

ORIGINAL ARTICLE

Global trends and epidemiological shifts in gastrointestinal cancers: insights from the past four decades

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Abstract

Background: The epidemiological profiles of gastrointestinal (GI) cancers vary across countries and over time, largely reflecting variations in risk factors and screening practices. We aimed to provide an overview of the current global burden of the five major types of GI cancers and conduct an updated evaluation of the long-term trends of GI cancers.

Methods: The updated numbers of new cases and deaths, and age-standardized rates (ASR), of the five GI cancers for 185 countries were sourced from the GLOBOCAN 2022, and presented by cancer site, continent, and human development index (HDI). For 43 countries, annual incidence and mortality data were obtained from the Cancer Incidence in Five Continents Plus and World Health Organization mortality databases, supplemented by the mortality data from the Disease Surveillance Points system for China. We compared the long-term trends of ASRs across countries since 1980, and estimated average annual percent changes (AAPCs) for the recent period 2003-2017.

Results: In 2022, there were 4,783,391 new cases and 3,235,719 deaths from the five GI cancers, accounting for 23.9% and 33.2% of all new cancer cases and deaths worldwide, respectively. Cancers of oesophagus, stomach, and liver were more common in Asian and high HDI countries, and colorectal and pancreatic cancer in western and very high HDI countries. Downward trends were observed in almost all countries for gastric cancer and most countries for oesophageal cancer. For colorectal cancer, the most favorable and unfavorable trends were found in 10 and 19 countries respectively. The largest decreases in liver cancer burden were mainly in eastern and southeastern Asia, while increases were seen in North America, Oceania, and Northern Europe, with AAPCs of 3%~7% for incidence and 2%~9% for mortality during 2003-2017. Half

List of abbreviations: GI, gastrointestinal; H. pylori, *Helicobacter pylori*; HBV, hepatitis B virus; HCV, hepatitis C virus; ASR, age-standardized rate; MIR, mortality-to-incidence ratio; HDI, human development index; CI5, Cancer Incidence in Five Continents; WHO, World Health Organization; DSPs, Disease Surveillance Points system; ICD-10, International Classification of Diseases 10th revision; AAPC, average annual percent change; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; NAFLD, non-alcoholic fatty liver disease.

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of the included countries showed increases in pancreatic cancer burden, with the largest AAPCs in Cyprus, Thailand, India, Türkiye, France, and Belarus for incidence, and Türkiye, Thailand, and China for mortality.

Conclusions: Deviating patterns were found for GI cancers worldwide. Multi-setting studies might provide insights into the underlying etiologies of these cancers, and identify areas where urgent cancer control strategies are needed.

KEYWORDS

colorectal cancer, epidemiology, gastric cancer, gastrointestinal cancer, global burden, liver cancer, oesophageal cancer, pancreatic cancer, time trend

1 | BACKGROUND

Gastrointestinal (GI) cancers refer to cancers that affect the digestive tract and other abdominal organs. The major types of GI cancers include cancers of oesophagus, stomach, colon and rectum, liver, and pancreas, each of which is estimated to have caused over 500,000 cases in 2022 [1, 2]. GI cancers share several common modifiable risk factors, such as smoking, alcohol consumption, obesity, unhealthy diet, and socioeconomic status, although the direction and magnitude of the effects vary by cancer site and subtype [3–6]. They also have distinct strong risk factors, such as *Helicobacter pylori* (*H. pylori*) for gastric cancer, and hepatitis B virus (HBV) and hepatitis C virus (HCV) for liver cancer [7].

Besides the potential role of prevention of GI cancers by reducing exposure to risk factors, early detection is also associated with lower death risk of several types of GI cancers, notably in high-risk areas and among high-risk populations [8–10]. However, countries vary greatly in whether screening programs are implemented, screening types (organized or opportunistic), screening strategies, participation rates, etc [7, 11, 12]. This can further reshape the epidemiological profiles of GI cancers. Similarities and differences in geographical and temporal variations in incidence and mortality rates across GI cancer types may shed light on the effect of past primary and secondary prevention programs, and identify populations where etiological studies and cancer control actions are needed in the future.

In a previous study, the evolving trends of the five major GI cancers were assessed in 26 countries (with incidence data up to 2012) [7]. With the rapid advances in the field, an updated evaluation of the global burden and time trends of GI cancers is crucial. In this study, we provided an overview of the current burden of GI cancers based on the latest estimates, and revealed their temporal patterns based on continuous high-quality population-based data from 43 countries distributed across six continents.

2 | MATERIALS AND METHODS

We obtained incidence and mortality data for the five major types of GI cancers in 2022 from the GLOBOCAN 2022 online database [13]. GLOBOCAN presents estimates of the burden of 36 cancer sites in 185 countries or territories [1]. The data sources and hierarchy of methods used for each country have been documented in detail elsewhere [13, 14]. Briefly, the national cancer estimates in 2022 are based on the best available cancer incidence and mortality data within each country, and their validity depends on the representativeness and quality of the data sources. Multiple methods are used, prioritizing short-term predictions where applicable. We present results based on the estimated new cases and deaths for the five GI cancers, their rankings across all cancer sites, and the age-standardized rates (ASRs) using the world standard population [15]. We also calculated the mortality-to-incidence ratios (MIRs) by dividing the ASRs of mortality by those of incidence. Results are shown by cancer site for each country, and are also aggregated by continent and human development index (HDI), the latter of which can be categorized into four levels: low (< 0.550), medium (0.550 – 0.699), high (0.700 – 0.799), and very high (≥ 0.800).

We obtained the annual incidence data of the five main GI cancers during 1980–2017, by 5-year age group and sex, from the Cancer Incidence in Five Continents (CI5) Plus [6]. Only registries that have passed a detailed quality assessment are published in the CI5 series, and the inclusion in the last three volumes is an indication of high quality over time. Therefore, we excluded cancer registries with less than 15 recent consecutive years of data. For the analysis of incidence trends, we finally selected 97 registries from 43 countries. Supplementary Table S1 shows the registries included for each country and their national coverage. When only regional registries were available, data were aggregated to obtain a proxy of the national estimates [16].

We retrieved the annual mortality data since 1980 from the World Health Organization (WHO) [17]. For countries in the Americas, the Philippines, Bahrain, and Thailand, the United Nations population estimates [18] were also utilized, due to the unavailability of population data for most years in the WHO database. Data quality, measured by completeness and proportion of ill-defined or non-specific causes, is high or medium (> 60%) in all studied countries except for Qatar (44%) [19]. For China, deaths and populations by 5-year age groups, sex, and cancer site, were extracted from the annual reports of the Disease Surveillance Points system (DSPs) between 2004 and 2021 [20]. The DSPs was established in 1990 and since 2004, the system was expanded to 161 sites, covering over 70 million population. In 2013, the system was combined with the Ministry of Health's vital registration system to cover 24.3% of the national population [21].

The five primary GI cancers were defined by using the International Classification of Diseases 10th revision (ICD-10) codes: esophagus (C15), stomach (C16), colorectum (C18-21), liver and intrahepatic bile ducts (C22, liver cancer for short), and pancreas (C25). We estimated annual ASRs of incidence and mortality for all ages by sex and cancer site using direct age standardization, with the world population as a reference [15]. Those aged 75 years and above were aggregated because the oldest age groups were combined in population counts in several low- and middle-income countries. We plotted the annual ASRs against years since 1980 whenever data were available. To enable direct quantitative comparisons across countries, we further selected the recent period of incidence data (2003-2017), when data were available for all countries, and calculated the average annual percent changes (AAPCs) of both incidence and mortality. The formula is $100 \times (e^{\beta} - 1)$, where β is the regression coefficient in the generalized linear regression models between $\ln$ natural logarithm of ASR and year, with a Gaussian distribution and identity link function [22]. All analyses were conducted in the R program (version 4.0.3).

3 | RESULTS

3.1 | Global burden of the main GI cancers and international variations

In 2022, there were 4,783,391 new cases and 3,235,719 deaths from the five major GI cancers, accounting for 23.9% and 33.2% of all new cancer cases and deaths worldwide, respectively (Figure 1). Colorectal cancer stood out as the most common GI cancer type, with an estimated 1,926,425 new cases and 904,019 deaths, corresponding to ASRs of 18.4 and 8.1 per 100,000, respectively. The other GI cancer

types combined accounted for 14.3% and 23.9% of all new cancer cases and deaths. The MIRs for the five cancer sites were 0.44 (colorectum), 0.66 (stomach), 0.86 (oesophagus and liver), and 0.90 (pancreas). The largest variations in the MIRs were observed for colorectal and gastric cancer, ranging from 0.30 and 0.41 in Northern America to 0.67 and 0.87 in Africa, and from 0.37 and 0.48 in very high HDI countries to 0.70 and 0.89 in low HDI countries. Cancers of oesophagus, liver, and pancreas showed smaller variations in MIRs, but the absolute values of ASRs differed by continent and HDI level (Supplementary Table S2).

Cancers of oesophagus, stomach, and liver are similar in the distribution of cases and deaths across continents and levels of human development, with around 70% of cases and deaths occurring in Asia, followed by Europe, Latin America and the Caribbean, and Africa. High HDI countries have higher proportions of cases and deaths, and ASRs, of these three cancer types (Figure 2; Supplementary Table S2). Opposite patterns were seen for colorectal and pancreatic cancer, with Europe, North America, and Oceania having higher ASRs for both incidence and mortality. Around half of all new cases of colorectal and pancreatic cancer occurred in very high HDI countries.

GI cancers were the most common cancers in 27 countries and the leading causes of cancer deaths in 36 countries in 2022. Colorectal cancer ranked first in cancer cases in 16 countries, notably in several Eastern European countries. Liver cancer and gastric cancer were the most common cause of cancer-related deaths in 18 and 12 countries, respectively. Oesophageal cancer ranked first in both cases and deaths in Bangladesh (Figure 3). The ASRs of incidence per 100,000 of all five GI cancers varied greatly across countries, ranging from 0 to 18 for oesophageal cancer, 1-35 for gastric cancer, 0-48 for colorectal cancer, 1-96 for liver cancer, and 1-11 for pancreatic cancer (Supplementary Figure S1). In general, cancers of oesophagus, stomach, and liver cancer are similar in geographical distribution, but with notable exceptions, such as the high risk of oesophageal cancer in southern and eastern Africa, gastric cancer in the western coast of South America, and liver cancer in several southeastern Asian countries.

3.2 | Temporal trends of GI cancer incidence and mortality

Figure 4 and Supplementary Table S3 show the incidence and mortality trends of ASRs for oesophageal cancer in men. The time trends of mortality were closely aligned with those of incidence for most countries, except for Japan, the Netherlands, the UK, Denmark, Norway, and Germany, where increasing incidence was accompanied by downward or stable mortality since the 2000s. For

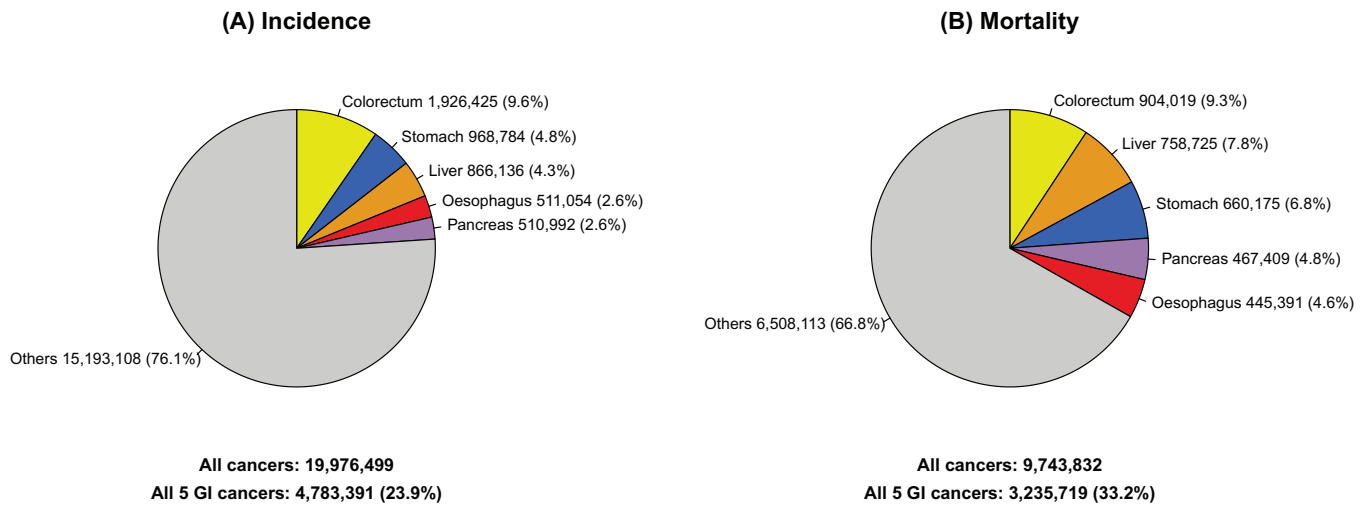


FIGURE 1 Numbers and proportions of new cases and deaths for the five major GI cancers in 2022. Abbreviations: GI, gastrointestinal.

instance, the annual percent changes in Japan were 0.81% (95% confidence interval [CI]: 0.39%, 1.23%) for incidence but -2.52% (95% CI: -2.78%, -2.27%) for mortality during 2003-2017. The majority of countries manifested decreasing trends or continuously low levels in both incidence and mortality rates throughout the study period. Slight increases since the 1980s were observed in some Eastern European countries, Thailand, and Uganda, with the annual percent increases in incidence ranging from 0.72% to 3.94%. The patterns in women were generally similar, although with much lower rates (Supplementary Figure S2; Supplementary Table S4).

For gastric cancer, consistent declines in both incidence and mortality were observed for almost all countries in both sexes (Figure 5; Supplementary Figure S3). The largest decrease in mortality was found in the Republic of Korea, from 58 and 25 per 100,000 women and men in 1985 to 9 and 4 per 100,000 in 2021. Similar favorable trends were also observed in other countries with historically high rates, such as Japan, Chile, and Costa Rica. A slight increase was found in Thailand, where age-standardized mortality increased annually by 1.68% (95% CI: 0.44%, 2.93%) in men and 2.75% (95% CI: 1.58%, 3.93%) in women during 2003-2017, although the ASRs were below 2.3 per 100,000 men and 1.7 per 100,000 women throughout the study period (Supplementary Tables S3-S4).

Four distinct patterns can be seen in the temporal variations for colorectal cancer (Figure 6; Supplementary Figure S4). In 19 countries, incidence rates increased over time, accompanied by increasing or stable mortality rates. The second pattern was contrary trend between incidence and mortality, which were notably seen in Denmark, Norway, the Netherlands, and Japan. The third pattern was an inverted-U incidence curve, peaking at around 2000/2010, which was represented by Slovenia, the Czech

Republic, and the Republic of Korea. The most favorable pattern, with continuous downward incidence and mortality, was observed in 10 countries, all located in North America, Oceania, and Europe. The age-standardized rates decreased annually by 1%~3% for incidence and 2%~3% for mortality during 2003-2017.

Figures 7 and Supplementary Figure S5 present the results for liver cancer. Declines in liver cancer burden were mainly observed in 11 countries, notably in Eastern Asia. Japan, the Republic of Korea, and China had the fastest decreases in incidence (-4%~2%) and mortality (-5%~3%) for both sexes. Unfavorable trends were found in most other countries, especially in countries of North America, Oceania, and Northern Europe, with AAPCs of 3%~7% for incidence and 2%~9% for mortality, starting from very low rates (< 4 per 100,000).

In Figures 8 and Supplementary Figure S6, increases in rates of pancreatic cancer can be seen in 21 countries, with a generally faster growth in incidence than mortality. During 2003-2017, the largest relative changes in incidence for both men and women were found in Cyprus (AAPCs: 3.46% in men and 5.19% in women), Thailand (4.05% and 2.61%), India (2.85% and 4.18%), Türkiye (2.37% and 3.02%), France (2.00% and 3.49%), and Belarus (2.30% and 2.27%). The highest AAPCs for mortality were observed in Türkiye, Thailand, and China, increasing by 2%~3% each year. In the remaining countries, the rates were relatively more stable over time.

4 | DISCUSSION

Based on high-quality population-based registries worldwide, this study reveals the long-term patterns of main GI cancers, and provides a comprehensive overview of

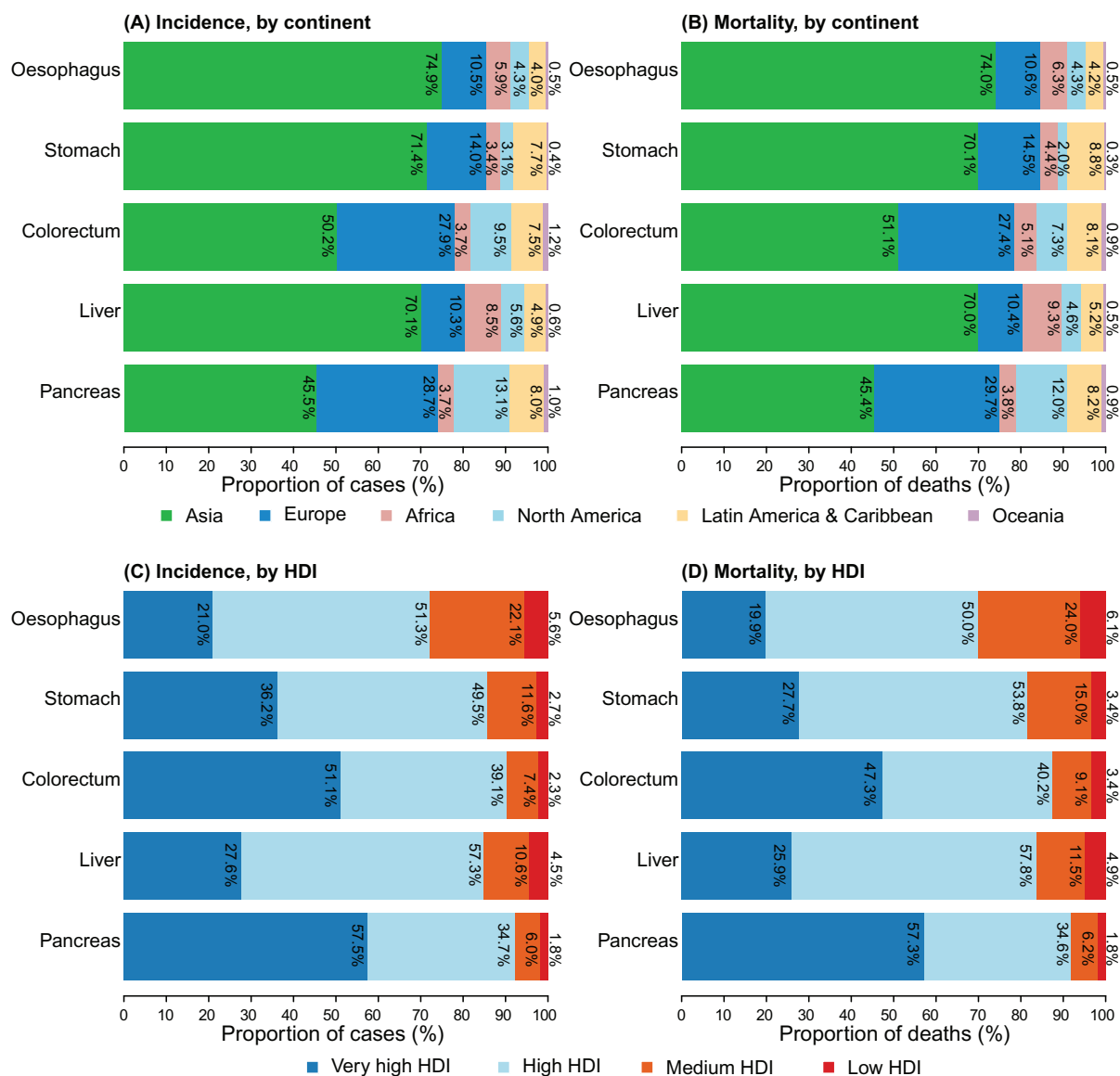


FIGURE 2 Proportions of new cases and deaths for the five major gastrointestinal cancers by continent (A-B) and HDI (C-D) in 2022. Abbreviations: GI, gastrointestinal; HDI, human development index.

their current global landscape. GI cancers contributed a larger proportion of all cancer deaths than of all new cancer cases, which were the most commonly diagnosed cancers in 27 countries and the leading causes of cancer deaths in 36 countries in 2022. Different types of GI cancers varied greatly across countries over time, with distinct profiles: (1) oesophageal cancer: most countries manifested decreasing trends or continuously low levels in incidence and mortality rates throughout the study period, except for some Eastern European countries, Thailand, and Uganda, where the rates had increased; (2) gastric cancer: consistent declines in both incidence and mortality were observed for almost all countries in both sexes; (3) colorectal cancer: four distinct patterns can be seen, with the most unfavorable pattern observed in 19 countries, and the

most favorable trends in 10 countries (all located in North America, Oceania, and Europe); (4) liver cancer: declines in disease burden were mainly observed in eastern and southeastern Asia, Italy, and Spain, and unfavorable trends were found in most other countries; (5) pancreatic cancer: increases in rates of pancreatic cancer can be seen in half of the included countries, with a general faster growth in incidence than mortality in recent years.

4.1 | Oesophageal cancer

The burden of oesophageal cancer varies greatly across countries and changes over time, which may be linked to the different distribution in subtypes, the varying

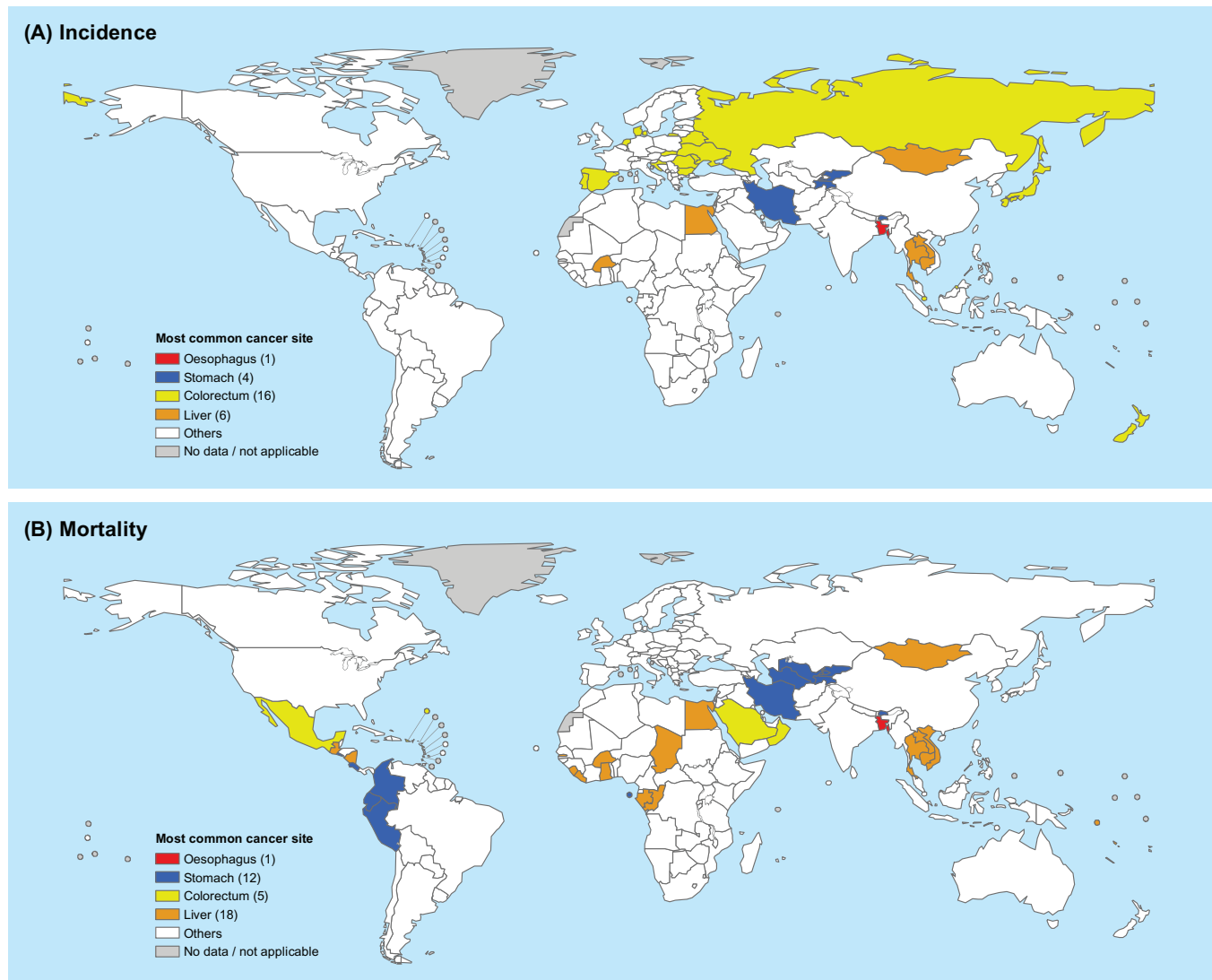


FIGURE 3 Countries where the five major gastrointestinal cancers ranked 1st in cases and deaths among all cancer sites in 2022.

prevalence of modifiable risk factors, and screening endeavors. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are the main subtypes of oesophageal cancer. ESCC is the dominant subtype in most countries, especially in high-risk areas [23]. Previous studies have documented the universal decline in the incidence of ESCC, with the exception of a few Eastern European countries; whereas the incidence rates of EAC have been generally increasing in most western countries, and it is now driving the overall trends in countries from North America, Northern Europe, and Oceania [24], which may explain the deviating patterns between incidence and mortality in our study for several countries such as Denmark, Norway, and the Netherlands.

Risk factors associated with oesophageal cancer include low socioeconomic status, tobacco, low intake of fruits and vegetables, and high intake of red and processed meat for both subtypes; poor oral health, alcohol, very hot

beverage, nitrosamines, and polycyclic aromatic hydrocarbons (eg, biomass combustion and opium use) for ESCC; and gastroesophageal reflux disease and high body mass index for EAC [4, 25]. In the high-risk areas, there is evidence of population groups with raised exposures to some of the aforementioned known risk factors [26]. However, no single dominant risk factor has been identified for the so-called Eastern Africa's corridor and Central Asian belt of oesophageal cancer [27]. The prevalence of obesity has increased in most countries [28], which might partially contribute to the increasing burden in EAC. While screening for oesophageal cancer is not adopted in most countries, China has launched several screening programs which cover this cancer type, and the mass gastric cancer screening in Japan and South Korea can also help detect oesophageal cancers [29]. These efforts may have accelerated the decline in mortality in these countries.

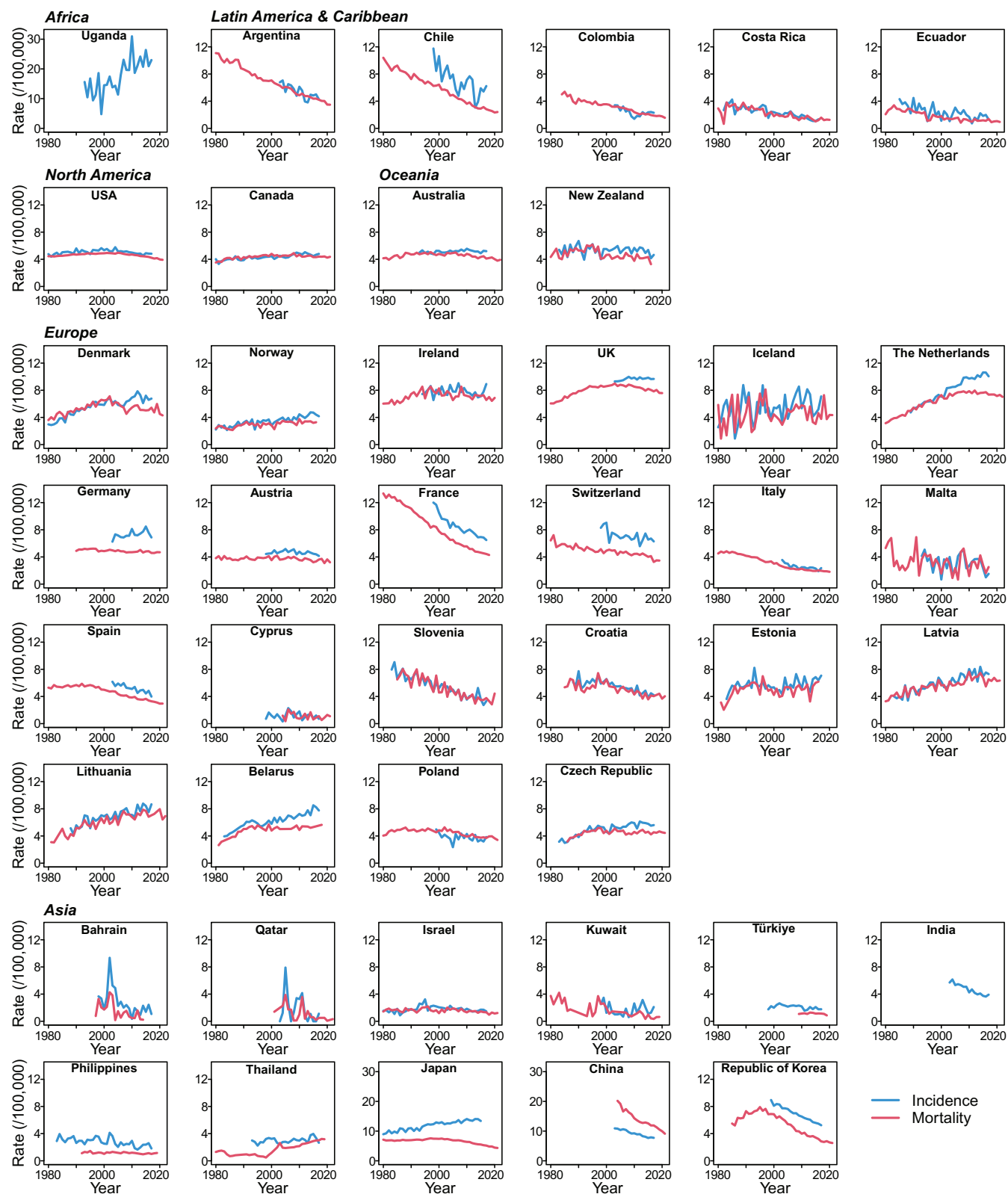


FIGURE 4 Time trends of age-standardized incidence and mortality rates (per 100,000) of oesophageal cancer in men. Note, the coverage of the included registries for the incidence data varies across countries, and it was below 5% for Argentina, Chile, Poland, India, and China. Caution is needed when interpreting the incidence trends for countries with low national coverage.

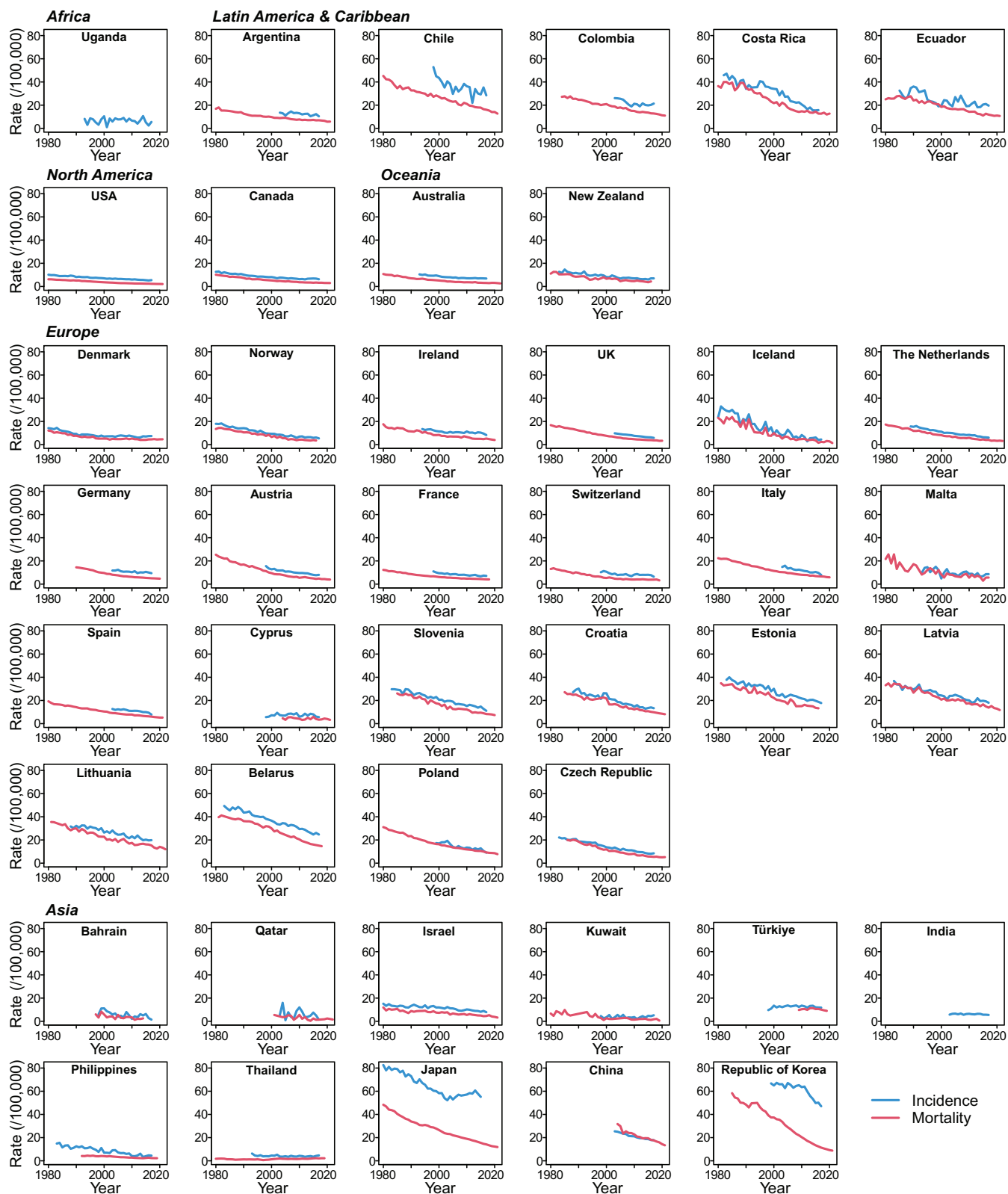


FIGURE 5 Time trends of age-standardized incidence and mortality rates (per 100,000) of gastric cancer in men.

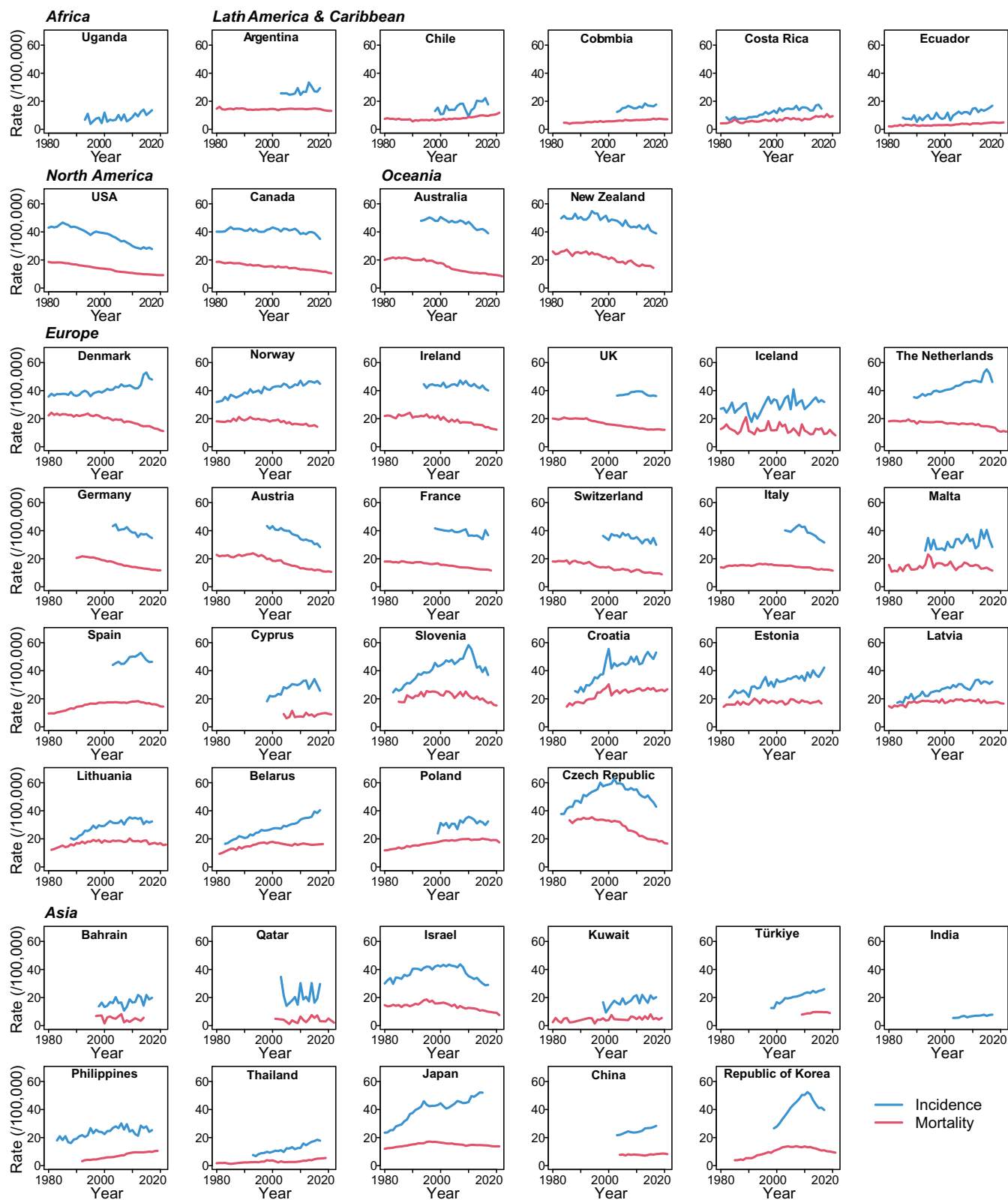


FIGURE 6 Time trends of age-standardized incidence and mortality rates (per 100,000) of colorectal cancer in men.

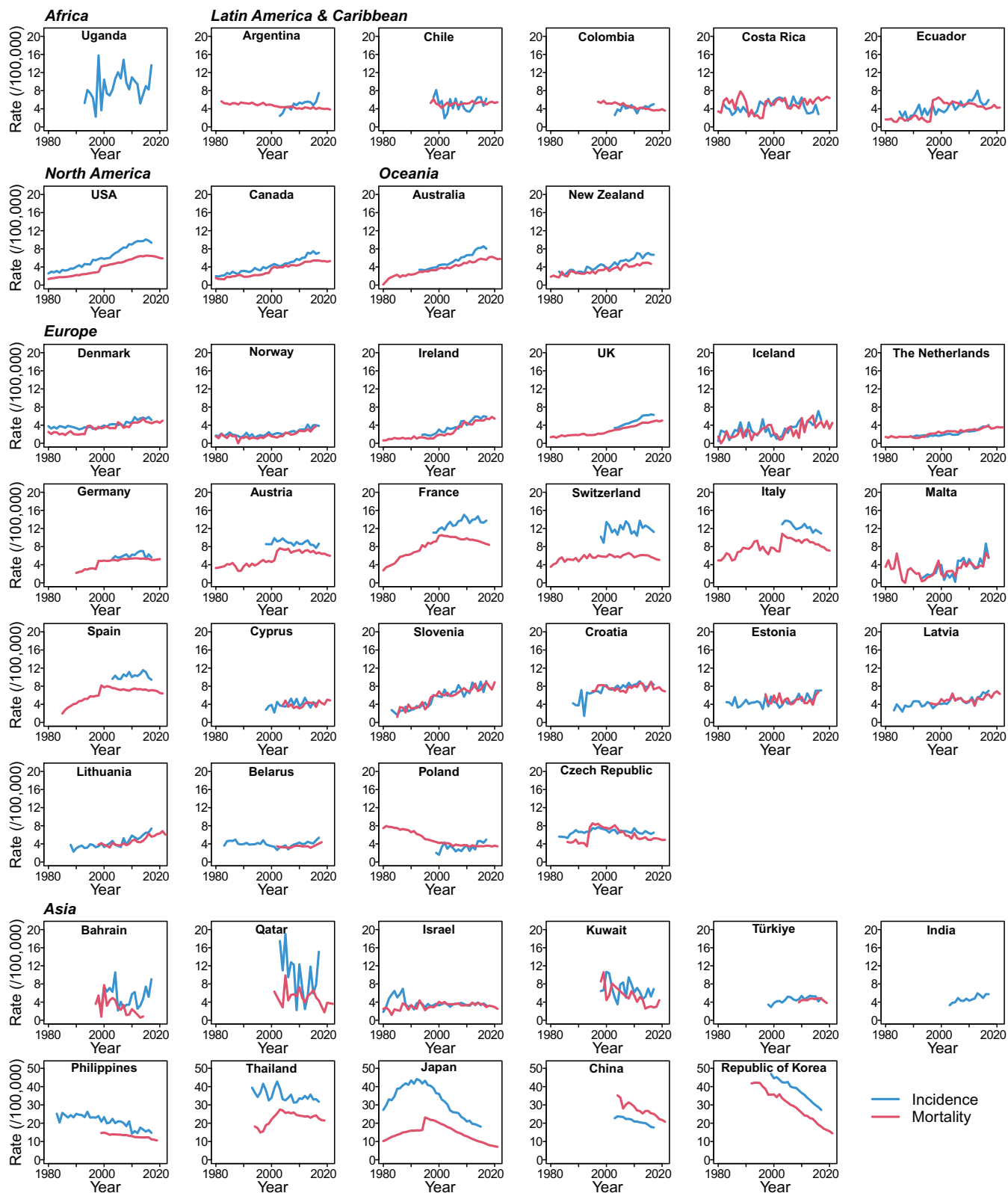


FIGURE 7 Time trends of age-standardized incidence and mortality rates (per 100,000) of liver cancer in men.

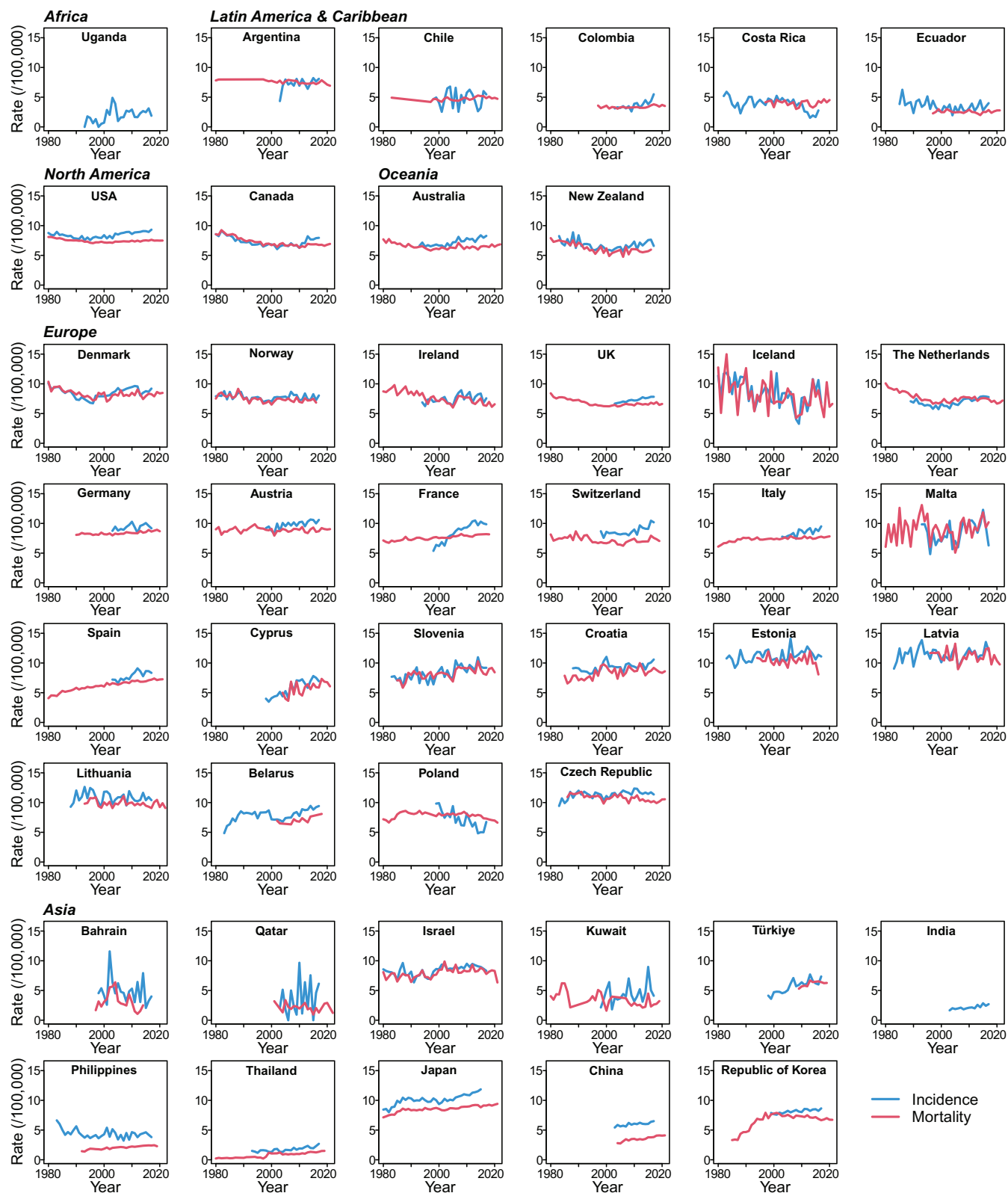


FIGURE 8 Time trends of age-standardized incidence and mortality rates (per 100,000) of pancreatic cancer in men.

4.2 | Gastric cancer

The steady decline in the global burden of gastric cancer, together with the favorable birth-cohort pattern since the last century [30], continues the support of the “unplanned triumph” declared 40 years ago [31]. However, it is important to highlight the uneven declines across countries in our study, which supports the effect of active prevention strategies. Meanwhile, despite downward trends in most countries, it is still too early to tell whether gastric cancer will become a rare disease globally, especially given the existence of high-risk regions and the possible generational transitions in the risk profile of gastric cancer [32].

As a well-established risk factor, *H. pylori* infection has been associated with 90% of non-cardia and 20% of cardia gastric cancer cases worldwide [33], and in China, the corresponding population attributable fraction goes to 78% and 62%, respectively [34]. Globally, *H. pylori* prevalence decreased from 53% before 1990 to 44% during 2015-2022 [35]; and in China, its prevalence reduced by 1% annually, but showed large geographical variations [36]. The improved socioeconomic and hygiene status, better food preservation, and *H. pylori* eradication therapy may all have played important roles in the primary prevention of gastric cancer. In our study, we also found faster decreases in gastric cancer mortality in South Korea, China, and Japan, where population-based screening programs are in practice [37], which helps reduce the risk of dying from the disease [8].

4.3 | Colorectal cancer

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer deaths worldwide in 2022, and it ranks first in the number of new cases in 16 countries. Several modifiable risk factors have been identified, such as smoking, alcohol consumption, intake of red and processed meat, physical inactivity, obesity, and inflammatory bowel disease [38]. It is alarming that both incidence and mortality have been rising in many transitioning countries, which might be linked to the adoption of westernized diet and lifestyle. Despite the generally favorable trends in high-income countries, there is evidence of the rise of early-onset colorectal cancer, suggesting the generational shift of risk factors and the importance of early-life exposures [38, 39]. There is sound proof that screening, either by lower endoscopy or fecal occult blood test, can reduce both the incidence and mortality of colorectal cancer [9, 40, 41]. Screening programs are being implemented in most countries in Western Europe, Oceania, specific regions in North and South America, Eastern Asia, and a few countries in South-

eastern Asia, but the screening strategy and participation rates vary greatly across countries [11, 12]. It is crucial to scale up evidence-based screening strategies globally, and for resource-constrained settings, the feasibility of such screening practices should be balanced and the screening strategies carefully designed.

4.4 | Liver cancer

Our study shows contrasting trends between high- and low-risk countries, implying distinct profiles in the underlying risk factors. The major well-established causes, HBV, HCV, and aflatoxin, have caused the largest fraction of liver cancer cases, mostly in high-risk areas. It is estimated that 56% of liver cancer cases were attributable to HBV [42], 20% to HCV [42], and 17% to aflatoxin [43], with HBV and aflatoxin showing a high degree of geographical aggregation in Eastern Asia and sub-Saharan Africa [42, 44]. The roll-out of HBV vaccination is a landmark event to prevent liver cancer, but the evidence of the continuous decline in liver cancer risk among the earlier birth cohorts in China [45] suggests the role of other factors, such as improved sanitary and hygiene status, public health interventions to reduce aflatoxin exposure, antiviral treatment, injection safety, mandatory screening for blood transfusion safety, and prevention of mother-to-child HBV transmission. However, the burden of liver cancer related to alcohol, obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) may have been on the rise. For example, NAFLD prevalence increased by 50% from 1990-2006 to 2016-2019 [46]. Non-alcoholic steatohepatitis and alcohol were considered the fastest-growing cause of age-adjusted liver cancer burden, especially in the Americas [47].

4.5 | Pancreatic cancer

Patterns of pancreatic cancer mortality closely followed those of incidence due to poor prognosis. Although survival of pancreatic cancer patients slightly improved over time, the 5-year survival rates remain < 10% in most countries [48]. The prevention of pancreatic cancer remains challenging. On the one hand, the risk factors are poorly understood, although several inherited DNA alterations and modifiable risk factors have been identified to be associated with a higher risk of pancreatic cancer, the strong role of a dominant cause in the population is not supported [49]. On the other hand, most pancreatic cancer patients are diagnosed at an advanced stage due to the lack of symptoms and sensitive biomarkers in the early stage, and therefore not eligible for curative surgery. Currently, screening is recommended mainly to the genetically

predisposed individuals with specific syndromes or carrying mutations in, such as, *STK11/LKB1*, *PRSS1*, P16 Leiden variant, and *CDKN2A* genes [50]. Inherited mutations only account for 10%-15% of pancreatic cases [50], and screening for sporadic pancreatic cancer is still under research. There are many ongoing efforts trying to establish predictive models to identify high-risk individuals from the general population and to discover novel biomarkers for the early detection of pancreatic cancer [51].

4.6 | Strengths and limitations

Based on the most recent estimates, we provide an up-to-date overview of the burden of five major GI cancers in 185 countries. Furthermore, we make use of almost 40 years of real-world high-quality population-based data to examine the time trends of GI cancers in 43 countries. The multi-country and multi-cancer analyses enable a comprehensive understanding of how GI cancers have been changing globally. However, there are several limitations. First, the 2022 estimates depend on the availability and quality of the source data in each country, and there might exist uncertainties for countries with no well-functioning population-based registries. Second, we were not able to analyze the distribution of GI cancers by stage and histological subtype, which may help us have a deeper understanding of the reasons underlying the spatial and temporal patterns that we observed. Third, in the incidence trend analysis, population coverage is low for some countries (below 5% for Argentina, Chile, Poland, India, and China), and therefore caution is needed when interpreting the representativeness of the included registries for these countries. Fourth, the DSPs experienced several changes over time—for instance, the coverage has been enlarged from 6% to 24% since 2013; data in 2004-2005 were collected through retrospective surveys, while those in the other years were based on routine surveillance—which may influence the consistency of mortality data for China. Lastly, under-reporting and misclassification can influence the accuracy of incidence and mortality data, especially in the early years, which should be borne in mind when interpreting the long-term trends of GI cancers.

5 | CONCLUSIONS

Currently, GI cancers remain a major threat globally, and cause larger proportions of cancer deaths than cancer cases due to their general poor prognosis. Several types of GI cancers share similarities in geographical distribution, but also with notable unique high-risk areas. Distinct patterns were found for the time trends of incidence and mortality across

countries and cancer types. Multi-setting studies of populations with common and distinct spatiotemporal patterns, as identified here, might provide insights into the underlying etiologies of these cancers, and identify areas where urgent cancer control strategies are needed.

AUTHOR CONTRIBUTIONS

Rui-Hua Xu and Mengmeng Li conceptualized and designed the study. Mengmeng Li did the formal analysis and wrote the original draft of the manuscript. Sumei Cao and Rui-Hua Xu contributed to data interpretation and writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

The datasets used in this study are all publicly available.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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