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Helicobacter pylori Risk Associated with Sibship Size and Family History of Gastric Diseases in Japanese Adults

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***Helicobacter pylori* is thought to be a cause of gastric cancer. Risk factors of *H. pylori* positivity were investigated among 4,361 public service workers in Japan. Sera and information on family history and lifestyle were collected, and *H. pylori* antibody was measured using the sera. Sex- and age-adjusted odds ratios of factors expected to influence *H. pylori* seropositivity were calculated. The factors with a significant influence were included in a logistic regression model and the final model was obtained by backward elimination. Sibship size (4 and more vs. 1), smoking habit (current vs. never), and paternal and siblings' histories of gastric diseases showed significant relationships to *H. pylori* seropositivity, with odds ratios (95% confidence intervals) of 1.5 (1.0–2.1), 0.8 (0.7–0.9), 1.5 (1.3–1.8) and 1.7 (1.1–2.6) respectively. However, spouse's history was not related. In the final model, sibship size and paternal history remained as positive factors, and smoking as a negative one. Contradictory results on the relationship between *H. pylori* status and smoking among recent studies indicate the existence of hidden confounding factors. It is suggested that infection from family members in childhood considerably affects the *H. pylori* status of Japanese adults, whereas infection between adults is rare.**

Key words: *Helicobacter pylori* — Family history — Sibship size — Serology — Epidemiology

It has been established that *Helicobacter pylori* is one of the pathogens in gastric diseases such as peptic ulcer and chronic gastritis,[1–3] and it may also cause gastric cancer.[4–6] A Japanese study has revealed a high odds ratio of 13.3 for gastric cancer in those aged under 40.[7] In spite of many epidemiological studies, the infection routes of *H. pylori* have not been established yet. In Japan, which has the highest incidence of gastric cancer among the developed countries, only a few studies have been carried out so far on the relationship between *H. pylori* positivity and family history. This study was performed to investigate the relationships by collecting sera and information from 4,361 Japanese public service workers.

METHODS

The subjects were from about 5,000 public service workers belonging to a bureau. The offices of the subjects were distributed from the east to the west coast in the middle of Honshu island. About 90% of the workers underwent a general health check program which was performed from August to September of 1996, and 4,361 workers responded to a questionnaire for this study. The residual sera of the health check program were collected and used. Serum *H. pylori* antibody was measured by BML Co., Ltd. (Tokyo) after serum examinations for the general health check program. Measurements were made by enzyme immunoassay with Pilika Plate G Helicobacter II (Biomerica Ltd., Newport Beach, CA) and values within the gray zone were defined as negative. Using the questionnaire, information was collected on expected risk factors of *H. pylori* positivity such as past history, family history, sibship size, and smoking and drinking habits.

Age- and sex-adjusted odds ratios for *H. pylori* seropositivity were calculated for the various factors. As for family history of gastric diseases, if the family had a history of gastric cancer, gastric ulcer, or duodenal ulcer, it was defined as positive. The factors showing a significant influence in the analyses were entered into a multiple logistic regression model with age and sex. The final model was obtained by backward elimination so that the *P* values of all explanatory variables were under 0.10. Calculations were carried out using statistical software "HALBAU" (Gendai-sugaku-sha, Kyoto).

RESULTS

Table I shows the age and sex distribution of the subjects and the *H. pylori* seropositive percent with respect to age and sex. Female subjects showed lower seropositivity than male subjects, but seropositivity depended on age more strongly than on gender. Seropositivity increased with age from 22 to 53%.

Past history of gastric diseases was related to *H. pylori* seropositivity. Age- and sex-adjusted odds ratios (95% confidence intervals) of history of chronic gastritis, gastric and duodenal ulcers were 2.06(1.52, 2.78), 2.98(2.29, 3.90) and 2.01(1.35, 2.98), respectively.

Table I. Age and Sex Distribution of the Subjects and *H. pylori* Seropositivity

Age (years)	Male[a)]	Female[a)]	Total[a)]
19–29	1,261 (22.3%)	425 (19.5%)	1,686 (21.6%)
30–39	1,526 (29.8%)	144 (26.4%)	1,670 (29.5%)
40–49	791 (46.4%)	63 (41.3%)	854 (46.0%)
50–69	121 (53.7%)	30 (50.0%)	151 (53.0%)
Total	3,699 (31.6%)	662 (24.5%)	4,361 (30.5%)

a) Number of subjects (seropositive %).

Table II. Age- and Sex-adjusted Odds Ratios for *H. pylori* Seropositivity

Risk factor	*n*	Odds ratio (95% CI)
Sibship size		P=0.030*
1	209	1.0
2,3	3,518	1.15 (0.84, 1.59)
4+	519	1.45 (1.01, 2.08)
Unknown	115	0.80 (0.47, 1.37)
Smoking habit		P=0.031
Never	1,970	1.0
Past	397	0.97 (0.76, 1.23)
Current	1,929	0.80 (0.69, 0.93)
Unknown	65	0.86 (0.49, 1.50)
Drinking habit		P=0.543
Never	350	1.0
Occasional	1,573	0.86 (0.66, 1.12)
Past	30	0.69 (0.30, 1.58)
Current	2,341	0.85 (0.66, 1.11)
Unknown	67	0.62 (0.33, 1.15)
Father's history of gastric disease		P<0.001
Negative	3,533	1.0
Positive	575	1.51 (1.25, 1.82)
Unknown	253	1.14 (0.86, 1.52)
Mother's history of gastric disease		P=0.315
Negative	3,897	1.0
Positive	183	1.25 (0.91, 1.72)
Unknown	281	1.10 (0.84, 1.44)
Siblings' history of gastric disease		P=0.041
Negative	3,937	1.0
Positive	97	1.71 (1.12, 2.60)
Unknown	327	1.07 (0.83, 1.37)
Spouse's history of gastric disease		P=0.993
Negative	3,332	1.0
Positive	60	0.99 (0.57, 1.71)
Unknown	969	1.01 (0.85, 1.20)

CI: confidence interval.
* *P* value for the factor.

Table II shows age- and sex-adjusted odds ratios of other factors for *H. pylori* seropositivity. Sibship size showed a dose-dependent positive association with *H. pylori* seropositivity. Smoking habit was negatively related to *H. pylori* seropositivity and drinking habit had no significant influence. With respect to family history of gastric diseases, paternal history and siblings' history showed significant positive relationships. Maternal history showed an elevated odds ratio but the 95% confidence interval included 1.0. Spouse's history showed an odds ratio of about 1.0.

Table III. Final Model Using Multiple Logistic Regression: Factors Associated with *H. pylori* Seropositivity

Explanatory variable	Odds ratio (95% confidence interval)	*P* value
Age (+1 year)	1.06 (1.05, 1.06)	P<0.001
Sex		P=0.010
Male	1.0	
Female	0.75 (0.60, 0.93)	
Sibship size		P=0.013
1	1.0	
2,3	1.17 (0.85, 1.61)	
4+	1.48 (1.02, 2.13)	
Unknown	0.62 (0.31, 1.23)	
Smoking habit		P=0.007
Never	1.0	
Past	0.95 (0.74, 1.20)	
Current	0.78 (0.67, 0.91)	
Unknown	1.54 (0.70, 3.36)	
Father's history of gastric diseases		P<0.001
Negative	1.0	
Positive	1.52 (1.26, 1.84)	
Unknown	1.16 (0.87, 1.55)	

Number of subjects was 4,361.

In addition to age and sex, sibship size, smoking habit, paternal and siblings' histories of gastric diseases were entered into a multiple logistic regression model. The final model is shown in Table III. Sibship size and paternal history of gastric diseases were positively and smoking habit was negatively related to *H. pylori* seropositivity. Female subjects showed significantly lower risk for *H. pylori* seropositivity.

DISCUSSION

About 500 workers did not undergo the health check program because they were admitted to hospitals to undergo more detailed clinical survey programs instead. Among the employees who underwent the health check program, about 3% did not respond to the questionnaire, mainly because they did not have enough time to fill out it. Thus, we consider that there should be little bias between the workers who participated in the study and those who did not in the bureau.

Past history of gastric diseases such as gastric and duodenal ulcer and chronic gastritis was related to *H. pylori* seropositivity. However, these factors were thought to be not the causes but the results of *H. pylori* infection, and thus were excluded from the analysis using the multiple logistic regression model.

The seropositive percent of the current study is lower than that in a previous Japanese study.[8] This may be because of differences in the calendar time of the phlebotomy. Infection in adulthood is known to be rare in developed countries and *H. pylori* prevalence mainly depends on infection in childhood.[9, 10] If this is true in Japan, gradual improvement of sanitary conditions, which affect infection in childhood, can cause a decrease of *H. pylori* prevalence with calendar time. In the current study and the previous study,[8] *H. pylori* prevalence increased with age in adulthood. This can be explained by the decrease of *H. pylori* prevalence with calendar time, when infection in adulthood is not frequent.

A significant sex-dependent difference in *H. pylori* prevalence was observed, but the difference was at most 5.1%. This result was consistent with a Northern Irish study.[11] In Germany, female subjects showed lower seropositivity, though the difference was not significant.[12] It seems that women are less likely to be infected with *H. pylori*, but the difference is not large.

Sibship size was positively and dose-dependently associated with *H. pylori* seropositivity. The association remained after adjustment for other factors. The dose-dependency seems to suggest a direct relationship between sibship size and *H. pylori* status. Several studies have shown that overcrowding in childhood is a risk factor for *H. pylori* infection.[11–15] A nested-case control study has shown that those with large sibship size are at high risk for gastric cancer and peptic ulcer and it is suggested that large sibship size contributes to infection between siblings in childhood.[16] The results of the current study were consistent with those in the above studies, and infection between siblings may be one of the main infection routes in Japan.

Smoking habit showed a negative association with *H. pylori* infection and the association remained after adjustment for other factors. There is a Japanese study suggesting that smoking is positively related to *H. pylori* infection, among outpatients without malignant diseases at a regional cancer center.[17] Another Japanese study found no relationship between smoking and *H. pylori* infection.[18] A Northern Irish group concluded that smoking is positively related to *H. pylori* seropositivity.[11] The relationship between smoking habit and *H. pylori* infection seems to depend on the subjects. The contradictory results indicate that hidden confounding factors may exist.

As family histories of gastric cancer, duodenal and gastric ulcer gave similar results, the three gastric diseases were combined into one factor in the analyses. If a person has history of gastric disease, the probability that he/she is infected with *H. pylori* is not less than 80%.[7, 19, 20] Infection of family members with *H. pylori* is a risk factor for *H. pylori* infection.[21] Paternal history had a significant influence, while maternal history did not. In the current study, the sex-related difference in *H. pylori* prevalence was also slight compared with the difference in the frequency of gastric diseases between the fathers and the mothers. The proportion of those who developed gastric diseases after *H. pylori* infection was larger among the fathers than among the mothers, which may account for the difference in relationships to *H. pylori* positivity.

Siblings' history gave a larger point estimate of odds ratio, but this factor was eliminated from the model. As discussed above, infection among siblings may be one of the infection routes. If a subject is infected with *H. pylori* and the infection occurred in childhood, the possibility that his/her siblings also have *H. pylori* is high. This may be the reason why the point estimate was large. However, frequency with which siblings of the subjects had a history of gastric disease was low compared with that of the fathers, which is thought to be the reason why the siblings' history was eliminated from the model. As siblings' history showed a stronger association than maternal history, it is unlikely that an inherited characteristic is a major cause of the significant relationships between family histories and *H. pylori* seropositivity. It is more likely that infection between family members is the cause of the relationship. It has been reported that infection occurred among family members.[22]

The subjects of the current study were in the age range of 19–65. Infection between siblings or from the parents presumably would have occurred mainly in their childhood, but the odds ratios of these factors may be underestimated owing to infection in adulthood. We believe that infection in childhood predominantly influences the *H. pylori* status of Japanese adults.

Spouse's history showed no relation to *H. pylori* seropositivity, though intimate contact is to be expected. This supports the idea that infection of *H. pylori* between adults is not common. Fecal-oral transmission is suspected to be an infection route of *H. pylori*,[23] though there is a contradictory finding.[24] Fecal-oral transmission is thought to be frequent in childhood and rare in adulthood, and this is compatible with the results of the current study.

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