CANCER EPIDEMIOLOGY

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

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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 ≤ *t* ≤ 85) among the *H. pylori*-infected population ($Cp_{crude(0-t)}$) was calculated as follows:

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

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,

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

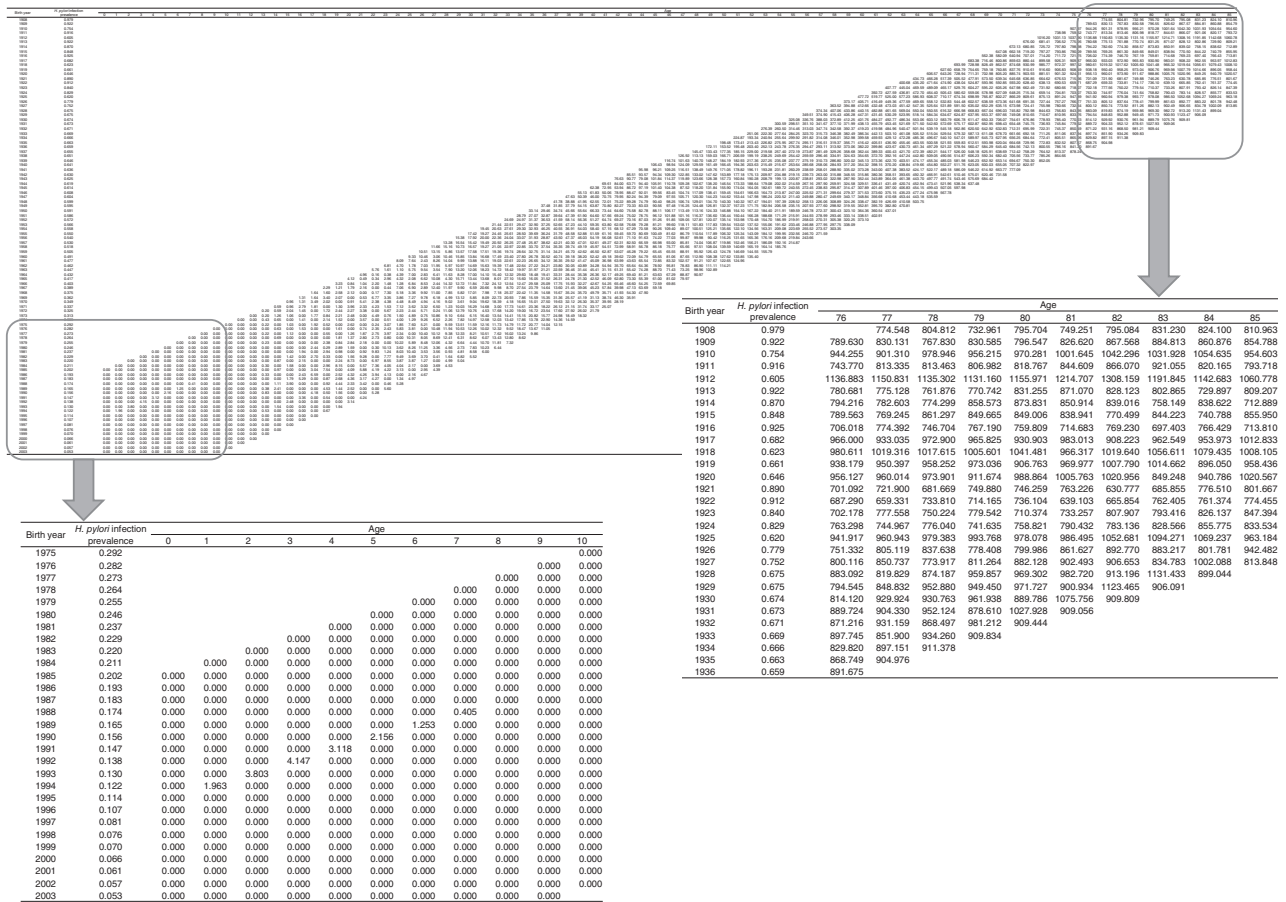$$s_{x+1} = s_x \times \exp[-(m_x - d_x + r_x)],$$

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

Lower-left detail (Age 0–10):

Birth year	H. pylori infection prevalence	0	1	2	3	4	5	6	7	8	9	10
1975	0.292											0.000
1976	0.282										0.000	0.000
1977	0.273									0.000	0.000	0.000
1978	0.264								0.000	0.000	0.000	0.000
1979	0.255							0.000	0.000	0.000	0.000	0.000
1980	0.246						0.000	0.000	0.000	0.000	0.000	0.000
1981	0.237					0.000	0.000	0.000	0.000	0.000	0.000	0.000
1982	0.229				0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1983	0.220			0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1984	0.211		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1985	0.202	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1986	0.193	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1987	0.183	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.405
1988	0.174	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1989	0.165	0.000	0.000	0.000	0.000	0.000	1.253					
1990	0.156	0.000	0.000	0.000	0.000	0.000	2.156					
1991	0.147	0.000	0.000	0.000	0.000	4.147	3.116					
1992	0.138	0.000	0.000	0.000	0.000	4.147						
1993	0.130	0.000	0.000	0.000	3.803							
1994	0.122	0.000	1.963									
1995	0.114	0.000	0.000									
1996	0.107	0.000	0.000									
1997	0.081	0.000										
1998	0.076	0.000	0.000									
1999	0.100	0.000										
2000	0.066	0.000	0.000									
2001	0.061	0.000	0.000									
2002	0.057	0.000	0.000									
2003	0.053	0.000	0.000									

Lower-right detail (Age 76–85):

Birth year	H. pylori infection prevalence	76	77	78	79	80	81	82	83	84	85
1908	0.979		774.548	804.812	732.961	795.704	749.251	795.084	831.230	824.100	810.963
1909	0.922	789.630	830.131	767.830	830.585	796.547	826.620	867.568	884.813	860.876	854.788
1910	0.754	944.255	901.310	978.946	956.215	970.281	1001.645	1042.296	1031.928	1054.635	954.603
1911	0.916	743.770	813.335	813.463	806.982	818.767	844.609	866.070	921.055	820.165	793.718
1912	0.605	1136.883	1150.831	1135.302	1131.160	1155.971	1214.707	1308.159	1191.845	1142.683	1060.778
1913	0.922	780.681	775.128	761.876	770.742	831.255	871.070	828.123	802.865	729.897	809.207
1914	0.870	794.216	782.603	774.299	858.573	873.831	850.914	839.016	758.149	838.622	712.889
1915	0.848	789.563	769.245	861.297	849.665	849.006	838.941	770.499	844.223	740.788	855.950
1916	0.925	706.018	774.392	746.704	767.190	759.809	714.683	769.230	697.403	766.429	713.810
1917	0.682	966.000	933.035	972.900	965.825	930.903	983.013	908.223	962.549	953.973	1012.833
1918	0.623	980.611	1019.316	1017.615	1005.601	1041.481	966.317	1019.640	1056.611	1079.435	1008.105
1919	0.661	938.179	950.397	958.252	973.036	906.763	969.977	1007.790	1014.662	896.050	958.436
1920	0.646	956.127	960.014	973.901	911.674	988.864	1005.763	1020.956	849.248	940.786	1020.567
1921	0.890	701.092	721.900	681.669	749.880	746.259	763.226	630.777	685.855	776.510	801.667
1922	0.912	687.290	659.331	733.810	714.165	736.104	639.103	665.854	762.405	761.374	774.455
1923	0.840	702.178	777.558	750.224	779.542	701.733	733.257	807.907	793.416	826.137	847.394
1924	0.829	763.298	744.967	776.040	741.635	758.821	790.432	783.136	828.566	855.775	833.534
1925	0.620	941.917	960.943	979.383	993.768	978.078	986.495	1052.681	1094.271	1069.237	963.184
1926	0.779	751.332	805.119	837.638	778.408	799.986	861.627	892.770	883.217	801.781	942.482
1927	0.752	800.116	850.737	773.917	811.264	882.128	902.493	906.653	834.783	1002.088	813.848
1928	0.675	883.092	819.829	874.187	959.857	969.502	982.720	913.196	1131.433	899.044	
1929	0.675	794.545	848.832	952.880	949.450	971.727	900.934	1123.465	906.091		
1930	0.674	814.120	929.924	930.763	961.938	889.786	1075.756	909.809			
1931	0.673	889.724	904.330	952.124	878.610	1027.928	909.444				
1932	0.671	677.216	931.159	868.497	981.212	909.834					
1933	0.669	897.745	851.900	934.260	909.834						
1934	0.666	829.820	897.151	911.378							
1935	0.663	868.749	904.976								
1936	0.659	891.675									

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

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

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

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

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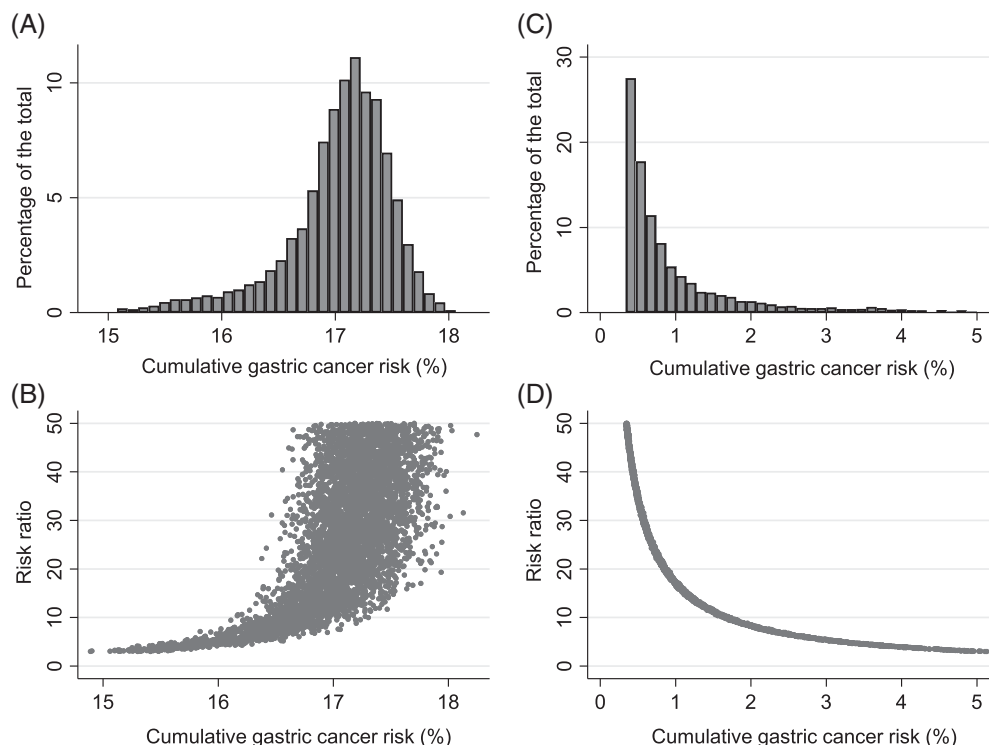
TABLE 1 Cumulative incidence risks[a] (%) of developing gastric cancer from birth to age 85 among *Helicobacter pylori*-infected and uninfected populations (estimated by performing 5000 Monte Carlo simulations using three available data sets)

				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).

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).
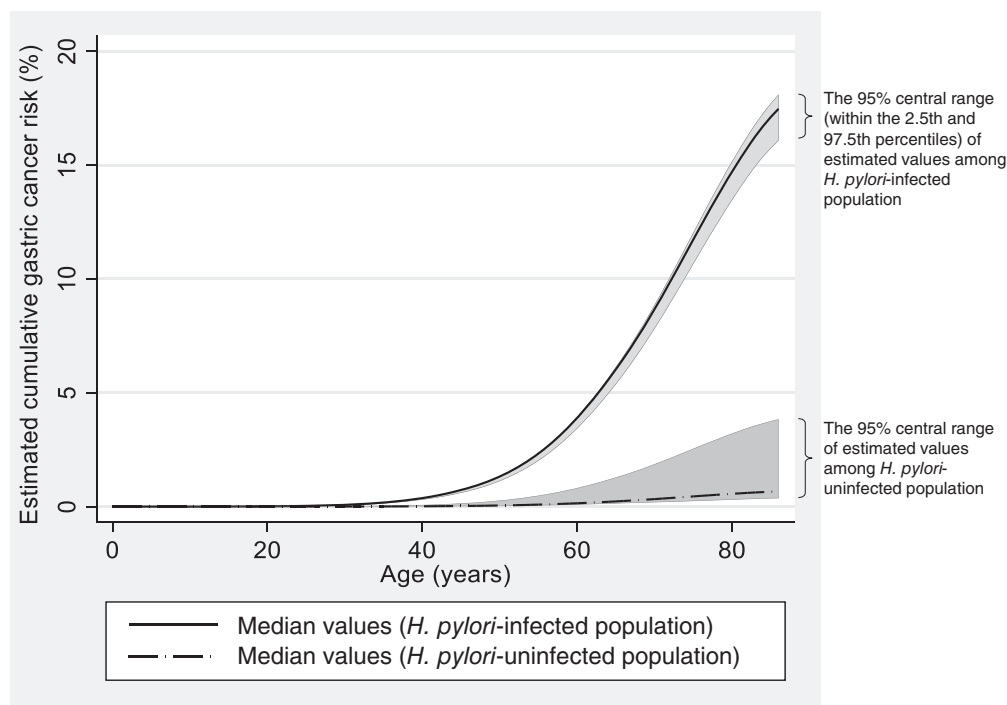
Table 2 shows the mean of the estimated cumulative incidence risks for gastric cancer based on Monte Carlo simulations at attained ages in certain age groups without gastric cancer among the *H. pylori*-infected population. Among all age groups, males who survived without developing gastric cancer until the age of 30 had the highest cumulative incidence risk for gastric cancer at 85. In females, those who survived

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.

FIGURE 3 Median values and 95% central ranges (within the 2.5th and 97.5th percentiles) of estimated cumulative incidence risks for gastric cancer from birth to attained age among male *Helicobacter pylori*-infected and uninfected populations based on 5000 Monte Carlo simulations

The 95% central range (within the 2.5th and 97.5th percentiles) of estimated values among *H. pylori*-infected population

The 95% central range of estimated values among *H. pylori*-uninfected population

Median values (*H. pylori*-infected population)
Median values (*H. pylori*-uninfected population)

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.

ETHICS STATEMENT
Since we used official Japanese statistical data, ethical approval was not required for our study.

DATA AVAILABILITY STATEMENT
The datasets used in this analysis are available from the corresponding author upon reasonable request.

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