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PREVALENCE OF *HELICOBACTER PYLORI* INFECTION MEASURED WITH URINARY ANTIBODY IN AN URBAN AREA OF JAPAN, 2008–2010

TAKASHI TAMURA[1], EMI MORITA[1], TAKAAKI KONDO[2], JUN UEYAMA[2], TETSUYA TANAKA[2], YUTO KIDA[2], YOKO HORI[2], SHIGERU INOUE[3], KOUTARO TOMITA[1], RIEKO OKADA[1], SAYO KAWAI[1], ASAHI HISHIDA[1], MARIKO NAITO[1], KENJI WAKAI[1] and NOBUYUKI HAMAJIMA[1]

[1]*Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Nagoya University School of Health Sciences*
[3]*Medical Student, Nagoya University School of Medicine*

ABSTRACT

Helicobacter pylori (*H. pylori*) has expanded to infect about half the world's population. Although there were many studies on the prevalence of *H. pylori* infection for defined areas in the 1990s throughout the world, there were only limited sources tracking its latest prevalence among large populations. In the present study, we estimated the prevalence of *H. pylori* among the inhabitants of Nagoya, an urban area of Japan. Study subjects were 5,167 participants (1,467 males and 3,700 females) aged 35 to 69 years from the Daiko Study, a part of the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study). A urinary anti-*H. pylori* antibody was used to detect *H. pylori* infection. The history of eradication treatments for *H. pylori* infection was obtained using self-administered questionnaires. The prevalence detected by the urinary test included 19.6% (95% confidence interval; 16.8–22.6%) for those aged 35–39 years, 25.8% (23.5–28.2%) for 40–49 years, 39.4% (36.8–42.1%) for 50–59 years, 50.3% (47.8–52.7%) for 60–69 years, and 36.4% (35.1–37.7%). Among 5,167 participants, 266 (5.1%) stated that they had received an eradication treatment. Since 167 subjects with negative urinary tests replied that they had been seropositive for *H. pylori* in the past, they were included among the ever-infected inhabitant group. Consequently, the overall rate of those with a history of persistent infection was 39.6% (38.3–40.9%). The prevalence of *H. pylori* infection observed in Nagoya seemed to be lower than the corresponding prevalence reported in other studies of Japan. That lower rate might be due to the reduced exposure from improved urban sanitary conditions.

Key Words: *Helicobacter pylori*, Prevalence, Eradication, Nagoya

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium colonizing human gastric mucosa identified by Marshall *et al.* in 1983, which increases the risk of gastric diseases, including stomach cancer.[1,2] The infection rate has been estimated to cover half of the world's population.[3,4] The infection rate in Japan has been reported to be higher than that in other industrialized countries, but lower than that in developing countries.[5] The gastric cancer incidence was higher

Corresponding Author: Takashi Tamura
Department of Preventive Medicine, Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Phone: +81-52-744-2132, Fax: +81-52-744-2971, E-mail: takashi.tamura@c.mbox.nagoya-u.ac.jp

in Japan because the strains of East Asian CagA are so dominant.[6,7] Persistent *H. pylori* infection also causes ulcers, atrophic gastritis, mucosa-associated lymphoid tissue lymphoma, and intestinal metaplasia.[8-11]

It is well known that *H. pylori* is transmitted from person to person through oral-oral or fecal-oral routes during childhood, and the infection lasts for decades unless the bacterium is eradicated.[12,13] Though infection among adults is possible, it is highly limited.[14,15] Factors directly affecting possible transmission routes, such as sewage systems, are considered among the essential environmental components of prevalence. Although the mechanism has not been clarified, lifestyle factors such as salty food intake,[16] low intake of fruits,[17] and smoking,[18-21] might play important roles in persistence of the infection.

Although several studies have reported the prevalence of *H. pylori* infection in different areas of Japan in the 1990s, they were mainly restricted to rural areas.[22-24] This study aimed to investigate the recent prevalence among the inhabitants of Nagoya (an urban area of Japan) in 2008–2010. Past eradication treatments were examined to estimate the influence on those ever-infected. The ethics committee of the Nagoya University School of Medicine approved the present study protocol (approval number 618).

SUBJECTS AND METHODS

Subjects

Subjects were 5,167 participants (1,467 males and 3,700 females) aged 35 to 69 years as reported in the Daiko Study, a part of the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study).[25,26] The participants were enrolled at the Daiko Medical Center from June, 2008 to May, 2010. All participants have provided a written informed consent form and completed a questionnaire on their lifestyles, including a history of *H. pylori* test and/or eradication treatments. Four who withdrew from this study, and one without a urine sample for the detection of anti-*H. pylori* antibody, were excluded. An antibody-kit for urine, Rapiran (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was used to detect persistent *H. pylori* infections.

Statistical analysis

Confidence intervals (CIs) of proportion were estimated based on a binominal distribution. Differences in the proportion between two groups were examined using a chi-square test. Differences in mean were examined with a Student's *t*-test. The age-standardized rates were calculated based on the distribution of all subjects of this study. The odds ratios (ORs) were estimated through a logistic regression model. A Stata MP/11 (Stata Corp., College Station, TX, USA) was used for the calculations.

RESULTS

Table 1 shows the characteristics of the study subjects. They were 1,467 males (28.4%) and 3,700 females (71.6%) in total 5,167. Among them, those aged 50 years or over accounted for 58.5%. The mean ± standard deviation of age was 53.6 ± 10.3 years in males and 52.2 ± 10.3 years in females. Current smokers were 24.1% in males and 6.9% in females, while current drinkers were 74.9% and 45.9%, respectively. Among 5,167 subjects, 487 (9.4%) replied that they had a history of a *H. pylori* test, 325 (6.3%) were found to be positive, and 171 (3.3%) were successfully treated. Three did not reply to any queries regarding *H. pylori*. Eleven failed

Table 1 Characteristics of subjects

Characteristics		Male n=1,467	Female n=3,700	Total n=5,167
Age (years)				
	35–39	191	571	762
	40–49	347	1,033	1,380
	50–59	403	945	1,348
	60–69	526	1,151	1,677
Wards				
	Central area	550	1,323	1,873
	Eastern area	825	2,096	2,921
	Western area	92	281	373
Drinking				
	Current	1,099	1,699	2,798
	Former	45	60	105
	Never	323	1,940	2,263
	Unknown	0	1	1
Smoking				
	Current	354	255	609
	Former	639	386	1,025
	Never	474	3,058	3,532
	Unknown	0	1	1
Past tests for *H. pylori*				
	No	1,235	3,366	4,601
	Yes	188	299	487
	Do not remember	44	32	76
	Unspecified	0	3	3
Results of past tests				
	Positive	133	192 (2)[a]	325 (2)[a]
	Negative	43 (1)[a]	104 (8)[a]	147 (9)[a]
	Forgotten	13	8	21
	Unspecified	0	5	5
Eradication treatments				
	No	19	36 (1)[b]	55 (1)[b]
	Yes: succeeded	74 (4)[b]	97	171 (4)[b]
	Yes: failed	19	24	43
	Yes: unknown	20	32	52
	Do not remember	4	4	8
	Unspecified	1	0	1

[a] In parentheses are those who did not specify "yes" to the question addressing "past tests for *H. pylori*."
[b] In parentheses are those who did not specify "positive" to the question addressing "results of past tests."

to specify "yes" for "past tests for *H. pylori*," but replied to "results of past tests." Although five did not reply to "results of past tests," one of them answered the question on "eradication treatments." In addition, four males replied that their "eradication treatments" had succeeded, though they forgot the "results of past tests" or stated it to be negative. One subject with a past positive result did not reply to the question about "eradication treatments." Since 24 (0.5%) of 5,167 subjects had inconsistent responses to questions regarding *H. pylori*, those with negative urinary tests were regarded as being negative.

The prevalence of persistent *H. pylori* infection detected by urinary testing according to sex is shown in Table 2, i.e. 19.6% (95% CI; 16.8–22.6%) for those aged 35–39 years, 25.8% (23.5–28.2%) for 40–49 years, 39.4% (36.8–42.1%) for 50–59 years, 50.3% (47.8–52.7%) for 60–69 years, and 36.4% (35.1–37.7%).

There were 167 participants with negative urine tests who replied that they had been *H. pylori* seropositive in the past, 113 of whom replied that they had successful eradication treatments, 27 that they had received eradication treatments with an unknown result, 13 that they had failed their eradication treatments, 11 that they had not had any eradication treatment, and 3 that they had forgotten to get their eradication treatments. Table 3 shows the number of all ever-infected inhabitants according to sex including the above 167 participants; 20.7% (17.9–23.8%) for those aged 35–39 years, 27.6% (25.3–30.0%) for 40–49 years, 43.3% (40.7–46.0%) for 50–59 years, 55.0% (52.6–57.4%) for 60–69 years, and 39.6% (38.3–40.9%). The percentage of ever-infected participants as a whole was higher in males than in females (χ^2=15.85, p<0.001).

The prevalence of *H. pylori* was examined among those in the Nagoya area. The central area (the six wards of Atsuta, Higashi, Kita, Mizuho, Naka, and Showa) was downtown, while the eastern area (the five wards of Chikusa, Meito, Midori, Moriyama, and Tenpaku) and the western area (the five wards of Minami, Minato, Nakagawa, Nakamura, and Nishi) were in the suburbs.

Table 2 Prevalence (%) of *H. pylori* infection and 95% confidence interval (95% CI) measured with a urinary anti-*H. pylori* antibody test

Age	Male		Female		Total	
	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)
35–39	191	23.0 (17.3–29.7)	571	18.4 (15.3–21.8)	762	19.6 (16.8–22.6)
40–49	347	25.6 (21.1–30.6)	1,033	25.8 (23.2–28.6)	1,380	25.8 (23.5–28.2)
50–59	403	39.5 (34.7–44.4)	945	39.4 (36.2–42.6)	1,348	39.4 (36.8–42.1)
60–69	526	54.0 (49.6–58.3)	1,151	48.6 (45.6–51.5)	1,677	50.3 (47.8–52.7)
Total	1,467	39.3 (36.8–41.8)	3,700	35.2 (33.7–36.8)	5,167	36.4 (35.1–37.7)

Table 3 Proportion of *H. pylori* ever-infection and 95% confidence interval (CI) measured with a urinary anti-*H. pylori* antibody test, when 167 subjects were added with negative results replying that they had been seropositive

Age	Male		Female		Total	
	N	Ever-infected (95% CI)	N	Ever-infected (95% CI)	N	Ever-infected (95% CI)
35–39	191	24.6 (18.7–31.3)	571	19.4 (16.3–22.9)	762	20.7 (17.9–23.8)
40–49	347	28.8 (24.1–33.9)	1,033	27.2 (24.5–30.0)	1,380	27.6 (25.3–30.0)
50–59	403	44.2 (39.3–49.2)	945	43.0 (39.8–46.2)	1,348	43.3 (40.7–46.0)
60–69	526	60.6 (56.3–64.8)	1,151	52.5 (49.5–55.4)	1,677	55.0 (52.6–57.4)
Total	1,467	43.9 (41.3–46.5)	3,700	37.9 (36.3–39.5)	5,167	39.6 (38.3–40.9)

The age-standardized rate was similar; 40.1% for the central area, 39.3% for the eastern area, and 38.3% for the western area. However, the rate among those aged 35–40 years in the western area (8.3%) was significantly lower (p=0.027) than that in the other areas.

The prevalence according to smoking habit was 39.1% (35.2–43.1%) for smokers, 38.0% (35.0–41.0%) for former smokers, and 35.4% (33.8–37.0%) for never smokers. The age-sex adjusted ORs of *H. pylori* infection were 1.21 (95% CI; 1.00–1.47, p=0.054) for smokers and 1.00 (0.85–1.18, p=0.976) for former smokers relative to never smokers among the subjects, excluding one without a reply to smoking history (N=5,166). The prevalence according to drinking habit was 35.3% (33.6–37.2%) for drinkers, 41.9% (32.3%–51.9%) for former drinkers, and 37.4% (35.4–39.4%) for never drinkers. The age-sex adjusted ORs of *H. pylori* infection were 0.95 (0.84–1.08, p=0.436) for drinkers and 1.25 (0.83–1.89, p=0.285) for former drinkers relative to never drinkers among the subjects, excluding one with no reply to drinking history.

DISCUSSION

In 2008–2010, we documented the prevalence of *H. pylori* infection among the inhabitants of Nagoya, an urban area of Japan. Although the persistent infection detected by the urinary tests was found to be relatively low as a whole (36.4%), that rate rose higher with age. The ever-infected inhabitants with negative urinary tests were 3.2% as a whole. The age-sex adjusted OR of *H. pylori* infection was marginally significantly higher for smokers relative to never smokers (p=0.054).

Several studies have so far reported the prevalence among the Japanese population in defined areas during periods when eradication treatments were not generally provided. After those uninfected with eradication treatments were added, the prevalence in the present study was lower than those from previous studies (Fig. 1). Even when the year of the survey was taken into account,

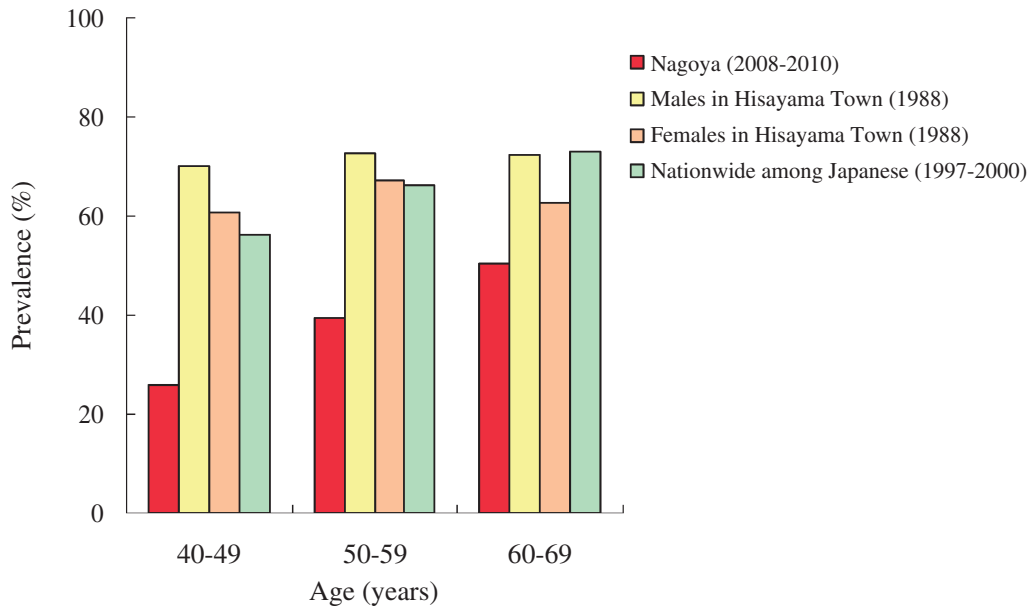

Fig. 1 Prevalence (%) in different areas of Japan within the survey year obtained from the references[22,23]

the reduction was marked. Although the prevalence among smokers (39.1%) was significantly higher than that among never smokers (35.4%), as noted in previous reports,[18-21] even such a small difference in the prevalence between smokers and never smokers could not account for the reduced prevalence. Though the influence of a transfer of populations was unknown, it seemed to be limited because the transfer to other areas of groups with high infection rates and/or the transfer to the city of groups with low infection rates were not plausible. Such transfers were regarded as being independent of the infection. Accordingly, the observed lower prevalence might be due to the high prevalence of washing toilet together with the sanitary drainage in Nagoya.

One limitation of this study was that the sensitivity and specificity of Rapiran[26-29] could not be measured directly. According to the document on Rapiran, the sensitivity was 89.6% and the specificity was 93.8%. As for the false-positives and false-negatives in this study, the following information was available. Of 1,879 participants with a positive urinary test, 112 (6.0%) visited the Daiko Medical Center for eradication treatments. Among them, we found that eight (7.1%) were negative both for an urea breath test (UBT) and a serum anti-*H. pylori* antibody, three (2.7%) were negative for a UBT and positive for a serum anti-*H. pylori* antibody as a false-positive, one (0.9%) was positive for a UBT and negative for a serum anti-*H. pylori* antibody, and one (0.9%) was without a UBT but was negative for a serum anti-*H. pylori* antibody. A total of 12 subjects (10.7% of 112) were determined not to be infected in spite of a positive urinary test when they had participated in the Daiko Study, indicating that the positive predictive value was 89.3%. Accordingly, the possibility of the false-positive should be taken into account. In addition, the false-negative must be similarly considered; 11 subjects who replied that they have been seropositive in the past without eradication treatments were found to be negative when given a urinary test. If the false-positives were similar to the false-negatives, the prevalence estimated in the present study may reflect the actual prevalence.

Although it is expected that the prevalence would be declining hereafter due to eradication treatments and sanitary condition improvements in many areas of the world, surveillance for *H. pylori* infection might be important for estimating the future risk of *H. pylori*-related diseases, including gastric cancer in each region. Thus, monitoring the prevalence of *H. pylori* infection in various regions worldwide would be required.

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