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Effects of *Helicobacter pylori* infection and smoking on gastric cancer incidence in China: a population-level analysis of trends and projections

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Abstract

Objective—Although gastric cancer incidence is declining in China, trends may differ from historical patterns in developed countries. Our aim was to (1) retrospectively estimate the effects of *Helicobacter pylori* (*H. pylori*) and smoking on past gastric cancer incidence and (2) project how interventions on these two risk factors can reduce future incidence.

Methods—We used a population-based model of intestinal-type gastric cancer to estimate gastric cancer incidence between 1985 and 2050. Disease and risk factor data in the model were from community-based epidemiological studies and national prevalence surveys.

Results—Between 1985 and 2005, age-standardized gastric cancer incidence among Chinese men declined from 30.8 to 27.2 per 100,000 (12%); trends in *H. pylori* and smoking prevalences accounted for >30% of overall decline. If past risk factor trends continue, gastric cancer incidence will decline an additional 30% by 2050. Yet, annual cases will increase from 116,000 to 201,000 due to population growth and aging. Assuming that *H. pylori* prevention/treatment and tobacco control are implemented in 2010, the decline in gastric cancer incidence is projected to increase to 33% with universal *H. pylori* treatment for 20-year-olds, 42% for a hypothetical childhood *H. pylori* vaccine, and 34% for aggressive tobacco control.

Conclusions—The decline in gastric cancer incidence has been slower than in developed countries and will be offset by population growth and aging. Public health interventions should be implemented to reduce the total number of cases.

Keywords

Gastric cancer; *Helicobacter pylori*; Smoking; Cancer prevention; China

Introduction

Gastric cancer is the second leading cause of cancer-related deaths, with an estimated annual 933,000 new cases and 700,000 deaths worldwide (10.4% of all cancer deaths) [1]. In most developed countries, gastric cancer incidence has declined dramatically without targeted interventions. The “unplanned triumph” has been attributed to improvements in sanitation, greater fruit and fresh vegetable consumption, and reduced *Helicobacter pylori* infection [2]. Responsible for 74–78% of all cases [3], *H. pylori* is the leading risk factor for gastric cancer. As prevalence has declined, <30% are infected in high-income countries such as the United States and the United Kingdom [4–6]. Other risk factors include low vegetable and fruit intake, high dietary salt, and smoking [7–11].

Helicobacter pylori treatment can potentially prevent gastric cancer by reducing the progress of precancerous lesions, defined as atrophy, intestinal metaplasia, or dysplasia, to invasive cancer. Several clinical trials are under way [12], and results from the first of such studies suggest that treatment for *H. pylori* has the potential to reduce the risk of gastric cancer development, with the optimal time for treatment being before precancerous lesions are present [13,14]. Clinical studies on intermediate outcomes also provide indirect support for a benefit on cancer risk via reduced progression of precancerous lesions to cancer [15,16]. Despite improved understanding of gastric cancer etiology and clinical interventions, the effects of changing risk factor trends and availability of *H. pylori* treatment on disease rates at the population level have not been quantified.

China accounts for 40% of all gastric cancer cases worldwide [1] and more than 30% of the world’s tobacco consumption [17]. Currently, an estimated 58% of the population is infected with *H. pylori* [3], and approximately 60% of adult men and less than 5% of adult women smoke [17–19]. To better understand the population-level dynamics of a disease with unique historical pattern of impressive decline in some populations, and large remaining burden in others, we retrospectively (1) estimated the effects of *H. pylori* and smoking on past gastric cancer trends and (2) projected how interventions on these two factors can reduce future incidence.

Materials and methods

Overview

We conducted a population-based analysis of gastric cancer among men in China to estimate the effects of risk factors on past trends and future projections of gastric cancer incidence. The analysis included all Chinese men born between 1905 and 2034, divided into 5-year birth cohorts. For each cohort, risk factor prevalence was based on community-based epidemiological studies and national prevalence surveys. We leveraged a previously published natural history model of gastric cancer [20], which includes *H. pylori* infection and smoking as factors that affect disease initiation and progression, to estimate the incidence of gastric cancer for each cohort in the analysis. (See supplementary materials for details.) Gastric cancer rates for the different birth cohorts were then weighted using population figures from the United Nations (UN) Population Division [21] to estimate

overall gastric cancer incidence and cases in all ages combined. We conducted the analysis separately for rural and urban regions because there are differences in infection and other epidemiological characteristics [22,23]. National incidence was based on rural and urban estimates, weighted by the corresponding share of the population.

To separate changes in age-specific incidence from changes in the population age structure, we report age-standardized incidence. We used the Segi world population for standardization [24]. Because population growth and aging are important determinants of the total number of cases, we also analyzed what proportion of the projected increase in gastric cancer cases is due to these demographic changes. To do this, we recalculated the expected number of cases in each year after 2005 using the modeled annual incidence in 2050 multiplied by year-specific population estimates (i.e., fixed incidence and changing population). Conversely, the effect of epidemiological change was estimated using annual incidence in each year and the 2005 population (i.e., changing incidence and fixed population).

Risk factor and mortality data by birth cohort

For each birth cohort, the prevalences of *H. pylori* seropositivity and smoking were estimated from community-based epidemiological studies and national prevalence surveys [11,19,22,23,25–28]. We assumed that prevalences were established by age 20 and remained unchanged through the life course of the cohort because (1) individuals become infected with *H. pylori* in childhood and remain infected unless treated [29] and (2) smoking starts between the ages of 15 and 23, with subsequent lifetime cessation rates of less than 10% in the absence of aggressive tobacco control [19,30]. We also assumed that prevalences of the two risk factors were not correlated because smoking initiation is unlikely to be related to infection. While individuals may move between rural and urban regions in adulthood, their *H. pylori* status, which reflects childhood socioeconomic factors [31–33], and smoking prevalence at age 20 were specific to their location at birth and maintained over time.

Epidemiological studies have shown that (1) *H. pylori*-seropositive individuals have a higher risk of progression to atrophy than those who are *H. pylori*-negative and (2) smokers face higher risks of progression to intestinal metaplasia and dysplasia than nonsmokers (relative risk = 1.3 and 2.2, respectively) [34,35]. When these data are used in the gastric cancer natural history model, the relative risks of disease associated with *H. pylori* and smoking were estimated as 4.9 and 1.5, respectively. These values are within the range of published estimates (3.0–5.9 and 1.4–2.2, respectively [9–11,36]). Additional model parameter details are provided in the supplementary materials.

Helicobacter pylori prevalence—A study of 46 rural counties estimated that *H. pylori* prevalence ranged from 55.8% among 35–39-year-olds (corresponding to the 1945–1949 birth cohort) to 67.1% among 50–54-year-olds (1925–1929 birth cohort) [22]. Based on these data, we estimated that *H. pylori* infection declined by 4.5% between successive 5-year birth cohorts. For urban populations, a study in Shanghai found that *H. pylori* prevalence varied from 50% among 50–59-year-olds (1935–1939 birth cohort) to 41.4% among 20–29-year-olds (1965–1969 birth cohort), suggesting a 3.1% decline in infection between successive 5-year birth cohorts [23]. We estimated *H. pylori* prevalence for other birth cohorts by extrapolating the inter-cohort decline rates [4].

Smoking—A retrospective mortality study on smoking-related deaths (1905–1929 birth cohorts) and a nationwide survey of smoking prevalence (1930–1979 birth cohorts) [11,19] estimated that birth-cohort-specific smoking prevalence in China ranged from 50% (1905–1909 birth cohort) to 75% (1950–1954 birth cohort) and declined again to 50% for the

1975–1979 birth cohort. Data from three rounds of the Ministry of Health National Health Service Survey also showed a decrease in smoking prevalence among 18-year-olds between 1993 and 2003 [25–27]. Based on these data, we estimated that smoking prevalence would decline by 9% between each successive 5-year post-1975 birth cohort. We used the same smoking prevalence for rural and urban areas because of their similar observed prevalence (68 vs. 64%) [19].

Mortality from competing causes and gastric cancer—Background mortality rates (i.e., mortality from causes other than gastric cancer) were estimated using data from 1953–1964, 1964–1982, 1982–1990, 1990–2000, 1999–2000, and 2005–2030 [37–40]. For birth cohorts born prior to 1953, we used 1953–1964 mortality rates because there were limited changes in adult mortality prior to the 1949 founding of the People’s Republic of China [41]. Because gastric cancer treatment has advanced little in the last century, we assumed that case-fatality for incident gastric cancer cases was the same for all birth cohorts.

Retrospective and prospective risk factor scenarios

We considered two types of scenarios to examine trends in gastric cancer and its major risk factors between 1985 and 2050 (Table 1) [11,13,15,16,^{19,22,23},25–28,42,43]. We report results for years after 1985, the earliest year for which the population consisted only of post-1905 birth cohorts included in our model.

Retrospective risk factor exposure, 1985–2005—To estimate the effects of risk factors on past disease trends, we compared the gastric cancer trend under the observed trends in *H. pylori* and smoking with those that would have been expected had *H. pylori* infection and smoking remained at 1905–1909 birth cohort levels (referred to as the “epidemiological halt” scenario). Each risk factor trend was also evaluated separately.

Prospective risk factor projection, 2005–2050—To quantify the potential effects of risk factor interventions on future gastric cancer in addition to risk factor trends, we used several *H. pylori* prevention/treatment and tobacco control scenarios. We assumed that these were implemented in 2010.

Results

Birth cohort risk factor trends

Figure 1 shows *H. pylori* and smoking prevalences for cohorts of men born between 1905 and 2034 in China. *H. pylori* prevalence declined from 81% in the 1905–1909 birth cohort to 39% in the 1985–1989 birth cohort in rural regions and from 60 to 37% in urban regions. If past trends continue, *H. pylori* prevalence for the 2030–2034 birth cohort is expected to decline to 26 and 28%, respectively, which is similar to the *H. pylori* prevalence among middle-aged Americans in 1990 [44]. If the decline in cohort smoking prevalence continues for post-1975 birth cohorts, less than 20% of individuals born in 2030 in China would become smokers. For comparison, currently 24% of all men in the United States smoke [45].

Retrospective risk factor exposure and gastric cancer incidence, 1985–2005

Modeled age-standardized incidence was 30.8 per 100,000 in 1985 and 27.2 per 100,000 in 2005 (a 12% decline; Table 2; Fig. 2a). The 2005 estimate was within 6–18% of reported rates, e.g., from GLOBOCAN [1], Global Burden of Disease study [40] and the national mortality routine reporting system (CHIS) [46]. The modeled 12% decline between 1985 and 2005, based on observed trends in *H. pylori* and smoking only, was approximately one-third of the observed decline in gastric cancer in China [46]. The effects of this decline reduced the cumulative risk of gastric cancer between 20 and 84 years of age from 4.5 to

4.0%. The decline in gastric cancer incidence was 10% in rural areas and 6% in urban areas. The national decline was larger than both of these because the proportion of the population in urban areas, where prevalence is lower, increased over this period.

Had the prevalence of *H. pylori* and smoking remained at the 1905–1909 birth cohort level (scenario *EPI*), age-standardized gastric cancer incidence would have decreased 4% between 1985 and 2005 (32.6 to 31.5 per 100,000). Had smoking prevalence remained unchanged at the 1905–1909 birth cohort level, the reduction in gastric cancer incidence from declining *H. pylori* prevalence (scenario *HP*) would have been even higher at 14%, versus the observed 12%.

Projection of risk factor exposure and gastric cancer incidence, 2005–2050

If observed birth cohort risk factor trends continue (scenario *CONT*), cumulative risk of gastric cancer between the ages of 20 and 84 will decline from 4.0 to 2.9% between 2005 and 2050. Age-standardized gastric cancer incidence will decline an additional 30% from 27.2 to 19.0 per 100,000 (Table 2; Fig. 2b). The annual rate of decline during this period would be approximately one-third higher than in 1985–2005, due largely to declining smoking prevalence among post-1960 birth cohorts.

Helicobacter pylori treatment at age 20 would reduce the lifetime risk of gastric cancer among infected individuals from 3.7 to 3.1% (17%). This effect is relatively small because treatment reduces disease progression only among individuals without advanced precancerous lesions and is not expected to benefit those who have already developed these lesions [13,15,16]. In birth cohorts that consist of infected and non-infected individuals, the benefits of treatment will depend on the prevalence of *H. pylori* infection. For example, universal treatment would reduce the lifetime gastric cancer risk of the 1990 birth cohort, which has an *H. pylori* prevalence of 35%, from 1.4 to 1.2%. When the effects of universal treatment in all birth cohorts are considered, the projected decline in gastric cancer between 2005 and 2050 would increase from 30 to 33% (18.3 per 100,000; Fig. 2b).

A hypothetical childhood *H. pylori* vaccine would have a larger benefit, leading to a 42% decline in gastric cancer because of its ability to prevent the development of pre-cancerous lesions present by age 20 in the vaccinated cohorts. The remaining incidence in 2050 will be 15.7 per 100,000 (16.4 per 100,000 if vaccine efficacy was only 80%). If young men do not take up smoking (*SM-C*), the incidence decline would be 34%, leading to an incidence of 17.9 per 100,000 in 2050. If gastric cancer risk among smokers aged 35 and younger were also reversible, tobacco control would reduce incidence to 16.2 per 100,000.

The benefits of lower *H. pylori* and smoking, seen as a declining age-specific incidence, will be outweighed by the fact that China is projected to have a larger and older population (Fig. 3). As a result, the number of cases among Chinese men is expected to nearly double from 116,000 in 2005 to 201,000 in 2050. Only after 2040 will the total number of cases begin to decline, by approximately 8,000 between 2040 and 2050 (<5%). Approximately 50% of gastric cancers in 2050 will be attributable to *H. pylori* infection (104,000 cases). Only 5–18% of these cases can be avoided with *H. pylori* interventions by 2050 as those benefiting will be too young to have realized the full benefits (Fig. 4). However, the benefits of prevention will increase substantially over time, as treated cohorts increase in number and age.

Discussion

Unlike the dramatic decline in developed countries, gastric cancer remains a major public health concern in China. We estimated that the combined changes in *H. pylori* and smoking

trends were associated with a 12% decline in gastric cancer incidence between 1985 and 2005 among Chinese men, although approximately 20% of the total benefits from reductions in *H. pylori* infection were offset by the rise in smoking. Even if declining *H. pylori* and smoking trends continue, gastric cancer incidence in China in 2050 will be six times that of current levels in the United States [1], with the vast majority of new cases stemming from *H. pylori* infections decades earlier. Population growth and aging will overshadow this decline and lead to near doubling of the number of new cases by 2050. Smoking and *H. pylori* interventions can reduce incidence, but the full benefits will be realized only after several decades. Nonetheless, even in the analysis period, reducing smoking and preventing or treating *H. pylori* infection can have significant benefits, with the largest benefits from preventing smoking or *H. pylori* at younger ages.

As with any projections of future disease burden, our estimates are uncertain and affected by our model assumptions and some limitations. First, our estimates of past cohort *H. pylori* and smoking were based on epidemiologic studies from China but may miss possible within-cohort dynamics that happen later in life. For example, progression of gastritis to atrophy or intestinal metaplasia can lead to loss of *H. pylori* among a small proportion, or some of the older cohorts in our retrospective analysis may have begun smoking later in life. Future prevalences of *H. pylori* and smoking are also uncertain, as are those of other factors responsible for the unaccounted portion of variation in incidence, including dietary changes [47]. Second, based on the available epidemiological evidence, we assumed that *H. pylori* and smoking influence disease progression at specific and distinct stages of gastric cancer natural history. The estimated effects of risk factors would be underestimated if they also affect other disease stages. Third, the estimated model parameters for the effects of *H. pylori* on gastric cancer were relatively uncertain [20], but the effects on the projected gastric cancer incidence were less than 10%; further, the relative ordering of scenarios was unchanged. Fourth, our model parameters were estimated using epidemiologic data of the high-risk region of Linqu [1,48]. We adjusted *H. pylori* and smoking to their national prevalence, but the etiological effects may vary by region. Risk factor interventions may also affect background mortality, especially for smoking because it is a risk factor for all-cause mortality. Lastly, our analysis focused only on men. Although *H. pylori* prevalence is similar among women, smoking is considerably lower and the projected decline in incidence and burden would likely be lower.

Despite these limitations, our analysis of risk factor trends and gastric cancer burden has several strengths. We used a state-transition model that was developed to reflect current scientific knowledge about the natural history of gastric cancer and which was parameterized using country-specific epidemiological data. The capability of the model to incorporate *H. pylori* infection and smoking allowed for a more complete representation of heterogeneity in disease progression. Incorporating these risk factors also allowed estimating how past exposure and future interventions affect disease trends and projections. As new data from clinical trials of *H. pylori* treatment and studies of smoking cessation become available, our results can be updated and refined to provide more accurate estimates of the burden and comparative benefits of gastric cancer prevention policies, providing a basis for discussing public health policy. Further, our estimates can be useful for assessing cost-effectiveness of various interventions, framing questions for epidemiological investigation, and highlighting high priority data that are needed to improve the precision of model estimates.

Projections of future cancer burden at the population level are inherently uncertain, but they are needed to guide the planning of cancer control programmes [49]. As has been observed in many developed countries, gastric cancer incidence is declining and is expected to continue declining in China. However, the relatively low decline rate, coupled with

population growth and aging, is expected to nearly double the number of cases over the coming decades. The large absolute burden demonstrates the need for *H. pylori* treatment and smoking cessation programmes to accelerate the underlying rate of decline. Finding effective strategies for early detection and treatment of gastric cancers should also be a research priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Birth cohort risk factor exposure at age 20. The graph shows the observed exposure for birth cohorts up to the 1975–1979 cohort and projected exposure for birth cohorts born after 1980

Fig. 2.

Age-standardized gastric cancer incidence for retrospective and prospective scenarios (see Table 1 for scenario definitions). **a** Age-standardized gastric cancer incidence between 1985 and 2005 for scenarios of past risk factor trends. Numbers show percentage of declines between 1985 and 2005. **b** Age-standardized gastric cancer incidence between 2005 and 2050 for future risk factor scenarios. Numbers show percentage of declines between 2005 and 2050. * A part of the decline in gastric cancer incidence is due to the increase in the proportion of urban population. For example, if proportion of urban population were held constant at 1985 level, age-standardized gastric cancer incidence between 1985 and 2005 would have increased for *EPI* (+0.2%) and *SM* (+2.2%)

Fig. 3.
Change in the projected number of gastric cancer cases attributed to demographic and epidemiological changes between 2005 and 2010/2050. Number of cases attributed to each component is depicted for each year

Fig. 4.
Gastric cancer cases between 1985 and 2050: proportions attributable to *H. pylori* and avoidable through interventions

Table 1

Risk factor scenarios used in the analysis

Scenario	Notation	Definition ^a
<i>Type 1: Retrospective risk factor exposure, 1985–2005</i>		
Epidemiologic changes halted	(EPI)	<i>H. pylori</i> and smoking prevalences remained at 1905–1909 birth cohort levels in subsequent cohorts
Observed <i>H. pylori</i> prevalence decline	(HP)	The prevalence of <i>H. pylori</i> declined by 4.5 and 3.1% every 5-year 1905–2034 birth cohort in rural and urban populations, respectively, as observed [22,23]. Smoking prevalence remained at 1905–1909 birth cohort levels for all cohorts
Observed smoking prevalence changes	(SM)	Smoking prevalence changed from 50 to 75% for 1905–1974 birth cohorts, and then declined by 9% for every post-1975 birth cohort as observed in China [11,19,25–28]. <i>H. pylori</i> prevalence remained at 1905–1909 birth cohort levels for all cohorts
Both observed <i>H. pylori</i> and smoking prevalence changes	(ALL)	Combination of observed changes in <i>H. pylori</i> prevalence and smoking for each birth cohort
<i>Type 2: Prospective risk factor projections^b, 2005–2050</i>		
Continued <i>H. pylori</i> and smoking trends	(CONT)	Birth cohort trends for <i>H. pylori</i> and smoking prevalences continue (as described above in <i>ALL</i>) for cohorts born between 1985 and 2034
<i>H. pylori</i> treatment	(HP-T)	Universal <i>H. pylori</i> treatment for 20-year-olds with 100% coverage. Based on clinical studies, we assumed that <i>H. pylori</i> treatment reduced disease progression only among individuals without advanced precancerous lesions (i.e., gastritis or atrophy) [13,15,16]. We also assumed that treated individuals remain uninfected as adult reinfection is rare [42,43]. See supplementary materials for additional details
<i>H. pylori</i> vaccine	(HP-V)	Hypothetical childhood <i>H. pylori</i> vaccination with 100% coverage and efficacy, including a catch-up program for those aged 5–19 years. We assumed vaccination reduces the risk of infection to zero, thereby reducing disease risk from 3.7 to 0.7% (96%)
Tobacco control	(SM-C)	Tobacco control to reduce initiation among 20-year-olds reduced to 0% ^c

^a All scenarios also incorporated change in background mortality risk from other diseases. Population growth (medium fertility variant) and urbanization were also included, using estimates from the UN population division

^b All interventions begin in 2010

^c We also estimated the additional benefit if risk among smokers ages 35 and younger in 2010 was reversible to non-smoking levels

Table 2

Modeled gastric cancer incidence and number of cases for select scenarios

Age-standardized gastric cancer incidence (per 100,000 men) ^a		Crude gastric cancer incidence (per 100,000 men)				Number of cases							
		1985	2005	2030	2050	1985	2005	2030	2050				
Type 1: Retrospective													
ALL	30.8	27.2	22.6	22.6	19.0	23.7	25.0	35.2	37.6	74,900	116,200	194,800	200,800
Type 2: Projected													
CONT	–	27.2	22.6	22.6	19.0	–	25.0	35.2	37.6	–	116,200	194,800	200,800
Hp-T	–	27.2	22.5	22.5	18.3	–	25.0	35.1	36.8	–	116,200	194,300	196,300
Hp-V	–	27.2	22.2	22.2	15.7	–	25.0	34.8	34.1	–	116,200	192,700	182,100
SM-C	–	27.2	22.4	22.4	17.9	–	25.0	35.0	36.2	–	116,200	193,700	193,400

^a Age-standardized using the Segi world population