CANCER EPIDEMIOLOGY

Lifetime incidence risk for gastric cancer in the *Helicobacter pylori*-infected and uninfected population in Japan: A Monte Carlo simulation study

Sayo Kawai[1] 🔘 | Chaochen Wang[1] | Yingsong Lin[1] 🔘 | Tae Sasakabe[1] | Masumi Okuda[2] | Shogo Kikuchi[1] 🔘

[1]Department of Public Health, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan

[2]Department of Pediatrics, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

Correspondence
Shogo Kikuchi, Department of Public Health, Aichi Medical University School of Medicine, 1-1 Yazako-karimata, Nagakute, Aichi 480-1195, Japan.
Email: kikuchis@aichi-med-u.ac.jp

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Abstract

Helicobacter pylori (H. pylori) infection is considered the leading cause of gastric cancer. Gastric cancer is currently a common cancer with high incidence and mortality rates, but it is expected that the incidence rate will gradually decrease as the *H. pylori* infection prevalence decreases in the future. When evaluating the effectiveness of gastric cancer prevention strategies, it is essential to note the differences in long-term cumulative risks between *H. pylori*-infected and uninfected populations, but this has not yet been precisely evaluated. In our study, we aimed to estimate the cumulative incidence risks of developing gastric cancer from birth to 85 years among *H. pylori*-infected and uninfected populations by using population-based cancer registry data and birth year-specific *H. pylori* infection prevalence rates. Death from gastric cancer and other causes of death were considered in the estimations of the adjusted cumulative incidence risks stratified by sex and *H. pylori* infection status. After performing 5000 Monte Carlo simulations with repeated random sampling using observed cancer incidence in selected three prefectures (Fukui, Nagasaki, Yamagata) of prefectural population-based cancer registry in Japan, the mean adjusted cumulative incidence risk for gastric cancer in the *H. pylori*-infected population was 17.0% for males and 7.7% for females and 1.0% for males and 0.5% for females in the uninfected population. These results calculated with Japanese cancer registry data may be useful in considering and evaluating future prevention strategies for gastric cancer in Japan.

KEYWORDS
cancer prevention strategies, cancer registry, cumulative incidence risk, gastric cancer, *Helicobacter pylori*

What's new?

Helicobacter pylori infection is considered the leading cause of gastric cancer. This study estimated the cumulative incidence risk for gastric cancer from birth to 85 years of age, stratified by *H. pylori* infection status, for the first time in Japan. The cumulative risk among *H. pylori*-infected individuals was 17.0% in males and 7.7% in females, after adjusting for gastric cancer incidence and other causes of death. The cumulative risk in the population without *H. pylori* infection was low. These results offer essential information for future cost-effectiveness and cost-benefit analyses and new gastric cancer prevention programs in Japan.

1 | INTRODUCTION

Gastric cancer is the fifth most frequent cancer and the fourth most common cause of cancer deaths worldwide.[1,2] *Helicobacter pylori* is known as the leading risk factor for gastric cancer.[3-5] The virulence or carcinogenicity of *H. pylori* depends on the strain. East Asian type *H. pylori* strains, which prevail in Japan, have a stronger carcinogenic effect than European type *H. pylori* strains.[6]

In Japan, age-standardized gastric cancer incidence and mortality have been decreasing over the past decades.[7] The decrease is thought to be mainly because of decreasing *H. pylori* prevalence.[8,9] Gastric cancer incidence in those with *H. pylori* infection may be consistent unless a remarkable change occurs in the genetic background of the Japanese population or the *H. pylori* strains. Thus, the lifetime cumulative incidence risk for gastric cancer among those with *H. pylori* infection in a specific region is a good marker for the virulence of the *H. pylori* strains prevailing in that region and might help predict the future gastric cancer situation. We adopted the lifetime cumulative incidence risk instead of relative risk, mainly for the following reasons. Relative risk provides limited information on the absolute value of the risk. In contrast, lifetime cumulative incidence risk can show the absolute value concretely, which helps to directly predict an individual's gastric cancer risk in the future, and is useful and convenient in calculating the costs and benefits of a gastric cancer prevention program.

Utilizing the causal relationship between *H. pylori* and the development of gastric cancer, several preventive strategies for gastric cancer have been put into practice. For example, several local Japanese governments have been practicing the "test and treat" approach for *H. pylori* infection among senior or junior high school students[10] to prevent the future development of gastric cancer in not only the students themselves but also the next generations because the infection route of *H. pylori* in Japan is mainly from parents to their children.[11,12] When considering the effectiveness of these prevention strategies for gastric cancer, especially in cost-effectiveness analyses, it is inevitable that the lifetime cumulative incidence risk of the *H. pylori*-infected population in the region needs to be considered, and the risk ratio needs to be calculated depending on the presence or absence of infection. Nevertheless, few studies to date have directly evaluated these risks in *H. pylori*-infected subjects, and the current national gastric cancer strategies are based on cancer statistics that do not consider *H. pylori* infection, including lifetime cumulative risk for gastric cancer.

Our study aimed to calculate the long-term cumulative risk of developing gastric cancer among *H. pylori*-infected and uninfected Japanese populations using existing cancer registry data.

2 | MATERIAL AND METHODS

In estimating the cumulative gastric cancer incidence risk, the distribution and mean of the estimated values were calculated by performing 5000 Monte Carlo simulations under the conditions described below. The simulation was performed using R version 4.0.3 (http://www.R-project.org/), and subsequent statistical analyses were performed with Stata16 (StataCorp LLC, Texas).

2.1 | Source of gastric cancer incidence and mortality data

Japan consists of 47 prefectures, and each prefecture has collected and registered data on cancer patients. Until the start of the national cancer registry in 2016, the accuracy of regional cancer registries varied because the cooperation among the medical institutions in each prefecture differed. Gastric cancer (ICD-10 code C16) incidence rates were obtained from observed cancer incidence of prefectural population-based cancer registry in selected three prefectures (Fukui, Nagasaki, Yamagata) for trend analysis from 1985 to 2012 (Source A),[13-15] national estimates of cancer incidence in Japan based on regional cancer registries from 9 to 32 prefectures from 1985 to 2012 (Source B),[16] and Japan's national cancer registry established by the Act on Promotion of Cancer Registration (Law No. 111, issued on December 13, 2013) from 2016 to 2017 (Source C).[17] Source A has been recommended for assessments of the year-to-year differences in the cancer incidence rate, but there are prefectures that are thought to have a relatively high prevalence of gastric cancer among the included prefectures.[18] Therefore, we mainly performed the calculation using Source A, and Sources B and C were used to compare the resulting estimations.

The data of all-cause and gastric cancer (ICD-10 code C16) death rates (per 100 000 population) from the 2018 Vital Statistics of Japan[19] were used for adjustments.

2.2 | Estimation of age-specific *H. pylori* infection prevalence

For the calculation of each gastric cancer incidence rate at a certain age among the *H. pylori*-infected population, we used birth-year specific *H. pylori* infection rates estimated from our previous meta-analysis.[9] According to the meta-analysis, the prevalence of *H. pylori* infection in the population born in 1908 is lower than that in those born in 1928, which seems unnatural. The reasons for this may be the spontaneous disappearance of *H. pylori* due to the progression of gastric mucosal atrophy, which is common in the elderly population,[20,21] and the infection tests for those born before 1928 were performed when they became elderly. Since it was difficult to know the real *H. pylori* prevalence in this population, we hypothesized that the prevalence of *H. pylori* among the population born between 1908 and 1928 was uniformly distributed between 60% and 100%.

2.3 | Estimation of gastric cancer incidence rates among specific populations

In addition to the distribution pattern of *H. pylori* prevalence, we hypothesized that the risk ratios of developing gastric cancer in *H. pylori*-infected and uninfected populations were between 3 and 50. Uniformly distributed risk ratios were adopted in each simulation.

The calculation formula used in the simulation is as follows. We estimated the gastric cancer incidence rate (*Io*) at each age *x* by birth year based on the observed gastric cancer incidence rates from the three prefecture registries from 1985 to 2012. Since gastric cancer incidence rates from the cancer registries were obtained annually for the 5-year age classes ($I_{(age\,range)}$), we estimated the incidence rate for each age *x* (Io_x) as follows:

$$Io_{x(=g+q)} = 0.5 \times \left(I_{(g \sim g+4)} + I_{(g-5 \sim g-1)}\right) + q \times 0.2 \times \left(I_{(g \sim g+4)} - I_{(g-5 \sim g-1)}\right),$$

where $g = 5, 10, 15, ..., 80, 85$ and $q = -2, -1, 0, 1, 2$.

For ages 0 to 2,

$$Io_{x(=g+q)} = I_0 + q \times 0.4 \times \left(I_{(g \sim g+4)} - I_0\right),$$

where $I_0 = 0, g = 0$ and $q = 0, 1, 2$.

The groups of gastric cancer incidence rates for age *x* among the *H. pylori*-infected (Ip_{xy}) and uninfected (In_{xy}) populations was calculated based on the predicted prevalence of the *H. pylori* infection rate (P_y) for each birth year *y* from 1908 to 2003. Based on the hypothesized gastric cancer risk ratios (uniformly distributed between 3 and 50) between those with and without *H. pylori* infection, Ip_{xy} and In_{xy} were calculated as follows:

$$Ip_{xy} = \frac{RR \times Io_{xy}}{1 + P_y \times (RR - 1)},$$

$$In_{xy} = \frac{Io_{xy}}{1 + P_y \times (RR - 1)}.$$

Since multiple Ip_{xy} and In_{xy} values were calculated for each age *x* from 0 to 85 years, their mean values Ip_x and In_x were used for further calculations. In practice, the number of values calculated for each age *x*, except for ages ≤8 or ≥78, was 28 (Figure 1).

2.4 | Estimation of cumulative gastric cancer risk

Then, we estimated the two cumulative incidence risk values for gastric cancer among *H. pylori*-infected and uninfected populations for each sex. The crude cumulative risks were calculated using the same method as described by Schouten et al,[22] and the adjusted cumulative risks, which considered competing causes of death and gastric cancer death and incidence, were also calculated using the same method as described by Wun et al.[23] The calculations were performed under the condition that the risk ratio did not differ depending on age.

The crude cumulative incidence risk for gastric cancer[22] from birth through age *t* ($0 \le t \le 85$) among the *H. pylori*-infected population ($Cp_{crude(0-t)}$) was calculated as follows:

$$Cp_{crude(0-t)} = 1 - \exp\left(-\sum_{x=0}^{t} Ip_x\right). \quad (1)$$

The crude cumulative risk among the population with *H. pylori* infection ($Cn_{crude(0-t)}$) was given by Equation (1) with In_x substituted for Ip_x.

The adjusted cumulative incidence risks for gastric cancer[23] was calculated as follows based on a hypothetical cohort of 100 000 individuals.

n_x: number alive at the beginning of age *x*.
m_x: all-cause mortality rate at age *x*.
d_x: gastric cancer mortality rate at age *x*.
Ip_x: gastric cancer incidence rate at age *x* among the *H. pylori*-infected population.
In_x: gastric cancer incidence rate at age *x* among the uninfected population.
s_x: number of gastric cancer-free population at the beginning of age *x*.
r_x: gastric cancer incidence rate at age *x* among a gastric cancer-free population.
a_x: number of newly developed gastric cancers through age *x* among a gastric cancer-free population.

With n_0 and s_0 defined as 100 000 live births,

$$n_{x+1} = n_x \times \exp(-m_x),$$

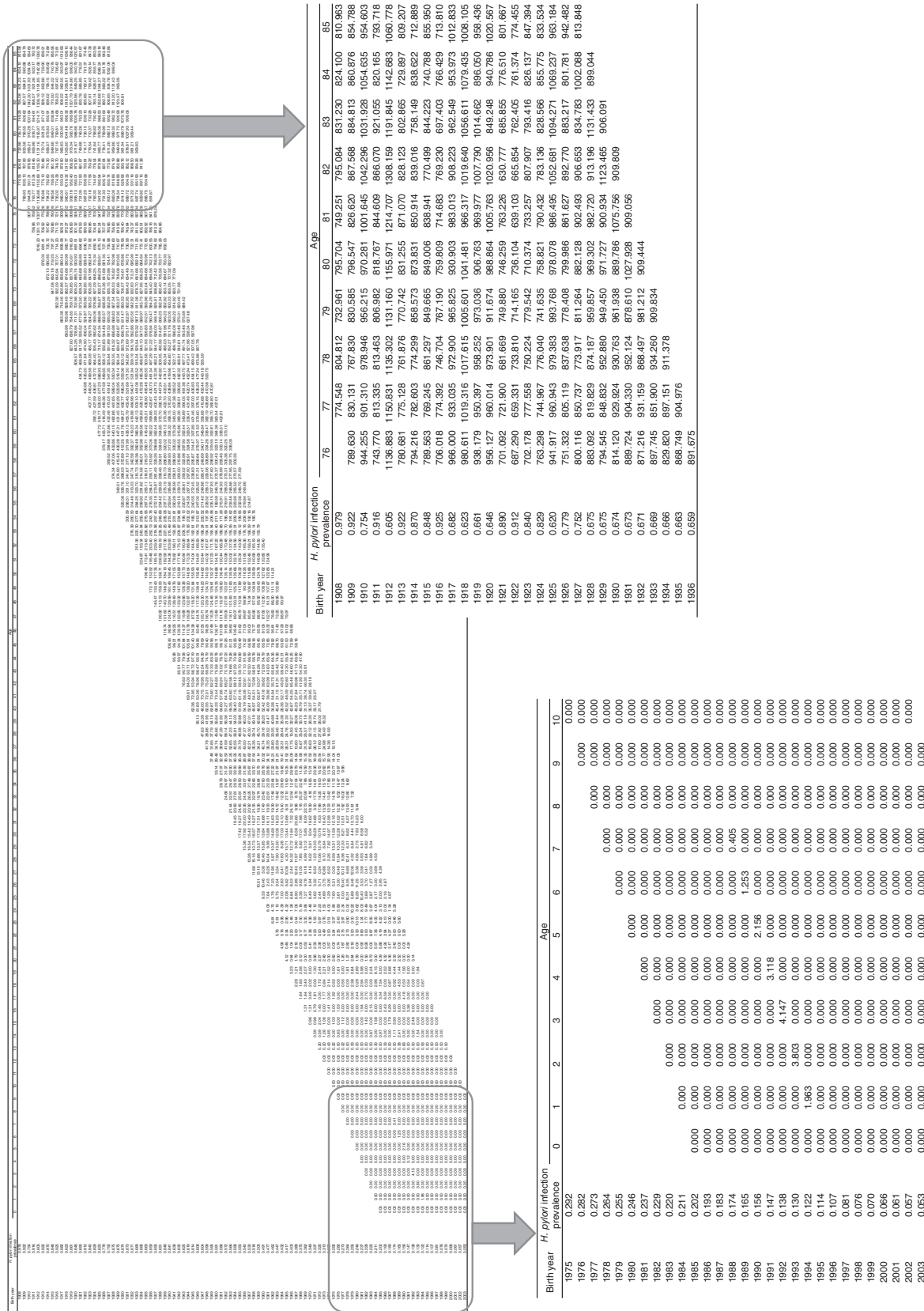$$s_{x+1} = s_x \times \exp[-(m_x - d_x + r_x)],$$

FIGURE 1 Example of a simulation of gastric cancer prevalence in the male *Helicobacter pylori*-infected population
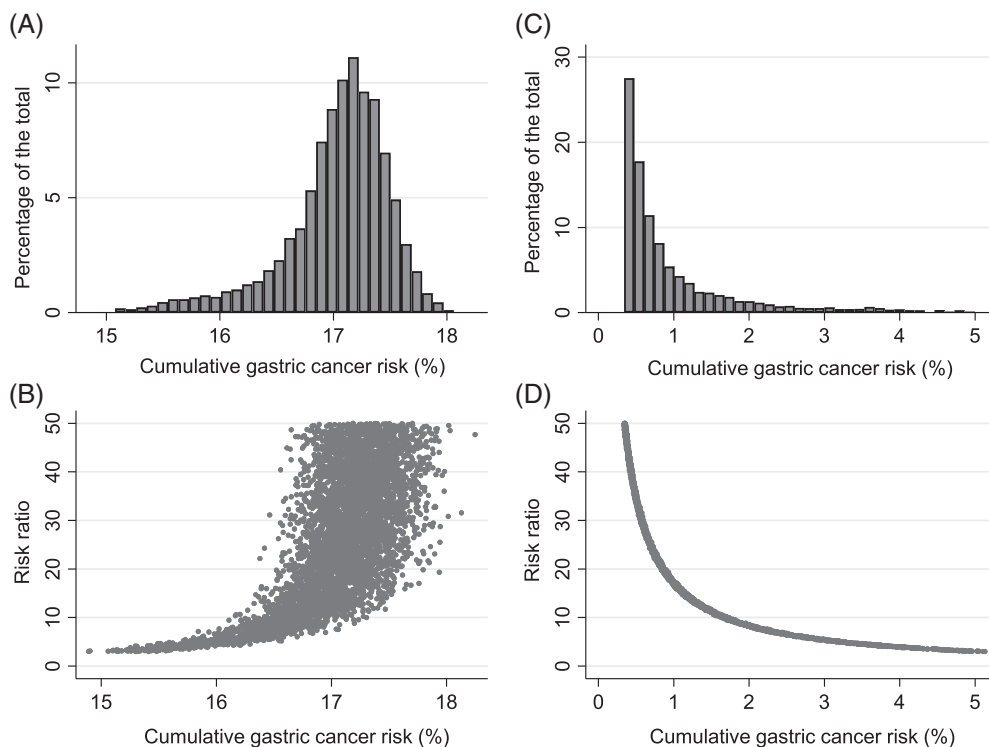
(A)

(C)

FIGURE 2 Scatter plots and histograms of estimated cumulative risk distribution for gastric cancer from 0 to 85 years among Japanese males determined by performing 5000 Monte Carlo simulations when various conditions for *Helicobacter pylori* infection rate and gastric cancer risk ratio were set. (A), Histogram for the *H. pylori*-infected population; (B), scatter plot for the *H. pylori*-infected population; (C), histogram for the population without *H. pylori* infection; (D), scatter plot for the population without *H. pylori* infection

(B)

(D)

TABLE 1 Cumulative incidence risks[a] (%) of developing gastric cancer from birth to age 85 among *Helicobacter pylori*-infected and uninfected populations (estimated by performing 5000 Monte Carlo simulations using three available data sets)

				Estimated value at each percentile points				
Gender	*H. pylori* infection	Data sources[b]	Mean (95% CI)	2.5th percentile	25th percentile	Median	75th percentile	97.5th percentile
Males	Positive	A	17.03 (15.73-17.72)	15.73	16.84	17.11	17.34	17.72
		B	15.23 (14.08-15.83)	14.08	15.07	15.30	15.49	15.83
		C	14.87 (13.22-15.26)	13.22	14.78	15.08	15.20	15.26
	Negative	A	1.01 (0.36-3.76)	0.36	0.46	0.65	1.15	3.76
		B	0.88 (0.32-3.39)	0.32	0.40	0.57	1.00	3.39
		C	0.85 (0.31-3.17)	0.31	0.40	0.56	0.97	3.17
Females	Positive	A	7.66 (7.05-8.00)	7.05	7.57	7.70	7.81	8.00
		B	6.66 (6.14-6.94)	6.14	6.59	6.70	6.78	6.94
		C	6.07 (5.36-6.26)	5.36	6.02	6.17	6.23	6.26
	Negative	A	0.45 (0.16-1.70)	0.16	0.20	0.29	0.52	1.70
		B	0.39 (0.14-1.48)	0.14	0.18	0.25	0.44	1.48
		C	0.35 (0.13-1.24)	0.13	0.16	0.23	0.40	1.24

[a]Cumulative gastric cancer incidence risks adjusted for all cause of deaths and gastric cancer deaths and incidences.
[b]Data source: A, observed cancer incidence in selected three prefectures (Fukui, Nagasaki, Yamagata) of prefectural population-based cancer registry in Japan (1985-2012); B, national estimates of cancer incidence based on prefectural population-based cancer registries of 9 to 32 prefectures in Japan (1985-2012); C, Japan's national cancer registry (2016-2017).

$$a_x = s_x \times [1 - \exp\{-(m_x - d_x + r_x)\}] \times \frac{r_x}{m_x - d_x + r_x}.$$

In the case of the *H. pylori*-infected population, r_x was given as follows:

$$r_x = -\ln\left[1 - \frac{n_x}{s_x} \times \{1 - \exp(-lp_x)\}\right]. \quad (2)$$

Then, the cumulative incidence risk for gastric cancer (the probability of developing gastric cancer) through age t from age j ($0 \leq j < t \leq 85$) among the *H. pylori*-infected population

TABLE 2 Subsequent cumulative incidence risks[a] for gastric cancer in a gastric cancer-free population at each age in the *Helicobacter pylori*-infected population (estimated by performing 5000 Monte Carlo simulations with a risk ratio of 3 to 50 using the incident rates obtained from selected three prefecture cancer registry data in Japan [1985–2012])

Gender	H. pylori infection	Current age (years)	Number of gastric cancer-free population (±SD)	Means and 95% central ranges (the 2.5th percentile to 97.5th percentile) of estimated risks at attained ages (years)									
				40	45	50	55	60	65	70	75	80	85
Males	Positive	0 (at birth)	100 000	0.36 (0.30-0.38)	0.72 (0.60-0.75)	1.30 (1.12-1.35)	2.30 (2.01-2.37)	3.85 (3.43-3.96)	5.97 (5.37-6.14)	8.59 (7.81-8.87)	11.64 (10.65-12.04)	14.63 (13.47-15.18)	17.03 (15.73-17.72)
	Positive	10	99 654 (±0)	0.36 (0.30-0.38)	0.72 (0.60-0.75)	1.30 (1.12-1.35)	2.30 (2.02-2.37)	3.86 (3.44-3.97)	5.99 (5.39-6.16)	8.62 (7.84-8.90)	11.68 (10.68-12.08)	14.68 (13.51-15.23)	17.09 (15.78-17.78)
	Positive	20	99 474 (±1)	0.36 (0.29-0.38)	0.71 (0.60-0.74)	1.30 (1.12-1.34)	2.30 (2.02-2.37)	3.86 (3.44-3.97)	5.99 (5.40-6.16)	8.63 (7.85-8.91)	11.70 (10.70-12.10)	14.70 (13.53-15.25)	17.11 (15.80-17.81)
	Positive	30	98 960 (±6)	0.30 (0.25-0.32)	0.66 (0.56-0.68)	1.25 (1.08-1.29)	2.26 (1.99-2.32)	3.82 (3.41-3.93)	5.96 (5.38-6.14)	8.62 (7.84-8.89)	11.70 (10.71-12.10)	14.72 (13.56-15.27)	**17.14 (15.84-17.84)**
	Positive	40	98 042 (±20)		0.41 (0.35-0.42)	1.01 (0.88-1.04)	2.02 (1.79-2.08)	3.60 (3.23-3.70)	5.76 (5.22-5.93)	8.44 (7.70-8.71)	11.55 (10.60-11.95)	14.60 (13.46-15.15)	17.05 (15.77-17.74)
	Positive	50	95 818 (±53)				1.19 (1.07-1.22)	2.81 (2.54-2.88)	5.02 (4.57-5.17)	7.76 (7.10-8.01)	10.94 (10.06-11.33)	14.07 (13.00-14.60)	16.57 (15.36-17.26)
	Positive	60	90 030 (±121)						2.75 (2.51-2.85)	5.67 (5.21-5.88)	9.05 (8.36-9.42)	12.38 (11.47-12.91)	15.04 (13.97-15.73)
	Positive	70	77 301 (±220)								4.68 (4.33-4.91)	8.55 (7.92-8.98)	11.65 (10.82-12.28)
	Positive	80	55 018 (±302)										5.39 (4.98-5.75)
Females	Positive	0 (at birth)	100 000	0.36 (0.29-0.38)	0.61 (0.51-0.64)	0.94 (0.80-0.98)	1.36 (1.18-1.41)	1.94 (1.70-1.99)	2.67 (2.38-2.75)	3.63 (3.27-3.75)	4.87 (4.43-5.05)	6.30 (5.77-6.55)	7.66 (7.05-8.00)
	Positive	10	99 680 (±0)	0.36 (0.29-0.38)	0.61 (0.51-0.64)	0.95 (0.81-0.98)	1.37 (1.18-1.41)	1.94 (1.71-2.00)	2.67 (2.38-2.76)	3.64 (3.28-3.76)	4.89 (4.44-5.06)	6.32 (5.79-6.57)	7.69 (7.08-8.02)
	Positive	20	99 567 (±1)	0.35 (0.29-0.37)	0.61 (0.51-0.63)	0.94 (0.80-0.97)	1.36 (1.18-1.41)	1.94 (1.70-1.99)	2.67 (2.38-2.75)	3.64 (3.28-3.75)	4.88 (4.44-5.06)	6.32 (5.79-6.57)	**7.69 (7.08-8.02)**
	Positive	30	99 289 (±6)	0.29 (0.24-0.30)	0.55 (0.46-0.57)	0.88 (0.76-0.91)	1.30 (1.14-1.34)	1.88 (1.66-1.93)	2.61 (2.34-2.69)	3.58 (3.24-3.70)	4.83 (4.41-5.01)	6.27 (5.76-6.52)	7.65 (7.05-7.98)
	Positive	40	98 678 (±20)		0.30 (0.26-0.31)	0.63 (0.55-0.65)	1.06 (0.94-1.09)	1.64 (1.46-1.68)	2.38 (2.15-2.45)	3.35 (3.05-3.46)	4.61 (4.23-4.78)	6.06 (5.58-6.30)	7.44 (6.89-7.77)
	Positive	50	97 285 (±42)				0.51 (0.45-0.52)	1.09 (0.99-1.12)	1.84 (1.68-1.90)	2.83 (2.60-2.93)	4.11 (3.79-4.26)	5.58 (5.16-5.81)	6.98 (6.48-7.30)
	Positive	60	94 494 (±70)						0.91 (0.83-0.94)	1.92 (1.78-2.00)	3.24 (3.00-3.38)	4.75 (4.42-4.97)	6.20 (5.77-6.51)
	Positive	70	89 013 (±107)								1.64 (1.52-1.72)	3.25 (3.02-3.42)	4.78 (4.45-5.05)
	Positive	80	77 051 (±156)										2.14 (1.99-2.29)

[a]Cumulative gastric cancer incidence risks adjusted for all cause of deaths and gastric cancer deaths and incidences.
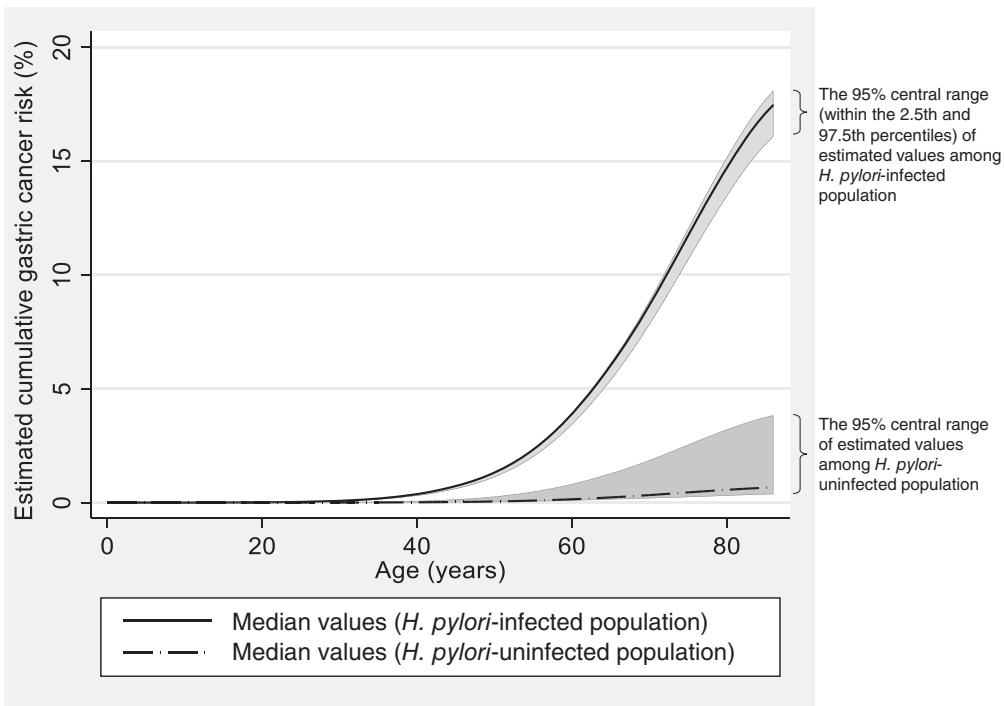
without a history of gastric cancer ($Cp_{(j-t)}$) was calculated as follows:

$$Cp_{(j-t)} = \sum_{x=j}^{t} a_x/s_j.$$

The adjusted cumulative risk among the population without *H. pylori* infection ($Cn_{(j-t)}$) was obtained through a_x and s_x given by Equation (2) with In_x substituted for Ip_x.

The above calculation was performed by Monte Carlo simulation randomly 5000 times for each of the three data sources and each sex, and the mean values and 95% confidence intervals (CIs) were calculated. Furthermore, we examined the relationship between the hypothesized risk ratio and the distribution of estimated cumulative risk values.

3 | RESULTS

As a result of 5000 simulations based on selected three prefectures (Fukui, Nagasaki, Yamagata, 1985-2012) cancer registry (Source A), the crude cumulative risk of developing gastric cancer from birth to 85 years of age among the *H. pylori*-infected population was 22.26% (95% CI, 20.63-23.21) for males and 8.74% (95% CI, 8.07-9.14) for females. The adjusted cumulative risks estimated by the same data (Source A) were 17.03% (95% CI, 15.73-17.72) for males and 7.66% (95% CI, 7.05-8.00) for females. As shown in Figure 2, taking the male population as an example, the simulation's estimated values were not normally distributed and depended on the risk ratio setting. The mean values were slightly lower than the median values. For males, the median was 17.11%, and the interquartile range (IQR) was 16.84% to 17.34%; for females, the

median was 7.70%, and the IQR was 7.57% to 7.81%. Among the population without *H. pylori* infection, the adjusted cumulative incidence risks for gastric cancer from birth to 85 years of age were 1.01% (95% CI, 0.36-3.76) for males and 0.45% (95% CI, 0.16-1.70) for females (Table 1). Similar simulations were performed to calculate cumulative incidence risks for gastric cancer among *H. pylori*-infected and uninfected males and females based on the other two sources of data (Sources B and C), and their estimated values were slightly lower than those obtained from Source A (Table 1).

Table 2 shows the mean of the estimated cumulative incidence risks for gastric cancer based on Monte Carlo simulations at attained ages in certain age groups without gastric cancer among the *H. pylori*-infected population. Among all age groups, males who survived without developing gastric cancer until the age of 30 had the highest cumulative incidence risk for gastric cancer at 85. In females, those who survived without gastric cancer until age 20 showed the highest risk at 85. No sex difference was observed under 40 years of age between males and females with or without *H. pylori* infection, while the *H. pylori*-infected male population over 40 years showed a higher gastric cancer incidence. Figure 3 shows the median values and 95% central ranges (within the 2.5th and 97.5th percentiles) of the estimated cumulative incidence risks for gastric cancer from birth to attained age among *H. pylori*-infected and uninfected populations based on 5000 Monte Carlo simulations.

4 | DISCUSSION

4.1 | Summary of findings

As shown in Table 1, we calculated the cumulative incidence risks for developing gastric cancer from birth to age 85 among *H. pylori*-

infected and uninfected populations. In the male population, the mean cumulative incidence risks for gastric cancer were 17.0% for *H. pylori*-infected individuals and 1.0% for uninfected individuals. The corresponding risks for females were 7.7% and 0.5%. For the cumulative risk of developing gastric cancer from a certain age to 85, males who survived without developing gastric cancer by age 30 had the highest cumulative risk. Among the female population, those who did not develop gastric cancer by age 20 had the highest cumulative risk. These results may be because there is less gastric cancer among those who die young.

4.2 | Analysis methods and conditions

Since the relative risk of developing gastric cancer between individuals infected and uninfected with *H. pylori* is not yet clear, we estimated these values through extensive random simulations calculated from three available data sets. We also ran 20 000 simulations under the same conditions, but the results did not substantially change; therefore, we determined that 5000 iterations would be sufficient.

In a Japanese cohort study, the relative risk between those with and without infection exceeded 15, and no incidence was observed in subjects without *H. pylori* infection,[4] whereas a Swedish study[24] showed a relative risk of approximately 20. Considering that the Japanese *H. pylori* strain is more virulent than the Swedish strain,[6] the relative risk could possibly be as high as 30 to 50 in the Japanese population. In the main analysis, we set the risk ratio to be distributed between 3 and 50. We also performed calculations after restricting the risk ratios between 3 and 10, accounting for the possibility that the actual relative risk would be small, but the cumulative risks were similar to the main results.

Regarding the unnatural change in *H. pylori* infection rate among people born before 1928, we hypothesized that the prevalence of *H. pylori* infection among the population born between 1908 and 1928 was uniformly distributed between 60% and 100% because spontaneous disappearance of *H. pylori* might be common in that age group. Although it is difficult to predict the true prevalence, we reestimated the cumulative risks with a hypothesis of a beta distribution with a median of 85%, 80%, 75% and 70% for age groups divided in 5-year increments from 1908 to 1928. The risk value calculated by this method (17.27% for the *H. pylori*-infected male population) was close to the estimated value based on a hypothesized uniform distribution of 60% to 100%.

4.3 | Differences in results among data sources

The estimated cumulative incidence risks for gastric cancer calculated from selected three prefectures cancer registry for trend analysis (Source A) was slightly higher than the values calculated based on the other two sources: national estimates of cancer incidence in Japan based on regional cancer registries of 9 to 32 prefectures (Source B) and Japan's national cancer registry (Source C). The accuracy of

cancer registries in Japan varied among prefectures in the past, and it is recommended that "high-quality" data from three prefectures are used when examining year-to-year transitions.[15] According to the latest report from the National Cancer Center's "Monitoring of Cancer Incidence in Japan" (MCIJ2015),[18] the age-standardized incidence rates of gastric cancer (male, female and overall) in Yamagata (63.5 per 100 000 population) and Fukui (54.7 per 100 000 population) were higher than the national average (45.3 per 100 000 population) and that in Nagasaki (43.0 per 100 000 population) was similar. This tendency has not changed for many years.[25] The higher rates calculated in our study, which were from Source A, may be due to the higher accuracy of cancer registries and/or differences in risk factors other than *H. pylori* infection, as discussed later. Although it is difficult to understand the real effects of these reasons, the results of our study might slightly overestimate the risk value for the whole of Japan.

4.4 | Comparisons with existing findings

To date, few studies have evaluated the lifetime risk of gastric cancer among the *H. pylori*-infected population. The few Japanese studies considering *H. pylori* infection did not stratify patients by the prevalence of *H. pylori*.[26,27] The reported lifetime cumulative incidence risks for gastric cancer without considering *H. pylori* infections were 11.4% for males and 5.7% for females.[26] Our results, estimated from the same data source, showed 17.0% in the *H. pylori*-infected population, with the risk not exceeding 1.0% in the *H. pylori*-uninfected population. From this result, it is clear that a consideration of *H. pylori* infection is indispensable. According to the cancer statistics from the Surveillance, Epidemiology and End Results (SEER) Program of the United States in 2015 to 2017, lifetime risks for gastric cancer among Asian Pacific/Islander inhabitants were 1.89% in males and 1.30% in females.[28] This can be explained by the fact that the *H. pylori* prevalence in the United States is much lower than that in Japan.[29] In addition, the weaker virulence of the *H. pylori* strains prevailing in the United States compared to that of the strains in East Asia, including Japan, may play a role.[30]

4.5 | Future developments based on the results of our study

Significant differences in the long-term cumulative incidence risks for gastric cancer between *H. pylori*-infected and uninfected populations suggest that tailored gastric cancer prevention strategies are needed. Since the effect of successful eradication of *H. pylori* infection on future gastric cancer risk has already been clarified,[31,32] the risk of gastric cancer in *H. pylori*-infected individuals can be predicted in both cases: with and without eradication therapy. In addition, from the results of our study, it is possible to evaluate the effect of preventing parent-to-child transmissions of *H. pylori* infection on reducing the risk of gastric cancer in the next generation.

4.6 | Study limitations

Because the calculations are based on many postulations and hypotheses, our study has several limitations. First, we assumed that the prevalence of *H. pylori* infection was determined by the year of birth, and the rate did not change until the age of 85. Most *H. pylori* infections occur in childhood and therefore, new infections in adulthood are rare.[21,33] Although the *H. pylori* infection rate in childhood is unstable, the effect of variations in the prevalence of *H. pylori* infection in childhood is negligible on the long-term cumulative risk because the incidence of gastric cancer in childhood is very low. In the elderly population, persistent infection with *H. pylori* sometimes causes advanced atrophy of the gastric mucosa, which can cause *H. pylori* to spontaneously disappear. Some cohort studies have shown that those who experienced spontaneous disappearance of *H. pylori* had a higher risk for gastric cancer than those with persistent infection,[27,34,35] seemingly indicating that the risk increased after disappearance. However, we think the spontaneous disappearance of *H. pylori* exerts little influence on the cumulative risk for gastric cancer. The severity of atrophic gastritis increases with age in *H. pylori*-infected patients,[36] and severity shows a positive relationship with gastric cancer risk.[27,34,35,37,38] Those with a history of spontaneous disappearance of *H. pylori* have more severe gastric mucosal atrophy than those with persistent infection. The higher hazard ratio of gastric cancer in those with the spontaneous disappearance of *H. pylori* in the cohort study may be because those with spontaneous disappearance have a higher risk of developing gastric cancer due to severe gastric mucosal atrophy. Second, we postulated that the risk ratio of developing gastric cancer between *H. pylori*-infected and uninfected populations is the same at all ages because no studies have reported such a relationship to date. A few studies have reported relationships of age and the magnitude of *H. pylori* infection with gastric carcinogenesis. In our previous studies,[3,20] the magnitude was more substantial in the younger population. This may be because more severe gastric mucosal atrophy and consequently more spontaneous disappearances of *H. pylori* occurred in older gastric cancer patients than in younger gastric cancer patients or control subjects.[21] Third, we hypothesized that the mortality rates are the same between *H. pylori*-infected and uninfected populations. Since gastric cancer may be the most common cause of *H. pylori*-induced death, higher mortality is expected in the *H. pylori*-infected population. However, the effect is diminished when the incidence of gastric cancer is treated as a censored variable. Fourth, we did not rule out the impacts of other risk factors for gastric cancer, including smoking.[39] Fifth, we considered the cumulative incidence risk from birth to age 85 as the lifetime cumulative incidence risk here because examinations for gastric cancer, including endoscopy, are performed less frequently for those aged over 85, and the incidence rates in patients of those ages are not necessarily stable or reliable. The average healthy life expectancy is increasing year by year around the world, including in Japan. If stable and reliable data in age groups above 85 years are obtained, the lifetime cumulative incidence risk should be calculated to include ages older than 85.

4.7 | Conclusion

Based on the considerations above, the estimated values in our study are similar to the actual values. In the future, the incidence of gastric cancer in this population will be expected to decrease steadily as the *H. pylori* prevalence decreases. Our study showed that the long-term cumulative risk of gastric cancer differed substantially depending on the presence or absence of *H. pylori* infection and revealed that the cumulative risk in the population without *H. pylori* infection was low. These results may help us consider and evaluate prevention strategies for gastric cancer, including what screening programs should be applied in Japan.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

ORCID

Sayo Kawai [ID] https://orcid.org/0000-0002-5156-4880
Yingsong Lin [ID] https://orcid.org/0000-0003-0214-3649
Shogo Kikuchi [ID] https://orcid.org/0000-0001-9499-9668

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
3. Kikuchi S, Wada O, Nakajima T, et al. Serum anti-*Helicobacter pylori* antibody and gastric carcinoma among young adults. Research group on prevention of gastric carcinoma among young adults. *Cancer*. 1995;75:2789-2793.
4. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med*. 2001;345:784-789.
5. Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1-241.
6. Satomi S, Yamakawa A, Matsunaga S, et al. Relationship between the diversity of the cagA gene of *Helicobacter pylori* and gastric cancer in Okinawa, Japan. *J Gastroenterol*. 2006;41:668-673.
7. Katanoda K, Hori M, Saito E, et al. Updated trends in cancer in Japan: incidence in 1985-2015 and mortality in 1958-2018—a sign of decrease in cancer incidence. *J Epidemiol*. 2021;31:426-450.
8. Kobayashi T, Kikuchi S, Lin Y, et al. Trends in the incidence of gastric cancer in Japan and their associations with *Helicobacter pylori* infection and gastric mucosal atrophy. *Gastric Cancer*. 2004;7:233-239.

9. Wang C, Nishiyama T, Kikuchi S, et al. Changing trends in the prevalence of *H. pylori* infection in Japan (1908-2003): a systematic review and meta-regression analysis of 170,752 individuals. *Sci Rep*. 2017;7: 15491.

10. Kakiuchi T, Matsuo M, Endo H, et al. A *Helicobacter pylori* screening and treatment program to eliminate gastric cancer among junior high school students in Saga Prefecture: a preliminary report. *J Gastroenterol*. 2019;54:699-707.

11. Konno M, Fujii N, Yokota S, et al. Five-year follow-up study of mother-to-child transmission of *Helicobacter pylori* infection detected by a random amplified polymorphic DNA fingerprinting method. *J Clin Microbiol*. 2005;43:2246-2250.

12. Okuda M, Osaki T, Lin Y, et al. Low prevalence and incidence of *Helicobacter pylori* infection in children: a population-based study in Japan. *Helicobacter*. 2015;20:133-138.

13. Katanoda K, Ajiki W, Matsuda T, et al. Trend analysis of cancer incidence in Japan using data from selected population-based cancer registries. *Cancer Sci*. 2012;103:360-368.

14. Katanoda K, Hori M, Matsuda T, et al. An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. *Jpn J Clin Oncol*. 2015;45:390-401.

15. Katanoda K, Sobue T, Tanaka H, Miyashiro I, eds. *JACR Monograph Supplement No. 2*. Tokyo: Japanese Association of Cancer Registries; 2016.

16. Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol*. 2015; 45:884-891.

17. Cancer Registry and Statistics Cancer Information Service, National Cancer Center, Japan (Ministry of Health, Labour and Welfare, National Cancer Registry). https://ganjoho.jp/reg_stat/statistics/dl/index.html. Accessed June 24, 2020.

18. National Cancer Center, Center for Cancer Control and Information Services. *Monitoring of Cancer Incidence in Japan, MCIJ2015*; 2019.

19. Vital Statistics Japan (Ministry of Health, Labour and Welfare). https://www.mhlw.go.jp/toukei/list/81-1.html. Accessed February 3, 2020.

20. Kikuchi S, Nakajima T, Kobayashi O, et al. Effect of age on the relationship between gastric cancer and *Helicobacter pylori*. Tokyo Research Group of Prevention for Gastric Cancer. *Jpn J Cancer Res*. 2000;91:774-779.

21. Kikuchi S. Epidemiology of *Helicobacter pylori* and gastric cancer. *Gastric Cancer*. 2002;5:6-15.

22. Schouten LJ, Straatman H, Kiemeney LA, Verbeek AL. Cancer incidence: life table risk versus cumulative risk. *J Epidemiol Community Health*. 1994;48:596-600.

23. Wun LM, Merrill RM, Feuer EJ. Estimating lifetime and age-conditional probabilities of developing cancer. *Lifetime Data Anal*. 1998;4:169-186.

24. Ekström AM, Held M, Hansson LE, Engstrand L, Nyrén O. *Helicobacter pylori* in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology*. 2001;121:784-791.

25. Okui T. An age-period-cohort analysis of mortality rates for stomach, colorectal, liver, and lung cancer among prefectures in Japan, 1999-2018. *Environ Health Prev Med*. 2020;25:80.

26. Taniyama Y, Katanoda K, Charvat H, et al. Estimation of lifetime cumulative incidence and mortality risk of gastric cancer. *Jpn J Clin Oncol*. 2017;47:1097-1102.

27. Charvat H, Sasazuki S, Inoue M, et al. Prediction of the 10-year probability of gastric cancer occurrence in the Japanese population: the JPHC study cohort II. *Int J Cancer*. 2016;138:320-331.

28. National Cancer Institute (U.S.), SEER Program (National Cancer Institute (U.S.)), National Center for Health Statistics (U.S.). *Cancer Statistics Review*. Bethesda, MD: U.S. Dept. of Health and Human Services Public Health Service National Institutes of Health National Cancer Institute; 1991.

29. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology*. 2017; 153:420-429.

30. Yamaoka Y, Kato M, Asaka M. Geographic differences in gastric cancer incidence can be explained by differences between *Helicobacter pylori* strains. *Intern Med*. 2008;47:1077-1083.

31. Doorakkers E, Lagergren J, Engstrand L, Brusselaers N. *Helicobacter pylori* eradication treatment and the risk of gastric adenocarcinoma in a Western population. *Gut*. 2018;67:2092-2096.

32. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2014;348:g3174.

33. Malaty HM, El-Kasabany A, Graham DY, et al. Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. *Lancet*. 2002;359:931-935.

34. Ohata H, Kitauchi S, Yoshimura N, et al. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. *Int J Cancer*. 2004;109:138-143.

35. Mizuno S, Miki I, Ishida T, et al. Prescreening of a high-risk group for gastric cancer by serologically determined *Helicobacter pylori* infection and atrophic gastritis. *Dig Dis Sci*. 2010;55:3132-3137.

36. Ohkuma K, Okada M, Murayama H, et al. Association of *Helicobacter pylori* infection with atrophic gastritis and intestinal metaplasia. *J Gastroenterol Hepatol*. 2000;15:1105-1112.

37. Yanaoka K, Oka M, Yoshimura N, et al. Risk of gastric cancer in asymptomatic, middle-aged Japanese subjects based on serum pepsinogen and *Helicobacter pylori* antibody levels. *Int J Cancer*. 2008; 123:917-926.

38. Tatsuta M, Iishi H, Nakaizumi A, et al. Fundal atrophic gastritis as a risk factor for gastric cancer. *Int J Cancer*. 1993;53:70-74.

39. Kikuchi S, Nakajima T, Kobayashi O, et al. U-shaped effect of drinking and linear effect of smoking on risk for stomach cancer in Japan. *Jpn J Cancer Res*. 2002;93:953-959.