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Disparities, Trends, and Predictions to 2040 in Gastrointestinal Cancer Incidence, Mortality in the United States

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INTRODUCTION: **Growing gastrointestinal cancers in the United States necessitate further research due to substantial health care and economic impacts. The aim of this study was to analyze trends and future projections for 5 major gastrointestinal cancers (colorectal, pancreatic, liver, stomach, and esophageal).**

METHODS: **Data were sourced from the Surveillance, Epidemiology, and End Results database; National Center for Health Statistics; and Global Burden of Diseases databases. An age-period-cohort model using the Bayesian Information Criterion method was applied to project incidence and mortality rates to 2040.**

RESULTS: **Men consistently exhibited higher incidence and mortality rates across all gastrointestinal cancers, with significant variation across the 51 US states. From 2000 to 2020, colorectal cancer incidence and mortality rates declined across all racial groups, except for the incidence rates of American Indian and Alaska Native (AIAN) men, Hispanic men, and Hispanic women, which remained stable. Pancreatic cancer incidence increased across all groups except for AIAN men, while mortality rates rose only for White men and Hispanic women. Liver cancer incidence rose among AIAN men and White, AIAN, and Hispanic women, while mortality rates declined for most groups. Stomach cancer incidence and mortality either declined or stabilized, and esophageal cancer rates showed a general decline. By 2040, increases in incidence and mortality are projected for most gastrointestinal cancers, particularly in men.**

DISCUSSION: **Despite varied trends over the past 2 decades, an overall increase in gastrointestinal cancer incidence and mortality rates is anticipated in the next 20 years in the United States, underscoring the need for effective prevention and intervention strategies.**

KEYWORDS: gastrointestinal cancer; incidence; mortality; trend; prediction

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D465; http://links.lww.com/AJG/D466; http://links.lww.com/AJG/D467; http://links.lww.com/AJG/D468; http://links.lww.com/AJG/D469; http://links.lww.com/AJG/D470; http://links.lww.com/AJG/D471

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INTRODUCTION

Gastrointestinal malignant tumors refer to a group of cancers originating from the digestive system, including the stomach, esophagus, pancreas, hepatobiliary duct, large intestine, and small intestine, which are among the most common cancers in humans (1). Approximately 343,040 newly diagnosed gastrointestinal cancer cases and 171,920 deaths are expected to occur in 2022 in the United States, accounting for 18% of all cancer cases and 28% of all cancer deaths in the country (2). Given the growth and aging of the population, it is anticipated that these numbers will continue to rise, exerting even greater pressure on an already overburdened health care system and imposing a staggering economic burden (3). Understanding the patterns and projected trends of gastrointestinal cancers is crucial for evaluating the effectiveness of preventive measures implemented over the past decades, formulating future public health

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policies and allocating health care resources. Further study of the incidence and mortality patterns, along with estimated projections, is essential for informed decision making in health care.

Although prior studies have provided valuable insights into the trends and disparities of individual gastrointestinal cancers (4–6), a comprehensive assessment of the entire gastrointestinal cancer spectrum remains limited. Furthermore, research forecasting future trends of gastrointestinal cancers primarily focuses on global or non-US populations (7,8), leaving a gap in understanding the US-specific projections. Our study comprehensively describes the sociodemographic disparities and trends in incidence and mortality, and forecasts the changes to 2040 for 5 major gastrointestinal cancers, including colon and rectum, pancreas, liver and intrahepatic bile duct, stomach, and esophageal cancers in the United States. These data offer valuable insights into the significance of gastrointestinal cancers in the United States.

METHODS

Data sources

Population-based 5 gastrointestinal cancers incidence data (2000–2020) were sourced from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) 22-registry database (covering about 50% of the US population). Primary site and histology were coded using *International Classification of Diseases* (*ICD*) *for Oncology*, *Third Edition* (*ICD*-O-3) (9). The *ICD*-O-3 codes for colorectal cancer in the SEER database are C180-C189, C199, C209-C212, C218, and C260; for pancreatic cancer, the codes are C250-C259; for liver cancer, C220-C221; for stomach cancer, C160-C169; and for esophageal cancer, C150-C159.

Mortality data from 2000 to 2020 were obtained from the SEER mortality database, with the mortality information collected and compiled by the National Center for Health Statistics (NCHS, nearly covering 100% of the population). The mortality data are based on death certificates provided by state vital statistics offices and consolidated into a national data set to ensure the data accuracy and comprehensiveness (10). The causes of death were determined based on the *ICD* codes applicable at the time of death (*ICD-10*). These were subsequently categorized using the SEER cause of death recoding system to enhance consistency between *ICD* and *ICD*-O coding systems (10). Only primary cancers were considered (colorectal [C180, C182-C189, C19, and C20], pancreatic [C250-C254 and C257-C259], liver [C220-C224, C227, and C229], stomach [C160-C166 and C168-C169], and esophageal [C150-C155 and C158-C159]) (10).

To forecast the variations in incidence and mortality rates up to 2040, we sourced specific data (1990–2019) from the Global Burden of Disease 2019 database. Data sources used to inform the cancer estimates were obtained from vital registration systems, sample vital registration systems, verbal autopsy reports, and national and subnational population-based cancer registries (11). Five major gastrointestinal cancers were also classified according to the *ICD-10* based on their primary sites (12): colorectum (C18-C19.0, C20, C21-C21.8), pancreas (C25-C25.9), liver (C22-C22.4, C22.7-C22.8), stomach (C16-C16.9), and esophagus (C15-C15.9). Population forecast data were extracted from the Global Population Forecasts 2017–2100.

Statistical methods

Cross-sectional incidence (2016–2020) and mortality (2016–2020) rates with their 95% confidence intervals were calculated by gender (where relevant) and by distinct racial and ethnic groups as documented in medical records or death certificates (non-Hispanic White [White], non-Hispanic Black [Black], non-Hispanic Asian American and Pacific Islander [AAPI], non-Hispanic American Indian and Alaska Native [AIAN], Hispanic, and all races/ethnicities) using SEER*Stat v8.4.2 (NCI, Bethesda, MD). Incidence and mortality were age-adjusted to the 2000 US standard population and expressed per 100,000 persons. The Tiwari method was used to calculate the 95% confidence intervals, and differences between groups were deemed significant if their intervals did not overlap. The Tiwari method was also used to calculate male/female and non-White race/ethnicity/White population incidence and mortality rate ratios for all 5 cancers. Owing to issues of racial misclassification, the mortality data pertaining to AIAN individuals has been omitted (13).

Temporal trends in age-standardized cancer incidence (2000–2019) and mortality (2000–2020) rates were estimated using the Joinpoint Trend Analysis Software (Version 4.9). The default number of Joinpoints ranged between 0 and 5, using the Monte Carlo permutation analysis to estimate best-fitting model with the estimated annual percentage change (APC) for each segment (14). The Monte Carlo permutation analysis is a statistical method to detect significant changes in trends by randomly permuting the data and comparing different models (14). It identifies the best-fitting model by testing whether observed Joinpoints are significantly different from what would occur by chance (14). This approach controls for Type I error and is flexible, making it reliable for analyzing complex cancer incidence and mortality trends (14). The short-term temporal trends for incidence (2015–2019) and mortality (2016–2020) rates were expressed as the average APC (AAPC) as calculated with Joinpoint. The AAPC was equal to the APC when the AAPC was entirely within the last Joinpoint segment. Trends were characterized as ascending or descending when the APC or AAPC was statistically meaningful based on a two-sided *P*-value less than 0.05, and were otherwise considered to be steady. In 2020, cancer incidence data were significantly lower than predicted due to delays in cancer diagnosis and screening caused by the COVID-19 pandemic. This discrepancy introduced a larger variance, reducing the statistical power of Joinpoint models used for trend analysis (15). Consequently, we excluded the 2020 incidence data from the trend analysis to maintain the accuracy of our findings.

To visualize the geographical disparities in current incidence (2016–2020) and mortality (2016–2020) rates, maps were generated using the US Cancer Statistics Data Visualizations Tool to display age-standardized incidence and mortality rates by state, with rates based on fewer than 16 cases or deaths being withheld. Owing to sparse data, the mapping of incidence and mortality data was restricted to the 5 major gastrointestinal cancers for White individuals.

To predict the incidence and mortality rates from 2020 to 2040, we used the Bayesian Age-Period-Cohort (BAPC) model implemented within the Integrated Nested Laplace Approximations framework, which was selected for its computational efficiency and lower error rates compared with traditional methods (16–19). The Integrated Nested Laplace Approximations framework, when used in conjunction with the BAPC model, effectively approximates the marginal posterior

distributions, thereby avoiding the mixing and convergence issues typically associated with traditional Bayesian methods that rely on Markov Chain Monte Carlo sampling techniques. The model was established using the "BAPC" and "INLA" packages in R software. All statistical analyses and data visualizations were executed using GraphPad Prism version 9.0 and R software (V.4.3.2).

RESULTS

Colorectal cancer

Between 2016 and 2020, male individuals exhibited higher average annual age-standardized incidence and mortality rates for colorectal cancer compared with female individuals. Incidence rates were highest among AIAN individuals (male: 56.1 [51.8 to 60.8], female: 48.2 [44.6 to 52.0]), while mortality rates were greatest among Black individuals (male: 22.3 [21.9 to 22.6], female: 14.3 [14.1 to 14.5]) (Tables 1 and 2). Geographically, Kentucky recorded the highest incidence rates (male: 54.1 [52.7 to 55.5], female: 39.4 [38.3 to 40.5]), whereas West Virginia had the highest mortality rates (male: 20.2 [19.0 to 21.5], female: 13.8 [12.9 to 14.7]) (see Figures S1, http://links.lww.com/AJG/D465 and S2, http://links.lww.com/AJG/D466; Tables S1, http://links.lww.com/AJG/D467 and S2, http://links.lww.com/AJG/D468). During the most recent period, colorectal cancer incidence showed a declining trend across most racial and ethnic groups for both men and women, with rates stabilizing among AIAN men, Hispanic men, and Hispanic women (Figure 1; Table S3, http://links.lww.com/AJG/D469). Mortality rates between 2000 and 2020 also declined across all racial and ethnic groups (Figure 2; Table S4, http://links.lww.com/AJG/D470). By 2040, incidence rates are projected to increase by 9.8% in men and 11.5% in women, while mortality is expected to rise by 27.9% in men and 21.9% in women (Figures 3 and 4).

Pancreatic cancer

For pancreatic cancer, between 2016 and 2020, male individuals exhibited higher average annual age-standardized incidence and mortality rates compared with female individuals. Black individuals had the highest average annual age-standardized incidence and mortality rates (male incidence: 17.8 [17.4 to 18.3], female incidence: 15.0 [14.7 to 15.4]; male mortality: 15.3 [15.0 to 15.6], female mortality: 12.3 [12.1 to 12.5]) (Tables 1 and 2). Geographically, New Jersey had the highest average annual incidence rates for men (17.6 [17.0 to 18.2]) and women (13.4 [12.9 to 13.9]), while Rhode Island recorded the highest male mortality (15.8 [14.3 to 17.5]) and Hawaii the highest female mortality (10.7 [8.8 to 13.1]) (see Figures S1, http://links.lww.com/AJG/D465 and S2, http://links.lww.com/AJG/D466; Tables S1, http://links.lww.com/AJG/D467 and S2, http://links.lww.com/AJG/D468). Between 2000 and 2019, pancreatic cancer incidence increased across all racial and ethnic groups for both men and women, with stable trends for AIAN women (Figure 1; Table S3, http://links.lww.com/AJG/D469). Mortality rates from 2000 to 2020 increased for White men (AAPC: 0.40 [0.32 to 0.50]) and Hispanic women (AAPC: 0.25 [0.09 to 0.43]), while declining for Black men (AAPC: −0.18 [−0.34 to −0.00]) and Black women (AAPC: −0.24 [−0.39 to −0.06]) (Figure 2; Table S4, http://links.lww.com/AJG/D470). By 2040, pancreatic cancer incidence is projected to increase by 3.6% in men and decrease by 1.3% in women, with mortality expected to rise by 5.0% in men while remaining stable in women (Figures 3 and 4).

Liver cancer

For liver cancer, the average annual age-standardized incidence rates from 2016 to 2020 were notably higher among male individuals. AIAN had the highest incidence rates (male: 28.3 [25.4 to 31.4], female: 12.2 [10.4 to 14.1). Mortality rates were highest among Hispanic individuals (male: 13.1 [12.9 to 13.4], female: 6.0 [5.8 to 6.2]) (Tables 1 and 2). Geographically, Texas recorded the highest incidence rates for men (14.5 [14.1 to 14.8]) and Mississippi for women (5.2 [4.7 to 5.8]) (Table 1). Mississippi also reported the highest mortality rates for both men (11.9 [11.0 to 12.9]) and women (5.1 [4.6 to 5.7]) (see Figures S1, http://links.lww.com/AJG/D465 and S2, http://links.lww.com/AJG/D466; Tables S1, http://links.lww.com/AJG/D467 and S2, http://links.lww.com/AJG/D468). In recent years, there have been significant differences in recent years by gender and race/ethnicity, among male individuals, the incidence was reducing among Black (AAPC: −2.86 [−4.02 to −1.42]) and AAPI (AAPC: −1.79 [−3.96 to −1.15]) individuals, increased among AIAN (AAPC, 3.71 [1.94 to 6.09], but remained stable among white and Hispanic individuals. However, among women, the incidence of liver cancers were increased in White (AAPC, 1.71 [0.17 to 2.91]), AIAN (AAPC: 3.52 [2.29 to 5.13]) and Hispanic (AAPC: 2.42 [2.07 to 2.89]), declined in AAPI (AAPC: −2.10 [−5.16 to −1.33]), and stabilized in Black individuals (Figure 1; Table S3, http://links.lww.com/AJG/D469). From 2000 to 2020, mortality rates decreased among most male groups, except for White men, where the rate remained stable, while mortality rates decreased among AAPI women and remained stable in other female groups (Figure 2; Table S4, http://links.lww.com/AJG/D470). By 2040, liver cancer incidence is projected to increase by 32.2% in men and decrease by 7.0% in women, while mortality is expected to rise by 33.0% in men but decrease by 5.2% in women (Figures 3 and 4).

Stomach cancer

Stomach cancer between 2016 and 2020 followed the same pattern, with male individuals having significantly higher average annual age-standardized incidence and mortality rates than female individuals. The highest incidence rates were observed in AIAN men (14.2 [12.1 to 16.6]), while Hispanic women had the highest incidence (8.4 [8.2 to 8.6]) and mortality rates (3.9 [3.8 to 4.0]) (Tables 1 and 2). Geographically, New York had the highest average annual incidence rates for men (8.9 [8.5 to 9.2]), and New Jersey had the highest rates for women (4.6 [4.4 to 4.8]). Delaware recorded the highest average annual mortality rates for men (4.4 [3.5 to 5.4]), while Mississippi had the highest rates for women (2.1 [1.7 to 2.5]) (see Figures S1, http://links.lww.com/AJG/D465 and S2, http://links.lww.com/AJG/D466; Tables S1, http://links.lww.com/AJG/D467 and S2, http://links.lww.com/AJG/D468). Between 2000 and 2019, incidence rates decreased across most racial and ethnic groups, except among White women, Hispanic women, and AIAN men and women, where rates either stabilized or increased (Figure 1; Table S3, http://links.lww.com/AJG/D469). Mortality rates from 2000 to 2020 decreased across all groups, except for Hispanic women, where the rates remained stable (Figure 2; Table S4, http://links.lww.com/AJG/D470). By 2040, stomach cancer incidence is projected to rise by 15.5% in men and 12.1% in women, with mortality expected to increase by 18.9% in men and 10.6% in women (Figures 3 and 4).

Table 1. Average annual age-standardized incidence (2016–2020) rates[a] and rate ratios with 95% confidence intervals for major gastrointestinal cancers by race and ethnicity and sex in the United States

	All races	White	Black	AIAN	AAPI	Hispanic
Incidence[b]						
Colorectal cancer						
Male						
Rate	42.5 (42.3–42.7)	42.7 (42.4–42.9)	51.3 (50.5–52.1)	56.1 (51.8–60.8)	36.0 (35.3–36.6)	40.4 (39.8–40.9)
Rate ratio[c]	—	Reference	1.20 (1.18–1.22)*	1.32 (1.21–.42)*	0.84 (0.83–0.86)*	0.95 (0.93–0.96)*
Female						
Rate	32.2 (32.1–32.4)	32.8 (32.5–33.3)	37.8 (37.2–38.3)	48.2 (44.6–52.0)	25.5 (25.0–26.0)	28.9 (28.5–29.3)
Rate ratio[c]	—	Reference	1.15 (1.14–1.17)*	1.47 (1.36–1.59)*	0.78 (0.76–0.80)*	0.88 (0.87–0.90)
M:F rate ratio	1.32 (1.31–1.33)*	1.30 (1.29–1.31)*	1.36 (1.33–1.39)*	1.17 (1.04–1.30)*	1.41 (1.37–1.45)*	1.40 (1.37–1.42)*
Pancreatic cancer						
Male						
Rate	15.3 (15.2–15.4)	15.9 (15.7–16.0)	17.8 (17.4–18.3)	17.2 (14.8–19.8)	11.1 (10.7–11.5)	12.9 (12.6–13.2)
Rate ratio[c]	—	Reference	1.12 (1.09–1.15)*	1.08 (0.93–1.25)	0.70 (0.67–0.72)*	0.81 (0.79–0.83)*
Female						
Rate	11.9 (11.8–12.0)	11.8 (11.7–11.9)	15.0 (14.7–15.4)	11.5 (9.8–13.4)	9.3 (9.0–9.6)	11.4 (11.2–11.7)
Rate ratio[c]	—	Reference	1.27 (1.24–1.30)*	0.98 (0.83–1.14)	0.79 (0.76–0.81)*	0.97 (0.94–0.99)*
M:F rate ratio	1.28 (1.27–1.30)*	1.35 (1.33–1.37)*	1.19 (1.15–1.23)*	1.49 (1.20–1.86)*	1.19 (1.14–1.25)*	1.13 (1.09–1.17)*
Liver cancer						
Male						
Rate	14.4 (14.3–14.5)	11.4 (11.3–11.5)	17.6 (17.2–18.0)	28.3 (25.4–31.4)	18.7 (18.2–19.2)	22.2 (1.8–22.6)
Rate ratio[c]	—	Reference	1.54 (1.50–1.58)*	2.48 (2.22–2.75)*	1.64 (1.59–1.68)*	1.94 (1.90–1.98)
Female						
Rate	5.3 (5.2–5.4)	4.2 (4.1–4.3)	5.6 (5.4–5.8)	12.2 (10.4–14.1)	6.7 (6.5–7.0)	9.2 (9.0–9.5)
Rate ratio[c]	—	Reference	1.34 (1.29–1.40)*	2.90 (2.49–3.37)*	1.60 (1.54–1.67)*	2.20 (2.14–2.27)*
M:F rate ratio	2.71 (2.67–2.75)*	2.72 (2.67–2.78)*	3.13 (3.00–3.27)*	2.32 (1.93–2.79)	2.78 (2.65–2.91)*	2.40 (2.33–2.48)*
Stomach cancer						
Male						
Rate	9.1 (9.0–9.2)	7.4 (7.3–7.6)	13.2 (12.8–13.6)	14.2 (12.1–16.6)	12.4 (12.0–12.7)	12.0 (11.7–12.3)
Rate ratio[c]	—	Reference	1.77 (1.72–1.83)*	1.91 (1.62–2.23)*	1.66 (1.60–1.72)*	1.61 (1.57–1.66)*
Female						
Rate	5.2 (5.2–5.3)	3.6 (3.6–3.7)	7.7 (7.4–7.9)	7.7 (6.4–9.3)	7.1 (6.8–7.3)	8.4 (8.2–8.6)
Rate ratio[c]	—	Reference	2.11 (2.03–2.19)*	2.13 (1.75–2.57)*	1.95 (0.87–2.03)*	2.30 (2.23–2.38)*
M:F rate ratio	1.75 (1.72–1.77)*	2.05 (2.00–2.10)*	1.72 (1.65–1.80)*	1.83 (1.43–2.6)*	1.75 (1.66–1.83)	1.43 (1.38–1.48)*
Esophageal cancer						
Male						
Rate	7.2 (7.1–7.3)	8.4 (8.3–8.5)	5.6 (5.3–5.8)	9.4 (7.8–11.4)	3.7 (3.5–3.9)	4.8 (4.7–5.0)
Rate ratio[c]	—	Reference	0.67 (0.64–0.70)*	1.12 (0.92–1.36)	0.44 (0.42–0.47)*	0.58 (0.55–0.60)*
Female						
Rate	1.7 (1.7–1.7)	1.9 (1.8–1.9)	2.0 (1.9–2.1)	2.7 (1.9–3.6)	1.0 (0.9–1.1)	1.0 (1.0–1.1)
Rate ratio[c]	—	Reference	1.05 (0.98–1.12)	1.42 (1.02–1.92)*	0.51 (0.46–0.57)*	0.55 (0.51–0.60)*
M:F rate ratio	4.26 (4.16–4.37)*	4.47 (4.34–4.60)*	2.83 (2.62–3.06)*	3.55 (2.46–5.18)*	3.83 (3.42–4.31)*	4.60 (4.27–5.06)*

AAPI, Asian American and Pacific Islander; AIAN, American Indian and Alaska Native; F, female; M, male.
[a]All racial groups are exclusive of individuals identifying as Hispanic. Rates are per 100,000 and age-adjusted to the 2000 US standard population. Mortality data for AIAN individuals are excluded due to racial misclassification. Incidence data are from the National Cancer Institute Surveillance, Epidemiology, and End Results database, and mortality data are from the National Center for Health Statistics database.
[b]Rates are adjusted for delays in case reporting.
[c]Rate ratios are based on rates age-adjusted to the 2000 US standard population, with White population as the reference group.
*Significant difference in rate ratio in comparison with the reference group ($P < 0.05$).

Table 2. Average annual age-standardized mortality (2016–2020) rates[a] and rate ratios with 95% confidence intervals for major gastrointestinal cancers by race and ethnicity and sex in the United States

	All races	White	Black	AIAN	AAPI	Hispanic
Mortality						
Colorectal cancer						
Male						
Rate	15.6 (15.5–15.7)	15.5 (15.4–15.6)	22.3 (21.9–22.6)	—	10.9 (10.6–11.2)	13.5 (13.3–13.8)
Rate ratio[b]	—	Reference	1.44 (1.42–1.47)*	—	0.71 (0.69–0.73)*	0.88 (0.86–0.89)*
Female						
Rate	11.0 (10.9–11.1)	11.1 (11.0–11.1)	14.3 (14.1–14.5)	—	7.7 (7.5–8.0)	8.5 (8.3–8.7)
Rate ratio[b]	—	Reference	1.29 (1.27–1.31)*	—	0.70 (0.68–0.72)*	0.77 (0.75–0.78)*
M:F rate ratio	1.42 (1.41–1.43)*	1.40 (1.39–1.41)*	1.56 (1.53–1.59)*	—	1.42 (1.36–1.48)*	1.60 (1.55–1.64)*
Pancreatic cancer						
Male						
Rate	12.7 (12.7–12.8)	13.1 (13.0–13.2)	15.3 (15.0–15.6)	—	8.2 (8.0–8.5)	9.6 (9.4–9.8)
Rate ratio[b]	—	Reference	1.17 (1.15–1.19)*	—	0.63 (0.61–0.65)*	0.73 (0.72–0.75)*
Female						
Rate	9.6 (9.6–9.7)	9.6 (9.6–9.7)	12.3 (12.1–12.5)	—	7.0 (6.8–7.2)	8.0 (7.8–8.2)
Rate ratio[b]	—	Reference	1.27 (1.25–1.30)*	—	0.72 (0.70–0.75)*	0.83 (0.81–0.85)*
M:F rate ratio	1.32 (1.31–1.33)*	1.36 (1.34–1.37)*	1.25 (1.22–1.28)*	—	1.18 (1.13–1.24)*	1.20 (1.16–1.24)*
Liver cancer						
Male						
Rate	9.6 (9.5–9.6)	8.4 (8.4–8.5)	12.9 (12.7–13.2)	—	12.5 (12.1–12.8)	13.1 (12.9–13.4)
Rate ratio[b]	—	Reference	1.53 (1.50–1.56)*	—	1.48 (1.44–1.52)*	1.56 (1.52–1.59)*
Female						
Rate	4.1 (4.0–4.1)	3.6 (3.6–3.7)	4.8 (4.7–4.9)	—	5.1 (4.9–5.3)	6.0 (5.8–6.2)
Rate ratio[b]	—	Reference	1.32 (1.29–1.36)*	—	1.41 (1.36–1.47)*	1.65 (1.60–1.70)*
M:F rate ratio	2.35 (2.33–2.38)*	2.32 (2.29–2.35)*	2.69 (2.60–2.77)*	—	2.43 (2.32–2.54)*	2.19 (2.12–2.26)*
Stomach cancer						
Male						
Rate	3.8 (3.7–3.8)	2.9 (2.9–2.9)	7.2 (7.0–7.4)	—	5.9 (5.7–6.2)	5.9 (5.8–6.1)
Rate ratio[b]	—	Reference	2.47 (2.39–2.55)*	—	2.04 (1.95–2.13)*	2.04 (1.97–2.11)*
Female						
Rate	2.1 (2.1–2.1)	1.5 (1.5–1.5)	3.5 (3.3–3.6)	—	3.7 (3.5–3.8)	3.9 (3.8–4.0)
Rate ratio[b]	—	Reference	2.33 (2.24–2.41)*	—	2.48 (2.36–2.60)*	2.63 (2.54–2.73)*
M:F rate ratio	1.79 (1.76–1.83)*	1.96 (1.91–2.01)*	2.08 (1.99–2.17)*	—	1.61 (1.52–1.71)*	1.52 (1.46–1.58)*
Esophageal cancer						
Male						
Rate	6.7 (6.6–6.8)	7.6 (7.5–7.7)	4.8 (4.7–5.0)	—	2.6 (2.5–2.8)	3.6 (3.4–3.7)
Rate ratio[b]	—	Reference	0.64 (0.61–0.66)*	—	0.34 (0.32–0.36)*	0.47 (0.44–0.49)*
Female						
Rate	1.4 (1.4–1.4)	1.5 (1.5–1.5)	1.5 (1.5–1.6)	—	0.7 (0.6–0.8)	0.7 (0.6–0.7)
Rate ratio[b]	—	Reference	1.03 (0.98–1.08)	—	0.46 (0.41–0.51)*	0.44 (0.41–0.48)*
M:F rate ratio	4.84 (4.75–4.93)*	5.08 (4.98–5.18)*	3.14 (2.96–3.32)*	—	3.81 (3.38–4.30)*	5.37 (4.93–5.85)*

AAPI, Asian American and Pacific Islander; AIAN, American Indian and Alaska Native; F, female; M, male.

[a]All racial groups are exclusive of individuals identifying as Hispanic. Rates are per 100,000 and age-adjusted to the 2000 US standard population. Mortality data for AIAN individuals are excluded due to racial misclassification. Incidence data are from the National Cancer Institute Surveillance, Epidemiology, and End Results database, and mortality data are from the National Center for Health Statistics database.

[b]Rate ratios are based on rates age-adjusted to the 2000 US standard population, with White population as the reference group.

*Significant difference in rate ratio in comparison with the reference group ($P < 0.05$).

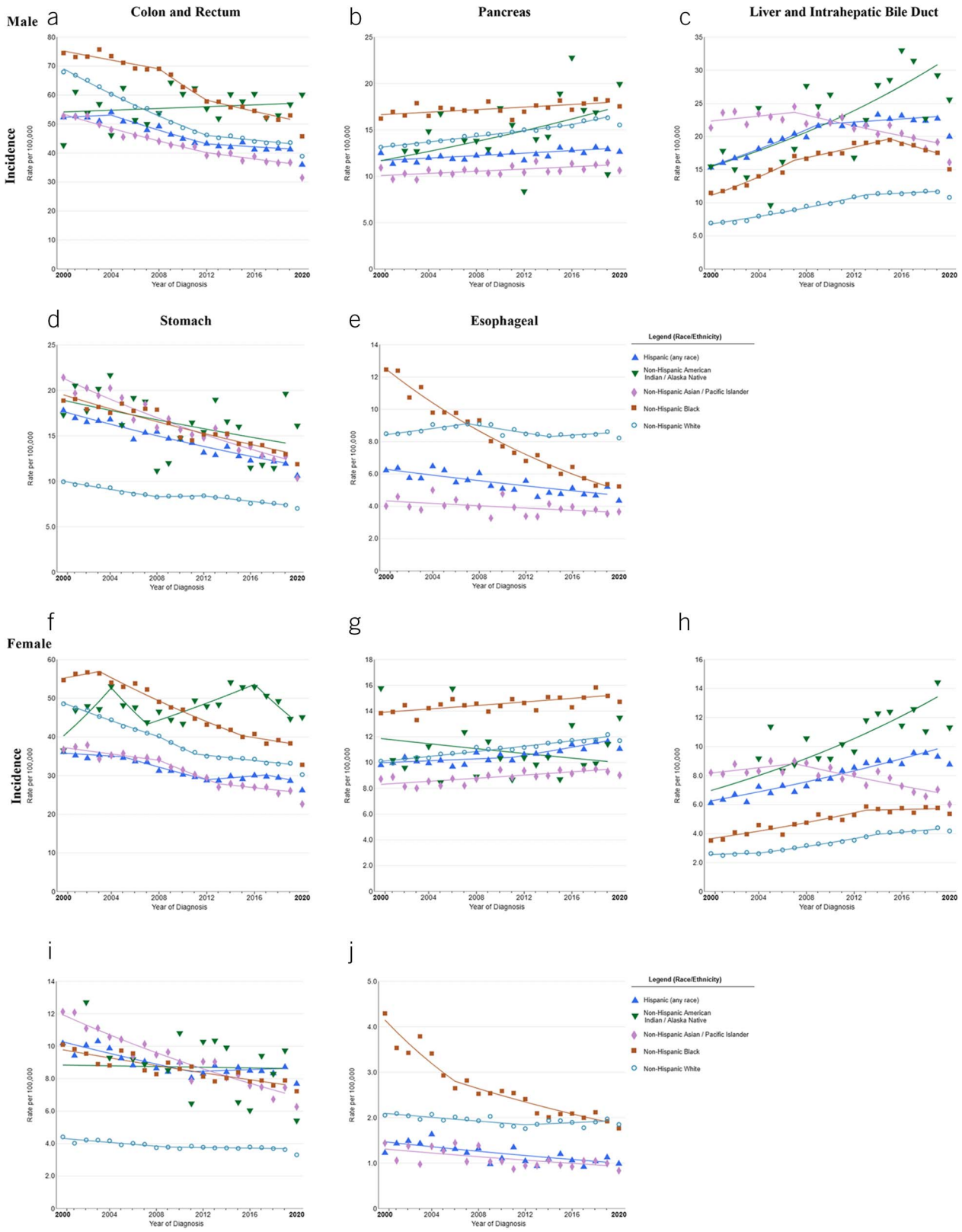

Figure 1. Trends in annual age-standardized rates for 5 major gastrointestinal cancers incidence (2000–2019) by race and ethnicity and sex in the United States. Trends in age-standardized incidence rates among (**a**) colorectal cancer in men, (**b**) pancreatic cancer in men, (**c**) liver cancer in men, (**d**) stomach cancer in men, (**e**) esophageal cancer in men, (**f**) colorectal cancer in women, (**g**) pancreatic cancer in women, (**h**) liver cancer in women, (**i**) stomach cancer in women, and (**j**) esophageal cancer in women. Owing to sparse data, incidence for American Indian/Alaska Native individuals of esophageal cancer are excluded.

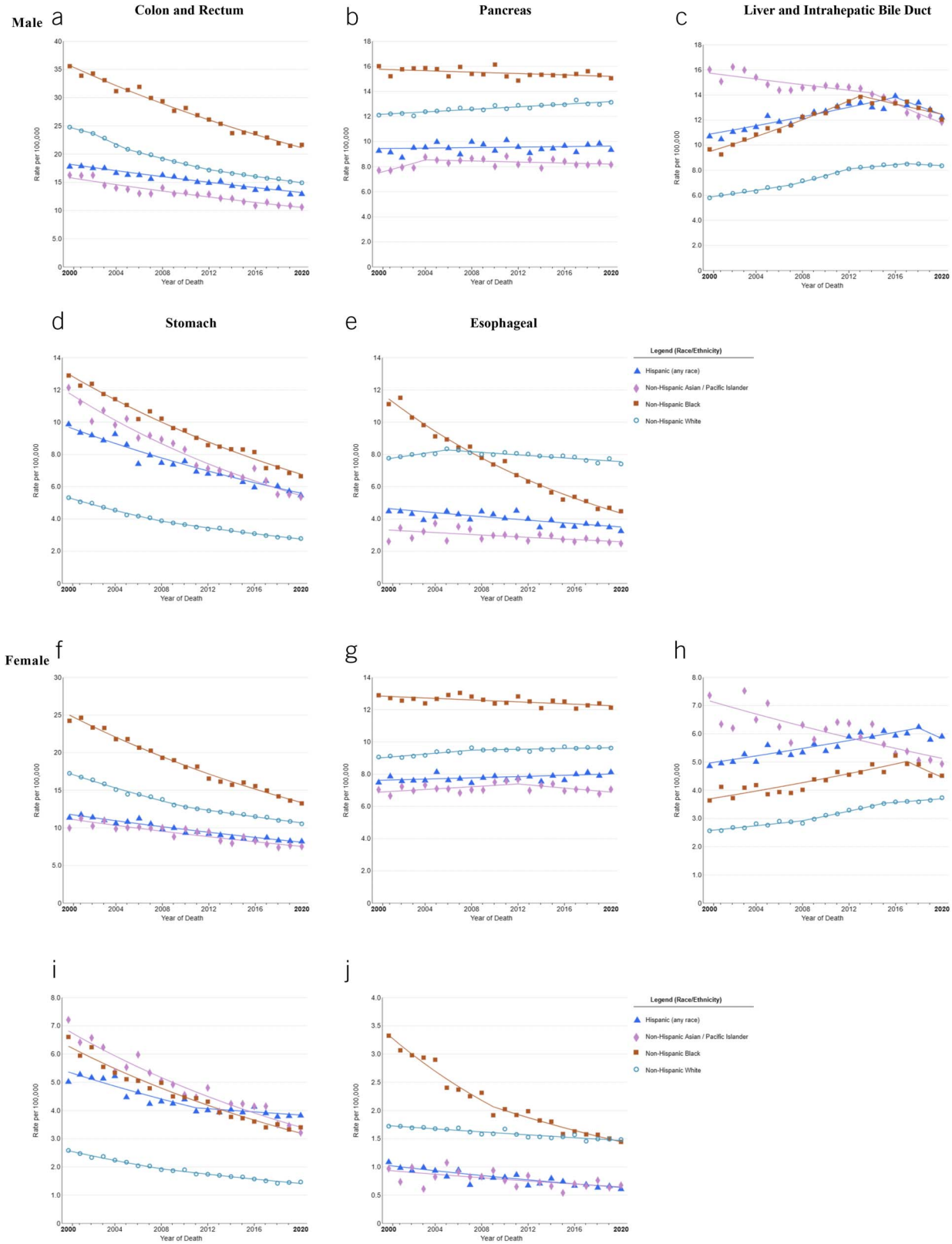

Figure 2. Trends in annual age-standardized rates for 5 major gastrointestinal cancers mortality (2000–2020) by race and ethnicity and sex in the United States. Trends in age-standardized mortality rates among (a) colorectal cancer in men, (**b**) pancreatic cancer in men, (**c**) liver cancer in men, (**d**) stomach cancer in men, (**e**) esophageal cancer in men, (**f**) colorectal cancer in women, (**g**) pancreatic cancer in women, (**h**) liver cancer in women, (**i**) stomach cancer in women, and (**j**) esophageal cancer in women. Owing to issues of racial misclassification, the mortality data pertaining to American Indian/Alaska Native individuals has been omitted.

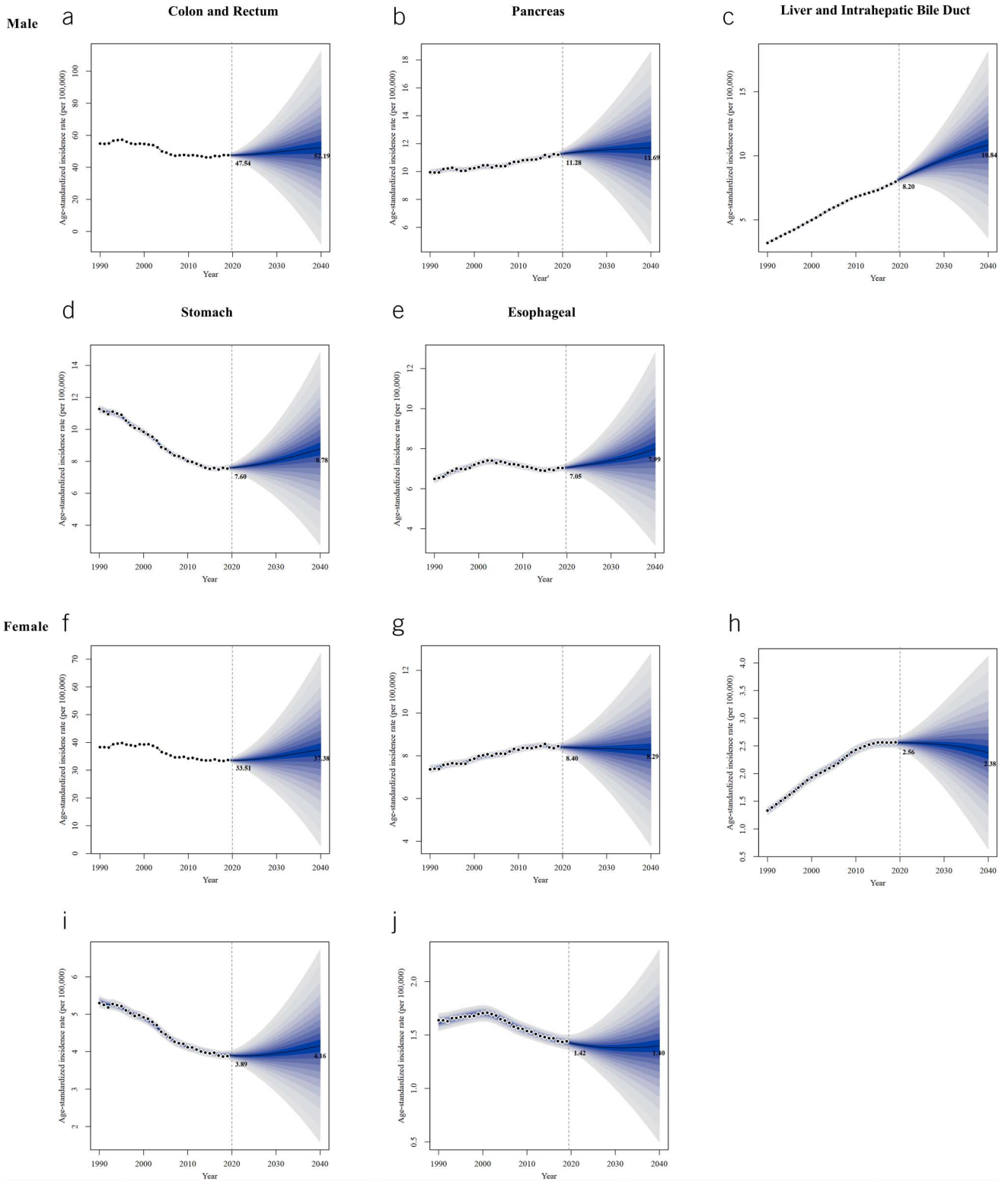

Figure 3. The temporal trends of age-standardized incidence rates (ASRs, per 100,000) of 5 major gastrointestinal cancers between 1990 and 2040 at the United States: (**a**) colorectal cancer in men, (**b**) pancreatic cancer in men, (**c**) liver cancer in men, (**d**) stomach cancer in men, (**e**) esophageal cancer in men, (f) colorectal cancer in women, (**g**) pancreas cancer in women, (**h**) liver cancer in women, (**i**) stomach cancer in women, and (**j**) esophageal cancer in women. In the Global Burden of Disease data set, observational values are represented by open dots. The dark blue shadow signifies the 95% highest density interval of predicted values. The mean predictive value is depicted as a solid black line. The point at which the prediction commences is marked by a vertical dashed line. ASRs, age-standardized rates.

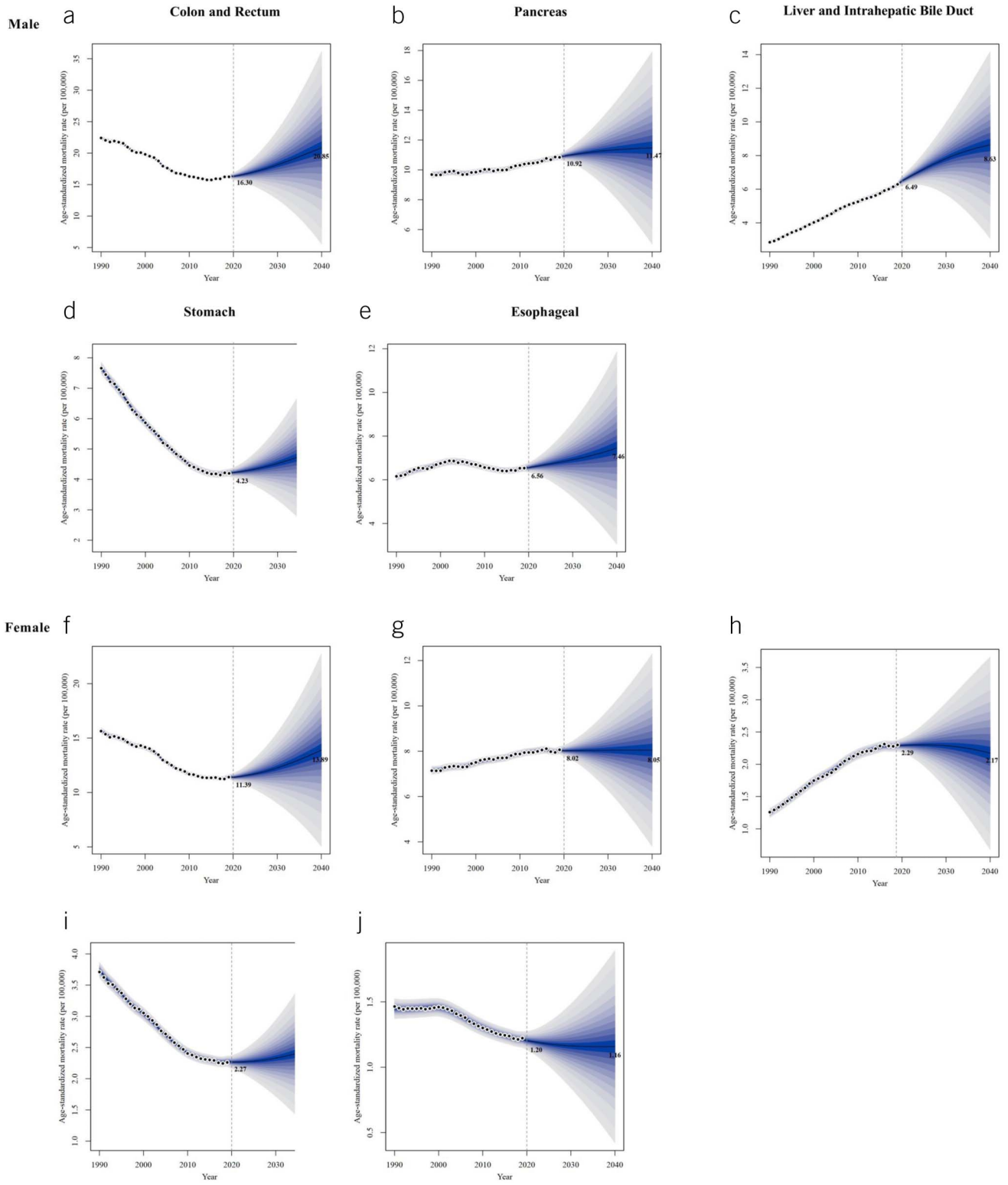

Figure 4. The temporal trends of age-standardized mortality rates (ASRs, per 100,000) of 5 major gastrointestinal cancers between 1990 and 2040 at the United States: (**a**) colorectal cancer in men, (**b**) pancreatic cancer in men, (**c**) liver cancer in men, (**d**) stomach cancer in men, (**e**) esophageal cancer in men, (**f**) colorectal cancer in women, (**g**) pancreas cancer in women, (**h**) liver cancer in women, (**i**) stomach cancer in women, and (**j**) esophageal cancer in women. In the Global Burden of Disease data set, observational values are represented by open dots. The dark blue shadow signifies the 95% highest density interval of predicted values. The mean predictive value is depicted as a solid black line. The point at which the prediction commences is marked by a vertical dashed line. ASRs, age-standardized rates.

Esophageal cancer

Owing to sparse data, incidence for AIAN individuals of esophageal cancer is excluded. For esophageal cancer, from 2016 to 2020, male individuals also had significantly higher average annual age-standardized incidence and mortality rates compared with female individuals. Incidence was highest among AIAN men (9.4 [7.8 to 11.4]), followed by White men (8.4 [8.3 to 85]), and among women, AIAN individuals also had the highest incidence (2.7 [1.9 to 3.6]). Mortality rates were highest in White men (7.6 [7.5 to 7.7]), while among women, rates were similar between White (1.5 [1.5 to 1.5]) and Black (1.5 [1.5 to 1.6]) individuals (Tables 1 and 2). Geographically, Maine had the highest average annual incidence rates for men (11.9 [10.9 to 13.0]) and Rhode Island had the highest incidence for women (2.5 [1.9 to 3.1]). West Virginia recorded the highest average annual male mortality (10.1 [9.3 to 11.0]), and Alaska recorded the highest female mortality (2.7 [1.8 to 3.8]) (see Figures S1, http://links.lww.com/AJG/D465 and S2, http://links.lww.com/AJG/D466; Tables S1, http://links.lww.com/AJG/D467 and S2, http://links.lww.com/AJG/D468). From 2000 to 2019, incidence rates decreased in Black men (AAPC: −4.48 [−4.95 to −4.04]), AAPI women (AAPC: −1.70 [−2.92 to −0.29]), and Hispanic (men: [AAPC: −1.47 (−1.99 to −0.89)]; women: [AAPC: −1.90 (−2.84 to −0.87)]), while stabilizing in other groups (Figure 1; Table S3, http://links.lww.com/AJG/D469). Owing to sparse data, incidence for AIAN individuals of esophageal cancer was excluded from trend analysis. From 2000 to 2020, mortality showed a declining trend across all racial and ethnic groups and genders (Figure 2; Table S4, http://links.lww.com/AJG/D470). By 2040, esophageal cancer incidence is projected to increase by 13.3% in men and decrease by 1.4% in women, while mortality is expected to increase by 13.7% in men and decrease by 3.3% in women (Figures 3 and 4).

DISCUSSION

In this study, we systematically analyzed the disparities and trends in incidence and mortality for 5 major gastrointestinal cancers, and forecasted the changes by 2040 with high spatial resolution and high-quality input data.

Colorectal cancer

We observed that male individuals consistently exhibit a higher burden of colorectal cancer, which may partially be explained by lifestyle factors such as higher rates of cigarette smoking, alcohol consumption, and intake of red and processed meats among men (20). However, a recent study estimated that known risk factors, including cigarette smoking and diet, can only explain about 33% of the sex difference in the incidence of colon cancer and 39% for rectal cancer (21), suggesting that undetermined risk factors played a role in these disparities.

The high incidence of colorectal cancer in Kentucky may be linked to elevated smoking and obesity rates (22). Despite state efforts to increase screening, significant barriers such as fear of screening, cost concerns, and limited access to free services, particularly in rural areas, have hindered progress (23,24). Moreover, limited funding for statewide screening programs exacerbates these challenges (22). The high colorectal cancer mortality rate in West Virginia is likely related to delayed diagnoses, low screening rates, and restricted healthcare access, especially in rural regions. While legislation supports screening, barriers such as lack of awareness, and insufficient provider recommendations persist, hindering uptake (25). Consequently, many cases are diagnosed at an advanced stage, resulting in poorer outcomes (26). High rates of comorbidities, including obesity, diabetes, and smoking, further contribute to the elevated mortality rates in this state (26).

From 2000 to 2020, the decrease in colorectal cancer rates was largely due to better lifestyle choices and widespread screening that allowed for the early detection and removal of precancerous lesions (27). However, the projected rise in colorectal cancer mortality in the United States from 2020 to 2040 could be driven by population aging, increasing incidence among younger individuals, and lifestyle factors such as rising obesity rates (28,29). Access disparities in screening also likely play a role. These findings underscore the importance of maintaining preventive measures and early detection strategies, although the specific contribution of each factor remains to be fully understood.

Pancreatic cancer

Pancreatic cancer incidence and mortality have consistently been higher in men than women and in Black individuals compared with other racial and ethnic groups. Cigarette smoking, which accounts for approximately 12% of the cases in men and 9% of the cases in women in the United States, may partly explain the difference in incidence between men and women (30), but not between White and Black men, as cigarette smoking continues to be higher among Black men and White women (31).

The high pancreatic cancer incidence of New Jersey may be associated with its dense population, industrial history, and common lifestyle risk factors such as smoking and obesity (32,33). In Rhode Island, an older population and late-stage diagnoses likely contribute to the state's highest male mortality rates (34). Similarly, Hawaii's high female mortality rate may be linked to limited healthcare access, leading to delayed treatment (32,34).

Advances in diagnostic techniques, such as more effective imaging and biomarker detection, may explain part of the increased incidence from 2000 to 2020, as cancers are now detected earlier (35). The projected increase in pancreatic cancer mortality from 2020 to 2040 could result from an aging population, the rising prevalence of risk factors such as obesity, diabetes, and smoking, and delays in diagnosis and limited treatment options (36–38). The improvements in survival rates likely reflect better management and targeted treatments for those diagnosed early or at a resectable stage, but these advancements do not yet compensate for the overall rise in incidence driven by aging and lifestyle factors. Given the poor prognosis associated with pancreatic cancer, these trends highlight the need for enhanced preventive strategies, earlier diagnostic interventions, and more effective therapeutic options.

Liver cancer

The higher burden of liver cancer in men could be linked to higher rates of smoking, alcohol consumption, and hepatitis C virus (HCV) infection (30). Among AIAN populations, the high liver cancer incidence is likely driven by metabolic, viral, and behavioral factors. Obesity and diabetes, 2 major contributors to metabolic-associated steatotic liver disease (MASLD), are particularly prevalent among AIAN individuals, leading to progression into nonalcoholic steatohepatitis, cirrhosis, and eventually liver cancer (39,40). Obesity and diabetes are also linked to an increased risk of HCV infection, which further

exacerbates liver cancer risk (41). In addition, high levels of alcohol consumption and tobacco use in AIAN communities contribute to the risk of cirrhosis, chronic liver disease, and liver cancer (39,42). Recent studies have shown that genetic factors, especially related to the development of MASLD and its progression, might be more prominent in specific ethnic groups, suggesting further exploration into these pathways could shed light on disparities (43). Higher mortality rates from hepatocellular carcinoma (HCC) in Hispanic populations may be related to several interrelated factors. First, MASLD has become a leading cause of HCC-related mortality, particularly among older individuals, with Hispanic populations experiencing the highest burden (44,45). Hispanic individuals are often diagnosed with liver cancer at more advanced stages due to delayed access to health care and a lack of regular screening programs, reducing their chances of receiving curative treatments such as liver transplants (46–48). In addition, barriers to liver transplant eligibility, such as high rates of comorbid conditions and cultural factors, significantly limit treatment options (49–51). In addition, potential genetic predispositions may further contribute to these observed disparities (52).

Texas continues to report the highest liver cancer incidence in the United States (53), likely driven by widespread alcohol-related liver disease and metabolic syndrome, including obesity and diabetes (53,54). High mortality rates of Mississippi are similarly linked to elevated levels of obesity, smoking, chronic hepatitis infections, and significant healthcare access disparities, which result in delayed diagnoses and poorer outcomes (55).

From 2000 to 2020, liver cancer incidence rates increased among AIAN men, and White, AIAN, and Hispanic women, while stabilizing or declining in other groups. While HCV has been a traditional risk factor (52), its impact has been diminishing in the United States. Conversely, MASLD has emerged as a leading contributor to HCC, particularly in the Hispanic and White populations (56). However, MASLD carried a lower progression risk compared with viral hepatitis infections (56). Research indicates that HBV is a primary risk factor of HCC among AAPI individuals (57), and the decline in HCC incidence in this group can be linked to improved HBV management strategies, including enhanced screening and vaccination for US-born children (57). Regular biannual monitoring for chronic HBV in AAPI individuals has played a crucial role in reducing HCC mortality (58). Our study shows that the incidence of liver cancer in men is expected to increase by 2040. This rise was likely due to escalating obesity and diabetes epidemics, compounded by disruptions to hepatitis B and C diagnostics and treatment during the COVID-19 pandemic, threatening to reverse gains in viral hepatitis control (59). Similar to global trends (59), liver cancer mortality is also expected to rise by 2040, with several factors potentially contributing to this increase. While advancements have been made in HCV prevention and treatment, the long-term effects of chronic HCV infection may continue to impact mortality (60). In addition, chronic alcohol use, which can lead to cirrhosis, and the increasing prevalence of MASLD associated with obesity and diabetes, may exacerbate liver damage and elevate mortality risks over time (60,61).

Stomach cancer

Stomach cancer incidence and mortality rates have historically been higher in male individuals than female individuals, with significant disparities observed in AIAN and Hispanic women. Approximately 20% of stomach cancer cases in the United States are linked to excess body weight and cigarette smoking (30), factors that may partially explain the higher incidence rates observed in Hispanic women, given the high prevalence of overweight conditions in this demographic (31).

The high incidence rates in New York and New Jersey may be associated with urban lifestyle factors, including smoking and diets high in processed or pickled foods (62,63). By contrast, higher mortality rates of Delaware and Mississippi may result from delayed diagnoses and limited access to healthcare services (64).

Stomach cancers can be categorically divided into 2 primary topographical subsites: noncardia and the cardia (CGC). From 2000 to 2020, the overall decline in stomach cancer rates across most racial and ethnic groups may be linked to improved food preservation and hygiene, leading to a reduction in H. pylori infection (65). However, there has been a notable rise in the incidence of CGC among non-Hispanic Whites, potentially affecting the overall declining trend of stomach cancer in this demographic (66). Projections indicate that contrary to the anticipated decline in stomach cancer rates observed in most countries, the United States was seeing an uptick, especially in younger generations, with a notable rise in proximal and noncardia stomach cancers linked to excess weight and obesity (67,68). Lifestyle factors such as consumption of salt-preserved foods, alcohol, and body fat, particularly for cardia gastric cancer, remained significant. In addition, increased consumption of processed, barbecued meats; low fruit and vegetable intake; and smoking have also been implicated (69). The projected increase in US stomach cancer mortality from 2020 to 2040 could be driven by several factors. While efforts to prevent Helicobacter pylori infection have been somewhat effective, the emergence of antibiotic-resistant strains over time may contribute to higher mortality rates (70). Poor dietary habits, the increasing prevalence of obesity, and conditions associated with obesity, such as gastroesophageal reflux disease (GERD), further elevate the risk (69). In addition, the aging population and delays in diagnosis are likely to worsen outcomes, particularly in economically disadvantaged populations (69).

Esophageal cancer

The disproportionate burden of esophageal cancer incidence among men and AIAN individuals may be partially explained by higher levels of obesity within these populations. For example, in 2017–2018, the rate of overweight adults was 77% among men and 69% among women (30). In addition, in 2018, the obesity rate was 48% for the AIAN population and 31% for the White population (3).

Certain geographic regions, such as Maine and Rhode Island, also exhibit distinct characteristics that may explain their higher incidence of esophageal cancer. In Maine, elevated rates of obesity and tobacco use among adolescents and young adults may partly account for the increased incidence of esophageal cancer (71). In Rhode Island, the rising adult obesity rate, combined with relatively high levels of alcohol consumption, could contribute to the state's elevated esophageal cancer incidence (72). Furthermore, smoking and alcohol consumption are likely significant contributors to the high esophageal cancer mortality observed in West Virginia and Alaska. The socioeconomic challenges in West Virginia and the geographic isolation of Alaska, which leads to

unequal access to health care, may further exacerbate the high mortality rates in these regions (73,74).

From 2000 to 2020, esophageal cancer incidence and mortality were decreasing, which may reflect declining smoking rates (75). Last, a slight increase in esophageal cancer rates among men was projected, likely due to a rise in esophageal adenocarcinoma associated with Barrett esophagus, GERD, obesity, and a decrease in Helicobacter pylori infection rates (76). The projected increase in esophageal cancer mortality in the United States from 2020 to 2040 may be attributed to several factors. The rising prevalence of obesity and GERD may elevate the risk of esophageal adenocarcinoma, leading to higher mortality (76). Moreover, high-risk groups continue to experience elevated rates of tobacco and alcohol use, which may sustain esophageal cancer mortality. In addition, the aging population may play a significant role, as older adults are more susceptible to esophageal cancer and tend to have poorer treatment outcomes.

Limitations

However, this study had some limitations. Owing to the limited data on incidence and mortality among non-White individuals, our examination was confined to geographic differences in incidence and mortality among White individuals. In addition, inaccuracies in the classification of race and ethnicity in medical records and death certificates could have led to an underestimation of the incidence and mortality rates for race/ethnicity groups other than White and Black individuals. Furthermore, the Global Burden of Disease database lacked racial data, thereby making it impossible to predict future cancer incidence and mortality trends among different racial groups.

In conclusion, using high-quality population-based incidence and mortality data, our study revealed a strong heterogeneity in the incidence and/or mortality trends for 5 gastrointestinal cancers in the United States, with a projected increase in incidence and mortality for most diseases by 2040. Further research is needed to elucidate the underlying reasons for these patterns, informing interventions aimed at halting the rising burden of gastrointestinal cancers and mitigating the sociodemographic disparities. Meanwhile, improving access to care and health promotions for all populations is essential to reduce persistent racial/ethnic and geographic mortality and incidence disparities for some gastrointestinal cancers. A long-term best practice approach must include the primary prevention of smoking and obesity, along with careful monitoring of trends using high-quality population-based cancer registries and corresponding national registration sources.

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CONFLICTS OF INTEREST

Guarantor of the article: Fan Li, PhD.

Specific author contributions: Y.H. (Conceptualization: Equal; Data curation: Equal; Methodology: Equal; Software: Lead; Visualization: Lead; Writing—original draft: Lead). H.H. (Conceptualization: Equal; Data curation: Equal; Methodology: Equal). T.W. (Conceptualization: Equal; Data curation: Equal; Methodology: Equal). A.Z. (Conceptualization: Equal; Data curation: Equal). H.Z. (Conceptualization: Equal; Data curation: Equal). Z.Z. (Conceptualization: Equal; Data curation: Equal). Y.X. (Conceptualization: Equal; Data curation: Equal). R.W. (Data curation: Equal; Investigation: Equal). N.W. (Data curation: Equal; Investigation: Equal). X.L. (Data curation: Equal; Investigation: Equal). J.L. (Data curation: Equal). Y.L. (Conceptualization: Equal; Data curation: Equal; Resources: Equal; Supervision: Equal; Writing—review & editing: Equal). F.L. (Conceptualization: Equal; Data curation: Equal; Resources: Equal; Supervision: Equal; Writing—review & editing: Equal).

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Potential competing interests: None to report.

Data statement: The data utilized in this study can be found in the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/), National Center for Health Statistics (NCHS), and 2019 Global Burden of Disease (GBD) study (https://vizhub.healthdata.org/gbd-results/). Analytic code and any additional information required to reanalyze the data reported in this paper can be obtained from the corresponding author upon reasonable request, following the publication of this article.

Study Highlights

WHAT IS KNOWN

- ✓ Gastrointestinal cancers present a significant burden in the United States.
- ✓ It is urgent to understand the incidence and mortality trends for effective healthcare planning.
- ✓ Previous studies reported on incidence and mortality patterns for individual gastrointestinal cancers in the United States.
- ✓ These studies addressed individual cancer types rather than gastrointestinal cancers overall.

WHAT IS NEW HERE

- ✓ Men's incidence and mortality for gastrointestinal cancers are 1 to 5 times higher than women's.
- ✓ The incidence and death rates of 5 major gastrointestinal cancers varied remarkably across 51 states.
- ✓ Incidence rates for pancreas cancer increased, except for a stabilization for American Indian and Alaska Native women.
- ✓ The incidence for liver cancer increased among White women, Hispanic men, and American Indian and Alaska Native.
- ✓ Mortality rates for pancreas cancer increased among White men and Hispanics women.
- ✓ Future incidence and mortality of 5 gastrointestinal cancers are expected to continue to rise.

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