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Title:
Rising early-onset and declining late-onset gastrointestinal cancers in Spain, 1999-2023

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Trends in Gastrointestinal Cancer Incidence in Spain, 1999–2023: Divergence Between Early- and Late-Onset Disease

Background & Methods

Aim: This study examines incidence trends in early-onset gastrointestinal cancers (<50 years) in Spain from 1999 to 2023, and compares them with trends observed in late-onset cases (50+ years).

Data Source: Global Burden of Disease (GBD) 2023 database, Spanish National Statistics Institute (INE) population data.

Analysis: Age-standardized Incidence Rates (ASIRs) & Joinpoint Regression to calculate Annual Percentage Change (APC) and Average Annual Percentage Change (AAPC)

Results

Cancer Site	Men (< 50 yrs)	Men (≥ 50 yrs)	Women (< 50 yrs)	Women (≥ 50 yrs)
Colorectal	Decline (−0.8%) ↓	Modest increase (+0.4%) ↑	Decline (−0.8%) ↓	Stable ↔
Oesophageal	Sharp decline (−3.7%) ⇓	Moderate decline ↓	Initial rise, then decline ↑↓	Minimal change ↔
Gastric (Stomach)	Moderate decline ↓	Moderate decline ↓	Moderate decline ↓	Moderate decline ↓
Liver	Stable ↔	Increase (+0.9%) ↑	Slight increase (+0.5%) ↑	Modest decrease ↓
Pancreatic	Moderate decline ↓	Increase (+0.7%) ↑	Stable/slight decrease (−0.2%) ↔	Sharp increase (+1.6%) ⇑
Gallbladder/Biliary	Decline, recent uptick ↓↑	Fluctuating ~	Decline, then stable ↓↔	Steady decline ↓

Conclusions

Key action

LATE-ONSET SUCCESS
↓ Gastric & esophageal (≥50 yrs)

Public health works: Sustain infection control & anti-tobacco efforts.

METABOLIC BURDEN
↑ Pancreatic & liver

Target metabolic health (obesity, diabetes, NALFD) to counter steep rise

EARLY-ONSET CONCERNS
↓ early colorectal/esophageal, but stabilizing

Intensify prevention to halt the predicted early-onset rise

POLICY
GI cancer trends evolving

Optimize Screening (CRC) and Risk Reduction strategies for all ages

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Rising Early-Onset and Declining Late-Onset Gastrointestinal Cancers in Spain, 1999–2023

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Final Declarations

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Ethics Statement: Formal ethical review and the requirement for patient consent were waived because this study utilized de-identified and publicly available data. The research was conducted in compliance with the Declaration of Helsinki and adheres to the STROBE reporting guideline.

Data Availability: The data that support the findings of this study are publicly available through the Global Burden of Disease (GBD) 2023 database. The specific results were obtained via the GBD online query tool (available at: https://vizhub.healthdata.org/gbd-results/), and no specific permissions were required to access the data for research purposes.

Rising Early-Onset and Declining Late-Onset Gastrointestinal Cancers in Spain, 1999–2023

Abstract

Introduction:

Gastrointestinal cancers (GICs) constitute a major and evolving public health challenge. Global trends indicate a decline in infection-related malignancies and a rise in cancers associated with metabolic risk factors. This study analysed long-term incidence trends of early- and late-onset GICs in Spain between 1999 and 2023.

Methods:

A retrospective, ecological time-trend analysis was performed using incidence data from the Global Burden of Disease (GBD) 2023 database. Age-standardised incidence rates (ASIRs) for oesophageal, gastric, colorectal, liver, pancreatic, and gallbladder/biliary tract cancers were calculated by sex and age group (<50 years, ≥50 years), using the 2013 European standard population. Temporal trends were assessed with Joinpoint regression to estimate annual (APC) and average annual percentage change (AAPC).

Results:

Among adults aged ≥50 years, marked declines were observed for gastric and oesophageal cancers, whereas pancreatic and liver cancers increased steadily in both sexes. Colorectal cancer incidence stabilised in women and rose slightly in men. In individuals <50 years, overall GIC incidence decreased, most notably for oesophageal (–3.7%) and colorectal (–0.8%) cancers, although a plateau emerged from 2016–2017 onwards. Pancreatic and liver cancers in young women showed early signs of stabilisation or mild increase.

Conclusions:

From 1999 to 2023, Spain achieved substantial reductions in infection- and tobacco-related GICs, reflecting effective prevention strategies. However, the rising incidence of metabolic-related malignancies, particularly pancreatic and liver cancers, and the recent stagnation in early-onset colorectal cancer trends highlight the need to strengthen metabolic health policies and optimise national screening programmes.

Keywords: Gastrointestinal cancers, incidence trends, Spain, early-onset cancer, metabolic risk, Joinpoint regression

Rising Early-Onset and Declining Late-Onset Gastrointestinal Cancers in Spain, 1999–2023

Lay Summary

Cancers of the digestive system, which include the oesophagus, stomach, colon, liver, pancreas and bile ducts, are among the most common and deadly worldwide. Their causes are changing as lifestyles, diets and medical care evolve. This study looked at how often these cancers have been diagnosed in Spain over the past 25 years, and whether the trends differ between younger and older adults.

Researchers analysed national data on new cancer cases recorded between 1999 and 2023. They examined how the number of people diagnosed each year changed over time and compared patterns in men and women under and over 50 years of age.

The results showed that cancers related to infections and smoking, such as stomach and oesophageal cancer, have fallen sharply, which reflects better hygiene, less smoking and healthier diets. In contrast, cancers linked to obesity and metabolic problems, such as those of the pancreas and liver, have increased steadily in both men and women. Among people under 50, most digestive cancers became less common, but the decline in colon cancer has stopped in recent years.

These findings show major progress in preventing infection-related cancers in Spain, but also reveal new challenges. Rising rates of pancreatic and liver cancer, and the stabilisation of colon cancer in younger adults, point to the growing influence of modern lifestyles. Promoting healthy habits, maintaining active lifestyles and improving participation in screening programmes are essential to continue reducing the impact of digestive cancers in the future.

Rising Early-Onset and Declining Late-Onset Gastrointestinal Cancers in Spain, 1999–2023

Key points

What is known about the subject:

- Gastrointestinal cancers (GICs) remain a major cause of morbidity and mortality worldwide.
- In Spain, population-based colorectal cancer screening and lifestyle improvements have reduced mortality and late-onset disease burden.
- Early-onset gastrointestinal cancers (EOGICs), particularly colorectal cancer, are rising in many high-income countries, but national incidence data in Spain have been limited.

What this study adds:

- This study provides the first comprehensive national analysis of age-standardised GIC incidence trends in Spain from 1999 to 2023, stratified by sex and age group.
- Marked declines were observed in infection- and tobacco-related cancers (gastric and oesophageal), while metabolic-related malignancies (pancreatic and liver) increased steadily.
- Early-onset colorectal cancer incidence initially declined in both sexes but has plateaued since 2016–2017, indicating potential unfavourable cohort effects.

What the clinical implications are:

- The stabilisation of early-onset colorectal cancer suggests emerging metabolic and environmental risk factors among younger cohorts.
- Strengthening population screening adherence and extending eligibility to older adults could maximise current gains.

Integrated metabolic health strategies addressing obesity, diabetes, and physical inactivity are essential to curb the growing burden of pancreatic and liver cancers.

Rising Early-Onset and Declining Late-Onset Gastrointestinal Cancers in Spain, 1999–2023

Introduction

Gastrointestinal cancers (GICs) represent a major and escalating global health burden (1). In 2022, they accounted for approximately 4.9 million new cases and 3.3 million deaths worldwide, figures projected to increase substantially by 2040 (1,2). Despite advances in prevention, early detection, and treatment, incidence patterns remain heterogeneous across cancer types, sexes, and regions (3,4).

The global epidemiological landscape of GICs is shifting. Malignancies historically linked to chronic infection and tobacco exposure, such as esophageal squamous cell carcinoma and gastric cancer, are declining. Conversely, those associated with obesogenic lifestyles—including colorectal, liver, and pancreatic cancers—are increasing, particularly in high-income Western countries(2,4–6).

A critical public health concern is the rise of Early-Onset Gastrointestinal Cancers (EOGICs), diagnosed before age 50. Nearly 490,000 new EOGIC cases were reported globally in 2021, marking a 31% increase since 1990(3,4). Early-onset colorectal cancer (EOCRC) shows the steepest rise, followed by gastric, pancreatic, and hepatobiliary cancers(3,4). Modifiable risk factors driving this shift include excess adiposity, Westernized diets, physical inactivity, and alterations in gut microbiota(4,7,8,8,9).

In Spain, prevention strategies have focused on tobacco control, the Mediterranean diet, and population-based colorectal cancer screening since the 2000s(10,11). While these measures have improved survival and reduced overall mortality(12–15), incidence trends remain complex: gastric cancer has declined but increased among younger men(16); pancreatic cancer continues rising, driven by ageing and cohort effects (17); and colorectal cancer remains the most frequent GIC in men (18). Despite a recorded fall in EOGIC mortality(13), comprehensive national data on EOGIC incidence by sex and cancer subtype in Spain remain scarce.

This study addresses this crucial gap by examining age-standardized incidence trends for six key early- and late-onset GICs in Spain between 1999 and 2023, stratified by sex.

Methods

This retrospective, ecological time-trend study analysed population-level incidence data for GICs in Spain over the period 1999–2023. The primary objective was to characterise

temporal trends in age-standardised incidence rates (ASIRs) by sex and age group, enabling direct comparison with previously reported mortality patterns and providing evidence to inform targeted public health strategies.

Data Sources

Incidence data for oesophageal, gastric, colorectal, liver, pancreatic, and gallbladder/biliary cancers in Spain were retrieved from the Global Burden of Disease (GBD) 2023 database (available at https://vizhub.healthdata.org/gbd-results/). The study period (1999–2023) was selected to match that used in a previous national analysis of EOGIC mortality (13), facilitating direct comparison of incidence and mortality trends. Data were stratified by sex and five-year age groups. Mid-year population estimates from the Spanish National Statistics Institute (INE; https://www.ine.es) were used as denominators for rate calculations.

Statistical Analysis

ASIRs per 100,000 population were calculated using direct standardisation, with the 2013 European standard population as reference (19). Analyses were performed for three age categories: all ages combined, individuals younger than 50 years (early-onset), and those aged ≥50 years (late-onset).

Temporal trends were analysed using the Joinpoint Regression Program (version 5.2.0.0; National Cancer Institute, USA), which identifies statistically significant inflection points (joinpoints) where trends change in direction or magnitude. Default settings were used to estimate joinpoints and calculate two summary statistics: the annual percentage change (APC) for each segment and the average annual percentage change (AAPC) across the study period (20). Trends were considered increasing or decreasing when statistically significant ($p < 0.05$), and stable otherwise(20).

Results

Table 1 shows the absolute number of GIC cases in Spain in 1999 and 2023. The largest absolute increases were observed among individuals aged ≥50 years. In men, colorectal cancer cases rose from 14,964 to 26,864 (79.5%), followed by liver (92.8%) and pancreatic cancers (84.7%). Among women, pancreatic cancer showed the steepest increase, more than doubling from 2,400 to 5,149 cases (114.6%). Trends in those aged <50 years were

heterogeneous; young men exhibited a modest 11.3% rise in colorectal cancer but marked declines in oesophageal (-42.3%) and stomach cancers (-26.5%). Young women experienced notable rises in pancreatic (32.7%), liver (30.6%), and colorectal cancers (9.9%).

ASIRs and long-term trends, expressed as AAPC, are summarised in Table 2. Among older adults (≥50 years), two contrasting patterns emerged. Pancreatic cancer in women increased from 31.5 to 44.8 per 100,000 (1.6%), with men also experiencing increases in pancreatic (0.7%) and liver (0.9%) cancers. Conversely, stomach, oesophageal and gallbladder and biliary tract cancers declined in both sexes. Colorectal cancer showed a modest rise in men (0.4%) and remained stable in women. For EOGICs (<50 years), ASIRs generally declined. Colorectal cancer decreased significantly in both young men and women (–0.8%). The steepest decline was observed for oesophageal cancer in young men, from 1.9 to 0.8 per 100,000 (–3.7%). Liver and pancreatic cancer incidence in young women remained stable (0.5% and -0.2%, non-significant). These patterns suggest a largely declining EOGIC incidence, although some sites show emerging stabilisation (Table 2).

Joinpoint regression analysis revealed varied temporal trends across different age groups, sexes, and cancer types (Fig. 1–3). For adults under 50 (Fig. 1.), colorectal cancer rates initially decreased in both sexes, then experienced a sharper decline before levelling off around 2016/2017. Oesophageal cancer declined steadily in men, whereas women experienced an early rise followed by sustained decreases. Gallbladder and biliary tract cancer declined in both sexes, although there has been a recent uptick in men since 2017 and it has stabilised in women since 2015. Liver cancer rose early in both sexes, then declined, with a late upturn in women around 2020. Pancreatic cancer rates declined in men after a stable period, while in women, they initially rose before eventually decreasing. Stomach cancer rates steadily dropped in both sexes, with a more pronounced decline in men.

In adults aged ≥50 years (Fig. 2.), colorectal cancer initially increased before declining in both sexes, whereas oesophageal cancer steadily decreased in men with minimal change in women. Gallbladder and biliary tract cancer trends fluctuated in men but declined steadily in women. Liver cancer increased in men until 2015 before declining and modestly decreased in women. Pancreatic cancer steadily increased in both men and women, while stomach cancer showed consistent declines, with a more noticeable decrease in men,

stabilizing in both sexes around 2019/2020.

Across all ages combined (Fig. 3.), trends largely mirrored those observed in older adults. Colorectal cancer showed initial rises followed by declines, especially in women. Oesophageal cancer declined in men with limited change in women. Gallbladder and biliary tract cancer declined in women but was variable in men. Liver cancer increased in men before decreasing and declined modestly in women. Pancreatic cancer rose steadily in both sexes, and stomach cancer consistently decreased.

Discussion

Our findings delineate two contrasting epidemiological narratives for GICs in Spain. Late-onset malignancies, including gastric cancer and oesophageal squamous cell carcinoma (SCC), have declined markedly, whilst pancreatic and liver cancers continue to rise and early-onset colorectal cancer trends have plateaued. These divergent trajectories reflect an ongoing epidemiological transition—from cancers historically driven by infections, smoking, and dietary insufficiency to malignancies associated with metabolic dysfunction, obesity, and other contemporary risk factors(21). Emerging cardio-hepato-metabolic frameworks provide a unifying lens for understanding these trends, emphasising the shared pathophysiological mechanisms—including insulin resistance, chronic inflammation, and ectopic fat accumulation—that drive both cardiovascular disease and metabolic-associated malignancies such as pancreatic and hepatocellular carcinoma(22).

The sustained reduction in gastric cancer represents a considerable public health achievement. Once the predominant GIC, its decline closely parallels decreasing Helicobacter pylori prevalence, driven by improved sanitation, refrigeration reducing reliance on salt-preserved foods, and widespread antibiotic use (16,23–25). Similarly, oesophageal cancer incidence has declined steadily, particularly amongst men, in line with falling smoking and alcohol consumption rates (26,27). This reduction is predominantly attributable to decreased SCC incidence, whilst oesophageal adenocarcinoma (AC)—linked to gastro-oesophageal reflux disease and obesity—has stabilised or increased modestly in some regions (28,29). Notably, ASIRs continue to decline, indicating that gains from reduced SCC outweigh rises in AC.

The decline in colorectal cancer incidence among adults aged ≥50 years highlights the effectiveness of Spain's national screening programme. Population-based faecal occult blood testing for individuals aged 50–69 has enabled the early detection and removal of precursor adenomas, thereby reducing the incidence of invasive disease (10,30). However, participation remains suboptimal, with completion rates around 62.5%, increasing to 77.1% among those invited (30). Improving adherence is essential to maximise the impact of screening and to consolidate current gains. Additionally, extending the upper screening age to 74 years—consistent with European Union recommendations and practices already adopted by several member states—represents a key opportunity to further enhance programme effectiveness (10).

Pancreatic cancer is the fastest-growing GIC in Spain. This rise is largely linked to the increasing prevalence of metabolic syndrome, specifically obesity and type 2 diabetes, and declining physical activity (31–33). The steeper increase in women suggests a need to investigate sex-specific risk factors, such as hormonal influences and differing exposure patterns. Meanwhile, liver cancer incidence is also on the rise, primarily driven by metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), and the lingering impact of viral hepatitis. This trend highlights the urgent need for integrated metabolic health strategies and comprehensive management of chronic diseases.

EOGICs patterns in Spain differ markedly from those observed in North America and Northern Europe, where sharp increases have been reported (4,8). In Spain, EOCRC rates initially declined (–0·8%) in both sexes, likely reflecting favourable lifestyle changes and cohort effects (18). However, joinpoint analysis reveals a critical inflection point, with rates plateauing from 2016–2017 onwards. This stagnation may herald Spain's entry into the adverse cohort phase observed internationally, driven by increased consumption of ultra-processed foods, sedentary behaviour, early-life antibiotic exposure, and gut microbiome perturbation (34) . Whilst absolute EOCRC incidence remains low, the arrested decline signals a concerning potential future burden, initially affecting individuals aged 20–29 years before extending to older young adults (35).

The pronounced decline in oesophageal cancer amongst young men likely reflects generational reductions in smoking prevalence, whereas modest rises in pancreatic and liver cancers amongst young women suggest early metabolic risk emergence. These early-onset

trends serve as sentinel indicators that metabolic carcinogenesis—characterised by obesity, insulin resistance, and NAFLD—is accelerating, particularly for aggressive malignancies such as pancreatic adenocarcinoma and hepatocellular carcinoma.

Strengths and Limitations

A principal strength of this study is the use of the comprehensive GBD 2023 dataset, enabling robust age-standardisation and 25-year trend analysis via Joinpoint regression. By harmonising high-quality data from multiple Spanish regional cancer registries, local variability is minimised, allowing nuanced interpretation of national patterns across multiple GIC sites.

Several limitations warrant consideration. First, reliance on GBD estimates precludes direct evaluation of individual risk factors, such as obesity, genetic susceptibility, or socioeconomic determinants, limiting causal inference. Second, regional registry differences, evolving diagnostic practices, and potential disruptions during the COVID-19 pandemic (2020–2021) may have influenced incidence estimates. Third, caution is needed when interpreting EOCRC trends due to low absolute case numbers and associated statistical variability; nevertheless, the observed plateau remains epidemiologically concerning and warrants continued surveillance.

Conclusions

Between 1999 and 2023, Spain achieved substantial reductions in late-onset gastric and oesophageal cancers, reflecting successes in infection control and lifestyle interventions. Nevertheless, the rising incidence of pancreatic and liver cancers, particularly amongst older adults, highlights the growing impact of metabolic risk factors on cancer burden. Whilst early-onset colorectal and oesophageal cancers have continued to decline, recent stabilisation may presage increases in younger cohorts exposed to adverse metabolic and environmental conditions. Sustained investment in public health measures—including metabolic risk reduction, early detection strategies, and population-based screening programmes—is essential to consolidate past gains and address the evolving epidemiological landscape of GICs in Spain.

Table 1. Absolute Number of New Gastrointestinal Cancer Cases in Spain, by Site, Sex, and Age Group (1999 vs. 2023)

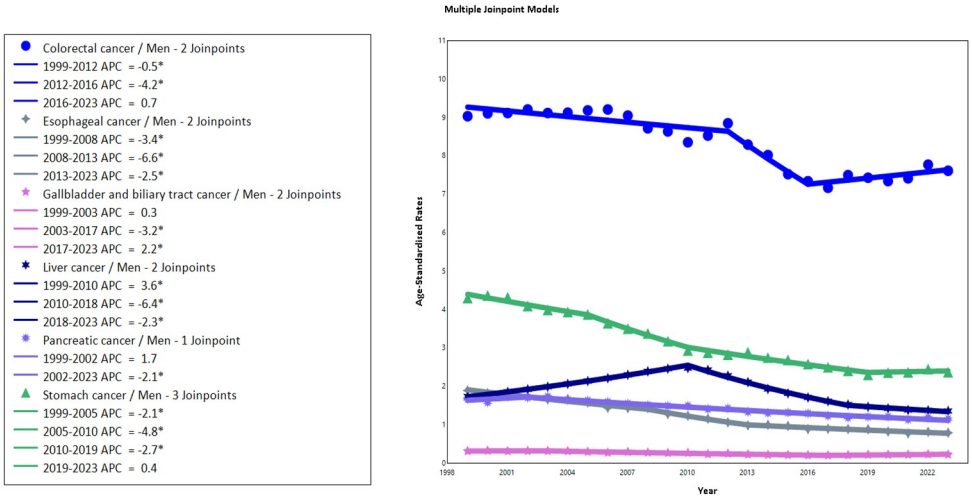
	AGE <50			AGE 50+			ALL AGES		
CANCER SITE	**1999**	**2023**	**% Change**	**1999**	**2023**	**% Change**	**1999**	**2023**	**% Change**
					Men				
COLORECTAL CANCER	1,099	1,223	11.3%	14,964	26,864	79.5%	16,063	28,087	74.9%
ESOPHAGEAL CANCER	223	129	-42.3%	1,907	2,085	9.3%	2,130	2,214	3.9%
GALLBLADDER AND BILIARY TRACT CANCER	40	36	-10.6%	645	1,033	60.1%	685	1,069	56.0%
LIVER CANCER	211	213	0.9%	2,980	5,746	92.8%	3,192	5,959	86.7%
PANCREATIC CANCER	197	193	-2.0%	2,372	4,381	84.7%	2,569	4,574	78.1%
STOMACH CANCER	520	382	-26.5%	6,114	6,070	-0.7%	6,633	6,452	-2.7%
					Women				
COLORECTAL CANCER	915	1,006	9.9%	12,181	18,631	52.9%	13,096	19,636	49.9%
ESOPHAGEAL CANCER	24	21	-11.8%	381	486	27.5%	405	507	25.2%
GALLBLADDER AND BILIARY TRACT CANCER	35	28	-20.4%	1,196	1,028	-14.1%	1,232	1,056	-14.3%
LIVER CANCER	69	90	30.6%	1,318	1,843	39.8%	1,387	1,933	39.3%
PANCREATIC CANCER	95	126	32.7%	2,400	5,149	114.6%	2,495	5,275	111.4%
STOMACH CANCER	299	257	-13.8%	3,782	3,675	-2.8%	4,080	3,933	-3.6%

Table 2: Age-Standardized Incidence Rates (ASIR) and Annual Average Percentage Change (AAPC) for Gastrointestinal Cancers in Spain, Stratified by Site, Sex, and Age Group: 1999 vs. 2023

	Men			Women		
	ASIR			ASIR		
Cancer site	**1999**	**2023**	**AAPC [C.I.]**	**1999**	**2023**	**AAPC [C.I.]**
Age <50						
Colorectal cancer	9.0	7.6	-0.8 [-1.4 ; -0.3]	7.5	6.4	-0.8 [-1.3 ; -0.3]
Esophageal cancer	1.9	0.8	-3.7 [-4.2 ; -3.1]	0.2	0.1	-1.6 [-2.3 ; -0.9]
Gallbladder and biliary tract cancer	0.3	0.2	-1.3 [-1.9 ; -0.7]	0.3	0.2	-1.8 [-2.8 ; -0.9]
Liver cancer	1.7	1.4	-1.1 [-1.2 ; -0.9]	0.6	0.6	0.5 [0 ; 1]
Pancreatic cancer	1.7	1.2	-1.6 [-2 ; -1.1]	0.8	0.8	-0.2 [-0.5 ; 0.2]
Stomach cancer	4.3	2.4	-2.5 [-3 ; -2]	2.4	1.7	-1.5 [-2 ; -1.1]
Age 50+						
Colorectal cancer	276.8	308.2	0.4 [0.2 ; 0.6]	161.7	161.9	0 [-0.3 ; 0.2]
Esophageal cancer	32.8	23.3	-1.4 [-1.7 ; -1.1]	5.1	4.3	-0.5 [-1.2 ; 0.1]
Gallbladder and biliary tract cancer	12.2	12.0	0 [-0.6 ; 0.7]	15.7	8.7	-2.4 [-2.7 ; -2.2]
Liver cancer	52.6	65.0	0.9 [0.6 ; 1.1]	17.3	16.1	-0.3 [-0.4 ; -0.2]
Pancreatic cancer	42.4	49.8	0.7 [0.6 ; 0.8]	31.5	44.8	1.6 [1.5 ; 1.6]
Stomach cancer	113.1	69.4	-1.9 [-2.3 ; -1.5]	49.7	31.2	-1.8 [-2.1 ; -1.5]
All ages						
Colorectal cancer	113.5	124.9	0.3 [0.1 ; 0.5]	67.6	67.1	0 [-0.3 ; 0.3]
Esophageal cancer	13.9	9.6	-1.5 [-1.8 ; -1.2]	2.1	1.8	-0.6 [-1.1 ; -0.1]
Gallbladder and biliary tract cancer	5.0	4.8	0 [-0.7 ; 0.6]	6.3	3.5	-2.4 [-2.7 ; -2.2]
Liver cancer	21.6	26.2	0.8 [0.6 ; 0.9]	7.1	6.6	-0.3 [-0.4 ; -0.2]
Pancreatic cancer	17.5	20.1	0.6 [0.5 ; 0.7]	12.8	18.0	1.5 [1.4 ; 1.6]
Stomach cancer	46.7	28.5	-2 [-2.3 ; -1.6]	20.9	13.2	-1.8 [-2.1 ; -1.5]

Age < 50

Men



Women

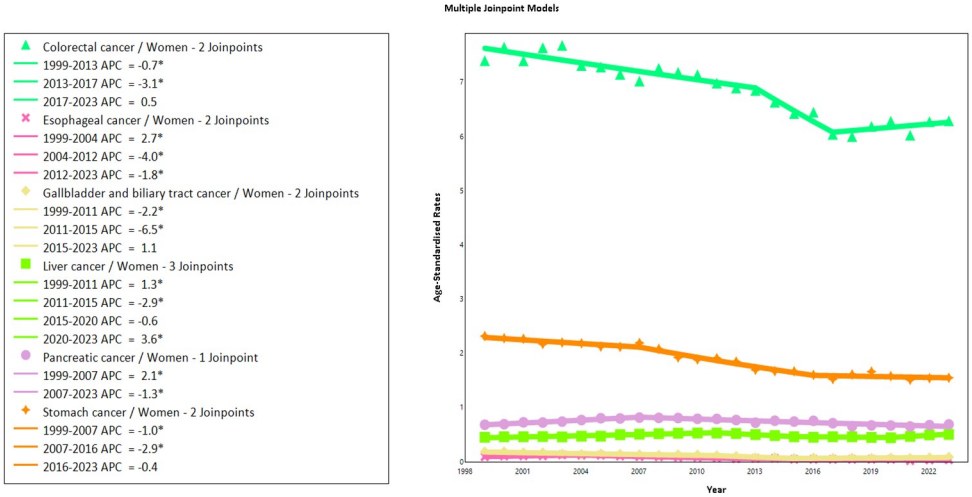
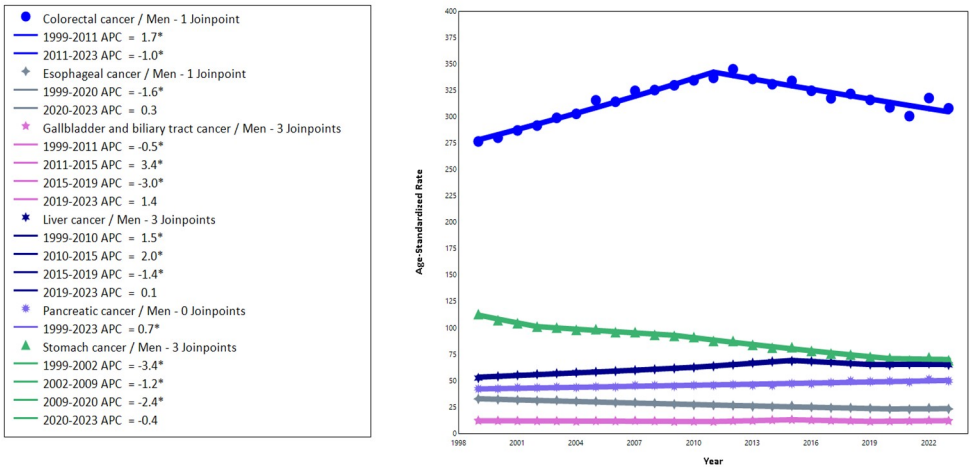


Figure 1. Trends in Age-Standardized Incidence Rates (ASIR) for Cancers of the Digestive System in the Age < 50 Population (1999–2023).

Age 50+

Men



Women

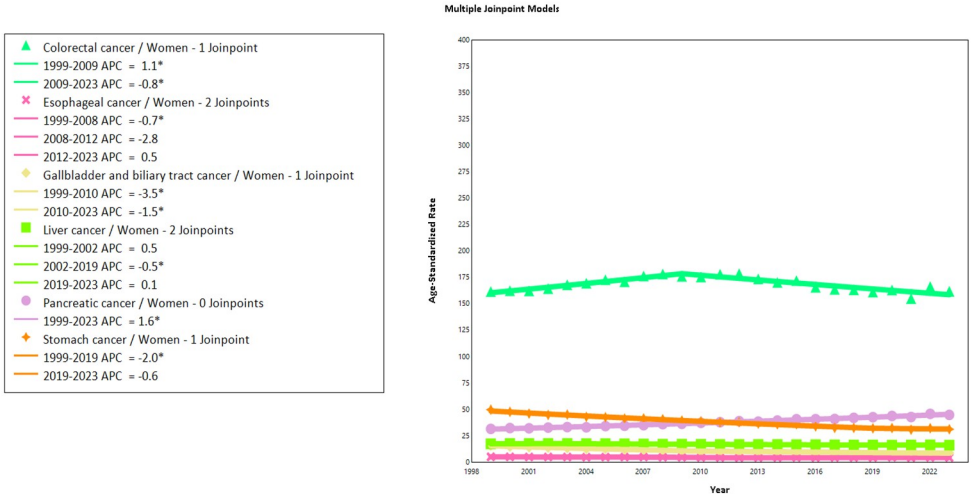


Figure 2. Trends in Age-Standardized Incidence Rates (ASIR) for Cancers of the Digestive System in the Age 50+ Population (1999–2023).

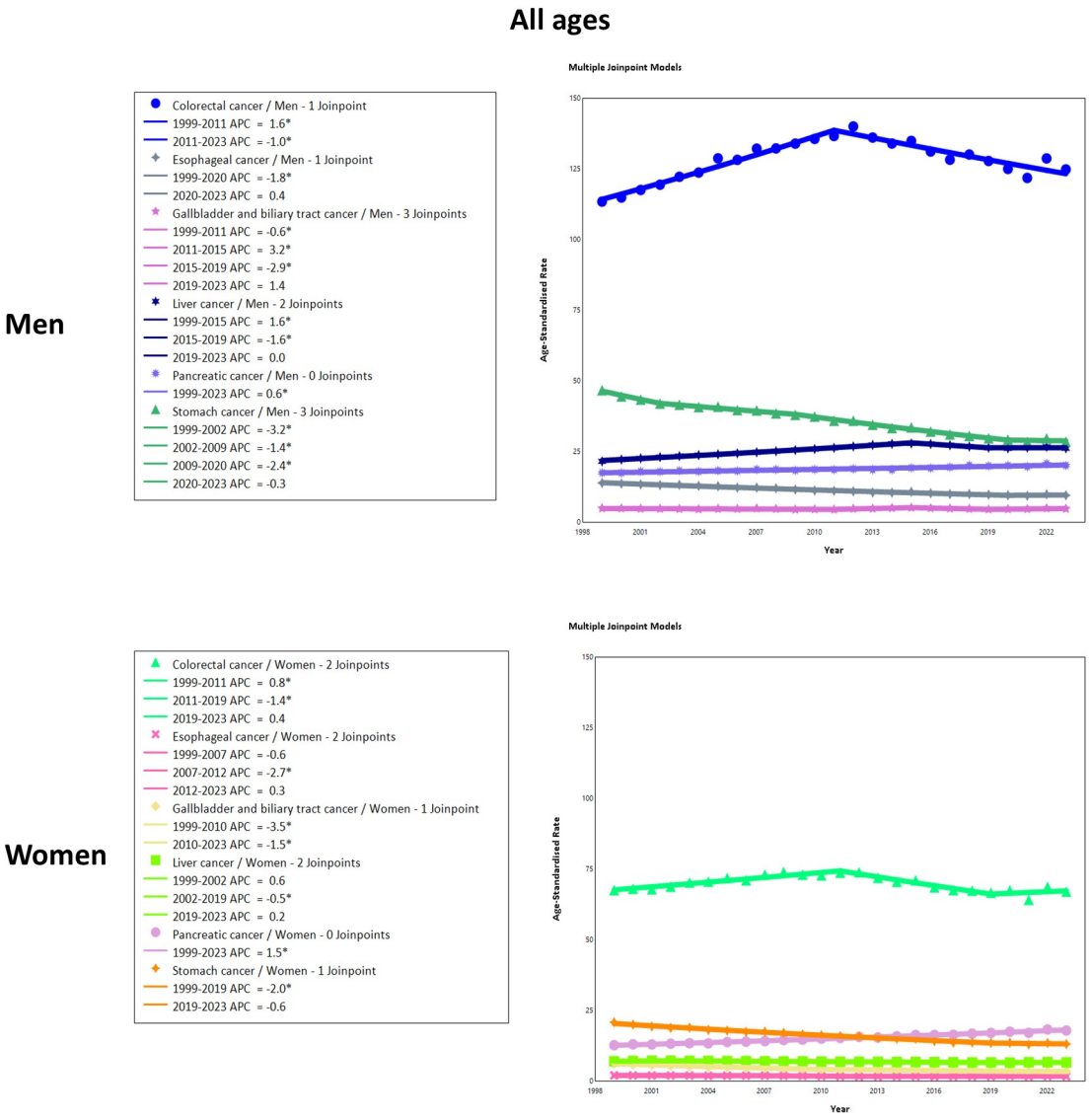


Figure 3. Trends in Age-Standardized Incidence Rates (ASIR) for Cancers of the Digestive System in the All Ages Population (1999–2023)

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