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The Global, Regional, and National Early-Onset Colorectal Cancer Burden and Trends from 1990 to 2021: Based on the Global Burden of Disease Study 2021

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Abstract

Background: The early-onset colorectal cancer (EOCRC) refers to the diagnosis of colorectal cancer before the age of 50 years. The global incidence and mortality rates of EOCRC in individuals under 50 years old continue to rise.

Methods: Based on the Global Burden of Disease 2021 (GBD2021) data, the estimated annual percentage changes and Joinpoint regression model were utilized to analyze the temporal trend of global disease burden of EOCRC from 1990 to 2021. Pearson rank correlation analysis was employed to examine the association between disease burden and Socio-Demographic Index (SDI). The contribution factors of EOCRC were analyzed using decomposition analysis. Additionally, the Autoregressive Integrated Moving Average Model (ARIMA) was employed to forecast future trends.

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Result: The findings of the study revealed that in 2021, there was a higher incidence and mortality rates of EOCRC among males compared to females. Furthermore, between 1990 and 2021, there was a direct correlation between the social development and the rate of decline in EOCRC mortality. Individuals aged 30-34 experienced the highest disease burden. Simultaneously, population growth emerged as the primary contributor to the escalating disease burden of EOCRC. It was projected that the incidence rate of EOCRC would continue to rise within the next three decades.

Conclusion: The global burden of EOCRC have continued to rise from 1990 to 2021 and was projected to further increase over the next three decades. Therefore, EOCRC remained a paramount global public health challenge necessitating the development of more precise and effective strategies to address this epidemic.

Keywords: *Early-onset colorectal cancer, Global Burden of Disease 2021, estimated annual percentage changes, Joinpoint regression model, decomposition analysis*

1. Introduction

The incidence of colorectal cancer (CRC) ranks third globally among all malignancies, and it stands as the second leading cause of cancer-related mortality [1, 2]. Early-onset colorectal cancer (EOCRC) typically refers to the diagnosis of colorectal cancer in individuals under the age of 50 [3]. Although some developed countries have witnessed the decrease in incidence and mortality rates of CRC among individuals aged over 50 due to lifestyle changes and widespread screening programs [4], there is still a global increase in both EOCRC (< 50 years) incidence and mortality rates [3, 5]. For instance, the incidence of EOCRC in the United States has witnessed a 50% increase over the past three decades, with projections indicating that by 2030, CRC is going to emerge as the primary cause of cancer-related mortality among individuals under the age of 50 in the country. Furthermore, previous studies have demonstrated that EOCRC frequently presents at an advanced stage, a poor histological type and a higher likelihood of distant metastasis [6, 7], but further investigation is warranted to elucidate the underlying reasons for this phenomenon.

Some studies have demonstrated that the rise in EOCRC is related to factors including obesity, sedentary lifestyle, high consumption of red meat, alcohol intake, smoking, and other unhealthy behaviors [8, 9]. Additionally, it is also influenced by geographical and sociodemographic aspects like race, income levels, and the adoption of screening measures like colonoscopy [7, 9]. Currently, the increasing prevalence of EOCRC has led to significant economic burden and loss of life-years among young patients worldwide. The Global Burden of Disease 2021 (GBD2021) offered comprehensive global estimates on the incidence, prevalence, and mortality rates for 371 diseases and injuries across 204 countries and territories and 811 subnational regions from 1990 to 2021 [10, 11]. This study was the first to dissect the

latest global burden trends of EOCRC and predict their future trends over a longer time horizon using the newly updated GBD2021 dataset. Our objective was to offer robust evidence supporting policymakers in developing more accurate and effective public health strategies to reduce the burden imposed by EOCRC.

2. Methods

2.1. Overview

Based on GBD2021 data, this study estimated the temporal trends of incidence and mortality rates across regions, genders, and different age-groups from 1990 to 2021. Additionally, it provided predictions for potential future trends. This study adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).

2.2. Definitions

GBD2021 is a comprehensive international research collaboration, supported by over 11,500 collaborators from 164 countries [12]. It aims to quantify and compare the global health and disease burden from 1990 to 2021 through extensive data provision, review, and analysis [12]. EOCRC usually refers to the diagnosis of CRC in individuals under the age of 50 [13, 14]. The most widely recommended definition for adolescents and young adults in oncology sets the lower age limit at 15 years, as endorsed by the National Cancer Institute and the European Society for Medical Oncology [15]. Therefore, we utilized an age range of 15 to 49 years in this study. This investigation employed GBD2021 data to analyze temporal trends of the incidence, mortality and their corresponding rates for EOCRC, based on gender, region, and age-group from 1990 to 2021. Further this study further predicted the future trend of the EOCRC. Based on the Socio-demographic Index (SDI), data for the 204 countries and territories included in GBD2021 are categorized into five regions: low SDI region, middle-low SDI region, middle SDI region, middle-high SDI region, and high SDI region [16]. In this study, individuals aged between 15-49 years were further divided into seven distinct age-groups: 15-19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years and 45-49 years. The data obtained from the publicly accessible data platform of the Global Health Data Exchange website (Link) did not involve the collection of personal information, thus obviating the need for ethical approval.

2.3. Statistical Analysis

The Joinpoint regression model was utilized to calculate the average annual percentage change (AAPC) for each gender, each SDI region and each age-group providing an overview of corresponding temporal trend of incidence and mortality rates for EOCRC from 1990 to 2021. In addition, we computed estimated annual percent change (EAPC) in Rate to evaluate the temporal trend by natural logarithm of Rate fit the linear regressions model: $\gamma = \alpha + \beta\chi + \varepsilon$, where γ represents ln (Rate) and χ denotes calendar year. Thus: $\ln(\text{Rate}) = \alpha + \beta x + \varepsilon$. EAPC was then calculated as follows: EAPC with 95% CI $=100 \times (e\beta - 1)$. If EAPC falls within its respective positive or negative range within a given confidence interval greater than zero or less than zero respectively; this indicates an increasing or decreasing trend over time for Rate values. Here, Rate represents incidence rate or mortality rate. Considering the substantial variations in the distribution of SDI across 21 regions and 204 countries and territories, from 1990 to 2021, Pearson's rank correlation analysis was utilized to evaluate the correlation between the incidence and mortality rate of EOCRC and SDI in 21 regions and 204 countries and territories, respectively.

Furthermore, decomposition analysis was utilized to quantify the contributions of three population-level factors: population aging, population growth, and epidemiological changes to the total change in incidence and mortality rates from 1990 to 2021. Additionally, the autoregressive integrated moving average (ARIMA) models were employed to forecast future trends in the incidence and mortality rate of EOCRC. The equation is represented as $Y_t = \varphi_1 Y_{t-1} + \varphi_2 Y_{t-2} + ... + \varphi_p Y_{t-p} + e_t - \theta_1 e_{t-1} - ... - \theta_q e_{t-q}$, where $(\varphi_1 Y_{t-1} + \varphi_2 Y_{t-2} + ... + \varphi_p Y_{t-p} + e_t)$ denotes the autoregressive (AR) model, $(e_t - \theta_1 e_{t-1} - ... - \theta_q e_{t-q})$ represents the moving average (MA) model, Y_{t-p} signifies the observed value of the (t-p) period, p and q denote the orders of AR and MA models, while e_t stands for the random error during period of t [17]. All statistical analyses and graphical representations were conducted using R software (version 4.2.1), Joinpoint software (version 5.2.0). A significance level set at $P < 0.05$ to indicate statistical significance.

3. Results

3.1. Temporal Trends of Incidence, Mortality and Rates Worldwide for EOCRC, from 1990 to 2021

The results of incidence, mortality, their corresponding rates, and the Joinpoint regression models based on incidence and mortality rates for EOCRC worldwide from 1990 to 2021 are presented in (Figure 1 & Table 1). Striking heterogeneity in the temporal trends of incidence and mortality rates for EOCRC among different genders, SDI regions, and age-groups was found in this study. Although the incidence rate for EOCRC was steadily increasing in both genders from 1990 to 2021, the upward trend in men was more pronounced (male, AAPC = 1.31 (1.25, 1.36) vs. female, AAPC = 0.57 (0.52, 0.64)), as shown in (Table 1 & Figure 1A). Notably, a divergent trend of mortality rate was observed between men and women, there was a slight increase in male mortality rate and a decreasing trend in female mortality rate (Male, AAPC = 0.06 (0.01, 0.11) vs. female, AAPC = -0.61 (-0.66, -0.55)), as presented in (Table 1 & Figure 1B). From 1990 to 2021, the High-middle SDI region (AAPC = 1.96 (1.86, 2.03)) exhibited the most significant upward trend of incidence rate for EOCRC, followed by the Middle SDI region (AAPC = 1.79 (1.73, 1.86)), while the Low SDI region (AAPC = -0.02 (-0.04, 0.02)) exhibited the slightly downward trend (Table 1 & Figure 1C). The temporal trend of EOCRC mortality rate from 1990 to 2021 revealed a pronounced decline in the high SDI region (AAPC = -0.48 (-0.54, -0.43)), followed by a similar downward trend in the low SDI region (AAPC = -0.42 (-0.45, -0.39)) (Table 1 & Figure 1D).

TABLE 1: Incidence, Mortality, Rate, and Average Annual Percentage Change (AAPC) of early-onset colorectal cancer (EOCRC), 1990-2021.

	1990		2021		AAPC (95% CI)
	Number (95%UI)	Rate per 100,000 (95%UI)	Number (95%UI)	Rate per 100,000 (95%UI)	
Sex					
Both					
Incidence	107309·8 (99971·3, 114184·5)	3·96 (3·69, 4·21)	211890·4 (193832·2, 231271·9)	5·37 (4·91, 5·86)	0·99 (0·95, 1·01)
Mortality	59231·5 (54391·3, 63963·1)	2·19 (2·01, 2·36)	79504·3 (72699·2, 86539·5)	2·01 (1·84, 2·19)	-0·23 (-0·27, -0·19)
Male					
Incidence	58100·1 (52189·3, 63006)	4·23 (3·8, 4·59)	126665·9 (110037·1, 144644·7)	6·33 (5·5, 7·23)	1·31 (1·25, 1·36)
Mortality	32451·2 (28468·1, 35780·5)	2·36 (2·07, 2·61)	47359 (41410·6, 53363·6)	2·37 (2·07, 2·67)	0·06 (0·01, 0·11)
Female					
Incidence	49209·7 (44835·5, 53755·3)	3·68 (3·35, 4·02)	85224·5 (77873, 93406·8)	4·37 (4, 4·79)	0·57 (0·52, 0·64)
Mortality	26780·3 (23916·7, 29934·8)	2 (1·79, 2·24)	32145·3 (29390·9, 35098·1)	1·65 (1·51, 1·8)	-0·61 (-0·66, -0·55)
SDI level					
High					
Incidence	35483·5 (34724·6, 36268·9)	7·7 (7·53, 7·87)	50984·8 (49340·5, 52745·4)	10·15 (9·82, 10·5)	0·89 (0·83, 0·94)
Mortality	13064·1 (12770, 13392·8)	2·83 (2·77, 2·91)	12316·1 (11904·5, 12747·1)	2·45 (2·37, 2·54)	-0·48 (-0·54, -0·43)
High-middle					
Incidence	31203·4 (28545·1, 33777·3)	5·53 (5·06, 5·98)	62133·7 (54171·5, 72026·5)	9·87 (8·6, 11·44)	1·96 (1·86,2·03)
Mortality	17681·8 (16052·9, 19290·8)	3·13 (2·84, 3·42)	19428·2 (17107·2, 22241·9)	3·09 (2·72, 3·53)	-0·03 (-0·09,0·06)
Middle					
Incidence	29451·9 (25921·7, 32913·7)	3·23 (2·85, 3·61)	70156·6 (61013·6, 78921·6)	5·59 (4·86, 6·29)	1·79 (1·73, 1·86)
Mortality	19817·7 (17430·6, 22197·3)	2·18 (1·91, 2·44)	29245·5 (25664·3, 32573·9)	2·33 (2·04, 2·6)	0·22 (0·17, 0·28)

Low-middle								
Incidence	8199·3	(7120·4, 9361·8)	1·32 (1·16, 1·52)	21402	(18751·8, 24494·8)	2·11	(1·85, 2·41)	1·12 (1·09, 1·14)
Mortality	6272·9	(5426·8, 7185·6)	1·14 (0·98, 1·3)	13387·6	(11781·8, 15442·1)	1·49	(1·29, 1·7)	0·47 (0·44, 0·51)
Low								
Incidence	2860·3	(2211·8, 3361·8)	1·29 (1, 1·52)	7036·8	(6070, 8090·3)	1·3	(1·12, 1·49)	-0·02 (-0·04, 0·02)
Mortality	2335·4	(1799·2, 2743·8)	1·06 (0·81, 1·24)	5057·6	(4354·6, 5858)	0·93	(0·8, 1·08)	-0·42 (-0·45, -0·39)
				age (years)				
15-19								
Incidence	1994·7	(1682·6, 2213·7)	0·38 (0·32, 0·43)	1798·6	(1596·5, 2021·1)	0·29	(0·26, 0·32)	-0·92 (-0·99, -0·84)
Mortality	1293·4	(1071·2, 1447·4)	0·25 (0·21, 0·28)	805·1 (705·1, 922)		0·13	(0·11, 0·15)	-2·11 (-2·16, -2·06)
20-24								
Incidence	3377·6	(2955·5, 3765·6)	0·69 (0·6, 0·77)	3886·5	(3507·9, 4254)	0·65	(0·59, 0·71)	-0·24 (-0·29, -0·19)
Mortality	2242	(1931·6, 2519·5)	0·46 (0·39, 0·51)	1786·8	(1591·1, 1985·8)	0·3	(0·27, 0·33)	-1·38 (-1·42, -1·33)
25-29								
Incidence	5831·4	(5247·9, 6349·2)	1·32 (1·19, 1·43)	8703·2	(7944·7, 9492)	1·48	(1·35, 1·61)	0·30 (0·22, 0·38)
Mortality	3351·9	(2972·6, 3695·3)	0·76 (0·67, 0·83)	3308·5	(2996·2, 3626·4)	0·56	(0·51, 0·62)	-0·98 (-1·07, -0·89)
30-34								
Incidence	11036·9	(10020·2, 11859·5)	2·86 (2·6, 3·08)	21807·6	(19800·6, 23950·1)	3·61	(3·28, 3·96)	0·81 (0·74, 0·89)
Mortality	6096·1	(5456·5, 6640·4)	1·58 (1·42, 1·72)	7774·3	(7046·5, 8520·6)	1·29	(1·17, 1·41)	-0·60 (-0·67, -0·54)
35-39								
Incidence	19143·3	(17630·8, 20595·6)	5·43 (5·01, 5·85)	34004·9	(30763·6, 37356)	6·06	(5·49, 6·66)	0·40 (0·36, 0·44)
Mortality	10509·6	(9501, 11471·9)	2·98 (2·7, 3·26)	12547·8	(11408·2, 13639·2)	2·24	(2·03, 2·43)	-0·94 (-1·01, -0·88)
40-44								

Incidence	27425·2	(25645·7, 29160·5)	9·57 (8·95, 10·18)	53182·7	(48359·8, 58356·5)	10·63	(9·67, 11·67)	0·31 (0·25, 0·37)
Mortality	14706·8	(13517·9, 15897)	5·13 (4·72, 5·55)	19580·6	(17861·2, 21179)	3·91	(3·57, 4·23)	-0·89 (-0·96, -0·84)
45-49								
Incidence	38500·6	(36197·9, 40771·6)	16·58 (15·59, 17·56)	88506·9	(80432·4, 97666·7)	18·69	(16·99 ,20·63)	0·45 (0·34, 0·51)
Mortality	21031·7	(19511·4, 22591·3)	9·06 (8·4, 9·73)	33701·3	(30773·4, 37042·7)	7·12	(6·5 ,7·82)	-0·75 (-0·8, -0·7)

SDI: Sociodemographic Index; EAPC: estimated annual percentage change; AAPC: Average Annual Percentage Change; UI: Uncertainty Interval; CI: Confidence Interval; *: P-value < 0·05; EOCRC: Early-Onset Colorectal Cancer.

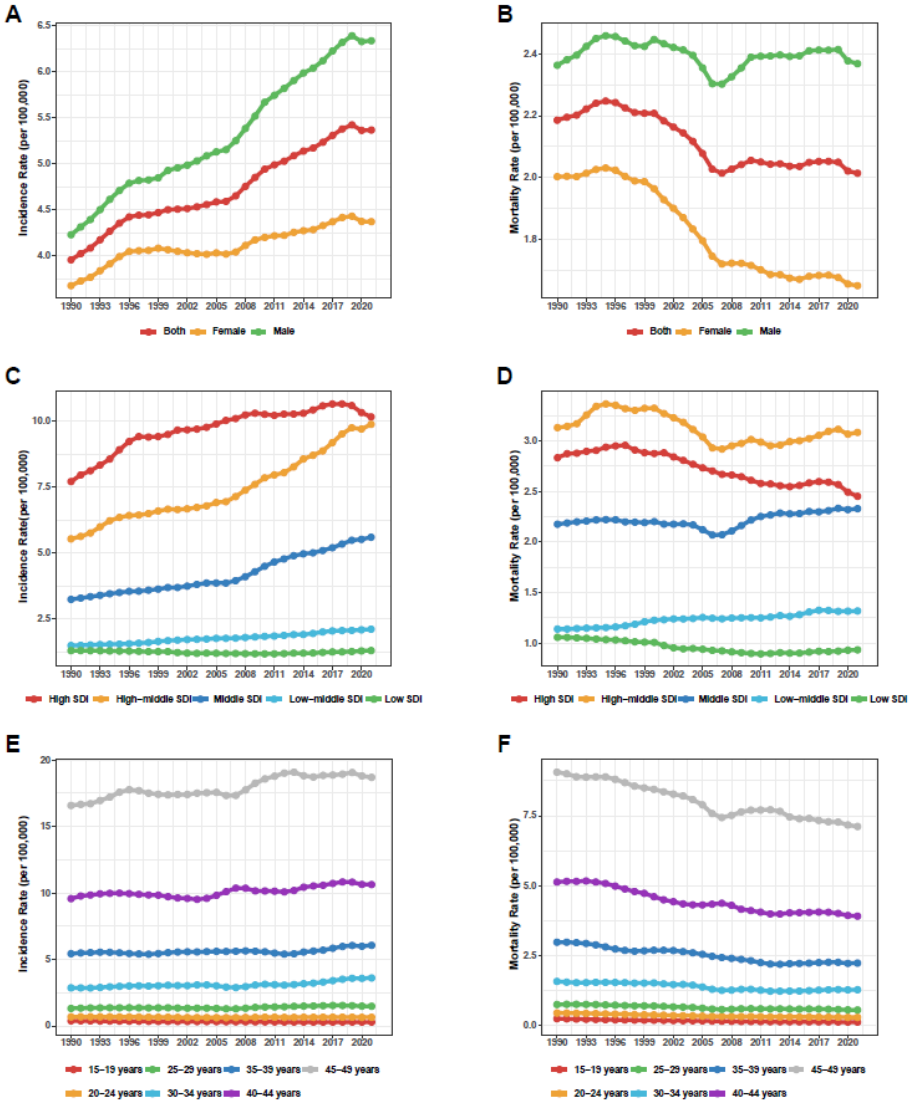

FIGURE 1: Temporal trends of incidence and mortality rates in early-onset colorectal cancer (EOCRC) from 1990 to 2021. **A)** Showed the temporal trend of incidence rate by sex. **B)** Illustrated the temporal trend of incidence rate by

region. **C)** Displayed the temporal trend of mortality rate by sex. **D)** Presented the temporal trend of mortality rate by region.

Surprisingly, the low-middle SDI region (AAPC = 0.47 (0.44, 0.51)) exhibited an unexpected upward trend in mortality rate. From 1990 to 2021, in both men and women, the incidence rate of EOCRC showed the highest proportion in high SDI region, while it exhibited the lowest proportion in low SDI region; furthermore, both proportions were showing a declining trend (Supplementary Figure 1A). The highest proportion of mortality rate among both genders displayed in middle-high SDI region, whereas it remained lowest in low SDI region, which also exhibited a downward trend (Supplementary Figure 1B). The incidence rate of EOCRC demonstrated a significant decrease in the 15-19 age-group (AAPC = -0.92 (-0.99, -0.84)), followed by the 20-24 age-group (AAPC = -0.24 (-0.29, -0.19)) (Table 1 & Figure 1E). Conversely, there was an upward trend in EOCRC incidence across all age-groups between 25 and 49 years, with the most notable increase observed in the 30-34 age-group (AAPC = 0.81 (0.74, 0.89)). Furthermore, a significant downward trend in mortality rates was observed across all age-groups ranging from 15 to 49 years, with the most notable decline observed within the 15-19 age-group (AAPC = -2.11 (-2.16, -2.06)) (Table 1 & Figure 1F).

3.2. Global Disease Burden Assessment of Total Cancers Attributed to EOCRC for 204 Countries and Territories, in 2021

The global map exhibited significant heterogeneity in incidence rate and their corresponding EAPCs, as well as mortality rate and their corresponding EAPCs, for EOCRC across 204 countries and territories in 2021, as displayed in (Figure 2 & Supplementary Figure 2). The global incidence rate of EOCRC in 2021 was notably high, particularly in China, Thailand, Iran, Colombia, Venezuela, Costa Rica, Cuba, Uruguay. Conversely, most African countries exhibited a low incidence rate of EOCRC. In particular, Mauritania, Senegal, Guinea, Mali, Niger, Ghana, and Nigeria in West Africa, Namibia and Mozambique in South Africa, Kenya in East Africa. Additionally, Bhutan in South Asia also presented low incidence rate, as shown in (Figure 2A). Similarly, the world map presented in (Supplementary Figure 2A) showed comparable results for the mortality rate in 2021. Figure 2B showed the temporal trend of the burden of EOCRC incidence rate from 1990 to 2021, which was evaluated by EAPC analysis based on incidence rate, and it was clear that the temporal trend presented significant regional heterogeneity. In South America, Brazil, Paraguay, Chile, Argentina, Peru, Colombia, Venezuela, Costa Rica, Ecuador, and Mexico; in North Africa, Egypt and Libya; in the Middle East, Yemen, Saudi Arabia, Iran, and Iraq; in Southeast Asia, Thailand and Vietnam; and in East Asia, Mongolia displayed a striking upward trend. However, the United States in North America, Spain in southern Europe, Norway in northern Europe, Austria, Switzerland and Serbia in central Europe, Ukraine in Eastern Europe, Ethiopia in East Africa, Kazakhstan, Kyrgyzstan, Tajikistan and Australia in Central Asia exhibited a significant downward trend. The global disease burden for EOCRC, as assessed by EAPC values based on mortality rate, demonstrated similar trends, as depicted in (Supplementary Figure 2B).

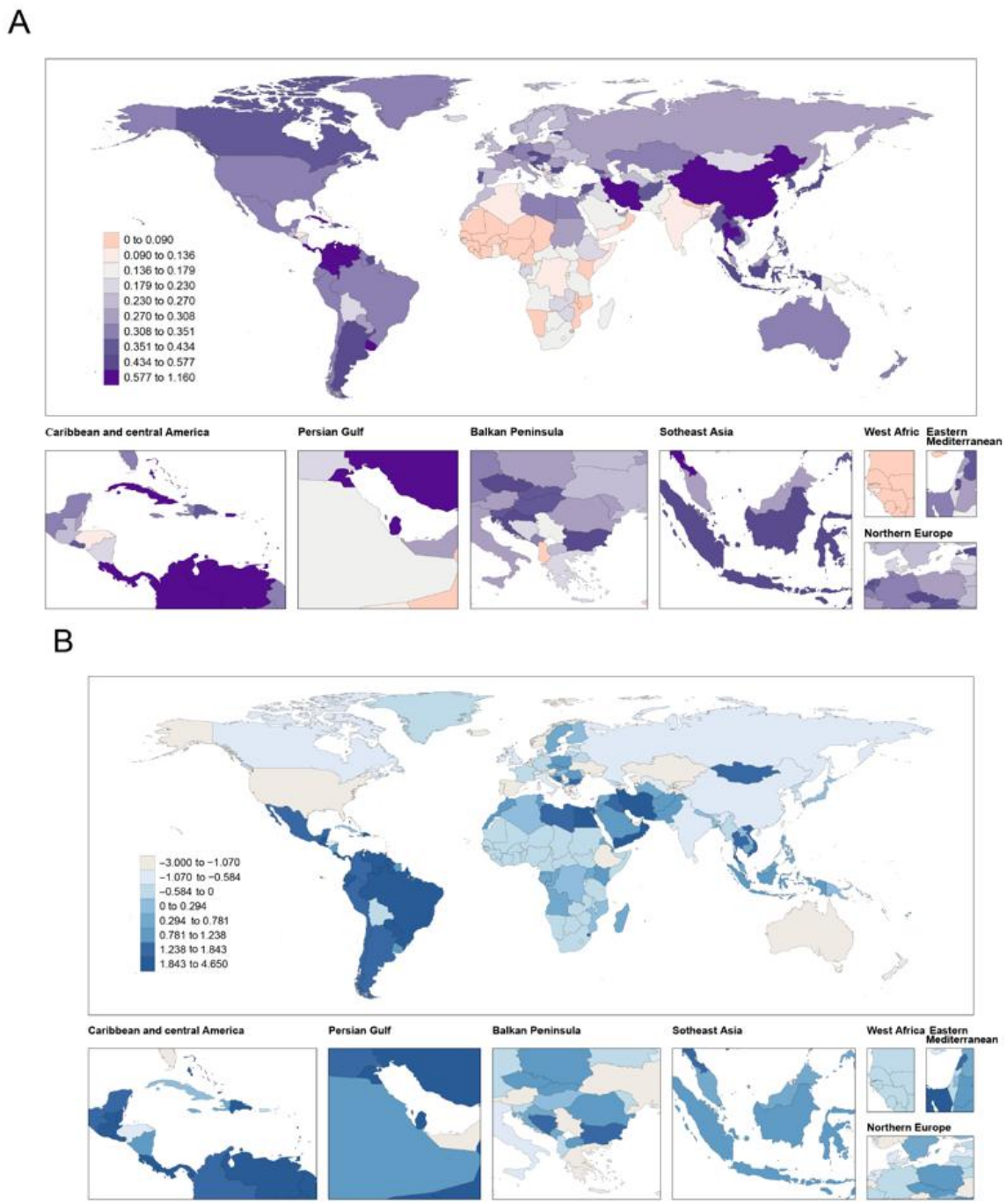

FIGURE 2: A) The incidence rate and **B)** estimated average percentage change (EAPC) of early-onset colorectal cancer (EOCRC) across 204 countries and territories from 1990 to 2021.

3.3. The Trend in Incidence and Mortality Rates for EOCRC among 21 Regions and 204 Countries and Territories based on SDI, from 1990 to 2021

The observed and expected incidence and mortality rates for EOCRC across 21 regions and 204 countries and territories from 1990 to 2021 were presented in (Figure 3). The global incidence rate of EOCRC in 2021 was similar to expectations, while the mortality rate was significantly lower than expectations. Up to 2021, the incidence (Figure 3A) and mortality (Figure 3C) rate of EOCRC has been lower than anticipated in

over two-thirds of regions, including South Asia and Andean Latin America, while the remaining regions, represented by East Asia and Caribbean, continue to experience higher-than-expected rates. Additionally, the incidence rate for EOCRC in 21 regions (Figure 3A) and 204 countries and territories (Figure 3B & Supplementary Table 1) basically showed increased trend with increasing SDI, which indicated a positive correlation between incidence rate for EOCRC and SDI. The trends of mortality rate for EOCRC in 21 regions (Figure 3C) and 204 countries and territories (Figure 3D & Supplementary Table 2) were initially increased with increasing SDI, then declined at SDI of 0.75. Those demonstrated a positive correlation between mortality rate for EOCRC and SDI at initial and then negatively at last, indicating the burden of EOCRC exhibited a trend of initial growth followed by subsequent decline with higher SDI values.

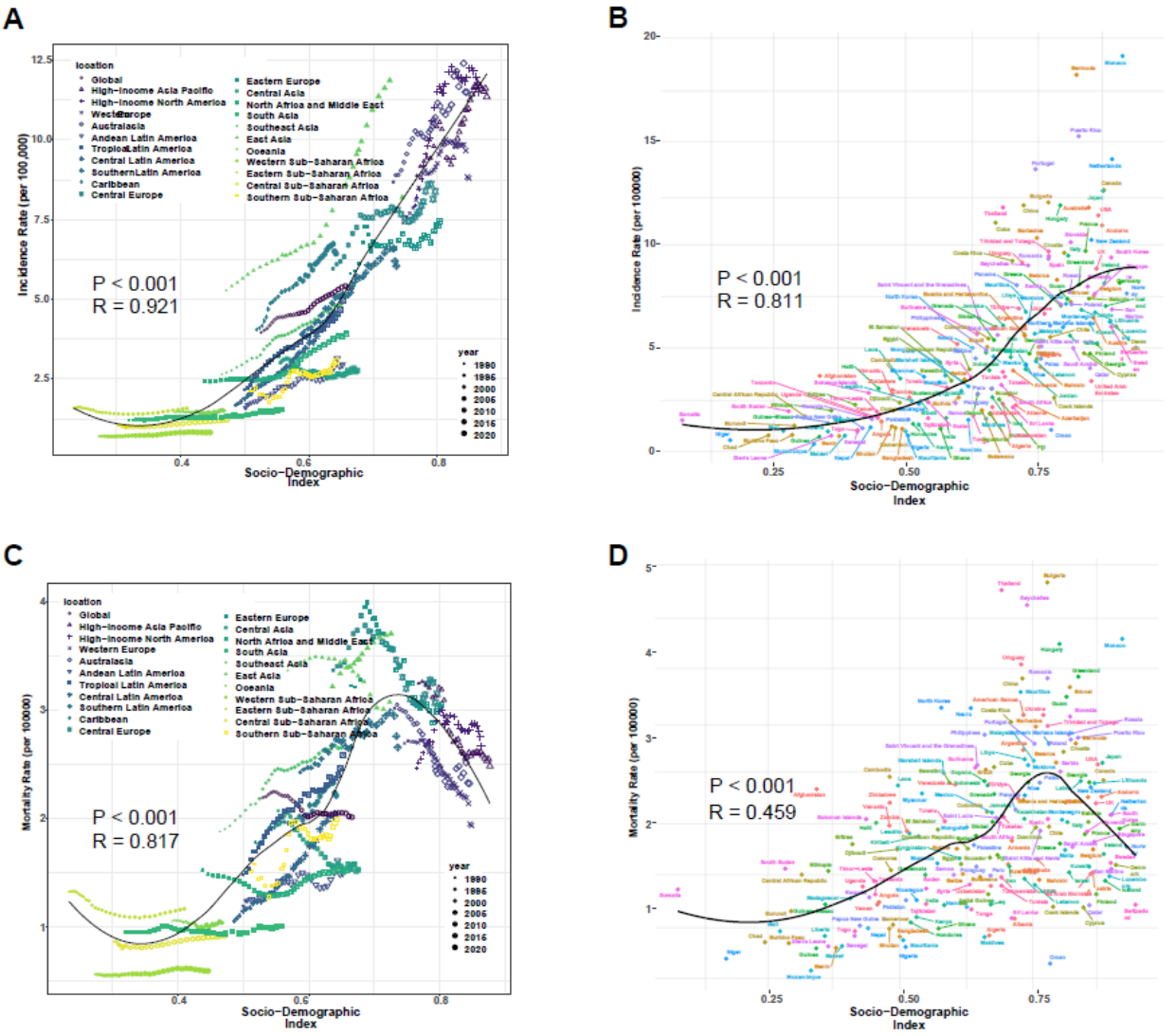

FIGURE 3: A & B) Trend of incidence and **C & D)** mortality rate of EOCRC among 22 regions and 204 countries and territories based on the Sociodemographic Index (SDI) from 1990 to 2021. For each region, points from left to right depict annual estimates from 1990 to 2021, with expected values displayed as the black line.

3.4. Decomposition Analysis of the Change in Incidence and Mortality Rates for EOCRC from 1990 to 2021

A decomposition analysis was performed to determine the contribution of three population-level determinants: population aging, population growth, and epidemiological change, to the change in incidence and mortality rates for EOCRC, as shown in (Figure 4). The incidence rates of EOCRC in both men and women have significantly increased due to population growth, epidemiological change, and population aging, particularly driven by population growth. In contrast to the contribution of population growth was more significant in men, the impact of population aging on EOCRC was more pronounced in women (Figure 4A). The findings in Figure 4B demonstrated a significant contribution of population growth and aging, particularly population growth, to the observed increase in mortality rates for EOCRC among both men and women as well as the overall population. The impact of epidemiological changes on reducing mortality rate was completely counteracted by the effects of population growth and aging, resulting in a net increase in mortality. The results depicted in (Figures 4C & 4D) demonstrated that population growth exerted the most significant influence on both the incidence and mortality of EOCRC in low, low-middle, middle SDI regions. Conversely, population aging emerged as the predominant factor in high-middle and high SDI regions.

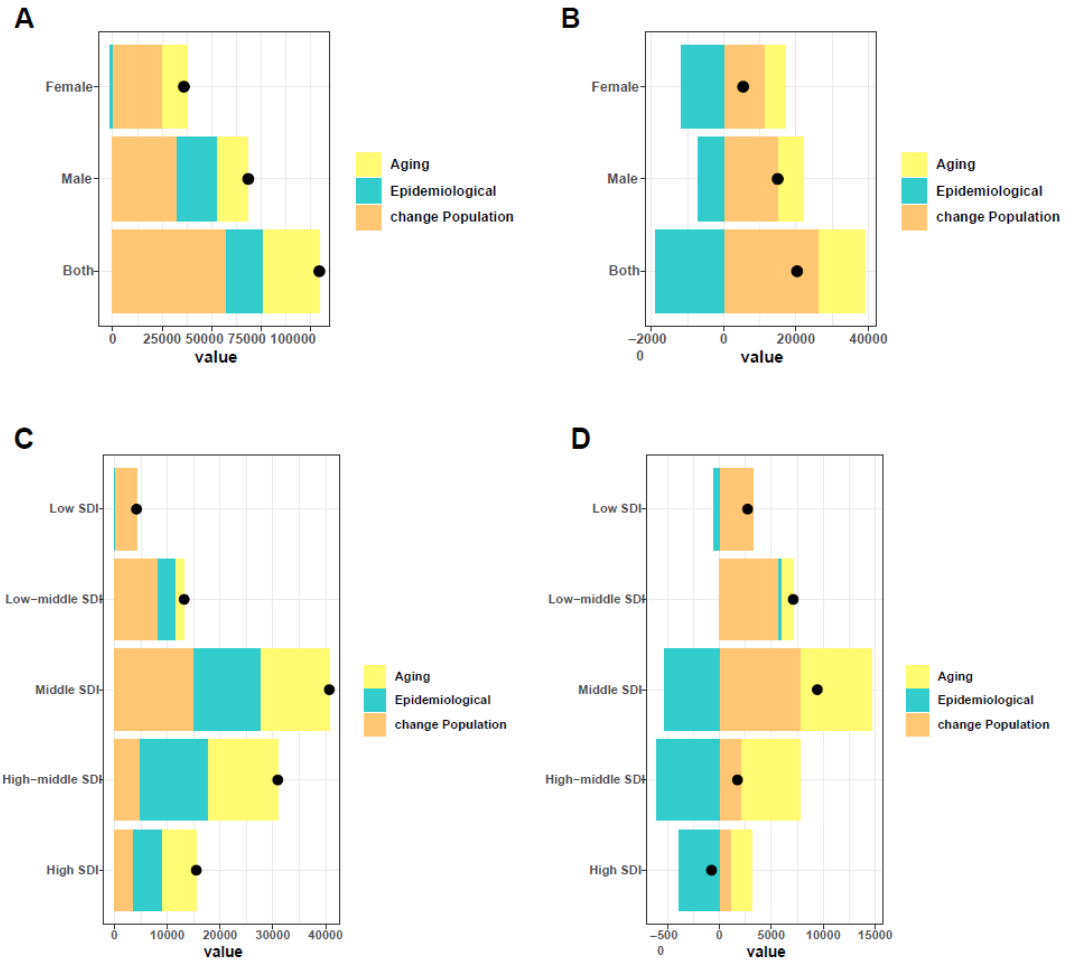

FIGURE 4: A & C) Decomposition analysis of changes in incidence and **B & D)** mortality rates of early-onset colorectal cancer (EOCRC) by sex and SDI region. Changes are decomposed into three population-level determinants:

population aging, population growth, and epidemiological change from 1990 to 2021. The black dots indicated the total value of change attributable to all three components.

Additionally, (Figure 4D) revealed that in low, middle and high SDI regions, the decline in mortality rate resulting from epidemiological changes was completely counterbalanced by population growth and aging, leading to a net increase in mortality rates. In contrast, high SDI regions experienced a net reduction in mortality rate due to the prevailing impact of epidemiological changes outweighed the other two factors.

3.5. Predicted Global Trends of EOCRC Incidence and Mortality Rate over the Next Three Decades

The ARIMA models were utilized to quantitatively depict the trends of EOCRC incidence and mortality from 2022 to 2050, as shown in (Figure 5). The EOCRC incidence rate was expected to increase from 5.37 per 100 000 in 2021 to 6.78 per 100 000 in 2050 (Supplementary Table 3 & Figure 5A). The predicted mortality rate was going to plateau from 2.01 per 100 000 in 2022 to 2050 at 2.00 per 100 000 (Supplementary Table 4 & Figure 5B).

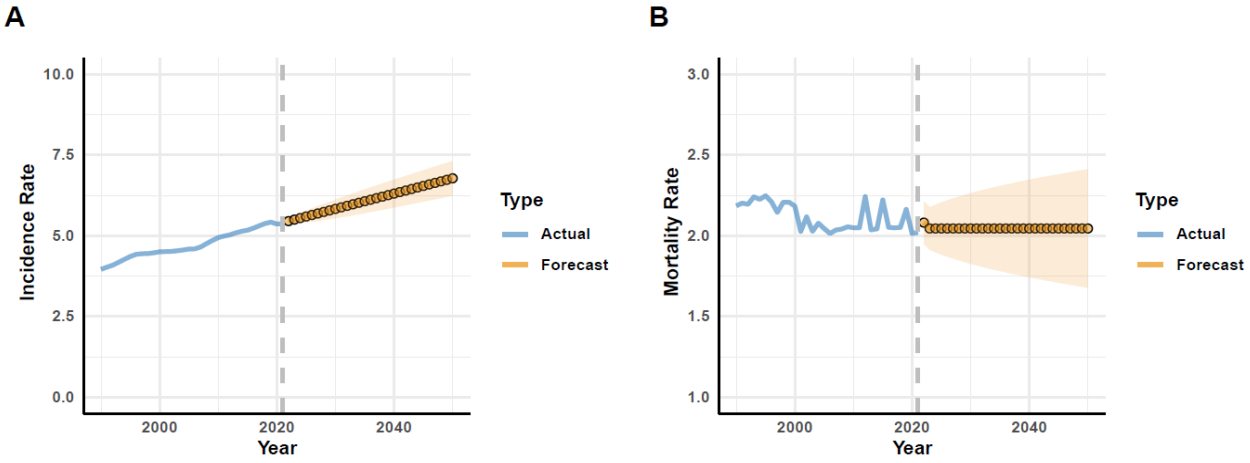

FIGURE 5: A) Predicted global trends of EOCRC incidence and **B)** mortality rate of early-onset colorectal cancer (EOCRC) for the next 28 years (2022-2050). Blue lines represented the historical trends from 1990 to 2021, while yellow dotted lines and shaded regions represent the predicted trends and their 95% confidence intervals (CIs).
CI: Confidence Interval.

4. Discussion

To the best of our knowledge, this study was the first comprehensive analysis to examine temporal trends in the global burden of EOCRC from 1990 to 2021, utilizing updated GBD2021 data. Our findings revealed a consistent and significant increase in EOCRC incidence rate worldwide over the past three decades, with rates rising from 3.96 per 100000 in 1990 to 5.37 per 100000 in 2021. Conversely, global mortality rate for EOCRC have demonstrated a steady decline from 2.19 per 100000 in 1990 to an estimated rate of approximately 2.01 per 100000 in 2021. The findings aligned with the outcomes of prior investigation [18, 19].

Significant disparities in temporal trends were observed in the incidence and mortality rates of

EOCRC between genders. The upward trend of incidence rate among men exhibited a significantly steeper incline compared to women, while the decline in mortality rate displayed a comparatively less pronounced pattern. This gender discrepancy became increasingly evident over the study period spanning from 1990 to 2021. The incidence rate of men was significantly higher than that of women, as indicated by previous studies [18]. This disparity might be attributed to variations in lifestyle factors such as higher rates of visceral fat accumulation, smoking, and alcohol consumption among men [20]. Heme iron played a role in the development of colorectal cancer by facilitating the production of reactive oxygen species (ROS) and influencing the composition of gut microbiota [21, 22]. Additionally, there was a higher prevalence of iron deficiency among women compared to men, which might contribute to the lower incidence rate of EOCRC in women than in men [23]. Furthermore, female exhibited a lower mortality rate of EOCRC compared to their male counterparts, potentially attributed to disparities in sex hormone levels. The presence of endogenous estrogens and the use of oral contraceptives in women have demonstrated a reduction in cancer risk. Additionally, it was worth noting that most women were postmenopausal at the time of colorectal cancer diagnosis, and employing postmenopausal hormone replacement therapy (HRT) has also been proven to decrease the risk of developing colorectal cancer [24, 25].

Significant regional heterogeneity in the incidence and mortality rates of EOCRC was found in our study. With the exception of the low SDI region, all other four SDI regions exhibited an upward trend in incidence rates. Interestingly, the low SDI region demonstrated a decline in mortality rates second only to that observed in the high SDI region, while middle-low SDI region displayed a distinct increasing trend. The SDI served as an indicator of the economic and social progress achieved by a country or region. The analysis of the correlation between SDI and mortality and morbidity rates revealed that there was a positive association, indicating that as the SDI increased, both morbidity and mortality rates also increased. However, once the social development level reached a higher stage, there was an observed decline in mortality rate. Our study also revealed that the incidence and mortality rates of EOCRC were higher in developed countries such as the United States, Japan, and European nations; however, there was an overall declining trend. This could be attributed to the sedentary lifestyle, consumption of red meat, tobacco use, alcohol intake, as well as a higher prevalence of obesity or overweight observed among individuals residing in these highly developed countries [26]. We hypothesized that the decline in mortality rate could potentially be attributed to the advancements in healthcare systems and screening strategies. Furthermore, we have observed a significant surge in the incidence rate of EOCEC and a concurrent decline in mortality rate in China and other rapidly developing countries. These trends could be attributed to the adoption of Western lifestyle practices leading to an increase in risk factors, as well as advancements made in healthcare systems and screening strategies within these countries. In addition, the Global Burden of Disease (GBD) incorporates data from well-established registries in developed countries, and the higher incidence rate of EOCRC in these countries might be attributed to the presence of more robust registries, resulting in more comprehensive and accurate reporting of incidences. The rapid increase in incidence rate observed in rapidly developing countries could also be attributed to advancements made in the quality of cancer registries during this period. Similarly, suboptimal registries might account

for why the declining mortality trend observed in low SDI region ranked second only to that seen in high SDI region.

Our study revealed an age-related increase in the incidence and mortality rates of EOCRC. Moreover, there was notable heterogeneity among different age-groups regarding temporal trends in both incidence and mortality rates. Specifically, our findings indicated that between 1990 and 2021, the most substantial reduction in incidence and mortality rates occurred in the 15-19 age-group, whereas the highest increase in incidence rate was observed in the 30-34 age-group with minimal reduction in mortality rate. Previous research has demonstrated a correlation between risk factors such as consumption of sugar-sweetened beverages and high Body Mass Index (BMI) during adolescence with an elevated risk of EOCRC [9, 27]. However, an increasing number of countries were prioritized adolescent health in past three decades, resulting in a decrease in unhealthy diets and lifestyles among adolescents. Consequently, noteworthy reductions have been observed in both incidence and mortality rates of CRC among this population segment. Individuals aged 30-34 years face heightened risk factors for CRC due to economic freedom and high work-life stress levels including smoking, alcohol consumption, excessive red meat intake, as well as sedentary behavior. Additionally, current recommendations suggested colonoscopy screening at the age of 50 [28], although some countries have lowered it to 45 years old [29, 30]. As a result, screening coverage for individuals under the age of 45 was significantly inadequate leading to delayed detection of CRC within this demographic cohort which might explain their higher incidence and mortality rates.

The decomposition analysis revealed that the rise in incidence and mortality rates of EOCRC was attributed to population growth and population aging, with population growth having the greatest impact. Although epidemiological changes could mitigate EOCRC mortality rate, this effect would be counteracted by population growth and aging. Therefore, given the global increase in population and exacerbation of aging trends, EOCRC remained a significant global public health concern. Furthermore, utilizing the ARIMA model, we projected that the incidence rate of EOCRC would continue to escalate over the next 30 years; however, mortality rate was expected to reach a plateau during this period. Consequently, the enhancement of relevant policies and regulations by policy makers is imperative in order to foster individual health awareness, modify unhealthy lifestyles, and expedite the advancement of early detection and precision treatment measures, thereby alleviating the burden posed by EOCRC.

Previous studies have identified several molecular and genomic risk factors associated with EOCRC. For instance, mutations in specific genes, such as APC [31] and TP53 [32], were believed to elevate the risk of developing colorectal cancer. Furthermore, hereditary genetic syndromes, including Lynch syndrome [33, 34] and familial adenomatous polyposis (FAP) [31, 35], have been shown to significantly increase susceptibility to EOCRC. In addition, epigenetic modifications, such as DNA methylation [32] and histone alterations [32], might also contribute to the pathogenesis of this disease. A more comprehensive understanding of these molecular and genomic risk factors may enhance early detection and enable the development of targeted therapeutic strategies; however, further research is necessary to clarify their underlying mechanisms and clinical implications.

Our study had several limitations. Firstly, the GBD2021 data utilized in our analysis were derived from a predictive database of disease burden rather than real-world data. Secondly, the GBD database was deficient in reliable data on diseases in underdeveloped or developing countries with inadequate registration systems. Consequently, this study did not encompass the global population comprehensively. Lastly, due to the selection of an age group below 50 years for this study, it was not available to simultaneously obtain age-standardized relevant data. Despite these constraints, this study offered valuable insights into both current and temporal patterns of EOCRC burden worldwide and furnishes robust evidence for formulating more accurate and effective public health strategies.

5. Implications for Practice

In conclusion, our study revealed a general increase in the incidence rate of EOCRC and a decreasing trend in mortality rate from 1990 to 2021. Furthermore, it is projected that the incidence rate of EOCRC would continue to rise over the next three decades, with variations observed across regions, genders, and age groups. Therefore, proactive measures must be taken by countries and regions to effectively address this issue and mitigate the incidence, mortality rates as well as alleviate the economic burden and strain on healthcare systems caused by EOCRC.

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Author contributions

Conceptualization, data curation, formal analysis, investigation, resources and software were conducted by Ting Ma, Zhaofu Qin, Shiqi Zhou, Ziyan Weng, Guidong Chen, Xinyi Gao and Dening Ma. Ting Ma and Zhaofu Qin were responsible for validation, visualization and methodology. Project administration and supervision were conducted by Xinyi Gao and Dening Ma. Ting Ma performed the writing - original draft. Xinyi Gao and Deing Ma performed the funding acquisition and writing - review & editing. All authors read and approved the final manuscript.

Consent for Publication

Not applicable.

Competing Interests

None.

Data Availability

Data for this study can be obtained from the Global Health Data Exchange website (Link).

Ethics Approval and Consent to Participate

Not required as this study used public data aggregated on the level of country and global, and no personal information was collected.

Abbreviations

AR: Autoregressive

AAPC: Average annual percentage change

ARIMA: Autoregressive Integrated Moving Average Model

BMI: Body Mass Index

CRC: Colorectal cancer

EOCRC: Early-onset colorectal cancer

EAPC: Estimated annual percentage change

GBD2021: Global Burden of Disease 2021

GATHER: Guidelines for Accurate and Transparent Health Estimates Reporting

HRT: Hormone replacement therapy

MR: Moving average

ROC: Reactive oxygen species

SDI: Socio-Demographic Index

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