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Lifestyle and Anti-*Helicobacter pylori* Immunoglobulin G Antibody among Outpatients

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Since eradication of *Helicobacter pylori* (*H. pylori*) is thought to be a preventive measure against stomach cancer, several studies have examined factors associated with the infection. This paper reports the association of the infection with lifestyle factors observed in a hospital-based case-control study. Cases were 140 anti-*H. pylori* IgG antibody-positive outpatients (75 males and 65 females). Controls were 52 antibody-negative outpatients (22 males and 30 females). Both groups had undergone gastroscopy at Aichi Cancer Center Hospital between February 1995 and February 1997, and lifestyle data collected on the first visit were linked to calculate odds ratios. A strong association was observed with smoking among males; age-adjusted odds ratio (OR) = 7.85, 95% confidence interval (CI), 2.03–30.4. Rice breakfast (OR = 3.74; 95%CI, 1.30–10.8) and soybean paste soup (every day vs. occasionally, OR = 5.24; 95%CI, 1.80–15.2) were also associated with antibody positivity in males, but not in females. In females, pickled Chinese cabbage (≥1/week vs. ≤3/month, OR = 2.82; 95%CI, 1.06–7.48) and lettuce (≥1/week vs. ≤3/month, OR = 2.90; 95%CI, 1.09–7.76) were significantly associated with positivity. Multivariate analysis gave similar estimates for the above factors. Although the association between smoking and *H. pylori* infection has not been detected in past studies of a general population, except one recent one, this study on outpatients suggested a possible association. Smoking may work as a cofactor disturbing incidental eradication of *H. pylori* by antibacterial agents administered for other reasons.

Key words: Case-control study — *Helicobacter pylori* — Smoking

Helicobacter pylori (*H. pylori*) infection causes chronic atrophic gastritis,[1–3] which is considered to be a state with an elevated risk of gastric cancer.[4] *H. pylori* has been detected in the feces, saliva and dental plaque of infected patients.[5–7] Recently, it has been found in drinking water in Peru.[8] Although transmission is assumed to occur mainly in childhood through the fecal-oral and/or oral-oral route,[9] transmission details remain unclear.

In Japan, the prevalence of the infection exceeds 70% among persons aged 40 years or over, while it is about 20% among those below 20 years of age.[10, 11] This could be explained by the relatively poor sanitary conditions more than 30 years ago, though specific risk factors have not been clarified.[9] The risk factors for having *H. pylori* can be classified into two categories: factors for infection and factors for the continuation of the infected state. Non-steroidal anti-inflammatory drugs, smoking, and alcohol were examined as risk factors mainly in the latter context, but a clear association with *H. pylori* infection has not been observed so far. We conducted a case-control study on the association between *H. pylori* infection and lifestyle among outpatients who underwent gastroscopy at Aichi Cancer Center Hospital, where HERPACC (Hospital-based Epidemiologic Research Program at Aichi Cancer Center) started in 1988.[12]

MATERIALS AND METHODS

The subjects were 201 outpatients whose first visit to Aichi Cancer Center Hospital was in and after 1988, and who underwent gastroscopy between February 1995 and February 1997. They had given informed, consent in writing for anti-*H. pylori* IgG antibody testing before gastroscopy. The study was approved by the Institutional Review Board of Aichi Cancer Center. Patients diagnosed as having stomach cancer, those who underwent gastrectomy, and those under treatment for cancer of other sites were excluded from the study.

Information on lifestyle was obtained through HERPACC.[12] HERPACC has routinely been collecting lifestyle information from first-visit patients since 1988; about 7,000 per year, totalling some 67,000 subjects as of February 1996. The self-administered questionnaire was handed out to all outpatients on the first visit and retrieved on the same day. Accordingly, the information was obtained before diagnosis for all outpatients, except a small percentage of patients who had been diagnosed at another hospital. This group of outpatients did not include any cancer patients, as stated above.

Blood samples were obtained before gastroscopy. Anti-*H. pylori* immunoglobulin G (IgG) antibodies, which

were reported to decrease within six months after eradication,[13] were measured, in addition to pepsinogens, at SRL Co., Ltd., where routine measurement of the IgG antibody has been established using an enzyme immunoassay kit (Pirika Plate G *Helicobacter* until June 1996, and Detaminor *H. pylori* antibody after July 1996). Ratings of (−) or (±) in the Pirika Plate test or an Elisa Value of 2.2 or less in the Detaminor *H. pylori* test were regarded as uninfected (controls), and higher ratings or values were considered as infected (cases). The odds ratios were calculated by means of an unconditional logistic model using the SAS Logistic Procedure.[14]

RESULTS

Of the 201 participants in the study, 192 (95.5%) could be linked to HERPACC data; 22 IgG-negative males, 75 IgG-positive males, 30 IgG-negative females, and 65 IgG-positive females. Table I shows the age distribution of the subjects according to antibody status. The number of patients with atrophic gastritis defined as pepsinogen I <70 ng/ml and pepsinogen I/II ratio <3 is also shown in the Table I; those with atrophic gastritis were 22.7% among the negative group and 46.7% for the positive group in males ($\chi^2=4.02$, $P<0.05$, Fisher's exact test $P=0.052$), and 16.7% and 58.5% in females ($\chi^2=12.47$, $P<0.001$), respectively.

Table II shows the age-adjusted odds ratio (OR) of lifestyle factors for antibody-positive males. Smoking was the most powerful factor among those examined. The OR for smokers was 7.85 with a 95% confidence interval (CI) of 2.03–30.4. Ex-smokers were found to have a 2.04 times higher risk than non-smokers, although this was not significant. When adjusted for the kit used in the antibody test as an independent variable in the logistic model, there was no change in the results; OR for smokers was 8.57 (2.11–34.7), and that for ex-smokers was 2.20 (0.61–7.90).

Alcohol consumption yielded an odds ratio estimate above unity, but it was not statistically significant. The OR for green tea, coffee, and black tea were also not significant. These three items were added to the questionnaire in 1990, and accordingly the numbers of subjects were 62 infected and 21 uninfected.

Type of breakfast was assessed in five categories; "rice," "bread," "rice or bread," "other food," and "no breakfast." When compared with "bread" or "other food," those who answered "rice" or "rice or bread" had a 3.74 times higher OR. This finding was reflected by questions on the number of cups of rice per day (≥ 3 cups vs. ≤ 2 cups) and soybean paste soup (miso soup) intake per day (every day vs. occasionally), giving an elevated OR of infection. Both were closely related to breakfast type ("rice" or "rice or bread" vs. the others); the concordant pairs were 70.1% (68/97) and 77.3% (75/97), respectively. No other food intakes were related to antibody status.

Table I. Age Distribution according to Anti-*Helicobacter pylori* IgG Antibody (Ab) Status and Number of Atrophic Gastritis Patients[a] in Parentheses

Age	Males			Females		
	Ab (−)	Ab (+)	Total	Ab (−)	Ab (+)	Total
20–29	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)
30–39	2 (0)	12 (3)	14 (3)	7 (0)	3 (0)	10 (0)
40–49	10 (3)	12 (4)	22 (7)	12 (2)	12 (6)	24 (8)
50–59	4 (1)	31 (17)	35 (18)	6 (2)	29 (21)	35 (23)
60–69	4 (1)	18 (10)	22 (11)	2 (1)	18 (10)	20 (11)
70–	2 (0)	1 (1)	3 (1)	3 (0)	3 (1)	6 (1)
Total	22 (5)	75 (35)	97 (40)	30 (5)	65 (38)	95 (43)

a) Pepsinogen I <70 and pepsinogen I/II ratio <3.

In females, there were only five smokers (7.7%) among the cases, which did not allow proper evaluation of the effect of smoking. There were no significant factors except pickled Chinese cabbage (hakusai) and lettuce (Table III). The age-adjusted OR and its 95% CI were 2.82 and 1.06–7.48 for pickled Chinese cabbage (≥ 1 times/week vs. ≤ 3 times/month), and 2.90 and 1.09–7.76 for lettuce (≥ 1 times/week vs. ≤ 3 times/month), respectively.

Table IV shows the result of a multivariate analysis, which included age, smoking, type of breakfast, pickled Chinese cabbage, and lettuce. Smoking and rice for breakfast remained statistically significant in males. The estimate for smokers did not change substantially when number of cups of rice or soybean paste soup intake replaced breakfast type in the multivariate analysis; OR $=7.97$ and 11.8, respectively. In females, pickled Chinese cabbage and lettuce remained statistically significant with a slightly larger point estimate. In the multivariate analysis, the estimates for breakfast type and pickled Chinese cabbage were above unity in both sexes.

DISCUSSION

A strong association between smoking and *H. pylori* infection in males was clearly demonstrated in this study. Since several studies have reported no significant association between smoking and *H. pylori* infection,[15–18] except for a recent report,[19] many investigators presume that smoking does not affect the continuation of *H. pylori* infection, and may consider that the results obtained from this study were caused by biases. However, the lifestyle information was obtained on the first visit, and *H. pylori* antibody positivity was tested prior to gastroscopy. The subjects were outpatients, not a general population,

Table II. Age-adjusted Odds Ratio (OR) and Its 95% Confidence Interval (CI) for Lifestyle Factors for the Anti-*Helicobacter pylori* IgG Antibody in Males

	Cases (positive)	Controls (negative)	OR	95% CI
Smoking				
non-smokers	22	14	1	
ex-smokers	16	5	2.04	0.60–6.95
smokers	37	3	7.85	2.03–30.4
Alcohol				
non-drinkers	27	11	1	
drinkers	48	11	1.84	0.68–5.00
Green tea[a)]				
0–6 cups/day	54	19	1	
7≤ cups/day	8	2	1.39	0.12–2.60
Coffee[a)]				
occasionally	28	6	1	
every day	34	15	0.48	0.16–1.44
Black tea[a)]				
occasionally	59	20	1	
every day	3	1	1.00	0.10–10.2
Breakfast				
no rice	18	11	1	
rice	49	8	3.74	1.30–10.8
no breakfast	8	3	1.63	0.35–7.47
Rice				
≤2 cups/day	26	15	1	
≥3 cups/day	49	7	4.05	1.46–11.2
Soybean paste soup				
occasionally	26	16	1	
every day	49	6	5.24	1.80–15.2
Milk				
occasionally	38	12	1	
every day	37	10	1.17	0.45–3.05
Fresh vegetables				
occasionally	21	3	1	
every day	54	19	0.41	0.11–1.52
Fruit				
occasionally	33	6	1	
every day	42	16	0.47	0.17–1.36
Pickled Chinese cabbage				
≤3 times/month	50	16	1	
≥1 times/week	25	6	1.36	0.46–3.97
Dried/salted fish				
≤3 times/month	54	15	1	
≥1 times/week	21	7	0.83	0.29–2.37
Cooked/raw fish				
≤3 times/month	22	3	1	
≥1 times/week	52	19	0.37	0.10–1.40
Bean curd				
≤3 times/month	15	7	1	
≥1 times/week	60	15	1.88	0.65–5.47
Green vegetables				
≤3 times/month	16	4	1	
≥1 times/week	59	18	0.82	0.24–2.78
Carrot				
≤3 times/month	22	6	1	
≥1 times/week	53	16	0.90	0.31–2.62
Pumpkin				
≤3 times/month	43	13	1	
≥1 times/week	32	9	1.07	0.41–2.82
Cabbage				
≤3 times/month	15	5	1	
≥1 times/week	60	16	1.25	0.39–3.98
Lettuce				
≤3 times/month	24	7	1	
≥1 times/week	51	14	1.06	0.38–3.00
Potato/sweet potato				
≤3 times/month	24	7	1	
≥1 times/week	51	15	0.99	0.36–2.75
Egg				
≤3 times/month	8	1	1	
≥1 times/week	67	21	0.40	0.05–3.38
Chicken				
≤3 times/month	28	6	1	
≥1 times/week	47	16	0.63	0.22–1.79
Beef				
≤3 times/month	36	6	1	
≥1 times/week	38	16	0.35	0.12–1.05
Pork				
≤3 times/month	37	8	1	
≥1 times/week	38	14	0.54	0.19–1.53
Ham/sausage				
≤3 times/month	43	10	1	
≥1 times/week	32	12	0.58	0.21–1.60
Instant noodles				
≤3 times/month	60	14	1	
≥1 times/week	15	8	0.43	0.15–1.22

a) Subjects whose first visits were on or after 1990.

which did not bias the association. From an epidemiological viewpoint, the association should be valid.

We conducted a comprehensive review of the relevant research papers, and found previous studies to support our finding. Recently, a significantly elevated OR of smoking for *H. pylori* infection has been reported for black patients (males and females combined, OR=3.09, 95% CI, 1.48–6.45). The subjects were patients who had undergone endoscopy at a hospital in New Orleans.[20] The study found that there was no association among white patients, who had a lower positive rate of *H. pylori* infection (52.4%) than the black patients (80.0%). The

Table III. Age-adjusted Odds Ratio (OR) and Its 95% Confidence Interval (CI) for Lifestyle Factors for the Anti-*Helicobacter pylori* IgG Antibody in Females

	Cases (positive)	Controls (negative)	OR	95% CI
Smoking				
non-smokers	59	25	1	
ex-smokers	1	2	0.14	0.01–2.08
smokers	5	3	1.18	0.23–6.22
Alcohol				
non-drinkers	47	23	1	
drinkers	18	7	1.46	0.51–4.21
Green tea[a)]				
0–6 cups/day	44	21	1	
7≤ cups/day	5	3	0.65	0.13–3.31
Coffee[a)]				
occasionally	27	12	1	
every day	22	12	1.03	0.36–2.91
Black tea[a)]				
occasionally	44	22	1	
every day	5	2	1.52	0.26–8.87
Breakfast				
no rice	21	9	1	
rice	44	20	0.94	0.35–2.52
no breakfast	0	1	–	
Rice				
≤2 cups/day	41	15	1	
≥3 cups/day	24	15	0.55	0.22–1.39
Soybean paste soup				
occasionally	27	13	1	
every day	38	17	1.08	0.43–2.71
Milk				
occasionally	26	14	1	
every day	38	16	1.22	0.49–3.05
Fresh vegetables				
occasionally	19	11	1	
every day	45	19	1.62	0.61–4.30
Fruit				
occasionally	12	8	1	
every day	53	22	1.10	0.36–3.33
Pickled Chinese cabbage				
≤3 times/month	30	22	1	
≥1 times/week	35	8	2.82	1.06–7.48
Dried/salted fish				
≤3 times/month	35	15	1	
≥1 times/week	29	15	0.84	0.34–2.09
Cooked/raw fish				
≤3 times/month	7	5	1	
≥1 times/week	58	25	1.14	0.30–4.32
Bean curd				
≤3 times/month	6	4	1	
≥1 times/week	59	26	1.33	0.31–5.74
Green vegetables				
≤3 times/month	5	3	1	
≥1 times/week	60	27	1.25	0.24–6.41
Carrot				
≤3 times/month	7	3	1	
≥1 times/week	58	27	0.65	0.14–2.98
Pumpkin				
≤3 times/month	30	17	1	
≥1 times/week	35	13	1.35	0.54–3.36
Cabbage				
≤3 times/month	5	4	1	
≥1 times/week	60	25	2.26	0.52–9.96
Lettuce				
≤3 times/month	15	13	1	
≥1 times/week	50	17	2.90	1.09–7.76
Potato/sweet potato				
≤3 times/month	8	5	1	
≥1 times/week	57	25	1.65	0.45–6.05
Egg				
≤3 times/month	3	0	1	
≥1 times/week	62	30	–	
Chicken				
≤3 times/month	15	8	1	
≥1 times/week	49	22	1.46	0.51–4.24
Beef				
≤3 times/month	29	14	1	
≥1 times/week	36	16	1.16	0.46–2.87
Pork				
≤3 times/month	22	10	1	
≥1 times/week	43	20	1.38	0.51–3.71
Ham/sausage				
≤3 times/month	39	23	1	
≥1 times/week	26	7	2.73	0.95–7.81
Instant noodles				
≤3 times/month	62	29	1	
≥1 times/week	3	1	1.81	0.16–21.1

a) Subjects whose first visits were on or after 1990.
–: Estimate was not obtained as there were no subjects among cases or controls.

prevalence rate of *H. pylori* infection in Japanese is closer to that of black patients. Of interest is another report which provides clearer evidence; the eradication rate for *H. pylori* with omeprazole and amoxicillin was much lower among smokers (38.8%; 7/18) than among non-smokers (73.1%; 19/26, this was not shown in the table, but was calculable from the overall eradication rate, 26/44), while the difference was not observed in triple therapy with azithromycin, omeprazole, and amoxicillin because of its strong eradication effect (91.6%).[21] A lower eradication rate for smokers was observed in a clinical study using omeprazole, clarithromycin, and tinida-

Table IV. Odds Ratio (OR) and Its 95% Confidence Interval (CI) for Lifestyle Factors for the Anti-*Helicobacter pylori* IgG Antibody Estimated by Multivariate Analysis Including Age, Smoking, Type of Breakfast, Pickled Chinese Cabbage, and Lettuce

	Males		Females	
	OR	95% CI	OR	95% CI
Smoking				
non-smokers	1		1	
ex-smokers	1.63	0.43–6.25	0.06	0.00–0.95
smokers	6.93	1.64–29.2	0.91	0.14–5.74
Breakfast				
no rice	1		1	
rice	3.37	1.08–10.6	1.65	0.52–5.27
no breakfast	0.87	0.15–4.94	—	
Pickled Chinese cabbage				
≤3 times/month	1		1	
≥1 times/week	1.49	0.42–5.30	4.53	1.47–14.0
Lettuce				
≤3 times/month	1		1	
≥1 times/week	1.01	0.32–3.25	3.88	1.38–11.8

—: Estimate was not obtained as there were no subjects among cases.

zole.[22] These reports indicate that among those who receive antibiotic medication for therapeutic reasons, smoking may disturb incidental *H. pylori* eradication by the antibiotic medication. Unfortunately, the history of medication of the subjects was not available in this study.

Some possible reasons for the association found in this study are as follows. Firstly, the association with smoking would be more evident in patients than in the general population, because patients would be more likely to have received treatment with antibiotics. Secondly, the association would be more marked in groups with a high prevalence of the infection than in groups with a lower prevalence, because smoking affects the eradication process. In the study reporting a positive association for the general population in Northern Ireland, the prevalence was more than 60% among the subjects aged 45 years or over.[19] A high percentage of smokers would have been infected, which might favor detection of the association. A epidemiological study in which only a few subjects were smokers could not evaluate the effect of smoking on *H. pylori* infection,[23] as in the analysis of female outpatients in this study.

The association of the *H. pylori* antibody with rice for breakfast, frequent rice intake, and frequent soybean paste soup intake was observed in males, and with pickled Chinese cabbage and lettuce in females. It was reported in another Japanese study that pickled vegetables and soybean paste soup were associated with IgG antibody titer in males.[17] The Japanese diet may have some role in the continuation of *H. pylori* infection for both sexes, though clearer evidence is required. The association with lettuce in females observed in this study remains to be further investigated; it may be a chance association.

H. pylori resides around the gastric epithelium, not around intestinalized epithelium,[24–26] and in an environment with a range of pH.[27] The continuation of *H. pylori* infection is considered to be dependent on the lumen environment. The biological mechanism which creates a favorable environment for *H. pylori* through smoking or Japanese diet is not clear. However, the findings obtained here are interesting epidemiologically, when we consider the role of smoking and diet in stomach cancer risk elevation.[28, 29] Besides direct carcinogenesis by substances derived from smoking, smoking may play a role as a co-factor in increasing stomach cancer risk through *H. pylori* infection. Similarly, Japanese food may increase the risk through *H. pylori* infection. Further epidemiologic studies are necessary to assess the quantitative contribution of the interaction between these factors and *H. pylori* infection to the development of stomach cancer.

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