

Emerging trends in the global burden of colorectal cancer

David J. Lee^{1,2}, Aparna Parikh¹, Bhawna Sirohi³, Yin Cao^{4,5,6} & Andrew T. Chan^{7,8,9,10,11} ✉

Abstract

Globally, colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths, although these epidemiological patterns show substantial geographical variation. In this Review, we discuss the emerging global patterns of CRC incidence, which historically has been the highest among Western, high-income countries but is now increasing globally beyond these regions. This rise has mainly been driven by early-onset CRC – that is, cancers diagnosed in individuals aged <50 years. A birth cohort effect beginning with individuals born in the 1960s indicates that factors beyond genetic susceptibility or changes in screening practice underlie this increase. A changing landscape of established and emerging risk factors occurring worldwide has been proposed to underlie these epidemiological trends in CRC. Hypothesized risk factors include dietary and lifestyle aspects, shifts in the gut microbiota and the rise in environmental contaminants associated with the rapid urbanization occurring globally. Substantial advances in the characterization of genomic and epigenomic profiles of CRCs as well as their gut microbiomes not only hold potential for providing insight on the aetiology of this disease but could also be leveraged for early detection and interception strategies. The under-representation of non-Western populations in these studies, however, greatly limits progress and, if not addressed, could widen the existing gaps in global CRC prevention and control.

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¹Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA. ²Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. ³Department of Medical Oncology, Balco Medical Centre, Vedanta Medical Research Foundation, Raipur, India. ⁴Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, MO, USA. ⁵Alvin J. Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA. ⁶Division of Gastroenterology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA. ⁷Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. ⁸Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. ⁹Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. ¹⁰Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ¹¹Harvard Chan Microbiome in Public Health Center, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ✉e-mail: achan@mgh.harvard.edu

Key points

- Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with substantial geographical variation in incidence patterns.
- A rising incidence of early-onset CRCs (those diagnosed before the age of 50 years) was first observed in the mid-1990s in Western high-income countries and has since expanded globally, including in Asia and Latin America.
- Although genetic predisposition contributes to a substantial proportion of the global CRC burden, emerging global epidemiology trends in CRC implicate that non-hereditary factors have a strong role.
- Potentially modifiable risk factors, including adverse dietary and lifestyle patterns, alterations in gut microbiota and exposure to environmental contaminants, have been hypothesized to contribute to the rise of early-onset CRC.
- Limited data from low-income and middle-income countries hinder progress in collective understanding of CRC risk factors and mechanisms essential for identifying precision prevention strategies to curb the current global epidemiological trends for CRC.

Introduction

Globally, colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths^{1,2}. According to data from the Global Cancer Observatory (GLOBOCAN) database of the WHO International Agency for Research on Cancer (IARC), an estimated 1.9 million new CRC diagnoses and 904,000 CRC-related deaths occurred worldwide in 2022, constituting 10% of all incident cancers and 9% of all cancer-related deaths¹. Patterns of CRC incidence vary across world regions and are changing, with a notable rise in early-onset disease – that is, newly diagnosed CRCs among individuals aged <50 years – since the 1990s^{3,4}. In this Review, we examine these emerging global patterns and discuss proposed exposure-related and contextual risk factors that might underlie them.

Global incidence patterns

CRC incidence trends have shown marked geographical variation, with rates being historically higher in Europe, Australia and New Zealand, North America and high-income countries (HICs) in Asia Pacific and lower in South Asia and most parts of Africa^{1,5,6} (Fig. 1). On the basis of GLOBOCAN estimates for 2022, the incidence of colon cancer differed tenfold between regions with the highest and lowest rates in both sexes, whereas the incidence of rectal cancer showed a sevenfold and fourfold difference in males and females, respectively¹. When grouped according to the Human Development Index (HDI), countries with a high or very high HDI had a threefold to fourfold higher incidence of CRC in 2020 than those with a low or medium HDI, whereas mortality differences in the same year were more modest (twofold to threefold) owing to a higher CRC-related mortality in countries with a lower HDI^{1,5,7–9}.

The correlation between CRC incidence and HDI has been largely attributed to higher life expectancies in countries with a high HDI that result in older, more cancer-susceptible populations as well as to the influence of Western dietary and lifestyle behaviours in these

regions^{6,10,11}. Further insights on this pattern emerge when examining temporal trends by age groups across different regions. Countries in regions with historically the highest incidence of CRC were among those that experienced a rise in early-onset CRC, a trend that began during the mid-1990s⁴. For example, in the USA, the incidence of CRC among younger individuals (aged 20–49 years) rose by 1.3% annually from 1998 to 2019 and by 6.4% annually from 2019 to 2022, with increases observed across all racial and ethnic groups from 2013 to 2022 (ref. 12). Among countries with data available in IARC Cancer Incidence in Five Continents Plus (CI5plus), a compendium of high-quality population-based cancer registries that serves as the foundation for GLOBOCAN estimations, nine HICs in Europe, North America and Oceania saw a distinct rise in CRC among younger individuals (aged 20–49 years) starting in 1992–1996, whereas the incidence of CRC among older individuals (aged ≥50 years) remained stable or declined over the same time period⁴. Notably, eight of these nine HICs had shown declining or stable trends in CRC incidence among younger individuals (aged 20–49 years) before this rise in the mid-1990s.

The term birth cohort refers to individuals who are born in the same time period and age through life together, sharing the same environmental and lifestyle exposures¹³. A birth cohort effect in CRC epidemiology has been suggested, whereby individuals born since the 1960s are being diagnosed with early-onset CRC at progressively higher rates in later generations¹³. In the USA, for example, a population-based analysis of cancer registry data available until 2013 revealed that individuals born circa 1990 have more than twice the risk of colon cancer (incidence rate ratio (IRR) 2.40, 95% CI 1.11–5.19) and more than a fourfold higher risk of rectal cancer (IRR 4.32, 95% CI 2.19–8.51) relative to those born circa 1950 (ref. 14). Similarly, individuals born in the 1960s and successive birth cohorts in the UK have progressively higher age-specific incidence rates of rectal cancer compared with those born circa 1935: 35% for 1975 (IRR 1.35, 95% CI 1.27–1.43), 139% for 1985 (IRR 2.39, 95% CI 2.14–2.67) and 419% for 1995 (IRR 5.19, 95% CI 4.13–6.53)¹⁵. The same analysis also showed increases in age-specific incidence rates for colon cancer in successive birth cohorts in this country: 19% for 1975 (IRR 1.19, 95% CI 1.14–1.25), 96% for 1985 (IRR 1.96, 95% CI 1.80–2.14) and 294% for 1995 (IRR 3.94, 95% CI 3.30–4.69). Strikingly parallel trends have been noted for other HICs in North America, Europe and Oceania over a similar time period^{4,15,16}, raising hypotheses regarding shared risk factors for CRC⁶.

Although initially observed in Western HICs⁴, the global rise of CRC, including early-onset disease, is becoming increasingly evident³. According to Global Burden of Disease (GBD) estimates (Fig. 2), the incidence of CRC rose in Asia (notably in Southeast Asia), Latin America and the Caribbean, North Africa and sub-Saharan Africa over the 1990–2023 period, both among older (aged 50–74 years) and younger individuals (aged 15–49 years)^{17–20}. When evaluating these trends at the country and territory level, specifically among the 50 countries that were included in the latest IARC CI5plus database analysis, CRC diagnosed in younger individuals (aged 25–49 years) increased for regions in Asia (Israel, Japan, Thailand and Turkey), Eastern Europe (Belarus), and Latin America and the Caribbean (Argentina, Chile, Costa Rica, Ecuador, Martinique and Puerto Rico³; Table 1). Notably, three of these regions (Argentina, Israel and Puerto Rico) had an age-related divergence in CRC trends – that is, increasing incidence among younger individuals, occurring alongside decreasing or stable incidence among older individuals (aged 50–74 years) – whereas the rest had concurrent increases in CRC incidence in both age groups³. CRC in younger individuals did not increase in Uganda, the only sub-Saharan African country included in this CI5plus analysis³, consistent with the known broader CRC trends

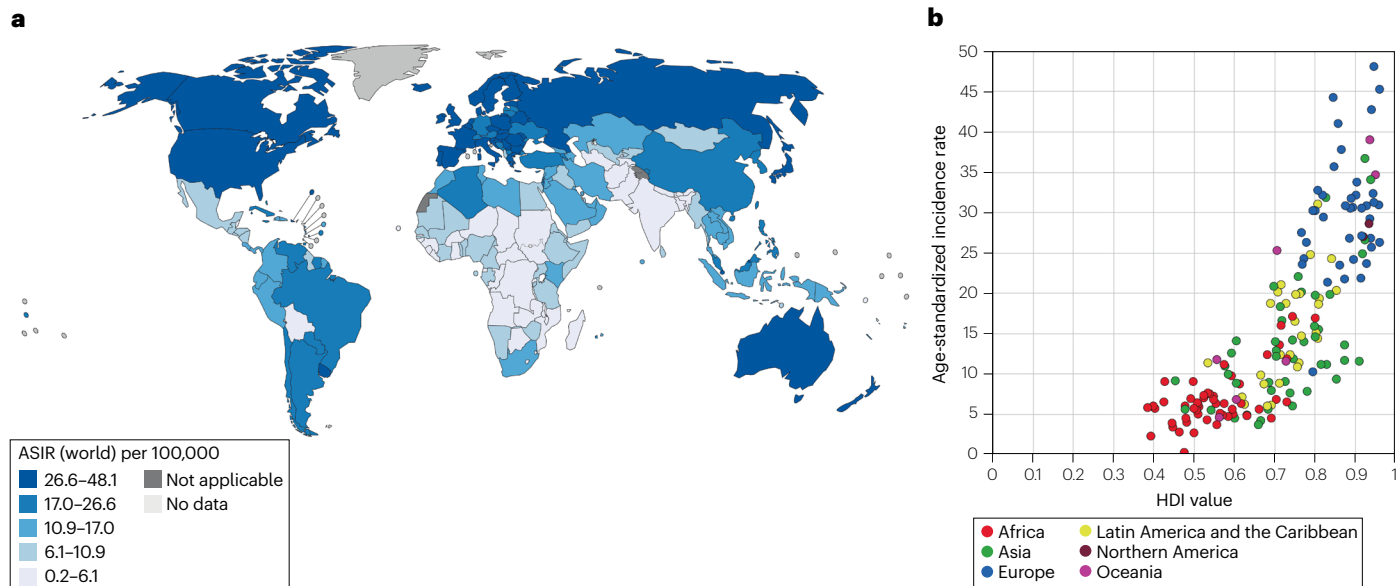


Fig. 1 | Estimated age-standardized CRC incidence worldwide in 2022 according to GLOBOCAN. **a**, Estimated age-standardized incidence rates (ASIRs) for colorectal cancer (CRC) worldwide, categorized by country, according to the Global Cancer Observatory (GLOBOCAN) in 2022 (ref. 209). **b**, Estimated ASIRs of CRC plotted against Human Development Index (HDI) values for countries across different world regions, according to GLOBOCAN 2022 (ref. 209). Each

point represents a country, with colours indicating regions (see colour key). HDI is a summary measure that incorporates life expectancy at birth (health), mean and expected years of schooling (education), and gross national income per capita (standard of living)²¹⁰. Reprinted with permission from ref. 209; accessed 3 February 2026.

in Eastern sub-Saharan Africa^{17,20}. Major gaps in high-quality cancer registry data across much of sub-Saharan Africa and other world regions obscure trends in CRC epidemiology, although these emerging trends suggest that factors beyond increasing life expectancy underlie the increasing CRC burden in these regions.

The plateauing and declining incidence of average-onset CRC – that is, newly diagnosed CRCs among individuals aged ≥ 50 years – in certain regions might be partially attributable to the implementation of national CRC screening programmes over the past few decades. In Israel, for example, the previously increasing CRC trends in both younger (aged 25–49 years) and older (aged 50–74 years) individuals began to diverge in the mid-2000s³, possibly reflecting a downstream effect of a stool-based screening programme that was initiated in 1999 and expanded over subsequent years^{21,22}. CRC incidence of both age groups declined sharply in South Korea in the early 2010s³, possibly reflecting the delayed effects of the implementation of a national CRC programme for adults aged ≥ 50 years in 2004, together with the extensive uptake of opportunistic CRC screening among adults aged ≥ 40 years occurring alongside organized gastric and breast cancer screenings recommended for this age group^{23,24}.

Changes in the regional epidemiology of CRC are shaped by the availability and extent of screening programmes, their uptake among patients and the varying prevalence of CRC risk factors. The latter two elements could explain why, in some countries, the availability of organized screening programmes has not always involved a stabilization or decrease in CRC incidence. For example, Chile and Japan saw a rise in CRC incidence in both younger (aged 25–49 years) and older adults (aged 50–74 years) over the 2008–2017 period³ despite having implemented national CRC screening programmes in 2012 and 1992, respectively^{25,26}. Furthermore, Argentina and Puerto Rico observed a

stabilization of CRC incidence among older adults (aged 50–74 years) during the same 10-year period³ despite their screening programmes not being implemented until the mid-2010s^{27–29}, making it unlikely that these programmes were the sole contributors to the already plateauing trends. Wide variations in screening uptake owing to system-level barriers (including differential insurance coverage, regional availability and awareness, or disruption resulting from natural disasters)^{30–33}, as well as the pace of adoption (or mitigation) of a Western diet and other lifestyle risk factors that have accompanied the rapid economic growth in these regions^{34–37}, might explain why the mere availability of screening programmes does not always correlate with changes in CRC incidence.

Inherited susceptibility

Approximately 20–30% of CRCs have a familial component^{10,38}. Meta-analyses have demonstrated that individuals with at least one first-degree relative diagnosed with CRC have an approximately twofold increased risk of developing CRC compared with those without a family history^{10,39}. The relative risk is further elevated when the affected first-degree relative was diagnosed before the age of 50 years, exceeding a threefold risk in pooled case–control and cohort studies⁴⁰, and rising to a fourfold to sixfold increased risk when two or more first-degree relatives are affected regardless of age³⁹. Given that epidemiological data from non-Western regions remain limited, these estimates are heavily influenced by studies performed in HICs in North America and Europe. Nonetheless, the available evidence suggests that the relative increase in CRC risk associated with family history is broadly comparable across regions worldwide. For example, a prospective multicentre study conducted in 16 Asia-Pacific regions, inclusive of both HICs and LMICs, demonstrated that individuals with at least one first-degree relative diagnosed with CRC had a twofold increased risk (adjusted OR for parent probands 2.02,

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95% CI 1.03–3.96; $P=0.04$; adjusted OR for sibling probands 2.25, 95% CI 1.00–5.04; $P=0.05$) compared with individuals with no family history of CRC⁴¹. Similarly, a meta-analysis of observational studies conducted in the Eastern Mediterranean region showed that having a first-degree relative diagnosed with CRC was associated with a twofold increased risk of CRC (OR 2.19, 95% CI 1.22–3.91; $P=0.008$)⁴². Although data from Latin America^{43,44} and Africa^{45–47} are sparse, the available evidence suggests that the magnitude of associations is similar, together indicating that family history accounts for a substantial proportion of the global CRC burden.

Pathogenic germline variants of high and moderate penetrance account for ~10% of all CRCs^{48,49} and a higher proportion of familial CRCs (16%)⁴⁸ and early-onset CRCs (16–25%)^{50,51}. Accounting for individuals who develop de novo high-penetrance germline mutations without having a family history⁵², the estimated prevalence of hereditary CRC syndromes in the general population is 3–6%^{10,38}. Among hereditary CRC syndromes, Lynch syndrome is the most common, occurring in approximately one in 300–400 individuals of the general population in Western countries^{53–56}. Lynch syndrome arises from germline mutations in one of four genes related to the mismatch repair (MMR) machinery (*MLH1*, *MSH2*, *MSH6* and *PMS2*) or 3' deletions in *EPCAM* that lead to epigenetic silencing of the adjacent *MSH2* (ref. 57). Familial adenomatous polyposis, caused by pathogenic variants in *APC*, is the next most common hereditary syndrome and occurs in approximately one in 10,000 individuals^{57,58}.

The mutational spectrum of high-penetrance genes in hereditary syndromes shows regional variation^{4,59–62}. Regarding Lynch syndrome,

for example, both the relative frequencies and mutational profiles of MMR genes differ by geography and ancestry^{60,62–64}. Yet, despite the observed variation, the available epidemiological evidence indicates that the prevalence of Lynch syndrome as a diagnosable condition is broadly consistent across populations worldwide⁶⁵.

The broad heterogeneity in CRC penetrance among carriers of Lynch syndrome variants is also strikingly consistent across regions^{55,66}. A study of 5,255 families with Lynch syndrome across 15 countries found a wide within-gene variation in the risk of developing CRC⁵⁵. The variation in CRC penetrance across gene, sex or continent was especially pronounced among carriers of *MLH1* or *MSH2* variants, the majority of whom could be clustered either near the lower end of the spectrum (approaching the risk in the average population) or in the upper end (indicating near certainty of developing CRC). This study also reported substantial variation in penetrance among carriers of the specific *MSH2* c.942 + 3A > T variant, indicating that the penetrance for CRCs in Lynch syndrome carriers is not solely determined by the pathogenic variant and the affected MMR gene. Overall, these data suggest that unmeasured modifiers, such as shared environmental factors and polygenic risk, might have a prominent role in influencing CRC development among Lynch syndrome carriers. Furthermore, the observation that this wide variation in CRC penetrance exists across continents suggests that region-specific environmental and genetic factors might shape the local risk of CRC⁵⁵.

The expansion of large-scale genome-wide association studies (GWAS) is also facilitating discovery of additional low-penetrance

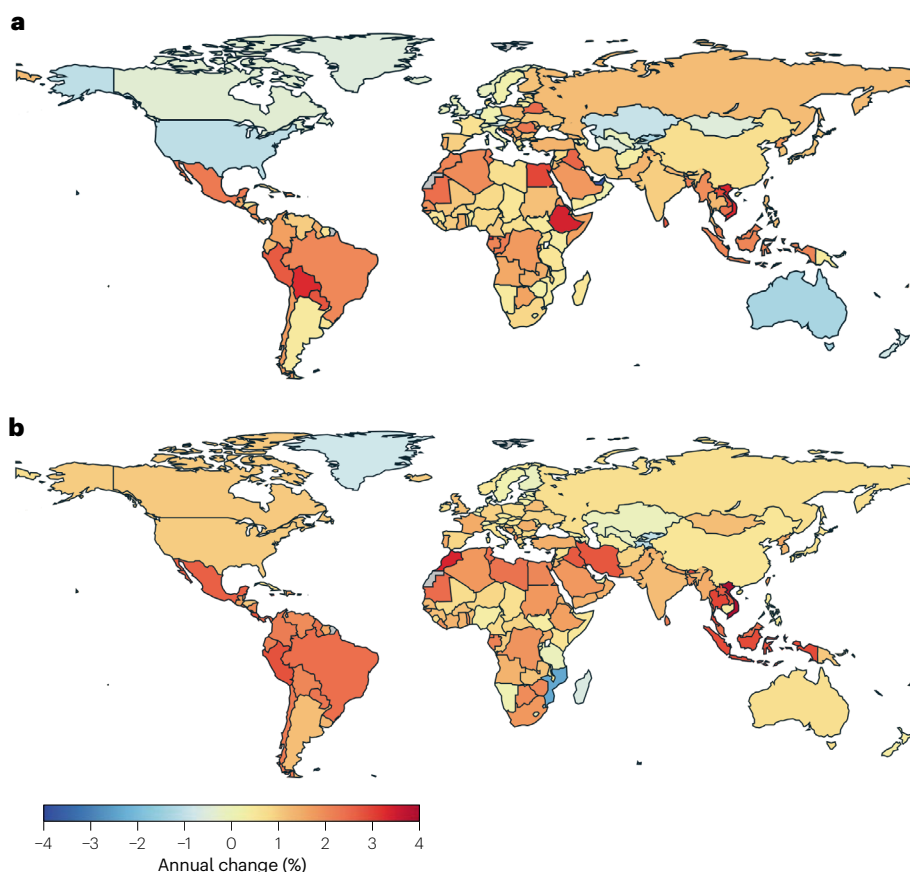


Fig. 2 | Temporal changes in CRC incidence worldwide according to GBD. a, Average annual percentage change of colorectal cancer (CRC) incidence among older individuals diagnosed at the age of 50–74 years from 1990 to 2023, as estimated by the Global Burden of Disease (GBD) study¹⁹. **b,** Average annual percentage change of CRC among younger individuals diagnosed at the age of 15–49 years from 1990 to 2023, as estimated by the GBD study¹⁹. Adapted with permission from the Institute for Health Metrics and Evaluation. All rights reserved.

germline variants that might influence CRC risk. Thus far, approximately 200 low-penetrance variants have been identified as being associated with CRC risk⁶⁷, and a fine-mapping analysis with results published in 2024 resolved these associations to 238 independent signals and 136 putative CRC susceptibility genes⁶⁸. The inclusion of populations of East Asian ancestry in large-scale GWAS has expanded the number of CRC-associated genetic variants identified^{68,69}, and the incorporation of populations of African and other origins in trans-ancestry analyses will probably further increase variant discovery and improve generalizability and clinical applicability across global populations⁷⁰. Although the cumulative effect of low-penetrance variants (or polygenic risk score) currently accounts for only a minor proportion of the risk of CRC attributable to family history^{71,72}, these variants are nonetheless independently associated with CRC susceptibility. One study demonstrated that study participants without a family history but in the top 30% of the polygenic risk score distribution had an approximately twofold increased risk of CRC, an estimate similar to the relative risk conferred by having a first-degree relative diagnosed with CRC⁷³. The risk estimate for early-onset CRC is higher, approaching a fourfold increased risk versus a threefold risk for average-onset CRC in another study⁷⁴. Thus, family history, pathogenic germline variants with high and moderate penetrance, and polygenic risk from low-penetrance variants are overlapping but distinct forms of inherited susceptibility that meaningfully contribute to the global burden of CRC.

Lifestyle factors

The rapidly changing global incidence of CRC, particularly for early-onset CRC, points to drivers beyond age and genetic susceptibility. Indeed, the predominance of sporadic CRCs, the wide heterogeneity in penetrance among Lynch syndrome carriers and the large proportion of familial aggregation that remain unexplained by pathogenic variants suggest that lifestyle and environmental factors might have a major aetiological role.

In the GBD 2019 assessment of the global cancer burden attributable to potentially modifiable risk factors, CRC ranked second (after cancers of the lung and related airways) in terms of risk-attributable deaths and disability-adjusted life years⁷⁵. Globally, smoking and diets low in milk and calcium are the main contributors to all-age disability-adjusted life years attributable to CRC⁷⁵, although the relative contributions of individual risk factors differ across regions⁶. For example, a high body mass index (BMI), alcohol intake and smoking are prominent contributors in Australasia, Europe and North America (USA and Canada), whereas dietary deficiencies in milk and calcium generally account for a greater share in sub-Saharan Africa and South and Southeast Asia⁶.

Epidemiological and ecological studies indicate that region-specific CRC incidence patterns can quickly shift in response to changes in local, population-level risk factor profiles. For example, rapid urbanization and economic growth have often been accompanied by shifts towards Western diets and sedentary lifestyles – a trend observed in parts of Asia, Latin America and sub-Saharan Africa, where CRC incidence has also increased concomitantly^{76–78}. The rising incidence in early-onset CRC in non-Western countries has also coincided with the liberalization of food trade, which was accelerated in the late 1980s to early 1990s, leading to rapid accessibility and consumption of red meats and processed foods, contributing to the subsequent rise of obesity rates in economically transitioning countries^{79,80}. Furthermore, studies indicating that migrants from countries with a low incidence

Table 1 | Temporal change in age-standardized CRC incidence by age group according to IARC CI5plus

Region	10-year AAPC (95% CI) ^a	
	Aged 25–49 years at diagnosis	Aged 50–74 years at diagnosis
Rise in CRC among younger individuals only		
Argentina	2.92 (0.80–5.10)	0.33 (–0.80 to 1.46)
Australia	3.01 (2.43–3.58)	–2.62 (–3.09 to –2.15)
Canada	2.83 (2.29–3.37)	–1.97 (–3.34 to –0.59)
France	2.09 (0.88–3.32)	–0.11 (–0.60 to 0.39)
Germany	1.99 (1.23–2.75)	–1.69 (–2.05 to –1.33)
Ireland	0.62 (0.07–1.18)	–1.65 (–3.52 to 0.26)
Israel	0.46 (0.03–0.89)	–4.01 (–4.64 to –3.38)
New Zealand	3.97 (2.44–5.52)	–2.40 (–2.67 to –2.12)
Norway	3.52 (1.94–5.13)	0.20 (–0.01 to 0.41)
Slovenia	0.65 (0.31–0.99)	–4.16 (–5.68 to –2.62)
UK, England	3.59 (3.12–4.06)	–0.72 (–1.38 to –0.07)
UK, Scotland	0.64 (0.39–0.88)	–2.27 (–3.57 to –0.95)
USA	2.13 (1.90–2.36)	–1.49 (–2.47 to –0.50)
USA, Puerto Rico	3.81 (2.68–4.96)	–0.44 (–2.21 to 1.37)
Rise in CRC among older individuals only		
Bahrain	–0.27 (–2.63 to 2.15)	3.36 (2.29–4.45)
China	1.86 (–2.29 to 6.18)	0.92 (0.58–1.26)
Estonia	0.54 (–0.11 to 1.19)	1.09 (0.85–1.33)
Iceland	7.33 (–0.77 to 16.10)	0.88 (0.61–1.15)
India	1.26 (–0.03 to 2.57)	2.59 (2.05–3.15)
Kuwait	0.49 (–1.61 to 2.62)	1.65 (0.34–2.98)
Latvia	–0.06 (–0.59 to 0.48)	0.53 (0.02–1.05)
Uganda	0.22 (–1.85 to 2.34)	2.37 (1.19–3.56)
Rise in CRC among both younger and older individuals		
Belarus	3.24 (0.17–6.41)	1.95 (1.83–2.06)
Chile	3.96 (1.26–6.74)	1.55 (0.13–2.99)
Costa Rica	1.49 (1.02–1.97)	2.38 (2.02–2.74)
Croatia	1.39 (0.69–2.09)	0.80 (0.22–1.37)
Denmark	1.67 (1.03–2.31)	2.40 (1.24–3.58)
Ecuador	2.10 (1.29–2.91)	1.76 (1.14–2.38)
Finland	0.89 (0.65–1.13)	0.61 (0.40–0.83)
France, Martinique	1.74 (0.13–3.37)	3.85 (2.80–4.90)
Japan	2.94 (1.39–4.52)	2.03 (1.71–2.35)
Sweden	2.32 (1.85–2.79)	0.34 (0.24–0.45)
Thailand	2.76 (2.17–3.36)	3.77 (3.40–4.15)
Netherlands	1.77 (1.56–1.99)	1.25 (0.10–2.40)
Turkey	2.15 (1.57–2.74)	1.83 (1.18–2.49)

Data adapted from an analysis conducted on behalf of the WHO International Agency for Research on Cancer (IARC) Cancer Incidence in Five Continents Plus (CI5plus) database³. Among 50 countries and territories included in this study, the table delineates those that have observed a positive 10-year average annual percentage change (AAPC) in the age-standardized incidence rates of colorectal cancer (CRC) among younger individuals only (aged 25–49 years), older individuals only (aged 50–74 years) and both age groups concurrently. Countries and territories with 10-year AAPCs that were negative or neutral-stable (such as those with a 95% confidence interval (CI) including 0) in both the younger and older age groups have not been included in the table for simplicity. ^aThe 10-year AAPC in age-standardized incidence rates in CRC are from 2008 to 2017. Exceptions are Costa Rica (2005–2016) and Japan (2006–2015).

Table 2 | Dietary, nutritional and lifestyle factors affecting CRC risk according to the WCRF/AICR Third Expert Report

Factor	Quality of evidence	Exposure increment (or category)	Relative risk of CRC (95% CI)
Increases CRC risk			
Adult-attained height	Strong–convincing	5 cm	1.05 (1.02–1.07)
Alcoholic drinks	Strong–convincing	10 g (ethanol) per day	1.07 (1.05–1.08)
Body fatness	Strong–convincing	5 kg/m ² (BMI)	1.05 (1.03–1.07)
		per 10 cm (WC)	1.02 (1.01–1.03)
		per 0.1 unit (WHR)	1.02 (1.01–1.04)
Processed meat	Strong–convincing	50 g per day	1.16 (1.08–1.26)
Red meat	Strong–probable	100 g per day	1.12 (1.00–1.25)
Foods containing haem iron	Limited–suggestive	1 mg per day	1.04 (0.98–1.10) ^a
Low intakes of fruits	Limited–suggestive	100 g per day	0.96 (0.93–1.00) ^a
Low intakes of non-starchy vegetables	Limited–suggestive	100 g per day	0.98 (0.96–0.99)
Decreases CRC risk			
Calcium supplements	Strong–probable	Highest vs lowest ^b	0.76 (0.65–0.89) ^c
Dairy products	Strong–probable	400 g per day	0.87 (0.83–0.90)
Foods containing dietary fibre	Strong–probable	10 g (fibre) per day	0.93 (0.87–1.00)
Physical activity	Strong–convincing	Highest vs lowest ^b	0.80 (0.72–0.88)
Whole grains	Strong–probable	90 g per day	0.83 (0.78–0.89)
Fish	Limited–suggestive	100 g per day	0.89 (0.80–0.99)
Foods containing vitamin C	Limited–suggestive	40 mg per day	0.94 (0.89–0.99)
Multivitamin supplements	Limited–suggestive	Users vs non-users	0.88 (0.79–0.98)
Vitamin D	Limited–suggestive	30 nmol/l (plasma or serum)	0.92 (0.85–1.00)

Data are adapted from World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project (CUP) Third Expert Report (2018)⁸⁹. Factors for which the evidence is ‘limited–no conclusion’ have been excluded from this table for simplicity. The relative risk estimates are pooled results from meta-analyses^{89,90}. ^aAlthough the association was not statistically significant, the data provide evidence of a non-linear association with a numerical increase in CRC risk for higher levels of the exposure. ^bThe pooled effect estimate in the meta-analysis represents a crude harmonization of ‘highest versus lowest’ comparisons from individual studies. ^cEstimate derived from a separate meta-analysis²⁰⁸. BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

of CRC often acquire the higher risk of this disease associated with their host countries – a phenomenon known as the cancer risk transition, which has been well documented in multiple contexts^{81–87} – provide further evidence that non-heritable exposure can shape population-specific incidence patterns. Studies in Australia^{83,88}, North America^{85–87} and Western Europe^{81,82,84} have shown that immigrants,

many from non-Western birth countries, initially have a statistically significantly lower risk of CRC than the native-born population but that this advantage diminishes with duration of residence, with trajectories varying by sex and age at immigration. A study of Mexico-born US immigrants found that the shift from traditional to Westernized diets and the parallel acquisition of an elevated risk of CRC can occur rapidly, within one generation⁸⁵. Together, these data underscore the influence of modifiable lifestyle and dietary factors in shaping regional patterns of CRC incidence.

Global estimations of CRC risk attributable to lifestyle and dietary determinants, such as those provided by the GBD study^{6,75}, are based on factors recognized by the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) to have well-established associations with CRC. In their Third Expert Report of 2018, the WCRF/AICR concluded that strong evidence (probable or convincing) indicates that physical activity and the consumption of wholegrains, dietary fibre, dairy products and calcium supplements reduce CRC risk, whereas high body fatness (measured by BMI, waist circumference and waist-to-hip ratio), adult-attained height and the consumption of alcoholic drinks and red and processed meats increase risk^{89,90} (Table 2). These risk and protective factors for CRC have been identified based on a critical assessment⁸⁹ of available epidemiological and experimental studies, many of which have shown evidence of a dose–response relationship and biological plausibility. Since the publication of the WCRF/AICR Third Expert Report, growing evidence points to sugar-sweetened beverages as a potential risk factor for CRC, including early-onset CRC^{91,92}. Further research in low-income and middle-income countries (LMICs), including those in Africa, Asia (other than East Asia) and Latin America, is warranted to validate previously defined CRC risk factors and potentially identify additional dietary and lifestyle determinants.

Outside of factors related to diet and physical activity, the WCRF/AICR has also recognized smoking and inflammatory bowel disease (which encompasses Crohn’s disease and ulcerative colitis) as risk factors of CRC⁸⁹. With regard to medications, studies have suggested that long-term use of aspirin, non-steroidal anti-inflammatory drugs or, for post-menopausal women, hormone therapy might reduce CRC risk, although not all guidelines currently recommend them for population-wide chemoprevention. For example, considerations on the long-term use of aspirin include its toxicity profile (particularly, the risk of gastrointestinal bleeding) and delayed protective effect typically observed after 10–20 years of follow-up^{93–96}. As a result, some guidelines (including those by the American Gastroenterological Association, the National Comprehensive Cancer Network and Cancer Council Australia) recommend CRC chemoprevention with aspirin only in selected groups, such as individuals who have Lynch syndrome and individuals who are aged <70 years, with a life expectancy of ≥10 years and an elevated risk of cardiovascular disease^{94,97–99}.

Beyond the role of individual foods, nutritional components and lifestyle factors, experts are increasingly recognizing the need for holistic analyses of dietary and lifestyle patterns that better reflect real-world scenarios and evaluate their combined effects on CRC risk¹⁰⁰. Patterns can be derived a priori on the basis of culturally defined dietary habits as well as established dietary and dietary–lifestyle guidelines, a posteriori through exploratory statistical modelling approaches of observational data to identify patterns, or using a hybrid approach¹⁰¹. The Empirical Dietary Inflammatory Pattern (EDIP) and Empirical Dietary Index for Hyperinsulinemia (EDIH), for example, are dietary pattern scores derived using a hybrid approach that incorporated

biomarker data (specifically, inflammatory markers in EDIP and fasting C-peptide in EDIH) and quantify the inflammatory and insulinaemic potential of habitual diets, respectively^{102,103}. In large prospective cohort studies, study participants in the highest quintile of EDIP and EDIH scores had a 32% and 26% higher risk of developing CRC, respectively, relative to those in the lowest quintile (HR for EDIP 1.32, 95% CI 1.12–1.55; $P_{\text{trend}} < 0.001$; HR for EDIH 1.26, 95% CI 1.12–1.42; $P_{\text{trend}} < 0.0001$)^{102,103}. On the basis of these and other findings showing that EDIP and EDIH have an overall consistent direction of positive associations with CRC risk and grounds for biological plausibility^{104–106}, the WCRF/AICR Global Cancer Update Programme (CUP Global) concluded in 2025 that the evidence for higher EDIP and/or EDIH scores predicting an increased risk of CRC is ‘strong–probable’¹⁰¹. CUP Global also concluded that the Empirical Lifestyle Index for Hyperinsulinemia, an extension of EDIH that also includes key lifestyle factors (BMI and physical activity) in addition to diet, has strong–probable evidence of a positive association with CRC risk¹⁰⁷. The evidence for most other dietary and dietary–lifestyle patterns that have been investigated for CRC risk, including a Mediterranean diet and the Healthful Plant-Based Diet Index, is currently considered ‘limited–suggestive’ (Table 3 and Supplementary Table 1)^{101,107}.

Gut microbiota

The influence of lifestyle factors on CRC risk is in part modulated by the gut microbiota. For example, the protective effects of dietary fibre and physical activity might be mediated by the increased abundance of short-chain fatty acid-producing bacteria, which are important regulators of metabolic homeostasis¹⁰⁸. Fibre is a substrate for fermentation by gut microbiota, producing short-chain fatty acids (notably butyrate), which support healthy colonocytes as their primary energy source and contribute to tumour suppression through pro-apoptotic and anti-inflammatory mechanisms^{109,110}. Conversely, adverse dietary patterns can cause shifts in the gut microbiota, enriching for bacterial species that facilitate a chronic inflammatory milieu¹¹¹, disrupt a healthy intestinal epithelial barrier¹¹² and/or produce metabolites and metabolic byproducts, including hydrogen sulfide¹¹³ and secondary bile acids¹¹⁴. These interrelated mechanisms can cause DNA damage and promote tumorigenesis¹¹². Obesity, a comorbidity closely associated with Western dietary patterns, can exacerbate these microbiota-mediated mechanisms in addition to independently contributing to CRC risk through separate pathophysiological mechanisms¹¹⁵.

An increasing body of research is seeking to elucidate the causal, functional roles of individual microbial taxa in colorectal tumorigenesis. *Fusobacterium nucleatum*, a typically oral species, is rarely detected in the healthy lower gut but significantly enriched in tumour tissue and stools from patients with CRC, as observed and replicated in multiple independent cohorts^{116–118}. In preclinical models, *F. nucleatum* has been demonstrated to drive tumorigenesis by indirectly leading to upregulation of the expression of oncogenic and pro-inflammatory genes^{119,120}, modulating the tumour immune microenvironment and thus facilitating immune evasion^{121–123}, and potentiating oncogenic signalling in *KRAS* p.G12D-mutant CRC by activating a convergent, pro-tumorigenic pathway. Another striking example is provided by *Escherichia coli* strains that carry the *pks* pathogenicity island, which encodes the enzymatic machinery responsible for synthesizing colibactin. Colibactin is a genotoxic compound that can cause oncogenic transformation through induction of distinct mutational signatures in host epithelial cells, specifically the single-base substitution signature SBS88 and the indel signature ID18 catalogued in the COSMIC

database^{124,125}. Importantly, a study of the genomes from 981 patients with CRC across 11 countries and 4 continents found a robust correlation between mutational load in SBS88 and ID18 and CRC incidence rates¹²⁶. Moreover, these signatures were 3.3-fold more common in patients diagnosed at an age of <40 years than in those diagnosed at ≥70 years of age¹²⁶, suggesting that exposure to colibactin-producing bacteria might be contributing to the global rise in early-onset CRC.

Beyond the identification of certain microbiota strains, an expanding area of research is seeking to identify universal microbiome signatures in CRC that are consistent across populations and settings worldwide. A pooled analysis of 3,741 stool samples from study participants with or without CRC from 11 countries identified 125 bacterial groups, including both known and previously uncharacterized species, with relative abundance in CRC¹²⁷. CRC-associated microbiome signatures shift along the adenoma–carcinoma sequence and vary by tumour stage and location^{128–130}. In addition, the considerable overlap in gut microbiota patterns associated with CRC and those associated with obesity and/or metabolic syndrome has raised hypotheses regarding convergent and potentially modifiable pathogenic mechanisms^{108,127}. This overlap, however, also underscores the need for rigorous control for anthropomorphic and biomarker measures (such as BMI and markers of inflammation) because potential confounding by obesity and/or metabolic syndrome can obscure the identification

Table 3 | Summary of evidence on the associations of dietary and dietary–lifestyle patterns on CRC risk according to CUP Global

Pattern	Derivation method	Direction of CRC association	Quality of evidence
Dietary patterns			
Empirical Dietary Index for Hyperinsulinemia	Hybrid	Positive	Strong–probable
Empirical Dietary Inflammatory Pattern	Hybrid	Positive	Strong–probable
Dietary Approaches to Stop Hypertension	A priori	Negative	Limited–suggestive
Healthful Plant-Based Diet Index	A priori	Negative	Limited–suggestive
HEI and AHEI	A priori	Negative	Limited–suggestive
Mediterranean diet	A priori	Negative	Limited–suggestive
Dietary–lifestyle patterns			
Empirical Lifestyle Index for Hyperinsulinemia and modifications	Hybrid	Positive	Strong–probable
WCRF/AICR recommendations score	A priori	Negative	Strong–probable
American Cancer Society guidelines score	A priori	Negative	Limited–suggestive
Healthy Lifestyle Index and modifications	A priori	Negative	Limited–suggestive

Data adapted from systematic reviews of the literature^{101,107}. Patterns for which the evidence is ‘limited–no conclusion’ have been excluded from this table for simplicity. None of the patterns had ‘strong–convincing’ evidence. Descriptions of these dietary and dietary–lifestyle patterns are provided (Supplementary Table 1). AHEI, Alternative Healthy Eating Index; CRC, colorectal cancer; CUP Global, WCRF/AICR Global Cancer Update Programme; HEI, Healthy Eating Index; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

of CRC-specific microbiome signatures¹³¹. Collectively, reliable patterns will not only provide insight on CRC biology but also inform biomarker-based strategies for early detection and interception¹²⁷.

A major limitation of large-scale microbiome analyses is the lack of representation of populations from LMICs, particularly from sub-Saharan Africa^{127,132}. Although a study involving participants from South Africa identified some microbiome signatures that overlap with those described in Western cohorts¹³³, the largely uncharacterized microbial diversity of non-Western populations¹³⁴ limits our understanding of the biology and epidemiology of CRC as well as the generalizability of clinical and public health interventions derived from these findings.

Research on transkingdom interactions that might influence carcinogenesis in the colorectum is an emergent area of interest, although data on the enteric virome^{135–137}, mycobiome¹³⁸ and archaeome^{139,140} remain limited. Initiatives such as the National Institutes of Health Human Virome Program¹⁴¹ will enable a deeper investigation of their roles in CRC.

Pollutants and toxins

The influence of exposure to chemicals and environmental contaminants on CRC risk is currently not well established, although the emerging shifts in the global epidemiology of CRC – particularly in early-onset disease – have raised questions about their potential contribution. The rise in early-onset CRC, first observed in the mid-1990s, temporally aligns with the large-scale expansion in the use of industrial and consumer products containing hazardous chemicals that started in the post-World War II period, raising the possibility of a delayed effect from exposure to these substances^{142–144}. For example, the global production of plastics exponentially increased in the 1950s, leading to widespread environmental plastic pollution and human exposure to microplastics through ingestion, inhalation and dermal contact¹⁴³. The production of perfluoroalkyl and polyfluoroalkyl substances (PFAS; synthetic compounds used in a wide variety of industrial and commercial applications because of their chemical and thermal stability, water and oil repellency, and distinct surfactant properties) also began to increase substantially in the 1950s, following their initial development and commercial introduction in the 1940s¹⁴⁵. Microplastics and PFAS persist in environmental media and biota worldwide (including in remote regions) owing to their bioaccumulation and long-distance transport potential, raising concerns of their enduring effects on human health (including CRC risk) potentially for generations to come^{146,147}.

Chemical exposure includes exposure to persistent environmental pollutants (such as PFAS and heavy metals) as well as occupational exposure (to agents including asbestos, benzene and agricultural pesticides), exposure to food-related contaminants (such as bisphenol A and phthalates) and consumer product-related and lifestyle-related exposures (for example, microplastics and flame retardants)^{142,144,148}. As of June 2025, the IARC has classified 135 agents as Group 1 carcinogens and 95 Group 2A carcinogens (indicating that they are carcinogenic or probably carcinogenic to humans, respectively)¹⁴⁹; exposure to these agents can occur in a dietary, microbial, occupational and/or environmental manner. The IARC Monographs Programme continues to review suspected carcinogens nominated for consideration, with more than 210 distinct candidate agents considered in the March 2024 Advisory Group meeting¹⁵⁰. Currently, only a small subset of Group 1 and Group 2 agents are established or implicated risk factors for CRC. This subset includes red and processed meats, alcoholic beverages and tobacco smoking as well as their associated compounds, such as some polycyclic aromatic

hydrocarbons and heterocyclic aromatic amines generated during high-temperature cooking of meat and present in tobacco smoke as well as some *N*-nitroso compounds found in processed meats and tobacco¹⁴⁹. However, the range of potential culprits of chemical risk might be wider, as suggested by reports of elevated CRC risk among industrial workers with high exposure to chemical agents (such as asbestos, benzene, pesticides, leather, basic metals and rubber)^{151–154} as well as studies indicating that certain environmental pollutants (microplastics) are present at higher levels in stool from study participants with CRC relative to participants without cancer¹⁵⁵ and in CRC tumour tissue relative to adjacent non-cancerous tissue¹⁵⁶.

The associations of environmental contaminants with CRC remain largely speculative. Given that many chemical contaminants affect human health through chronic, low-level exposure with long latency periods between the exposure and outcome, establishing their link with CRC faces substantial methodological challenges^{142,157}. Furthermore, standardized, scalable methods for biomonitoring exposure to complex, co-occurring chemical mixtures in humans remain a high priority^{135,148,158,159}. Yet, mechanistic evidence from preclinical studies evaluating the role of chemical exposure in carcinogenesis, including intestinal barrier disruption¹⁶⁰, genotoxicity and DNA damage^{160,161}, epigenetic alterations^{161,162}, endocrine disruption¹⁵⁷ and induction of chronic inflammation^{163,164}, indicate that the influence of long-term exposure to chemical pollutants in CRC risk is an underexplored area of research. The need for further investigation is particularly relevant given that rapid urbanization continues to occur worldwide – indeed, approximately two-thirds of the world's population are projected to be living in cities and towns by 2050, and 90% of the urban growth in the global South in the same time period is estimated to occur in Asia and Africa^{165,166}, which will lead to the global expansion of population-level environmental and occupational exposure to potential carcinogens.

Screening and care delivery

The changing epidemiology of CRC underscores the need to both adapt current public health strategies and identify new ones to meet the rising burden of this disease occurring worldwide. These approaches will range from implementing CRC screening programmes to addressing modifiable risk factors. For example, identifying the optimal screening strategy for a specific region involves assessing regional incidence trends and considering them alongside projected clinical benefits, harms and costs of potential interventions – in summary, strategies must be informed by the local context^{167,168}. In the USA, the starting age for CRC screening among individuals at average risk was lowered from 50 to 45 years to address the rising incidence of early-onset CRC through screening pathways involving stool-based assays and direct visualization tests (for example, colonoscopy)^{168,169}. Data have shown that lowering the screening age in the USA has increased the detection rate of localized stage CRC among individuals aged 45–49 years and reduced subsequent CRC incidence^{12,170,171}. Most other Western HICs have maintained the starting age for screening at 50 years, although some, including Canada and Australia, are considering guideline revisions^{99,172–174}. Taiwan also expanded its faecal immunochemical testing (FIT)-based screening programme in 2025 by lowering the starting age for screening to 45 years of age¹⁷⁵.

In LMICs, where historically national CRC screening programmes have been largely absent, the growing incidence of CRC has motivated increasing adoption and evaluation of organized screening initiatives, most commonly predicated around stool-based tests given their non-invasiveness and affordability¹⁷⁶. Evidence from

upper-middle-income countries in Latin America suggests that such programmes can achieve high levels of acceptability: a meta-analysis demonstrated a high uptake of FIT-based screening (86%) and colonoscopy completion rate exceeding 75% after a positive finding, resulting in detection rates of adenoma and CRC on par with those in screening programmes from North American and European countries¹⁷⁷. However, within-country studies have observed that screening uptake may not be uniform within a population and can vary substantially by socioeconomic status, reflecting both individual-level and health system-level factors^{30–32}. Furthermore, particularly in low-income and lower-middle-income countries, challenges extend beyond issues of screening uptake. For example, a study in Nigeria demonstrated that although FIT-based screening was feasible and well accepted¹⁷⁸, a high rate of false-positive findings owing to benign conditions (such as haemorrhoids) imposed a substantial burden for endoscopic follow-up that would overwhelm the current national capacity under a nationwide scale-up¹⁷⁸. Collectively, these studies indicate that effective CRC screening programmes in LMICs extend beyond identifying a single low-cost screening test, with the need to address bottlenecks throughout the screening-to-treatment continuum.

The balance between patient acceptability and test performance characteristics will become especially relevant for emerging screening and diagnostic tests, including blood-based tests that detect genomic and epigenomic alterations associated with CRC in circulating cell-free DNA^{179,180}. Indeed, the potentially higher acceptability and practicality of administration of blood-based tests compared with stool-based or endoscopy approaches^{181,182} make them especially attractive for lower-resourced settings. However, their lower performance, especially for the detection of advanced adenomas and other precancerous lesions^{179,180,183}, underscores the need for careful evaluation of their role within multimodal screening pathways and the importance of their close integration with the development of diagnostic and treatment capacity, especially in LMICs, to achieve meaningful reductions in the global CRC burden.

Identifying optimal screening strategies tailored to the local context is only one component of the broader efforts needed for developing or expanding care delivery models to meet the rising tide of early-onset CRC^{184,185}. In general, current guidelines recommend that patients diagnosed with early-onset CRC should be treated similarly to patients with average-onset CRC^{184,186}. Thus far, studies suggest that although patients with early-onset CRC often receive more intensive treatment regimens, they do not derive a clear survival benefit^{49,187–193}. As the demand for management of patients diagnosed with early-onset CRC continues to rise worldwide, however, not all healthcare systems will have the immediate capacity to provide certain aspects of care. For example, despite universal germline testing being recommended for patients with early-onset CRC, and MMR deficiency and microsatellite instability (MSI) testing being recommended for all patients with newly diagnosed CRC^{98,184}, relevant large multigene panels, immunohistochemistry, PCR and/or next-generation sequencing assays are not necessarily available in, or affordable for, all healthcare systems – especially in LMICs¹⁸⁴. These potential limitations are relevant because MMR-deficient and MSI-high tumours are more common among patients with early-onset CRC, owing to a higher incidence of Lynch syndrome in this population¹⁸⁴. In terms of treatment implications, these tumour subtypes tend to have high responsiveness to immune-checkpoint inhibitors^{184,194}. However, many healthcare systems currently lack access to these immunotherapies and capacity to accommodate the more intensive screening approaches

recommended for Lynch syndrome carriers^{98,195}. As such, optimizing CRC care delivery models will require context-specific treatment pathways that are aligned with local epidemiological patterns and can evolve alongside strengthening of healthcare systems and efforts for developing capacity.

Conclusions

The global epidemiology of CRC is changing, and our current understanding of modifiable (diet, lifestyle, and potentially microbiota and chemical exposure) and non-modifiable (family history and hereditary syndromes) risk factors for this disease presents opportunities for early detection and interception strategies. For example, given the high, globally stable prevalence of Lynch syndrome, refined risk prediction tools that integrate personal and family history to estimate the probability of carrying a pathogenic or likely pathogenic germline variant could be combined with MMR immunohistochemical staining and germline testing in an optimal, cost-conscious manner to address a substantial portion of early-onset CRCs in less-resourced settings^{196–198}. Furthermore, the current knowledge of established dietary and lifestyle risk factors has public health and policy implications for curbing the global obesity epidemic, addressing dietary deficiencies in milk and calcium (especially in LMICs), and strengthening control of smoking and alcohol intake^{6,199}. As populations around the world rapidly become urbanized (especially in Asia and Africa)¹⁶⁶, thoughtful design of the built environment could mitigate social, behavioural and potential environmental risk factors for CRC by fostering physical activity, countering the widespread adoption of adverse dietary patterns and reducing exposure to carcinogens at the workplace and community level^{200–202}.

Despite advances in our understanding of the global epidemiology of CRC and its risk factors, the stark lack of representation of many world regions in research remains a major hindrance to progress. Current knowledge of global incidence of CRC, including the rise of early-onset CRC in LMICs, is largely derived from a 2025 analysis of the IARC CI5plus database, which is widely considered the gold standard for international cancer registries. This knowledge, however, remains substantially limited by the scarcity of high-quality data from many non-Western regions, particularly across Africa and Asia. For example, Uganda is the only country in sub-Saharan Africa with a cancer registry that met the IARC CI5plus quality standards to be included in the latest analysis³. Also, in many countries, cancer incidence estimates are derived from subnational registry data. For example, the cancer registries of China and India, which are included in CI5plus, cover only 0.6% and 1.5% of the population, respectively³, despite being the world's most populous nations and containing regions with a high prevalence of CRC risk factors^{203–205}. Finally, although substantial advances have been made to identify and validate universal microbiome¹²⁷ and mutational signatures¹²⁶, and polygenic risk scores^{68,69} that can be leveraged for precision prevention strategies, the lack of representation of non-Western populations – particularly those in sub-Saharan Africa, despite having the most genomic and microbiota diversity^{134,206} – in large-scale analyses can inadvertently exacerbate, rather than mitigate, global CRC disparities²⁰⁷. Thus, prioritizing the expansion of high-quality cancer registries and building research capacity in LMICs could substantially advance collective understanding of CRC aetiology and, in turn, guide prevention strategies to curb the global tide in rising CRC incidence.

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Competing interests

In the past 36 months, A.P. has held equity in Cadex, Khora, OneCell, Parithera and XGenomes; has been an adviser and/or consultant for 3T Biosciences, AbbVie, Adroya, Amgen, AstraZeneca, Bristol Myers Squibb, CVS, CareSet, Caris, Delicate, DoMore Diagnostics, Eli Lilly, Exact Sciences, Foundation Medicine, GSK, Guardant, Hookipa, Incyte, Johnson & Johnson, Kahr, Merck, Mirati, MPM Capital, Naterara, Neogenomics, Pfizer, Pheon, Phesi, PMV Pharma, Regeneron, Science For America, Seagen, Sirtex, Summit Therapeutics, Takeda, Third Rock Ventures, Value Analytics Labs, Xilio and Zola; is Chief Scientist of Reversing Early Recurrence; receives author fees from Up to Date; has received travel fees from Karkinos Healthcare; and works in an institution that has received research funding from Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Erasca, Genentech, Incendia, Mirati, Pheon, PMV Pharma, Revolution Medicine, Syndax and Xilio. Y.C. has been a consultant for Bayer Need for unrelated work. A.T.C. has been a paid consultant for Boehringer Ingelheim and Pfizer for work unrelated to this article and receives grant support from Freenome for work unrelated to this article. D.J.L. and B.S. declare no competing interests.

Additional information

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