Chapter 1.

The global epidemiology of gastric cancer and *Helicobacter pylori*: current and future perspectives for prevention

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Summary

- Gastric cancer remains and will remain a major global public health problem because of a substantial demographic-driven increase in burden, despite the decreasing incidence trends observed in many countries.
- The largest relative increases in the absolute numbers of new cases of gastric cancer and deaths from gastric cancer are predicted for countries with low and medium levels of the Human Development Index.
- The majority of gastric cancer cases are attributable to chronic infection with *H. pylori*, which is highly preventable. This highlights the importance of coordinated global action for prevention of *H. pylori* infection, to reduce suffering and death from gastric cancer.

1.1 Introduction

This chapter examines the global landscape of gastric cancer incidence and mortality in 2022. Overall comparisons of gastric cancer incidence and mortality rates between countries are presented using age-standardized rates (ASRs). This chapter focuses on variations in gastric cancer incidence and mortality rates in countries with different levels of the Human Development Index (HDI) using the databases of recorded data and estimates that are collected and disseminated by IARC. The trends in incidence of gastric cancer over time are presented for selected countries. Where possible, global patterns of incidence rates are examined for the two main subsites of gastric cancer: cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC). CGC, which occurs in the part of the stomach adjoining the gastro-oesophageal junction, and NCGC, which occurs in the distal regions of the stomach, have overlapping and distinct risk factors, which warrant independent investigation. Predictions for the future global burden of these cancers and the preventable cases are made based on the current estimates. Finally, the global patterns of gastric cancer described in this chapter are presented in the context of the known risk factors for gastric cancer, with a focus on *H. pylori* infection and its contribution to the global burden of gastric cancer incidence.

1.2 Data sources and methods

This chapter explores the current patterns and trends of gastric cancer using the recorded trends and estimates hosted at IARC and distributed on the IARC Global Cancer Observatory platform [1]. Estimates of new gastric cancer cases and deaths from gastric cancer in 2022 in 185 countries and territories worldwide were extracted from the GLOBOCAN database. The sources and methods that were used to estimate country-specific incidence and mortality have been documented elsewhere [2]. Incidence and mortality across countries and regions with different HDI levels are described in terms of the numbers of new cases and deaths, as well as the ASRs, so that comparisons across countries can be made. *Cancer Incidence in Five Continents* Volume XII is an IARC publication that uses high-quality incidence data provided by population-based cancer registries [3]. This chapter provides the incidence patterns for the two main subsites of gastric cancer: CGC, which is defined as International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code C16.0, and NCGC, which is defined as ICD-10 codes C16.1–C16.9, whereby cancers with overlapping or undefined topography were considered to be NCGC. In instances in which > 75% of all cases of gastric cancer in a population were coded as "not otherwise specified", which is defined as ICD-10 code C16.9, these were excluded from any subsite analyses. Sex- and age-specific proportions of CGC and NCGC subtypes were calculated for the countries in *Cancer Incidence in Five Continents*, and these proportions were then applied to the total number of estimated gastric cancer cases by 5-year age group, sex, and country in GLOBOCAN 2022. The ASRs of incidence and mortality (per 100 000 person-years) were calculated based on the world standard population [4], sex, and HDI level. Patterns by HDI level were examined to investigate variations in gastric cancer incidence and mortality in terms of the level of resources and societal development of countries. HDI was defined using the predefined four-tier distribution described in the United Nations Development Programme's Human Development Report 2021–2022 [5]. Trends in gastric cancer incidence over time were examined using data from population-based cancer registries of cases diagnosed in 1980–2017 [3, 6, 7]. The numbers of new gastric cancer cases by 2050 were predicted using demographic projections assuming that rates as estimated in 2022 remained stable over the prediction period (2022–2050).

1.3 Global patterns of gastric cancer

Gastric cancer is the fifth most commonly diagnosed cancer and the fifth leading cause of cancer death worldwide, with an age-standardized incidence rate of 9.2 per 100 000 person-years and an age-standardized mortality rate of 6.1 per 100 000 person-years in 2022 [8]. In absolute numbers, an estimated 969 000 new cases of gastric cancer (4.8% of all cancer cases) were diagnosed and 660 000 deaths from gastric cancer (6.8% of all cancer deaths) occurred in 2022 [1].

A wide variation in gastric cancer incidence and mortality rates is observed across world regions (Fig. 1.1). The regions of eastern Asia (male ASR, 23.0 per 100 000 person-years; female ASR, 9.7 per 100 000 person-years; 521 000 new cases combined) and eastern Europe (male ASR, 16.2; female ASR, 7.7; 66 400 new cases combined) have the highest incidence rates. By World Health Organization (WHO) region, the Western Pacific Region has the highest incidence (ASR, 15.2; 543 757 new cases), followed by the European Region (ASR, 8.4; 161 553 new cases), the Eastern Mediterranean Region (ASR, 6.6; 37 781 new cases), the Region of the Americas (ASR, 6.4; 103 924 new cases), the South-East Asia Region (ASR, 4.4; 95 622 new cases), and the African Region (ASR, 4.1; 25 851 new cases) [1].

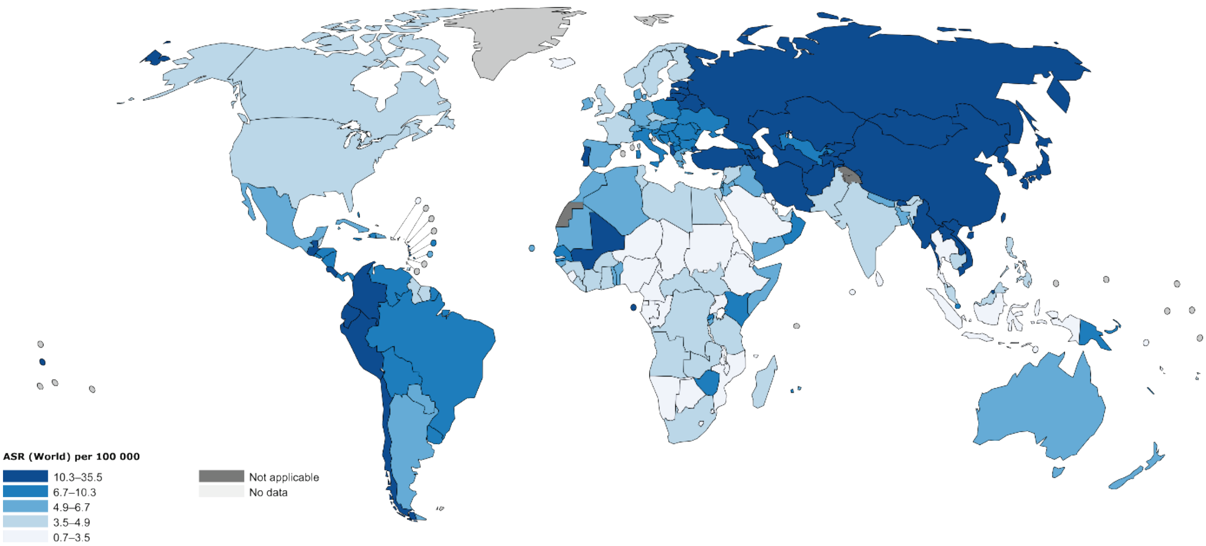


Fig. 1.1. Global incidence of gastric cancer in 2022 by country. ASR, age-standardized rate. Source: Ferlay et al. (2024) [1].

Of the top 25 countries for incidence of gastric cancer worldwide, Mongolia (male ASR, 53.0 per 100 000 person-years; female ASR, 21.9 per 100 000 person-years), Japan (male ASR, 40.9; female ASR, 15.9), and the Republic of Korea (male ASR, 38.4; female ASR, 16.9) have the highest incidence rates in both males and females (Fig. 1.2) [1]. Similar patterns in mortality are observed, with high mortality rates observed in countries with high incidence rates of gastric cancer. Japan and the Republic of Korea are exceptions to this pattern, because the mortality rates are about one quarter of the incidence rates observed in these countries. This is probably due to the introduction of radiographic screening in the 1960s in Japan, which was expanded to a nationwide screening programme in 1983 [9], and the introduction of an endoscopic-focused national screening programme in the Republic of Korea in 2000 [10], which have led to a shift in the stage at diagnosis and markedly improved the survival proportion of this cancer, which generally has a poor prognosis [11, 12].

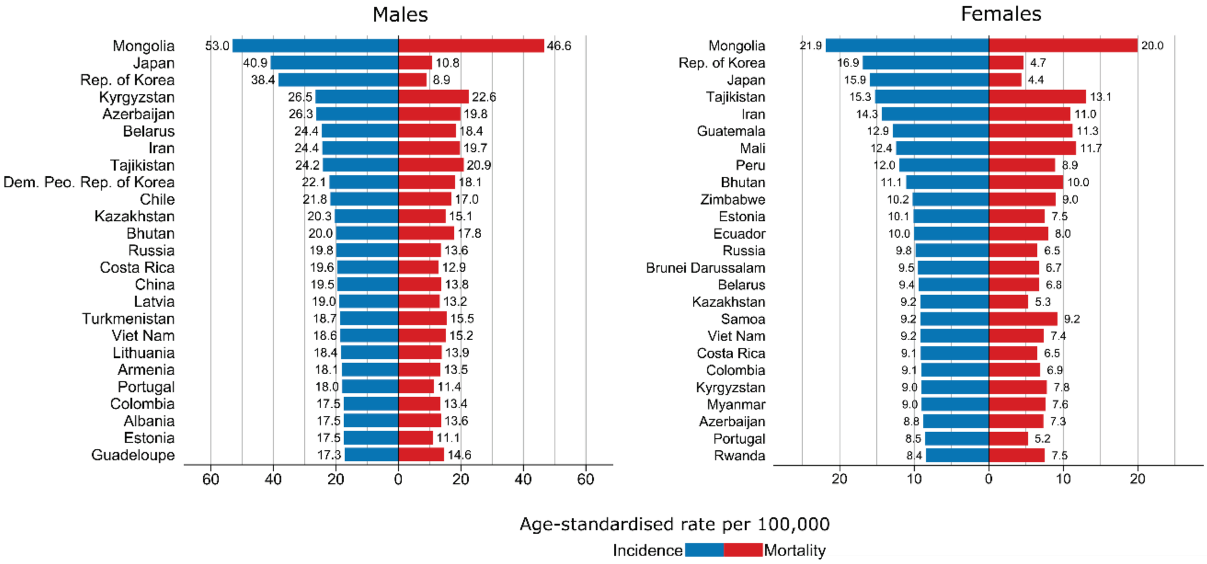


Fig. 1.2. Age-standardized incidence and mortality rates (per 100 000 person-years) for the 25 countries with the highest incidence rates of gastric cancer, from GLOBOCAN 2022. Source: Ferlay et al. (2024) [1].

The risk of gastric cancer varies substantially even within the same region (Fig. 1.3) [1]. Also, certain populations within low-incidence countries have a higher risk of gastric cancer, for example specific ethnic groups (see Chapter 4).

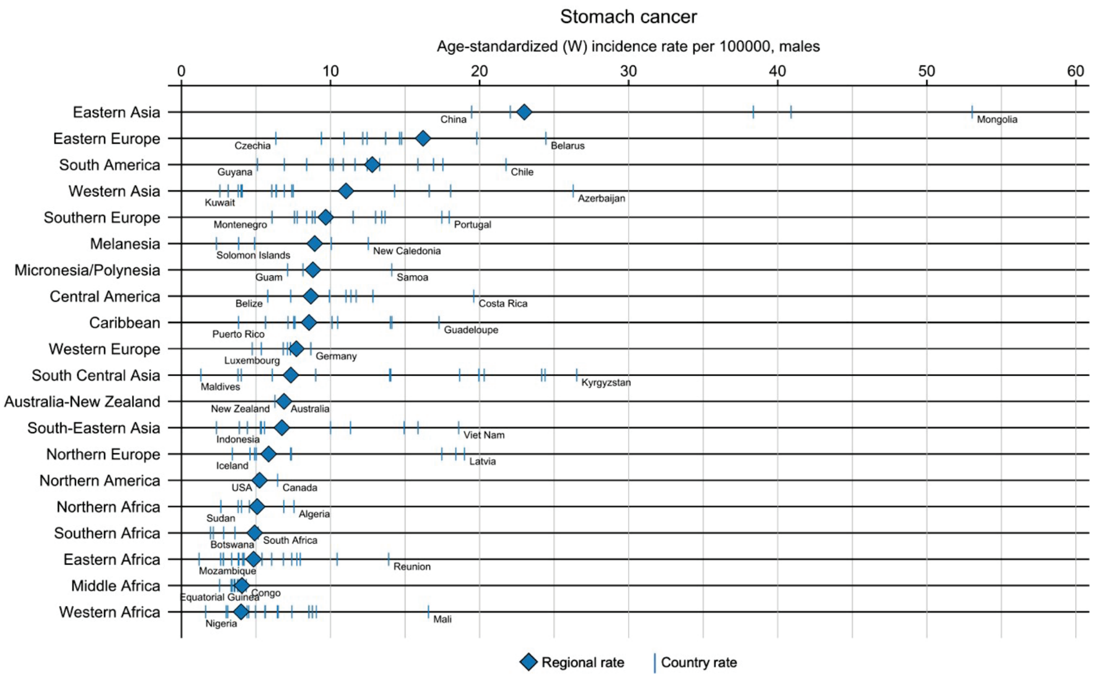


Fig. 1.3. Age-standardized incidence rates (per 100 000 person-years) of gastric cancer, in males, by world region. Source: Ferlay et al. (2024) [1].

Gastric cancer incidence was higher in areas with higher levels of HDI; 830 000 cases (85.7% of all gastric cancer cases) occurred in countries with high or very high HDI, compared with 138 000 cases (14.3% of all cases) in countries with low or medium HDI. This is driven by the high incidence rates in a few countries: the Republic of Korea and Japan in the group with very high HDI and China in the group with high HDI. China, the most populous of the countries with high or very high HDI, accounts for 43% of the cases of gastric cancer in the countries with high and very high HDI (359 000 cases), which is 37% of all gastric cancer cases worldwide. For mortality from gastric cancer, countries with low and medium HDI contribute to an important proportion of deaths from gastric cancer (18.4% of all gastric cancer deaths) relative to their contribution to the global gastric cancer burden (14.3% of all gastric cancer cases). This indicates a need to initiate dialogue to enable more affordable preventive strategies for gastric cancer to be made available in these countries.

1.4 Overview of gastric cancer incidence by subsite (cardia and non-cardia)

NCGC is the most common subtype of gastric cancer (853 000 cases), and this subtype contributes 82% of all gastric cancer cases worldwide, compared with CGC (181 000 cases), which contributes 18% of all cases. NCGC is consistently the more common subtype in all regions worldwide. The highest incidence rates of both subtypes are observed in East Asia (Fig. 1.4) [3]. Although both overlapping and distinct risk factors for the two subtypes have been identified, with much focus on the association of *H. pylori* infection and NCGC, there is increasing evidence for an association of *H. pylori* infection and CGC; about 62% of CGC cases in Asia could be attributable to *H. pylori* infection [14]. Given that the majority of the global NCGC and CGC burden is in East Asia [13], population-based *H. pylori* screen-and-treat strategies may have even larger beneficial effects in these high-risk settings.

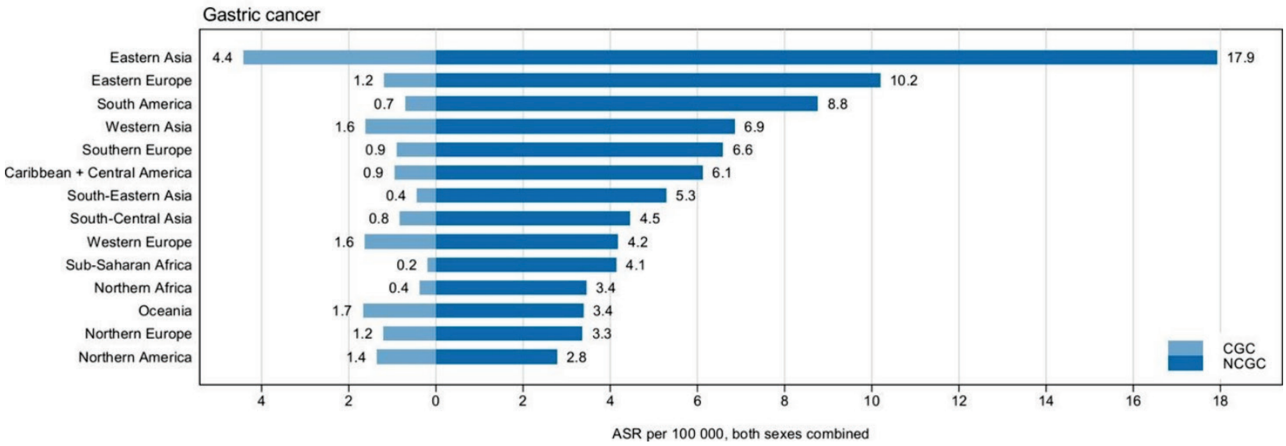


Fig. 1.4. Age-standardized incidence rates (per 100 000 person-years) of gastric cancer for each subsite, cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC), by world region. Source: Reproduced from Arnold et al. (2020) [13], © 2020 with permission from BMJ Publishing Group Ltd.

1.5 Trends in gastric cancer incidence over time

Fig. 1.5 shows the trends in the annual ASR of gastric cancer incidence in the countries for which data are available, and Fig. 1.6 shows the estimated annual percentage change (EAPC) of gastric cancer incidence rates in selected countries for the most recent 10 years (2008–2017). The decreasing prevalence of *H. pylori* infection as well as improved sanitation, changes in diet, and widespread use of antibiotics may have resulted in decreases in the incidence of gastric cancer, predominantly in countries with higher HDI [16]. During the most recent 10 years (2008–2017), gastric cancer incidence rates mostly decreased across countries, with incidence rates decreasing by more than 3% per year in several countries, including Bahrain, Costa Rica, Cyprus, Czechia, Denmark, Malta, Norway, Qatar, the Netherlands, the Republic of Korea, and the United Kingdom (England) [15].

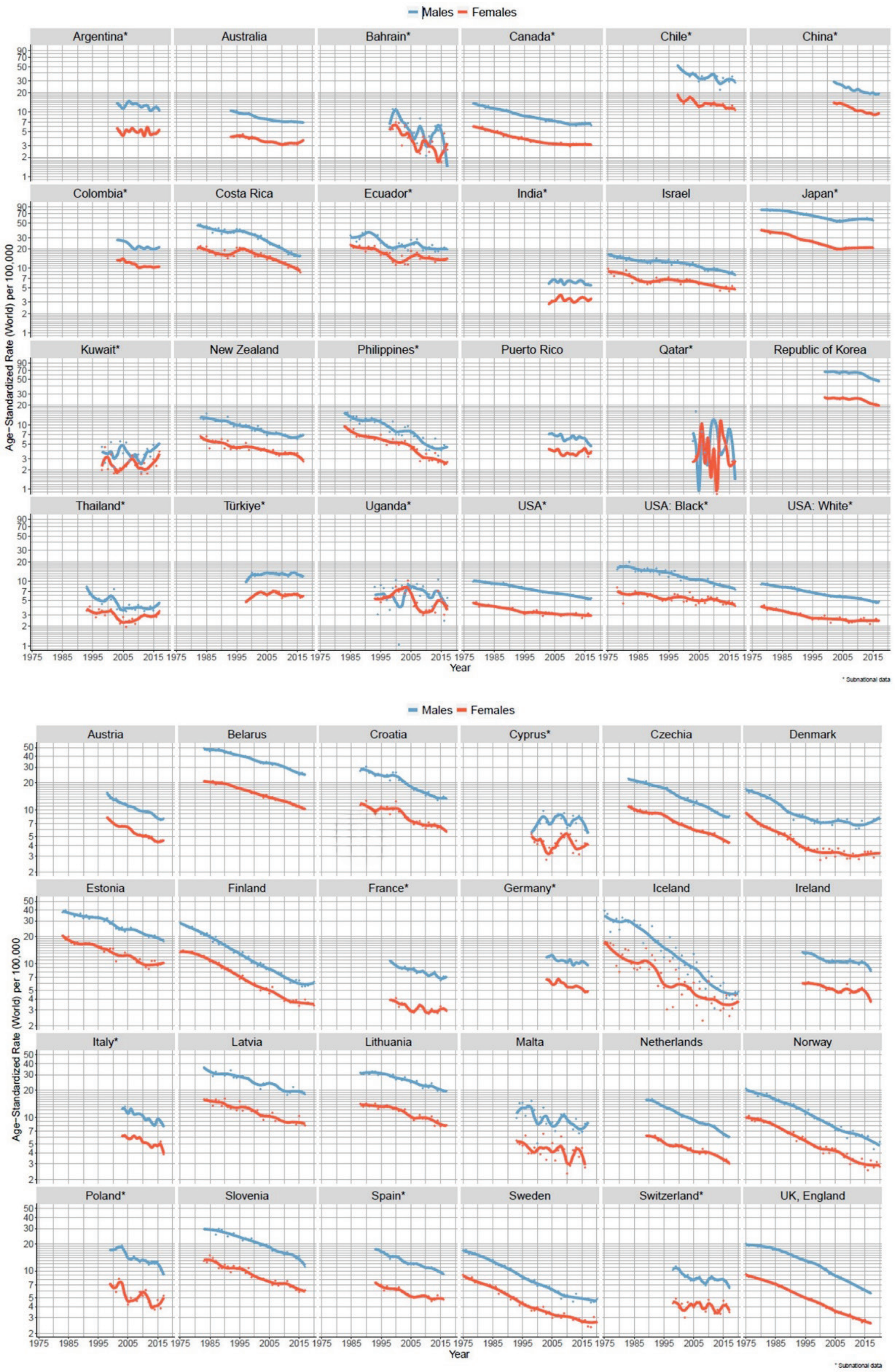


Fig. 1.5. Trends in age-standardized incidence rates (per 100 000 person-years) for gastric cancer in selected countries, 1980–2017. Source: Ervik et al. (2024) [15].

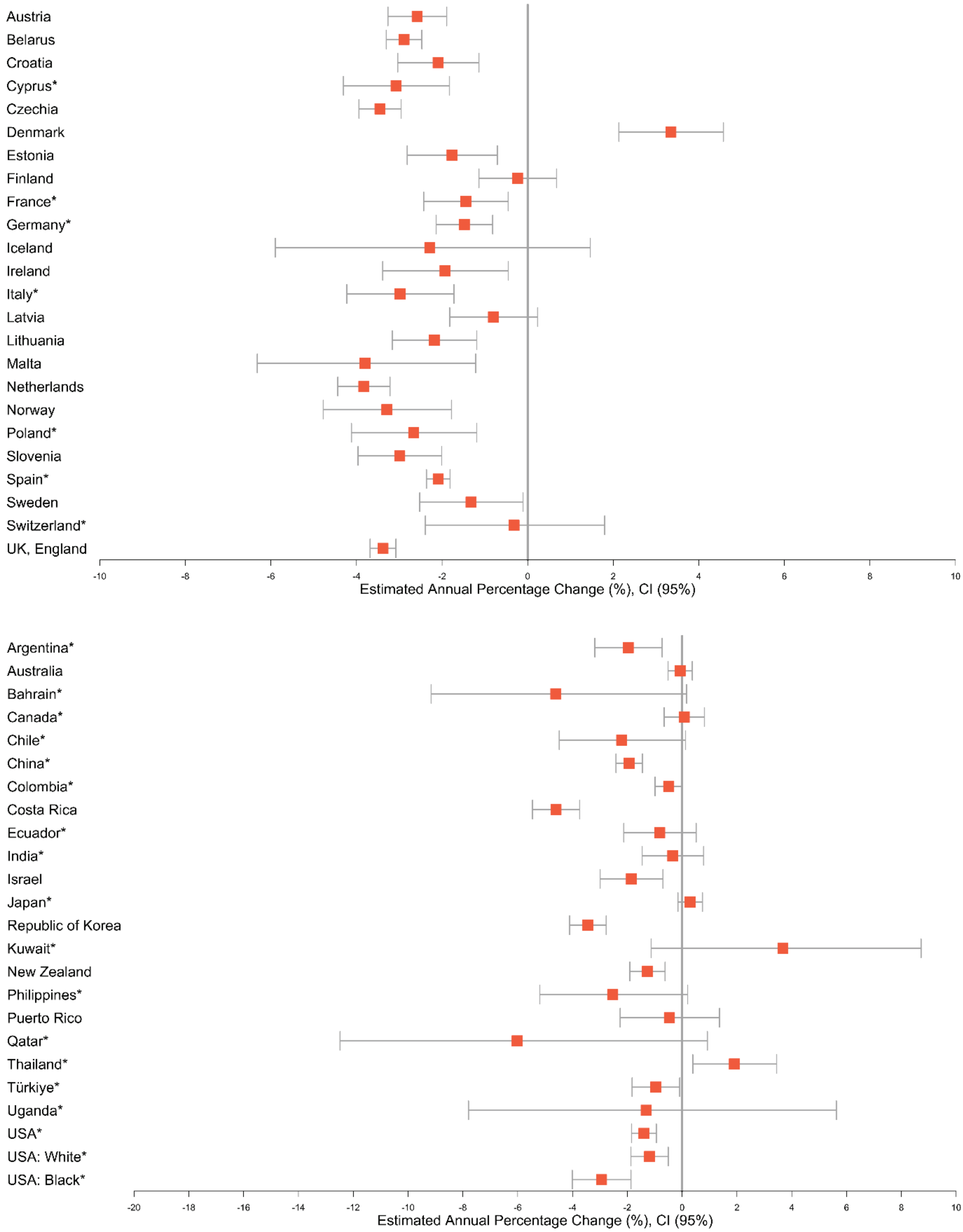
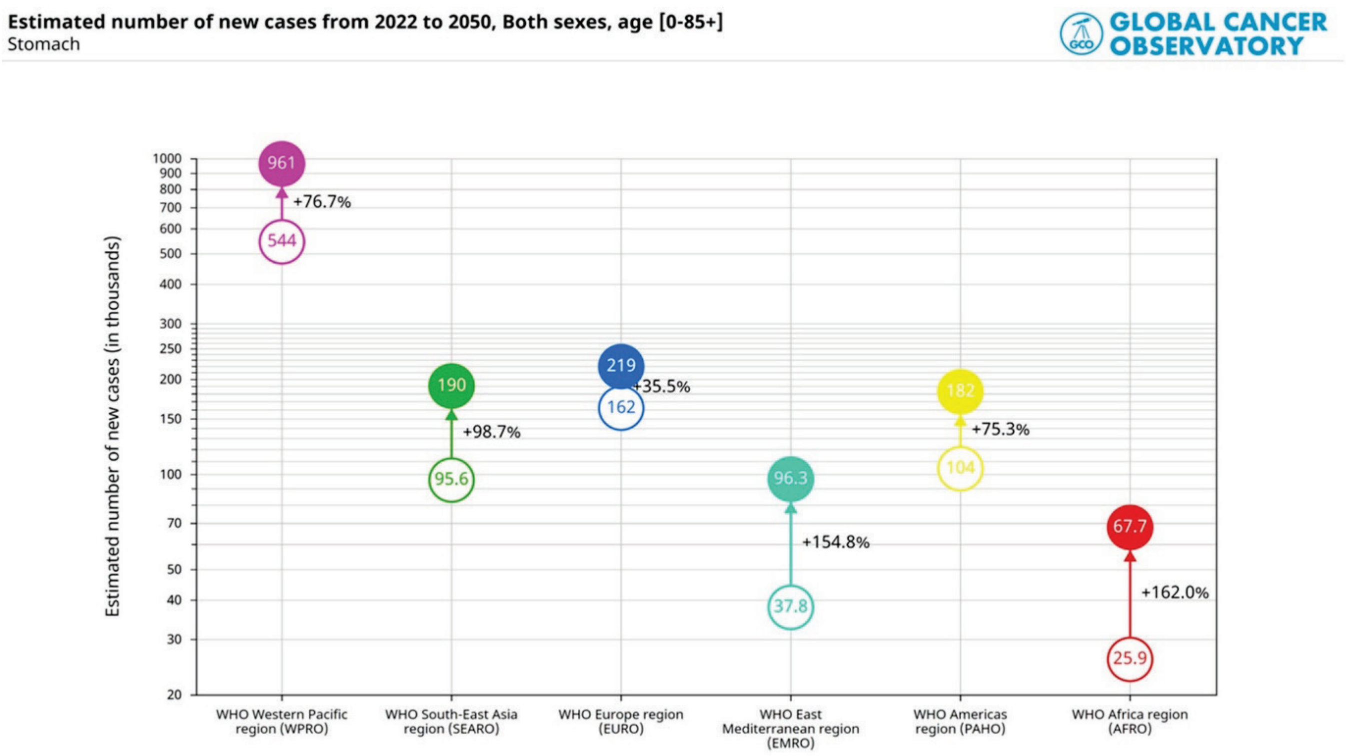


Fig. 1.6. Estimated annual percentage change (EAPC) of gastric cancer incidence rates for the most recent 10 years (2008–2017) in selected countries. CI, confidence interval. Source: Ervik et al. (2024) [15].

Previous studies have noted that the decreasing trends in gastric cancer incidence observed in some countries were more pronounced in older age groups, and an equivalent decrease has not always been seen in younger age groups [17, 18]. In younger populations (aged < 50 years) in 15 of 34 countries with both low and high incidence rates, increases in incidence have been observed [17]. In the same age group, increasing incidence rates of 1.3% per year in 1995–2013 for NCGC in non-Hispanic White Americans were reported using data from a population-based registry in the USA [19]. These increases were especially pronounced for women (EAPC, 2.6%). Although these observations are important, they require careful interpretation, because some of the observed increases may be due to the redistribution of unspecified tumours [13].

1.6 The burden of gastric cancer incidence and mortality by 2050

Although incidence rates of gastric cancer have been generally decreasing in countries, the absolute number of new gastric cancer cases is expected to increase because of demographic changes in populations (i.e. population growth and increasing longevity). Globally, it is predicted that there will be an 87.5% increase in the number of gastric cancer cases, assuming that current rates remain stable, from the 969 000 new cases estimated in 2022 to 1.82 million new cases estimated in 2050 [20]. By WHO region, the Western Pacific Region is expected to have the highest numbers of new cases and deaths in 2050 (961 000 new cases, 646 000 deaths) and the African Region to have the lowest numbers (67 700 new cases, 59 500 deaths). However, the largest relative increases are expected in the African Region, with increases of 162.0% in the number of new cases and 163.9% in the number of deaths (Fig. 1.7). The absolute number of new cases predicted in 2050 will be highest in countries with higher HDI (1.4 million cases) compared with countries with lower HDI (306 190 cases). The largest relative increases in new cases are predicted to occur in countries with low and medium HDI, with an increase of 153.2% in countries with low HDI and an increase of 114.0% in countries with medium HDI (Fig. 1.8A). The number of deaths from gastric cancer is predicted to increase by 94.7% by 2050, from the 660 000 deaths estimated in 2022 to 1.29 million deaths estimated in 2050. The largest relative increases in gastric cancer deaths are predicted to occur in countries with lower HDI, with an increase of 154.2% in countries with low HDI and an increase of 116.2% in countries with medium HDI, contributing about 271 195 deaths in 2050 (Fig. 1.8B).



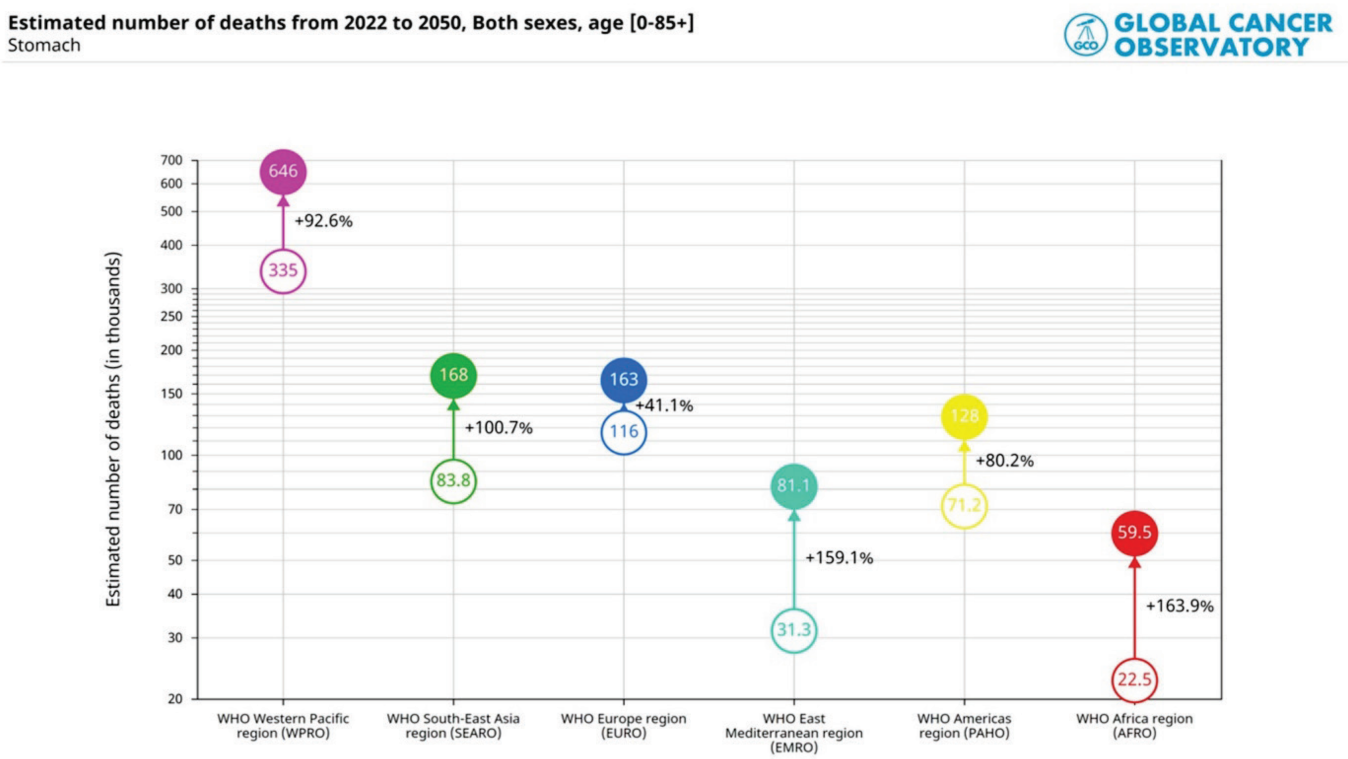
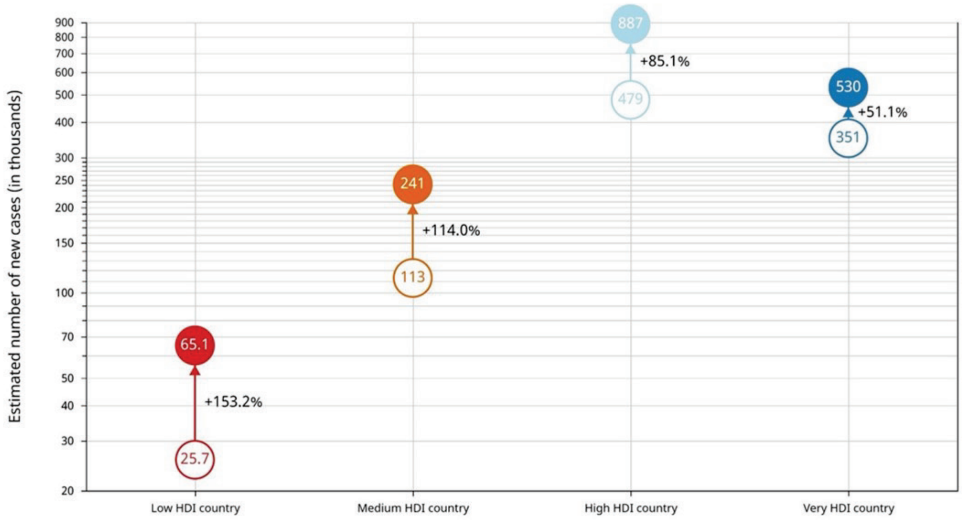


Fig. 1.7. Estimated number of (top) new cases of gastric cancer and (bottom) deaths from gastric cancer, 2022 to 2050, by WHO region. Source: Ferlay et al. (2024) [20].

These predictions are based on the assumption that current rates will remain stable. In many countries, a decrease in gastric cancer incidence and mortality has been observed, with an annual percentage decrease of ≥ 3% in many countries. However, even if the 3% annual decrease is assumed to be observed globally, there will still be a 50% increase in the predicted numbers of gastric cancer cases by 2050, with an estimated 1.45 million new cases.



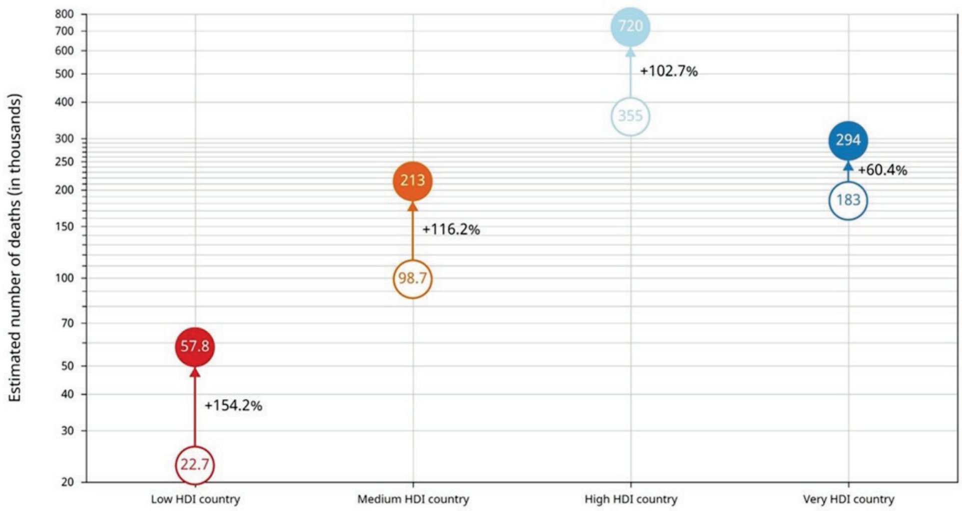


Fig. 1.8. Estimated number of (top) new cases of gastric cancer and (bottom) deaths from gastric cancer, 2022 to 2050, by level of Human Development Index (HDI). Source: Ferlay et al. (2024) [20].

1.7 Lifetime estimates of expected and preventable gastric cancers

IARC estimated the numbers of expected and preventable gastric cancer cases for people born between 2008 and 2017 globally [21]. Based on data from GLOBOCAN 2022, the lifetime global burden of gastric cancer in these birth cohorts is expected to reach 15.6 million cases in the absence of any additional preventive efforts. By applying the reference-standard attributable fractions given in Table 1.1, it was estimated that about 76% of the gastric cancer burden in these birth cohorts was attributable to *H. pylori* infection and therefore was theoretically preventable.

Table 1.1. Proportions of non-cardia gastric cancer (NCGC) and cardia gastric cancer (CGC) attributable to *H. pylori* infection, by world region

Gastric cancer type and country or region	Gastric cancer cases		Controls		Odds ratio (95% CI)	Attributable fraction (%) (95% CI)
	Number	*H. pylori* positivity (%)	Number	*H. pylori* positivity (%)		
NCGC in China	500	94	500	76	5.9 (3.3–10.8)	78 (65–86)
CGC in China	500	92	500	76	3.1 (1.5–6.1)	62 (32–77)
NCGC in Australia, Europe, USA	230	93	803	61	15.0 (7.9–28.6)	87 (82–90)[a]

CI, confidence interval.
[a] Considered to be representative of the world outside China.
Source: Adapted from Gu et al. (2023) [22]. Reprinted by permission of Taylor & Francis Ltd (http://www.tandfonline.com).

The results showed Asia as the main contributor of the total estimated lifetime burden of gastric cancer in these birth cohorts, as expected, but also highlighted Africa and the Americas as the second most important regions to target for gastric cancer prevention in the future. The impact of demographic change is substantial, and it is expected that the gastric cancer burden will increase 4–8-fold across a lifetime in an average single birth cohort in Africa, mostly in sub-Saharan Africa, compared with the total number of cases estimated for the region in 2022. Africa is considered as an area of low gastric cancer incidence, despite having a very high prevalence of *H. pylori* infection; this is often referred to as the African enigma [23]. The data suggest that this may be a historical artefact of population structure, and indicate the need for local policy discussions and cancer control planning in the region to prevent increases in the numbers of gastric cancer cases linked to the substantial demographic changes expected in the future in Africa.

1.8 Risk factors for gastric cancer

The main risk factor for gastric cancer is chronic infection with *H. pylori*, which is classified by IARC as carcinogenic to humans (Group 1) [24, 25]. In 2021, the National Toxicology Program's 15th Report on Carcinogens added chronic infection with *H. pylori* to its list of substances that are known or reasonably anticipated to cause cancer in humans [26].

Chronic infection with *H. pylori* is responsible for the large majority of NCGC [22, 27, 28] (see Section 1.9). *H. pylori* infection causes a sequence of changes in the gastric mucosa: gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia, which eventually leads to the development of cancer [29]. The global prevalence of *H. pylori* infection was 48% in an analysis of data from 62 countries [30], with substantial geographical variations. For example, the prevalence of *H. pylori* infection was highest in Africa, with a pooled estimate of 70%, and Oceania had the lowest prevalence (24%) [30]. These regional prevalence estimates indicated that 4.4 billion individuals worldwide had *H. pylori* infection in 2015 [30]. A recent review over various time periods showed that the crude global prevalence of *H. pylori* infection was 44% in adults and 35% in children and adolescents in 2015–2022 [31]. In adults, the prevalence of *H. pylori* infection has decreased by 16% during the past 30 years, but a corresponding decrease has not been observed in children and adolescents [31]. However, the reviews of the prevalence of *H. pylori* infection worldwide found substantial heterogeneity between studies, for example in terms of study design, diagnostic methods for *H. pylori* infection, population subgroups, and population age [31, 32].

In addition to *H. pylori* infection, the role of Epstein–Barr virus infection is implicated in about 10% of cases of gastric cancer [33, 34], but it is not known whether Epstein–Barr virus is a risk factor for gastric cancer that is independent of *H. pylori* infection, or whether it is a co-factor. Smoking and familial predisposition are also associated with increased risk of gastric cancer. Other modifiable risk factors that are linked to increased risk of gastric cancer include being overweight or obese (for CGC), consuming alcohol (≥ 3 alcoholic drinks per day), and consuming foods that have been preserved by salting, including pickled vegetables and salted or dried fish [35]. The interactive role of risk factors has also been investigated; for example, in Asian populations, the presence of *H. pylori* infection along with a high dietary salt intake was associated with a higher risk of gastric cancer compared with the absence of infection and a low salt intake [36].

An increased risk of gastric cancer was also found to be associated with the consumption of red meat and processed meat, and with the endogenous formation of nitrosamines; however, this association was observed only in people with *H. pylori* infection [37]. These results are based on small, mainly case–control studies; larger, prospective cohort studies are needed to confirm these findings.

1.9 Fraction of gastric cancer attributable to *H. pylori* infection

Accurate quantification of the fraction of gastric cancer attributable to *H. pylori* infection is highly dependent on obtaining accurate estimates of relative risk, and recent improvements in study designs have increased the accuracy of these estimates [22, 27]. First, *H. pylori* antibodies can spontaneously disappear during the carcinogenic process and thus require assessment in blood long before the development of gastric cancer, so that relative risks are higher in prospective study designs than in classic case–control studies. Second, the use of more sensitive immunoblotting, rather than the older enzyme-linked immunosorbent assay (ELISA) technology, has further increased the estimates of relative risk (and hence the attributable fraction) [27].

The significant relative risks for *H. pylori* infection were first established for NCGC, predominantly in studies in Australia, Europe, and the USA [25, 27, 38]. More recently, a large prospective study in China found significant associations not only for NCGC but also for CGC [14].

Based on relative risks and prevalence of *H. pylori* infection in gastric cancer cases from reference-standard studies (i.e. those testing for *H. pylori* by immunoblotting in samples > 10 years before gastric cancer diagnosis), the attributable fractions for cases of NCGC were recently estimated to be 87% in the low-risk settings for gastric cancer of Australia, Europe, and the USA and 78% in the high-risk setting for gastric cancer of China [22]. Furthermore, 62% of cases of CGC in China were also estimated to be attributable to *H. pylori* infection. The apparent discrepancy in the etiological role of *H. pylori* infection in CGC in China versus in Australia, Europe, and the USA, where earlier studies found no, or even inverse, associations of *H. pylori* infection and CGC [22], may be due to differences in the anatomical location of cancer, with CGC in Australia, Europe, and the USA tending to involve the distal oesophagus and CGC in East Asia involving the proximal stomach. Given the substantial role of *H. pylori* infection in CGC in China, which is the region that accounts for the majority of gastric cancer cases worldwide, any beneficial effects of *H. pylori* eradication will extend beyond NCGC as a target for gastric cancer prevention.

Given the very high seroprevalence of *H. pylori* infection in gastric cancer cases, the attributable fractions assessed in these reference-standard studies remain highly sensitive to the presence of only a few false-negative results. Thus, even these current best estimates may still be underestimates, and the true attributable fractions for *H. pylori* infection, particularly for NCGC, could approach 100% if *H. pylori* exposure could be measured perfectly.

1.10 Global burden of *H. pylori*-attributable cancer

By extrapolating the subsite- and region-specific attributable fractions given in Table 1.1 to the worldwide gastric cancer burden, IARC estimated that 850 000 (4.3%) of all cancers diagnosed worldwide in 2020 were directly attributable to *H. pylori* infection; of these *H. pylori*-attributable cancers, NCGC contributed 94%, CGC contributed 4%, and gastric lymphoma contributed 2%. This cancer burden is higher than that of any other cancer-causing infection, including human papillomavirus (HPV) (730 000 attributable cases) and hepatitis B virus and hepatitis C virus combined (550 000 attributable cases). For these infections, WHO launched the Cervical Cancer Elimination Initiative (in 2020) [39] and the hepatitis elimination initiative (in 2016) [40]; this highlights the need to prioritize a global *H. pylori* prevention strategy.

In line with the geographical disparities in gastric cancer risk and burden discussed earlier, the majority (62%) of *H. pylori*-attributable cancers are diagnosed in East Asia, where the corresponding incidence rates are the highest in the world [28] (Fig. 1.9).

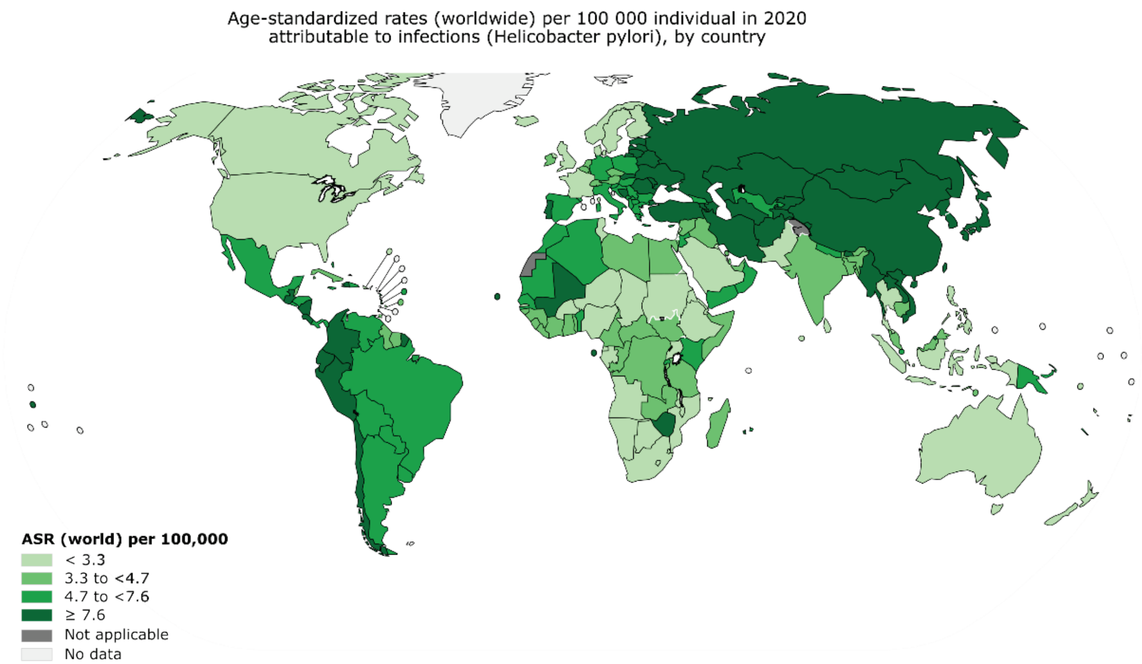


Fig. 1.9. Age-standardized incidence rate of *H. pylori*-attributable gastric cancer. ASR, age-standardized rate. Source: Reproduced from de Martel et al. (2019) [28]. © 2019 International Agency for Research on Cancer; licensee Elsevier.

1.11 Conclusions

These findings highlight that gastric cancer will remain a major global public health problem, with the projected demographic-driven increase in burden in low-risk areas in addition to the continuing burden in high-risk areas. Furthermore, these data highlight the potential public health impact of population-based *H. pylori* screen-and-treat approaches, which are evidence-based, relatively simple and effective, safe, and inexpensive to implement compared with cancer treatment, to reduce the *H. pylori*-attributable burden of gastric cancer.

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