (reference)	
1-2 times per week	135	0.87	0.61 - 1.24	167	0.90	0.66 - 1.24	40	1.64	0.72 - 3.73	158	0.87	0.63 - 1.21
3-4 times per week	130	0.89	0.62 - 1.28	128	0.83	0.59 - 1.16	34	1.67	0.72 - 3.86	118	0.77	0.55 - 1.08
Everyday	74	0.84	0.56 - 1.25	62	0.95	0.64 - 1.40	22	1.84	0.75 - 4.50	59	0.95	0.64 - 1.42
p for trend			0.55			0.61			0.28			0.54
Japanese pickles												
Never or 1-2 times per month	72	1.00 (reference)		87	1.00 (reference)		23	1.00 (reference)		82	1.00 (reference)	
1-2 times per week	45	0.50	0.34 - 0.73	91	0.91	0.67 - 1.23	15	0.53	0.27 - 1.04	89	0.93	0.68 - 1.27
3-4 times per week	87	0.79	0.58 - 1.09	87	0.93	0.68 - 1.27	23	0.67	0.36 - 1.22	82	0.95	0.69 - 1.30
Everyday	168	0.82	0.61 - 1.09	147	0.93	0.69 - 1.24	40	0.64	0.37 - 1.13	137	0.95	0.70 - 1.29
p for trend			0.99			0.70			0.28			0.82
Soy food												
Never or 1-2 times per month	16	1.00 (reference)		18	1.00 (reference)		5	1.00 (reference)		18	1.00 (reference)	
1-2 times per week	64	0.95	0.54 - 1.65	92	0.76	0.45 - 1.29	16	0.65	0.23 - 1.84	89	0.75	0.45 - 1.28
3-4 times per week	108	0.84	0.49 - 1.44	153	0.74	0.44 - 1.23	31	0.81	0.31 - 2.13	143	0.71	0.43 - 1.19
Everyday	195	0.82	0.48 - 1.38	149	0.57	0.34 - 0.96	51	0.72	0.28 - 1.86	140	0.56	0.33 - 0.95
p for trend			0.29			0.01			0.78			0.01
Miso soup (including data for intake per day)												
Never or 1-2 times per month	13	1.00 (reference)		20	1.00 (reference)		6	1.00 (reference)		20	1.00 (reference)	
1-2 times per week	15	0.80	0.37 - 1.73	27	1.00	0.54 - 1.87	5	0.45	0.13 - 1.58	25	0.91	0.48 - 1.71
3-4 times per week	32	0.53	0.27 - 1.02	53	0.72	0.42 - 1.24	10	0.34	0.12 - 0.98	51	0.70	0.40 - 1.22
Everyday (<1 bowl per day)	74	0.63	0.34 - 1.15	100	0.81	0.48 - 1.35	28	0.49	0.19 - 1.24	95	0.78	0.47 - 1.31
Everyday (1-2 bowls per day)	107	0.54	0.30 - 0.98	102	0.77	0.46 - 1.29	24	0.27	0.11 - 0.71	95	0.74	0.44 - 1.24
Everyday (>2 bowls per day)	119	0.53	0.29 - 0.97	92	0.77	0.45 - 1.30	26	0.27	0.11 - 0.72	87	0.72	0.42 - 1.23
p for trend			0.07			0.36			0.01			0.31
Quartile of sodium intake per day												
1 (low)	63	1.00 (reference)		93	1.00 (reference)		20	1.00 (reference)		92	1.00 (reference)	
2	73	1.00	0.71 - 1.41	112	0.88	0.66 - 1.18	22	1.23	0.65 - 2.34	103	0.82	0.61 - 1.11
3	95	1.12	0.81 - 1.55	83	0.96	0.70 - 1.32	24	1.07	0.57 - 2.01	81	0.96	0.70 - 1.33
4 (high)	94	0.90	0.63 - 1.27	85	0.92	0.64 - 1.33	22	0.81	0.40 - 1.62	81	0.89	0.62 - 1.29
p for trend			0.67			0.82			0.47			0.82

^aAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II), histological type (adeno, other), referral status (from screening, other), occupation (professional or office worker, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), family history of stomach cancer (no, yes), comorbidities (no, yes), BMI (<18.5, 18.5 - <23.0, 23.0 - <25.0, ≥25.0, missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^bAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (III, IV), histological type (adeno, other), referral status (from screening, other), occupation (professional or office worker, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), family history of stomach cancer (no, yes), comorbidities (no, yes), BMI (<18.5, 18.5 - <23.0, 23.0 - <25.0, ≥25.0, missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^cStatistical test for interaction between stage group (0-II and III-IV) and food intake.

had consumed soy food and miso soup more frequently than those with advanced-stage cancer, suggesting that intake of these foods might have prevented the progression of stomach tumors. Meanwhile, miso soup intake tended to be closely associated with the risk of death among patients with early-stage cancer, whereas frequent intake of soy food was significantly associated with a reduced risk of death among patients with advanced-stage cancer. These differences in mortality risk between early-stage and advanced-stage cancer may reflect the impacts of other lifestyle factors related to the intake of soy food and miso soup. However, inverse associations of soy food and miso soup intake with survival of stomach cancer patients are biologically plausible. Soybean products, including soy food and miso soup, are a good source of isoflavones.³² In vitro studies have shown that isoflavones inhibit the growth and proliferation of stomach cancer cells.^{33,34} Hypothetically, among patients frequently consuming soybean products during the pretreatment period, stomach cancer may grow more slowly. In addition, studies using cachectic mouse models employing cell lines established from advanced stomach cancer have shown that isoflavone treatment induces tumor cytostasis and attenuation of cachexia, thus prolonging survival.³⁵ These biological studies

suggest that intake of soybean products would likely favorably impact the survival of patients with stomach cancer, regardless of the tumor stage at the time of diagnosis. Second, patients with advanced-stage stomach cancer might have had poor nutritional status due to eating disorders, and, consequently, their frequencies of soy food and miso soup intake might have been reduced (Table 4). However, the intake frequencies of food items other than soybean products were similar between the early-stage and advanced-stage cancer groups. Therefore, it is unlikely that eating disorders caused by disease progression would have completely explained the differences in food intake frequency and mortality risk between the two groups. Even if patients with advanced-stage stomach cancer had suffered eating problems, consumption of soybean products, especially soy food, would have reduced their risk of death, as shown in Table 5. For patients with cancers of the colon and rectum, an inverse association between seaweed intake and the risk of death was pronounced in those with advanced-stage cancer (Tables S3 and S4). These results must be interpreted carefully, because the risk estimates according to stage were based on a limited number of events. Furthermore, the cause of death was different between patients with colon and rectal cancer,

TABLE 6 Hazard ratio of all-cause and disease-specific death for stomach cancer according to intake of soy food and miso soup stratified by family history of stomach cancer and histories of smoking and alcohol consumption

	All-cause death						Stomach cancer death					
	Absent			Present			Absent			Present		
	Number of deaths	HR	95% CI	Number of deaths	HR	95% CI	Number of deaths	HR	95% CI	Number of deaths	HR	95% CI
Family history of stomach cancer ^a												
Soy food												
Never or 1-2 times per month	24	1.00 (reference)		10	1.00 (reference)		18	1.00 (reference)		5	1.00 (reference)	
1-2 times per week	116	0.98	0.62 - 1.53	42	0.73	0.35 - 1.51	79	0.85	0.50 - 1.44	26	0.64	0.22 - 1.86
3-4 times per week	190	0.89	0.57 - 1.37	76	0.61	0.31 - 1.21	130	0.83	0.50 - 1.39	47	0.56	0.21 - 1.51
Everyday	267	0.80	0.52 - 1.23	88	0.50	0.25 - 1.00	147	0.66	0.39 - 1.11	50	0.50	0.18 - 1.39
p for trend			0.06			0.02			0.04			0.20
p for interaction ^d				0.42						0.70		
Miso soup (including data for intake per day)												
Never or 1-2 times per month	24	1.00 (reference)		10	1.00 (reference)		20	1.00 (reference)		7	1.00 (reference)	
1-2 times per week	30	1.10	0.63 - 1.94	12	0.64	0.26 - 1.55	22	1.00	0.52 - 1.92	8	0.34	0.11 - 1.06
3-4 times per week	64	0.68	0.42 - 1.12	24	0.56	0.25 - 1.22	48	0.74	0.43 - 1.30	15	0.29	0.10 - 0.80
Everyday (≤ 1 bowl per day)	135	0.73	0.47 - 1.16	43	0.53	0.25 - 1.12	97	0.76	0.46 - 1.28	28	0.33	0.12 - 0.89
Everyday (1-2 bowls per day)	154	0.73	0.46 - 1.15	59	0.48	0.23 - 0.98	85	0.68	0.40 - 1.14	36	0.36	0.14 - 0.92
Everyday (> 2 bowls per day)	160	0.71	0.44 - 1.12	54	0.52	0.25 - 1.07	85	0.65	0.38 - 1.12	29	0.27	0.10 - 0.73
p for trend			0.14			0.15			0.05			0.17
p for interaction				0.73						0.97		
History of smoking ^b												
Soy food												
Never or 1-2 times per month	11	1.00 (reference)		22	1.00 (reference)		7	1.00 (reference)		15	1.00 (reference)	
1-2 times per week	56	1.00	0.51 - 1.96	98	0.83	0.52 - 1.33	41	0.76	0.32 - 1.85	62	0.72	0.41 - 1.29
3-4 times per week	99	0.78	0.41 - 1.51	163	0.78	0.49 - 1.23	70	0.69	0.30 - 1.62	105	0.71	0.41 - 1.25
Everyday	137	0.60	0.31 - 1.15	207	0.80	0.51 - 1.27	74	0.47	0.19 - 1.11	117	0.75	0.42 - 1.32
p for trend			0.01			0.51			0.01			0.71
p for interaction				0.05						0.12		
Miso soup (including data for intake per day)												
Never or 1-2 times per month	15	1.00 (reference)		19	1.00 (reference)		14	1.00 (reference)		13	1.00 (reference)	
1-2 times per week	13	1.39	0.63 - 3.07	28	0.64	0.35 - 1.19	8	0.98	0.38 - 2.55	21	0.59	0.28 - 1.25
3-4 times per week	32	1.03	0.54 - 1.98	54	0.40	0.23 - 0.70	24	0.89	0.43 - 1.87	38	0.41	0.21 - 0.81
Everyday (≤ 1 bowl per day)	66	0.76	0.42 - 1.36	108	0.50	0.30 - 0.86	45	0.58	0.30 - 1.11	77	0.58	0.30 - 1.12
Everyday (1-2 bowls per day)	86	0.82	0.46 - 1.48	121	0.47	0.27 - 0.79	52	0.61	0.32 - 1.17	67	0.51	0.26 - 1.00
Everyday (> 2 bowls per day)	69	0.81	0.44 - 1.48	140	0.45	0.26 - 0.77	37	0.60	0.30 - 1.22	75	0.46	0.23 - 0.91
p for trend			0.15			0.10			0.05			0.30
p for interaction				0.86						0.39		
History of alcohol drinking ^c												
Soy food												
Never or 1-2 times per month	13	1.00 (reference)		19	1.00 (reference)		11	1.00 (reference)		12	1.00 (reference)	
1-2 times per week	63	0.90	0.49 - 1.67	88	0.92	0.55 - 1.52	43	0.52	0.26 - 1.04	59	0.92	0.48 - 1.76
3-4 times per week	102	0.80	0.44 - 1.45	150	0.86	0.52 - 1.40	71	0.58	0.30 - 1.13	96	0.87	0.46 - 1.62
Everyday	142	0.66	0.36 - 1.19	198	0.84	0.51 - 1.37	76	0.43	0.22 - 0.85	112	0.85	0.45 - 1.60
p for trend			0.03			0.41			0.05			0.55
p for interaction				0.14						0.13		
Miso soup (including data for intake per day)												
Never or 1-2 times per month	14	1.00 (reference)		20	1.00 (reference)		13	1.00 (reference)		14	1.00 (reference)	
1-2 times per week	19	1.13	0.55 - 2.35	22	0.93	0.49 - 1.78	13	0.66	0.29 - 1.51	17	1.16	0.52 - 2.61
3-4 times per week	42	1.11	0.59 - 2.09	44	0.46	0.26 - 0.81	28	0.88	0.43 - 1.77	33	0.47	0.23 - 0.95
Everyday (≤ 1 bowl per day)	69	1.03	0.57 - 1.87	102	0.57	0.34 - 0.96	46	0.93	0.48 - 1.79	73	0.58	0.30 - 1.12
Everyday (1-2 bowls per day)	79	0.80	0.44 - 1.46	126	0.59	0.35 - 0.99	43	0.65	0.33 - 1.26	73	0.58	0.30 - 1.13
Everyday (> 2 bowls per day)	80	0.74	0.40 - 1.35	121	0.74	0.43 - 1.25	48	0.63	0.32 - 1.26	62	0.70	0.35 - 1.40
p for trend			0.02			0.80			0.16			0.63
p for interaction				0.04						0.35		

^aAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), smoking (never, ever, missing), alcohol drinking (never, ever, missing), comorbidities (no, yes), BMI (< 18.5 , $18.5 \leq < 23.0$, $23.0 \leq < 25.0$, ≥ 25.0 , missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^bAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), alcohol drinking (never, ever, missing), family history of stomach cancer (no, yes), comorbidities (no, yes), BMI (< 18.5 , $18.5 \leq < 23.0$, $23.0 \leq < 25.0$, ≥ 25.0 , missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^cAdjusted by age (continuous), year of diagnosis (continuous), sex, stage (0-I, II, III, IV, unknown), histological type (adeno, other), referral status (from screening, other), occupation (professional or office work, other, missing), smoking (never, ever, missing), family history of stomach cancer (no, yes), comorbidities (no, yes), BMI (< 18.5 , $18.5 \leq < 23.0$, $23.0 \leq < 25.0$, ≥ 25.0 , missing), curative resection (no, yes), chemotherapy (no, yes), and energy intake (tertile groups, missing).

^dStatistical test for interaction between confounder used for stratification and exposure.

as shown in Table 1. It would be difficult to clearly explain respective effects of seaweed on the risk of all-cause and disease-specific death. However, seaweed is known to exert various biological effects, such as anticancer effects,^{36,37} which may explain the improved survival observed among patients with advanced-stage colorectal cancer.

In addition to the hypothetical direct effects of the various food items mentioned above, we also considered that interactions between pre-treatment dietary intake and the gut microbial community might impact

subsequent patient survival. For example, seaweed is a major source of dietary fiber in the Japanese diet,^{38,39} and this may affect the microbiota composition of the gastrointestinal tract. A high-fiber diet increases the population of microbiota producing short-chain fatty acids (SCFA). SCFAs, in particular butyrate, have anti-inflammatory and anticarcinogenic properties,⁴⁰⁻⁴² which may contribute to improved survival among patients with colon and rectal cancer. A recent study conducted in the USA has shown that higher fiber intake after colorectal cancer diagnosis

is associated with better survival, thus supporting this consideration.⁴³ In addition, although hypothetical, interaction of certain gut microbiota with dietary fiber may have the capacity to alter the metabolism of chemotherapeutic agents,⁴² thus strengthening the effects of chemotherapy for patients with colorectal cancer, especially advanced-stage cancer. Modulation of the gut microbiota by dietary fiber may also influence the survival of patients with stomach cancer. However, a proportion of stomach cancers are associated with *Helicobacter pylori* infection. Antibiotic therapy prior to disease diagnosis might alter microbial species.^{42,44} It is likely that the stomach has a diverse microbiota population.⁴⁵ Some studies have suggested that soy-based diets may increase the population of "good bacteria" such as lactobacilli in the microbial community.^{46,47} Thus, among the patients with stomach cancer, pretreatment intake of soybean products may exert greater effects than intake of seaweed on survival.

Stratified analyses among patients with stomach cancer demonstrated variations in the association between intake of soybean products and survival across the levels of each confounder. An inverse association was observed among both patients with and without a family history of stomach cancer, suggesting that for intake of soybean products the risk of death is unlikely to be modified by inherited genetic factors. In contrast, the effects of soybean product intakes on survival of stomach cancer patients tended to be unclear among both ever-smokers and ever-alcohol drinkers. Any beneficial effects of soybean products may be interrupted by inflammation and immunological deterioration due to smoking and alcohol consumption.^{13,48,49}

The present study had both strengths and limitations. One of its strengths was the high quality of patient recruitment and follow up. Few patients were lost to follow up, and all patients with colon cancer were completely followed up. Another strength was that confounding factors, including treatment methods and other prognostic factors, were appropriately controlled for.

The limitations of the study were as follows. First, some patients whose FFQ data were incomplete were excluded from the analysis. However, the background characteristics of the analytic subjects were similar to those of the original cohort subjects (data not shown in tables). It is unlikely that incomplete data from the FFQ have distorted the results. Second, as we were unable to collect information on changes in dietary habits subsequent to cancer diagnosis and surgery, evaluation of the effects of behavioral change was not possible. However, analysis according to stage may have been informative for considering the interrelationships between dietary habits and disease progression. Third, the risk of mortality was mainly evaluated for the average frequency of food intake. The effect of the absolute amount of intake could not be fully investigated.²⁴ Furthermore, the generalizability of our results may have been limited because our study was performed at a single hospital in Miyagi Prefecture. To validate our results, further studies using FFQ including exact portion size information will be required in other regions.

In conclusion, this prospective cohort study has clarified the associations between pretreatment intake of traditional Japanese food and the risk of death among Japanese patients with digestive tract cancers. For patients with stomach cancer, intake of soy food

and miso soup was inversely associated with the risk of all-cause and stomach cancer death. Among patients with colon cancer, intake of seaweed was inversely associated with the risk of all-cause death, and patients with rectal cancer who had frequently consumed seaweed tended to have a lower risk of rectal cancer death. These findings indicate that pretreatment intake of Japanese food such as soybean products and seaweed may significantly and favorably impact mortality risk in patients with stomach and colorectal cancer, although this must be investigated further in future studies.

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DISCLOSURE

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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