Food/nutrient intake and risk of atrophic gastritis among the *Helicobacter pylori*-infected population of northeastern Japan

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Although *Helicobacter pylori* (*H. pylori*) infection is considered a key risk factor for atrophic gastritis, along with other environmental factors, it is still unclear which factor is involved in the development of atrophic gastritis among *H. pylori*-infected subjects. In the present cross-sectional study, therefore, we analyzed various dietary factors in relation to the presence of atrophic gastritis among *H. pylori*-infected subjects who participated in a health check-up program in a town in northeastern Japan. One thousand and seventy-one subjects (362 males and 709 females) who provided both self-administered validated food frequency questionnaires and blood samples were the basis for the study, and all of them were serologically positive for *H. pylori* immunoglobulin G (IgG) antibody. Among them, 663 (223 males and 440 females) were diagnosed as having atrophic gastritis on the basis of serum pepsinogen levels. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated based on tertile categories of subjects without atrophic gastritis, using logistic regression analysis. Among females, high consumptions of rice (OR=1.6, 95% CI: 1.1–2.3), cod roe (OR=1.5, 95% CI: 1.0–2.2) and cuttlefish (OR=1.5, 95% CI: 1.0–2.3) were associated with a moderately increased risk of atrophic gastritis after adjustment for age (*P* for trend=0.02 for these items). Among males, high consumptions of rice and miso soup showed a tendency toward an increased risk (*P* for trend=0.12 and 0.13, respectively). Vegetables and fruits showed no association among either males or females. From these results, it is suggested that the dietary habits of consumers of traditional Japanese foods may play a role in the development of atrophic gastritis after *H. pylori* infection. (Cancer Sci 2003; 94: 372–377)

Atrophic gastritis is considered to be a pre-cancerous lesion of the stomach.[1–6] The relationship of gastric cancer with *Helicobacter pylori* (*H. pylori*) infection has been reported by many authors.[4,7] It is also known that *H. pylori* infection increases the risk of atrophic gastritis, although the relative risk varied in the range of 2–10.[4,8–16] These studies indicate that *H. pylori* may not be the sole cause of atrophic gastritis, because not all infected subjects eventually develop atrophic gastritis. Environmental factors, especially dietary intake, could also be important in explaining differences between subjects who do or do not develop atrophic gastritis.

Epidemiological studies investigating the association between environmental factors and atrophic gastritis have been limited, mainly because the proper diagnosis of atrophic gastritis earlier relied on endoscopic findings with/without biopsy, which is difficult to conduct outside a clinical setting. However, the serum levels of pepsinogen I (PG I) and pepsinogen II (PG II), together with the pepsinogen I/II ratio (PG I/II), have recently been used as markers for atrophic gastritis.[4,8–10,12,14,17] PG I/II in combination with PG I was demonstrated to be predictive of the histologic status of gastric mucosa,[18] and is considered as the most predictive marker for gastric cancer risk.[4,8–10,12,14,17] This method is less invasive than the endoscopic approach and is easy to use if blood samples are available, making it rather easy to employ in a community-based health check-up.

Previous epidemiological studies have suggested that not only *H. pylori* infection, but also a variety of environmental factors are important risk factors for atrophic gastritis,[4,8–16] e.g., low vegetable intake[9,12] and use of salt for seasoning.[19] However, food intake was assessed using frequency of food consumption only, and no studies have assessed food intake quantitatively with a validated questionnaire to evaluate the possible association between diet and atrophic gastritis. In the present study, therefore, we assessed the food intake quantitatively using a validated questionnaire, and evaluated the possible association between 20 dietary factors (especially vegetables and salty food intake) and the presence of atrophic gastritis diagnosed in terms of serum pepsinogen levels. Furthermore, which environmental factor is involved in the development of atrophic gastritis among persons infected with *H. pylori* has rarely been investigated. Therefore, we also investigated this point among *H. pylori*-infected subjects.

Subjects and Methods

Study subjects. The subjects were participants of a health check-up program in a town in northeastern Japan, where the mortality from gastric cancer is one of the country's highest. They were a subgroup of participants in the Japan Public Health Centers-based prospective study on cancer and cardiovascular diseases (JPHC Study) cohort I launched in 1990, and they were born between 1930 and 1949.[20] Self-administered food-frequency questionnaires (FFQ) were distributed through the public health centers to subjects on the occasion of a 5-year follow-up survey of the JPHC study in 1995. Of the 3399 subjects whose addresses were registered in the town as of 1990, 2872 (84.5%) filled out the questionnaire. Blood samples were obtained with written informed consent from 1566 (46.1%) subjects at the health check-up during that same year. A total of 1407 subjects (484 males and 923 females) who answered the self-administered questionnaires and provided blood samples were eligible.

Blood samples were tested for serum PG I and PG II as well as for *H. pylori* IgG antibody. Serum levels of PG I and PG II were used as a diagnostic tool for atrophic gastritis. Of 1407 eligible subjects, the analysis was restricted to 1141 (81.1%) whose *H. pylori* IgG antibody in the serum was positive.

Questionnaires. This self-administered questionnaire was composed of items such as general characteristics, the medical history of participants, cigarette smoking, alcohol consumption, vitamin supplement intake and dietary information. All subjects were asked about the average frequency of intake and portion

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size of 138 items over the past year.[21] Alcohol intake (g/day) of current drinkers was assessed based on reported consumption frequencies and amounts of five alcoholic beverages (sake, shochu, beer, whisky and wine). Daily consumption of rice was ascertained by categorized answers (numbers of rice bowls consumed per day: <1, 1, 2, 3, 4, 5, 6, 7–9, 10≤ bowls/day; the portion size: small, medium or large bowl). The frequency of miso soup consumption was classified into 6 categories (never, 1–3/month, 1–2, 3–4, or 5–6 per week and almost once/day), and the numbers of bowls per day were categorized in the same way as for rice intake. The frequency of other food items was classified into 9 categories (never, 1–3/month, 1–2, 3–4, or 5–6/week, almost once/day, 2–3, 4–6 or 7+ times/day), and the portion size was classified into 3 categories (more than 1.5 portion, same as the usual portion size, or less than half a portion). The intakes of sodium for each food were calculated using the food composition table developed for the food frequency questionnaire (FFQ) based on the Standard Tables of Food Composition in Japan, the 4th revised edition.[22] The salt intake from cooking salt and salty seasonings such as soy sauce was estimated from the cooking methods frequently used for meats, fish and vegetables.[23] To confirm the validity of this questionnaire, we collected questionnaires and 28-day dietary records (7 days in each of the four seasons) from 215 subjects in four areas, and estimated the amount of intake per food group from them. Spearman correlation coefficients for the intakes of the fish group, vegetable group, and fruit group and sodium from the questionnaire and those from the dietary record were 0.46, 0.33, 0.61 and 0.59 in males, and 0.42, 0.35, 0.50 and 0.55 in females, respectively.[24] The validity indices of food items that were consumed less frequently were inevitably unreliable against dietary records over a short duration, and are not listed here. We concluded that this questionnaire had reasonable validity for use in large-scale epidemiological studies.

H. pylori. *H. pylori* infection was determined by measuring serum *H. pylori* IgG antibodies. Specific anti-*H. pylori* antibodies in sera stored at −80°C were measured with an enzyme-linked immunosorbent assay (ELISA) kit using an acid-extracted antigen (Helico G, Porton Cambridge, Oxford, UK). The sensitivity and specificity of the assay was 96% and 86%, respectively, compared with gastric biopsy findings.[25]

Criteria for atrophic gastritis. The serum levels of PG I and PG II were measured by radioimmunometric assay kits (PG I/PG II RIABEAD, Dainabot Co., Ltd., Tokyo) at an outside laboratory (SRL, Inc., Tokyo). Atrophic gastritis was diagnosed according to two criteria: a PG I level below 70 ng/ml and a PG I/II ratio below 3.0. This was because these criteria show a high geographic correlation with the age-adjusted mortality rate of gastric cancer among five Japanese populations (r=0.99) and have the best predictive ability for gastric cancer mortality.[17] Recent studies have adopted these criteria, and their reliability has been recognized.[4, 8–10, 12, 14]

Data analysis. Three people with a prior history of gastrectomy were excluded from the study along with three others with a history of gastric cancer. Fifty-five subjects with energy intakes that were unreasonably high (≥4000 calories/day for males; ≥3600 calories/day for females) or low (<900 calories/day for males; <800 calories/day for females), or thirteen subjects who failed to answer questions about dietary intake, were also excluded from the analysis (n=64). In this study, we analyzed data from 1071 eligible subjects (362 males and 709 females) and examined the possible association between serologically determined atrophic gastritis and food intake among subjects with *H. pylori* infection.

For statistical analysis, the total intake of each food was divided into 3 categories at the nearest tertile based on the distribution in the control group. As regards smoking habits, subjects were classified as never, past, or current smokers. As for alcohol use, subjects were classified as non-drinkers or drinkers consuming <50 or 50≤ g per day. The trend was assessed by assigning ordinal values for categorical variables and median values for continuous variables.

Table 1. Characteristics of serologically determined atrophic gastritis cases and controls

Characteristics	Males			Females		
	AG[1] n=223	NAG[2] n=139	P for difference	AG[1] n=440	NAG[2] n=269	P for difference
Age	57.5 (0.4)	55.0 (0.5)	<0.0001	57.1 (0.3)	55.8 (0.3)	0.001
Cigarette smoker (%)[3]	47.1	39.6	0.16	2.1	2.6	0.63
Alcohol (g/day)	30.8 (1.9)	31.1 (2.4)	0.90	0.6 (0.1)	0.8 (0.2)	0.38
Total fish (g/day)	110.7 (4.8)	116.3 (6.1)	0.47	110.4 (3.1)	104.7 (4.0)	0.26
Salted fis >1/week (%)	61.0	66.9	0.26	68.6	66.5	0.56
Dried fis >1/week (%)	27.4	25.9	0.76	27.5	33.1	0.11
Cod roe >1/week (%)	64.1	60.4	0.48	58.2	48.0	0.01
Cuttlefish >1/week (%)	41.7	38.1	0.50	38.0	29.0	0.01
Meat (g/day)	58.7 (3.1)	71.8 (3.9)	0.01	55.6 (2.2)	59.3 (2.8)	0.29
Rice (g/day)	366.3 (8.7)	361.7 (11.0)	0.75	287.0 (5.0)	276.7 (6.3)	0.20
Fruit (g/day)	201.6 (12.1)	175.6 (15.3)	0.18	274.8 (10.6)	260.9 (13.5)	0.42
Green-yellow vegetables (g/day)	68.7 (3.6)	65.7 (4.6)	0.61	84.7 (3.2)	79.5 (4.1)	0.32
Broccoli >1/week (%)	46.2	48.9	0.61	62.7	70.6	0.03
Other vegetables (g/day)	130.9 (9.3)	122.9 (11.8)	0.60	143.2 (4.7)	135.5 (6.0)	0.31
Cabbage <1/week (%)	87.4	92.1	0.17	92.1	91.8	0.92
Pickled vegetables (g/day)	57.1 (4.1)	55.1 (5.2)	0.75	63.6 (2.8)	65.0 (3.6)	0.76
Soybean products (g/day)	113.5 (4.3)	110.7 (5.4)	0.68	108.0 (3.2)	112.2 (4.1)	0.42
Miso soup (g/day)	414.7 (10.8)	381.3 (13.7)	0.06	318.9 (7.0)	311.9 (9.0)	0.53
Sodium (mg/day)	6384.8 (185.7)	6415.4 (235.2)	0.92	6245.6 (122.3)	6134.9 (156.5)	0.58
Carotene (μg/day)	3036.1 (144.5)	2829.7 (183.1)	0.38	3642.0 (127.0)	3400.1 (162.7)	0.24
Vitamin C (mg/day)	153.9 (6.3)	149.3 (8.0)	0.65	193.6 (5.3)	178.4 (6.8)	0.08
Calcium (mg/day)	579.9 (18.2)	586.3 (23.0)	0.83	592.3 (13.6)	599.7 (17.4)	0.74

Based on Student's t test or χ^2 test.
Figures are means (SE) unless otherwise specified.
1) AG=atrophic gastritis. *2*) NAG=non-atrophic gastritis. *3*) Current male smokers, current and past female smokers.

Student's t test or the χ^2 test was used to compare the characteristics of subjects with and without atrophic gastritis. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were obtained by logistic regression analysis. The ORs of smoking and alcohol consumption were compared with those of never smokers and non-drinkers, respectively, for reference. As for the other foods, the ORs were compared with the lowest tertile of intake as the reference. The dose-response association was tested by a χ^2 estimate of the linear trend in the medians of each category. Two-sided P values <0.05 were considered statistically significant. All statistical analyses were performed using the SAS statistical software package.[26)]

Results

Of 1071 subjects with *H. pylori* infection, 663 were diagnosed with serologically determined atrophic gastritis. The overall prevalence of atrophic gastritis was 61.9% (male 61.6%, female 62.1%).

Table 1 shows the characteristics and distribution of dietary factors among subjects with *H. pylori* infection. The average age of subjects with and without atrophic gastritis was 57.5 and 55.0 in males, and 57.1 and 55.8 in females, respectively. Among females, subjects with atrophic gastritis had a higher consumption of cod roe and cuttlefish than subjects without it (P<0.05). On the contrary, the proportion of subjects with atrophic gastritis who consume broccoli one or more times per week was lower than in subjects without atrophic gastritis (P<0.05). The average consumption of miso soup tended to be lower in male subjects with atrophic gastritis compared to those without it. No substantial differences were observed for the intake of other foods between subjects with and without atrophic gastritis.

The analysis of cigarette smoking or alcohol use in the present study was restricted to males. The crude OR for current smokers was 1.2 (95% CI: 0.7–1.9) compared with never smokers. Current smoking statistically significantly increased the OR of atrophic gastritis with the adjustment for age (OR=1.7, 95% CI: 1.0–2.9). There was no clear association between total alcohol use and atrophic gastritis. The effect on atrophic gastritis did not differ by alcohol beverage type. Smoking and drinking risks for atrophic gastritis were not evaluated among females because female smokers and drinkers were so few in this study population. When we estimated ORs of atrophic gastritis for each food, we adjusted for smoking status only in the analysis for males.

Table 2 shows the ORs of serologically determined atrophic gastritis in relation to sodium and some traditional Japanese foods including rice, fish and miso soup. Among females, an increased OR was observed for the highest consumption category of both cod roe (OR=1.5, 95% CI: 1.0–2.2) and cuttlefish (OR=1.5, 95% CI: 1.0–2.3) after adjustment for age. We found a steady increase in the OR of atrophic gastritis as the intake of rice increased (OR for intermediate tertile=1.3, high tertile=1.6, P for trend<0.05) after adjustment for age. After a further adjustment for age and cod roe, high consumption of rice statistically significantly increased the OR of atrophic gastritis (P for trend<0.05). Although the estimated OR for the intermediate tertile of sodium intake was 1.9 (95% CI: 1.3–2.7) compared with the low tertile, sodium intake did not show a statistically significant trend. High consumption of dried fish tended to decrease the OR for atrophic gastritis.

Among males, no notable association was observed between atrophic gastritis and various types of fish intake after adjustment for age and smoking status. High consumption of miso soup and rice was associated with a slightly increased OR of atrophic gastritis but without statistical significance (miso soup: for high tertile, OR=1.6, 95% CI: 0.9–2.8, trend P=0.13, rice: for high tertile, OR=1.6, 95% CI: 0.9–2.9, trend P=0.12).

Table 3 shows the results of multivariate analysis (including selected vegetables and fruits, which affected the OR of atrophic gastritis in univariate analysis). Among both males and fe-

Table 2. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) for serologically determined atrophic gastritis among subjects with *H. pylori* infection

Food items		Males						Females					
		Median	AG[1)] *n*	NAG[2)] *n*	Adjusted OR[3)]	95% CI	*P* for trend	Median	AG[1)] *n*	NAG[2)] *n*	Adjusted OR[4)]	95% CI	*P* for trend
Salted fish	Low	4.7	87	46	1.0			4.7	138	90	1.0		
	Intermediate	15.0	76	53	0.7	0.4–1.1		15.0	174	109	1.0	0.7–1.5	
	High	35.0	60	40	0.7	0.4–1.2	0.28	35.0	128	70	1.2	0.8–1.7	0.45
Dried fish	Low	0	77	41	1.0			0	153	81	1.0		
	Intermediate	3.3	83	60	0.6	0.4–1.1		3.3	166	99	0.9	0.6–1.4	
	High	10.7	63	38	0.9	0.5–1.5	0.85	10.7	122	89	0.7	0.5–1.1	0.11
Cod roe	Low	0.7	77	53	1.0			0.7	111	75	1.0		
	Intermediate	4.3	86	45	1.3	0.8–2.2		1.3	130	96	1.0	0.7–1.5	
	High	10.0	60	41	1.0	0.6–1.8	0.93	5.0	199	98	1.5	1.0–2.2	0.02
Cuttlefish	Low	3.3	86	57	1.0			1.7	84	56	1.0		
	Intermediate	5.0	83	52	1.1	0.6–1.7		3.3	189	135	1.0	0.7–1.5	
	High	16.1	55	30	1.1	0.6–2.0	0.76	10.7	167	78	1.5	1.0–2.3	0.02
Miso soup	Low	150	34	30	1.0			150	136	83	1.0		
	Intermediate	300	55	36	1.3	0.7–2.6		300	160	100	1.0	0.7–1.4	
	High	450	134	73	1.6	0.9–2.8	0.13	450	144	86	1.0	0.7–1.5	0.90
Rice	Low	247.4	57	46	1.0			202.0	122	90	1.0		
	Intermediate	339.8	85	47	1.6	0.9–2.8		247.4	146	90	1.3	0.9–1.8	
	High	472.8	81	46	1.6	0.9–2.9	0.12	354.7	172	89	1.6	1.1–2.3	0.02
Sodium	Low	4040.1	71	46	1.0			3700.1	107	90	1.0		
	Intermediate	5853.8	69	46	1.0	0.5–1.6		5763.3	198	90	1.9	1.3–2.7	
	High	8774.2	83	47	1.1	0.6–1.9	0.73	8454.7	135	89	1.3	0.9–2.0	0.30

The total intake of each food was divided into 3 groups (low tertile, intermediate tertile, or high tertile) based on the distribution in the control group.
Calculated by logistic analysis.
1) AG=atrophic gastritis. *2*) NAG=non-atrophic gastritis. *3*) Adjusted for age and smoking. *4*) Adjusted for age.

Table 3. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) for serologically determined atrophic gastritis among subjects with *H. pylori* infection

Food items		Males						Females					
		Median	AG[1] *n*	NAG[2] *n*	Adjusted OR[3]	95% CI	*P* for trend	Median	AG[1] *n*	NAG[2] *n*	Adjusted OR[4]	95% CI	*P* for trend
Green-yellow vegetables	Low	26.8	78	46	1.0			30.4	134	90	1.0		
	Intermediate	54.3	62	47	0.7	0.4–1.3		62.6	142	89	1.0	0.7–1.5	
	High	107.1	83	46	1.0	0.6–1.7	0.87	122.7	164	90	1.2	0.8–1.7	0.38
Other vegetables	Low	56.9	79	46	1.0			60.8	147	89	1.0		
	Intermediate	104.2	61	47	0.7	0.4–1.3		115.4	137	90	0.9	0.6–1.3	
	High	188.9	83	46	1.0	0.6–1.8	0.72	214.3	156	90	1.1	0.7–1.6	0.59
Pickled vegetables	Low	17.1	80	47	1.0			18.6	143	89	1.0		
	Intermediate	36.3	58	46	0.7	0.4–1.3		42.3	152	90	1.0	0.7–1.5	
	High	87.0	85	46	1.0	0.6–1.6	0.93	112.5	145	90	1.0	0.7–1.5	0.98
Fruits	Low	51.2	87	47	1.0			96.4	132	89	1.0		
	Intermediate	136.7	56	46	0.7	0.4–1.3		205.3	144	90	1.1	0.7–1.6	
	High	334.0	80	46	1.0	0.6–1.8	0.73	407.0	164	90	1.2	0.8–1.8	0.32
Broccoli	Low	0.7	66	36	1.0			1.4	188	98	1.0		
	Intermediate	1.4	64	40	0.8	0.4–1.5		4.5	116	78	0.8	0.5–1.1	
	High	5.3	93	63	0.8	0.5–1.4	0.63	10.5	136	93	0.8	0.6–1.1	0.25
Cabbage	Low	5.9	71	38	1.0			5.9	141	90	1.0		
	Intermediate	13.8	71	45	0.9	0.5–1.6		13.8	149	99	1.0	0.7–1.4	
	High	20.7	81	56	0.7	0.4–1.3	0.28	32.5	150	80	1.2	0.8–1.8	0.30

The total intake of each food was divided into 3 groups (low tertile, intermediate tertile, or high tertile) based on the distribution in the control group.
Calculated by logistic analysis.
1) AG=atrophic gastritis. *2*) NAG=non-atrophic gastritis. *3*) Adjusted for age and smoking. *4*) Adjusted for age.

males, neither vegetables nor fruits demonstrated an inverse trend. Intake of pickled vegetables, a diet high in salt, did not show any association with atrophic gastritis. No association of vitamin C or carotene with atrophic gastritis was observed.

Discussion

The present study focused on the food intake of subjects with *H. pylori* infection. It contributed to clarification of the association between various dietary factors and atrophic gastritis after *H. pylori* infection.

A positive association between traditional Japanese food (rice and cod roe) and atrophic gastritis in females was clearly observed in this study. In males, rice and miso soup were associated with an increased risk for atrophic gastritis, although this was not statistically significant. The result that a high consumption of cod roe or miso soup was associated with an increased risk of atrophic gastritis may be regarded as supportive of the association between salt intake and atrophic gastritis, because cod roe and miso soup are generally salt-rich. Our study showed a trend of increasing risk of atrophic gastritis with the consumption of rice in females. The association between rice intake and gastric cancer has been inconsistent, with some studies showing a positive association,[3, 27–29] and others finding none at all.[6, 30] The results from the previous epidemiological studies are likewise inconsistent regarding the association between rice and atrophic gastritis. One study demonstrated a severe reduction in the PG I/II ratio with high rice/pasta consumption in Venezuela,[31] whereas another reported a decreased risk of atrophic gastritis, but an increased risk of gastric cancer from rice intake.[3] The mechanism by which a high consumption of rice increases the risk of gastric cancer is unclear. Ji *et al.* suggested that carbohydrate could possibly irritate the gastric mucosa physically (especially in the form of rough whole-grain cereals).[32] Although rice is a typical source of carbohydrate, it is unclear whether or not it physically affects the mucosa. An indirect effect of rice intake on atrophic gastritis may exist. Rice may correlate with other dietary factors and it may act as a marker of intake of traditional Japanese foods or salted foods.

As to fish consumption (including salted and dried fish), we did not find any association with atrophic gastritis, in contrast to a previous experimental study showing that fish meal enhanced *H. pylori*-induced gastritis in Mongolian gerbils.[33] Fish meal might contain factors, other than salt, that greatly enhance *H. pylori*-induced gastritis. In another epidemiological study, traditional Japanese foods (rice, miso soup, raw fish and cod roe) increased the risk of gastric cancer.[29] It was suggested that such foods might accelerate the development of atrophic gastritis and gastric cancer, though the mechanisms involved need to be clarified.

The significant increase in the risk of atrophic gastritis associated with high cuttlefish consumption was unexpected. If the cuttlefish is in the form of "shiokara" (salted cuttlefish, a traditional Japanese food), it might increase the risk of atrophic gastritis, although data on the cooking methods were not available from this questionnaire. No other epidemiological or experimental studies have shown such a positive association between cuttlefish and atrophic gastritis. This result may well be only a chance finding. As in the case of cuttlefish, we can not deny that the positive association between cod roe and atrophic gastritis may be coincidental. However, although cod roe is a minor contributor of salt/sodium in terms of its portion size and intake frequency, it contains a high concentration of sodium per serving. Therefore, it is possible that cod roe is a risk factor for atrophic gastritis.

We could not detect a statistically significant association between atrophic gastritis and any food item in males, though some food items (rice, cod roe and cuttlefish) were associated with atrophic gastritis in females. The negative results for several food items among males must be interpreted with caution because of the small number of male subjects. One possibility is that the effect may be truly confined to females. Alternatively, it may be owing to the residual confounding effect of smoking and dietary factors in males.

If high consumption of sodium indeed affects the development of atrophic gastritis, the lack of a positive association between atrophic gastritis and salted fish or pickled vegetables

would be unexpected. But there are two possible interpretations of this lack of an association. First, our study subjects were residents in the high-risk area in Japan, and there was a possibility that they had homogeneous dietary habits, making it difficult to detect such a positive association. Second, it might be difficult to identify risk factors in recent dietary habits, if dietary risk factors, especially in early life, play a more important part in the development of atrophic gastritis as Kato *et al.* suggested.[34)]

High salt intake and its association with gastric cancer have been reported in many studies.[5, 30, 35)] Sodium chloride exerts a dose-dependent, tumor-promoting activity on gastric carcinogenesis in rats when given after N-methyl-N′-nitrosoguanidine.[36)] Several epidemiological studies have reported an increased risk for atrophic gastritis associated with high salt intake[37)] or salt seasoning.[19)] In our study, the adjusted OR for the intermediate tertile of sodium intake compared to the low tertile was 1.9, whereas sodium intake did not show any significant trend in females, and no association at all was observed in males. The lack of a significant positive association with sodium intake could be due to three reasons, one related to dietary assessment, another to the stage of atrophic gastritis development and the third, to the range of individual consumption of sodium. First, a dietary assessment of sodium may not be appropriate. We compared the intake levels of sodium assessed with this questionnaire and two corresponding 24-h urinary excretion levels in residents of 3 JPHC study areas including the present study area. The Spearman rank correlation coefficients between dietary sodium assessed with this questionnaire and the urinary excretion data were weak or null; 0.24 and −0.10 in males and females, respectively,[38)] although 24-h urinary excretion is not necessarily a reliable biomarker, due to day-to-day variation. Sodium intake is from consumption of miso soup (20%), fish and shellfish (16%) and pickled vegetables (12%). Seasonings such as table salt and soy sauce are major contributors of sodium intake (approximately 30%). However, the amount of sodium intake from such seasonings could not be assessed by this FFQ.[39)] The Spearman correlation coefficients for sodium intakes from the questionnaire and those from the dietary record were moderate (r=0.59 in males, r=0.55 in females) across four areas with a relatively large range of variation; however, they may be relatively low only in this study area. Additionally, our previous study suggested that even though the sodium concentration in the food items is different, the uniform composition table gives the same sodium value, making exact evaluation impossible.[40)] Therefore, the fact that it is somewhat difficult to quantify the intake of sodium using this questionnaire may explain in part the absence of any association between sodium intake and gastritis in this study. Intake of highly salted food such as cod roe may be a more reliable marker for dietary sodium intake. Second, an experimental study has reported that excessive NaCl intake enhances *H. pylori* colonization in mice and in humans and that chronic salt intake may exacerbate gastritis by increasing colonization.[41)] In this previous experimental study, no significant exacerbation of inflammation was associated with high salt intake among *H. pylori*-infected mice. In the light of this result, high salt intake may not be associated with development of atrophic gastritis after *H. pylori* infection. Third, the mean intake of sodium was relatively high, and the standard deviation was within narrow limits in this study area compared with that in 3 other areas in Japan.[23)] This may make it difficult to detect a positive association.

Many studies have suggested that the intake of vegetables and fruits plays a protective role against gastric cancer.[34, 42)] Vegetables/fruits are rich in micronutrients, especially vitamin C, which may inhibit the endogenous formation of carcinogenic nitrosamines.[43)] Some researchers reported that vegetables and fruits protected against atrophic gastritis,[9, 12, 31)] while others found no such association.[3, 6, 8, 10, 11, 13, 16)] Our results revealed no association in either males or females. One possible reason for the apparent lack of a protective association is that vegetable/fruit intake may have no effect on the development of atrophic gastritis, although it may influence carcinogenesis in the stomach. Another may be the relatively low green and yellow vegetable intake within this region compared with other Japanese areas.[44)] In other words, the consumption level of green-yellow vegetables even in the highest tertile group may not be high enough to prevent atrophic gastritis.

Of 3399 residents selected from the study area, 1407 (41.4%) who provided both questionnaires and blood samples proved to be eligible. Thus, the proportion of subjects with available information was not very high, although it was comparable with that in other studies of this kind. Though the low response rate could have introduced selection bias, both questionnaires and blood samples were collected independently, and thus we believe bias should be negligible. Information bias, particularly recall bias, needs consideration, since the questionnaire was self-administered, and subjects were asked about their dietary intake over the past year. In a correlation analysis of dietary intakes estimated from the questionnaire with those from the 28-day dietary record, we confirmed that this questionnaire has reasonable validity for use in epidemiological studies. *H. pylori* infection and atrophic gastritis were classified using biological tests to minimize misclassification. Although the possibility of misclassification of both exposure and outcome status cannot be excluded, it would be non-systematic, and the estimates of the association presented here would be distorted towards the null, and therefore would represent conservative estimates of the effects.

Because of our analysis by cross-sectional design, we cannot rule out the possibility that the diet developed atrophic gastritis, or that the presence of atrophic gastritis leads to changes in the dietary pattern; in other words, a causal link cannot be established by the present study.

Allowing for these methodological issues, our results indicate that traditional Japanese food, including rice and cod roe, appears to moderately increase the risk for atrophic gastritis. Most epidemiological studies (including ours) dealing with the association between food intake and atrophic gastritis were conducted as cross-sectional or case-control studies. A prospective study will be necessary to clarify the risk factors for causing atrophic gastritis.

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