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Declining trends in prevalence of *Helicobacter pylori* infection by birth-year in a Japanese population

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Key words

Gastric cancer, *Helicobacter pylori* antibody, *Helicobacter pylori* infection, high-risk individuals, pepsinogen

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Gastric cancer incidence and mortality have been decreasing in Japan. These decreases are likely due to a decrease in prevalence of *Helicobacter pylori* infection. Our aim was to characterize the trends in prevalence of *H. pylori* infection focused on birth-year. We carried out a cross-sectional study that included 4285 subjects who were born from 1926 to 1989. We defined *H. pylori* infection by the serum *H. pylori* antibody titer. Individuals having *H. pylori* infection and those with negative *H. pylori* antibody titer and positive pepsinogen test were defined as high-risk individuals for gastric cancer. We estimated the birth-year percent change (BPC) of the prevalence by Joinpoint regression analysis. The prevalence of *H. pylori* infection among the subjects born from 1927 to 1949 decreased from 54.0% to 42.0% with a BPC of −1.2%. It was followed by a rapid decline in those born between 1949 (42.0%) and 1961 (24.0%) with a BPC of −4.5%, which was followed by those born between 1961 (24.0%) and 1988 (14.0%) with a BPC of −2.1%. The proportion of high-risk individuals for gastric cancer among the subjects born from 1927 to 1942 decreased from 62.0% to 55.0% with a BPC of −0.8%. A subsequent rapid declining trend was observed in those born between 1942 (55.0%) and 1972 (18.0%) with a BPC of −3.6%, and then it became stable. These remarkable declining trends in the prevalence of *H. pylori* infection by birth-year would be useful to predict the future trend in gastric cancer incidence in Japan.

*H*elicobacter pylori (*H. pylori*) infection is regarded as a major risk factor for gastric cancer.[1,2] It is typically acquired in childhood through unsanitary an environment.[3,4] Once infection is established, it usually lasts for life. Chronic infection with *H. pylori* has certain carcinogenicity which induces gastric cancer through chronic atrophic gastritis.[5,6]

In Japan, the age-adjusted incidence and mortality rate of gastric cancer have been declining over the past 30 years.[7,8] These decreasing trends have been thought to be due to a decline in the prevalence of *H. pylori* infection over time. The prevalence examined in the early 1990s in Sapporo city was over 70% among those aged 50 years and over.[9] Another study carried out in Kyushu reported that the prevalence of *H. pylori* infection increased with age, and the prevalence among those aged 50 years and over was 60–70% during the investigation period of 2002–2006.[10] This cross-sectional study was conducted again in 2007–2011, showing a prevalence of 40–60% among those aged 50 years and over.[11] The difference in the prevalence of *H. pylori* infection in the same geographic area and age group over time might be due to the birth cohort effect. Similarly, Ueda *et al.*[12] recently reported changes in the prevalence of *H. pylori* infection in 10-year birth cohorts between the 1940s and 1980s, showing a birth cohort effect with declining tendency of the prevalence in the Japanese population. However, the degree of change by a single birth year effect remains to be clarified.

In this study, we undertook a cross-sectional study to characterize trends by birth-year in the prevalence of *H. pylori* infection and the proportion of high-risk individuals for developing gastric cancer in Japan, which would provide useful information to estimate the future trend of gastric cancer incidence.

Materials and Methods

Study subjects. We recruited participants through the Hospital-based Epidemiological Research Program III at Aichi Cancer Center (HERPACC III) from November 2005 to March 2013. Briefly, all first-visit outpatients at Aichi Cancer Center Hospital (Nagoya, Japan) aged 20–79 years were asked to fill out a self-administered questionnaire regarding their lifestyle before development of the current symptom, and were also asked to provide blood samples.[13,14] Approximately 66.4% of the outpatients provided written informed consent to participate in the HERPACC III study carried out during this period. The process of subject selection from HERPACC III participants is shown in Figure 1. A total of 11 559 participants, born between 1926 and 1989, filled out the self-administered questionnaire and provided blood samples between November 2005 and March 2013. Of these, we selected 3828 participants

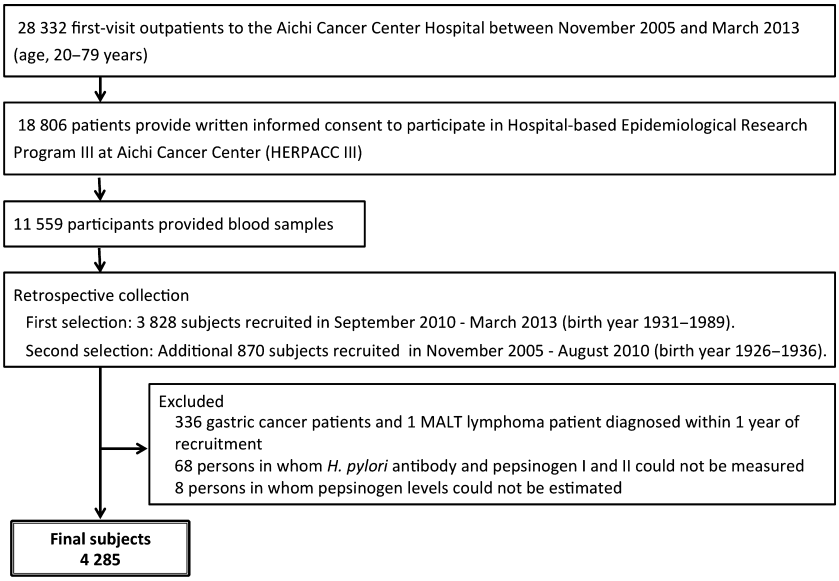

Fig. 1. Flowchart showing the selection of eligible subjects for the study of prevalence of *Helicobacter pylori* infection and proportion of high-risk individuals for gastric cancer. The study was undertaken within the framework of the Hospital-based Epidemiology Research Program III at Aichi Cancer Center (Nagoya, Japan).

who were born between 1931 and 1989, and who were recruited between September 2010 and March 2013 through HERPACC III. As the number of participants born between 1926 and 1936 was small, we additionally selected 870 individuals who were born in this period from those recruited between November 2005 and August 2010. The data were entered into the HERPACC database, which was periodically linked to the hospital-based cancer registry system until March 2014, to update the data on cancer incidence. Among the 4698 selected participants, we excluded 336 gastric cancer patients and one with mucosa-associated lymphoid tissue (MALT) lymphoma who were diagnosed within 1 year after recruitment, 68 individuals whose stored serum volume was insufficient for measurement of *H. pylori* antibody and pepsinogen levels, and eight persons in whom the result of the pepsinogen test could not be determined. The remaining 4285 subjects (male, $n = 2431$; female, $n = 1854$) were included in this study (Fig. 1). During the 1-year follow-up period, we identified 259 colorectal cancer cases (6.0%), 186 esophagus cancer cases (4.3%), 67 liver cancer cases (1.6%), 101 pancreatic cancer cases (2.4%), 339 lung cancer cases (7.9%), 221 head and neck cancer cases (5.2%), and 826 cases with other cancers (19.3%) among the 4285 study subjects, and the remaining 2286 subjects (53.3%) were designated as cancer-free subjects. As there was little evidence for the association between *H. pylori* infection and risk of cancer except gastric cancer and MALT lymphoma, we included patients who developed cancers other than these two cancer types in our study.

This study was approved by the Institutional Ethics Committee at Aichi Cancer Center (approval no. 19-7, 15 August 2005).

Determination of *H. pylori* antibody titer and pepsinogen levels. The *H. pylori* antibody titer and pepsinogen levels were measured in the blood sample obtained at the time of the first visit. The serum *H. pylori* antibody titer was measured using an enzyme immunoassay kit (E-plate Eiken *H. pylori* antibody or E-plate Eiken *H. pylori* antibody II; Eiken Kagaku, Tokyo, Japan). Positivity for *H. pylori* antibody was defined as higher than 10 U/mL *H. pylori* antibody titer. This cut-off value in the kit showed the sensitivity and specificity to be 90.7% and 91.5%, respectively, when the ^{13}C urea breath test was used for validation.[15] Individuals with *H. pylori* infection were defined as *H. pylori* antibody-positive individuals.

Serum pepsinogen levels were measured using the latex agglutination reaction kit (LZ test Eiken pepsinogen I and LZ test Eiken pepsinogen II; Eiken Kagaku). We adopted the level of pepsinogen I $\leq$ 70 ng/mL and the ratio of pepsinogen I /II $\leq$ 3.0 as showing a positive result in the pepsinogen test. The cut-off value was reported to provide a sensitivity and specificity for chronic gastritis of 87.5% and 84.9%, respectively, validated by histological examination.[16]

In the natural history of *H. pylori* infection, some *H. pylori* antibody-positive individuals develop chronic atrophic gastritis with negative conversion of *H. pylori* antibody and positive conversion of the result of the pepsinogen test.[1,17] Patients with positive *H. pylori* antibody and those with chronic atrophic gastritis have a high risk of developing gastric cancer.[18] Therefore, we defined both *H. pylori* antibody-positive individuals and pepsinogen test-positive individuals with negative *H. pylori* antibody as high-risk individuals for gastric cancer.

Statistical methods. We calculated the prevalence of *H. pylori* infection and proportion of high-risk individuals for gastric cancer using the three-birth-year moving-average method. The moving-average prevalence in the first birth-year (1927) was calculated as the sum of the number of positive individuals born in the first three birth-years (1926, 1927, 1928) divided by the total number of subjects born in those three birth-years. The following moving-average prevalence was calculated by using the subsequent three adjoining birth-years (1927, 1928, 1929). We calculated the moving-average prevalence in the last birth-year (1988) using the last three birth-years (1987, 1988, 1989). Their trends were characterized by Joinpoint regression analysis,[19] which is widely used to analyze trends over time. The technique identifies the time point(s), also referred to as joinpoint(s), at which there is a statistically significant change in the trend. We assigned the birth-year as an independent variable and the prevalence of *H. pylori* infection and the proportion of high-risk individuals for gastric cancer as dependent variables while setting a maximum of five join-

points. Then, all possible combinations of the joinpoints were tried to evaluate the best-fitting number of joinpoints to maximize the log-likelihood estimate.[19] The resulting trend segments, as delimited in time by joinpoints, were described by the birth-year percent change (BPC), that is, the slope of the line segment. In describing the trends, the terms "increase" or "decrease" were used when the slope (BPC) of the trend was statistically significant ($P < 0.05$); otherwise, the terms "stable" or "level" were used.

Joinpoint regression analysis was carried out using the Joinpoint Regression Program version 4.1.0 provided by the Surveillance, Epidemiology, and End Results Program (National Cancer Institute; http://surveillance.cancer.gov/joinpoint/). All statistical analyses were performed with 95% confidence intervals (CI); statistical significance was set at $P < 0.05$.

Results

Table 1 shows the number of study subjects according to birth-year and age at the time of recruitment in this study. The median birth-year of the 4285 study subjects was 1948. The age (mean ± SD) of the subjects was 60.5 ± 12.8 years (males, 64.1 ± 11.1 years; females, 55.8 ± 13.4 years). There were 1607 persons who were positive for *H. pylori* antibody (37.5%; 95% CI, 36.1–39.0%) and 198 persons who had a positive pepsinogen test but were negative for *H. pylori* antibody (4.6%; 95% CI, 4.0–5.3%). Table S1 shows the prevalence of *H. pylori* infection and the proportion of high-risk individuals for gastric cancer in each of the 13 birth cohorts that classified the subjects from 1926–29 to 1985–89.

Figure 2 and Table 2 show the trends in the prevalence of *H. pylori* infection and the proportion of high-risk individuals for gastric cancer using Joinpoint regression analysis. There were two significant joinpoints in the prevalence of *H. pylori* infection in 1949 and 1961 (Fig. 2a). The prevalence of *H. pylori* infection in subjects born between 1927 and 1949 decreased from 54.0% to 42.0%, with a BPC of −1.2% (95% CI, −1.6% to −0.8%). It was followed by a rapid decline in those born between 1949 (42.0%) and 1961 (24.0%) with a BPC of −4.5% (95% CI, −6.0% to −3.0%). The third decreasing trend was observed between 1961 (24.0%) and 1988 (14.0%) with a BPC of −2.1% (95% CI, −3.3% to −0.8%) (Table 2).

As for the proportion of high-risk individuals for gastric cancer, there were two significant joinpoints in 1942 and 1972 (Fig. 2b). The proportion of high-risk individuals for gastric cancer in the subjects born between 1927 and 1942 decreased from 62.0% to 55.0%, and the BPC of the period was −0.8% (95% CI, −1.4% to −0.1%). A subsequent rapid declining trend was observed in those born between 1942 (55.0%) and 1972 (18.0%) with a BPC of −3.6% (95% CI, −3.9% to −3.2%). It was followed by a stable trend until 1988 (BPC, +0.1% [95% CI, −3.1% to +3.4%]) (Table 2).

Table 1. Number of study subjects by birth-year and age at the time of recruitment to this study of prevalence of *Helicobacter pylori* infection in a Japanese population

Birth-year	Age, years						
	70–79	60–69	50–59	40–49	30–39	20–29	Total
1926–1929	76	0	0	0	0	0	76
1930–1934	519	0	0	0	0	0	519
1935–1939	579	18	0	0	0	0	597
1940–1944	205	307	0	0	0	0	512
1945–1949	0	654	0	0	0	0	654
1950–1954	0	218	270	0	0	0	488
1955–1959	0	0	354	0	0	0	354
1960–1964	0	0	162	196	0	0	358
1965–1969	0	0	0	291	0	0	291
1970–1974	0	0	0	104	127	0	231
1975–1979	0	0	0	0	120	0	120
1980–1984	0	0	0	0	29	24	53
1985–1989	0	0	0	0	0	32	32
Total	1379	1197	786	591	276	56	4285

Discussion

Our results showed that the prevalence of *H. pylori* infection in the Japanese population decreased as the birth year increased, with a drastic decline in those born between 1949 and 1961. A similar decreasing trend was observed in the proportion of high-risk individuals for gastric cancer, with a rapid decline among those born between 1942 and 1972. The different first joinpoints between the two proportions (1949 *vs* 1942) might be due to the latency of chronic inflammation. The negative conversion of *H. pylori* antibody and positive conversion of pepsinogen test accompany the development of chronic atrophic gastritis with increasing age.[20,21]

The drastic decline in the prevalence of *H. pylori* infection by birth-year can be explained by the change in sanitary conditions during childhood, when *H. pylori* infection is predominantly acquired. The main routes of transmission of *H. pylori* infection are known to be person-to-person transmission[22–25] and the waterborne route by drinking well water.[4,26,27] In particular, close intrafamilial contact, including mother/parent-to-child, sibling-to-sibling, and spouse-to-spouse has been consistently demonstrated as a risk factor for transmission of *H. pylori* infection.[1] In a population-based study, the risk of *H. pylori* infection in children increased according to the number of positive parents when the number of the children was the same,[25] and large sibship size was associated with increased risk of *H. pylori* infection in childhood.[28] Similarly in Japan, family size and the number of older siblings were reported to show significant positive correlations with the risk of *H. pylori* infection during childhood.[23] The number of live births and the number of persons per household decreased from the 1950s in Japan,[29] which might be correlated with the decrease in the prevalence of *H. pylori* infection in our data. Drinking well water in childhood is reported to be another risk factor for *H. pylori* infection.[4,26] A previous study in Japan reported that the prevalence of *H. pylori* infection increased with longer period of drinking well water in childhood.[30] There was rapid development of distribution of municipal water supply in Japan from 26.2% of households in 1950 to 80.8% of households in 1970.[31] In those days, Japan experienced a drastic economic expansion that brought improvements in social infrastructure, including water supply. The rapid decline in the proportion of those with positive *H. pylori* antibody among those born between 1949 and 1961 in our study was possibly attributed to these drastic improvements in sanitary conditions.

H. pylori infection is a major cause of gastric cancer. The population attributable fraction (PAF) of *H. pylori* infection for gastric cancer incidence (the fraction of gastric cancer incident cases that is attributable to *H. pylori* infection) was estimated to

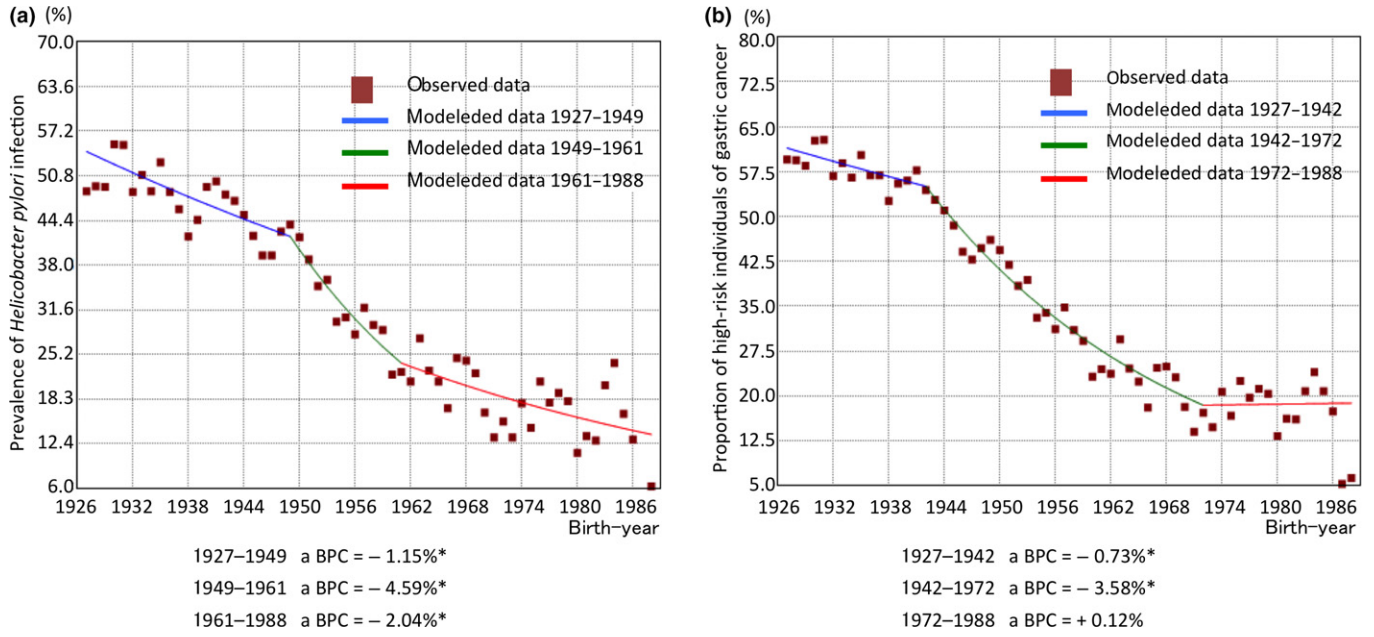

Fig. 2. Trends in the prevalence of *Helicobacter pylori* infection (a) and proportion of high-risk individuals for gastric cancer (b) by three-birth-year moving-average method in Joinpoint regression analysis. *Statistical significance was set at $P < 0.05$. BPC, birth-year percent change.

Table 2. Results of Joinpoint regression analysis of the trends of prevalence of *Helicobacter pylori* infection and proportion of high-risk individuals for gastric cancer in a Japanese population

	Prevalence of *H. pylori* infection				Proportion of high-risk individuals for gastric cancer			
	Birth-year	Observed data (SE), %	Modeled data, %	BPC (95% CI)	Birth-year	Observed data (SE), %	Modeled data, %	BPC (95% CI)
	1927	48.6 (8.2)	54.0		1927	59.5 (8.1)	62.0	
				−1.2* (−1.6 to −0.8)				−0.8* (−1.4 to −0.1)
1st Joinpoint	1949	43.5 (2.4)	42.0		1942	54.3 (2.8)	55.0	
				−4.5* (−6.0 to −3.0)				−3.6* (−3.9 to −3.2)
2nd Joinpoint	1961	22.7 (2.7)	24.0		1972	17.2 (3.3)	18.0	
				−2.1* (−3.3 to −0.8)				+0.1 (−3.1 to +3.4)
	1988	6.3 (6.1)	14.0		1988	6.3 (6.1)	19.0	

Observed data is the proportion calculated in this study. Modeled data is based on the observed data, and modified by Joinpoint regression analysis. *Statistical significance was set at $P < 0.05$. BPC, birth-year percent change; CI, confidence interval.

be 84.1% from data in a Japanese cohort study.[32] As a result of the high PAF, the trend in prevalence of birth-year-specific *H. pylori* infection would be closely linked to the trends in gastric cancer incidence and mortality rate in Japan. A previous age-period-cohort analysis of Japanese gastric cancer mortality showed that there was a cohort effect for the accelerated declining trend among those born after 1940.[7,33] This result is in accordance with our finding that the prevalence of *H. pylori* infection rapidly declined in those born after 1949.

There are some limitations to this study. First, our study subjects were all first-visit outpatients at our hospital. To avoid selection bias, we excluded 336 gastric cancer patients and one MALT lymphoma patient as having high probability of a past history of *H. pylori* infection. As a result, our study subjects included 46.7% of patients who developed other cancers during the 1-year follow-up period and 53.3% of cancer-free subjects who had mostly been referred for detailed examination of the possibility of cancer. Although there was little evidence of any association between *H. pylori* infection and cancer except gastric cancer and MALT lymphoma, the representativeness of our study subjects might have some vulnerability. Therefore, we re-analyzed the prevalence of *H. pylori* infection in only cancer-free subjects. As a result, the first joinpoint was in 1950, and the first and second BPC was −1.1% and −3.9%, respectively. This trend was similar to the result that was obtained when cancer subjects except for gastric cancer and MALT lymphoma subjects were included. Therefore, we considered that inclusion of cancer patients in our analysis would not lead to selection bias.

Second, as the recruiting period of the subjects was limited, there would be potential for contamination of the age-effect in our study. However, as *H. pylori* infection is predominantly acquired in childhood, we thought that the impact of the age-effect would be limited.

Third, the relatively low sensitivity and specificity of the serum *H. pylori* antibody titer kit and the pepsinogen test we used in this study might attenuate the accuracy of the prevalence. However, the limited accuracy would not influence the trend in prevalence of birth-year-specific *H. pylori* infection and the trend in birth-year-specific proportion of high-risk individuals for gastric cancer as the accuracy is thought to be consistent regardless of the subjects' age distribution.

Finally, three-quarters of our study subjects consisted of those who lived in Aichi Prefecture (75.2%). A previous study revealed that there was geographic variation in the prevalence of *H. pylori* infection in Japan, and that it was relatively low in Aichi Prefecture.[12] As this area has been one of the largest metropolitan areas in Japan, the spread of sanitary infrastructure, including water supply, is considered to have occurred earlier than in other areas in Japan. This condition might have shifted the first joinpoint, making a rapid declining trend towards older birth year in this study.

In summary, the prevalence of *H. pylori* infection in our study population decreased with increasing birth year. A dramatic decline in the prevalence of *H. pylori* infection was observed in those born between 1949 and 1961. As the PAF of *H. pylori* infection for gastric cancer is considerably large, this declining trend in prevalence of *H. pylori* infection would contribute to projection of the future trend in gastric cancer incidence in Japan. Fortunately, the Japanese government expanded national health insurance coverage for eradication therapy of *H. pylori* from patients with gastric/duodenal ulcer to those with chronic atrophic gastritis in February 2013. As this situation might have introduced a period effect to reduce the *H. pylori*-infected populations, we need to continue monitoring the prevalence of *H. pylori* infection in the Japanese population.

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Disclosure Statement

The authors have no conflict of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Prevalence of *Helicobacter pylori* infection and the proportion of high-risk individuals for gastric cancer in each of the 13 birth cohorts.

Supplemental Table 1. The prevalence of *H. pylori* infection and the proportion of high-risk individuals for gastric cancer in each of the 13 birth cohorts

Birth year	Number of study subjects	*H. pylori* infection (%) (95%CI)	Pepsinogen test positive with *H. pylori* antibody negative (%) (95%CI)	High-risk individuals for gastric cancer (%) (95%CI)
1926–1929	76	51.3 (39.6–63.0)	11.8 (5.6–21.3)	63.2 (51.3–73.9)
1930–1934	519	52.0 (47.6–56.4)	7.5 (5.4–10.1)	59.5 (55.2–63.8)
1935–1939	597	47.2 (43.2–51.3)	9.2 (7.0–11.8)	56.2 (52.1–60.2)
1940–1944	512	47.5 (43.1–51.9)	6.6 (4.6–9.2)	54.3 (49.9–58.6)
1945–1949	654	41.9 (38.1–45.8)	3.4 (2.1–5.0)	45.5 (41.7–49.4)
1950–1954	488	37.1 (32.8–41.5)	3.3 (1.9–5.3)	40.2 (35.9–44.7)
1955–1959	354	28.0 (23.3–33.0)	2.3 (1.0–4.4)	30.2 (25.5–35.3)
1960–1964	358	25.1 (20.7–30.0)	1.7 (0.6–3.6)	26.8 (22.3–31.7)
1965–1969	291	21.0 (16.4–26.1)	0.7 (0.1–2.5)	21.6 (17.1–26.8)
1970–1974	231	13.9 (9.7–19.0)	1.3 (0.3–3.7)	15.2 (10.8–20.4)
1975–1979	120	20.0 (13.3–28.3)	1.7 (0.2–5.9)	21.7 (14.7–30.1)
1980–1984	53	15.1 (6.7–27.6)	1.9 (0.05–10.1)	17.0 (8.1–29.8)
1985–1989	32	12.5 (3.5–29.0)	3.1 (0.08–10.1)	15.6 (5.3–32.8)
Total	4,285	37.5 (36.1–40.0)	4.6 (4.0–5.3)	42.1 (40.6–43.6)

H. pylori infection (%) : proportion of *H. pylori* antibody-positive subjects

Pepsinogen positive with *H. pylori* antibody negative (%) : proportion of subjects with positive pepsinogen test but who were negative *H. pylori* antibody

High-risk individuals for gastric cancer (%) : prevalence of subjects with *H. pylori* infection or subjects with positive pepsinogen test but who were negative *H. pylori* antibody

95%CI : 95% confidence interval