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A Prospective Study of Atrophic Gastritis and Stomach Cancer Risk

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The relation of atrophic gastritis, other gastric lesions and lifestyle factors to stomach cancer risk was prospectively studied among 3,914 subjects who underwent gastroscopic examination and responded to a questionnaire survey at the Aichi Cancer Center Hospital. During 4.4 years of follow-up on average, 45 incident cases of stomach cancer were identified at least three months after the initial examination. If the baseline endoscopic findings indicated the presence of atrophic gastritis, the risk of developing stomach cancer was increased 5.73-fold, compared with no indication at the baseline. The risk further increased with advancing degree of atrophy and increasing extension of atrophy on the lesser curvature. These trends in the relative risks were statistically significant ($P=0.027$ and $P=0.041$, respectively). The risk of developing stomach cancer was statistically significantly increased among subjects with gastric polyps, but not among those with gastric ulcer. Stomach cancer cases tended to consume more cigarettes, alcohol, rice, pickles and salted fish gut/cod roe and less fruits and vegetables and to have more family histories of stomach cancer than noncases, although these differences were not statistically significant. The results of the present study provide additional evidence on the relation between atrophic gastritis and stomach cancer and suggest a need for intensive follow-up of patients with atrophic gastritis and gastric polyps.

Key words: Atrophic gastritis — Gastric polyp — Stomach cancer — Prospective study

Stomach cancer is one of the most common cancers worldwide,[1)] and in Japan it is still the leading cancer despite a declining trend.[2)] There is a remarkable geographical variation in stomach cancer mortality/incidence, and high incidence and mortality are observed in Asia, Central and South America and Eastern Europe.[1, 2)] While dietary habits, such as foods rich in nitrate or nitrite and their derivatives, a high salt diet, a high carbohydrate diet and a diet low in fresh fruits and vegetables have been associated with these chronological and geographical variations in stomach cancer incidence,[3)] several types of pathological changes in the stomach, i.e., atrophic gastritis, intestinal metaplasia, gastric ulcer and polyps, have been suspected as premalignant lesions for stomach cancer.[4)] In particular, a close geographical correlation between prevalence of atrophic gastritis or intestinal metaplasia and stomach cancer has been reported[5–8)] in addition to the histological observation that carcinoma developed frequently in areas of intestinal metaplasia.[5, 9–11)] Although the association between atrophic gastritis and stomach cancer risk has rarely been evaluated in analytical epidemiologic studies, our recent cross-sectional analysis has strongly supported this association.[12)] However, because of the nature of cross-analyses, we could not determine the temporal relationship of the two events. If the association is also observed in a prospective study, it would be helpful in establishing a causal relationship. As reported previously,[13)] we have conducted a clinico-epidemiological study on atrophic gastritis and stomach cancer risk among subjects who received gastroscopic examination. One of the principal aims of this study is to identify high-risk individuals for developing stomach cancer, and study subjects are supposed to be followed up for 10 years in the study protocol. Because we have obtained some significant results among the baseline endoscopic findings, these results will be presented here, together with those on lifestyle factors.

MATERIALS AND METHODS

Details of this study were described elsewhere.[13)] From April, 1985 to March, 1989, a questionnaire survey was conducted for the patients who received gastroscopic examination at Aichi Cancer Center Hospital. A total of 7,019 questionnaires were distributed and 6,226 were collected (88.7%). After excluding prevalent cases of cancer and the subjects with resected stomach, a total of 5,395 subjects comprised the original cohort of this prospective study.

The gastroscopic findings were evaluated by the six gastroenterologists in the Aichi Cancer Center Hospital with respect to presence of atrophic gastritis, degree and extension of atrophy, and presence of gastric ulcer, polyps and other lesions. The degree of atrophy was

classified into three groups; mild, moderate and severe, according to the size of transparent blood vessels and discoloration in the gastric mucosa. This was supported by the previous report about the consistency between endoscopic and histological findings on atrophic gastritis.[14] Mild atrophic gastritis was defined as gastric mucosa with transparent fine blood vessels and yellowish discoloration. Moderate atrophic gastritis was defined as gastric mucosa with clearly transparent blood vessels and yellow-grayish discoloration. Severe atrophic gastritis was defined as gastric mucosa with transparent large blood vessels and gray-greenish discoloration.

The questionnaire was self-recorded and included items on medical history, family history, diet, smoking and drinking habits. Frequencies of intakes of the 10 food items including salty foods (pickled vegetable, salted or dried fish, salted fish gut or cod roe, foods boiled down in soy and pickled Japanese apricot) and other foods (soybean paste soup, raw vegetable, green-yellow vegetable, fruit and meat) were divided into the three categories; 'almost daily,' '2–3 times per week' and 'once or twice per month or less.' Respondents were instructed to choose the closest category. Frequencies of alcohol and cigarette consumptions were divided into the four categories; 'almost daily,' 'occasionally,' 'formerly' and 'never.' Consumptions of rice and cigarettes were reported as amounts consumed per day. Family history of cancer was restricted to parents and siblings.

After the baseline survey, incidence of cancer and deaths among the study subjects have been identified through linkage with gastroendoscopic records at the Aichi Cancer Center Hospital, the data from the Aichi Cancer Registry and death certificates. Additional mail surveys have been conducted to identify cancer incidence and deaths among all subjects including those living outside of Aichi Prefecture. If necessary, the diagnoses at these surveys were ascertained by contact with physicians in charge. The length of the observation period was computed for each subject as the time from the baseline survey to the diagnosis of stomach cancer, death, date of the last gastroscopic examination or the last mail survey that a subject responded to. Nine cases of stomach cancer that developed within 3 months of the initial survey and 1,472 subjects who had never responded to mail surveys and never received gastroscopic examination after the initial examination but whose death and cancer incidence had not been identified were excluded from the analyses. As a result, 3,914 subjects remained in the study. Sex and age distributions of these subjects are presented in Table I. Cox's proportional hazards regression model[15] was used to estimate the relative risks (RR) and the 95% confidence intervals (CI) associated with various baseline characteristics, adjusted for sex (a dummy variable), age (a continuous variable) and residence (metropolitan area in Aichi prefecture, other areas of Aichi prefecture and other prefectures). A test for trend in the log of the relative hazard was also performed by using Cox models.

RESULTS

During the follow-up period, representing 17,289 person-years at risk, a total of 45 incident cases of stomach cancer (35 males and 10 females) were identified. Of those, 37 cases were identified by linkage with the Aichi Cancer Registry and/or gastroendoscopic records at the Aichi Cancer Canter Hospital, 1 by death certificate and the remaining 7 by mail survey. The incidence markedly increased with advancing age, especially after age 65 in both sexes combined (Table II).

Table III shows the relative risks for stomach cancer by baseline endoscopic findings. If the baseline endoscopic findings indicated the presence of atrophic gastritis, the risk of developing stomach cancer was increased 5.73-fold, compared with no indication at the baseline. The risk further increased with advancing degree of atrophy and increasing extension of atrophy on

Table I. Age and Sex Distributions of Study Subjects

Age	Male		Female		Total	
	No.	(%)	No.	(%)	No.	(%)
–44	464	(25.1)	595	(28.8)	1059	(27.1)
45–49	260	(14.0)	299	(14.5)	559	(14.3)
50–54	296	(16.0)	332	(16.1)	628	(16.0)
55–59	264	(14.3)	351	(17.0)	615	(15.7)
60–64	241	(13.0)	251	(12.2)	492	(12.6)
65–69	155	(8.4)	135	(6.5)	290	(7.4)
70–74	110	(5.9)	74	(3.6)	184	(4.7)
75+	61	(3.3)	26	(1.3)	87	(2.2)
Total	1851	(100.0)	2063	(100.0)	3914	(100.0)

Table II. Age- and Sex-specific Incidence Rates for Stomach Cancer per 100,000 Person-Years

Age	Male		Female		Total	
	Rate	(No.)	Rate	(No.)	Rate	(No.)
–44	49.6	(1)	77.5	(2)	65.3	(3)
45–49	261.9	(3)	238.6	(3)	249.7	(6)
50–54	380.6	(5)	67.3	(1)	214.4	(6)
55–59	671.6	(8)	0.0	(0)	286.9	(8)
60–64	666.9	(7)	0.0	(0)	312.3	(7)
65–69	733.4	(5)	326.9	(2)	541.2	(7)
70–74	1013.1	(5)	0.0	(0)	619.3	(5)
75+	381.3	(1)	2023.6	(2)	830.8	(3)
Total	429.3	(35)	109.5	(10)	260.3	(45)

Table III. Sex-, Age- and Residence-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Stomach Cancer by Baseline Endoscopic Findings

Gastroscopic findings	No. of cases /person-years	Rate[a]	RR	95% CI
Atrophic gastritis				
Absent	1/2931.0	34.1	1.00	
Present	44/14321.2	307.2	5.73	0.78–41.90
Degree of atrophy				
None	1/2931.0	34.1	1.00	
Mild	19/8566.0	221.8	4.50	0.60–33.78
Moderate/severe	23/5558.7	413.8	6.69	0.89–50.11
			$P=0.027$[b]	
Extension on the greater curvature				
None	1/2931.0	34.1	1.00	
Lower third	6/2310.0	259.7	5.47	0.66–45.62
Upper two-thirds	33/11303.3	291.9	5.28	0.72–38.96
			$P=0.130$	
Extension on the lesser curvature				
None	1/2931.0	34.1	1.00	
Lower third	21/8413.6	249.6	5.09	0.68–37.96
Upper two-thirds	19/4496.3	422.6	6.87	0.90–51.94
			$P=0.041$	
Gastric ulcer				
Absent	41/16046.5	255.5	1.00	
Present	4/1242.6	321.9	0.97	0.35–2.72
Gastric polyp				
Absent	37/15957.9	231.9	1.00	
Present	8/1331.2	601.0	2.43	1.12–5.27

a) Per 100,000 person-years.
b) *P*-value for the trend.

the lesser curvature. These trends in the relative risks were statistically significant ($P=0.027$ and $P=0.041$, respectively). The increasing trend in the relative risks associated with extension on the greater curvature was neither clear nor statistically significant. The risk of developing stomach cancer was statistically significantly increased among subjects with gastric polyps (RR=2.43, 95% CI: 1.12–5.27), but not among those with gastric ulcer. The proportion of adenomatous polyps among total polyps was especially higher in subjects who developed stomach cancer (50%) than in those who did not (9%).

Table IV shows the relative risks associated with various other baseline habits. There was an increased risk of stomach cancer among current smokers who smoked 20 or more cigarettes per day, daily alcohol drinkers, subjects who consumed three or more cups of rice per day, daily pickles consumers, subjects who ate salted fish gut or cod roe at least twice a week and subjects with a family history of stomach cancer. But, none of these relative risks or their trends was statistically significant. Conversely, there was a decreased risk of stomach cancer associated with frequent intakes of fruits and raw and green-yellow vegetables, although these relative risks and their trends were not statistically significant.

DISCUSSION

Although the follow-up period of the present study was not long enough, the findings confirmed the observation in our recent cross-sectional analysis that the presence of atrophic gastritis substantially increased the risk of stomach cancer.[12] The estimated risk, 5- to 6-fold, was also similar in the two studies. Additionally, a kind of dose-response relationship, i. e., correlation with severity of the disease, was also observed in both studies. To date, few follow-up studies have been conducted to clarify this association prospectively. Almost all cases of stomach cancer arose from patients with atrophic gastritis or intestinal metaplasia in those studies, but the results have not been evaluated statistically because of the small number of the observed cases.[16–18] Therefore, the present prospective study provides additional new evidence on the association between atrophic gastritis and stomach cancer.

Table IV. Sex-, Age- and Residence-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Stomach Cancer by Various Baseline Habits

Dietary habits	No. of cases /person-years	Rate[a]	RR	95% CI
Smoking status				
Never	15/9800.6	153.1	1.00	
Past	11/2697.5	407.8	1.17	0.47–2.94
≤19 cigarettes/day	5/1629.8	306.8	1.08	0.36–3.26
≥20 cigarettes/day	14/2645.9	529.1	2.24	0.92–5.44
Alcohol intake				
None	12/7205.8	166.5	1.00	
Past	6/885.9	677.2	2.19	0.78–6.19
Occasional	11/5196.8	211.7	1.10	0.47–2.60
Daily	16/3671.5	435.8	1.51	0.65–3.54
Rice				
≤2 cup/day	11/6170.1	178.3	1.00	
3 cup/day	20/5771.0	346.6	1.95	0.93–4.08
≥4 cups/day	13/4969.9	262.8	1.22	0.53–2.78
			P=0.645[b]	
Pickles				
≤1–2/month	5/3017.5	165.7	1.00	
2–3/week	15/7330.5	204.6	1.26	0.46–3.48
Daily	21/6479.3	324.1	1.77	0.67–4.70
			P=0.186	
Salted fish gut, cod roe				
≤1–2/month	30/12932.9	232.0	1.00	
≥2–3/week	10/3358.7	297.7	1.35	0.66–2.77
≥2–3/week	10/3358.7	297.7	1.35	0.66–2.77
Raw vegetables				
≤1–2/month	6/1908.3	314.4	1.00	
2–3/week	25/9582.8	260.9	0.97	0.40–2.40
Daily	11/5228.3	210.4	0.80	0.29–2.18
			P=0.595	
Green-yellow vegetables				
≤2–3/week	27/9079.0	297.4	1.00	
Daily	17/8062.8	210.8	0.83	0.45–1.54
Fruits				
≤1–2/month	5/1189.0	420.5	1.00	
2–3/week	21/7167.6	293.0	0.71	0.27–1.90
Daily	18/8801.8	204.5	0.55	0.20–1.52
			P=0.250	
Family history of stomach cancer				
No	25/12095.0	206.7	1.00	
Yes	20/5194.1	385.1	1.71	0.95–3.09

a) Per 100,000 person-years.
b) *P*-value for the trend.

Although earlier studies on the etiology of atrophic gastritis have produced rather inconsistent results, cigarette smoking,[19] high consumptions of alcohol,[19] hot tea,[19] dried fish[20] and cured meats[21] and low consumptions of fruits[22] and vegetables[23] have been suspected to increase the risk of atrophic gastritis/intestinal metaplasia. In addition, *Helicobacter pylori* infection, that has recently been linked with gastric carcinogenesis,[24, 25] has also been associated with atrophic gastritis.[26–28] These similarities in risk factors between atrophic gastritis and stomach cancer mean we should consider the possibility that the observed association in the present study is solely because the two diseases share common risk factors in their pathogenesis.

The relationship between gastric ulcer and gastric carcinoma has been the subject of much controversy. Studies in western countries tend to support the view that gastric ulcers are not a significant source of gastric

carcinoma.[4] Our present study also supported this view. Gastric polyps, especially adenomatous ones, are believed to have some malignant potential, similarly to colorectal adenoma. Ming reported that adenomatous polyps in the stomach showed carcinomatous changes in 25% to 72% of studied lesions and over 80% are 2 cm in diameter or larger.[4] Although the present study also supported this potential, there is another possibility that the carcinoma already existed in the polyp, but could not be identified due to the limitation of biopsy. Based on the endoscopic findings, we can suggest that patients with atrophic gastritis and gastric polyps should be intensively followed up to prevent deaths from stomach cancer.

The absolute values of stomach cancer incidence in the present study should be cautiously interpreted. The study subjects were not representative of the general population, but visitors to a hospital, most of whom had gastrointestinal symptoms or suspicious gastric X-ray findings. Thus, they should be considered a high risk population of stomach cancer. Although subjects who had never responded to mail surveys were excluded from the analysis, most of these subjects were likely to be free from stomach cancer. This should result in overestimates of stomach cancer incidence. Lastly, atrophic gastritis in the present study was based on endoscopical diagnoses, not histological ones. Biopsy provides a definitive diagnosis, but it represents only a small portion of gastric mucosal surface area, which tends to yield false-negative findings. Compared with histological examination, endoscopic diagnoses may produce less false-negative, but more false-positive diagnoses. This should not much influence the results, if misclassification occurs with a similar frequency in cases and noncases.

Since all of the study subjects were examined gastroscopically at the baseline and since we excluded stomach cancer cases diagnosed within three months from the initial examination, misclassification of cases and noncases was less likely to occur in the present study than in ordinary prospective studies based on deaths or incidence of stomach cancer. In addition, prospective studies generally have the advantage of collecting information earlier in time before the subjects are diagnosed with cancers. Therefore, the results of studies are more likely to reflect causes, rather than effects, of the disease.

Several researchers have found that alcohol drinkers[29-31] and cigarette smokers[31-33] have a greater risk of stomach cancer than nondrinkers and nonsmokers. It has been suggested that excessive salt intake and carbohydrate intake can injure the gastric mucosa, acting as chemical and physical irritants, thus facilitating gastric carcinogenesis.[34] Nitroso compounds, present in salted fish products, have been considered as important gastric carcinogens[34] and vitamin C, present in fruits and vegetables, has been demonstrated to inhibit the formation of nitroso compounds in the stomach.[35] In addition, earlier studies have shown that family members of a stomach cancer case have around two times the risk of developing stomach cancer, compared with the general or referent population.[36, 37] Our results related to these factors generally supported the earlier findings, although none of the associations was statistically significant. This project is still on-going. Final results, especially on lifestyle factors, will be obtained in further follow-up.

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