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ORIGINAL RESEARCH

Disease Burden of Total and Early-Onset Colorectal Cancer in China from 1990 to 2019 and Predictions of Cancer Incidence and Mortality

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Background: Understanding the temporal trends in the epidemiology of colorectal cancer (CRC) and early-onset CRC (EOCRC) in China is essential for policymakers to develop appropriate strategies to reduce the CRC burden.

Methods: The prevalence, incidence, mortality, years of life lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life years (DALYs) of CRC were obtained from the Global Burden of Disease (GBD) Study 2019. The incidence and mortality of CRC over the next 25 years were predicted.

Results: From 1990 to 2019, the prevalence, incidence, and mortality of total CRC and EOCRC significantly increased in males, with milder trends in females. In 2019, the number of people living with CRC (or EOCRC) in China was approximately 3.4 (0.59) million, which was over seven (five) times higher than that in 1990. The DALYs, YLDs, and YLLs moderately increased from 1990 to 2019 in both sexes. The age-standardized mortality rate (ASMR) for females has shown a stable trend in total CRC, and a downward trend in EOCRC since 2000. While the ASMR for males showed increasing trends in total CRC and EOCRC. In 2019, the highest incidence, prevalence, YLDs, YLLs, and DALYs were all observed in the 65 to 69 age group, while the highest mortality was in the 70 to 74. By 2044, the incidence and deaths of CRC are expected to reach 1310 thousand and 484 thousand, respectively. For EOCRC, the incidence will peak at about 101 thousand around 2034, and the mortality will continuously decrease to a nadir at about 18 thousand around 2044.

Conclusion: Although the age-standardized incidence and mortality of total CRC and EOCRC in China will reach a plateau, the number of incident cases and deaths of CRC have been increasing in the last three decades and will continue to increase in the next 25 years.

Keywords: early-onset colorectal cancer, prevalence, incidence, mortality, disability-adjusted life years, age-period-cohort analysis

Introduction

The incidence and mortality of colorectal cancer (CRC) are rising rapidly worldwide. CRC is becoming the third most common cancer and the second leading cause of cancer-related deaths.[1] It is estimated that there will be over 1.9 million newly diagnosed CRC patients and nearly one million CRC-related deaths in 2020 globally, accounting for approximately one-tenth of cancer cases and deaths.[1] The burden of CRC is also crucial in China, ranking as the fourth leading cause of cancer-related deaths.[3] The interest in early-onset CRC (EOCRC) has been increasing, which is defined as CRC that occurs under the age of 50 years. A previous study conducted in nine high-income countries found that the incidence of EOCRC was increasing.[2] A recent study showed that the incidence and mortality of CRC had decreased in some European and North American countries. However, the burden of CRC and EOCRC continues to increase in many low- and middle-income countries, including China.[4]

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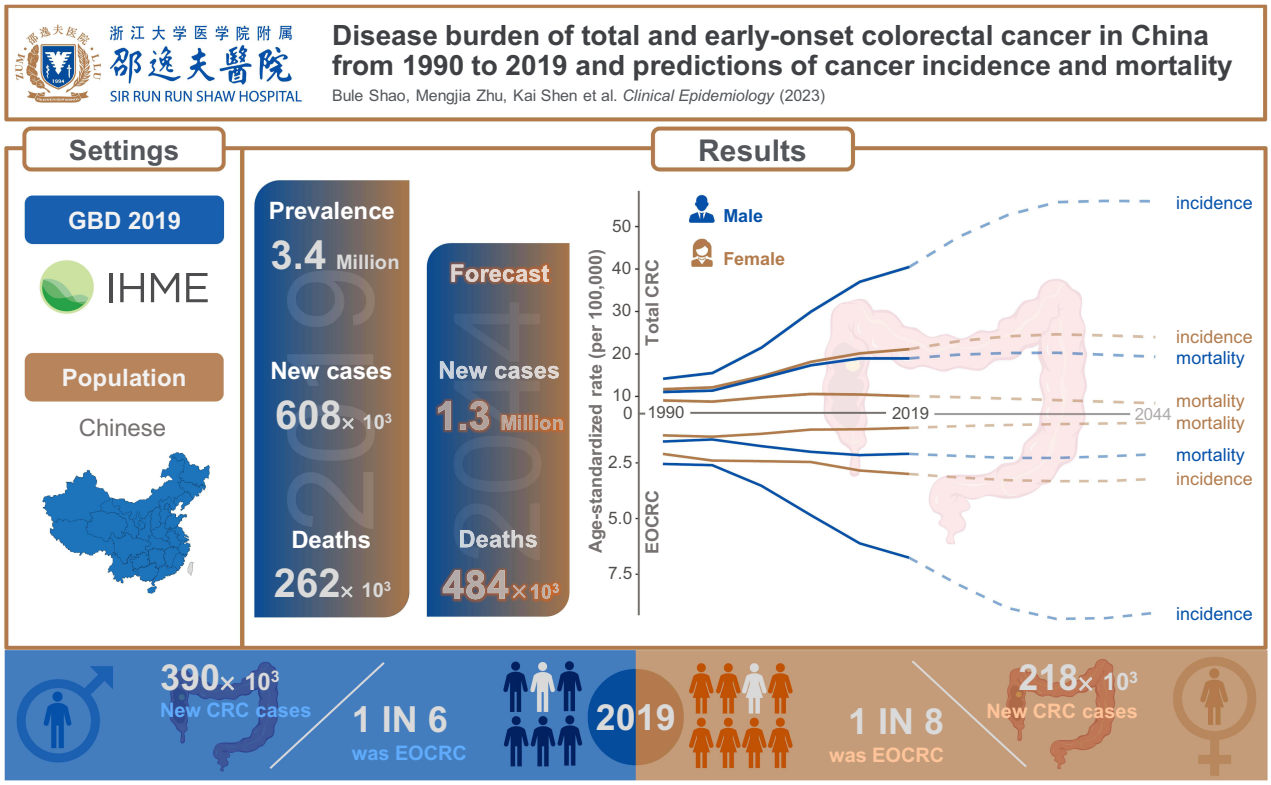
Graphical Abstract



Nearly 70% of all deaths worldwide are caused by noncommunicable diseases, including heart disease, stroke, cancer, diabetes, and chronic lung disease.[5] It is estimated that 75% of the deaths are caused by noncommunicable diseases and 82% of the premature deaths (before 70 years of age) occur in low- and middle-income countries.[5] The disease spectrum in China has gradually shifted from communicable to noncommunicable diseases with China's rapid economic development.[6] A stable or decreasing temporal trend of the incidence and mortality rates of CRC is observed in highly developed countries. However, the trend of CRC has been rising rapidly in China.[7] The growing incidence of CRC in low- and middle-income countries can be explained by two essential factors. First, economic advances have improved awareness of CRC and healthcare access, revealing undiagnosed CRC. Second, the urbanization of society, such as the westernization of diets and lifestyles, genuinely increases the number of CRC patients.[8] In contrast, the stable or decreasing trends of CRC deaths observed in high-income countries might contribute to the early screening and effective treatment developed in recent decades.[7] According to the cancer statistics of China, approximately 3.48 million new cases of CRC were diagnosed in 2013, accounting for 9.45% of new cancer cases in the country.[9] As the incidence of CRC continues to rise, the burden of CRC in China has become extremely heavy. Additionally, the epidemiological trends of EOCRC in China were poorly understood. Understanding the current and future trends in total CRC and EOCRC is imperative for policymakers to develop appropriate strategies.

A previous study analyzed the trends of CRC incidence and mortality from 1990 to 2016 in China and further predicted the trends up to 2025 using the Global Burden of Disease (GBD) Study 2017.[10] However, this study is likely to underestimate the predicted incidence and mortality of CRC in China by not considering population structure. China has one of the fastest-growing aging populations worldwide. By 2040, China is expected to have 28% of people over the age of 60 due to longer life expectancy and declining fertility.[11] Due to the large population base, people over 60 years of age are estimated to reach 402 million by 2040 in China. It is well known that the incidence of CRC increases exponentially

with age, making the population structure a vital factor in predicting the trend of CRC. Additionally, owing to algorithm and model improvements, the up-to-date GBD 2019 results presently supersede those of the prior GBD versions. Thus, in the present study, the disease burden of total CRC and EOCRC in the past three decades in China was demonstrated using the latest data obtained from the GBD 2019. Furthermore, the incidence and mortality of total CRC and EOCRC over the next 25 years were predicted by an age-period-cohort analysis, which took the changing population structure as an essential variable to make the forecast more accurate and solid.

In the present study, disability-adjusted life years (DALYs) were used as an important metric to evaluate the burden of total CRC and EOCRC. DALYs are the most representative and most widely used disease burden evaluation index, which includes healthy life years due to early death years of life lost (YLLs) and years lived with disability (YLDs).[12,13] DALYs not only synthesize early death and disability caused by diseases harmful to population health but also the relative importance of age, disease severity, and discount rates are taken into account. More detailed information on DALY, YLL, and YLD had been described in the previous study.[14]

The objective of this study was to provide an updated overview of the total CRC burden in China and to predict its trends over a longer period of time. Furthermore, revealing the epidemiological trends of EOCRC in China, which was scarcely reported, would help policymakers develop more appropriate strategies to curtail the burden of CRC.

Materials and Methods

Data Source

GBD is an ongoing regional and global research program that assesses the burden of diseases, injuries, and risk factors for a total of 369 diseases and injuries in 204 countries. Standardized approaches were employed in this study for estimating different epidemiologic metrics, including prevalence, incidence, deaths, YLLs, YLDs, and DALYs. GBD 2019 utilized a variety of data sources. DisMod-MR 2.1, a Bayesian meta-regression tool, was employed as the primary estimation method.[15] More detailed information regarding data resources, definitions, statistical methods, and data quality improvement can be found in previous studies.[15,16]

We obtained GBD 2019 data on colorectal cancer in China from 1990 to 2019.[17] The selected variables included the year, age, sex, incidence, prevalence, YLLs, YLDs, DALYs, and mortality. Additionally, China's predicted population was retrieved from the United Nations World Population Prospects (https://population.un.org/wpp/Download/Standard/Population/) to predict its future CRC burden.

Definition of CRC and EOCRC

All cancers coded as C18–21, D01.0–D01.2, and D12–D12.9 in the 11th revision of the International Classification of Diseases were considered to be CRC.[18] EOCRC was defined as CRC diagnosed <50 years of age.

Estimation of the Disease Burden of CRC in GBD 2019

The prevalence rate (per 100,000) is calculated as all new and preexisting cases divided by the population size, and the incidence rate (per 100,000) is calculated by dividing the number of new cases by the number of people in the population. The YLLs were calculated by multiplying the death rates by the standard life expectancy at each age, and the YLDs were calculated by multiplying the number of new cases by the disability weight, then by the average time lives with the disease before remission or death. DALYs were the sum of YLLs and YLDs. The mortality rate was calculated as the number of deaths per 100,000 people per year divided by the total population size.

Statistical Analysis

All rates were age-standardized according to the world standard population reported by GBD 2019. Uncertainty was estimated using each metric and propagated throughout the GBD modeling process. The 95% uncertainty intervals (95% UIs) were demonstrated using the 2.5th and 97.5th percentiles.[15]

The age-standardized rates of early-onset CRC were calculated by a direct method based on the world standard population distribution, and the corresponding 95% confidence intervals (95% CIs) were estimated by a method based on

gamma distribution.[19] Rates are shown per 100,000 population. The average annual percent change and corresponding 95% CI of total CRC and EOCRC were calculated by joinpoint regression in the Joinpoint Regression Program software (version 4.9.1.0, April 2022; Statistical Research and Applications Branch, National Cancer Institute, USA).[20] The program took trend data and fitted the simplest joinpoint model allowed by the data. The program starts with zero joinpoint (a straight line) and tests whether more joinpoints are statistically significant and must be added to the model (up to five joinpoints). The Monte Carlo Permutation method was employed for tests of significance.

Age-period-cohort (APC) analysis, which had shown a great performance in predicting the incidence and mortality trends of multiple cancers,[21] was conducted to predict the incidence and mortality of CRC in the next 25 years, considering both the changing rates and dynamic population structure. The power5 and Poisson APC models can be used in APC to calculate predictions of cancer incidence and mortality. As recommended by Møller et al,[22] the power5 function was used as a link function to level off the exponential growth. The model can be written as:

$$R_{ap} = \left(A_a + D.p + P_p + C_c\right)^5$$

where R_{ap} is the incidence rate in age group a in calendar period p, D is the common drift parameter,[23] A_a is the age component for age group a, P_p is the non-linear period component of period p, and C_c is the non-linear cohort component of cohort c.

The predicted numbers of new cancer cases and deaths in the five periods, 2020 to 2024, 2025 to 2029, 2030 to 2034, 2035 to 2039, and 2040 to 2044 were calculated by predicting the incidence and death rate in each age stratification, based on observed rates up to 2019, then multiplying the rates by the predicted population. All analyses were carried out using the R program version 4.0.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The Nordpred package (https://github.com/haraldwf/nordpred) was used to employ APC analyses, and the ggplot2 package was used to visualize the results.[24]

Results

Prevalence, Incidence, Death, YLD, YLL, and DALY of Total CRC and EOCRC from 1990 to 2019

The prevalence, incidence, and death of total CRC increased remarkably in both sexes from 1990 to 2019. In 2019, the prevalent cases of total CRC and EOCRC in China were 3.4 million and 0.59 million, respectively. The age-standardized prevalence rate of total CRC significantly increased from 54.0 (95% 95% UI 46.1, 62.3) per 100,000 to 221 (95% UI 176, 272) per 100,000 in males (Figure 1A). However, the increase was relatively milder among females, increasing from 44.5 (95% UI 38.0, 51.2) per 100,000 to 118 (95% UI 95.6, 145) per 100,000 (Figure 1A). Since 2010, the age-standardized incidence rate (ASIR) of total CRC had stabilized in females, whereas it had increased remarkably in males (Figure 1C). In females, incident cases of total CRC increased from 49.0 thousand to 218 thousand from 1990 to 2019, with the ASIR increasing from 11.3 to 21.1 per 100,000 at an AAPC of 2.16 (95% CI 1.94, 2.38) (Table 1, Appendix Table 1). Among males, incident cases of total CRC increased from 56.9 thousand to 390 thousand during the past three decades, with the ASIR increasing from 14.2 (95% UI 12.0, 16.4) to 41.4 (95% UI 33.4, 50.9) per 100,000 at an AAPC of 3.75 (95% CI 3.44, 4.07) (Figure 1C, Table 1).

For EOCRC, the temporal trends of prevalence and incidence were similar to those of total CRC (Figure 1). Both the age-standardized prevalence and ASIR of EOCRC in males remarkably increased from 1990 to 2019, with an AAPC of 5.01 (95% CI 4.73, 5.30) and 3.90 (95% CI 3.36, 4.45), respectively. However, more stable trends were observed in females, with an AAPC of 2.71 (95% CI 2.62, 2.80) for age-standardized prevalence and 1.73 (95% CI 1.03, 2.44) for ASIR (Table 1). Incident cases of EOCRC increased from 13.7 (95% UI 12.5, 14.9) thousand in 1990 to 61.8 (95% UI 53.8, 69.7) thousand in 2019 in males, and from 10.5 (95% UI 9.49, 11.5) thousand to 25.8 (95% UI 22.4, 29.1) thousand in females (Appendix Table 2).

The number of deaths due to CRC gradually increased during the study period, from 42.0 thousand to 165 thousand in males, and 37.3 thousand to 97.0 thousand in females (Appendix Table 1). The age-standardized mortality rate (ASMR)

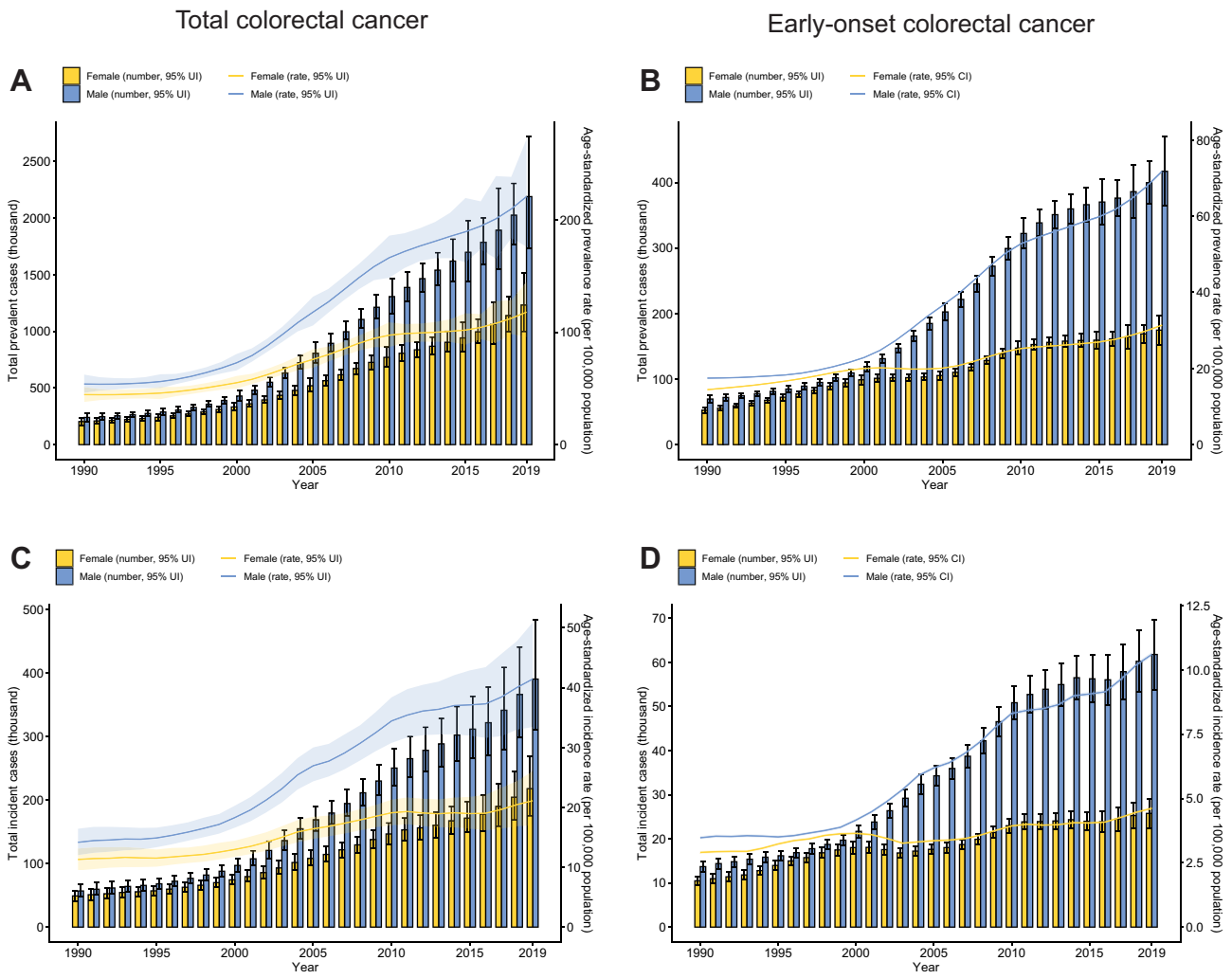


Figure 1 Prevalence and age-standardized prevalence rate (**A** and **B**), incidence and age-standardized incidence rate (**C** and **D**) of total CRC and EOCRC by sex from 1990 to 2019 in China.
Abbreviations: CRC, colorectal cancer; EOCRC, early-onset colorectal cancer.

in males increased from 11.7 (95% CI 9.9, 13.6) in 1990 to 19.3 (95% CI 15.8, 23.1) in 2019 with an AAPC of 1.71 (95% CI 1.36, 2.06). Meanwhile, ASMR in females showed a steady trend from 1990 to 2019 with an AAPC of 0.16 (95% CI −0.06, 0.38) (P>0.5) (Table 1, Appendix Table 1).

Table 1 Average Annual Percent Change of Epidemiological Metrics of Total CRC and EOCRC in China from 1990 to 2019

Metrics[a]	Total CRC			EOCRC		
	Both	Male	Female	Both	Male	Female
Prevalence rate	4.38 (4.20, 4.55)[c]	4.92 (4.74, 5.11)[c]	3.42 (3.29, 3.56)[c]	4.16 (4.05, 4.28)[c]	5.01 (4.73, 5.30)[c]	2.71 (2.62, 2.80)[c]
Incidence rate	3.11 (2.87, 3.35)[c]	3.75 (3.44, 4.07)[c]	2.16 (1.94, 2.38)[c]	3.06 (2.69, 3.44)[c]	3.90 (3.36, 4.45)[c]	1.73 (1.03, 2.44)[c]
Mortality rate	1.05 (0.82, 1.28)[c]	1.71 (1.36, 2.06)[c]	0.16 (−0.06, 0.38)[ns]	0.46 (0.20, 0.72)[c]	1.26 (1.03, 1.49)[c]	−0.89 (−1.56, −0.21)[c]
DALYs rate	0.91 (0.71, 1.10)[c]	1.60 (1.33, 1.86)[c]	−0.13 (−0.27, 0.01)[ns]	0.49 (0.22, 0.75)[c]	1.30 (1.03, 1.56)[c]	−0.81 (−1.52, −0.09)[b]
YLDs rate	3.70 (3.59, 3.80)[c]	4.34 (4.21, 4.47)[c]	2.74 (2.63, 2.85)[c]	3.62 (3.48, 3.77)[c]	4.45 (4.31, 4.58)[c]	2.21 (2.03, 2.40)[c]
YLLs rate	0.81 (0.61, 1.01)[c]	1.50 (1.24, 1.77)[c]	−0.22 (−0.37, −0.08)[c]	0.41 (0.14, 0.68)[c]	1.21 (0.95, 1.48)[c]	−0.98 (−1.62, −0.33)[c]

Notes: [a]Age-standardized rate. [b]P <0.05, [c]P <0.01.
Abbreviations: CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; DALYs, disability-adjusted life years; YLDs, years of life lived with disability; YLLs, years of life lost; ns, not significant.

Similar to total CRC, deaths of EOCRC in males increased from 8.47 (95% UI 7.67, 9.27) thousand in 1990 to 18.5 (95% UI 16.1, 20.9) thousand in 2019, with ASMR increasing from 2.17 (95% CI 2.13, 2.22) to 3.14 (95% CI 3.09, 3.19) per 100,000 at an AAPC of 1.26 (95% CI 1.03, 1.49) (Figure 2B and D, Appendix Table 1). However, deaths of EOCRC showed a downward trend in females. Although deaths of EOCRC in females increased from 6.51 (95% UI 5.88, 7.14) thousand in 1990 to 7.81 (95% UI 6.79, 8.84) thousand in 2019, the ASMR decreased from 1.82 (95% CI 1.78, 1.87) to 1.38 (95% CI 1.35, 1.42) per 100,000 with an AAPC of −0.89 (95% CI −1.56, −0.21) (Table 1).

Overall, YLDs, the non-fatal burden, of total CRC and EOCRC increased in both sexes during the last three decades. While the fatal burden (YLLs) differed by sex in either total CRC or EOCRC, showing increasing trends in males and decreasing trends in females. The AAPC of the age-standardized rate of YLDs was 3.70 (95% CI 3.59, 3.80) in total CRC and 3.62 (95% CI 3.48, 3.77) in EOCRC, both with an apparent male predominance (Appendix Figure 1).

DALYs, the sum of fatal burden (YLL), and non-fatal burden (YLD) showed generally increasing trends in males for both total CRC and EOCRC. In total CRC, the DALYs for males increased from 1238 (95% UI 1024, 1470) thousand in 1990 to 4169 (95% UI 3354, 5155) thousand in 2019, with the age-standardized rate of DALYs increasing from 273 (95% UI 229, 321) to 434 (95% UI 353, 532) per 100,000 at an AAPC of 1.60 (95% CI 1.33, 1.86) (Figure 2B and D, Table 1, Appendix Table 1). The temporal trend of DALYs for EOCRC was similar to that of all CRC, the DALYs were 920 (95% UI 812, 1028) thousand for males in 2019 with an age-standardized rate of 159 per 100,000. In contrast to males, DALYs for females showed a steady trend

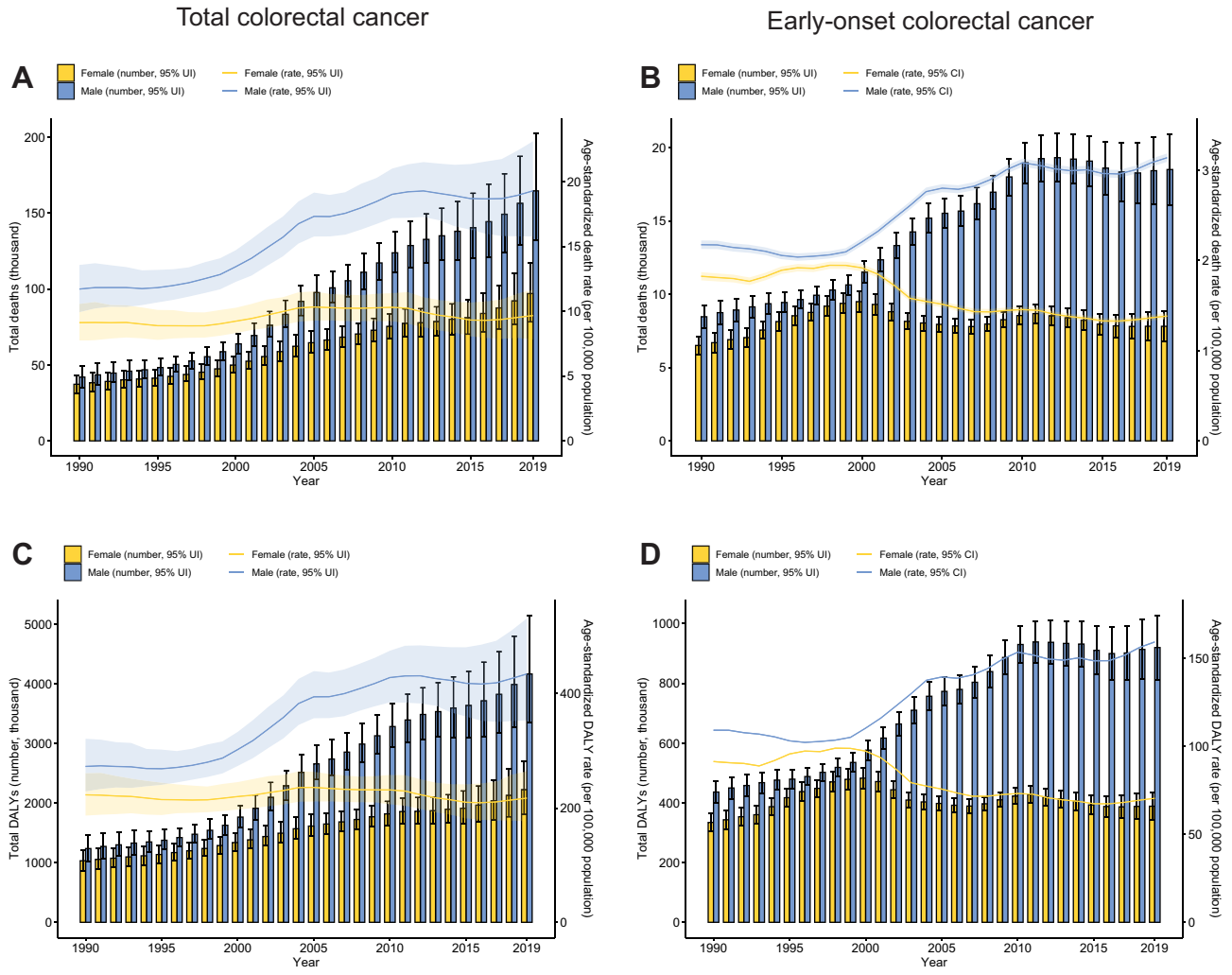


Figure 2 Number of deaths and age-standardized mortality rate (**A** and **B**), total DALYs and age-standardized DALYs rate (**C** and **D**) of total CRC and EOCRC by sex from 1990 to 2019 in China.

Abbreviations: CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; DALYs, disability-adjusted life years.

in total CRC (AAPC: −0.13 (−0.27, 0.01), $P>0.5$) and a declined trend in EOCRC (AAPC: −0.81 (−1.52, −0.09), $P<0.5$). In 2019, DALYs for females in total CRC were 2226 (95% UI 1812, 2708) thousand with an age-standardized rate of 217 (95% UI 177, 264) per 100,000. Although the DALYs for females in EOCRC increased from 334 (95% UI 304, 365) thousand in 1990 to 389 (95% UI 343, 435) thousand in 2019, the age-standardized rate of DALYs decreased from 91.2 (95% CI 90.9, 91.5) to 70.4 (95% CI 70.2, 70.6) per 100,000 with an AAPC of −0.81 (95% CI −1.52, −0.09) (Figure 2B and D, Table 1, Appendix Table 1).

Prevalence, Incidence, Death, YLD, YLL, and DALY of CRC in 2019

The burden of CRC showed both distinct sex and age-specific patterns in Chinese. Generally, males had a greater burden of CRC than females in each age group. In 2019, age-specific rates of prevalence and incidence peaked among people aged 75 to 79 years and 85 to 89 years in both sexes, respectively (Appendix Figure 2A and B); meanwhile, numbers of YLLs, YLDs, and DALYs all peaked at 65 to 69 years old (Appendix Figure 2D–F). The highest prevalent cases and age-specific prevalence rates were observed among aged 65 to 69 and 75 to 79 years in both sexes, respectively. In the 65 to 69 age group, incident cases peaked at 59.4 (95% UI 47.0, 74.2) thousand in males and 34.1 (95% UI 27.6, 41.6) thousand in females. The highest age-specific death rate was observed among males aged 90 to 94 (484 [95% UI 407, 557] per 100,000), whereas for females, the death rate continuously increased with age (Appendix Figure 2C). The rates of YLDs increased with age in both sexes and decreased after the age of 85 to 89 in males (160 [95% UI 117, 206] per 100,000), and 75–79 in females (73.0 [95% UI 51.2, 97.2] per 100,000) (Appendix Figure 2E). The rates of YLLs and DALYs both pronouncedly increased in males before the age of 85 to 89 and then decreased, while the rate reached a plateau around the age of 75 to 79 in females (Appendix Figure 2D and F). For males, the rates of YLLs and DALYs at the age of 85 to 89 were 3467 (95% UI 3016, 3913) per 100,000 and 3627 (95% UI 3167, 4093) per 100,000, respectively. For females, the rates of YLLs and DALYs at age of 75 to 79 were 1307 (95% UI 1069, 1582) per 100,000 and 1380 (95% UI 1135, 1657) per 100,000, respectively.

Predictions of Incidence and Death of Total CRC and EOCRC from 2020 to 2044

In the next 25 years, the incident cases and deaths of total CRC will increase linearly in both sexes (Figure 3C and E). The ASIR for males will significantly increase in the next 25 years, while the ASMR show a stable trend, fluctuating between 19 and 20 per 100,000; for females, the ASMR will show a decreasing trend, while the ASIR will reach a plateau around 2030 and fluctuate between 22 and 24 per 100,000.

By 2044, the incident cases and deaths of total CRC will be expected to dramatically increase to 1310 thousand and 484 thousand, respectively (Table 2). Among males, the number of new CRC cases will surge to 879 thousand, and the number of deaths will boost to 319 thousand in 2044 (Appendix Table 4). Among females, the incident cases of total CRC will increase from 52.5 thousand to 428 thousand during this period, and the number of CRC-related deaths will increase from 39.1 thousand to 164 thousand (Appendix Table 4). In general, the increments of both incident cases and deaths will be steeper among males than females (Figure 3C and E).

Although the predicted trends for ASIR and ASMR of EOCRC were similar to those of total CRC, the highest incident cases of EOCRC in both sexes were predicted to be 101 thousand around 2030 to 2034 (Table 2). After that, the incident cases of EOCRC showed a decreasing trend, which was predominantly driven by males (Figure 3D). The deaths of EOCRC were decreasing since 2014 (27.6 thousand) and will reach a nadir around 2044 at about 18.1 thousand (Figure 3F).

Discussion

In China, the prevalence, incidence, deaths, YLLs, YLDs, and DALYs of total CRC and EOCRC had been generally increasing from 1990 to 2019, with an evident male predominance. In 2019, the number of people living with CRC in China was approximately 3.4 million, which was over seven times higher than that in 1990. Among the 3.4 million people with CRC, about one in six (0.59 million) were EOCRC. The non-fatal burden (YLDs) of CRC increased during the last three decades, while the fatal burden (YLLs) differed by sex, showing increasing trends in males and decreasing trends in females. In addition, the present study found that the incidence of total CRC and CRC-related deaths will

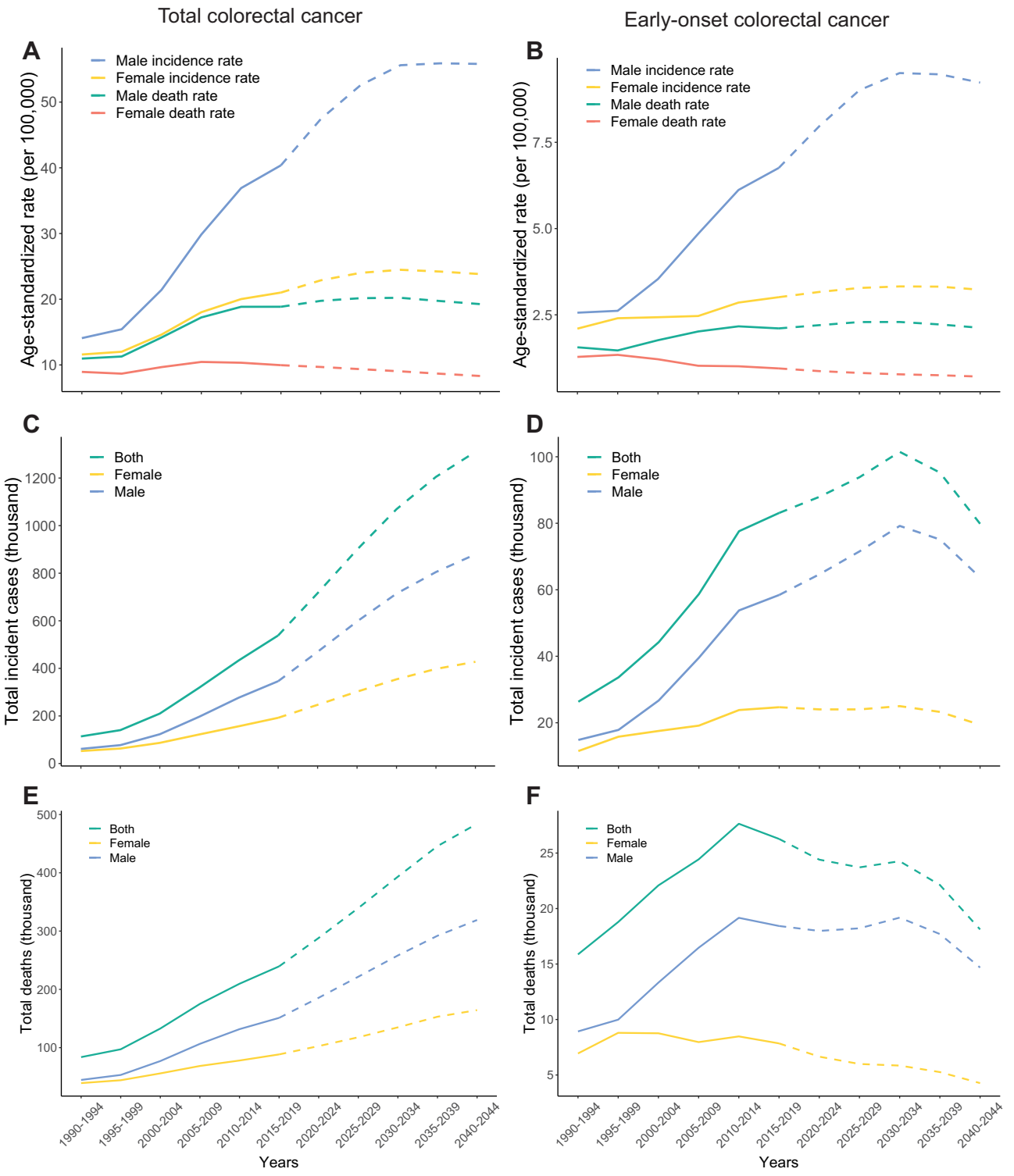


Figure 3 Observed and forecasted temporal trends of age-standardized rates of incidence and death (**A** and **B**), incident cases (**C** and **D**), and deaths (**E** and **F**) of total CRC and EOCRC by sex from 1990 to 2044 in China.
Abbreviations: CRC, colorectal cancer; EOCRC, early-onset colorectal cancer.

continuously increase in the next 25 years, and there will be almost twice as many incident cases and deaths among males as among females in 2044. Although ASMR for both sexes will decline slightly, the future burden of CRC in China is still quite huge due to the large population size, severe aging problem, and the rising incidence of EOCRC.

Table 2 Observed Number of Incident Cases and Deaths of Total CRC and EOCRC for Both Sex from 1990 to 2019 and Its Prediction from 2020 to 2044

Year	Total CRC[a]		EOCRC[a]	
	Incident Cases (×10³)	Deaths (×10³)	Incident Cases (×10³)	Deaths (×10³)
1990 to 1994	114	83.7	26.3	15.9
1995 to 1999	140	97.2	33.7	18.8
2000 to 2004	210	133	44.2	22.1
2005 to 2009	319	175	58.7	24.4
2010 to 2014	433	210	77.6	27.6
2015 to 2019	538	239	83.1	26.3
2020 to 2024	716	288	87.9	24.4
2025 to 2029	899	339	93.9	23.7
2030 to 2034	1069	393	101	24.3
2035 to 2039	1205	446	95.2	22.1
2040 to 2044	1310	484	79.9	18.1

Notes: [a]Average annual number.
Abbreviations: CRC, colorectal cancer; EOCRC, early-onset colorectal cancer.

Variations in the data between the up-to-date GDB 2019 and GBD 2017 were observed. The ASIR and prevalence rate of CRC in 2017 released by the GBD 2017 were 22.42 and 118.40 per 100,000, respectively. Meanwhile the GBD 2019 published ASIR and prevalence rate as 28.34 and 152.92 per 100,000, respectively. As previously reported, the difference could be attributed to the advanced algorithm and the improved model.[15] Therefore, it is essential to use the latest data to illustrate the current and future epidemiological trends of CRC in China.

In line with a previous study, the incidence and prevalence of CRC in the present study showed an upward trend over the past three decades in China.[10] The present study also found an evident sex difference in CRC incidence as previously reported in other studies.[25] Risk factors for CRC, such as alcohol consumption and smoking, were more frequently observed in males than females, which may partly explain the steeper increase in CRC incidence among males.[18] The incidence of CRC is decreasing or remaining stable in some highly developed countries, as the incidence increases with the growth of the Human Development Index, resulting in a high level of prevalence in those countries.[26] In 2020, new CRC cases in China accounted for 28.8%, and the number of deaths accounted for 30.6% of all CRC globally.[1] Many factors might account for the increasing incidence of CRC. As a developing country with over 1.4 billion people, the incidence of CRC in China showed an increasing trend due to economic advances, which led to increased awareness of CRC, improved diagnostic methods, easier and greater access to health care, and improved disease screening and surveillance.[27–29] In the meantime, well-known risk factors for CRC, including obesity, physical inactivity, poor diet, alcohol consumption, smoking, and ingestion of red meat and processed meat, have become more popular with China's westernization of society.[18,30–32]

The prevalence of CRC in China has significantly increased over the past three decades, with an evident male predominance, which could be attributed to the continuously increasing incidence and relatively stable or even decreasing trends in the fatal burden of CRC (ie, mortality and YLLs). With the rapidly growing aging population, China's aging problem could not be ruled out to aggravate the burden of CRC, since similar prevalence trends were observed in gastric cancer with a decreasing incidence rate and a stable mortality rate in China.[33]

In contrast to the global upward trends of incidence for CRC, the number of deaths due to CRC is decreasing in some developed countries, with improved screening and prevention approaches. However, it is still increasing in most developing countries.[34,35] The present study showed that the total deaths due to CRC gradually increased during the study period, while the ASMR was relatively stable or even decreased in females. The amelioration in ASMR might be attributed to advances in surgery, chemotherapy, radiotherapy, and, more importantly, remarkable progress in immunotherapy.[36,37] In line with a previous study, the ASMR of CRC in China was consistently higher in males than females.[25] A possible explanation for this might be that the severity of the risk factors depends on sex.[18] For instance, the

contribution of a high BMI to CRC is different in males and females, 11.1% in males and 4.6% in females.[18] Estrogen may also be a crucial factor driving sex differences in CRC.[38]

According to the present study, the CRC burden in China will continue to increase over the next 25 years. Zhang et al[10] reported the burden of CRC in China from 1990 to 2016 and predicted trends up to 2025. According to the present study, the expected incident cases of CRC in 2025 is approximately 900 thousand, while estimated 642 thousand new cases of CRC were reported by Zhang et al. It is well known that the incidence of CRC increases exponentially with age (Appendix Figure 2). The substantial difference between the present study and Zhang et al's might be attributed to the rapidly growing aging population. According to the United Nations Population Division, China, is expected to have over 1.4 billion population in 2020. Moreover, China has one of the fastest-growing aging populations in the world. Hence, the study by Zhang et al[10] is likely to underestimate the future incidence and mortality of CRC in China by not considering the changing structure of the population. Compared to Zhang et al's study, the present study not only took the dynamic population structure into account to provide a more precise and solid prediction but also further predicted the incidence and mortality of CRC to a greater extent, from 2020 to 2044. In addition, the improvement in algorithms and models in the latest GBD 2019 made the forecast more reliable. Our study demonstrated that the average annual number of incident CRC cases between 2040 and 2044 would be around 1.31 million, and the average annual mortality in this period would be about 484 thousand, implicating a considerable burden on China's healthcare system and economy in the near future.

With the worldwide prevalence of EOCRC expected to increase over the next decade, there is now arousing awareness of EOCRC. Compared with late-onset colorectal cancer, EOCRC is more likely to be detected at a more advanced stage (stage III–IV).[39] Epidemiological studies on EOCRC in China were scarcely reported. The present study showed that incidence of EOCRC in males was over two times higher than that in females, in 2019. This was consistent with a prior study, which demonstrated that males had a 2.2-fold increased risk for EOCRC compared with females.[40] The AAPC of ASIR for EOCRC in the present study was 3.06 (95% CI 2.69, 3.44), which had been reported to be 4 in New Zealand, 2.8 in Canada and Australia, and 2.2 in the USA.[2] Although the present study showed a steady ASMR of total CRC in females, the ASMR of EOCRC in females showed a declining trend with an AAPC of −0.89 ($P = 0.01$). In contrast to females, ASMRs in males with total CRC and EOCRC both presented increasing trends. The rapidly increasing incidence of EOCRC was poorly understood since common CRC risk factors reported during adulthood cannot fully explain this phenomenon. Most epidemiological studies of EOCRC collected data on exposure during adulthood but not early-life exposures, and recent data revealed that high intake of dairy products during childhood, obesity in adolescence, and childhood radiation exposure were associated with a higher risk for EOCRC.[41] More studies are needed to focus on evaluating early-life exposures with the future risk of EOCRC. In addition, prognostic differences between EOCRC and late-onset CRC were reported inconsistently and may account for heterogeneity in study designs and populations.[2] Thus, well-designed studies in different ethnicities are needed to further answer this question.

Given the tremendous future burden of CRC, and the increasing incidence of EOCRC in China, the development of new screening strategies, interventions, and treatments is critical for national policymakers and public health. The reduction of known modifiable risk factors could prevent at least half of CRC cases, according to previous research.[32,42] Public health policymakers should establish regulations and policies regarding these modifiable risk factors (eg, alcohol consumption, smoking, obesity, and physical inactivity) to curtail the future burden of CRC in China.[18] The high-risk population should be distinguished for earlier and more intensive screening. Additionally, more research programs should be supported to elucidate the underlying biological mechanisms of CRC to enable early diagnosis and precision treatment. Studies have revealed that genetic and environmental factors and their interactions play vital roles in CRC progression.[43] Previous studies have shown that specific foods and their interactions with genetic variations might affect CRC risk.[44] Choi et al[45] also reported that individuals with higher genetic susceptibility might benefit much more from a healthier lifestyle than their counterparts with lower genetic risk. These studies provide abundant evidence to support dietary and lifestyle modifications for CRC prevention. Although we are still at an early stage in addressing these questions, technological advances in the form of new experimental models and methodological tools will eventually yield mechanistic and causal insights that can be utilized to inform public health recommendations and reduce CRC incidence and mortality.

CRC has been preceded by colorectal adenomas for several years. In other words, removing cancerous adenomas at an early age has a profoundly beneficial effect on mortality.[46] Over the past few decades, the screening of CRC has

obtained significant progress. As the incidence of EOCRC increases, in 2021, the US Preventive Services Task Force updated the guidance on CRC screening; people should start CRC screening after 45 years of age, which has been proven to reduce the number of incidences and deaths.[47] China's CRC screening programs were initially launched in a limited number of regions with a high risk for CRC in 1970s. Screening programs have been promoted in numerous areas over the past decade. In the EOCRC, screening of some key populations such as young adults with first-degree relatives with CRC should be advanced and emphasized. Additionally, people who are diagnosed with inflammatory bowel disease (IBD) in adolescence should probably be under a more extensive follow-up, since the incidence of IBD, an established risk factor for CRC, has increased dramatically in China.[48] It has been demonstrated that fecal occult blood tests and flexible sigmoidoscopy for CRC screening can effectively reduce the mortality of CRC in China.[49] However, colonoscopy remains the gold standard nowadays.[42] Artificial intelligence for endoscopy has developed rapidly in the past few years, which can assist endoscopists in making more accurate and sensitive diagnoses.[36] In recent years, biomarkers for CRC screening have made new progress in screening areas.[50,51] With developments in screening techniques and the enlarged number of people screened, a considerable number of early CRC cases, could be detected and effective treatments can be accessed.[52,53] Economically, early screening of CRC also showed a reduction in the cost of treatment.[54]

Using the latest data from GBD 2019, the present study provides a comprehensive and long-term assessment of the burden of CRC. To the best of our knowledge, this is the first study to project trends in the incidence and mortality of CRC and EOCRC in China up to 2044. In addition to these strengths, this study had several limitations. First, the risk factors were not taken into account when predicting the incidence and mortality of CRC. Second, CRC could not be divided into colon and rectal cancers due to the limitations of the data source. Third, our study is subject to the general limitations of GBD studies, such as the availability and quality of primary data, especially for non-fatal outcomes.

Conclusions

In summary, China has experienced a rapidly increasing CRC burden over the past three decades. It is worth noting, although the fatal burden of CRC is on a stable or even slightly downward trend, the overall burden of CRC will continuously increase in the next 25 years due to China's large population size, rapidly growing aging population, and the increasing incidence of EOCRC. The tremendous future burden of CRC in China calls for intensive collaboration among policymakers, researchers, and health-care professionals to inform public health recommendations on modifiable risk factor interventions, precise screening strategies, and promising treatments to reduce CRC incidence and mortality.

Data Sharing Statement

The data presented in this study are available from the Global Burden of Disease Study 2019 (https://vizhub.healthdata.org/gbd-results/) and the United Nations World Population Prospects 2019 Revision (https://population.un.org/wpp/Download/Standard/Population/).

Ethic Statement

The Institutional Review Board of the Sir Run Run Shaw Hospital of Zhejiang University determined that the study did not require approval because the data were publicly available. This study complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations.[55]

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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