World Journal of Gastroenterology, Hepatology and Endoscopy ISSN 2766-788X | Volume 31

Research Article Open Access

Epidemiology of Early-Onset Gastrointestinal Cancers: A Systematic Analysis from The Global Burden of Disease Study 2021

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Received: 09 May 2026
Accepted: 22 May 2026
Published: 25 May 2026
J Short Name: WJGHE

Keywords:

Global Burden of Disease; Early-Onset Gastrointestinal Cancers; Incidence and Death; Risk Factor; Temporal Trends

Citation:

Jianjun Yang, Epidemiology of Early-Onset Gastrointestinal Cancers: A Systematic Analysis from The Global Burden of Disease Study 2021.World Jour of Gastro and Hepatology® 2026; V31(8): 1-11

1. Summary

The increasing incidence of early-onset gastrointestinal cancers (EOGCs) is becoming a primary global health concern. A comprehensive understanding of the disease burden of EOGCs is crucial for developing effective prevention and treatment strategies. Data on these cancers were extracted from the GBD 2021 database. The caseloads, age-standardised rates (ASRs) per 100 000 people, and risk factors were determined at the global, regional and country levels. There were 499,801 new cases of EOGCs and 285,895 related deaths. The most common cancer and the leading cause of cancer-related death was colon and rectum cancer. The burden of EOGCs was notably greater among males than among females, which was reflected by male-to-female ratios of 1.92 for incidence and 2.00 for death. East Asia had the heaviest burden of EOGCs. The AAPC in the incidence of colon and rectum cancer slightly increased (AAPC: 0.37 [95% CI 0.24 to 0.50]). Countries and territories with higher Sociodemographic Index (SDI) tended to have lower growth of AAPC in terms of the ASIR and ASDR. It was projected that by 2035, the global incidence of colon and rectum cancer will increase by 28.55% compared with that in 2021, with the total number of cases expected to reach approximately 272450.25 (95% UI 175889.95 to 369010.55). This study provided a basis for future investigations of aetiological factors for the occurrence of EOGCs; the development of prevention strategies based on local characteristics and socioeconomic and other conditions; and the formulation of more targeted interventions.

2. Introduction

Gastrointestinal (GI) malignancies represent a critical challenge to global health systems. Recent epidemiological studies reveal that during 2022, approximately 20 million cancer diagnoses and 9.7 million cancer-related fatalities were recorded worldwide, with GI-related neoplasms responsible for 26.3% of total cases and 38.1% of death outcomes [1,2]. While GI cancer predominantly affects older adults, epidemiologic data have indicated a significant increase in the incidence of early-onset GI cancers in the past three decades [3-5]. Notably, several GI tract malignancies consistently rank among the most prevalent and lethal cancers globally, imposing substantial socioeconomic pressures on healthcare infrastructures worldwide [6].

Younger adults aged 15–49 years diagnosed with early-onset gastrointestinal cancers (EOGCs) – such as colon and rectum, stomach, liver, esophageal, pancreatic, gallbladder and biliary tract cancers – demonstrate distinct biological, epidemiological, and clinical

features that are notably different from those observed in older adults [3-5]. Furthermore, these younger cohorts encounter a variety of age-related challenges spanning fertility concerns, treatment-related sequelae, financial strains, and psychological distress [7,8]. Sung and colleagues revealed a considerable increase in the incidence rates of GI cancers among younger adults, including colon and rectum, gallbladder, and pancreatic cancers [9]. Moreover, a recent study demonstrated increases in the incidence rates of pancreatic cancer as well as gallbladder and biliary tract cancers among in individuals younger than 50 years [10].

While previous investigations have assessed gastrointestinal cancer burdens, such analyses have largely been confined to particular geographic regions or countries experiencing data scarcity, especially within East Asian populations [11,12]. Current epidemiological patterns concerning worldwide incidence and death trends of early-onset gastrointestinal cancers (EOGCs) remain insufficiently documented. Although emerging studies have investigated certain digestive tract malignancies in younger populations, a systematic analysis of their worldwide and subregional prevalence patterns remains outstanding [13-15]. This study aimed to examine the burden, trends, and potential determinants of EOGCs across various nations and territories from 1990 to 2021 by using data from the Global Burden of Disease (GBD) Study 2021. Additionally, this study aimed to project the cancer burden through 2035. A comprehensive grasp of current burden distributions is essential for helping policymakers allocate health resources more effectively and for alleviating the impact of EOGCs.

3. Methods

3.1. Data Source

The dataset originates from the GBD 2021 research initiative, which maintains an extensive repository containing in-depth evaluations of 369 distinct medical conditions and 88 health risk determinants across 204 global jurisdictions. Annual statistics on EOGC cases, including incidence and death rates, were retrieved via the Global Health Data Exchange platform, a digital epidemiological resource maintained by the Institute for Health Metrics and Evaluation.

3.2. Estimation Methods

The methodology for determining the cancer burden based on data from the GBD 2021 study has been described previously. In summary, information on EOGCs was obtained from population-based cancer registries, vital registration systems, and verbal autopsy studies and categorized according to the 10th revision of the International Classification of Diseases. In this analysis, EOGCs were defined as cancers occurring in the gastrointestinal tract of individuals aged 15–49 years [9, 16]. Our analysis encompassed six specific EOGC categories: colon and rectum cancer, stomach cancer, liver cancer, esophageal cancer, pancreatic cancer, gallbladder and biliary tract cancer [1]. We aimed to assess the burden of disease across different dimensions, including sexes, years, cancer types and locations (covering 21 GBD regions, 204 nations, and five SDI categories). The SDI serves as a multidimensional indicator of regional development, calculated through aggregated metrics of fertility patterns, educational attainment levels, and economic productivity.

The Socio-demographic Index (SDI) serves as a composite indicator integrating educational attainment, fertility rates, and income levels, classified into five distinct tiers: high, high-middle, middle, low-middle, and low [17]. Our investigation quantified death proportions linked to EOGCs stemming from modifiable risks including tobacco consumption, alcohol intake, elevated body mass index, hyperglycemia, physical inactivity, and suboptimal dietary patterns. Detailed operational definitions and epidemiological evidence supporting these risk factor associations are documented in established research.

3.3. Statistical Analysis

The study estimated of the incidence and death rates of EOGCs, with 95% uncertainty intervals (UIs) calculated as the 2.5th and 97.5th ranked values from a posterior distribution of 1000 draws. Monte Carlo simulations, representing the 2.5th-97.5th percentile range of posterior estimates. The standardization process employed the following formula to eliminate demographic variation:

$$\text{Age standardised rate}=\left(\sum_{i=1}^{A}[a_i w_i]\right)/\left(\sum_{i=1}^{A}a_i\right)\times 100{,}000$$

where ai is the age-specific rate, and wi is the weight in the same age subgroup of the chosen reference standard population (in which i denotes the ith age class); A is the upper age limit.

Additionally, a joinpoint regression model was employed to estimate the average annual percentage change (AAPC) and its corresponding 95% confidence interval (CI) based on the ASRs of EOGCs from 1990 to 2021. The specific equation for calculating the AAPC is presented below:

$$\text{AAPC}=\left\{\exp\left(\sum[(w_i b_i)]/\left(\sum w_i\right)\right)-1\right\}\times 100$$

Where bi is the slope coefficient for the ith segment with i indexing the segments in the desired range of years; and wi is the length of each segment in the range of years.

The AAPC quantifies directional trends as either positive (increase), negative (decrease), or neutral (no change). Statistical significance was determined by evaluating whether both the AAPC value and its 95% CI boundaries were concordant: trends were classified as increasing when both AAPC and its 95% CI exceeded zero, or decreasing when both values fell below zero. Stability was concluded if the confidence interval encompassed zero.

To project upcoming patterns, the study utilized the Bayesian age-period-cohort (BAPC) model integrated with the integrated nested Laplace approximation (INLA) framework. This combined approach enabled precise approximation of marginal posterior distributions while resolving computational challenges related to mixing efficiency and convergence stability that typically affect conventional Bayesian techniques dependent on Markov chain Monte Carlo (MCMC) sampling. Analysis of GBD records spanning 1990-2021 confirmed the BAPC model's reliability in forecasting long-term trajectories. Statistical computations and graphical

representations were generated using Joinpoint Regression (v5.0.2) alongside R programming language (v4.2.3), with a predefined significance level of $P < 0.05$.

4. Results

4.1. Global Landscape of EOGCs in 2021

The global incidence rates, death rates, and ASRs of EOGCs in 2021 among individuals aged 15–49 years are presented in Table 1. In 2021, a total of 499,801 new cases of cancer and 285,895 cancer-related deaths were reported globally among individuals aged 15–49 years (Table 1). Colorectal cancer was the most prevalent EOGC and the leading cause of EOGC-related death, with an ASIR of 5.15 (95% UI 4.68 to 5.67) and an ASDR of 1.93 (95% UI 1.76 to 2.11) per 100,000 people, followed by stomach and liver cancers (Table 1).

As age advanced, both sexes experienced notable increases in absolute caseloads, ASIRs, and ASDRs (Figure 1. A and B). Overall, the burden of EOGCs was notably greater among males than females, as reflected by male-to-female ratios of 1.92 for incidence and 2.00 for death (Table 1). Gallbladder and biliary tract cancer was the only malignancy that exhibited a marginally higher ASDR in females than in males. Among adolescents (15–24 years old), young and middle-aged adults (25–39 years old), and middle-aged individuals (40–49 years old), the primary factor contributing to the increasing incidence and death rates of EOGCs was colon and rectum cancer (Tables S1-3). The ASIRs per 100,000 people for colon and rectum cancer among the adolescents, young and middle-aged adults, and middle-aged individuals were 0.46 (95% UI 0.42 to 0.51), 3.64 (95% UI 3.30 to 3.99), and 14.44 (95% UI 13.13 to 15.90) (Tables S1-3), respectively. After colon and rectum cancer, stomach and liver cancers were the strongest contributing factors to the incidence and death rates of EOGCs. However, the ASDR (5.57 [95% UI 4.83 to 6.47]) of stomach cancer among middle-aged individuals ranked first among EOGCs (Table S3). With increasing age, the ASIR and ASDR indicated that the proportion of esophageal, pancreatic, gallbladder and biliary tract cancers among EOGCs gradually increased. Specifically, among individuals aged 15–19 to 45–49 years, the proportions of new cases and cancer-related deaths increased from 3.97% to 20.94% and from 5.99% to 28.11%, respectively (Figure 1. C-F).

Table 1: Burden of gastrointestinal cancers incidence and death among the population aged 15 to 49 years old worldwide in 2021.

Cancer types	Both sexes		Men		Women	
	Cases (95% UI)	**ASIR (95% UI)**	**Cases (95% UI)**	**ASIR (95% UI)**	**Cases (95% UI)**	**ASIR (95% UI)**
Colon and rectum	211890.37 (193832.21, 231271.92)	5.15 (4.68, 5.67)	126665.90 (15790.83, 144644.68)	6.11 (5.30, 7.00)	85224.46 (77872.97, 93406.82)	4.17 (3.80, 4.61)
Stomach	125121.53 (107273.82, 144782.62)	3.04 (2.61, 3.52)	81784.78 (66841.40, 101135.61)	3.94 (3.17, 4.83)	43335.75 (38787.65, 48812.97)	2.13 (1.89, 2.41)
Liver	74947.90 (65248.37, 87629.60)	1.82 (1.57, 2.16)	59036.65 (49997.92, 72069.14)	2.84 (2.36, 3.49)	15911.25 (14229.31, 17833.53)	0.78 (0.69, 0.89)
Oeophageal	42698.14 (38138.30, 47972.14)	1.24 (1.09, 1.40)	32787.09 (28342.25, 37779.99)	1.88 (1.62, 2.18)	9911.05 (8365.20, 11798.71)	0.58 (0.49, 0.70)
Pancreatic	31530.74 (28670.64, 34517.36)	0.76 (0.69, 0.84)	21170.80 (18931.01, 23780.58)	1.02 (0.90, 1.14)	10359.94 (9482.77, 11205.03)	0.50 (0.46, 0.55)
Gallbladder and biliary tract	13611.93 (10670.03, 15790.83)	0.40 (0.31, 0.46)	6921.55 (4621.56, 8285.57)	0.40 (0.27, 0.48)	6690.38 (5201.29, 8149.55)	0.39 (0.30, 0.48)
	Deaths (95% UI)	**ASDR (95% UI)**	**Deaths (95% UI)**	**ASDR (95% UI)**	**Deaths (95% UI)**	**ASDR (95% UI)**
Colon and rectum	79504.29 (72699.21, 86539.49)	1.93 (1.76, 2.11)	47358.97 (41410.58, 53363.61)	2.29 (2.00, 2.59)	32145.32 (29390.94, 35098.09)	1.57 (1.43, 1.73)
Stomach	78870.88 (68703.65, 90835.64)	1.92 (1.66, 2.20)	49813.87 (41140.07, 61050.50)	2.40 (1.94, 2.90)	29057.01 (26115.42, 32184.55)	1.43 (1.28, 1.59)
Liver	58825.09 (51340.38, 68517.47)	1.43 (1.23, 1.69)	45929.63 (38909.14, 55822.25)	2.21 (1.85, 2.70)	12895.46 (11581.97, 14375.11)	0.64 (0.56, 0.72)

Oeophageal	32921.65 (29481.11, 36952.57)	0.95 (0.85, 1.08)	25301.81 (22060.71, 28917.45)	1.45 (1.26, 1.68)	7619.84 (6454.63, 9119.71)	0.45 (0.38, 0.54)
Pancreatic	26995.59 (24492.85, 29597.71)	0.65 (0.59, 0.72)	18251.45 (16264.91, 20502.31)	0.88 (0.78, 0.99)	8744.14 (7986.45, 9485.56)	0.43 (0.39, 0.47)
Gallbladder and biliary tract	8777.92 (6942.23, 10235.13)	0.26 (0.20, 0.30)	4082.09 (2677.75, 4842.28)	0.24 (0.15, 0.28)	4695.83 (3586.10, 5755.14)	0.27 (0.21, 0.34)

Note: ASIR, age-standardized incidence rates per 100000 population; ASDR, age-standardized death rates per 100000 population; UI, uncertainty interval.

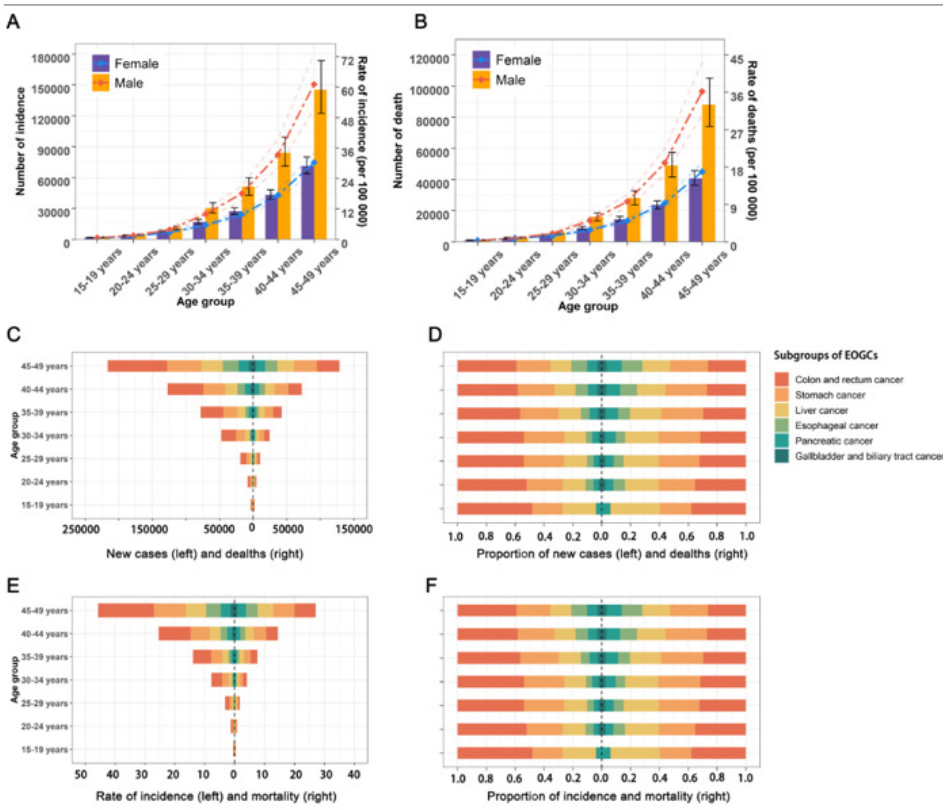

Figure 1: Global burden of EOGCs in2021. A. Global age-specific counts and rates of incident cases by sex. B. Global age-specific counts and rates of deaths by sex. C. Global age-specific counts of incident cases and deaths by cancer type. D. Global age-specific proportion of inc2 ident cases and deaths by cancer type. E. Global age-specific rates of incident cases and deaths by cancer type. F. Global age-specific proportion of incident cases and deaths by cancer type.

4.2. SDI-Related Disparities and Geographic Differences in The Burden of Eogcs

The global burden of EOGCs varied substantially across the five levels of the SDI (Figure 2. A and B). In 2021, colon and rectum, stomach, and liver cancers accounted for more than 70% of the total estimated EOGCs cases and related deaths (Table S4). The high-middle-SDI countries presented the highest ASIRs and ASDRs for EOGCs, whereas the low-SDI countries presented the lowest ASIRs, and the high-SDI countries presented the lowest ASDRs. Notably, in high-middle-SDI countries, colon and rectum cancer was the most prevalent EOGC and the leading cause of EOGCs-related death, with an ASIR of 8.10 (95% UI 6.92 to 9.54) and an ASDR of 2.53 (95% UI 2.20 to 2.93) per 100,000 people, followed by stomach cancer (Table S4).

Similarly, there were marked regional variations in the ASIRs and ASDRs for EOGCs in 2021 (Figure 2. A and B). East Asia recorded the highest ASIRs for stomach cancer and liver cancer at 6.99 and 4.58 per 100,000 people, respectively (Figure 2. C and D, Table S5). The highest ASDRs for colon and rectum cancer and liver cancer were also observed in East Asia, with ASDRs of 3.01 and 3.36, respectively, per 100,000 people in 2021 (Table S5). Western Sub-Saharan Africa reported the lowest ASIRs for colon and rectum, stomach, gallbladder and biliary tract cancers, with ASIRs of 1.07, 1.20 and 0.01 per 100,000 people, respectively, and reported the lowest ASDRs for colon and rectum cancer and gallbladder and biliary tract cancer, with rates of 0.78 and 0.01 cases per 100,000 people, respectively (Table S5).

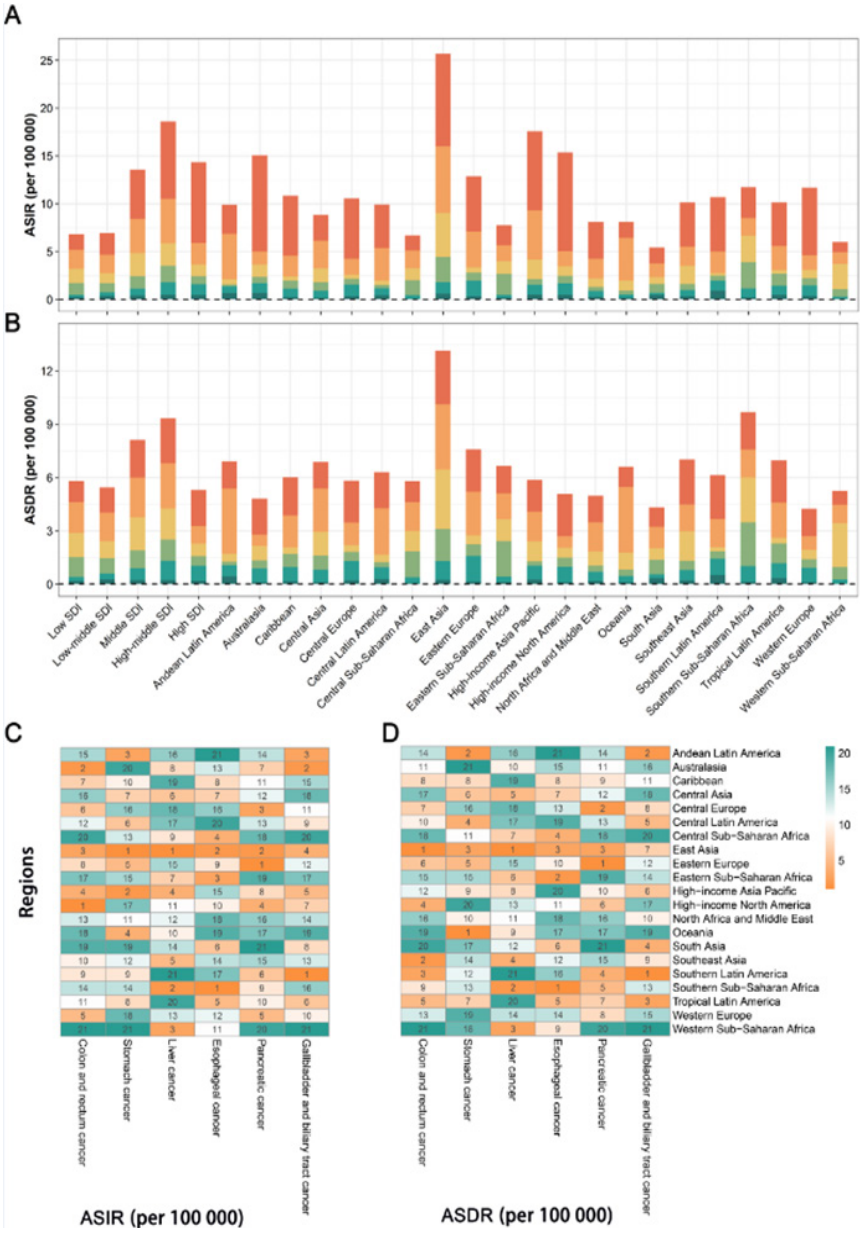

Figure 2: Regional burden of EOGCs in 2021.

A. ASIR by region and sociodemographic index for EOGCs.

B. ASDR by region and sociodemographic index for EOGCs.

C. Rankings of regions by ASIR for EOGCs.

D. Rankings of regions by ASDR for EOGCs.

4.3. Global Cancer Burden in Different Countries

The burden of EOGCs in 2021 showed significant variability across 204 countries or territories (Figure 3 and Figure S1). Monaco presented the highest ASIR for colon and rectum cancer (14.93 per 100,000 people [95% UI 9.13 to 22.66]), whereas Seychelles reported the highest ASDR for colon and rectum cancer (3.90 per 100,000 people [95% UI 2.87 to 5.17]) (Figure 3 and S1. A). In contrast, Mozambique had the lowest ASIR for colon and rectum cancer (0.49 per 100,000 people [95% UI 0.31 to 0.73]), whereas Oman presented the lowest ASDR (0.35 per 100,000 people [95% UI 0.22 to 0.54]). Afghanistan recorded both the highest ASIR (9.95 per 100,000 people [95% UI 4.86 to 15.65]) and the highest ASDR (9.00 per 100,000 people [95% UI 4.34 to 14.05]) for stomach cancer (Figure 3 and S1. B). Conversely, Morocco had the lowest ASIR for stomach cancer (0.48 per 100,000 people [95% UI 0.31 to 0.74]), whereas Kuwait presented the lowest ASDR (0.31 per 100,000 people [95% UI 0.24 to 0.39]). Mongolia demonstrated the highest ASIR for liver cancer (12.93 per 100,000 people [95% UI 8.43 to 19.22]) and ASDR (12.02 per 100,000 people [95% UI 7.85 to 17.76]). In contrast, Morocco demonstrated the lowest ASIR (0.11 per 100,000 people [95% UI 0.06 to 0.19]) and the lowest ASDR (0.10 per 100,000 people [95% UI 0.05 to 0.17]) for liver cancer (Figure 3 and S1. C). The highest ASIRs and ASDRs for esophageal, pancreatic, gallbladder and biliary tract cancers were observed in Malawi, Greenland, and Thailand, respectively. EOGCs impose a severe public health challenge in China, with colon and rectum, stomach, and liver cancers being especially severe (Figure 3 and S1. D-F). The ASDRs for these cancers reached 3.00 (95% UI 2.37 to 3.73), 3.66 (95% UI 2.84 to 4.69), and 3.38 (95% UI 2.58 to 4.42) per 100,000 people respectively.

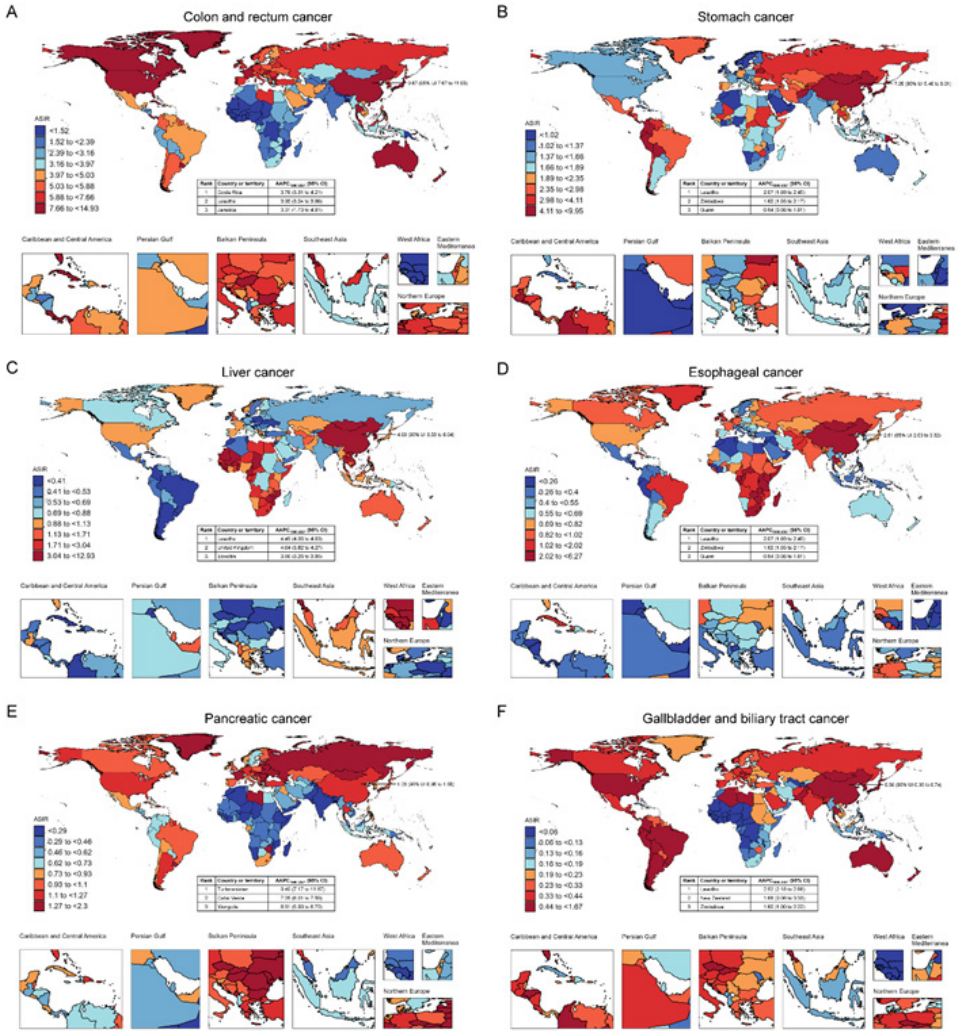

Figure 3: World maps depicting the ASIR burden of EOGCs in 2021.
A. The global burden of ASIR for colon and rectum cancer in 2021; B. The global burden of ASIR for stomach cancer in 2021; C. The global burden of ASIR for liver cancer in 2021; D. The global burden of ASIR for esophageal cancer in 2021; E. The global burden of ASIR for pancreatic cancer in 2021; F. The global burden of ASIR for gallbladder and biliary tract cancer in 2021.

4.4. Evolving Trend of EOGCs

The changes in the ASIRs and ASDRs of EOGCs from 1990 to 2021 were significant across the SDI and GBD regions (Figure 4 and S2). For high-middle-SDI regions, the AAPC in the incidence of colon and rectum cancer demonstrated the most pronounced upwards trend (AAPC: 0.96 [95% CI 0.66 to 1.26]) (Figure 4. A). However, the magnitude of decline in EOGCs was most pronounced in regions characterized by high-middle and high SDIs. The most notable decline in stomach, liver, pancreatic, gallbladder and biliary tract cancers was observed in high-SDI countries in terms of ASDRs (AAPC: -3.55 [95% CI -3.70 to -3.39], -1.50 [95% CI -1.99 to -1.00], -0.64 [95% CI -0.83 to -0.44] and -2.19 [95% CI -2.35 to -2.03]) (Figure S2. B-F). Overall, the incidence of colon and rectum cancer tended to increase (AAPC: 0.37 [95% CI 0.24 to 0.50]), and the most significant increases were observed in Central Latin America (AAPC: 2.56 [95% CI 2.28 to 2.85]). During the study period, the incidence of colon and rectum cancer increased most markedly in Costa Rica (AAPC: 3.76 [95% CI 3.31 to 4.21]), followed by Lesotho and Jamaica (Table S6). Similarly, the number of deaths from colon and rectum cancer increased most significantly in Lesotho (AAPC: 3.31 [95% CI 2.99 to 3.64]), followed by Costa Rica and Jamaica (Figure S1A). In Lesotho, the AAPC in the incidence and death rates of stomach cancer, liver cancer, esophageal cancer, and gallbladder and biliary tract cancers demonstrated the most pronounced increasing trends (Table S6). The incidence and death rates of pancreatic cancer rose most significantly in Turkmenistan (AAPC: 9.49 [95% CI 7.17 to 11.87], 9.48 [95% CI 7.12 to 11.89]), followed by Cabo Verde and Mongolia (Tables S6-7).

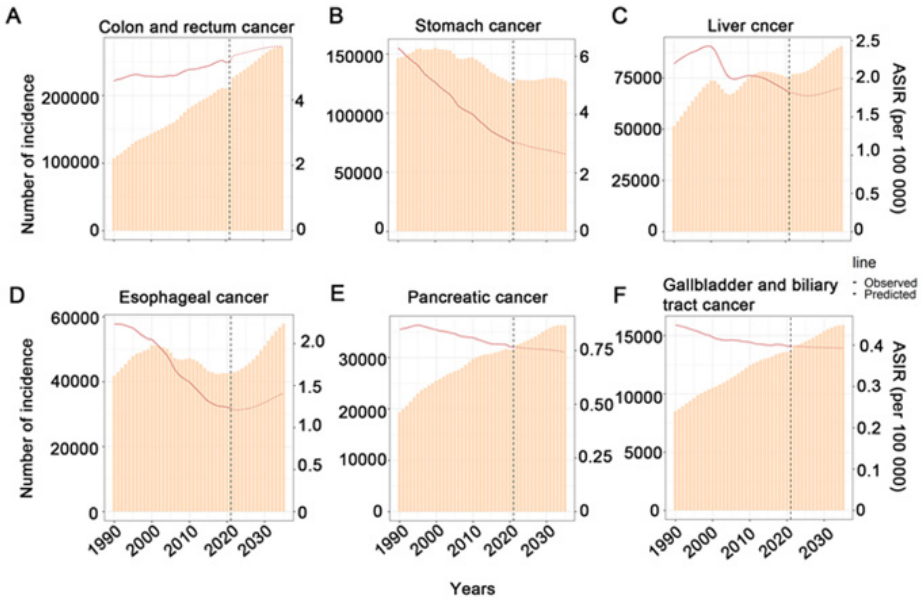

Figure 4: Temporal trend in burden of EOGCs in incidence from 1990 to 2021. A. Colon and rectum cancer; B. Stomach cancer; C. Liver cancer; D. Esophageal cancer; E. Pancreatic cancer; F. Gallbladder and biliary tract cancer.

4.5. Global Disease Burden Prediction for Eogcs To 2035

The future trends of ASIR, ASDR, and total cases of EOGCs from 2022 to 2035 were significant across the six distinct types of EOGCs. It was projected that by 2035, the global incidence of colon and rectum cancer will increase by 28.55% compared with that in 2021, with the total number of cases expected to reach approximately 272450.25 (95% UI 175889.95 to 369010.55) (Tables S8-9). Concurrently, the ASIR was expected to exhibit a gradual upwards trend after 1990, peaking at 5.63 (95% UI 3.63 to 7.62) per 100,000 people by 2035 (Figure 5. A, Table S8). Moreover, the number of global deaths due to colon and rectum cancer was forecasted to initially increase, peaking at an estimated 87,664.92 deaths (95% UI 55,370.37 to 119,959.46) by 2035 (Figure S3. A, Table S9). The ASIRs and ASDRs of stomach, pancreatic, gallbladder and biliary tract cancers were expected to exhibit a marked downwards trend (Figure 5 and S3, Tables S8 and S9). Among them, stomach cancer showed the most significant downwards trend (ASIR: 2.64 [95% UI 1.62 to 3.67], ASDR: 1.53 [95% UI 0.87 to 2.18] per 100,000 people) by 2035 (Figure 5 and S3. B). By 2035, the total number of cases was predicted to reach approximately 90469.32 (95% UI 19500.22 to 161579.81) for liver cancer and 57854.95 (95% UI 24614.28 to 91234.68) for esophageal cancer (Figure 5 and S3. C and D). Concurrently, the ASIRs were predicted to increase, reaching approximately 1.88 (95% UI 0.40 to 3.36) for liver cancer and 1.41 (95% UI 0.60 to 2.23 per 100,000 people) for esophageal cancer by 2035. The ASDR of liver cancer was predicted to increase and reach 1.48 (95% UI 0.09 to 2.93 per 100,000 people) by 2035. However, the ASDR of esophageal cancer was expected to follow an increasing trend, peaking at 1.04 (95% UI 0.41 to 1.68 per 100,000 people) by 2035.

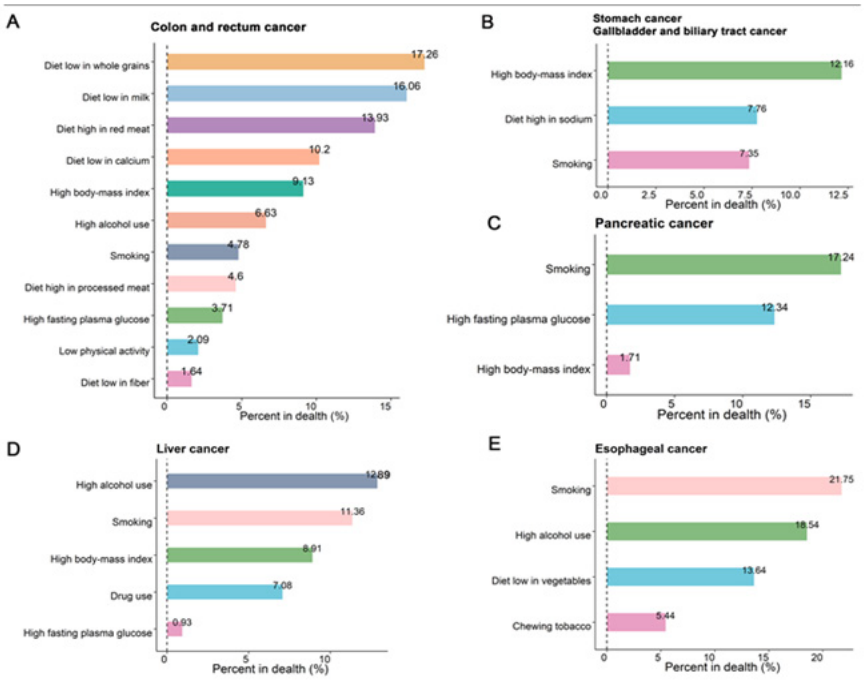

Figure 5: Projects the ASIR and cases of EOGCs for global from 2022 to 2035.
A. Colon and rectum cancer; B. Stomach cancer; C. Liver cancer; D. Esophageal cancer; E. Pancreatic cancer; F. Gallbladder and biliary tract cancer.

4.6. Risk Factors for EOGCs

Figure 6 presents a detailed analysis of the risk factors for EOGC-related death. At the global level, significant contributors to colon and rectum cancer-related death included diets low in whole grains (17.26%), diets low in milk (16.06%), diets high in red meat (13.93%), diets low in calcium (10.20%), high body mass index (9.13%), high alcohol use (6.63%), smoking (4.78%), diets high in processed meat (4.60%), high fasting plasma glucose (3.71%), low physical activity (2.09%), and diets low in fibre (1.64%) (Figure 6A). For stomach cancer-related death, the predominant risk factors were smoking (7.35%) and diets high in sodium (7.76%) (Figure 6B). A high body mass index (12.16%) was identified as the primary risk factor for gallbladder and biliary tract cancer-related death. Liver cancer-related deaths were predominantly attributed to high alcohol consumption (12.89%), smoking (11.36%), high body mass index (8.91%), drug use (7.08%), and high fasting plasma glucose levels (0.93%) (Figure 6. D). Esophageal cancer-related deaths were largely influenced by smoking (21.75%), high alcohol use (18.54%), diets low in vegetables (13.64%), and chewing tobacco (5.44%) (Figure 6E). Finally, smoking (17.24%), high fasting plasma glucose levels (12.34%), and high body mass index (1.71%) were major risk factors for pancreatic cancer-related death (Figure 6C).

5. Discussion

To our knowledge, this research represents an early attempt to present a comprehensive and up-to-date evaluation of the global burden and trends of EOGCs in individuals aged 15-49 based on data from the GBD 2021 study. To compensate for the limited results of the study, we provided up-to-date statistics on a comprehensive range of GBD data, including ASIRs, ASDRs, AAPCs, and major risk factors for EOGC-related deaths from 1990 to 2021. We revealed that (1) males had higher ASIRs and ASDRs than females, except for in cases of gallbladder and biliary tract cancer. (2) The aforementioned ASRs were distinctively high in East Asia. (3) Countries and territories with higher SDI levels tended to have weaker increases in the AAPCs of ASIRs and ASDRs. (4) The AAPC for the incidence rates of colon and rectum cancer slightly increased. (5) Trend analysis projected that the global burdens of colon and rectum, liver, and esophageal cancers would increase, while the burdens of stomach, pancreatic, gallbladder and biliary tract cancers were expected to exhibit a marked downwards trend from 2022 to 2035. (6) EOGC-related deaths were attributable to known risk factors, including smoking, high body mass index, high fasting plasma glucose, high alcohol use and diet.

Globally, males exhibited a higher incidence of EOGCs compared to females, with age-standardized rates for both occurrence and death being 1.9 times greater across GBD regions. Additionally, the disparity between males and females has been increasing over time. Epidemiological analyses attribute this male predominance to elevated rates of abdominal adiposity, tobacco use, and alcohol consumption patterns within male populations [18, 19]. Some studies have reported that alcohol and smoking more strongly contribute to EOGCs DALYs in males than in females [20, 21]. Additionally, these studies highlighted the protective role of endogenous oestrogen in reducing the risk of colon and rectum carcinogenesis among females. In addition to endogenous oestrogens, the use of oral contraceptives may also contribute to the reduced risk of colon and rectum cancer in females relative to males [22]. In addition to the disparity in incidence, there are also notable differences in death between males and females, with females generally exhibiting superior survival outcomes [23]. Sex appears to differentially modulate the circadian clocks of males and females, particularly in relation to the efficacy of chemotherapy for EOGCs, which may partly account for the sex-based disparities in survival and death [24]. Epidemiologic analyses of age-stratified EOGC burdens demonstrate contrasting patterns: while Global Burden of Disease 2019 data indicated higher incidence and death rates for colon and rectum malignancies among elderly women (≥65 years) [25]. Our findings emphasize the predominant impact on younger male populations. This age-dependent gender disparity in colon and rectum cancer epidemiology extends to biliary tract malignancies, where female patients exhibit elevated disease burdens across both early-onset and conventional onset cases [3]. The pathophysiological mechanisms underlying these sex-based variations remain incompletely understood, though current research suggests multifactorial interactions involving hormonal influences, metabolic differences, and distinct immune response profiles [3].

In the GBD 2021 study, East Asia recorded the highest ASIRs and ASDRs for EOGCs. This phenomenon may stem from the region's substantial demographic size coupled with the widespread adoption of comprehensive cancer surveillance initiatives. Contemporary epidemiological research by Li et al. [29] and Huang et al. [30] has specifically investigated emerging patterns of early-onset gastrointestinal malignancies in East Asia, emphasizing their disproportionate public health impact in this geographical area [26]. When contrasted against Western populations, East Asian communities demonstrate more substantial health challenges related to stomach, liver, esophageal, gallbladder and biliary tract cancers. Nevertheless, the escalating disease burden associated with colon and rectum and pancreatic cancers aligns with this investigation's conclusions [27]. Recent research has further revealed a progressive rise in early-onset cases involving colon and rectum, pancreatic, gallbladder and biliary tract cancers across East Asian populations, with parallel epidemiological patterns emerging in Western nations [28-31]. The East Asia region bears a relatively heavy disease burden in terms of EOGCs.

Overall, a negative correlation emerged between the annual percentage changes in age-standardized incidence and death rates of EOGCs and national SDI values. Existing research has revealed that cancer death and occurrence rates generally show a downward trend in areas with advanced development or elevated SDI scores, as quantified by the World Bank's Human Development Index (HDI) [32, 33]. Nevertheless, the distinct features of cancer exhibit considerable variation globally across nations. Our analysis identified high and middle-high SDI regions as bearing the higher burden of both incident cases and fatalities from EOGCs. However, these same regions demonstrated the most substantial

reductions in EOGC-related morbidity and death rates. Regional discrepancies in environmental exposures, behavioral patterns, and public health interventions might underlie the observed variations in age-standardized rates across different SDI tiers. Populations in high-SDI regions exhibit increased participation in preventive healthcare, supported by accessible and well-structured screening programs such as imaging based on computed tomography and serological surveillance of tumour biomarkers [34, 35]. These programs enable the systematic identification of oncological abnormalities through risk stratification, followed by timely therapeutic intervention. Therefore, these regions exhibit a higher disease burden alongside a consistent annual decline in age-standardized incidence and death rates. This trend may be attributed to the earlier diagnosis of diseases at more treatable stages of progression. Accordingly, to effectively manage the disease burden of EOGCs in the future, it is essential to focus increased attention on at-risk individuals residing in lower-SDI countries while continuing to address the needs of those in high-SDI settings.

Persistent epidemiological challenges in EOGCs are evident globally, with disproportionately elevated burden trajectories observed across geographically discrete populations despite decades of intensified prevention initiatives. Among these regions, notable examples include Seychelles (Southeast Asia, high-middle SDI), Afghanistan (North Africa and Middle East, low SDI), Mongolia (Central Asia, low-middle SDI), Malawi (Eastern Sub-Saharan Africa, low SDI), Greenland (High-income North America, high SDI), Thailand (Southeast Asia, middle SDI), and China (East Asia, high-middle SDI). Previous studies have shown that the ASIR and ASDR of EOGCs are negatively correlated with the SDI [3]. In this study, the majority of new cases and deaths attributable to EOGCs were observed in regions with medium-to-high and high SDI levels. However, potential reasonable interpretations of this phenomenon can be derived from the relevant literature. Both Afghanistan and Malawi have endured prolonged civil conflicts, during which the importance of cancer care has been largely neglected. This neglect has resulted in underdeveloped infrastructure and a shortage of human resources dedicated to cancer treatment. These inadequacies are reflected in the estimated global incidence and death rates of cancer. Therefore, it is critical to strengthen cancer care in these countries and advocate for global oncology support. Despite advanced healthcare infrastructure, in Seychelles, the death rates of colon and rectum cancer are 40% higher than the rates predicted by its SDI (0.73). This difference is attributable to metabolic mismatch where Westernized diets (obesity rate 34%) override preventive gains through the hyperactivation of the Wnt/β-catenin pathway [36, 37]. Similarly, Greenland's pancreatic cancer survival deficit (surgery rate <15%) stems from geographic-genetic synergy: TP53 germline mutations (carrier rate 7.2%) are amplified by traditional smoked meat carcinogens (BaP exposure >50 ng/m^3), compounded by Arctic healthcare fragmentation [38]. China's EOGCs epidemic represents a complex interplay between rapid socioeconomic development and enduring public health challenges [39]. China's EOGCs epidemic represents a complex interplay between rapid socioeconomic development and enduring public health challenges [40]. Accounting for the multifaceted nature of healthcare systems and the intricate interplay among socioeconomic, environmental, and public health factors is crucial when fluctuations in disease incidence rates are interpreted.

Our analysis revealed smoking, high body mass index, high fasting plasma glucose, and high alcohol use as key metabolic drivers of EOGCs. These findings are consistent with the global consensus on modifiable risk factors, particularly the WHO-IARC Monograph, which highlights obesity-associated carcinogenesis as a critical emerging threat in younger populations alongside 11 other aetiological agents [41, 42]. Previous studies have consistently shown that individuals under 50 years of age with a BMI exceeding 25 are at increased risk of EOGCs [42, 43]. Additionally, smoking and heavy alcohol consumption are associated with EOGCs, particularly among those consuming three or more alcoholic drinks per day, who are at significantly greater risk of developing EOGCs [44]. According to previous studies, the Western dietary pattern is associated with an increased risk of GCs [45]. Analysis of 26,320 participants from the National Health and Nutrition Examination Survey cycles from 2005-2018 revealed significant associations between combined dietary inflammatory/oxidative balance scores and the risk of gastrointestinal cancers. A higher dietary inflammatory index is linked to increased risk, whereas a higher dietary oxidative balance score is protective. A higher dietary inflammatory index is associated with increased risk, whereas a higher dietary oxidative balance score appears to be protective [46, 47]. EOGCs carcinogenesis is distinct from that in adults, with germline genetic alterations playing a predominant role [2]. This aetiological divergence underscores the need for expanded research into hereditary mechanisms to facilitate the development of targeted therapies for EOGCs. Consequently, in addition to addressing dietary and lifestyle risk factors, individuals with a documented family history of EOGCs should be prioritized for stratified surveillance, incorporating multimodal screening approaches (e.g., CT, EUS, MRI, serum biomarkers, and germline sequencing) to enable pre-emptive intervention and improve clinical outcomes.

This investigation presents global assessment to date of EOGCs burden, trends, and risk factors, spanning 204 countries and territories over 30 years. Key findings reveal an accelerating global EOGCs burden with disproportionate impacts in low-SDI regions and East Asia, which has the highest case incidence and number of deaths. However, the data and findings have certain limitations. First, ASRs demonstrate significant short-distance variation influenced by lifestyle and environmental gradients. Proximity to high-incidence countries may lead to artificially inflated estimates in regions lacking epidemiological reporting. Therefore, there is a need to collect more detailed geographical data in future studies. Second, the absence of molecular subtyping within the GBD framework precludes risk-stratified analysis, potentially leading to incomplete characterization of EOGCs heterogeneity. Third, data scarcity in under-resourced regions remains a critical challenge. The reliance on single registries in some countries highlights the

need for expanded surveillance infrastructure to ensure population representativeness. Finally, the cross-sectional design imposes inherent ecological limitations, allowing for hypothesis generation rather than causal inference. The temporal mismatch between exposure and outcome metrics further underscores the necessity for contemporary cohort studies to validate these findings.

6. Conclusions

With increasing global trends in the ASIRs and ASDRs across 204 countries and territories, EOGCs have emerged as a significant cause of cancer-related deaths and burdens worldwide. While there are several exceptions, regions with lower SDI levels tend to experience greater EOGC burdens, potentially due to inadequate environmental conditions, unhealthy lifestyles, limited health awareness, and insufficient disease control strategies. While the exact mechanisms driving this epidemiological shift require further investigation, well-documented risk elements encompass tobacco consumption, elevated adiposity measurements, impaired glucose metabolism, and excessive ethanol intake. This comprehensive assessment offers valuable insights for developing enhanced prevention protocols and optimizing EOGCs management strategies. While certain indicators for specific cancers have been previously reported, our results not only complement prior studies but also assist policymakers in evaluating the overall burden of EOGCs to inform targeted prevention strategies and the allocation of public health resources.

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