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ORIGINAL ARTICLE

Global landscape and temporal trends in lifetime risk of colorectal cancer in 185 countries: a population-based study

Li Li*, Kexin Sun*, Xiang Li*, Yifei Yao, Hengxi Li, Shaoming Wang, Wanqing Chen, Rongshou Zheng

Office for Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

ABSTRACT

Objective: Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related mortality worldwide. This study was aimed at estimating regional and national variations in lifetime CRC risk worldwide.

Methods: CRC data were extracted from GLOBOCAN 2022, including 185 countries, and population and all-cause mortality data were sourced from the United Nations. The world was divided into 20 geographical regions and categorized by Human Development Index (HDI). Lifetime CRC risk was estimated with the life table method, adjusted for multiple primary cancers.

Results: In 2022, the lifetime risks of developing and dying from CRC were 2.69% [95% confidence interval (CI): 2.68–2.70] and 1.39% (95% CI: 1.39–1.40), respectively. Men had a higher risk of colon cancer than rectal cancer, and higher CRC risk than women. Lifetime risk varied by region and HDI: regions with very high, high, moderate, and low HDI had incidence risks of 5.17%, 2.75%, 0.72%, and 0.57%, respectively, and mortality risks of 2.48%, 1.50%, 0.44%, and 0.41%, respectively. Australia/New Zealand had the highest incidence risk (7.41%, 95% CI: 7.30–7.52), and Northern Europe the highest mortality risk (3.28%, 95% CI: 3.24–3.32). Risks were stable before 40 years of age, peaked in middle age, and declined after 70 years of age. Temporally, Thailand had the highest increasing trend in lifetime risk, whereas the United States and Austria showed a decreasing trend.

Conclusions: Lifetime CRC risk differs by subtype, sex, HDI, and geography, and residual risk gradually decreases with age. Targeted primary prevention strategies should be implemented in various countries and regions to mitigate CRC burden.

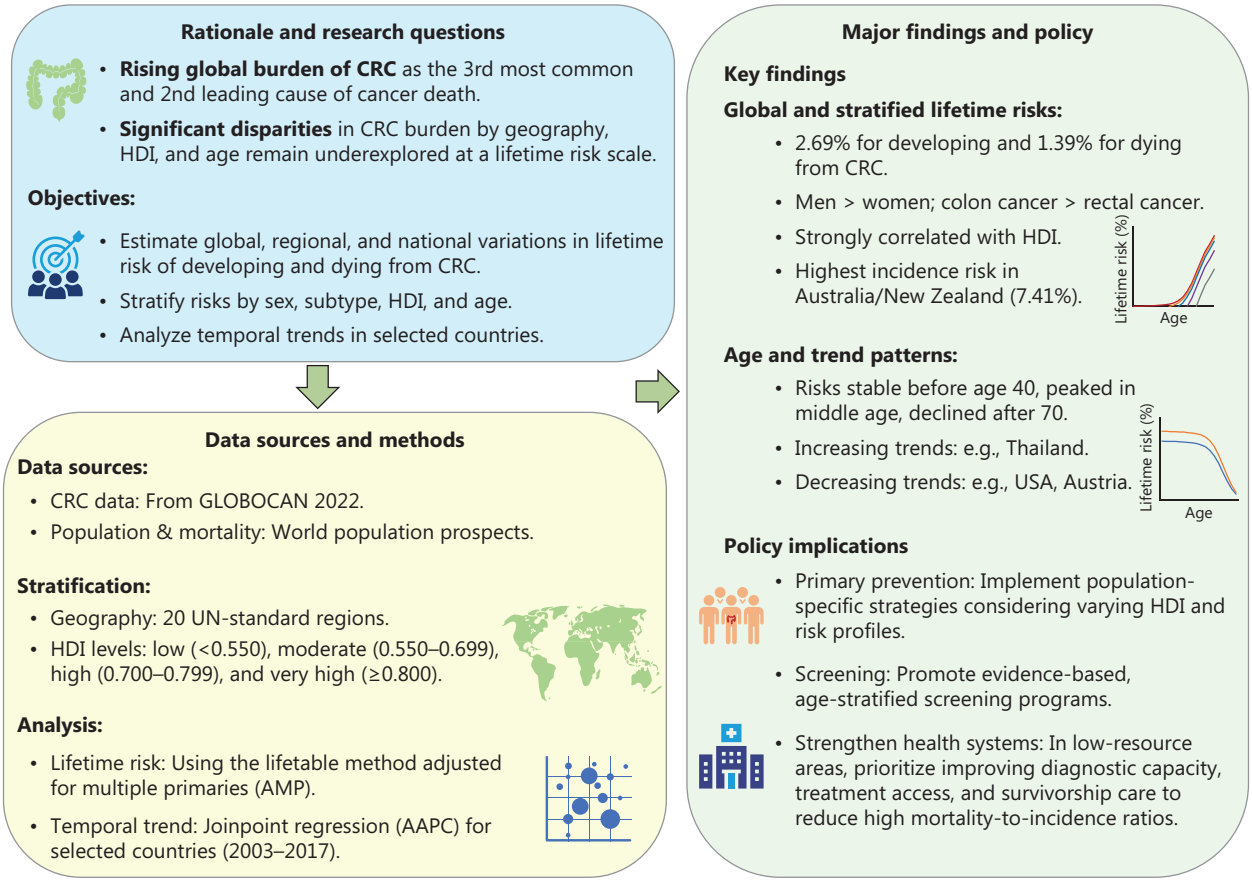
KEYWORDS Lifetime risk; colorectal cancer; incidence; mortality; epidemiology

Introduction

Globally, malignant neoplasms pose a major public health challenge: they are primary contributors to premature mortality, and they substantially affect healthcare systems and socioeconomic development[1,2]. Colorectal cancer (CRC) has become one of the most common malignant tumors in cancer diseases, and it accounts for a large proportion of cancer-related deaths. Current estimates suggest that the global cancer burden reached approximately 20 million incident cases in 2022, and the number of cancer deaths approached 9.7 million. Notably, CRC contributed nearly 1.93 million incident cases (representing approximately one-tenth of total new cancer diagnoses) and was associated with more than 900,000 deaths worldwide[3]. Recent trends in CRC show a paradoxical pattern: although the age-adjusted mortality rates have consistently declined, primarily because of advancements in early detection through endoscopic screening, substantial geographical disparities exist in CRC incidence. These variations are closely correlated with socioeconomic development indices and nutritional transition patterns, and pose a particularly high disease burden in industrialized nations[4]. Furthermore, the changing trends and regional variations in CRC result in unique challenges, particularly in transitional economies: population structures and increased CRC incidence among young people are serious public health concerns that place a substantial financial burden on medical resources[5,6].

The estimation of lifetime cancer risk typically integrates current disease incidence rates with all-cause mortality data. This risk, which refers to the cumulative probability of disease development throughout an individual's remaining lifespan, considering competing mortality risk, is a crucial epidemiological indicator for assessing population-level disease burden[7-9]. Notably, because individuals may experience multiple primary cancer diagnoses during their lifetime, the

*These authors contributed equally to this work.
Correspondence to: Wanqing Chen and Rongshou Zheng
E-mail: chenwq@cicams.ac.cn and zhengrongshou@cicams.ac.cn
ORCID ID: https://orcid.org/0000-0002-1159-1884 and https://orcid.org/0000-0003-4295-3398
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Study Flowchart This flowchart summarizes the rationale, methods, principal findings, and public health implications of this study. Data were derived from GLOBOCAN 2022 and UN population estimates. Analyses estimated lifetime risk, stratified by geography, HDI, sex, and age, and revealed substantial global disparities. The results underscore the need for context-specific strategies to decrease the CRC burden worldwide. AAPC, average annual percentage change; AMP, adjusted for multiple primaries; CRC, colorectal cancer; HDI, Human Development Index.

index of lifetime risk represents the probability of cancer occurrence. From a methodological perspective, the adjusted for multiple primaries (AMP) approach offers a theoretically robust framework for lifetime risk estimation. This method addresses a critical limitation in conventional cancer registry data by adjusting for multiple primary cancers. Specifically, the AMP method incorporates cancer incidence rates with probabilistic estimates of cancer-free survival, thereby enhancing the accuracy of risk assessments[10,11]. The application of lifetime risk estimation to CRC epidemiology is particularly valuable in public health planning. By evaluating age-specific lifetime risk, healthcare systems can develop stratified, evidence-based screening protocols and implement targeted prevention strategies that ultimately enhance the efficacy of CRC control programs.

This population-based study was aimed at systematically characterizing the global landscape and temporal trends in the lifetime risks of developing and dying from CRC. It highlights disparities in lifetime risk, stratified by cancer subtype, sex, human development index, and geographic region, and also explores age-related changes in lifetime risk. Our findings offer evidence-based insights with potential to inform the design of targeted, context-specific CRC prevention and control strategies tailored to the needs of different populations worldwide.

Materials and methods

Data sources

CRC was classified according to the International Classification of Diseases, 10th revision (ICD-10), encompassing three distinct anatomical categories: colon cancer (C18), rectosigmoid junction cancer (C19–C20), and anorectal cancer (C21). Epidemiological data were extracted from the GLOBOCAN 2022 database, containing data from 185 countries and territories worldwide across 36 cancer sites, by sex

and age (5-year intervals) (https://gco.iarc.who.int/today). Demographic parameters and all-cause mortality rates were obtained from the World Population Prospects (https://population.un.org/wpp/). For geographical analysis, we used the classification defined by the United Nations Population Division to classify the 185 countries and territories into 20 regions. Furthermore, to examine socioeconomic influences, we stratified global regions and individual nations according to Human Development Index (HDI) quartile, according to the United Nations Development Program's Human Development Report 2021–2022 (https://hdr.undp.org/). The HDI quantitatively assesses human development status according to three basic aspects: health, knowledge, and standard of living. We divided countries or regions into four categories by HDI: low (<0.550), moderate (0.550–0.699), high (0.700–0.799), and very high (≥0.800).

Time-series data on the incidence of CRC (ICD-10: C18–C21) during 2003–2017 were retrieved from Cancer Incidence in Five Continents Plus (CI5Plus) (https://ci5.iarc.fr/ci5plus/), an open-access online resource developed and maintained by the International Agency for Research on Cancer (IARC). This dataset compiles annual cancer statistics from population-based registries that meet quality standards for comparability, completeness, and validity. We extracted age-specific incidence rates from registries in the 36 countries included in the trend analysis and estimated the lifetime risk trends.

Statistical analysis

The lifetime risk assessment was conducted with the life table method with adjustment for multiple primary cancers and other causes of mortality, accounting for the incidence of multiple primary malignancies[8,9]. The formula for estimating lifetime risk (P_{AMP}) was as follows:

$$P_{AMP} = \int_0^{\infty} \hat{\lambda}_c(a)\,\hat{S}_0^*(a)\,da = \sum_{i=1}^{f} \frac{R_i}{R_i + M_i - D_i}\,\hat{S}_0^*(a_i) \times \left(1 - \exp\left(-\frac{W_i}{N_i}\left(R_i + M_i - D_i\right)\right)\right)$$

where $\hat{\lambda}_c$ denotes the observed cancer incidence or mortality rate, $\hat{S}_0^*(a_i)$ denotes the probability of being alive and cancer free at age i, and W_i denotes the 5-year age group.

The input data included the following:

Age- and sex-specific population (N_i)

Age- and sex-specific cancer incidence (R_i)

Age- and sex-specific cancer mortality (D_i)

Age- and sex-specific all-cause mortality data (M_i)

No country-specific external parameter for the proportion of multiple primary cancers was used.

More detailed information regarding the calculation and formulas is provided in the **Supplementary files**. The estimates were performed at the global, regional, and national scales, with stratification based on HDI levels. The Joinpoint Regression Program (version 5.4.0) was used to calculate the lifetime risk trend, and results are reported as average annual percentage change (AAPC). The statistical analyses were conducted in SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

To evaluate the potential effects of ignoring future changes, we conducted a short-term trend-extrapolation sensitivity analysis. Among the 36 countries included in the analysis, we selected 20 countries with statistically significant trends in CRC incidence during 2003–2017. For each selected country, age-specific incidence rates were projected to 2030 with a Bayesian age-period-cohort model informed by the Nordpred projection framework[12,13]. Lifetime risk was recalculated for each country and projection year with the same AMP-adjusted framework used in the primary analysis.

Results

Lifetime risk of developing CRC globally, regionally, and nationally

Table 1 shows the probabilities of developing and dying from CRC globally and by sub-region. The global lifetime risk of developing CRC was approximately 2.69% [95% confidence interval (CI): 2.68–2.70]: 1.64% (95% CI: 1.64–1.65) for colon cancer and 0.99% (95% CI: 0.99–1.00) for rectal cancer. The risk of CRC in men was 2.81% (95% CI: 2.80–2.82), a percentage higher than the 2.55% (95% CI: 2.54–2.56) observed in women. The highest morbidity was found in very high HDI (5.17%, 95% CI: 5.16–5.19), followed by high HDI (2.75%, 95% CI: 2.74–2.76), moderate HDI (0.72%, 95% CI: 0.71–0.73), and low HDI (0.57%, 95% CI: 0.55–0.58) countries/regions. Among the 20 world regions, the highest lifetime risk of incidence was in Australia/New Zealand (7.41%, 95% CI: 7.30–7.52), which was followed by Northern Europe (6.79%, 95% CI: 6.73–6.84) and Southern Europe (6.58%, 95% CI: 6.54–6.62), whereas the lowest risk was reported in West Africa (0.51%, 95% CI: 0.49–0.54). Nationwide, Norway had the highest risk of CRC, at 10.32% (95% CI: 10.00–10.63), thus indicating that approximately 1 in 10 people develop CRC, and was followed by Denmark, New Zealand, Japan, the Netherlands, and Singapore, all of which had a risk >8%. The three countries with the lowest lifetime risk of CRC were Gambia, Chad, and Sierra Leone (**Tables 1 and S1–S3, Figures 1, 2 and S1–S4**).

Lifetime risk of dying from CRC, globally, regionally, and nationally

The global lifetime risk of dying from CRC was approximately 1.39% (95% CI: 1.39–1.40), with 0.85% (95% CI: 0.84–0.85) for colon cancer and 0.51% (95% CI: 0.51–0.52) for rectal cancer. The risk of dying was 1.43% (95% CI: 1.42–1.44) among

Table 1 Lifetime risks (%) of developing and dying from colorectal cancer in 2022

Population	Developing (95% CI)	Dying (95% CI)
Colorectal cancer		
World	2.69 (2.68, 2.70)	1.39 (1.39, 1.40)
Very high HDI	5.17 (5.16, 5.19)	2.48 (2.47, 2.49)
High HDI	2.75 (2.74, 2.76)	1.50 (1.50, 1.51)
Moderate HDI	0.72 (0.71, 0.73)	0.44 (0.43, 0.44)
Low HDI	0.57 (0.55, 0.58)	0.41 (0.40, 0.42)
Colon cancer		
World	1.64 (1.64, 1.65)	0.85 (0.84, 0.85)
Very high HDI	3.42 (3.41, 3.44)	1.68 (1.67, 1.69)
High HDI	1.51 (1.51, 1.52)	0.80 (0.80, 0.81)
Moderate HDI	0.39 (0.39, 0.40)	0.24 (0.24, 0.25)
Low HDI	0.29 (0.28, 0.30)	0.21 (0.20, 0.22)
Rectal cancer		
World	0.99 (0.99, 1.00)	0.51 (0.51, 0.52)
Very high HDI	1.66 (1.66, 1.67)	0.76 (0.75, 0.76)
High HDI	1.20 (1.20, 1.21)	0.67 (0.67, 0.68)
Moderate HDI	0.29 (0.29, 0.29)	0.17 (0.17, 0.17)
Low HDI	0.22 (0.21, 0.23)	0.15 (0.15, 0.16)

CI, confidence interval; HDI, Human Development Index

men, which was higher than the 1.34% (95% CI: 1.33–1.34) observed in women. Countries/regions with very high HDI had the highest risk (2.48%, 95% CI: 2.47–2.49), and were followed by high HDI (1.50%, 95% CI: 1.50–1.51), moderate HDI (0.44%, 95% CI: 0.43–0.44), and low HDI (0.41%, 95% CI: 0.40–0.42) countries/regions. Among the 20 world regions, the lifetime risk of death was highest in Northern Europe (3.28%, 95% CI: 3.24–3.32), which was followed by Southern Europe (3.22%, 95% CI: 3.19–3.25) and Australia/New Zealand (3.22%, 95% CI: 3.14–3.30), and lowest in middle Africa (0.32%, 95% CI: 0.29–0.35). Singapore had the highest risk of CRC death, at 5.52% (95% CI: 5.24–5.80), and was followed by Norway, New Zealand, and Croatia, all of which had a risk >4%. The mortality-to-incidence (MI) ratio indicated delete disparities among regions. Developed regions such as Northern and Western Europe exhibited relatively low MI ratios (e.g., 0.45–0.49), whereas regions such as Africa had very high MI ratios (e.g., 0.62–0.76). In most regions, the MI ratio of colon cancer was similar to, or slightly higher than, that of rectal cancer. However, the difference was very obvious in South Africa, which had an MI ratio of 0.95 for colon cancer and only 0.39 for rectal cancer. The five countries with the lowest lifetime risk were Gambia, Guinea, Angola, Chad, and Sierra Leone, which had a risk <0.2% (**Tables 1 and S4–S6, Figures 1,2 and S1–S4**).

Lifetime risk of developing CRC by age

In 2022, the risk of developing CRC at different ages varied by subsite and region. The risk remained stable before the age of 40 years, at 2.64% (95% CI: 2.63–2.65), and the risks of colon and rectal cancer were 1.61% (95% CI: 1.61–1.62) and 0.97% (95% CI: 0.97–0.98), respectively. The residual risk after the age of 70 years was 1.55% (95% CI: 1.54–1.56), 1.01% (95% CI: 1.00–1.01), and 0.52% (95% CI: 0.52–0.53) for CRC, colon cancer, and rectal cancer, respectively. The risk in men and women at 40 years of age was 2.76% (95% CI: 2.74–2.77) and 2.50% (95% CI: 2.49–2.51), respectively. The residual risk gradually decreased with age: after the age of 70 years, the residual risk was 1.51% (95% CI: 1.50–1.53) in men and 1.57% (95% CI: 1.56–1.58) in women (**Tables 1, S2, S7 and S8, Figure 3**).

Lifetime risk of dying from CRC by age

In 2022, the risk of dying from CRC by age varied by subsite and sex. Before the age of 40 years, the risk remained stable, at 1.37% (95% CI: 1.37–1.38). Here, 0.84% and 0.51% are the risks of colon and rectal, respectively. The residual risk after the age of 70 years was 0.97% (95% CI: 0.97–0.98), 0.62% (95% CI: 0.61–0.62), and 0.34% (95% CI: 0.33–0.34) for CRC, colon cancer, and rectal cancer, respectively. The risk in men and women at the age of 40 years was 1.41% (95% CI: 1.40–1.42) and 1.32% (95% CI: 1.31–1.33), respectively. Similarly to the changes in the risk of developing CRC, the residual risk gradually decreased with age. The residual risk of dying was 0.97% (95% CI: 0.97–0.98) after the age of 70 years: 0.94 (95% CI: 0.93–0.96) in men and 0.99% (95% CI: 0.98–1.00) in women (**Tables 1, S5, S9 and S10, Figure 3**).

Trends in the lifetime risk of developing CRC by country and sex

Figure 4 shows the trends in lifetime risk across countries from 2003 to 2017, stratified by sex. In both men and women, Thailand, Belarus, and Estonia showed the highest positive AAPC, thus indicating the most significant increase in CRC risk. In contrast, the United States, Austria, and the Czech Republic exhibited negative AAPCs, reflecting decreasing risk. In men, Belarus had the highest AAPC, thus suggesting a marked rise in risk among men. The United States and Austria showed notable decreasing trends. In women, Thailand and Malta were among the countries with positive AAPC, signifying increasing risk. The United States and Austria demonstrated negative AAPC values. The risks in men and women in Iceland showed opposite trends (increasing among women and decreasing among men). These findings highlighted varying temporal trends in CRC risk across nations and sexes. Benjamini-Hochberg analysis of multiple lifetime risk trend

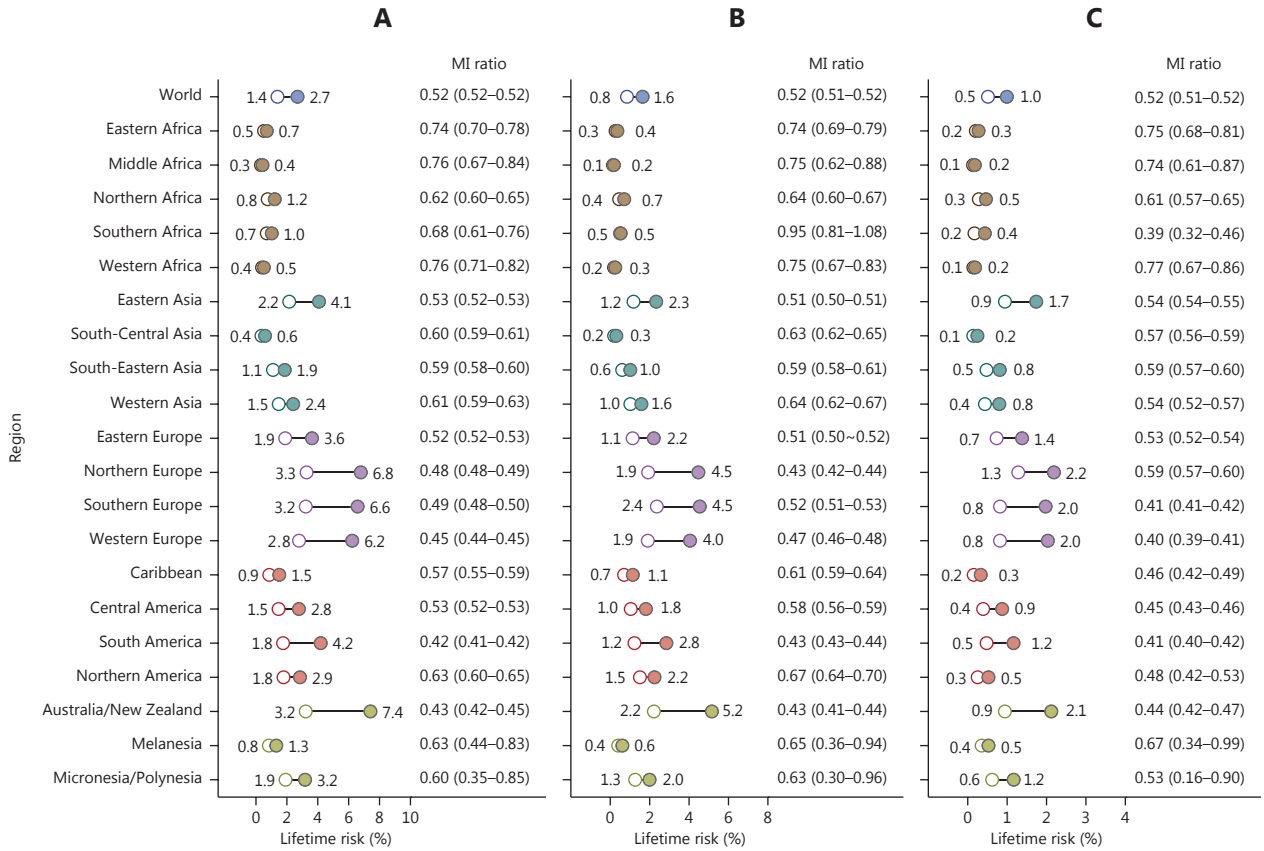


Figure 1 Lifetime risks of developing or dying from colorectal cancer in 2022 by region, in people of both sexes with (A) colorectal cancer, (B) colon cancer, and (C) rectal cancer. The hollow circle on the left represents the lifetime risk of dying from cancer, whereas the solid circle on the right represents the lifetime risk of developing cancer. The MI ratio represents the ratio of the lifetime risk of dying from cancer to the lifetime risk of developing cancer. MI, mortality-to-incidence.

significance indicated that the results before and after adjustment remained consistent (**Table S11**). In the trend-extrapolation sensitivity analysis of 20 countries with significant incidence trends (2003–2017), the projected lifetime risk with respect to a 2017 baseline in 20 countries changed by −7.95% to 11.91% by 2022; −12.56% to +16.30% by 2025; and −18.76% to +25.06% by 2030. The country ranking remained largely stable between the baseline and projected estimates (**Table S12, Figure S5**).

Discussion

The estimated lifetime probability of developing CRC was close to 3% in 2022. The risks of incidence and mortality were both higher for colon cancer than rectal cancer, and the risks in men were slightly higher than those in women. The incidence and mortality risk for colon cancer and rectal cancer were higher in men than in women across all age groups. However, analysis of mortality risk indicated a lower risk of dying from colon cancer in men than women across all age groups. With increasing HDI, both CRC incidence and mortality risk showed an upward trend. Norway had the highest lifetime risk, exceeding 10%, whereas Singapore had the highest mortality risk, surpassing 5%, in alignment with the global distribution of lifetime cancer risk[11]. CRC incidence and mortality risk were closely associated with age: they significantly increased after the age of 40 years and continued to rise thereafter.

The study findings are highly consistent with the results of the CRC burden assessment. CRC incidence and mortality rates significantly varied across countries and regions. Australia/New Zealand and the European regions had the highest incidence, whereas some African and South Asian regions showed the lowest incidence. CRC mortality rates also showed similar characteristics, and were highest in Eastern Europe and lowest in South Asia. More than two-thirds of CRC cases and approximately 60% of deaths

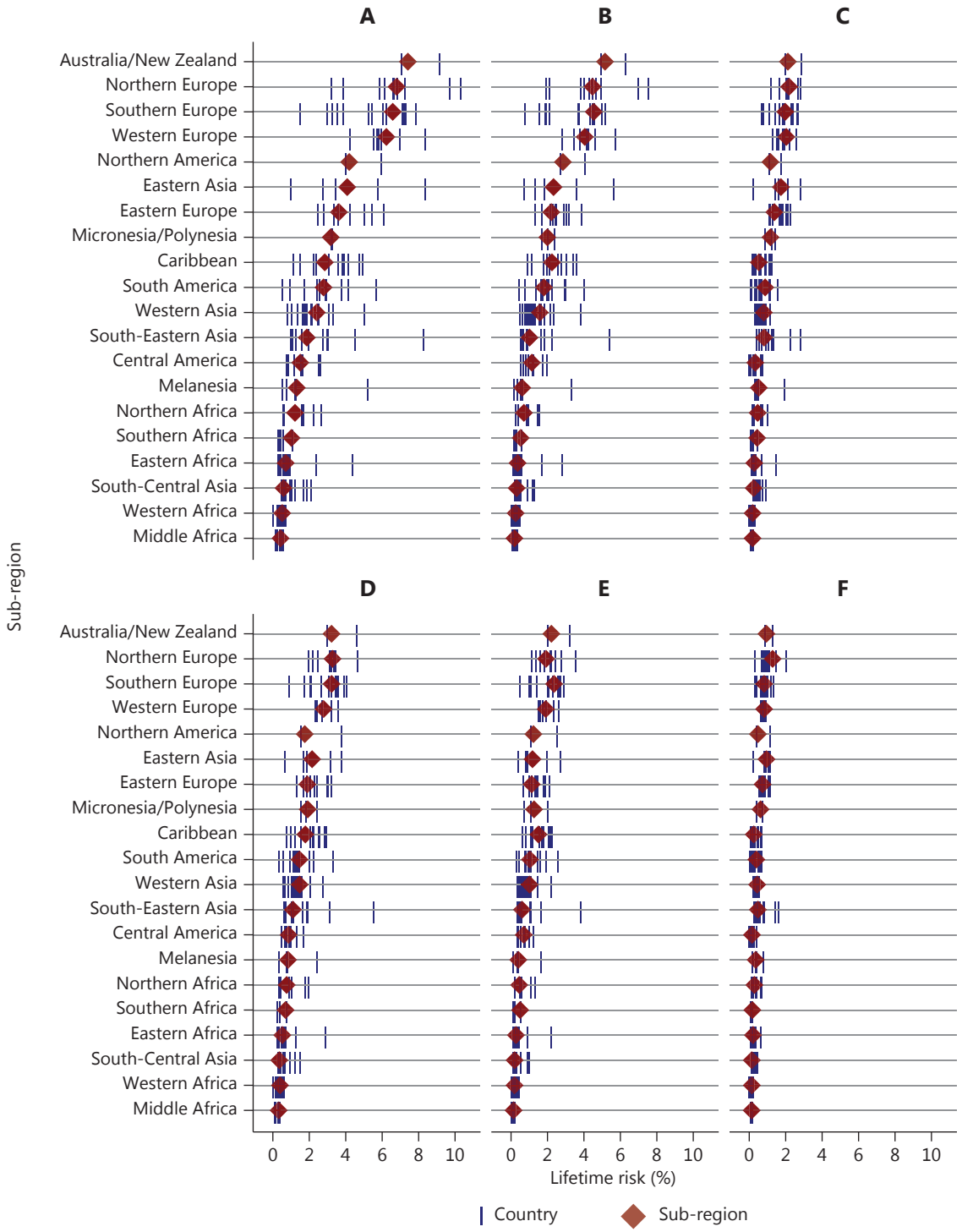


Figure 2 Lifetime risks of developing or dying from colorectal cancer by subtype in 2022, in people of both sexes. (A) developing colorectal cancer, (B) developing colon cancer, (C) developing rectal cancer, (D) dying from colorectal cancer, (E) dying from colon cancer, or (F) dying from rectal cancer. The diamonds denote the average lifetime risk in each selected geographic area. The vertical line denotes the lifetime risk in each country.

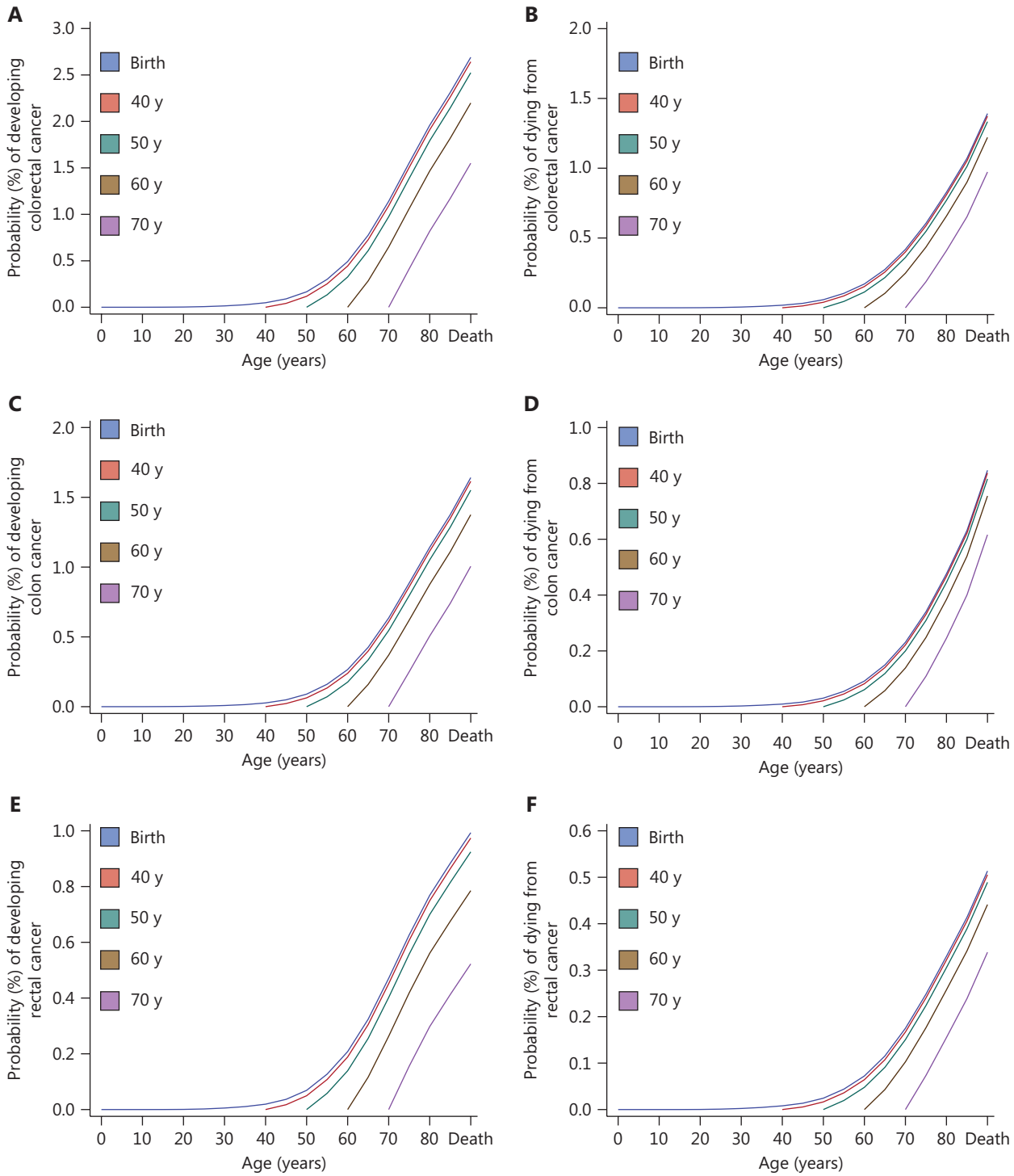


Figure 3 Lifetime risk of developing or dying from cancer within selected age intervals in 2022, in people of both sexes (A) developing colorectal cancer, (B) dying from colorectal cancer, (C) developing colon cancer, (D) dying from colon cancer, (E) developing rectal cancer, or (F) dying from rectal cancer. Curves are represented for baseline ages at birth, and 40, 50, 60, and 70 years of life free of colorectal cancer. Risks until death represent lifetime risks from the baseline age.

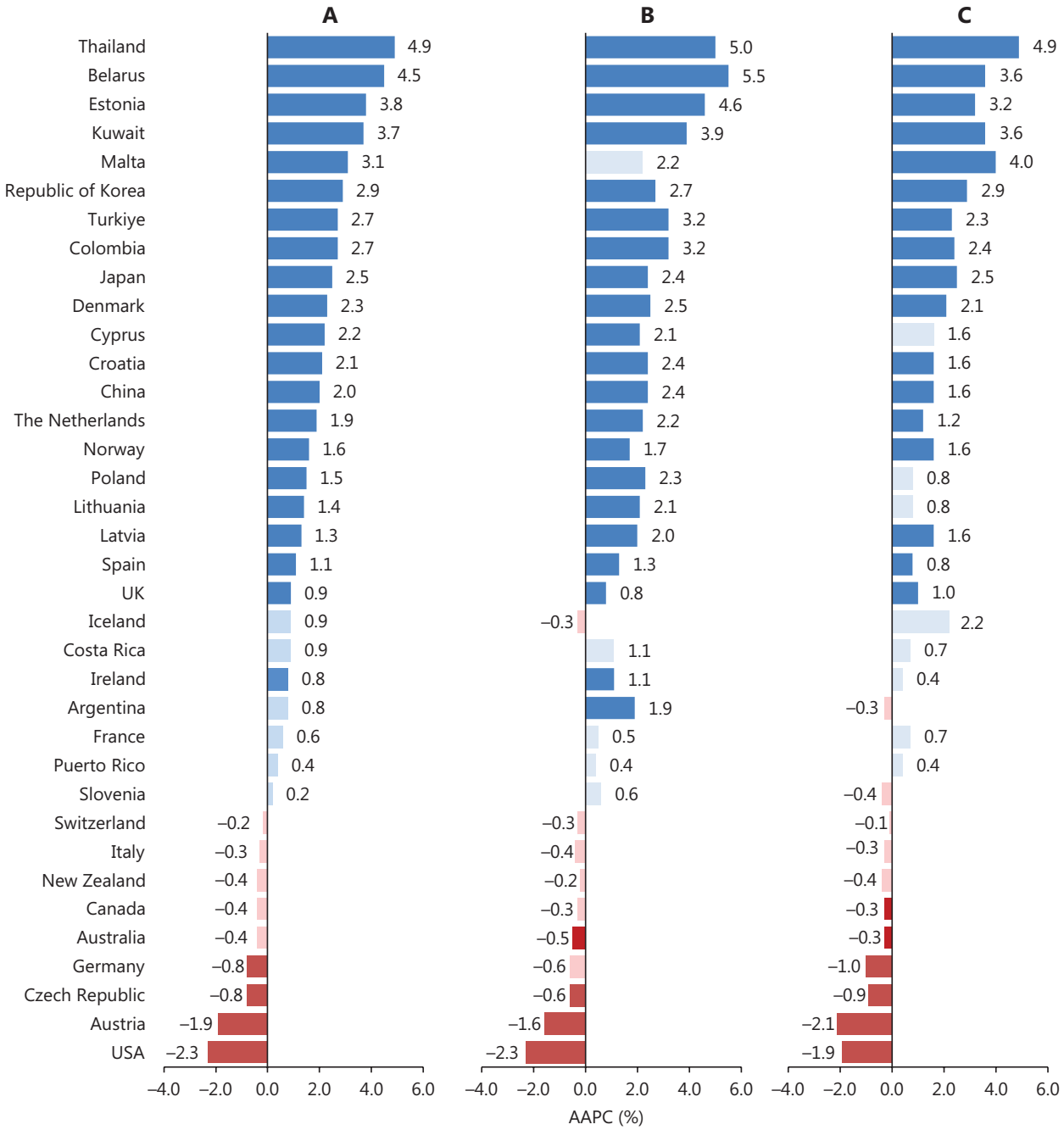


Figure 4 AAPC in the lifetime risk of developing colorectal cancer from 2003 to 2017, for (A) both sexes, (B) men, and (C) women. Dark blue bars represent countries with a statistically significant increasing trend (AAPC > 0, $P < 0.05$). Light blue bars represent countries with an increasing trend that is not statistically significant (AAPC > 0, $P > 0.05$). Dark red bars represent countries with a statistically significant decreasing trend (AAPC < 0, $P < 0.05$). Light red bars represent countries with a decreasing trend that is not statistically significant (AAPC < 0, $P > 0.05$). AAPC, average annual percentage change (%).

occurred in regions with high or very high HDI. By 2040, the number of new CRC cases has been projected to increase to 3.2 million, and deaths from CRC have been projected to reach 1.6 million in high or very high HDI countries[14]. The coefficient of variation for developing or dying from CRC in very high and high HDI regions was relatively small with respect to those in moderate and low HDI regions (**Table S13**). Moreover, 72.38% of the differences between

countries were attributed to HDI (**Table S14**). The intraclass correlation coefficient (ICC) indicated that the risk of developing colon cancer showed strong HDI clustering (ICC > 0.49), whereas the deaths were relatively more dispersed and exhibited weak national clustering; these findings suggested that HDI has more significant effects on developing than dying from CRC. Moreover different HDI regions have different CRC risks, and significant differences were observed even in high-income countries and regions. **Figure S6**, showing the relationship between the lifetime risk of CRC and HDI among countries or regions, clearly demonstrates the increasing lifetime risk trend with increasing HDI. This phenomenon might be due to prolonged life expectancy and relatively large proportions of older populations in those countries and regions. Moreover, the incidence of early onset CRC among adults younger than 50 years has increased and led to a relatively high incidence of CRC in these countries/regions[15,16]. Moreover, the burden is increasing with the increase in transition economies worldwide[17].

High-income countries increased their resource investments in expanding screening programs in the late 1990s, and the widespread global adoption of colonoscopy has increased screening, detection, and resection of precancerous lesions, thus favorably controlling CRC mortality in older people. In highly developed countries, CRC incidence and mortality rates have either stabilized or are decreasing. Rural residents often have lower educational levels and lower incomes than urban residents, as well as limited insurance coverage; together, these factors may further hinder their access to cancer screening[18]. These socioeconomic and demographic factors have increased the promotion of cancer screening in communities, thus potentially resulting in the observed increase in CRC incidence in people 40–50 years of age in many low- and middle-income countries, and particularly some transition countries[19,20]. Importantly, CRC is usually asymptomatic. When symptoms such as anemia, abdominal pain, or rectal bleeding develop, most patients are already in advanced stages of invasive, malignant, and metastatic cancers. Late diagnosis is a determinant of differences in patient survival and death, and the diagnosis of CRC at different stages partially explains the survival differences[21].

The rise in lifetime risk in Thailand might reflect increases in obesity/diabetes[22] as well as increased case detection through expanded diagnostic capacity. In contrast, the declines in the United States/Austria might be consistent with strengthened screening programs, decreased smoking rates[23], and concurrently improved treatment outcomes. These driving factors underscore that modifiable factors, including lifestyle, healthcare opportunities, and public health efforts, affect population level risks, thus providing insights for policy-making. Increased exposure to environmental risk factors associated with lifestyle changes and the westernization of diets are important factors in the rapid rise in CRC incidence[5,24,25]. Several studies have shown that alcohol consumption, smoking, and low-calcium diets are risk factors for CRC. Modern lifestyle shifts, including high-calorie diets, sedentary lifestyles, and widespread consumption of processed foods, have collectively contributed to the rising incidence of CRC. In particular, the westernization of diets (characterized by decreased intake of fiber-rich fruits, vegetables, and whole grains, and increased intake of red and processed meats) is strongly correlated with a significant rise in CRC risk. The extent to which these risk factors are affected across countries and regions may vary according to cultural, economic, and social factors. Studies have confirmed that diet and healthful lifestyle are important modifiable indicators for improving CRC prognosis[26,27]. Focusing on lifestyle intervention efforts in populations to improve dietary habits through public health measures would greatly contribute to the prevention of CRC in high-risk countries and regions.

The significant geographic disparities in MI ratios (calculated as lifetime mortality risk divided by incidence risk), which approximately reflect the 5-year relative survival rate of cancer, provided critical insights into the effectiveness of CRC care systems. Lower MI ratios in high-resource regions such as Europe and Australia/New Zealand indicated that a high incidence burden is met with relatively effective secondary and tertiary prevention, probably arising from established screening programs, timely diagnosis, and advanced therapeutics. In contrast, the high MI ratios in regions such as South Africa (0.95 for colon cancer) and other parts of Africa (0.61–0.76) indicated that, despite a lower incidence, a disproportionately high fraction of diagnosed patients died from the disease[21,28,29]. This pattern indicates disparities in early detection, access to high-quality treatment, and survivor care, and may also reflect differences in medical infrastructure and resource allocation[30]. These data support transforming the global cancer control model and further highlight that efforts to decrease mortality must consider factors such as diagnostic ability and equity of medical and health resources, rather than just monitoring trends in cancer incidence rates.

The index of lifetime risk is used to calculate the probability that an individual who is initially cancer-free will develop cancer at least once during the lifetime. However, routinely reported cancer incidence rates may include multiple primary cancers occurring in the same individual. Direct application of such cancer-based incidence rates in a conventional life-table calculation may therefore approximate the expected number of primary cancers per person rather than the probability of ever developing cancer. The AMP method addresses this issue by updating the population that remains both alive and cancer-free at each age interval[8]. At each age, cancer incidence is applied only to individuals who have not previously developed cancer and have not died. Individuals who develop cancer are removed from the cancer-free risk set for subsequent age

intervals, whereas individuals who die before cancer diagnosis are treated as competing events. Therefore, the method simultaneously considers multiple primary cancers, the life expectancy of the population, and competing mortality, without requiring an externally specified country-specific proportion of multiple primary cancers.

According to a sensitivity analysis based on the assumption that if the incidence and mortality rates of colorectal cancer were to remain unchanged globally, but the life expectancy and age-specific mortality rate were to maintain the level in Japan, the estimated increase in lifetime risk of developing CRC was approximately 63.6% (4.40% *vs.* 2.69%). Alternatively, if the life expectancy and age-specific mortality rate were to reach the level of South Africa (where the life expectancy is 65 years), the lifetime risk might decrease by 44.7% (1.49% *vs.* 2.69%). The sensitivity analysis of the 20 selected countries (**Table S12**) with statistically significant trends in CRC incidence during 2003–2017 demonstrated that although ignoring future trends might slightly under- or overestimate lifetime risk in countries with rapidly changing incidence or mortality, the magnitude of this bias was unlikely to materially alter the study's main conclusions regarding comparative risk levels, country rankings, or global and regional patterns. Even in scenarios beyond the 10-year forecast (to 2030), the comparative lifetime risk across countries remained largely unchanged. Nevertheless, the results should not be interpreted as a full projection of future lifetime risk. Long-term forecasting over the full lifespan would require strong assumptions regarding future diagnostic practice, screening, risk-factor prevalence, treatment improvement, and demographic change. Our sensitivity analysis was therefore designed only to quantify the approximate direction and magnitude of possible short-term bias under transparent and reproducible assumptions.

This study has several significant strengths. First, the data sources were authoritative and timely: the study used the most recent global cancer incidence data from the GLOBOCAN 2022 database and conducted a systematic analysis to provide comprehensive and reliable data support for the assessment of lifetime CRC risk worldwide. Second, compared with the traditional method using 0–74 year cumulative risk, the AMP method considers the competing risk of death caused by the extension of life expectancy and other reasons. Particularly in the context of population aging worldwide, traditional cumulative risk assessment methods may not accurately reflect true cancer risk (**Figure S7, Table S15**). With increasing population life expectancy, we observed significant differences between the cumulative risk (0–74 years) and lifetime risk, because of variations in competing risk of death. Compared with the life table method for directly calculating current probability, the AMP method adjusts for the occurrence of multiple primary cancers. The results of the AMP method (2.69% for global) and current probability (2.72% for global) were similar for most countries or regions (**Table S16**). The global differences were small, and the country-level analyses indicated that country rankings and temporal trends were highly stable between the AMP-adjusted and conventional life-table estimates. This finding suggested that the main conclusions were robust to the choice of method. Importantly, the stability of the results indicated that using the methodologically preferred population-based estimate did not introduce instability or distort the conclusions. Finally, this study systematically compared the differences in lifetime CRC risk by subtype across various countries and regions. This comparison has important practical value for optimizing the allocation of prevention and control resources, and improving the global efficiency of prevention and control.

This study also has several limitations. First, the GLOBOCAN 2022 estimates rely on cancer registration data (incidence) and vital statistics (mortality), whose accuracy depends on data coverage and quality in different countries worldwide. Globally, registration coverage is low in regions such as South America and Africa, and therefore cannot accurately reflect the local cancer burden[3]. Moreover, approximately 77 countries or regions worldwide lack effective data, and estimates can be made only on the basis of data from neighboring countries or regions. These countries or regions account for 23.1% of the global population, and their CRC incidence and mortality accounted for approximately 23.6% and 21.0% of the global total in 2022. After exclusion of those countries from the sensitivity analysis, the global risk of developing CRC increased from 2.69% to 2.70%, and the risk of mortality increased from 1.39% to 1.40%. However, the effects on lifetime risk were not identical among HDI regions (**Table S17**). The risk in high HDI regions has slightly increased, whereas that in other regions has remained relatively stable or slightly decreased. Although the data indicated stability, caution is necessary in interpreting the detailed results for countries or regions that lack data or have low data quality. Second, the estimates of lifetime risk were based on cross-sectional incidence and mortality data of CRC worldwide in 2022, which does not account for potential future trends in incidence and mortality rates. For countries with rising incidence or mortality rates, we might have underestimated lifetime CRC risk by using these cross-sectional data. In contrast, for countries or regions with declining rates, the lifetime risk might potentially have been overestimated. Despite this limitation, our study quantified lifetime risk under current conditions, thereby providing essential information for public health planning, resource allocation, and understanding the burden of CRC. This baseline is particularly useful for comparing subpopulations in which the relative differences in risk are less sensitive to short-term trend variations than absolute values. Third, this study reflects only the average risk of specific countries/regions. In populous nations (e.g., China, the United States, Russia, and India), regional disparities are inevitable.

Conclusions

In 2022, substantial disparities in CRC lifetime risk and mortality risk were observed across nations and regions. Despite the global trend of declining age-standardized mortality rates, CRC continues to pose a significant cancer disease burden in most countries and is an important public health issue globally as economies develop, countries transform, life expectancy increases, and lifestyles change. The findings of this study should have substantial value to policymakers seeking to advance cancer-specific prevention initiatives, control strategies, therapeutic interventions, and resource allocation planning, as well as to researchers seeking to design and implement appropriate CRC prevention strategies, early detection programs, and clinical treatment protocols.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Rongshou Zheng, Wanqing Chen.
Collected the data: Li Li, Kexin Sun, Xiang Li, Yifei Yao, Hengxi Li, Shaoming Wang.
Contributed data or analysis tools: Rongshou Zheng, Li Li.
Performed the analysis: Rongshou Zheng, Kexin Sun.
Wrote the paper: Li Li, Rongshou Zheng.

Data availability statement

All data used in this study were obtained from public databases. Cancer data in 2022 are available online from GLOBOCAN 2022 at https://gco.iarc.fr/today/. CI5 data are available online from IARC at https://ci5.iarc.who.int/. The full dataset is available from the corresponding author on request.

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