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Atrophic Gastritis and Stomach Cancer Risk: Cross-sectional Analyses

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The relationship between atrophic gastritis and stomach cancer risk was investigated in case-control analyses involving 387 cases with stomach cancer and 5,422 control subjects who received gastroscopic examination at Aichi Cancer Center Hospital from April, 1985 to March, 1989. The presence of atrophic gastritis, the degree and extension of the atrophy and the presence of granularity and erosion were diagnosed endoscopically by six gastroenterologists. The prevalence of atrophic gastritis increased with age and was higher in males than in females. The relative risk (RR) of stomach cancer was 5.13 (95% confidence interval (CI): 2.79–9.42) if a subject had any type of atrophic gastritis. The risk further increased with advancing degree of atrophy and increasing extension on the greater and lesser curvatures. The RR associated with severe atrophy was 7.73 (95% CI: 3.95–15.12). These associations remained significant when analyzed by sex and age. The presence of granularity and erosion did not much affect the estimated risks. A clear difference in risk appeared in the analyses by histological type of cancer. The RR associated with atrophic gastritis was 24.71 (95% CI: 3.46–176.68) for the intestinal type and 3.49 (95% CI: 1.77–6.87) for the diffuse type. These findings may suggest a need for intensive follow-up of patients with severe atrophic gastritis.

Key words: Atrophic gastritis — Stomach cancer

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 environmental factors, especially diet, have been suspected to account for these geographical variations,[3] the accumulated pathological and epidemiological evidence suggests that atrophic gastritis is a kind of precursor of stomach cancer. A close geographical correlation between prevalence of atrophic gastritis or intestinal metaplasia and stomach cancer has been reported[4–7] in addition to the histological observation that carcinoma developed frequently in areas of intestinal metaplasia.[4,8–10] However, there have been only a limited number of analytical epidemiological studies on the relationship between atrophic gastritis and stomach cancer risk. As reported previously,[11] we have conducted a clinicoepidemiological study to identify risk factors for atrophic gastritis and stomach cancer and to assess the risk of developing stomach cancer among individuals with atrophic gastritis. In this paper, we will report the results of cross-sectional analyses on the relation between baseline endoscopic findings and stomach cancer.

MATERIALS AND METHODS

Details of this study were described previously.[11] Between April, 1985 and March, 1989, the data on gastroscopic findings of 5,859 subjects were compiled at the Aichi Cancer Center Hospital. These findings were evaluated by six gastroenterologists in the Aichi Cancer Center Hospital with special reference to atrophic gastritis, i.e., the presence of atrophic gastritis, degree of atrophy, extension on the greater curvature side and the lesser curvature side and presence of granularity and erosion. This was supported by the previous report on the consistency between endoscopic and histological findings on atrophic gastritis.[12] 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. 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.

After excluding 50 subjects whose gastroscopic findings could not be evaluated with respect to atrophic gastritis, 5,809 subjects remained in the study. Among them, 387 cases of stomach cancer were identified by histological examination and the remaining subjects were taken as controls in the analyses. Sex and age distributions of cases and controls are shown in Table I. The histological type of stomach cancer was determined according to the classification of Lauren.[13] There were 199 intestinal, 180 diffuse and 8 other and unknown types.

Table I. Sex and Age Distributions of Cases and Controls

Age	Male		Female		Total	
	Case No. (%)	Control No. (%)	Case No. (%)	Control No. (%)	Case No. (%)	Control No. (%)
–29	1 (0.4)	133 (5.2)	0 (0.0)	106 (3.7)	1 (0.3)	239 (4.4)
30–39	15 (5.6)	332 (12.9)	11 (9.1)	435 (15.3)	26 (6.7)	767 (14.1)
40–49	43 (16.2)	732 (28.4)	22 (18.2)	811 (28.5)	65 (16.8)	1543 (28.5)
50–59	67 (25.2)	708 (27.4)	35 (28.9)	876 (30.8)	102 (26.4)	1584 (29.2)
60–69	82 (30.8)	474 (18.4)	32 (26.4)	479 (16.9)	114 (29.5)	953 (17.6)
70+	58 (21.8)	202 (7.8)	21 (17.4)	134 (4.7)	79 (20.4)	336 (6.2)
Total	266 (100.0)	2581 (100.0)	121 (100.0)	2841 (100.0)	387 (100.0)	5422 (100.0)

Table II. Sex- and Age-specific Prevalence (%) of Atrophic Gastritis in Total Study Subjects

Age	Male		Female		Total	
	All types	Moderate /severe	All types	Moderate /severe	All types	Moderate /severe
–29	59.7	9.0	54.7	5.7	57.5	7.5
30–39	81.8	21.9	68.2	17.8	74.1	19.6
40–49	83.6	36.1	75.9	22.2	79.6	28.9
50–59	89.4	41.8	84.2	32.6	86.6	36.8
60–69	92.8	46.9	87.7	38.9	90.3	43.1
70+	95.8	51.0	86.5	42.9	92.3	47.9
Total	86.8	38.1	79.1	28.1	82.9	33.0

The Walker-Duncan logistic regression model[14] was used to estimate the sex- and/or age-adjusted relative risks (RR) and the 95% confidence intervals (CI) associated with various types of atrophic gastritis.

RESULTS

In total, more than 80% of the subjects had some type of atrophic gastritis and 33% had moderate or severe type. These prevalences were higher in males than in females and increased with advancing age, although the prevalence of any type of atrophic gastritis in females leveled off after the 60s (Table II).

Table III shows the sex- and age-adjusted RRs associated with various types of atrophic gastritis in the total subjects. There was a five-fold-increased risk of stomach cancer among subjects with any type of atrophic gastritis (RR=5.13, 95% CI: 2.79–9.42). The risk further increased with advancing degree of atrophy and increasing extension on the greater and lesser curvatures. The presence of granularity and erosion did not much affect the risk associated with atrophic gastritis.

Females had higher RRs than males. The RR associated with any type of atrophic gastritis was 6.34 (95% CI: 2.33–17.23) among females and 4.44 (95% CI: 2.07–9.53) among males. The increasing trend in risk with the degree of atrophy was also clearer among females than among males (Table IV). The increased risks associated with various types of atrophic gastritis were also observed among both younger ($\leq$59) and older ($\geq$60) age groups and they were a little higher in the younger age group (Table V).

When analyzed by histological type of stomach cancer (Table VI), the risk for intestinal type of stomach cancer was specifically increased in relation to the presence of atrophic gastritis. The RR associated with any type of atrophic gastritis was 24.71 (95% CI: 3.46–176.68) and that associated with severe atrophy was 42.74 (95% CI: 5.75–317.99). There was a moderately, but statistically significantly, increased risk of diffuse type of stomach cancer in relation to the presence of atrophic gastritis. The RR associated with any type of atrophic gastritis was 3.49 (95% CI: 1.77–6.87) and that associated with severe atrophy was 4.62 (95% CI: 2.05–10.40). These RRs were still a little higher in females than in males when analyses were limited to the diffuse type.

Multivariate analyses in the total subjects revealed that the extension on both curvatures and the degree of atrophy had independent effects on the stomach cancer risk.

Table III. Sex- and Age-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer According to the Presence of Various Types of Atrophic Gastritis (AG)

Type of atrophic gastritis	No. of cases /controls	RR	95% CI
Presence/absence			
No	11/985	1.00	
Any type	376/4437	5.13	2.79–9.42
Degree of atrophy			
No	11/985	1.00	
Mild	170/2671	4.22	2.27–7.84
Moderate	134/1372	5.34	2.85–10.01
Severe	56/330	7.73	3.95–15.12
Extension on the greater curvature			
No	11/985	1.00	
Lower third	33/737	3.18	1.58–6.36
Middle third	152/2047	4.69	2.51–8.74
Upper third	167/1450	6.08	3.26–11.36
Extension on the lesser curvature			
No	11/985	1.00	
Lower third	155/2636	3.95	2.13–7.35
Middle third	124/1223	5.50	2.93–10.32
Upper third	36/189	8.90	4.39–18.04
Granularity			
No atrophic gastritis	11/985	1.00	
AG without granularity	253/3365	4.67	2.52–8.64
AG with granularity	104/986	5.47	2.89–10.35
Erosion			
No atrophic gastritis	11/985	1.00	
AG without erosion	228/2885	4.94	2.66–9.15
AG with erosion	130/1485	4.70	2.50–8.82

Table IV. Age-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer by Sex According to the Presence of Various Types of Atrophic Gastritis

Type of atrophic gastritis	Males			Females		
	No. of cases /controls	RR	95% CI	No. of cases /controls	RR	95% CI
Presence/absence						
No	7/370	1.00		4/615	1.00	
Any type	259/2211	4.44	2.07–9.53	117/2226	6.34	2.33–17.23
Degree of atrophy[a)]						
Mild	118/1241	3.91	1.81–8.49	52/1430	4.64	1.67–12.89
Moderate	95/726	4.73	2.16–10.35	39/646	6.45	2.28–18.21
Severe	41/207	6.37	2.78–14.58	15/123	11.61	3.75–35.96
Extension on the greater curvature[a)]						
Lower third	23/342	2.98	1.26–7.05	10/395	3.42	1.07–10.98
Middle third	110/991	4.46	2.05–9.69	42/1056	4.84	1.73–13.57
Upper third	114/759	5.12	2.35–11.17	53/691	8.22	2.95–22.94
Extension on the lesser curvature[a)]						
Lower third	100/1236	3.44	1.58–7.49	55/1400	4.92	1.78–13.64
Middle third	92/636	5.23	2.39–11.45	32/587	5.65	1.98–16.14
Upper third	27/104	8.34	3.49–19.92	9/85	9.51	2.83–31.92
Granularity[a)]						
Absence	176/1592	4.32	2.01–9.30	77/1773	5.21	1.90–14.29
Presence	77/571	4.79	2.18–10.56	27/415	7.02	2.43–20.28
Erosion[a)]						
Absence	158/1256	4.76	2.21–10.28	70/1692	5.14	1.87–14.13
Presence	95/917	3.97	1.82–8.66	35/568	6.81	2.40–19.34

a) Reference category is subjects with no atrophic gastritis.

Table V. Sex- and Age-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer by Age Group According to the Presence of Various Types of Atrophic Gastritis

Type of atrophic gastritis	≤59			≥60		
	No. of cases /controls	RR	95% CI	No. of cases /controls	RR	95% CI
Presence/absence						
No	7/854	1.00		4/131	1.00	
Any type	187/3279	5.61	2.62–11.98	189/1158	4.48	1.64–12.25
Degree of atrophy[a)]						
Mild	86/2077	4.28	1.97–9.29	84/594	4.01	1.45–11.14
Moderate	69/951	6.48	2.95–14.24	65/421	4.21	1.50–11.78
Severe	22/200	8.95	3.74–21.41	34/130	6.47	2.22–18.82
Extension on the greater curvature[a)]						
Lower third	19/602	3.32	1.39–7.94	14/135	2.93	0.94–9.16
Middle third	81/1550	5.18	2.38–11.27	71/497	4.03	1.45–11.24
Upper third	73/970	6.80	3.10–14.92	94/480	5.18	1.87–14.38
Extension on the lesser curvature[a)]						
Lower third	84/2061	4.18	1.93–9.09	71/575	3.57	1.28–9.94
Middle third	62/832	6.61	2.99–14.62	62/391	4.34	1.55–12.18
Upper third	12/113	8.95	3.42–23.40	24/76	8.12	2.70–24.41
Granularity[a)]						
Absence	126/2520	4.97	2.31–10.70	127/845	4.19	1.53–11.53
Presence	51/691	6.31	2.83–14.06	53/295	4.55	1.61–12.84
Erosion[a)]						
Absence	111/2140	5.28	2.45–11.39	117/745	4.43	1.61–12.19
Presence	66/1083	5.18	2.35–11.39	64/402	4.09	1.46–11.45

a) Reference category is subjects with no atrophic gastritis.

Table VI. Sex- and Age-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer by Histological Type According to the Presence of Various Types of Atrophic Gastritis

Type of atrophic gastritis	Intestinal type			Diffuse type		
	No. of cases /controls	RR	95% CI	No. of cases /controls	RR	95% CI
Presence/absence						
No	1/985	1.00		9/985	1.00	
Any type	198/4437	24.71	3.46–176.68	171/4437	3.49	1.77–6.87
Degree of atrophy[a)]						
Mild	86/2671	20.64	2.84–149.93	79/2671	2.78	1.39–5.57
Moderate	72/1372	25.78	3.53–188.11	60/1372	3.68	1.81–7.52
Severe	36/330	42.74	5.75–317.99	20/330	4.62	2.05–10.40
Extension on the greater curvature[a)]						
Lower third	16/737	15.40	2.01–117.80	17/737	2.24	0.99–5.04
Middle third	79/2047	23.19	3.19–168.83	70/2047	3.12	1.55–6.30
Upper third	97/1450	31.40	4.31–228.63	66/1450	3.79	1.86–7.71
Extension on the lesser curvature[a)]						
Lower third	76/2636	18.73	2.58–135.94	76/2636	2.71	1.35–5.43
Middle third	69/1223	27.34	3.75–199.38	54/1223	3.67	1.79–7.55
Upper third	22/189	47.28	6.23–358.84	13/189	5.26	2.18–12.67
Granularity[a)]						
Absence	133/3365	23.17	3.22–166.71	114/3365	3.06	1.54–6.08
Presence	59/986	27.66	3.80–201.42	44/986	3.61	1.74–7.50
Erosion[a)]						
Absence	125/2885	25.53	3.54–184.09	98/2885	3.09	1.55–6.17
Presence	68/1485	22.35	3.08–162.40	60/1485	3.31	1.62–6.75

a) Reference category is subjects with no atrophic gastritis.

DISCUSSION

The present study showed that the presence of atrophic gastritis was associated with a substantial increase in the risk of stomach cancer. The strength of the association was enough to suggest a causal relation. The risk was correlated with the severity of the disease, i.e., the degree and extension of atrophy, suggesting a kind of dose-response relationship. Another important finding of the present study was that atrophic gastritis was more specifically associated with the intestinal type of stomach cancer. This finding supports the hypothesis, proposed by Correa *et al.*,[15] that the intestinal type of stomach cancer develops on the basis of atrophic gastritis. It has been observed that the intestinal type of stomach cancer is predominant in high-risk areas and accounts for most of the reduction when its risk is reduced in a population.[16, 17] Earlier studies also found that high-risk populations for stomach cancer had a high prevalence of atrophic gastritis and intestinal metaplasia.[4–7] Although no systematic sex difference in the prevalence of atrophic gastritis and intestinal metaplasia was found in Colombia,[18] the prevalence was higher among males than among females in each age group in the present study. Our finding seems to be consistent with higher incidence of stomach cancer in males. On the contrary, the RR associated with atrophic gastritis was higher in females than in males. This may suggest fewer factors working in the progression from atrophic gastritis to stomach cancer in females than in males. The increasing trend in the prevalence of atrophic gastritis with age observed in the present study was consistent with the results of previous studies,[4, 6, 7] although the prevalence in the present study could be biased toward a higher value because of the nature of the study subjects, i.e., most of them had complained of some gastric symptoms. Although granularity and erosion can represent proliferation and degeneration of epithelial cells, they were not useful indices in predicting the risk of stomach cancer associated with atrophic gastritis.

Follow-up studies for patients with atrophic gastritis or intestinal metaplasia have been attempted in several countries. In those studies, almost all of the stomach cancer cases arose from patients with atrophic gastritis or intestinal metaplasia, but the results were not analyzed statistically because of the small number of observed cases of stomach cancer.[19–21] Based on cross-sectional analyses, Sipponen *et al.* reported that the prevalence of atrophic gastritis was statistically significantly higher in patients with the intestinal type of stomach cancer than in controls and that no such differences were seen with regard to the diffuse type.[22] The same authors estimated the relative risk of stomach cancer to be 18.1 for severe atrophy in the antrum and 4.6 for severe atrophy in the body.[23] The risk did not increase in the less severe gastritis and no RRs were calculated by type of stomach cancer. Thus, we can not compare our results directly with theirs.

There were several methodological limitations in the present study. First, the present study was based on endoscopic diagnoses, not histological ones. Although biopsy provides a definitive diagnosis, 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 controls. Because of the small number of cases without atrophic gastritis, the estimated risks for intestinal type of stomach cancer should be cautiously interpreted and are likely to be exaggerated. Second, because the diagnosis of atrophic gastritis was difficult in cases with advanced cancer, they tended to be excluded from this study, leading to a higher proportion of early cancers. This selection is, however, less likely to affect the estimated risks. Conversely, we should consider another possibility, that physicians may have examined subjects more carefully in the presence of gastric cancer, which could lead to higher RRs. Third, sex and age were not matched between cases and controls, but were adjusted by using a statistical model. This may be justified by the similar results obtained in separate analyses by sex and age group. Finally, because of the nature of a cross-sectional analysis, we could not determine which came first, atrophic gastritis or stomach cancer. The original cohort of the study subjects has been followed up except for those with stomach cancer at the baseline. We will be able to report results from prospective analyses in the near future.

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