Project MEPROT: Shaping the Future of Early Onset Colorectal Cancer Prevention

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Abstract

Early onset colorectal cancer (EOCRC) among individuals under age 50 is increasing globally. While lifestyle factors such as obesity, metabolic comorbid conditions, poor diet, and sedentary behaviours are linked to EOCRC, critical gaps remain in identifying additional risk factors, with growing evidence in early-life and gut microbial-related exposures. In addition, how or when the risk factors act, individually or collectively, to initiate or promote CRC at much younger ages remains unknown. Compounding the complexity are the unique challenges of developing and implementing effective prevention strategies among younger populations. In this review, I symmary the progress and challenges of risk factor discovery for EOCRC, highlight opportunities for prevention, and propose a transdisciplinary framework integrating population, mechanistic, behavioural, and implementation sciences to accelerate causal risk factor discovery and translate insights into strategies to reverse the rising EOCRC burden. While currently implemented by Project MEPROT, this framework is broadly adaptable and intended to inspire collaborative efforts across the field. I also emphasize the critical role of patient perspectives and public engagement in shaping these efforts. With the urgency in risk factor discovery, scientists, the public, and policymakers must unite to transform knowledge into life-saving solutions for future generations.

Introduction

Colorectal cancer (CRC), the third most commonly diagnosed cancer and the second leading cause of cancer-related death worldwide, accounts for more than 1.9 million new cases and almost 904,000 deaths in 2022 worldwide.[1] Traditionally considered as a disease of older adults, CRC is now exhibiting a troubling epidemiological shift to younger adults.[2]

The rise in early onset colorectal cancer (EOCRC), typically defined as diagnosis before age 50, was initially documented in the United States (U.S.)[3] in 2017 and subsequently in another 18 high-income countries.[4] More recently, this trend has extended to 27 countries and territories across Latin America, the Caribbean, Asia, and Eastern Europe, according to data available from 2013-2017 (**Figure 1**).[2] In the most recent five years, countries with the highest rate of increase (average annual percent change) were New Zealand (3.97%), Chile (3.96%), England (3.59%), Norway (3.52%), Belarus (3.24%) (**Table 1**). [2] Despite rising incidence, EOCRC remains uncommon in absolute terms. Countries with the highest incidence (age-standardized incidence rates per 100,000) are Australia (16.5), New Zealand (14.8), the U.S. (14.8), Puerto Rico (15.2), and South Korea (14.3) (**Table 1**). In screening-age populations, age-standardized incidence rates in younger adults are substantially lower than those observed in later onset colorectal cancer (LOCRC), which is from 23.5 to 168.4 per 100,000 globally. [2] Increases in EOCRC incidence vary substantially by age groups under 50. In the US, incidence rises steadily across one-year age increments, with higher annual percent increases observed among adults aged 30-39 years than among those aged 40-49 years, particularly among men.[5] In the UK, the most sustained incidence increases have been reported in the youngest adults, including those aged 20-29 years, largely driven by distal tumours,[6] while regional analyses further indicate pronounced increases among individuals aged 30-39 years.[7] Sex-specific patterns in EOCRC incidence trends have emerged, with steeper increases observed in men in some countries (e.g., Chile, U.S., Puerto Rico) and in women in others (e.g., United Kingdom [UK], Norway).[2] More strikingly, strong birth cohort effects, marked by higher EOCRC incidence in more recent generations, have been consistently observed in North America (U.S., Canada), Oceania (Australia, New Zealand) and some high-income European nations (UK, Norway).[3,8] In the U.S., for example, individuals born around 1990 have twice the risk of developing colon cancer and four times the risk of rectal cancer compared with those born around 1950.[3]

EOCRC represents a growing clinical challenge. In the U.S., EOCRC mortality has risen since the early 2000s,[9] suggesting that the increase in incidence is not solely attributable to greater adoption of screening. Among all EOCRC cases, over 70% are sporadic,[9] occurring in individuals without a known family history or genetic syndrome (e.g., Lynch syndrome, familial adenomatous polyposis (FAP)). Sporadic EOCRC often presents in the distal colon (left-sided) and rectum,[10,11] with more advanced stages at diagnosis[12] and higher risks of recurrence and metastasis.[13] The advanced stages are likely in part due to late patient presentation and lack of awareness of common CRC symptoms from both patients and providers,[14] and/or emerging molecular differences compared to later onset CRC (LOCRC).[15,16] Sporadic EOCRCs are characterized as microsatellite stable (MSS)[15] and CpG island methylator phenotype (CIMP)-low/negative.[17] Compared to LOCRC, relatively few molecular differences have been identified thus far. Notable distinctions include differences in mutational burden,[18] higher prevalence of long-interspersed nucleotide element 1 (LINE-1) hypomethylation, a modest enrichment of microsatellite instability (MSI)-high tumors,[15,16] and a lower prevalence of the CIMP-high, BRAF V600,[19,20] and KRAS mutations.[21] EOCRC lies along a continuous age-related spectrum of colorectal carcinogenesis. The EOCRC designation represents an epidemiologically defined subgroup in which differences in exposure timing, cumulative risk, and clinical presentation are observed on average, rather than a biologically discrete disease entity. However, much of this evidence stems from retrospective, single-institution sequencing studies that are often enriched for advanced-stage disease or missing clinicopathological characteristics, underscoring the need for additional comprehensive molecular profiling using population-based samples.

The major challenge in addressing the burden of EOCRC is to identify the set of causal drivers behind its emergence. While some established and emerging risk factors for CRC, such as obesity,[22,23] metabolic dysfunction,[24-28] poor diet,[29-32] and sedentary behavior,[33] have been linked to EOCRC, it remains unclear whether additional, unidentified exposures may be contributing to and/or accelerating early tumorigenesis. Further complicating this is the uncertainty around the timing, interactions, and mechanisms by which established and emerging risk factors initiate or promote CRC across the life course. Without clearer mechanistic understanding, translating epidemiological insights into actionable EOCRC prevention strategies remains challenging.

In this review, I outline the progress and challenges in identifying risk factors for sporadic EOCRC, highlight emerging opportunities for early diagnosis and prevention, and propose a transdisciplinary framework to move systematically from correlation to causation with an overarching goal of identifying actionable strategies for EOCRC prevention in younger generations. This approach will be advanced through the Project MEPROT: (Mechanisms and Prevention of Early Colorectal Tumours). I also underscore the vital role of patient and public involvement and engagement in guiding these important endeavours.

EOCRC aetiology

Accumulating evidence supports a multifactorial, life-course model for the aetiology of EOCRC, in which multiple exposures seem to accumulate earlier in younger generations rather than a single dominant risk factor. Population-based and modelling studies indicate that rising EOCRC incidence across birth cohorts reflects an increase in underlying risk and accelerated carcinogenesis rather than improved detection alone.[34,35] Epidemiologic data most consistently implicate metabolic dysregulation[28] and diet-related exposures,[36] which appear to exert stronger effects in younger adults, while emerging molecular and experimental studies highlight the gut microbiome as a key mediator linking diet, metabolism, immune regulation, and epithelial biology.[37-40] Early-life microbial perturbations and enrichment of genotoxic bacteria, particularly colibactin-producing Escherichia coli, have been associated with age-specific mutational signatures, stem-cell reprogramming, and altered tumour-immune interactions.[41] These processes likely interact with host susceptibility, epigenetic remodelling, and epithelial plasticity to create a pro-tumorigenic intestinal microenvironment that lowers the age threshold for malignant transformation.[42] Although causal pathways, critical exposure windows, and relative contributions remain incompletely defined, this integrative framework provides a testable basis for coordinated population and mechanistic studies to clarify EOCRC aetiology and inform precision prevention strategies.

Unveiling Risk Factors for EOCRC

Progress in EOCRC risk factor discovery

Substantial efforts to date have focused on identifying risk factors driving the rising incidence of EOCRC, with particular attention to chronic health conditions and lifestyle behaviours, and a growing interest in early-life and gut microbial-related exposures (**Figure 2**).

Obesity, an established CRC risk factor with a typically stronger association in men than women, has drawn particular attention due to its substantial increase throughout the life course globally.[43,44] A meta-analysis of 7 studies indicated that obesity during adolescence or adulthood, defined as BMI ≥30 kg/m², was associated with a 54% increased risk of EOCRC (RR 1.54, 95% CI 1.01-2.35), compared with BMI 18.5-<25 kg/m².[23] In the female-only Nurses' Health Study II (NHSII), such association was stronger for EOCRC compared to LOCRC.[22] Few studies have investigated the impact of weight change from adolescence through adulthood.[22,45] In the NHSII, both BMI at age 18 (≥23 vs. 18.5–20.9 kg/m²; RR 1.63, 95% CI 1.01 -2.61) and subsequent weight gain through mid-adulthood (RR per 5 kg: 1.09, 1.02-1.16) were associated with EOCRC risk.[22] Despite these findings, epidemiologic and mechanistic studies remain limited regarding how early-life and/or intergenerational obesity[46-48] may contribute to EOCRC. Although obesity is an established risk factor for colorectal cancer, it is unlikely to be a sufficient explanation for the contrasting incidence patterns observed across age groups. The rising burden of EOCRC alongside declining LOCRC[2] despite higher obesity prevalence in

older adults suggests that additional factors, including exposure timing, early-life influences, and interacting metabolic, microbial, and environmental processes, contribute to EOCRC risk.

Metabolic dysregulation, indicated by type 2 diabetes (T2DM), metabolic syndrome, and metabolic dysfunction-associated steatosis liver disease (MASLD, previously termed non-alcoholic fatty liver disease [NAFLD]), are increasingly linked with EOCRC.[28] T2DM is rising rapidly in western high-income countries, affecting 4.8% of U.S. adults aged 18-44 between 2017-2020.[49] Early onset T2DM tends to be more aggressive, with earlier complications, poorer outcomes,[50] and lower rates of glycaemic, lipid, and blood pressure control. A meta-analysis of 12 studies found that T2DM was associated with 43% increased risk of EOCRC (OR 1.43, 95% CI: 1.08-1.80),[25] driven by unmanaged (OR 1.28, 1.02-1.60) but not managed T2DM.[26,27] In addition, metabolic comorbidities show a dose-dependent link with EOCRC risk. In a U.S. claims-based study, having 1, 2, or ≥3 conditions (obesity, hypertension, hyperlipidaemia, hyperglycaemia/T2DM) was associated with 9%, 12%, and 31% higher risk (P_{trend}<0.001), mainly for proximal and distal colon cancer.[24] Epidemiologic evidence linking MASLD and risk of EOCRC are also emerging.[51,52] Consistent with consensus molecular subtypes (CMS) data, the metabolically dysregulated CMS3 subtype is more common in EOCRC versus LOCRC.[20] Overall, converging data support the contribution of metabolic dysregulation to rising EOCRC and a targetable subgroup for precision prevention, but modest effect sizes call for mechanistic studies to refine risk stratification.

Diet is the most studied lifestyle factor in EOCRC. In the U.S., overall diet quality is worse in younger adults than in older adults,[53] with more than half of American youth consuming poor-quality diets.[54] In the NHS II, adherence to a Western dietary pattern was associated with an increased risk of early onset colorectal adenomas, whereas prudent dietary patterns as well as recommendation-based indexes (Dietary Approaches to Stop Hypertension [DASH], Alternate Mediterranean Diet [AMED], and Alternative Healthy Eating Index [AHEI]-2010) were associated with reduced risk, particularly for high-risk lesions of malignant potential in the distal colon and rectum.[29] In contrast, these associations, particularly for recommendation-based indexes, were weaker for LOCRC,[55,56] suggesting a potentially stronger influence of diet on EOCRC. Subsequent studies on specific components, such as red meat[57] and alcohol intake,[32,57] further support diet's role. Notably, the empirical dietary and lifestyle index for hyperinsulinemia (ELIH), a score reflecting hyperinsulinemia dietary and lifestyle patterns, appeared to be a stronger risk factor for EOCRC than LOCRC, further underscoring the role of metabolic dysregulation in EOCRC.[58]

Several critical knowledge gaps remain, including sparse evidence on how dietary exposures during critical developmental windows influence EOCRC risk, and limited assessment of dietary patterns prevalent among adolescents and young adults. One understudied exposure is sugar-sweetened beverages (SSBs), the primary source of added sugar in the U.S. diet. From 1977 to 2021, daily caloric intake from SSBs more than doubled among young individuals, peaking in 2-18 years (2.6 servings/day).[59] Murine studies showed high-fructose corn syrup accelerates intestinal tumour growth independent of obesity.[60,61] Epidemiologic data from NHSII support this, with ≥2 daily servings of SSBs doubling EOCRC risk (RR 2.18, 1.10-4.35) versus <1 serving. In addition, each additional daily serving during adolescence raised risk by 32% (RR 1.32, 1.00-1.75), independent of adulthood intake and major dietary risk factors.[31] Another example is "drunkorexia," the intentional restriction of food before alcohol consumption, increasingly common among young Western adults, especially women, with prevalence nearing 40%.[62] A prospective analysis from the UK Biobank reported a positive association between alcohol consumption without meals and risk of early onset gastrointestinal cancers, independent of total alcohol intake.[63] Looking ahead, innovative and rigorous longitudinal assessments of emerging dietary patterns, such as high intake of ultra-processed foods[64,65] and sulphur microbial diets, which favour the growth of genotoxic hydrogen sulphide-producing microbes,[30] and chrono nutrition which capture effects of meal timing,[66] will clarify how these exposures influence intestinal homeostasis,[67] interact with other risk factors, and drive colorectal tumorigenesis in younger populations.

For physical activity, despite overall improvements, many adolescents and young adults still fall short of recommendations,[68] while sedentary behaviour in this group continues to rise substantially. In the U.S., estimated total sitting time increased from 7.0 to 8.2 h/d among adolescents and from 5.5 to 6.4 h/d among adults during 2007-2016.[69] In the NHSII, individuals reporting over 14 hours of TV viewing per week had a 69% higher risk of EOCRC (RR 1.69, 95% CI 1.07-2.67), primarily from rectal cancer, compared to those watching less than 7 hours.[33] While some effects may be mediated by poor diet and low vitamin D, prolonged, uninterrupted sitting, may increase risk via gut dysbiosis,[70,71] impaired glucose regulation,[72] and extended exposure to faecal carcinogen, such as secondary bile acids.[73,74]

With growing recognition of the gut microbiome's role in CRC,[75,76] interest has surged in how microbial-related exposures contribute to EOCRC risk, especially given rising microbial dysregulation linked to urbanization and Westernized lifestyle.[77] Yet, prospective cohorts rarely capture microbial-related exposures across the life course. Antibiotic use, a known disruptor of gut microbial balance,[78] has been an initial focus. While studies reported links between prolonged antibiotic exposure with adenoma risk[79] and in-utero exposure to long-acting sulphonamides with CRC risk,[80] most have not shown consistent associations between adulthood antibiotic use and EOCRC risk.[78,81,82] Another area of interest is caesarean delivery, which may impair early microbial colonization and immune development during critical windows.[83,84] A Swedish nationwide cohort analysis found that compared to vaginal birth, birth through caesarean delivery was associated with risk of EOCRC in females (OR 1.62, 95% CI 1.01-2.60), not in males,[85] suggesting possible sex-specific mechanisms that require further investigations.[86] Finally, longstanding evidence highlighted the role of genotoxic gut microbes, notably *E. coli* strains harbouring the *pks* island that produce colibactin, a compound capable of inducing DNA damage,[87] in CRC development.[88,89] Among 97 EOCRC and 705 LOCRC microsatellite-stable cases, colibactin-associated signatures SBS88 and ID18 were enriched in EOCRC (SBS88: 26% vs. 12%; ID18: 41% vs. 16%) and in countries with higher CRC incidence.[41] Further, colibactin exposure was linked to APC driver mutations, suggesting that mutagenic exposure to colibactin-producing bacteria in early life may contribute to EOCRC.[41] However, causal relationships, the influence of host and lifestyle factors, effects on the tumour microenvironment, and critical exposure timing remain to be elucidated.

With respect to protective factors, several factors or agents established for CRC prevention, such as vitamin D,[90,91] aspirin,[92] and other nonsteroidal anti-inflammatory drugs[57] have shown promise for EOCRC. However, clinical trials to date have not focused on EOCRC or its precursors as primary endpoints, and younger adults remain underrepresented in existing trials. Efficiently designing and evaluating prevention strategies in this population is critical to advancing age-appropriate prevention strategies.

Emerging exposures, mechanisms, and challenges

Beyond risk factors discussed above, increasing attention is focused on environmental exposures such as air pollution,[93,94] environmental pollutants such as microplastics,[95] endocrine disrupting chemicals such as bisphenol A (BPA),[96] and more broadly the exposome, which "encompasses life course environmental exposures (including lifestyle factors), from the prenatal period onwards".[97,98] These exposures, along with risk factors discussed previously, are increasingly implicated in colorectal carcinogenesis through several converging biological pathways, including metabolic reprogramming, persistent low-grade inflammation, and gut microbiome dysbiosis.[99] These alterations can impair intestinal barrier integrity and immune surveillance, promoting microbial translocation[100] and sustained mucosal immune activation. The gut microbiome may also modulate the biological activity of these exposures through microbial biotransformation, converting compounds into more genotoxic metabolites that enhance carcinogenic potential.[101] Yet, much of the gut microbial metabolic landscape, particularly in early life, remains poorly characterized.[102] Emerging data also point to epigenetic reprogramming, via DNA methylation and histone modifications, as a mechanism linking early-life exposures to long-term gene expression changes relevant to cancer risk.[103] Ultimately, a unifying hypothesis for EOCRC centres on the idea that early-life and cumulative exposures disrupt gut and immune homeostasis. These disruptions, likely further exacerbated by obesity and insulin resistance, can create a pro-tumorigenic microenvironment that accelerates the initiation and progression of CRC at younger ages (**Figure 2**).

While evolution-based frameworks like tumour 'age',[104] which estimates "the time (months or years) elapsed from the common ancestor cancer cell to invasion or the formation of distant metastases," may help illuminate EOCRC biology, overcoming key challenges in risk factor discovery remains foundational (**Box 1**). First, most existing epidemiologic cohorts followed individuals since mid-adulthood, and were not designed to capture early-life windows of vulnerability or track individual, long-term, low-dose environmental exposures. While establishing new cohorts is ideal, a more immediate and cost-effective strategy is to harmonize and integrate existing datasets through a prospective, life course lens. Second, although the exposome is a powerful concept, reliably capturing it remains methodologically challenging. Advances in profiling now allow measurement of the internal exposome, such as thousands of metabolites and chemical exposures, yet linking these to external exposures and identifying functional biomarkers remains a major challenge. Third, even if feasible, the optimal causal inference relies on pre-diagnostic, often repeated biospecimens, which are scarce in many cohorts. Third, progress also depends on better integration with mechanistic research, as current models rarely reflect cumulative or multi-generational effects of real-world exposures. Ultimately, advancing precision prevention of EOCRC will depend on a unified framework that integrates population, mechanistic, behavioural, and implementation sciences, anchored in robust causal inference, to distil the broad exposome into actionable prevention strategies (**Figure 2 and Figure 3**).

Early detection and prevention

EOCRC is more often diagnosed at advanced stages, largely due to the absence of routine screening in younger adults, limited awareness among patients and providers, delays in recognizing symptoms often mistaken for benign conditions, and possibly more aggressive tumour biology. In the U.S., the rising incidence of EOCRC in 2010-2019 is driven by 3% annual increase in regional and distant-stage diagnoses, while localized-stage diagnoses declined by 1% annually.[105] From 2015 to 2019, 27% of EOCRC cases had distant metastases, compared to 19% among those aged 65 and older.[105] As a result, early detection, through both timely diagnosis and screening, and primary prevention of EOCRC are urgent needs.

Early diagnosis

The majority of EOCRC cases are diagnosed based on symptoms, making the linkage between patient-reported signs and timely diagnosis a critical opportunity to improve outcomes. A meta-analysis of 78 studies reported the most common symptoms at diagnosis were haematochezia (45%), abdominal pain (40%), and bowel habit changes (27%).[14] While most studies focus on symptoms at diagnosis, a U.S. claims-based study of >5.000 EOCRC cases highlights the promise of detecting these red-flag signs earlier. Between 3 and 24 months before diagnosis, four signs and symptoms (abdominal pain, rectal bleeding, diarrhoea, and iron deficiency anaemia) were associated with elevated EOCRC risk (ORs: 1.3-5.1), with risk rising sharply as symptom count increased.[106]

While these findings highlight the promise of symptom-based triage tools, their impact depends on more than awareness—raising it among patients and providers is only a first step. On the patient side, studies from US and European countries suggests that structural and psychosocial barriers further hinder early detection, including difficulty interpreting gastrointestinal symptoms, embarrassment or fear of diagnosis, denial of symptoms, delayed care-seeking, declining engagement with primary care, especially among younger, commercially insured adults.[107-109] On the provider side, competing demands, inexperience with EOCRC and the perception of low EOCRC risk frequently result in missed or delayed workups.[108,110] Similar challenges have also been documented globally, although their manifestation varies depending on health system structure and cultural context. To shift diagnosis to earlier stages, practical and structured workflows that can rapidly flag and act on potential warning signs in younger patients are urgently needed.

Screening

CRC screening programs remain out of step with the shifting epidemiology of CRC.[111] The majority of countries with high burden of EOCRC begin screening at age 50 or later (**Table 1**). Even in countries like the U.S., where the United States Preventive Services Task Force (USPSTF) recently lowered the starting age to 45 in 2021,[112] over half of EOCRC cases are still diagnosed before that age.[105] Screening uptake remains suboptimal globally, especially among younger adults. For instance, in the U.S., only 63% of adults aged 50-64 are screened, compared to 79% of those over 65.

Low screening uptake among younger adults stems from perceived low risk, stigma or embarrassment around the procedure, competing work and caregiving demands, limited primary care engagement and access to gastroenterologists.[110,113,114] Overcoming these barriers requires a shift toward strategies that are not only clinically effective but also acceptable, accessible, and scalable for younger populations. Screening modality also plays a central role. In the U.S., colonoscopy remains the dominant screening method, with faecal immunochemical test (FIT) offered as a non-invasive alternative for those unable or unwilling to undergo the procedure.[112] Colonoscopy detects and removes precancerous lesions but its invasiveness and time demands deter younger, working-age adults,[115] and its scalability as a population-wide screening method at younger ages remains uncertain.[116] In contrast, many European, Asian, and middle-income countries use a "FIT-first" approach, reserving colonoscopy for positive non-invasive tests.[111] This strategy facilitates broader population reach but is limited by FIT's lower sensitivity for advanced adenomas and right-sided lesions.[117] Several novel, non-invasive alternatives, including multi-target stool DNA test (mt-sDNA-FIT)[118] and RNA test (mt-sRNA-FIT),[119] and blood-based assays detecting cell-free DNA (cf-bDNA),[120,121] demonstrate improved sensitivity (80-90%) for cancer over FIT (~70%) in ongoing trials, but with modestly reduced specificity (~90% vs ~95%).[117] Their effectiveness in average-risk younger populations remains uncertain, and high costs may limit widespread implementation (**Table 1**). Innovation must extend beyond test development to new delivery models, that is, how screening is offered and evaluated. For example, integrating screening in workplaces[122] and pairing low-burden tests with tailored outreach may improve access and equity in EOCRC screening.

Primary prevention

Primary prevention of EOCRC remains in its early stages and likely holds most promise by targeting well-established CRC[123] and EOCRC risk factors to promote behavioural changes with broad benefits across age groups. Key targets may include but not limited to obesity prevention, diet improvement such as limiting red/processed meats and sugar-sweetened beverages and increasing fibre intake, and promoting physical activity while reducing sedentary behaviour. However, implementing effective interventions has proven difficult. For example, large nutritional intervention trials in CRC prevention have shown limited benefit, often due to poor adherence and modest dietary changes.[124] Greater mechanistic insight into the role of specific nutrients, along with precision prevention strategies that leverage supplements and account for tumour–host interactions, are needed to advance the field.[125]

Primary prevention may also include molecular prevention and immunoprevention. Agents like aspirin, metformin, statins, glucagon-like peptide-1 receptor agonists, and inhibitors of sodium-glucose linked transporters inhibitors have shown potential to reduce CRC risk by targeting inflammation and metabolic pathways.[126-129] Among them, aspirin is the most promising, particularly for preventing formation and progression of precursors like colorectal adenomas.[126] However, current trials lack a focus on EOCRC prevention. Additionally, given the growing recognition of the immune system's role in CRC, novel approaches targeting immune-modulatory pathways are being explored. Immunoprevention by cancer vaccines stimulates the host immune system against tumour cells and promote elimination, a process in which the immune system detects and eliminates growing tumour cells. Several vaccines for CRC prevention have been developed which mostly target tumour-associated antigens including MUC1 antigen vaccines.[130,131] However, to date, the available vaccines are in phase I and II trials mostly targeting high-risk populations such as those with Lynch syndrome and familial adenomatous polyposis. Therefore, further research is needed to advance molecular and immunoprevention strategies specifically targeting sporadic EOCRC and younger populations of average-risk.

Unique challenges to engage younger adults for EOCRC prevention

An individual's ability to engage in prevention is influenced by factors across multiple levels of influence, including at the personal, interpersonal, organizational, community, and societal levels. To be maximally effective, prevention programs must target several levels simultaneously. A further challenge for individual-level interventions is recognizing that behaviour change occurs in non-linear stages, requiring different strategies as individuals progress from awareness to sustained behaviour change (**Figure 3**), and moving through each of these stages requires different types of interventions.[132,133]

Another key challenge to EOCRC prevention is that most CRC prevention interventions have focused on increasing CRC screening among individuals aged 50 and older,[134] with comparatively little emphasis on communicating about CRC risk, risk factors, and lifestyle-based prevention strategies among people younger than 50. This makes these interventions unsuitable for younger individuals. In addition, the scant research on young adults suggests that they often have limited awareness of CRC risk factors including genetic, lifestyle, environmental, and social ones,[135] do not typically see themselves as at-risk of developing CRC, and are either unsure of how to prevent CRC risk or are sceptical of lifestyle behaviours reducing CRC risk. Thus, it is reasonable to expect that most younger adults are still in the first two phases of behaviour change (i.e., unaware or unengaged, **Figure 3**), and therefore initial individual-level interventions for younger adults must aim towards increasing awareness and convincing them that, not only are they at risk of developing EOCRC, but they need to act to reduce their risk.

Despite these challenges, it is possible to make recommendations about general strategies for designing effective interventions for engaging younger adults in CRC prevention activities. Most critically, intervention developers should leverage community-engaged research practices that allow the intended audience to fully participate in the creation, testing, refinement, and dissemination of the intervention.[136] This increases the likelihood that the intervention participants will view the resulting intervention as personally relevant, culturally meaningful and appropriate, and practically useful.[137] Community-engaged research practices can also be useful for ensuring that intervention materials and procedures are accessible to people with limited literacy, limited health literacy, or who may not be fluent in the local language.

Another strategy for designing effective interventions involves matching intervention content to the characteristics of the participant; this is known as tailoring intervention content.[138] While evidence is limited on whether tailoring effectiveness varies by age,[138] inclusion of personalized cancer risk assessment tools might be promising.[139] Such tools use information about an individual's health history to calculate an estimate of the likelihood that they will develop CRC in the future,[140,141] and then communicate that information to either the individual or healthcare provider. There are many resources that provide practical guidance for communicating personalized risk estimates most effectively.[142,143] Encouragingly, personalized risk assessment tools can be valuable for calibrating people's perception of their personal risk, including their personal risk of CRC.[144] Because younger adults often have limited contact with traditional healthcare systems, effective prevention and

risk communication strategies will require digitally native, age-appropriate approaches. Short-form digital media may offer opportunities to deliver evidence-based messages on the EOCRC risk and prevention to younger populations.[145,146]

However, providing risk information alone is not sufficient to promote beneficial changes in lifestyle behaviors.[147] Instead, risk assessment tools must be treated as one component of a multilevel cancer prevention intervention that provides support across each of the phases of behaviour change and targets multiple levels of influence. Integrating the tools into typical clinical workflow and integrating messaging related to CRC prevention alongside other chronic disease prevention initiatives may be particularly efficient and effective.[148] It might also be worthwhile to integrate risk assessment tools into interventions that target multiple health behaviours simultaneously[149] and that target multiple aspects of behaviour change.

Finally, because there are so few interventions that are designed specifically to reducing CRC risk among younger adults, it might be beneficial to approach intervention development from an adaptation perspective. That is, begin with CRC prevention interventions that have demonstrated efficacy in older populations[134,150] and, through community-engaged practices, adapt them for younger adults. Another approach would be to identify lifestyle interventions that have demonstrated efficacy in younger adults like those for cardiovascular disease prevention,[151] and adapt them for the CRC context (**Box 2**). These efforts would be towards utilizing an evidence-based public health approach to inform efficient and effective policy development through the implementation of proven adapted interventions.

Patient and public involvement and engagement

Over recent decades, patient and public involvement and engagement (PPIE)[152] has transformed cancer research by embedding patients and the public as partners in health and social care research. Scientific societies such as the *American Association for Cancer Research (AACR)* and *European Association for Cancer Research (EACR)* have embraced advocacy by incorporating programming that connects researchers with patients and survivors. For instance, the *AACR's Scientist↔Survivor Program*®, launched in 1999, fosters partnerships to promote the exchange of information on key aspects of cancer research, survivorship, advocacy and public policy. The American Cancer Society (ACS), through its advocacy affiliate, ACS Cancer Action Network℠ (ACS CAN), engages with policymakers to ensure that cancer remains a top local, state, and national priority. However, advocacy and engagement around cancer prevention remain limited relative to treatment-focused initiatives.

To address the rising burden of EOCRC, CRC-focused patient advocacy organizations have launched targeted initiatives globally. In the U.S., Fight Colorectal Cancer's Global Early Onset Colorectal Cancer Workgroup brings together international researchers and advocates to explore underlying drivers and solutions, and the Colorectal Cancer Alliance's series of Never Too Young Survey Report elevates the voices and needs of EOCRC patients and caregivers. In the UK, Bowel Cancer UK's Never Too Young campaign has raised awareness in younger adults, advocated for early identification, and helped drive policy changes to improve early diagnosis and care.

Yet there remains a critical need to systematically integrate patient perspectives earlier in the research process—when questions and priorities are defined—as emphasized by the Cancer Grand Challenges interdisciplinary initiative described below. Doing so will help ensure research efforts are relevant, impactful, and trusted. At the same time, public discourse often highlights the urgency of EOCRC while overlooking the complexity and time required for risk factor discovery. Researchers must more effectively communicate both the significance and limitations of emerging evidence.[153]

First steps toward shaping our future

A transdisciplinary framework for next-generation cancer prevention

Reversing the global rise of EOCRC demands more than incremental progress—it calls for a collective, transdisciplinary response. I present a framework that provides the blueprint for next-generation EOCRC research and prevention, uniting population, mechanistic, behavioural, and implementation sciences (**Figures 2 and 3**). This framework advances cancer prevention science by creating a living, iterative system: population studies reveal emerging risk factor, mechanistic models uncover causality, behavioural research pinpoints leverage points, and implementation science delivers scalable solutions. Together, these elements form a powerful engine that accelerates the transition from correlation to causation and transforms discoveries into precision prevention strategies. By coupling the scale of epidemiology with the mechanistic precision of experimental models[154], this framework delivers biologically grounded, globally relevant insights and sets the stage for a new era of life-course cancer prevention. I call on epidemiologists, cancer biologists, behavioural researchers, clinicians, data scientists, and implementation experts to leverage this generational opportunity to transform the trajectory of EOCRC and other cancers with rising incidence among the younger population and deliver a future where prevention begins earlier, is more precise, and spares generations to come.

Project MEPROT

To accelerate risk factor discovery, I established Project MEPROT (Mechanisms and Prevention of Early Colorectal Tumours) in American Northwest University School of Medicine. Project MEPROT's vision is to unravel and ultimately reverse the intricate network of causal factors across the life course that disrupt biological homeostasis, thereby promoting CRC in young adults. Building on the previously discussed transdisciplinary framework, Project MEPROT applies a three-stage conceptual model to systematically advance correlation to causation for EOCRC prevention (**Figure 4**). The foundational stage identifies emerging and novel life-course risk factors. The pillar stage interrogates causal mechanisms and maps biochemical and molecular networks linking these factors to EOCRC. At the apex, these insights are translated into precision and community-based prevention trials designed to deliver near-term benefit to younger generations.

Project MEPROT exemplifies our vision of a transdisciplinary framework integrating global cohorts, mechanistic modelling, and intervention trials to systematically advance EOCRC prevention. Anchored in the foundation–pillar–apex model, Project MEPROT links life-course risk factor discovery with mechanistic dissection of causal pathways and translation into precision and community-based interventions. We hope that Project MEPROT serves as a prototype for how the field can accelerate progress to reverse the rising tide of EOCRC.

Conclusions

EOCRC presents a growing global challenge in cancer prevention and control. A transdisciplinary framework integrating population, mechanistic, behavioural, and implementation sciences is needed to accelerate EOCRC risk factor discovery, with an overarching goal to rapidly informing efforts to reverse the rising burden of EOCRC. It is imperative that scientists, the public, and policymakers join forces to transform knowledge into life-saving solutions that will protect future generations.

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Key points

- EOCRC incidence is rising globally, with distinct geographic, birth cohort, anatomical, and sex-specific patterns.
- Identified EOCRC risk factors have primarily centered on metabolic dysregulation, poor diet, and sedentary behaviour, with emerging evidence implicating the roles of early-life or microbial-related exposures.
- Major gaps remain in understanding risk factors across the life course and the mechanisms by which they interact to accelerate CRC development at much younger ages.
- This article presents a transdisciplinary, integrative framework, bridging population, mechanistic, behavioural, and implementation sciences, to advance from correlation to causation and enable actionable prevention strategies.
- A significant portion of EOCRC cases occur before the recommended screening age, underscoring the urgent need to raise awareness, enhance early detection, and advance precision-based primary prevention strategies.
- The integration of patient perspectives and public engagement is critical to advancing these initiatives, which must be supported by timely, collaborative efforts across scientific, policy, and societal spheres.

Glossary terms

- Age-standardized incidence rate (ASIR) – A population-based measure of cancer incidence adjusted for age distribution.
- Birth cohort effect – Epidemiological phenomenon where individuals born in the same time period share risk exposures, leading to distinct disease patterns.
- CIMP (CpG island methylator phenotype) – An epigenetic subtype of cancer defined by widespread promoter methylation.
- Colibactin – A genotoxin produced by certain human gut *E. coli* strains (*pks*$^{+}$) implicated in CRC initiation.
- Effect size – A quantitative measure of the strength or magnitude of an association in epidemiology, such as odds ratios or relative risks.
- EOCRC (Early onset colorectal cancer) – Commonly defined as colorectal cancer diagnosed before the age of 50.
- Exposome – The totality of environmental exposures (non-genetic factors) experienced by an individual across their lifetime.
- Exposomics – The comprehensive, untargeted measurement of the totality of environmental exposures (such as chemicals, diet, pollutants, and microbial metabolites).
- Haematochezia – The presence of fresh blood per rectum, typically indicating lower gastrointestinal bleeding.
- LOCRC (Later onset colorectal cancer) – Commonly defined as colorectal cancer diagnosed after the age of 50.
- MASLD (Metabolic dysfunction–associated steatosis liver disease) – A 2023 redefinition of non-alcoholic fatty liver disease (NAFLD), characterized by hepatic steatosis plus at least one cardiometabolic risk factor, emphasizing metabolic dysfunction rather than exclusion of alcohol use.
- MSI-H (Microsatellite instability-high) – A hypermutable phenotype due to impaired DNA mismatch repair.
- MSS (Microsatellite stable) – Tumours without microsatellite instability.
- Mutational signature (e.g., SBS88, ID18) – A characteristic patterns of somatic mutations imprinted by specific exogenous carcinogens or mutagens.
- Non-targeted analysis of small molecules – the combination of unbiased metabolomics, lipidomics, and exposomics.
- Patient advocates – Individuals faced a cancer diagnosis, had a friend or loved one affected by cancer, and/or have cared for a cancer patient.
- Patient and public involvement and engagement (PPIE) – Involvement is when patient advocates use their experiences of cancer to help shape research. Engagement is where information and knowledge about research is shared by researchers or patient advocates with other patient advocates and the public who are not associated with their research program.
- Prudent dietary patterns – A diet characterized by higher intake of fruits, vegetables, whole grains, legumes, poultry, and fish, often reflecting overall healthier eating habits.

Table 1 | **EOCRC burden, CRC screening programs and uptake in countries (top 10) with the most rapid increase and highest incidence.**

Country	Continent	Income	AAPC*		ASIR*		Screening+			
			%	Rank	per 100 000 person-years	Rank	Start Age	Modality	Interval (yr)	Uptake (%)
New Zealand	Oceania	High	3.97	1	14.8	2	58	FIT	2	NA
Chile	South America	High	3.96	2	10.7		50	FIT	1	NA
UK - England	Europe	High	3.59	3	11.4		60	gFOBT	2	54.9
Norway	Europe	High	3.52	4	13.3	7	55	FIT	2	NA
Belarus	Europe	Upper-middle	3.24	5	8.9		NA	NA	NA	NA
Australia	Oceania	High	3.01	6	16.5	1	50	FIT	2	42.4
Japan	Asia	High	2.94	7	13.5	5	40	FIT	1	11
Argentina	South America	Upper-middle	2.92	8	11.6		50	FIT	1	<20
Canada	North America	High	2.83	9	13.5	6	50	FIT	2	NA
Thailand	Asia	Upper-middle	2.76	10	7.6		50	FIT	2	NA
U.S.	North America	High	2.13 Puerto Rico: 3.81		14.8 Puerto Rico: 15.2	3	45	FIT/ gFOBT/ colonoscopy	1 to 10	63% (age 50-64) 79% (age 65-75)
Republic of Korea	Asia	High	-0.45 (non-significant)		14.3	4	50	FIT	1	29.3
Netherlands	Europe	High	1.77		12.1	8	55	FIT	2	64.5
Iceland	Europe	High	7.33 (non-significant)		12	9	60	FIT	2	NA
Croatia	Europe	High	1.38		11.9	10	50	gFOBT	2	15.3

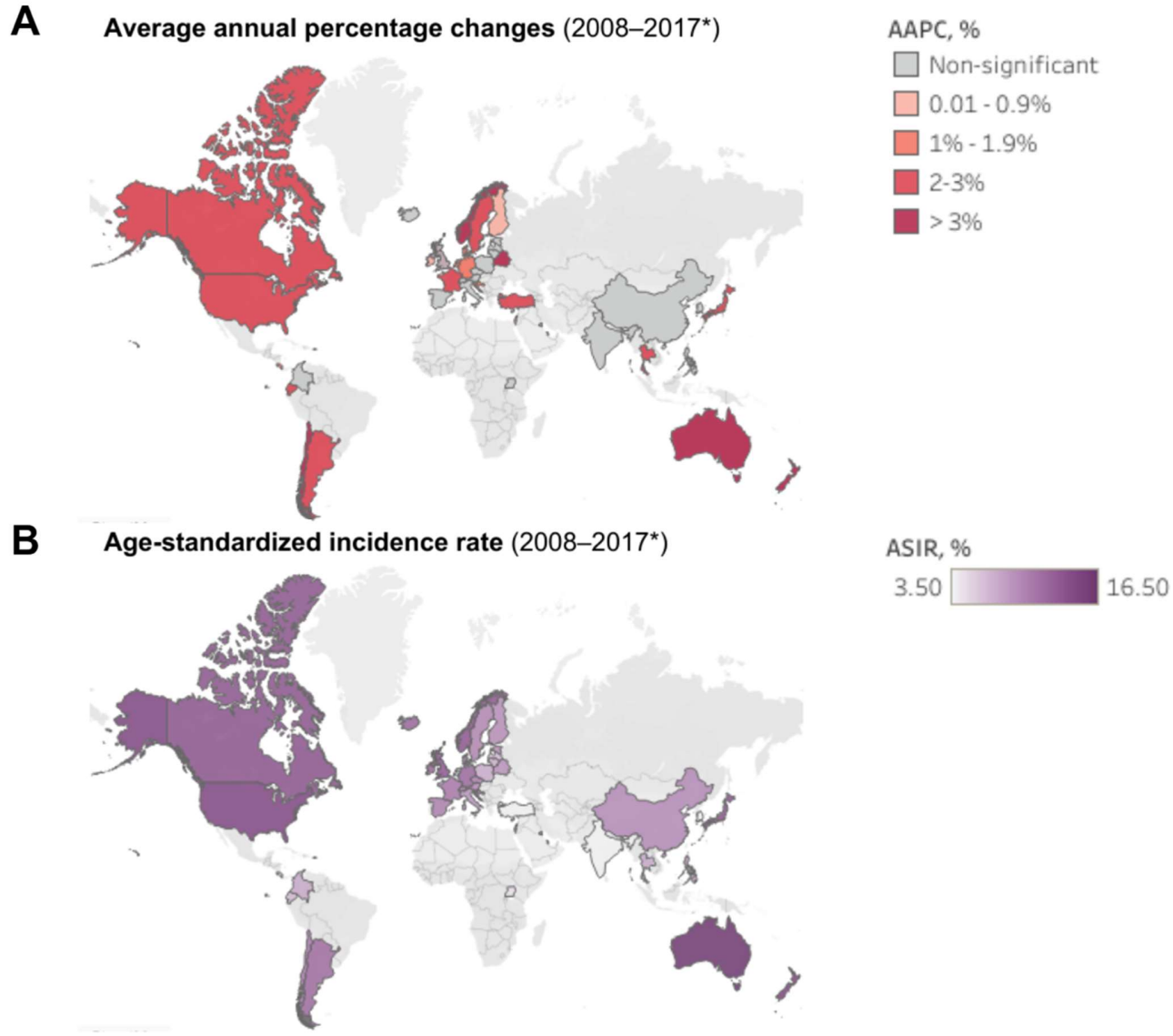
In most countries, screening eligibility begins after age 50, thereby missing a substantial proportion of EOCRC cases, which continue to rise in incidence. Even where screening is available, screening uptake is suboptimal. Income categories are classified according to the World Bank. Cells marked NA indicate data not available in published literature or public sources.

*AAPC and ASIR for EOCRC were estimated during 2008-2017 using the WHO–International Agency for Research on Cancer Incidence in Five Continents Plus database, as reported by Sung et al. (Lancet Oncol, 2025).

+ Screening information were reported in CanScreen5, except Iceland,[183] New Zealand,[184] Norway,[185] Belarus,[186] Argentina,[187] and U.S..[112]

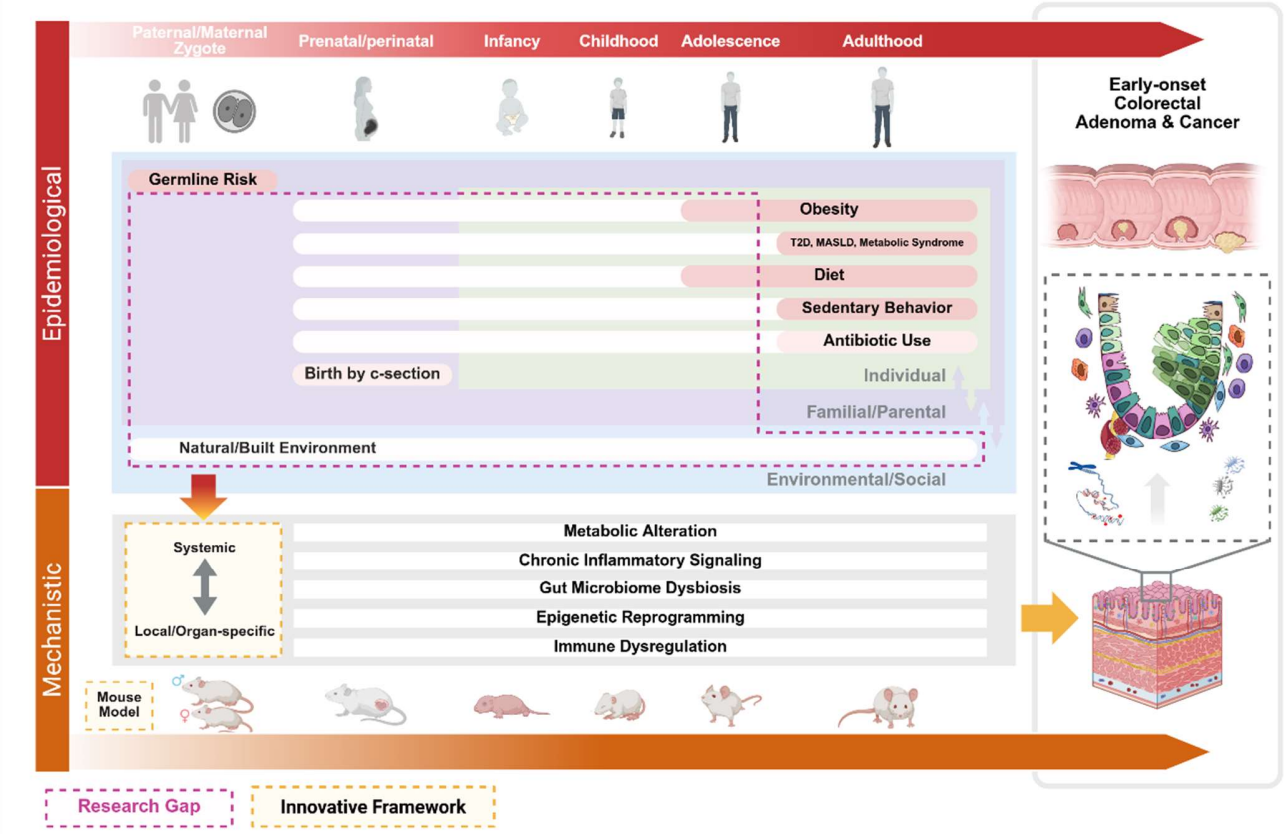
Abbreviations: AAPC, average annual percent change; ASIR, age-standardized incidence rate; gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test.

Figure 1 **Global trends in EOCRC: temporal changes and incidence rates.**



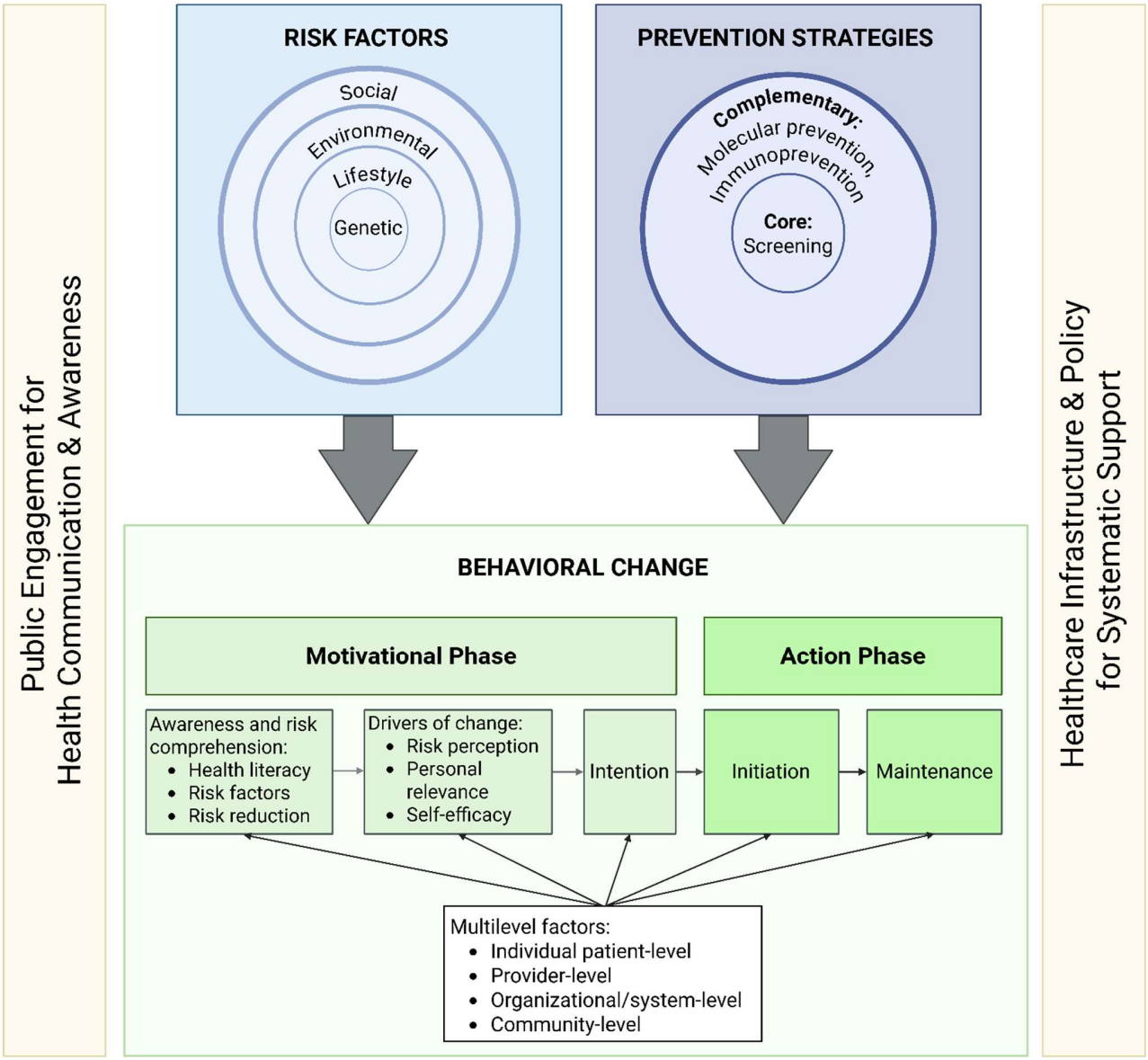
Global patterns of EOCRC incidence are illustrated using (A) average annual percentage change (AAPC) and (B) age-standardized incidence rates (ASIR) per 100,000 person-years across 2008-2017. Countries/territories shaded in darker red experienced the most rapid increases in EOCRC incidence (AAPC >3%), with notable trends observed in Australia, U.S., and several Northern and Western European countries. Concurrently, the highest ASIR were concentrated in Australia, New Zealand, and North America.

Figure 2 **EOCRC life-course causal risk factor discovery: integrating epidemiologic and mechanistic insights across the cancer continuum**



This figure depicts the first two components of the proposed transdisciplinary framework, highlighting how EOCRC risk emerges from cumulative interactions between genetic susceptibility and environmental exposures across the life course. Critical windows — from preconception through adulthood — represent opportunities for exposures to shape risk trajectories. Individual-level (green), familial/parental-level (purple), and environmental/social-level (blue) factors may converge to disrupt intestinal homeostasis through processes such as metabolic alteration, chronic inflammation, gut microbiome dysbiosis, epigenetic reprogramming, and immune dysregulation. Integrating epidemiologic evidence with mechanistic models enables identification of these pathways and accelerates discovery of causal risk factors across the cancer continuum. Bar lengths represent the life-stage span of exposure, with red highlighting periods supported by current evidence (darker intensity indicates stronger evidence). Pink dashed box circled the main research gaps on risk factors, including early-life exposures (zygote to adolescence) and environmental/social exposures. By integrating human epidemiologic data with mechanistic models in animals across life stages and cancer development, this framework provides a comprehensive approach to disentangle the temporal and biological underpinnings of EOCRC risk.

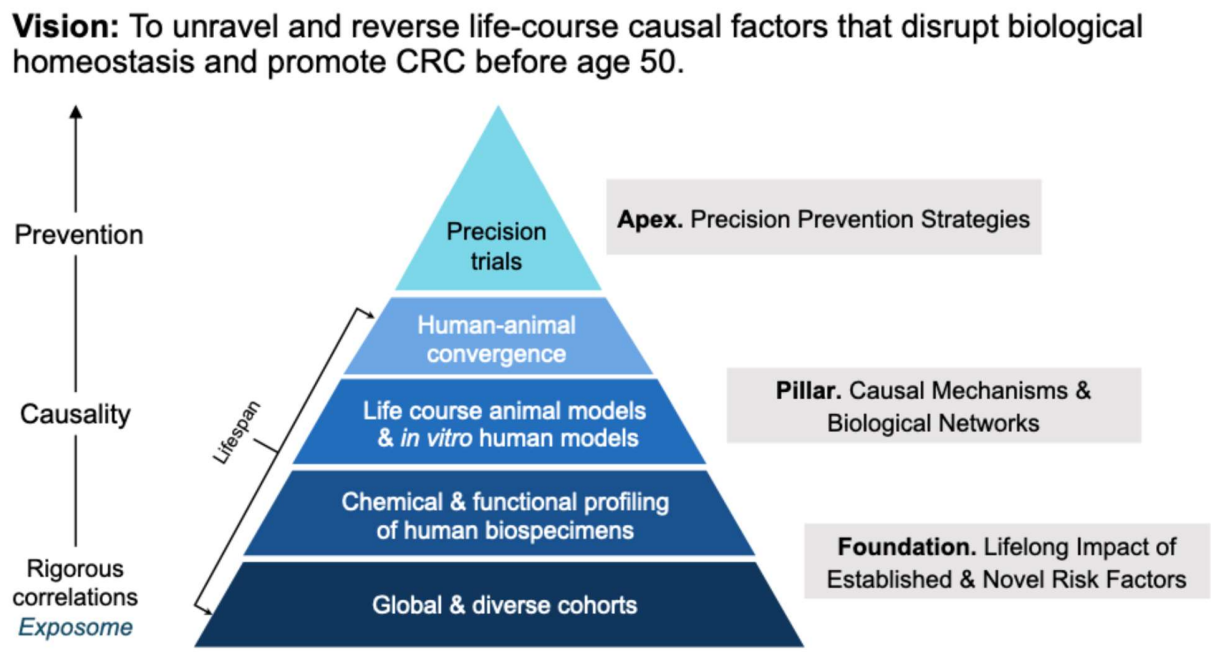
Figure 3 **EOCRC prevention: translating causal insights into behavioural change and implementation**



This figure illustrates the final components of the transdisciplinary framework, showing how identified risk factors like genetic, lifestyle, environmental, and social, can be integrated with prevention strategies to drive effective behavioural change. Screening remains the core strategy, complemented by emerging approaches such as molecular prevention and immunoprevention. Behavioural change is conceptualized in two phases: the *motivational phase*, where awareness of EOCRC risk factors, health literacy, and risk reduction strategies foster intention formation influenced by risk perception, personal relevance, and self-efficacy; and the *action phase*, which emphasizes initiating and sustaining preventive behaviours. These behaviours are shaped by multilevel determinants, including individual, provider, organizational, and community factors, supported by health communication, education, and enabling healthcare systems and policies. Together, these components

demonstrate how insights from population and mechanistic studies can be translated through behavioural and implementation sciences into comprehensive, multilevel interventions to prevent EOCRC in younger adults.

Figure 4 Project MEPROT**'s vision, conceptual model, and approach: advancing correlation to causation for actionable EOCRC prevention strategies.**



Project MEPROT operationalizes the proposed transdisciplinary framework, integrating population, mechanistic, behavioural, and implementation sciences to accelerate the transition from correlation to causation. The project's vision unfolds through a three-stage conceptual model ascending the causal pyramid: **foundation**, which maps the lifelong impact of established and novel risk factors using global cohorts; **pillar**, which investigates causal mechanisms and biological networks through advanced chemical and functional profiling of human biospecimens, innovative life-course animal models, in vitro human models, and comparative human–animal convergence studies; and **apex**, which applies these mechanistic insights to design and conduct precision and community-based prevention trials globally. Together, these stages exemplify how Project MEPROT seeks to generate biologically grounded, globally relevant, and actionable strategies to prevent EOCRC and engage younger populations in cancer prevention.

Box 1 Challenges and gaps in EOCRC risk factor discovery

- Gaps in exposure assessment: Most existing epidemiologic cohorts begin in mid-adulthood and are not designed to capture exposures during critical developmental periods or to monitor individual-level environmental exposures over time.
- From exposome to risk factors: Accurately measuring the full range of exposures across the life span remains methodologically complex and infeasible. Technological advances allow for detailed internal exposome profiling, but connecting these internal signals to external exposures and cancer initiation and progression remains a major unresolved challenge.
- Lack of longitudinal biospecimens: Identifying causal exposures requires access to high-quality, pre-diagnostic, and preferably repeated biospecimens—resources that are often lacking.
- Need for integrated conceptual model: Progress in EOCRC risk factor discovery and prevention will require mechanistic models that reflect real-world exposures, and a unified approach that integrates population data, experimental validation, and causal inference to translate complex exposome data into actionable prevention strategies.

Box 2 Strategies to engage younger populations in EOCRC and cancer prevention

- Leverage community-engaged research practices that includes stakeholder perspectives
- Include multiple components that, cumulatively, address multiple levels of influence (i.e., multilevel interventions)
- Accommodate literacy and language limitations
- Individual-level component(s) of multilevel interventions should be designed to (a) accommodate people who are at different stages of behaviour change, and (b) facilitate people's progression through the stages of behaviour change
- Correct misperceptions and incorrect beliefs
- Adapt existing effective interventions for EOCRC (e.g., behavioural and lifestyle interventions for CRC and other cancers)