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Global, regional, and national burden of early-onset colorectal cancer from 1990 to 2021: a systematic analysis based on the global burden of disease study 2021

Yang Meng[1†], Zongbiao Tan[2†], Junhai Zhen[3†], Di Xiao[1], Liwei Cai[1], Weiguo Dong[2*] and Changzheng Chen[1*]

Abstract

Background To provide estimates and trends for burdens of early-onset colorectal cancer (EOCRC) from 1990 to 2021 at the global, regional, and national levels, and to provide projections of EOCRC burden through 2030.

Methods A trend analysis based on the Global Burden of Diseases 2021. The joinpoint regression model was used to analyze the temporal trends on EOCRC burden by calculating the corresponding average annual percent changes (AAPCs). A decomposition analysis was used to understand the drivers of the changes in EOCRC burden. The relationship between socio-demographic index (SDI) and disease burden was assessed by the concentration index of inequality. In addition, we constructed a Bayesian age-period-cohort model to predict the burden of EOCRC worldwide from 2022 to 2030.

Results Globally, the burden of EOCRC increased significantly between 1990 and 2021, with the incidence rising from 5.43/100000 to 6.13/100000 (AAPC = 0.39), and the prevalence increasing from 29.65/100000 to 38.86/100000 (AAPC = 0.87). Over the same period, the death rate decreased from 2.98/100000 to 2.30/100000 (AAPC = − 0.84), whereas the disability-adjusted life-year (DALY) decreased from 148.46/100000 to 115.42/100000 (AAPC = − 0.82). In 2021, East Asia and China had the highest burden of EOCRC regionally and nationally. Decomposition analysis indicated the increase in EOCRC burden was mainly driven by population growth. The concentration index revealed that high-SDI countries had a greater burden of EOCRC than low-SDI countries. The global incidence and prevalence of EOCRC will rise continuously from 2022 to 2030.

Conclusions Between 1990 and 2021, the incidence and prevalence of EOCRC have escalated, whereas the death rate and DALY rate have declined. The burden varied with sex, SDI, and geographical locations. Given the rising trend of EOCRC burden, coordinated efforts are needed to reduce the burden posed by this malignancy.

Keywords Early-onset colorectal cancer, Disease burden, Global burden of disease study 2021

[†]Yang Meng, Zongbiao Tan and Junhai Zhen contributed equally as co-first authors.

*Correspondence:
Weiguo Dong
dongweiguo@whu.edu.cn
Changzheng Chen
whuchenchzh@163.com
Full list of author information is available at the end of the article

Background

Colorectal cancer (CRC) is currently the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality throughout the world [1]. Global patterns and trends of CRC vary greatly and are related to human development levels, suggesting that economic transition and the adoption of more Western lifestyles might increase the risk of this malignant disorder [2, 3]. Overall, the incidence of late-onset CRC (diagnosed after 50 years of age) has decreased in the past few decades, largely due to the implementation of screening [4]. However, there is growing evidence that the incidence of CRC among adults younger than 50 years (i.e., early-onset CRC; EOCRC) has increased worldwide over the past few decades [5]. Based on data from cancer registries in 20 European countries, the incidence of EOCRC increased annually by 7.9% from 2004 to 2016 for those aged 20–29, by 4.9% from 2005 to 2016 for those aged 30–39, and by 1.6% from 2004 to 2016 for those aged 40–49 [6]. Similar trends have also been reported in many other non-European countries, [7–10]. For example, the annual average increase in the incidence was 4.0% in New Zealand (2007–2016), 2.8% in Australia (2006–2015), 2.8% in Canada (2003–2012), and 2.2% in the USA (2007–2016) [3]. Meanwhile, the prevalence of EOCRC is also on the rise. It has been estimated that the prevalence increased by 56% between 1990 and 2019, from 16.3 to 25.4 per 100,000 population [11].

Although the elderly population still accounts for the majority of CRC cases, EOCRC exhibits significant clinical and pathological heterogeneity when compared to late-onset CRC, making it equally noteworthy [4, 12, 13]. For example, patients with EOCRC tend to be at a more advanced tumor–node–metastasis stage at diagnosis and have higher rates of signet-ring cell histology and poorly differentiated tumor, all of which are associated with a worse prognosis [4, 12, 13].

While some previous studies reported the incidence and trend of EOCRC in some countries, some issues still remain unclear [7–10]. For instance, many countries (especially low-resource ones) lack high-quality data on EOCRC. Additionally, the association between the burden of EOCRC and different sociodemographic index (SDI) levels has been rarely reported. The Global Burden of Disease Study (GBD) offers a unique opportunity to investigate the disease burden of EOCRC by quantifying health loss from various of diseases and injuries worldwide. Previous studies have analyzed the global burden of EOCRC between 1990 and 2019 based on GBD 2019 and have provided valuable information [11]. To our knowledge, the latest burden and pattern of EOCRC has not been documented yet. Besides, few studies have provided burden predictions of EOCRC.

In this study, we aimed to present the global trends of EOCRC incidence and deaths between 1990 and 2021 using latest data from GBD 2021 and to provide projections on EOCRC burden until 2030. In addition, we analyzed the contributions of major drivers to the changes in EOCRC burden. We also performed a health inequality analysis to determine the relationship between SDI and EOCRC burden.

Methods

Overview

In this analysis of data from GBD 2021, we extracted data from the Global Health Data Exchange (GHDx), which provides data on the burden of 371 diseases and injuries in 21 GBD regions and 204 countries and territories between 1990 and 2021, including CRC [14]. Details of the methodology have been previously described [14]. The datasets used in this study are publicly available and can be accessed elsewhere [15].

This study complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) [16]. Ethics approval was not required for this study due to the analysis of anonymized and publicly available data.

Study population and data collection

CRC is a category of GBD 2021 which is defined as codes C18-C21.9, D01.0-D01.3, D12-D12.9, and D37.3-D37.5 in the International Classification of Diseases (ICD)−10 and codes 153–154.9, 209.1, 209.5, 211.3–211.4, 230.3–230.6, and 569.0 in ICD-9. In accordance with previous studies, "EOCRC" was defined as CRC diagnosed in young adults aged 20–49 years [3, 7, 17–19]. GBD estimates for CRC were collected on four disease indicators [incidence, deaths, prevalence, and disability-adjusted life-years (DALYs)], for both sexes, in six age groups (20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, and 45–49 years), by 21 GBD-defined regions as well as 204 countries and territories [14, 20]. The 21 GBD-defined regions were 21 groups of countries/territories that were geographically proximate and epidemiologically similar, including Andean Latin America, Australasia, Caribbean, Central Asia, Central Europe, Central Latin America, Central Sub-Saharan Africa, East Asia, Eastern Europe, Eastern Sub-Saharan Africa, High-income Asia Pacific, High-income North America, North Africa and Middle East, Oceania, South Asia, Southeast Asia, Southern Latin America, Southern Sub-Saharan Africa, Tropical Latin America, Western Europe, and Western Sub-Saharan Africa [21].

The GBD 2021 also provided the SDI of each GBD 2021 location (Additional file 1: Table S1). SDI, which ranges from 0 to 1, is a summary indicator that identifies which level a country's or a region's health-related development status is located on the spectrum of development worldwide. SDI is the geometric mean of 0 to 1 indices of lag distributed income per capita, mean education for those ages 15 and older, and total fertility rate under the age of 25 [22]. For example, a country with an SDI of 0 suggests that it has theoretical lowest level of health-related development (i.e., the lowest income per capita, fewest EDU15+, and highest TFU25 when compared to other countries), whereas a country with an SDI of 1 has the highest level of development theoretically. According to the 2021 SDI values, all the 204 countries/regions were divided into one of the following SDI quintiles: high, high-middle, middle, low-middle, and low (Additional file 1: Table S2).

Statistical analysis

Joinpoint regression

First, we computed the average annual percentage changes (AAPCs), the 95% confidence intervals (CIs), and corresponding *P* values using Joinpoint regression to investigate the global trends in the burden of EOCRC between 1990 and 2021. AAPC is a summary indicator of the trend over a pre-specified fixed time interval. It is calculated as the weighted average of the annual percentage changes from the Joinpoint model.

Decomposition analysis

In order to understand the drivers of the EOCRC burden, we conducted a decomposition analysis. The decomposition analysis divides the overall difference in EOCRC burden into three factors: population growth, age structure aging, and epidemiological changes. Epidemiological changes refer to changes in the rates of corresponding indicators.

Health inequality analysis

To assess the influence of socioeconomic levels on the burden of EOCRC, we adopted the concentration index to measure the SDI-related cross-country inequalities in EOCRC burden. The concentration index can quantify the relative inequalities in health distribution among countries of varying socioeconomic backgrounds [23]. It ranges from −1 to 1, where a negative value indicates that the disease burden is more concentrated among people with lower socio-economic status, and vice versa.

Bayesian Age-Period-Cohort Analysis (BAPC)

Various models have been introduced for predicting cancer burden, including the Nordpred model, exponential regression model, generalized additive model, negative binomial regression model, and the BAPC model [24, 25]. Out of these, the BAPC model demonstrates a better predictive performance, particularly for near-term forecasts [24, 25]. As a result, we employed the BAPC model to forecast the incidence rate, death rate, prevalence rate, and DALY rate of EOCRC over the period from 2022 to 2030. The BAPC model is a common approach to understanding the trend of disease changes, utilizing the classic age-period-cohort model as its foundation.

Data for incidence, deaths, prevalence, and DALYs were all expressed as estimates per 100,000 population and their 95% uncertainty intervals (UIs). All statistical analyses and visualization were finished using R software (version 4.3.3) with the INLA package.

Results

Global burden of EOCRC

From 1990 to 2021, the global burden of EOCRC increased rapidly. Specifically, the number of EOCRC cases had doubled, rising from 105,315 (95% UI: 97,698 to 112,502) in 1990 to 210,092 (95% UI: 190,809 to 231,075) in 2021, as detailed in Table 1. Additionally, the age-standardized incidence rate (ASIR) of EOCRC climbed from 5.43 (95% UI: 5.04 to 5.79) to 6.13 per 100,000 population (95% UI: 5.57 to 6.74), reflecting a significant increase (AAPC: 0.39 [95% CI: 0.29 to 0.48], $P<0.001$). In 1990, the number of deaths attributed to EOCRC was 57,938 (95% UI: 52,891 to 62,815), corresponding to an age-standardized death rate (ASDR) of 2.98 per 100,000 population (95% UI: 2.72 to 3.23). By 2021, EOCRC-related fatalities had escalated to 78,699 (95% UI: 71,677 to 85,994), yet the ASDR had decreased to 2.30 per 100,000 population (95% UI: 2.09 to 2.51) (AAPC: −0.84 [95% CI: −0.99 to −0.70], $P<0.001$) (Table 1). During the same period, the age-standardized prevalence rate (ASPR) increased from 29.65 (95% UI: 27.77 to 31.40) to 38.86 per 100,000 population (95% UI: 35.34 to 42.86) (AAPC: 0.87 [95% CI: 0.72 to 1.01], $P<0.001$), whereas the age-standardized DALY rate decreased 148.46 (95% UI:135.44 to 160.9) to 115.42 per 100,000 population (95% UI:104.96 to 126.14)(AAPC: −0.82 [95% CI: −0.97 to −0.66], $P<0.001$) (Additional file 1: Table S3). In 2021, an estimated 1,332,091 (95% UI: 1,211,230 to 1,469,307) people worldwide had EOCRC, causing 3,943,287 (95% UI: 3,586,368 to 4,310,114) DALYs.

In terms of sex, in 1990, the global ASIR was higher in males (5.77 per 100,000 population) compared to females (5.07 per 100,000 population). By 2021, this trend persisted, with the ASIR for males rising to 7.28 per 100,000 population (AAPC: 0.74 [95% CI: 0.65 to 0.84], $P<0.001$), while for females, it remained relatively stable at 4.96 per 100,000 (Fig. 1 & Table 1). Between 1990 and 2021, the number of new EOCRC cases rose for both sexes, increasing from 56,978 to 125,636 in males and from 48,338 to 84,456 in females. Males represented approximately 54.1% of all new EOCRC cases in 1990, and this

Table 1 The incidence and deaths of EOCRC from 1990 to 2021 at the global and regional levels

	Incidence						Deaths					
Location	**Cases (n), 1990**	**Incidence (per 100,000 population), 1990**	**Cases (n), 2021**	**Incidence (per 100,000 population), 2021**	**AAPC, 1990–2021**	***P*. Value**	**Deaths (n), 1990**	**Deaths (per 100,000 population), 1990**	**Deaths (n), 2021**	**Deaths (per 100,000 population), 2021**	**AAPC, 1990–2021**	***P*. Value**
Global	105,315 (97,698 to 112,502)	5.43 (5.04 to 5.79)	210,092 (190,809 to 231,075)	6.13 (5.57 to 6.74)	0.39 (0.29 to 0.48)	< 0.001	57,938 (52,891 to 62,815)	2.98 (2.72 to 3.23)	78,699 (71,677 to 85,994)	2.30 (2.09 to 2.51)	−0.84 (−0.99 to −0.70)	< 0.001
Sex												
Male	56,978 (50,715 to 62,216)	5.77 (5.16 to 6.3)	125,636 (109,023 to 143,951)	7.28 (6.31 to 8.33)	0.74 (0.65 to 0.84)	< 0.001	31,712 (27,377 to 35,253)	3.21 (2.78 to 3.56)	46,897 (41,033 to 53,228)	2.72 (2.38 to 3.08)	−0.54 (−0.73 to −0.35)	< 0.001
Female	48,338 (43,761 to 53,199)	5.07 (4.6 to 5.57)	84,456 (76,927 to 93,214)	4.96 (4.52 to 5.48)	−0.07 (−0.20 to 0.06)	0.306	26,226 (23,175 to 29,366)	2.74 (2.43 to 3.07)	31,802 (28,899 to 34,927)	1.87 (1.70 to 2.05)	−1.24 (−1.35 to −1.13)	< 0.001
Sociodemographic index												
High SDI	35,205 (34,066 to 36,389)	8.86 (8.57 to 9.16)	50,764 (48,678 to 52,936)	10.05 (9.63 to 10.48)	0.41 (0.22 to 0.61)	< 0.001	12,955 (12,545 to 13,408)	3.26 (3.16 to 3.38)	12,265 (11,785 to 12,809)	2.42 (2.32 to 2.53)	−0.98 (−1.09 to −0.87)	< 0.001
High-middle SDI	30,625 (27,774 to 33,431)	7.24 (6.58 to 7.9)	61,745 (52,735 to 72,806)	9.62 (8.22 to 11.34)	0.92 (0.68 to 1.16)	< 0.001	17,324 (15,529 to 19,105)	4.1 (3.68 to 4.52)	19,302 (16,789 to 22,425)	3.00 (2.61 to 3.48)	−0.97 (−1.26 to −0.69)	< 0.001
Middle SDI	28,574 (24,813 to 32,319)	4.62 (4.02 to 5.22)	69,450 (60,100 to 79,205)	6.09 (5.27 to 6.94)	0.91 (0.65 to 1.16)	< 0.001	19,200 (16,635 to 21,717)	3.11 (2.7 to 3.51)	28,937 (25,370 to 32,642)	2.53 (2.22 to 2.86)	−0.67 (−0.91 to −0.44)	< 0.001
Low-middle SDI	8006 (6876 to 9211)	2.15 (1.85 to 2.47)	21,069 (18,355 to 24,441)	2.71 (2.36 to 3.14)	0.74 (0.64 to 0.83)	< 0.001	6120 (5240 to 7071)	1.65 (1.41 to 1.9)	13,178 (11,517 to 15,416)	1.70 (1.48 to 1.98)	0.09 (−0.05 to 0.22)	0.197
Low SDI	2796 (2150 to 3317)	1.98 (1.52 to 2.35)	6889 (5887 to 8052)	1.95 (1.67 to 2.27)	−0.06 (−0.2 to 0.07)	0.356	2280 (1744 to 2705)	1.62 (1.23 to 1.92)	4949 (4221 to 5821)	1.40 (1.20 to 1.65)	−0.48 (−0.55 to −0.4)	< 0.001
Region												
Andean Latin America	292 (238 to 353)	2.37 (1.93 to 2.86)	1014 (777 to 1308)	3.57 (2.74 to 4.61)	1.33 (0.76 to 1.89)	< 0.001	216 (176 to 260)	1.75 (1.43 to 2.11)	515 (397 to 656)	1.82 (1.4 to 2.31)	0.09 (−0.51 to 0.68)	0.772
Australasia	929 (800 to 1075)	10.18 (8.77 to 11.8)	1654 (1360 to 1986)	12.01 (9.88 to 14.43)	0.62 (−0.2 to 1.45)	0.139	323 (281 to 370)	3.55 (3.08 to 4.07)	334 (285 to 389)	2.42 (2.06 to 2.81)	−1.2 (−1.7 to −0.71)	< 0.001
Caribbean	724 (634 to 819)	5.71 (4.99 to 6.46)	1523 (1257 to 1809)	7.44 (6.14 to 8.84)	0.86 (0.54 to 1.17)	< 0.001	319 (277 to 360)	2.51 (2.18 to 2.84)	522 (426 to 638)	2.55 (2.08 to 3.12)	0.1 (−0.12 to 0.32)	0.379
Central Asia	1040 (977 to 1106)	4.82 (4.52 to 5.12)	1333 (1164 to 1507)	3.21 (2.8 to 3.62)	−1.25 (−1.78 to −0.72)	< 0.001	674 (634 to 717)	3.13 (2.94 to 3.33)	736 (643 to 834)	1.77 (1.55 to 2.01)	−1.81 (−2.35 to −1.27)	< 0.001

Table 1 (continued)

	Incidence						Deaths					
Central Europe	3674 (3472 to 3881)	6.84 (6.46 to 7.23)	4399 (3979 to 4842)	7.53 (6.8 to 8.28)	0.3 (−0.06 to 0.66)	0.098	2075 (1970 to 2182)	3.87 (3.67 to 4.07)	1653 (1504 to 1807)	2.81 (2.56 to 3.07)	−1.05 (−1.35 to −0.75)	< 0.001
Central Latin America	1322 (1249 to 1401)	2.48 (2.34 to 2.63)	6034 (5339 to 6809)	5.39 (4.77 to 6.09)	2.57 (2.35 to 2.78)	< 0.001	833 (790 to 880)	1.56 (1.48 to 1.65)	2682 (2382 to 3007)	2.4 (2.13 to 2.69)	1.41 (1.08 to 1.73)	< 0.001
Central Sub-Saharan Africa	250 (185 to 338)	1.71 (1.27 to 2.31)	782 (549 to 1128)	1.86 (1.3 to 2.68)	0.25 (0.09 to 0.42)	0.002	206 (152 to 278)	1.41 (1.05 to 1.9)	588 (409 to 866)	1.4 (0.97 to 2.06)	−0.05 (−0.19 to 0.09)	0.505
East Asia	35,317 (29,339 to 41,271)	7.3 (6.07 to 8.52)	81,105 (64,864 to 99,677)	11.47 (9.2 to 14.09)	1.44 (1.15 to 1.73)	< 0.001	22,602 (18,717 to 26,376)	4.68 (3.88 to 5.45)	25,294 (20,188 to 31,279)	3.57 (2.86 to 4.41)	−0.89 (−1.16 to −0.61)	< 0.001
Eastern Europe	6358 (6017 to 6735)	7.02 (6.64 to 7.44)	7129 (6489 to 7844)	6.93 (6.31 to 7.63)	−0.02 (−0.45 to 0.42)	0.934	3523 (3337 to 3719)	3.9 (3.7 to 4.12)	2920 (2639 to 3246)	2.83 (2.56 to 3.15)	−1.01 (−1.6 to −0.42)	0.001
Eastern Sub-Saharan Africa	1305 (980 to 1552)	2.64 (1.97 to 3.13)	3256 (2698 to 4129)	2.46 (2.05 to 3.11)	−0.22 (−0.33 to −0.12)	< 0.001	1082 (800 to 1290)	2.19 (1.61 to 2.61)	2398 (1982 to 3039)	1.82 (1.51 to 2.3)	−0.6 (−0.71 to −0.48)	< 0.001
High-income Asia Pacific	8184 (7756 to 8662)	9.65 (9.14 to 10.22)	8846 (7968 to 9827)	9.8 (8.82 to 10.9)	−0.01 (−0.38 to 0.36)	0.954	2983 (2836 to 3134)	3.54 (3.36 to 3.72)	1935 (1815 to 2072)	2.13 (2 to 2.29)	−1.62 (−1.78 to −1.47)	< 0.001
High-income North America	11,748 (11,340 to 12,150)	9.26 (8.94 to 9.58)	19,308 (18,392 to 20,246)	12.33 (11.74 to 12.93)	0.94 (0.48 to 1.41)	< 0.001	3643 (3540 to 3749)	2.88 (2.8 to 2.97)	4481 (4292 to 4662)	2.85 (2.73 to 2.97)	−0.03 (−0.48 to 0.42)	0.889
North Africa and Middle East	3808 (2922 to 4621)	3.67 (2.82 to 4.44)	12,919 (11,066 to 15,067)	4.55 (3.9 to 5.31)	0.7 (0.58 to 0.82)	< 0.001	2377 (1819 to 2894)	2.31 (1.77 to 2.8)	5027 (4229 to 5921)	1.78 (1.49 to 2.09)	−0.82 (−0.95 to −0.69)	< 0.001
Oceania	45 (32 to 60)	2.16 (1.54 to 2.85)	104 (81 to 134)	1.96 (1.52 to 2.51)	−0.29 (−0.44 to −0.15)	< 0.001	33 (23 to 44)	1.56 (1.1 to 2.07)	72 (55 to 92)	1.35 (1.03 to 1.73)	−0.46 (−0.64 to −0.28)	< 0.001
South Asia	6254 (5397 to 7140)	1.72 (1.48 to 1.96)	15,314 (13,247 to 18,438)	1.96 (1.7 to 2.35)	0.43 (0.16 to 0.71)	0.002	4950 (4261 to 5665)	1.36 (1.17 to 1.56)	10,035 (8656 to 12,139)	1.29 (1.11 to 1.55)	−0.16 (−0.43 to 0.11)	0.238
Southeast Asia	6106 (5005 to 7167)	3.88 (3.19 to 4.54)	17,738 (14,555 to 20,781)	5.47 (4.49 to 6.41)	1.15 (1 to 1.29)	< 0.001	4335 (3522 to 5114)	2.75 (2.24 to 3.24)	9694 (7969 to 11,316)	2.99 (2.46 to 3.49)	0.31 (0.18 to 0.43)	< 0.001
Southern Latin America	943 (819 to 1079)	4.88 (4.24 to 5.59)	2072 (1750 to 2430)	6.73 (5.68 to 7.9)	1.06 (0.61 to 1.51)	< 0.001	585 (508 to 667)	3.03 (2.63 to 3.46)	911 (780 to 1059)	2.95 (2.53 to 3.44)	−0.07 (−0.54 to 0.39)	0.758

Table 1 (continued)

	Incidence						Deaths					
Southern Sub-Saharan Africa	542 (482 to 612)	3.27 (2.91 to 3.7)	1307 (1109 to 1582)	3.85 (3.27 to 4.64)	0.55 (−0.1 to 1.19)	0.096	387 (344 to 437)	2.35 (2.08 to 2.65)	854 (721 to 1041)	2.52 (2.13 to 3.07)	0.26 (−0.41 to 0.93)	0.448
Tropical Latin America	1671 (1561 to 1790)	3.05 (2.85 to 3.26)	5884 (5476 to 6364)	5.42 (5.05 to 5.86)	1.8 (1.69 to 1.92)	< 0.001	1141 (1069 to 1219)	2.09 (1.96 to 2.23)	3073 (2868 to 3299)	2.83 (2.64 to 3.04)	0.88 (0.77 to 0.99)	< 0.001
Western Europe	14,212 (13,334 to 15,143)	8.36 (7.85 to 8.91)	16,513 (15,302 to 17,810)	8.43 (7.81 to 9.09)	0 (−0.28 to 0.28)	0.999	5178 (4877 to 5508)	3.04 (2.87 to 3.24)	3636 (3389 to 3897)	1.84 (1.72 to 1.97)	−1.67 (−1.89 to −1.45)	< 0.001
Western Sub-Saharan Africa	591 (482 to 711)	1.1 (0.89 to 1.32)	1854 (1372 to 2397)	1.27 (0.95 to 1.64)	0.47 (0.33 to 0.61)	< 0.001	474 (387 to 573)	0.88 (0.72 to 1.06)	1341 (1005 to 1725)	0.92 (0.69 to 1.19)	0.13 (0.03 to 0.23)	0.010

EOCRC Early-onset colorectal cancer, *AAPC* Average annual percentage change

Within parentheses were 95% uncertainty intervals for cases, incidence, and deaths, and 95% confidence intervals for AAPCs, respectively

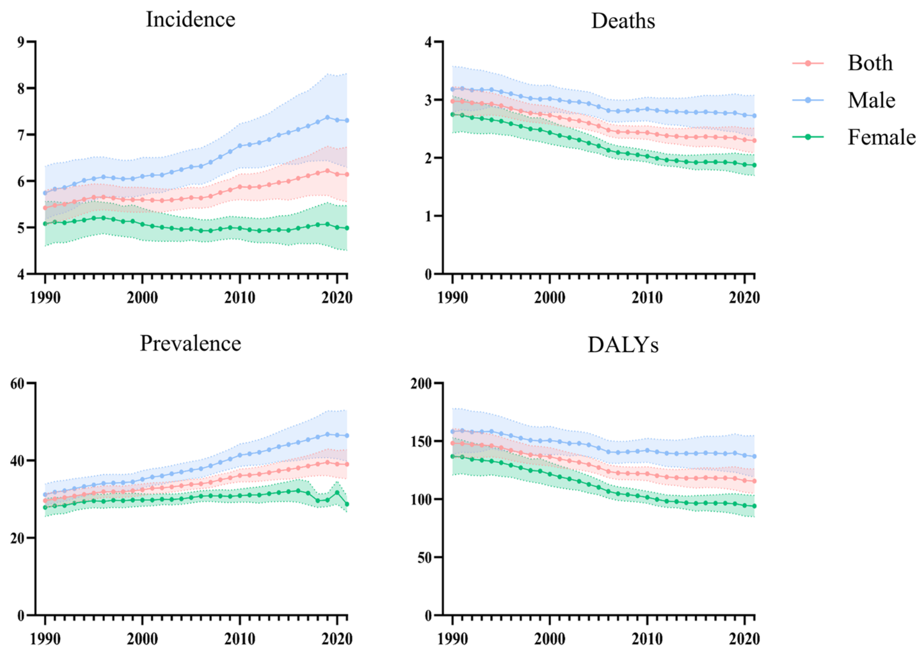

Fig. 1 Trends of global burden of early-onset colorectal cancer, 1990 to 2021. DALYs, disability-adjusted life-years. Data expressed as age-standardized rates per 100,000 population

proportion escalated to 59.8% by 2021. Over this period, the ASDR declined for both genders: from 3.21 to 2.72 per 100,000 population for males (AAPC: −0.54 [95% CI: −0.73 to −0.35], $P<0.001$), and from 2.74 to 1.87 per 100,000 population for females (AAPC: −1.24 [95% CI: −1.35 to −1.13], $P<0.001$).

Regional burden of EOCRC

Among the 5 SDI regions, the highest ASIR (10.05/100000 [95% UI: 9.63 to 10.48]) and ASPR (71.36/100000 [95% UI: 68.33 to 74.44]) were observed in the high-SDI region in 2021, whereas the highest ASDR (3.00/100000 [95% UI: 2.61 to 3.48]) and age-standardized DALY rate (152.74/100000 [95% UI: 132.76 to 177.22]) were noted in the high-middle SDI region (Table 1 & Additional file 1: Table S3). Between 1990 and 2021, the ASIR significantly increased in all SDI regions except for the low SDI region. Meanwhile, the ASPR significantly increased in all SDI regions, while the ASDR and age-standardized DALY rate significantly decreased in all these regions, except for the low-middle SDI region.

Among the 21 GBD regions, high-income North America had the highest ASIR of EOCRC in 2021 (12.33/100,000 [95% UI: 11.74 to 12.93]), closely followed by Australasia (12.01/100000 [95% UI: 9.88 to 14.43]). Notably, East Asia, one of the most densely populated regions globally, reported 81,105 new EOCRC cases in 2021 (95% UI: 64,864 to 99,677), accounting for nearly two-fifths of the global new cases. The highest ASDR in 2021 was also observed in East Asia (3.57/100000 [95% UI: 2.86 to 4.41]), followed by Southeast Asia (2.99/100000 [95% UI: 2.46 to 3.49]). High-income North America (88.37/100000 [95% UI: 84.11 to 92.61]) had the highest ASPR among all regions in 2021, while East Asia (543,916 [95% UI: 435,918 to 667877]) had the greatest number of EOCRC patients. In 2021, the highest age-standardized DALY rate (184.03/100000 [95% UI: 147.43 to 226.72]) and DALY number (1,279,602 [95% UI: 1,022,782 to 1579020]) were both documented in East Asia (Table 1 & Additional file 1: Table S3).

National burden of EOCRC

In 2021, among the 204 GBD countries/territories, Monaco had the highest ASIR (17.78/100000 [95% UI: 10.87 to 27.01]) and ASPR (127.72 [95% UI: 79.51 to 193.38]) of EOCRC, while Seychelles reported the highest ASDR (4.68 [95% UI: 3.45 to 6.21]) and age-standardized DALY rate (235.55 [95% UI: 173.09 to 313.27]) (Fig. 2, Additional file 1: Table S4 & S5). By contrast, Mozambique documented the lowest ASIR (0.58/100000 [95% UI: 0.37 to 0.87]) and ASPR (2.42 [95% UI: 1.54 to 3.58]), while Oman had the lowest ASDR (0.41/100000 [95% UI: 0.26 to 0.64]) and age-standardized DALY rate (20.7 [95% UI: 13.24 to 32.43]). Notably, in 2021, China ranked first in terms of incidence cases (78,129 [95% UI: 61,859 to 96574]), prevalent cases (524,949 [95% UI:416,604 to 649097]), death numbers (24,293 [95% UI: 19,153 to 30270]), and DALY numbers (1,229,897 [95%

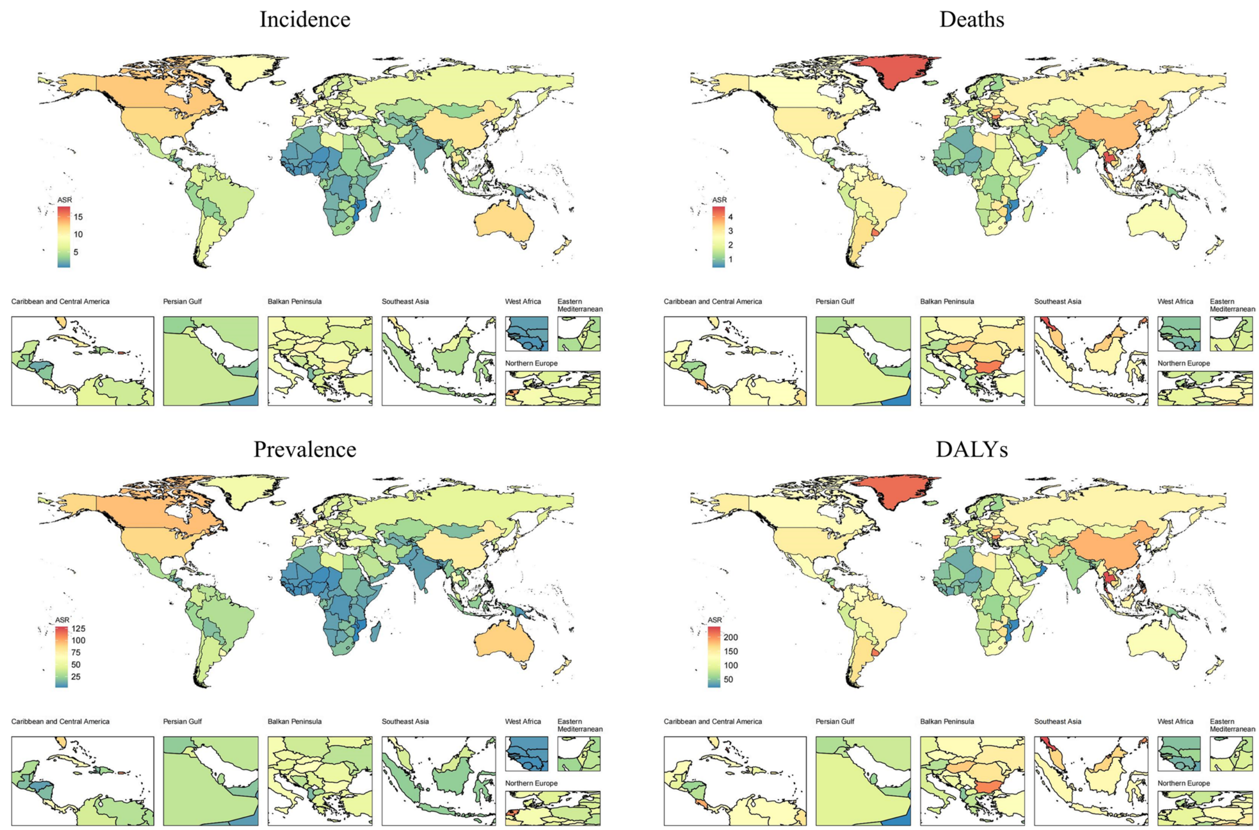

Fig. 2 Global map of the national burden of early-onset colorectal cancer in 2021. ASR, age-standardized rate; DALYs, disability-adjusted life-years. Data expressed as ASRs per 100,000 population

UI: 972,022 to 1528848]) among all countries/territories (Additional file 1: Table S4 & S5).

Between 1990 and 2021, the AAPCs were greater than zero in 149 countries/territories for ASIR, less than zero in 123 countries/territories for ASDR, greater than zero in 180 countries/territories for ASPR, and less than zero in 119 countries/territories for age-standardized DALY rate, basically consistent with the overall global trend (Additional file 1: Table S4 & S5).

Decomposition analysis of EOCRC

Figure 3 illustrated the contributions of population growth, age structure aging, and epidemiological changes to the shifts in EOCRC burden. Between 1990 and 2021, the increase in global EOCRC burden was mainly driven by population growth. Furthermore, the impact of population growth on EOCRC burden is more pronounced in low-income nations, whereas in high-income countries, the burden is more strongly influenced by epidemiological changes. It is noteworthy that epidemiological changes had contributed to an increase in the incidence cases and prevalent cases while playing a mitigating effect on the numbers of deaths and DALYs.

Health inequalities of EOCRC

The concentration index for ASIR, ASDR, ASPR, and age-standardized DALY rate were all greater than 0 in 1990, indicating that higher SDI countries have undertaken more EOCRC burden in comparison with their lower SDI counterparts (Fig. 4). In addition, by 2021, the concentration index of the four indicators further increased, indicating that inequalities in the burden of EOCRC among high and low SDI countries have become more prominent.

Prediction of disease burden of EOCRC from 2022 to 2030

According to the BAPC model, global burden of EOCRC is expected to increase between 2022 and 2030, with the ASIR and ASPR rising continuously (Fig. 5). By 2030, the global ASIR and ASPR are projected to escalate to 6.46/100000 (95% UI: 5.17 to 7.75) and 41.46/100000 (95% UI: 32.82 to 50.09), respectively. Fortunately, by 2030, the global ASDR is expected to decrease to 2.21/100000 (95% UI: 1.74 to 2.68), with the DALY rate dropping to 111.81 100,000 (86.99 to 136.62). Notably, males will remain the primary victims of EOCRC,

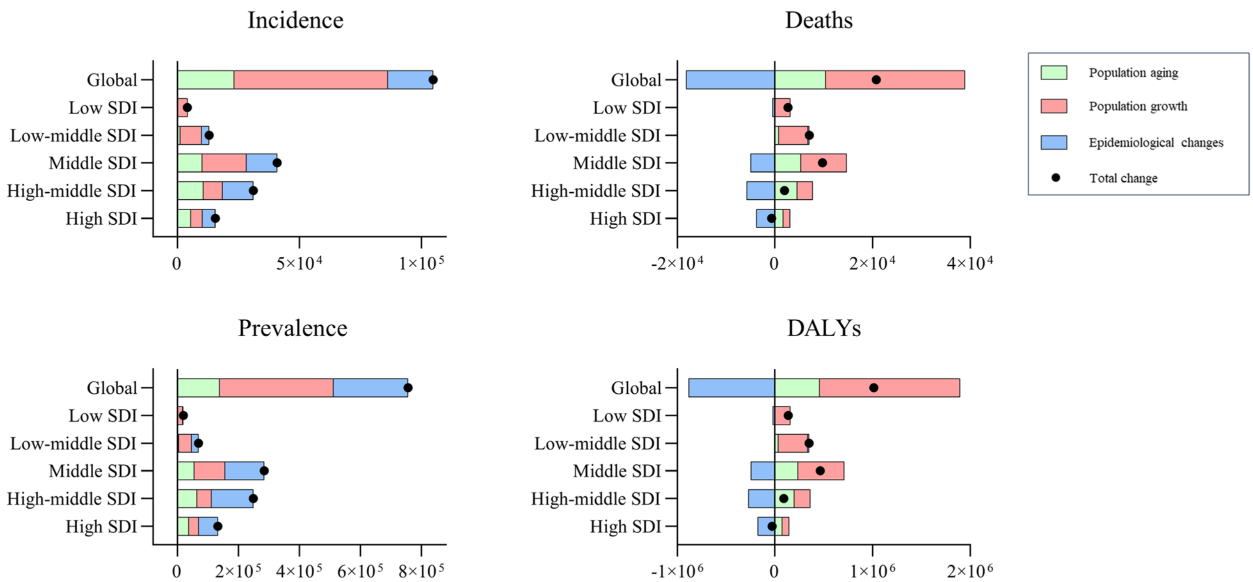

Fig. 3 Decomposition analysis of changes in the burden of early-onset colorectal cancer by SDI, 1990 to 2021. DALYs, disability-adjusted life-years; SDI, sociodemographic index. Epidemiological changes refer to changes in the rates of corresponding indicators

and the gap in ASIR and ASPR is anticipated to widen between males and females.

Discussion

In this study, we described and analyzed the global, regional, and national burdens of EOCRC from 1990 to 2021. By reporting high-quality disease data from 204 countries/territories worldwide, this study not only enhanced our understanding of EOCRC epidemiology but also provided crucial insights into the trends and variations of this disease across different geographical locations and time periods. These findings can inform targeted interventions aimed at reducing the EOCRC burden globally.

At the global level, from 1990 to 2021, the global incidence and prevalence of EOCRC increased remarkably. During the same period, there was an overall decreasing trend in its death rate and DALY rate. In 2021, the number of new cases, deaths, prevalent cases, and DALYs were 2 times, 1.4 times, 2.3 times, and 1.3 times, respectively, as compared to those 32 years ago. The "western diet" is frequently used to describe dietary intake patterns in the USA and other developed nations, which is mainly characterized by an increased consumption of energy-dense foods and sugared beverages, red and processed meats, as well as refined grains [26–28]. Western diet is ranked the most important modifiable risk factor of CRC [4]. In the past few decades, this unhealthy dietary pattern has also been more common in eastern and developing countries. A global assessment by the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group found that, since 1990, the consumption of unhealthy foods (e.g., red meats, processed meats, and sugared beverages) worsened among adults aged ≥ 20 years all over the world, although heterogeneity existed between countries [29]. In the same study, adults aged 20–49 years tended to have worse dietary patterns (i.e., lesser consumption of healthy dietary items and greater consumption of unhealthy ones) than those aged ≥ 50 years [29]. In the Nurses' Health Study II (1991–2015), female adults with sugar-sweetened beverages consumption ≥ 2 servings per day had a more than doubled risk of EOCRC, when compared with those who consumed less than one serving per week [30]. Unfortunately, young adults are the main consumers of sugar-sweetened beverages [4, 30]. Another global phenomenon that could likely have contributed to the increase in the burden of EOCRC is the growing obesity among young adults, a prevailing public health concern worldwide [31]. Several studies have demonstrated that early adulthood obesity is strongly associated with increased risk of EOCRC [32–34].

In the sex-stratified analysis, males had more cases and deaths of EOCRC than females and this sex-related difference kept growing over time. The male predominance of the global burden of EOCRC might be due to the greater tobacco and alcohol consumption and higher prevalence of visceral fat in this population [35]. Besides, oral contraceptives and endogenous estrogens were found to play a protective role for females in CRC [36, 37]. We also found sex-related differences in the death rate, with males consistently outpacing females and the

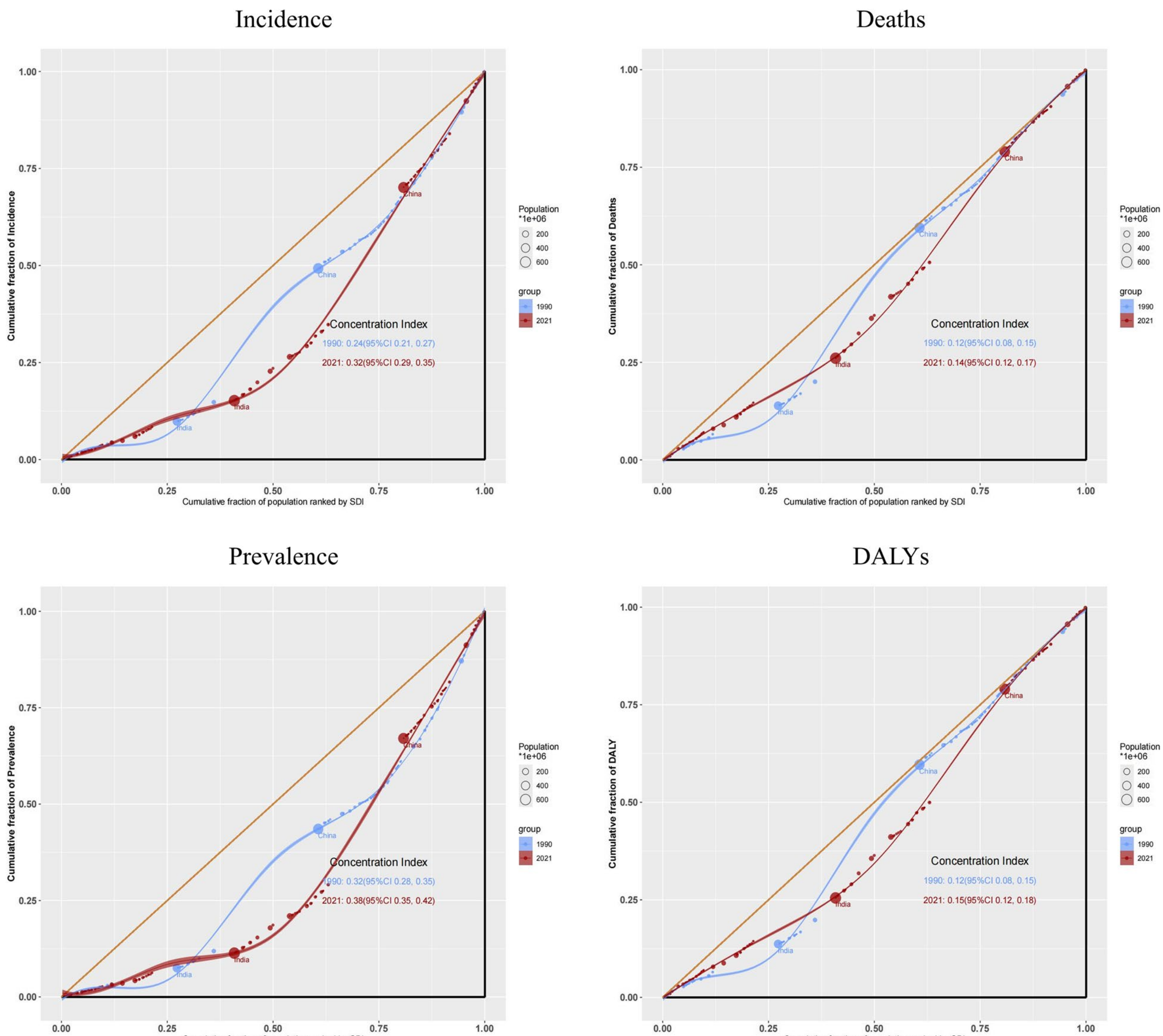

Fig. 4 Health inequality analysis for the burden of early-onset colorectal cancer, 1990 and 2021. DALYs, disability-adjusted life-years; SDI, sociodemographic index

gap widening between 1990 and 2021. Regarding the effect of surgery on CRC, females tend to have survive longer than males after CRC surgery, which may partly explain the gender difference in the death rate [38].

As the region with the heaviest EOCRC burden, East Asia had highest death rate and DALY rate of EOCRC in 2021. Additionally, due to its large population base, it also had the highest number of new EOCRC cases, deaths, prevalent cases, and DALYs. In 2021, East Asia contributed 38.6% and 32.1% of the global new cases and deaths of EOCRC, respectively. The major countries in East Asia, be it China, Japan, or South Korea, were all in the westernization of diet patterns and lifestyle in the past few decades, which can be responsible for the highest burden of EOCRC in this region [39–41]. Meanwhile, since southeast Asia had the third highest numbers of EOCRC deaths in 2021, the disease burden in the whole Asia is not optimistic as well. The whole Asian (5 regions) accounted for 59.2% and 60.6% of global new cases and deaths of EOCRC in 2021, outstripping the sum total of the other 5 continents (16 regions), highlighting the urgent need for EOCRC screening in Asia.

Nationally, China had the highest number of newly diagnosed cases, prevalent cases, deaths, DALYs among all countries in 2021. In 2021, 37 out of every 100 newly diagnosed cases of EOCRC occurred in China. Since

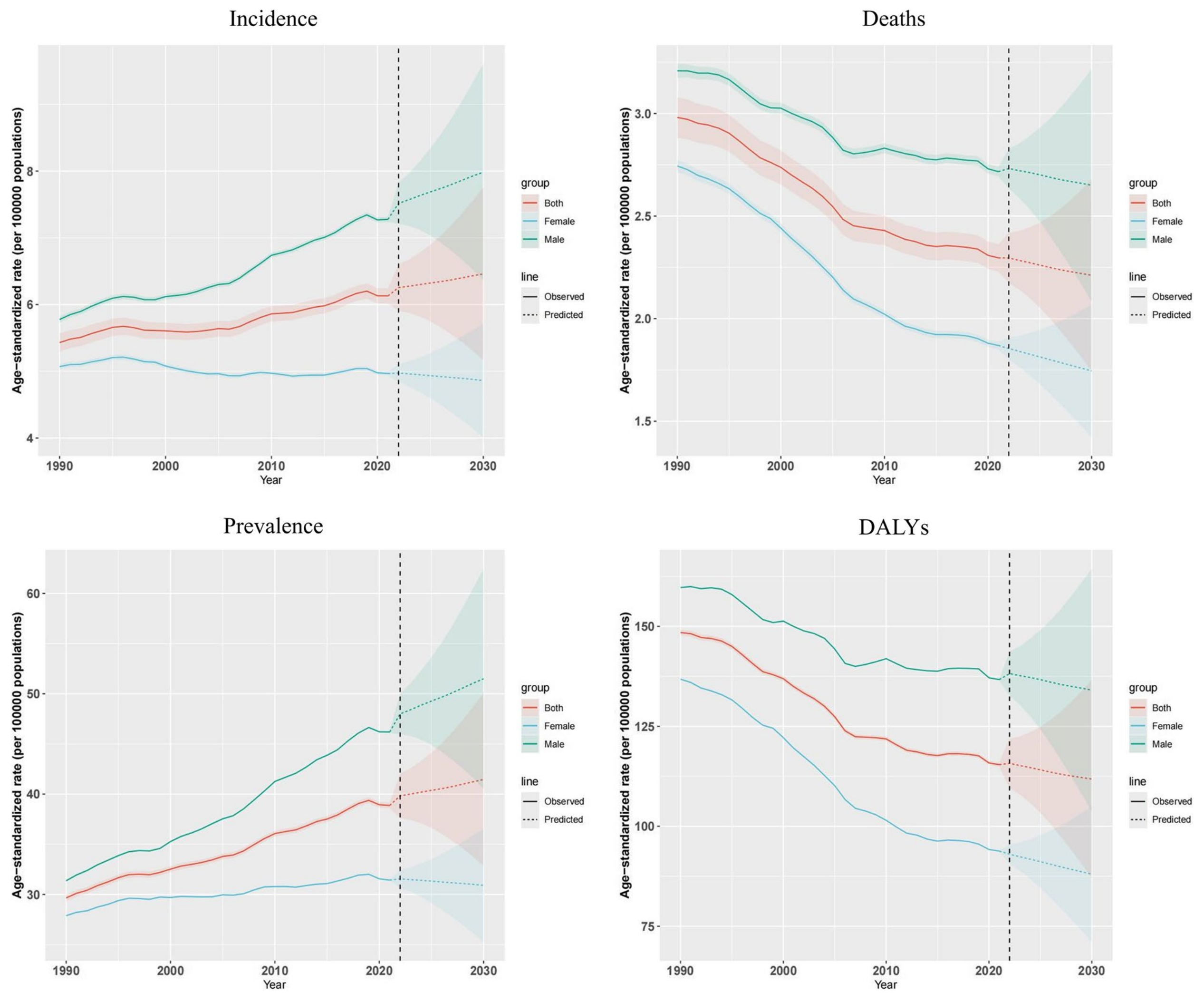

Fig. 5 Predictions of the global burden of early-onset colorectal cancer, 2022 to 2030. DALYs, disability-adjusted life-years

the 1990s, China has undergone many dramatic social and economic changes, as well as changes in people's lifestyles, which have been accompanied by a rapid rise in the prevalence of obesity [42]. Currently, China is the country with the highest number of overweight or obese people worldwide [42]. In China, approximately two-thirds of young men start smoking in early adulthood [43]. In addition, smoking and alcohol consumption are also prevalent among young Chinese women [44]. These changes may partly explain the rapid increase in the incidence and prevalence of EOCRC in China over the past three decades, which, combined with its large population, has made China the country with the highest disease burden of EOCRC globally. As of 2021, Austria had the earliest screening age (40 years) of all CRC screening programs [45]. Interestingly, among the 204 countries and territories, Austria's death rate was declining at the second fastest pace (AAPC = −2.82) between 1990 and 2021, more than three times the global average (AAPC = −0.84). Another nation that deserves attention is the USA. In recognition of the growing burden of EOCRC in the USA, in 2018, the American Cancer Society moved up the earliest CRC screening age from 50 to 45 years for average-risk adults [46]. It will be necessary to see if this move in the USA can reduce the burden of EOCRC in the future.

We observed SDI-related health inequalities in EOCRC burden, with people living in higher SDI countries tending to have higher incidence, prevalence, death, and DALY rates of EOCRC. This is consistent with a previous study, in which the ASIR and ASDR of CRC in developed countries were 2.6 and 1.9 times higher than those in less developed countries, respectively [47]. Thus, future efforts to reduce the burden of EOCRC should primarily focus on countries with higher SDI. However, this does not imply that lower SDI countries do not need to take action, as the incidence of EOCRC is showing an upward trend at the global level. It should be noted that developed countries often have more comprehensive registration systems and better medical conditions. In addition, several high SDI countries, like the USA, recommend start age of 45 years for CRC screening, which may lead to higher detection rate of EOCRC [46]. These may partly explain the higher ASIR and ASDR in high SDI countries.

Our findings revealed a concerning trend in the global burden of EOCRC. Using BAPC model, our analysis predicted a continuous rise in the global incidence and prevalence of EOCRC from 2022 to 2030, suggesting that EOCRC will remain a significant public health challenge in the coming years. Besides, the gap in ASIR will keep widening between sexes, with males bearing a greater burden compared to females. In the future, greater efforts should be made in health education to encourage young people to adopt healthier lifestyles. Additionally, methods for early detection of EOCRC should be optimized, and screening time for CRC should be appropriately advanced. This will not only enhance the detection rate of precancerous lesions, thereby reducing the occurrence of EOCRC, but also facilitate early diagnosis, thus improving patients' prognosis.

This study had several limitations. First, since GBD 2021 reported colon and rectal cancer together as "colorectal cancer," we were unable to assess the respective trends in colon and rectal cancer between 1990 and 2021. Second, in some countries, especially in underdeveloped ones, the misdiagnosis or omission due to inadequate medical care may lead to under-registration of CRC and thus causing underestimation of the burden of disease, although the GBD collaboration had used robust statistical methods to minimize this impact. Third, GBD 2021 did not provide data on sexual and gender minorities, a group that remains less understudied in CRC. Last but not least, in less developed countries, the low level of medical care, along with potential misdiagnosis, missed diagnosis, and inadequate registration system, may lead to an underestimation of the burden of EOCRC.

Conclusions

This study comprehensively reported the global burden of EOCRC from 1990 to 2021. Over the past 32 years, global ASIR and ASPR for EOCRC was on the rise, while ASDR and age-standardized DALY rate exhibited a downward trend. The burden varied with sex, sociodemographic factors, and geographical locations. Males and young adults in higher SDI countries undertook a heavier burden of EOCRC, which deserves attention. The burden of EOCRC is predicted to increase continuously over the next few years. The huge burden posed by EOCRC underscores the need for close collaboration among countries. Future efforts to mitigate the burden of EOCRC include health education, population-wide screening, and an earlier start age for screening.

Abbreviations

AAPCs	Average annual percentage changes
ASDR	Age-standardized death rate
ASIR	Age-standardized incidence rate
ASPR	Age-standardized prevalence rate
BAPC	Bayesian age-period-cohort analysis
CIs	Confidence intervals
CRC	Colorectal cancer
DALYs	Disability-adjusted life-years
EOCRC	Early-onset colorectal cancer
SDI	Sociodemographic index
GBD	Global Burden of Diseases
GHDx	Global Health Data Exchange
GATHER	Guidelines for Accurate and Transparent Health Estimates Reporting
ICD	International Classification of Diseases
UIs	Uncertainty intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03867-9.

Additional file 1. Tables S1-S5. Table S1. SDI values and quintiles of 204 countries/territories in GBD 2021. Table S2. SDI reference quintile values for GBD 2021. Table S3. The prevalence and DALYs of EOCRC from 1990 to 2021 at the global and regional levels. Table S4. The incidence and deaths of EOCRC from 1990 to 2021 at the national level. Table S5. The prevalence and DALYs of EOCRC from 1990 to 2021 at the national level.

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Authors' contributions
YM: Writing – original draft, Methodology, Investigation, Conceptualization. ZT: Writing – original draft, Methodology, Investigation, Conceptualization. JZ: Writing – original draft, Methodology, Investigation, Conceptualization. DX: Writing – review & editing, Resources. LC: Writing – review & editing, Resources. WD: Writing – review & editing, Validation, Supervision. CC: Writing – review & editing, Validation, Supervision. All authors read and approved the final manuscript.

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Data availability
The datasets for this study can be found in the Global Health Data Exchange database (https://ghdx.healthdata.org/gbd-2021).

Declarations

Ethics approval and consent to participate
Ethics approval was not required for this study due to the analysis of anonymized and publicly available data.

Consent for publication
Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan University, Wuhan 430060, China. [2]Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan University, Wuhan 430060, China. [3]Department of General Practice, Renmin Hospital of Wuhan University, Wuhan University, Wuhan 430060, China.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.
3. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, Jemal A. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179–85.
4. Sinicrope FA. Increasing Incidence of Early-Onset Colorectal Cancer. N Engl J Med. 2022;386(16):1547–58.
5. Patel SG, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol. 2022;7(3):262–74.
6. Vuik FE, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ, Zadnik V, Pellise M, Esteban L, Kaminski MF, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut. 2019;68(10):1820–6.
7. Siegel RL, Medhanie GA, Fedewa SA, Jemal A. State Variation in Early-Onset Colorectal Cancer in the United States, 1995–2015. J Natl Cancer Inst. 2019;111(10):1104–6.
8. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, Cantor SB, Chang GJ. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010. JAMA Surg. 2015;150(1):17–22.
9. Brenner DR, Heer E, Sutherland RL, Ruan Y, Tinmouth J, Heitman SJ, Hilsden RJ. National Trends in Colorectal Cancer Incidence Among Older and Younger Adults in Canada. JAMA Netw Open. 2019;2(7): e198090.
10. Araghi M, Soerjomataram I, Bardot A, Ferlay J, Cabasag CJ, Morrison DS, De P, Tervonen H, Walsh PM, Bucher O, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. Lancet Gastroenterol Hepatol. 2019;4(7):511–8.
11. Pan H, Zhao Z, Deng Y, Zheng Z, Huang Y, Huang S, Chi P. The global, regional, and national early-onset colorectal cancer burden and trends from 1990 to 2019: results from the Global Burden of Disease Study 2019. BMC Public Health. 2022;22(1):1896.
12. Yeo H, Betel D, Abelson JS, Zheng XE, Yantiss R, Shah MA. Early-onset Colorectal Cancer is Distinct From Traditional Colorectal Cancer. Clin Colorectal Cancer. 2017;16(4):293-299 e296.
13. Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K, Giannakis M, Wu K, Cao Y, Ng K, Ogino S. Rising incidence of early-onset colorectal cancer - a call to action. Nat Rev Clin Oncol. 2021;18(4):230–43.
14. Diseases GBD, Injuries C. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133–61.
15. Global Health Data Exchange database. Institute for Health Metrics and Evaluation, Seattle. 2024. https://ghdx.healthdata.org/gbd-2021. Accessed 31 May 2024.
16. Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, Grove JT, Hogan DR, Hogan MC, Horton R, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. Lancet. 2016;388(10062):e19–23.
17. Zahnd WE, Gomez SL, Steck SE, Brown MJ, Ganai S, Zhang J, Arp Adams S, Berger FG, Eberth JM. Rural-urban and racial/ethnic trends and disparities in early-onset and average-onset colorectal cancer. Cancer. 2021;127(2):239–48.
18. O'Sullivan DE, Ruan Y, Cheung WY, Forbes N, Heitman SJ, Hilsden RJ, Brenner DR. Early-Onset Colorectal Cancer Incidence, Staging, and Mortality in Canada: Implications for Population-Based Screening. Am J Gastroenterol. 2022;117(9):1502–7.
19. Jin EH, Han K, Shin CM, Lee DH, Kang SJ, Lim JH, Choi YJ. Sex and Tumor-Site Differences in the Association of Alcohol Intake With the Risk of Early-Onset Colorectal Cancer. J Clin Oncol. 2023;41(22):3816–25.
20. Collaborators GBDCoD: Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024, 403(10440):2100–2132.
21. Zhang J, Ma B, Han X, Ding S, Li Y. Global, regional, and national burdens of HIV and other sexually transmitted infections in adolescents and young adults aged 10–24 years from 1990 to 2019: a trend analysis based on the Global Burden of Disease Study 2019. Lancet Child Adolesc Health. 2022;6(11):763–76.
22. India State-Level Disease Burden Initiative Road Injury C. Mortality due to road injuries in the states of India: the Global Burden of Disease Study 1990–2017. Lancet Public Health. 2020, 5(2):e86-e98.
23. Wagstaff A. The bounds of the concentration index when the variable of interest is binary, with an application to immunization inequality. Health Econ. 2005;14(4):429–32.
24. Liu Y, Zhang C, Wang Q, Wu K, Sun Z, Tang Z, Zhang B. Temporal Trends in the Disease Burden of Colorectal Cancer with Its Risk Factors at the Global and National Level from 1990 to 2019, and Projections Until 2044. Clin Epidemiol. 2023;15:55–71.
25. Huang Q, Zi H, Luo L, Li X, Zhu C, Zeng X. Secular trends of morbidity and mortality of prostate, bladder, and kidney cancers in China, 1990 to 2019 and their predictions to 2030. BMC Cancer. 2022;22(1):1164.
26. Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Norat T. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS ONE. 2011;6(6): e20456.
27. Schwingshackl L, Schwedhelm C, Hoffmann G, Knuppel S, Laure Preterre A, Iqbal K, Bechthold A, De Henauw S, Michels N, Devleesschauwer B, et al. Food groups and risk of colorectal cancer. Int J Cancer. 2018;142(9):1748–58.
28. Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, Greenwood D, Norat T. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol. 2017;28(8):1788–802.
29. Imamura F, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, Mozaffarian D. Global Burden of Diseases N, Chronic Diseases Expert G: Dietary quality among men and women in 187 countries in 1990 and 2010: a systematic assessment. Lancet Glob Health. 2015;3(3):e132-142.
30. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, Meyerhardt JA, Chan AT, Willett WC, Wu K, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut. 2021;70(12):2330–6.
31. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766–81.
32. Li H, Boakye D, Chen X, Jansen L, Chang-Claude J, Hoffmeister M, Brenner H. Associations of Body Mass Index at Different Ages With Early-Onset Colorectal Cancer. Gastroenterol. 2022;162(4):1088-1097 e1083.
33. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, He X, Fuchs CS, Ogino S, Willett WC, et al. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. JAMA Oncol. 2019;5(1):37–44.
34. Li H, Boakye D, Chen X, Hoffmeister M, Brenner H. Association of Body Mass Index With Risk of Early-Onset Colorectal Cancer: Systematic Review and Meta-Analysis. Am J Gastroenterol. 2021;116(11):2173–83.
35. Collaborators GBDCC: Global, regional, and national burden of colorectal cancer and its risk factors, 1990–2019: a systematic analysis for the Global

Burden of Disease Study 2019. Lancet Gastroenterol Hepatol. 2022, 7(7):627–647.
36. Murphy N, Strickler HD, Stanczyk FZ, et al. A prospective evaluation of endogenous sex hormone levels and colorectal cancer risk in postmenopausal women. J Natl Cancer Inst. 2015;107(10):djv210.
37. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22(11):1931–43.
38. Yang Y, Wang G, He J, Ren S, Wu F, Zhang J, Wang F. Gender differences in colorectal cancer survival: A meta-analysis. Int J Cancer. 2017;141(10):1942–9.
39. Zhao G, Li H, Yang Z, Wang Z, Xu M, Xiong S, Li S, Wu X, Liu X, Wang Z, et al. Multiplex methylated DNA testing in plasma with high sensitivity and specificity for colorectal cancer screening. Cancer Med. 2019;8(12):5619–28.
40. Nakamura K, Hagihara K, Nagai N, et al. Ketogenic effects of multiple doses of a medium chain triglycerides enriched ketogenic formula in healthy men under the ketogenic diet: A randomized, double-blinded, placebo-controlled study. Nutrients. 2022;14(6):1199.
41. Cui LH, Shin MH, Kweon SS, Kim HN, Song HR, Piao JM, Choi JS, Shim HJ, Hwang JE, Kim HR, et al. Methylenetetrahydrofolate reductase C677T polymorphism in patients with gastric and colorectal cancer in a Korean population. BMC Cancer. 2010;10:236.
42. Wang Y, Zhao L, Gao L, Pan A, Xue H. Health policy and public health implications of obesity in China. Lancet Diabetes Endocrinol. 2021;9(7):446–61.
43. Chen Z, Peto R, Zhou M, Iona A, Smith M, Yang L, Guo Y, Chen Y, Bian Z, Lancaster G, et al. Contrasting male and female trends in tobacco-attributed mortality in China: evidence from successive nationwide prospective cohort studies. Lancet. 2015;386(10002):1447–56.
44. Wang JL, Ma JQ, Xu MY, Li F, Ren F, Guo YF, Sheng XY. Comparison of the effects of different growth standards on infants in Urban Shanghai: a cluster-randomized controlled trial. Chin Med J (Engl). 2019;132(1):4–10.
45. Tian Y, Kharazmi E, Sundquist K, Sundquist J, Brenner H, Fallah M. Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study. BMJ. 2019;364: l803.
46. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih YT, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250–81.
47. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.

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