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Changing Trends in Stomach Cancer Throughout the World

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Abstract

Purpose of Review—The paper aims to discuss the global trends in gastric cancer incidence in relation to important factors involved in the pathogenesis of gastric cancer.

Recent Findings—Despite a significant worldwide decline, gastric cancer remains a common cause of cancer death. The decline has been multifactorial and preceded the fall in *Helicobacter pylori* prevalence. The initial decline was associated with changes in food preservation and availability, especially of fresh fruits and vegetables, followed by a decline in the primary etiologic factor, *H. pylori*. Gastric cancer incidence remains high in East Asia, intermediate in Latin America, and low in developed countries. Significant racial/ethnic variability exists.

Summary—The rapid decline in incidence in East Asia will continue as primary and secondary prevention strategies are implemented. The incidence in Latin America is unlikely to decline significantly over the next few decades given high *H. pylori* prevalence in the young. Ultimately, global *H. pylori* eradication will be needed to largely eliminate gastric cancer.

Keywords

Gastric cancer; Disparities; *Helicobacter pylori*; Epidemiology; Risk factors; Natural history

Introduction

Gastric cancer incidence has declined significantly worldwide over the past half-century. Nevertheless, gastric cancer remains a global health problem as the fifth leading cancer and third most common cause of cancer-related deaths worldwide [1••]. Even today, gastric cancer incidence and mortality remain disproportionately high in East Asia, Latin America and Eastern Europe and within specific subgroups in the USA. Much of the reduction in gastric cancer incidence occurred coincident with economic improvements resulting in improved sanitation, hygiene, clean water supplies, and advances in food preservation,

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Compliance with Ethical Standards

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variety, and availability. In regions with currently high gastric cancer incidence, primary and secondary prevention strategies have helped reduce gastric cancer mortality [2••, 3••, 4].

Here, we review temporal changes, regional variations, and racial/ethnic disparities (specifically within the USA) in gastric cancer incidence and mortality. We focus on non-cardia gastric cancers and exclude adenocarcinoma of the esophagus related to Barrett's esophagus. We also discuss putative causes for global changes and variations in gastric cancer burden across populations. Finally, we present primary and secondary prevention strategies with proven effectiveness and propose future directions for reducing gastric cancer incidence and fatality among populations that still experience a high burden of gastric cancer.

Gastric Cancer Subtypes

Gastric adenocarcinoma accounts for approximately 90–95% of all stomach cancers, with lymphoma, leiomyosarcoma, gastrointestinal stromal tumor, and neuroendocrine tumors accounting for the remainder [5]. Gastric adenocarcinoma, although frequently discussed as a singular entity, actually encompasses two anatomic subtypes, cardia gastric cancer and non-cardia gastric cancer (here called gastric cancer), with distinct clinical and epidemiological characteristics. Cardia gastric cancer is defined as an adenocarcinoma in the proximal stomach located within 5 cm of and involving the gastroesophageal junction [6]. Cardia gastric cancer is associated with obesity, long-standing gastroesophageal reflux, and possibly tobacco smoking. Within the USA, it has the highest incidence among Caucasian men. Cardia cancer has a clinical course and epidemiology similar to that of esophageal adenocarcinoma [7] and a worse long-term survival than that of noncardia gastric cancer [8•]. Cardia gastric cancer incidence has remained stable or increased within specific subgroups [9].

Typical non-cardia gastric cancers encompass tumors arising more distally and are etiologically associated with *Helicobacter pylori* infection, tobacco smoking, and high dietary salt intake. A small proportion is related to EBV infection. Overall, non-cardia cancer has declined worldwide and is subtyped histologically into intestinal and diffuse types using the Lauren classification [10, 11]. Both types are associated with *H. pylori* infection which is involved with progressive and long-standing mucosal inflammation, followed by mucosal atrophy ultimately culminating in intraepithelial and finally advanced neoplasia. Gastric cancer is associated with well-defined precancerous lesions of mucosal atrophy and metaplasia. These can be readily identified endoscopically and confirmed by histology. Diffuse-type gastric cancer is strongly associated with loss of E-cadherin expression. Most diffuse-type cancers are also associated with atrophic gastritis but a definite precancerous lesion has not been identified. Diffuse-type gastric cancer includes signet ring adenocarcinoma which is also associated with non-*H. pylori*-associated hereditary gastric cancer. These are typically diagnosed in younger patients and carry a poor prognosis [10].

Gastric Cancer Pathogenesis and Risk Factors

Most cases of gastric cancers are sporadic and etiologically related with *H. pylori* infection. *H. pylori* is a class I carcinogen [12] that is estimated to account for approximately 89% gastric cancer cases (at least 95% of those in high gastric cancer incidence areas) [13]. *H. pylori* virulence, differences in host inflammatory response to infection, and specific environmental exposures additionally influence gastric cancer risk.

A strong association between gastric atrophy and gastric cancer has long been observed [14••]. The discovery of *H. pylori* in 1983 and subsequent demonstration that it was the main cause of gastritis culminated the long search for the cause of gastritis which had long been known to be tightly associated with gastric atrophy and with gastric cancer. *H. pylori* infections are usually acquired during childhood and typically remain latent for decades. Over the duration of a latent *H. pylori* infection, progressive gastric mucosal damage may occur resulting in progressive gastric atrophy which is associated with the development of metaplastic epithelia; first, as a progressive lawn of pseudopyloric metaplasia (now called spasmolytic polypeptide expressing mucosa or SPEM). Patches of intestinal metaplasia may then appear within the atrophic area. These islands of intestinal metaplasia give rise to the misnomer of a multifocal process [15]. Foci of dysplasia may appear within the lawn of atrophic mucosa which may then progress to invasive gastric neoplasia. In most developed countries, gastric cancer is a relatively rare event with only 1 to 3% of *H. pylori* infections progressing to gastric cancer [16]. In other countries, such as Japan and Korea, and in parts of China, the lifetime risk of gastric cancer is much higher and often may exceed 10%. The country or region-wide risk of gastric cancer directly relates to the proportion of the population that develops atrophic gastritis and the rate in which it develops [17]. Once atrophic gastritis is present, the annual risk of developing gastric cancer ranges increases to about 1% [15, 18].

H. pylori infection is considered a necessary but insufficient cause of gastric cancer as there are other factors that modulate the risk. For example, in India and tropical countries there is discordance between a relatively high *H. pylori* infection prevalence and low gastric cancer incidence (gastric cancer age-adjusted incidence in India: 7.8/100,000 and 6.1/100,000, respectively among males and females). In contrast, in Japan and China where *H. pylori* prevalence is also high, the gastric cancer incidence ranges from 62 to 69/100,000 and 26/100,000, respectively, among males and females [19•].

While *H. pylori* virulence and the host response to infection modulate gastric cancer risk [10], the dominant factor is environmental, most likely related to diet [20]. There has been considerable effort expended attempting to identify specific *H. pylori* virulence factors that increase the risk of gastric cancer. None have appeared, and overall, the data support the notion that *H. pylori* virulence factors that have been associated with gastric cancer share the common property of causing an increased host inflammatory response that underlies the risk increase in gastric cancer [21••]. The *H. pylori* virulence factors most often identified are the vacuolating cytotoxin, VacA, and the cytotoxin-associated antigen, CagA. However, even the most avirulent *H. pylori* strains have been associated with development of gastric cancer and peptic ulcer; the presence of the most virulent strains approximately doubles the risk [21••]. Host factors associated with an increased risk of gastric cancer are those associated with an

increased inflammatory response to the infection. One example is the pro-inflammatory interleukin (IL)-1. Some IL-1 genotypes are associated with an increased risk of gastric cancer whereas others are associated with reduced inflammation and reduced risk [21••]. For example, those infected with a virulent *H. pylori* strain and a pro-inflammatory IL-1 have been reported to have up to an 87-fold higher risk of gastric cancer [22].

Temporal Tends in Gastric Cancer Incidence and Mortality

Until the second half of the twentieth century, most gastric cancer epidemiological data came from local or regional epidemiological observations and fledgling local cancer registries predominantly in Northern America and Western Europe. Formal cancer registries developed more widely in the mid-1900s and global-level cancer tracking started with the launch of the International Association of Cancer Registries (IACR) in 1966 [23]. Since then, various estimation methods have been used to derive global cancer statistics from national, regional, or local-level cancer registry data [24]. A well-recognized limitation in global cancer data has been a paucity of high-quality, and in some cases any, data from low- and middle-income countries leading to potential underrepresentation of trends within those regions. Though a persistent problem, the number of countries included in global cancer estimations has recently expanded considerably from 29 to 184 [23, 25••].

Gastric cancer was common in the nineteenth century, and in the first half of the twentieth century, it was the most common cause of cancer death in Western countries [20]. For example, in 1919, James Ewing, who provided some of the earlier summary statistics of gastric cancer prevalence, reported that gastric cancer constituted 10% of 4131 cancer cases in Vienna, to as high as 41.5% of 27,511 cancers Switzerland; he also reported a relatively high mortality rate based on the 1912 US Census findings of 46,534 cancer-related deaths, 39.8% of which were stomach and liver in origin [26].

A decade later, as part of the Schorstein Lecture, Sir Arthur Hurst highlighted the continued high incidence and mortality of gastric cancer commenting that “every year about sixteen thousand people die in Great Britain from cancer of the stomach. It is the cause of death in 5 out of every 100 people dying after the age of 40, and accounts for about one-third of all deaths from carcinoma” [27]. Contemporary reports from regions within the USA also documented high gastric cancer incidence and mortality [28].

Gastric cancer continued to be the leading cause of cancer and cancer-related death until 1975. While the overall incidence did decrease over that time period, there was significant geographic variability [29]. Between 1930 and 1955, gastric cancer age-adjusted mortality fell in the USA, the Netherlands, and Canada. Conversely, in Japan during that same time period, gastric cancer incidence remained stable and cancer mortality actually rose [30]. By 1972, the standardized gastric cancer incidence rate per 100,000 among persons 35 to 64 years ranged from 14 to 35 in the USA, 31 to 67 in Europe, 110 to 160 in USSR, and 155 to164 in Japan [31••].

In 1975, gastric cancer had declined to where it represented the second leading cause of cancer worldwide, after lung cancer. This change was the result of both a rise in lung cancer and decline in gastric cancer incidence [32•]. From 1980 to 2011, gastric cancer mortality

rates continued to fall worldwide although with considerable regional variation in the direction and magnitude of change [33•]. Japan, Korea, the European Union (EU), and Russia had the most significant declines in gastric cancer mortality between 2000 and 2009 (estimated annual percent changes [EAPC] in men and women, respectively: Japan −3.1 and −3.9%; Korea −4.1 and −4.7%; EU −3.7 and −3.4%; Russia −3.0% in both sexes). In Japan, Korea, Russia, and the UK, the greatest reduction in mortality rates was observed among persons aged 35 to 64 years of age [33•]. Meanwhile, there was a leveling off in mortality rates in the USA and France. Notably, Japan, Korea, and Russia are among the countries with the greatest reductions in gastric cancer mortality over 1980 to 2011. They were also those with a higher proportion of non-cardia gastric cancer compared to cardia gastric cancer.

At present, gastric cancer is the fifth most incident cancer and the third leading cause of cancer deaths worldwide [34]. In 2012, the global age-standardized gastric cancer incidence rate was 12.1/100,000 [32•]. The total number of newly diagnosed gastric cancer cases was estimated at 952,000 representing 6.8% of all newly diagnosed malignancies and accounting for 8.8% of cancer-related deaths [34]. Incidence of gastric cancer occurs approximately twice as frequently in men compared to that in women with most cases occurring after the age of 60 [10, 32•]. Despite the decline in incidence, gastric cancer still has a dismal, 20%, 5-year survival rate [35••, 36] and high case fatality rate of74.5% throughout most of the world [19]. Gastric cancer is a main contributor to disability-adjusted life-year burden and early deaths from cancer and has a significant impact on overall health and life expectancy throughout the world [37].

Current Geographic Trends in Gastric Cancer Incidence and Mortality

There are significant regional differences in current gastric cancer incidence and mortality. The highest rates are observed in East Asia, Eastern and Central Europe, and South and Central America. Gastric cancer rates are also significantly lower in more economically developed regions of the world than in less developed (age-standardized incidence rate [ASIR] per 100,000: men = 15.6 vs. 18.1; ASIR women = 6.7 vs. 7.8; age-standardized mortality rate [ASMR] per 100,000: men = 9.2 vs. 14.4; ASMR women 4.2 vs. 6.5) [34]. More than 70% of gastric cancer cases occur in less-developed countries.

Currently, East Asia carries most of the world’s gastric cancer burden. In 2012, China, Japan, and Korea accounted for 60% of all newly diagnosed gastric cancer. Gastric cancer ASIRs in Korea, Mongolia, Japan, and China remain among the highest in the world, estimated at 41.8, 23.5, 29.9, and 22.7 per 100,000 respectively [32•]. Gastric cancer mortality rates are also high in East Asia (24 and 9.8 per 100,000 men and women, respectively) with the greatest number of cumulative gastric cancer deaths occurring in the Republic of Korea and Japan [32•]. Gastric cancer survival tends to be better in East Asia than in North America or Europe [38•]. For example, 5-year survival rates of 67 and 69% for primary gastric cancer have been reported in Korea and Japan, respectively [39•, 40]. Screening programs in East Asia that result in early detection of gastric cancer explain some of these differences. For example, greater than 50% of cancers are diagnosed at an early stage in Japan [41] as opposed to approximately 27% in the USA. Differences in tumor

biology and gastric cancer subtype (where the East has a higher proportion of non-cardia gastric cancer than the West) may also contribute to survival differences.

Central/Eastern Europe has the second highest gastric cancer rates after Eastern Asia with estimated ASIR of 13.5/100,000 and ASMR of 10.9/100,000. South and Central America have intermediate ASIRs (10.3 and 9.3 per 100,000 respectively) and ASMRs. Outliers within the region include Guatemala and Costa Rica, which have gastric cancer rates that compete with Eastern Asia with estimated ASIRs of 23.7 and 17.3 per 100,000 respectively [32•].

Western Europe, Northern Europe, and North America have intermediate to low rates of gastric cancer (ASIR: 6.3, 5.4, and 4 per 100,000 respectively). The USA specifically has an ASIR of 3.9/100,000 and the lowest gastric cancer mortality rate in the world (ASMR: 2.7 and 1.5 deaths per 100,000 in men and women, respectively) [32•]. In the USA, 5-year survival from gastric cancer has improved somewhat over the last 30 years from 15 to 29% [42]. However, the gastric cancer prognosis for the individual patient remains dismal as gastric cancer is typically diagnosed at an advanced stage (73% of cases) [43].

There are also differences in the anatomic subtype of gastric cancer that effect incidence and mortality. Globally and through much of East/Central Asia and Eastern Europe, non-cardia gastric cancer is the predominant anatomic subtype. Conversely, in North America and Western Europe, cardia gastric cancer is the predominant subtype due to the fact that non-cardia gastric cancer incidence has declined and cardia gastric cancer rates have remained stable or possibly increased [44••, 45–46].

Gastric Cancer Variability Within the USA

While gastric cancer burden is relatively low in the USA, there are persistent and significant ethnic/racial disparities in gastric cancer incidence and mortality. The few studies to examine gastric cancer by anatomic subtype have also shown that non-cardia gastric cancer specifically is disproportionately high among non-White populations [47, 48••] and indigenous populations [49•].

Non-White populations have nearly twice the incidence and mortality of gastric cancer compared to non-Hispanic White populations [47, 48••, 50••, 51–52•]. The Surveillance, Epidemiology, and End Results Program (SEER) reported ASIRs of 10.5, 10.6, and 10.2 per 100,000 in Hispanics, Asians/Pacific Islanders, and Blacks, respectively, versus 5.7 per 100,000 in non-Hispanic Whites over 2000–2014 [52•]. Similarly, a large US population study in a single health system in Southern California reported a 40–50% increased risk of gastric cancer in Hispanics (odds ratios [OR] 1.4), non-Hispanic Blacks (OR 1.5), and Asians (OR 1.5) compared to that in non-Hispanic Whites [51]. Gastric cancer mortality rates are the lowest among non-Hispanic Whites (ASMR 2.5 per 100,000) while double this rate was observed among all other ethnic/racial groups in 2010–2014 (5.3, 5.5, and 5.9 per 100,000 Hispanics, Asians/Pacific Islanders, and Blacks, respectively) [52•].

Indigenous populations within the USA are also disproportionately affected by gastric cancer. The estimated ASIR was much higher than observed in the general population at

30.8 and 9.4 per 100,000 Alaskan Inuit/Yupik/Inupiat men and American Indian/Alaskan Native men respectively over the 1990s to 2000s [49•]. The USA, however, is not unique in having such striking contrasts in gastric cancer patterns between indigenous and non-indigenous populations. Significantly higher gastric cancer burden is also observed among the indigenous populations of Canada, Northern Europe, Australia, New Zealand, and Russia as well [49•].

Gastric cancer disparities between subgroups in the USA have been observed as far back as the 1960s [30]. Ethnic/racial disparities in gastric cancer trends in the USA may be partly explained by an immigration effect, where individuals from higher gastric cancer incident regions of the world such as Eastern Asia, Eastern Europe, and Latin America account for higher rates. But, an immigration effect does not completely explain the trend given the disproportionately high gastric cancer rates observed among indigenous populations as well. Socioeconomic disparities are likely a strong contributing factor, mediated by greater exposure to *H. pylori* infection, risky environmental exposures, and barriers in accessing medical care [53••, 54•, 55••]. However, further work needs to be done to identify the root causes and rational prevention methods for the disparate gastric cancer trends observed in the USA. Also, an unexpected trend has been highlighted by recent data indicating a rise in non-cardia gastric cancer among young White men in the USA. Two separate analyses of SEER data noted unexpected increases in non-cardia gastric cancer among young White persons over the 1970s–2000s: one observed an increase among young Whites aged 25–39 years [56•] and the second, an unexpected increase in corpus cancers among young (25–39 years) and middle-aged Whites (40–59 years) [57••]. The significance of and reasons for this increase are still unclear.

Putative Mechanisms for the Decline in Gastric Cancer

H. pylori prevalence partially accounts for the observed trends in gastric cancer incidence over time and across populations. However, the cause for global declines and differences in gastric cancer incidence is multifactorial and related to trends in dietary, tobacco, and other environmental exposures in addition to *H. pylori* infection.

Countries and populations that have experienced marked improvements in public sanitation (linked to economic development) and access to clean water supplies have seen the most significant reductions in *H. pylori* infection. This is reflected by the “birth cohort effect” whereby *H. pylori* rates have been declining among younger generations in most regions of the world. Countries that have experienced the largest birth cohort effect include Korea, Japan, and the USA where observed *H. pylori* prevalence rates are markedly lower among younger compared to that among older age groups, reflecting a drop in acquisition of infection with successive generations. In Korea, *H. pylori* prevalence was estimated at 60% among 60-year-old versus 20% among 20-year-old persons in 2005 [58]; in Japan, cross-sectional studies have estimated *H. pylori* prevalence at 80% among pre-1950s-born persons versus 5% among 1980s-born persons [59••]; and in the USA, *H. pylori* prevalence was estimated at 40% among older adults versus 20% among younger adults in 1999–2000 [58]. On the other hand, Central and South American countries have not experienced a significant birth cohort effect [58] which is reflected in high *H. pylori* prevalence rates estimated at 70–

85% among all age groups in a cross-sectional study conducted from 2009 to 2012 across Mexico, Honduras, Costa Rica, Nicaragua, Chile, and Colombia [60••].

Environmental Factors and Gastric Cancer Incidence

Earlier reductions in gastric cancer incidence were not related to a change in *H. pylori* prevalence but more likely related to changes in diet [20••]. This is best seen in the West where high rates of gastric cancer and gastric ulcer were rapidly replaced by duodenal ulcer as the primary *H. pylori*-related disease (Fig. 1) [20••]. Gastric ulcer and gastric cancer are both related to progressive gastric injury and the development of atrophic gastritis. In contrast, duodenal ulcer is related to non-atrophic gastritis with high acid secretion and relative "protection" against gastric cancer. This change in the pattern of disease was therefore a reflection of the change in the pattern of gastric damage associated with *H. pylori* infections. This difference in the pattern of gastritis is also reflected in the differences in gastric cancer incidence between regions where fresh fruits and vegetables are available year round as opposed to those with seasonal diets. Reductions in gastric cancer risk are associated with diets rich in fruits, vegetables, fish, and whole grains rather than processed meats, refined grains, and high-fat products [61, 62••]. In the USA and Europe, the nineteenth and early twentieth centuries experienced marked changes in food production, processing, preservation, and especially transportation, such that in the second half of the twentieth century, *H. pylori* infection was in marked decline and fresh fruits and vegetables were available year round [20••]. This change was recently vividly illustrated by a study in Japan that evaluated gastric histology and *H. pylori* prevalence over a recent 40-year period. Despite the presence of *H. pylori* infection, there was a marked decrease in the rate of development and prevalence of atrophic changes (Fig. 2) [63••]. This change was also reflected in the rapid change in gastric cancer incidence between 1965 and 1995 where it fell to approximately 60% in every age group irrespective of the prevalence of *H. pylori* within that group (Fig. 3) [64••, 65•]. It is also important to note that these changes occurred despite no changes in virulence of the predominant strain of *H. pylori* or in host genetics.

Other important factors included a fall in salt consumption and patterns in tobacco smoking [63••]. A recent study evaluated the effect of tobacco smoking on gastric cancer incidence in 118 countries and found that the proportion of gastric cancers attributable varied by geographic region and sex with the highest attributable fractions observed among men in Eastern Asia and women in Western Europe. Importantly, the authors predicted an increase in the absolute number of gastric cancers attributable to smoking by the year 2020. This highlights a potential need to target smoking as a gastric cancer prevention strategy in regions where smoking is highly prevalent [66••].

In the USA and other developed countries, the change in the prevalence of the type of *H. pylori*-related diseases expressed as a rise in the incidence of duodenal ulcer was then noted to decline such that the incidence of all *H. pylori*-related diseases declined [20••]. This change reflected the progressive decline in *H. pylori* prevalence related to progressive improvements in sanitation, access to clean water, and improved household hygiene [20••]. A microsimulation model using National Health and Nutrition Examination Survey (NHANES) and National Health Interview Survey (NHIS) data estimated that between 1978

and 2008, the US gastric cancer incidence decreased 60% with the change in *H. pylori* prevalence alone accounting for 43% of the observed decline and the reduction in smoking for additional 3% [67].

Effect of Primary and Secondary Prevention Strategies on Gastric Cancer

Future efforts against gastric cancer likely consist of a combination of primary and secondary prevention strategies. The actual strategy utilized will depend on the resources available and the prevalence of *H. pylori*-related diseases. The report of an effective vaccine to reduce or prevent *H. pylori* infection suggests that it will be possible to extend *H. pylori* eradication to the developing world where it is most prevalent [68]. Meta-analyses have confirmed that eradication of *H. pylori* infection is effective in reducing gastric cancer incidence [69, 70]. Secondary preventive strategy using endoscopic screening and surveillance of those with high-risk histology is being performed in Japan and Korea with some success [2••, 3••, 4]. We predict that worldwide *H. pylori* eradication will soon be possible and will make gastric cancer a vanishing rare disease.

Conclusions

Gastric cancer incidence has declined dramatically throughout the world largely as a consequence of economic improvements that have brought about improved food preservation, availability, improved sanitation, access to clean water, and improved household hygiene which further led to a fall in *H. pylori* acquisition and a decline in prevalence among subsequent generations. Japan, Korea, and China currently carry the highest burden of gastric cancer. Overall, declining *H. pylori* prevalence and active gastric cancer screening and surveillance have resulted in reduced gastric cancer incidence and mortality. Tobacco smoking is emerging as an increasingly significant modifiable risk factor to target in the context of gastric cancer prevention.

Reductions in gastric cancer seen worldwide have not been universal. Central and South America both have intermediate to high rates of gastric cancer and have not yet experienced a significant decline in *H. pylori* prevalence in any age group. Even within the USA, a region with low gastric cancer burden, specific ethnic/racial groups and indigenous persons in the country experience a disproportionate burden of disease. Immigration effect and poverty may be contributing social factors to gastric cancer disparities across the world and within individual countries, but this needs to be understood more fully. Finally, primary and secondary prevention efforts among high-risk groups warrant consideration in the USA given the relative success of these interventions observed in East Asia.

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David Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *H. pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies.

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Key Points

(1) Gastric cancer incidence has declined worldwide but remains the fifth cause of cancer and the third cause of cancer deaths globally. However, there are significant differences in its incidence across the world and within ethnic/racial subgroups in developed countries.

(2) East Asia currently carries the highest gastric cancer burden; however, the risk is declining as the societies become westernized. Latin America is an outlier in that it has intermediate rates of gastric cancer but a decline is not predicted given the persistence of risk factors.

(3) Reductions in gastric cancer are largely the consequence of improvements in sanitation, food preservation, and availability as well as a decline in *H. pylori* infections. Reduction in tobacco smoking remains an important modifiable risk factor in gastric and other cancers.

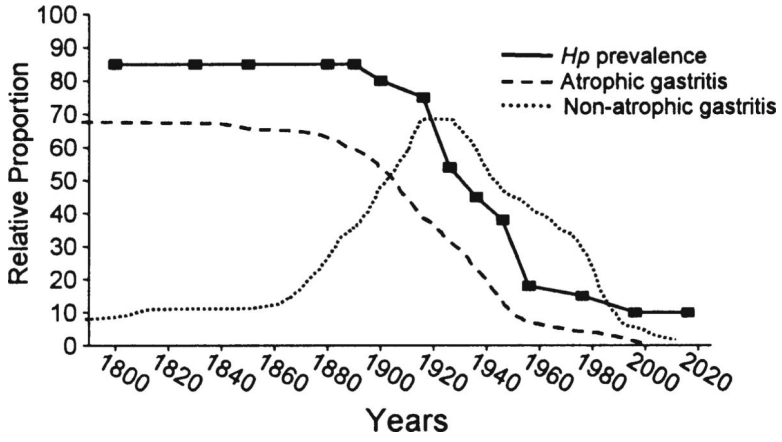

Fig. 1.

Changes in *H. pylori* prevalence among an asymptomatic White US population. Data from reference [71] for the birth cohorts born between 1916 and 1976, the data before and after, are estimated. The plot illustrates that until the late 1800s, most adults have *H. pylori* infection and atrophic gastritis. Late in the 1800s, the pattern of gastritis and the most common *H. pylori*-related disease changed from atrophic gastritis, gastric ulcer, and gastric cancer to a non-atrophic duodenal ulcer pattern and then with further decline in *H. pylori* prevalence, all *H. pylori*-related diseases tended to disappear

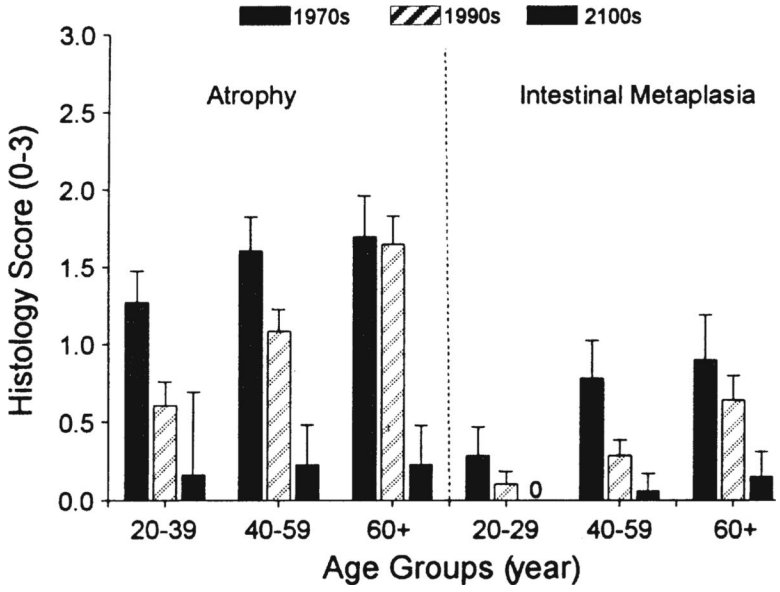

Fig. 2.

Mean ± 95% confidence intervals of atrophy and intestinal metaplasia scores of corpus mucosal biopsies in *H. pylori*-positive patients according to age group. Both mucosal atrophy and metaplasia in the corpus significantly decreased in time period setting in all age group and comparisons between all subgroups were significant ($p < 0.05$). Note the age-related increase between groups but the time-related decrease within groups. From reference [63••], with permission from John Wiley and Sons.

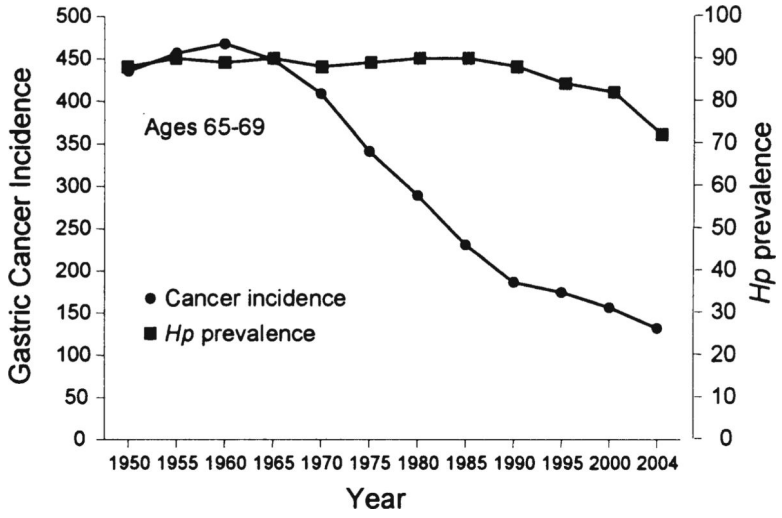

Fig. 3.

Changes in the incidence of gastric cancer and *H. pylori* infection among Japanese men aged 65–69 during the latter half of the twentieth century. Data from reference [64••]. Figure from reference [65•], with permission from Elsevier