



THE RISE OF EARLY ONSET COLORECTAL CANCER

Recent trends reveal a troubling rise in colorectal cancer rates among young adults in the past few decades. This white paper summarizes the risk factors linked to this rise and examines evolving screening practices in the US aimed at addressing this growing concern.

ABOUT THE AUTHOR

Thiviya Jeyakumar completed her PhD in Biochemistry at McGill University, where she investigated the genetic contribution to infectious and inflammatory diseases, including colitis-associated colorectal cancer

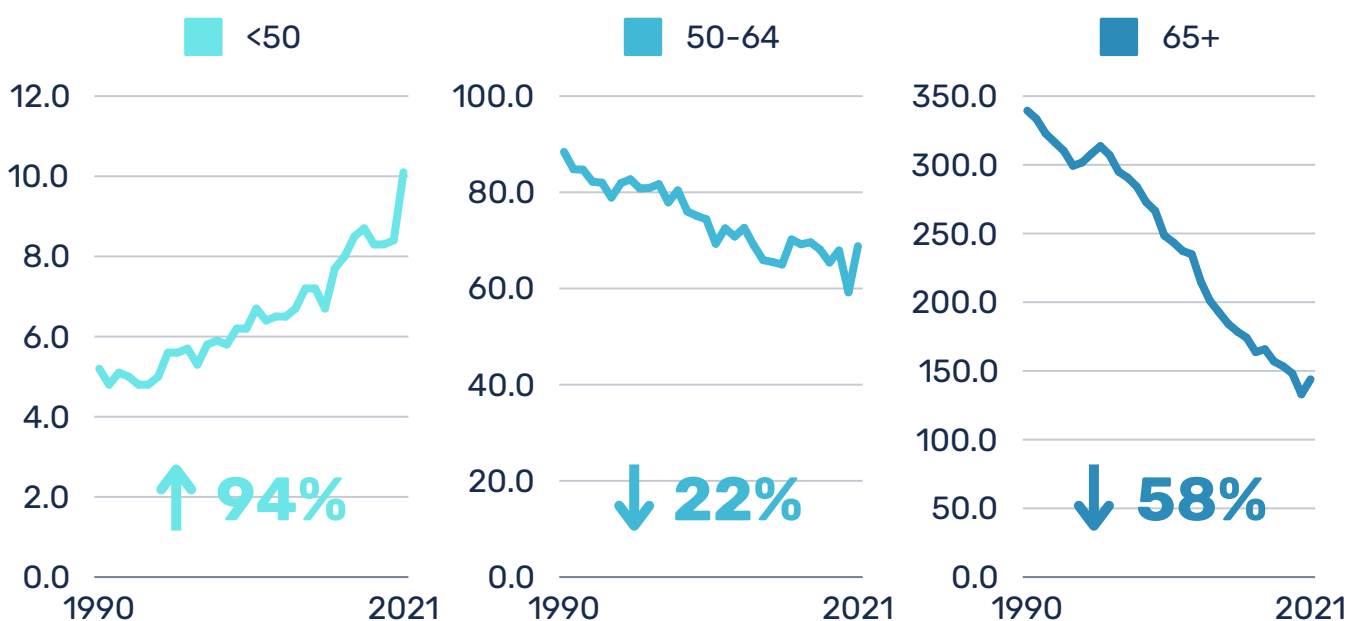
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The alarming rise in early-onset colorectal cancer cases

- Early-onset colorectal cancer (EOCRC) refers to colon and rectal cancer cases diagnosed in individuals under 50. Since the mid-1990s, EO CRC cases have increased by ~2% annually in the US, now making up and estimated ~13% of all CRC diagnoses in 2023
 - In 2024, CRC emerged as the leading cause of cancer deaths among men under 50 and the second leading cause among women under 50
 - This trend is also being seen across many countries worldwide, particularly those in the Global North
- While colorectal cancer rates are rising among young people, evidence suggests that in particular, it's rectal and distal colon cancers that are leading this surge
 - Those born after 1990 face 2x the risk of developing colon cancer and a staggering 4x the risk of rectal cancer compared to those born in 1950
- While CRC incidence rates remain significantly higher in older patients, they've been steadily declining in this group— an encouraging contrast to the alarming rise among younger adults
 - This drop is largely credited to the increased use of screening, particularly colonoscopies, which effectively detect and remove precancerous polyps

Trends in colorectal cancer incidence rates in the US by age group (1990-2021)



Graphs illustrate the age-adjusted SEER (Surveillance, Epidemiology and End Results) incidence rates of colorectal cancer (both colon and rectal cancer) from 1990 to 2021 in the labelled aged groups (<50, 50-64, 65+). On the Y-axis is the reported incidence rate per 100 000 and on the X-axis is the reported the year of diagnosis.

What is driving the rapid uptick in EOCRC?

The exact reason for the rise in colorectal cancer among young people is unknown, but it is likely due to a combination of factors, such as diets, sedentary lifestyles, obesity, smoking, and excessive alcohol consumption. A family history of CRC or polyps, or conditions such as inflammatory bowel disease, also significantly increases risk. Unravelling these factors is a key part of pinpointing individuals at heightened risk of EOCRC who would benefit most from early screening and intervention.

Genetics

An estimated 15-25% of EOCRC cases are linked to high-risk genetic variants and hereditary conditions. First-degree relatives of EOCRC patients were found to be 6X more likely to be diagnosed with the disease compared to the general population. However, genetic factors alone are unlikely to explain the sharp rise in CRC among younger adults over the past 30 years. Individuals with a genetic predisposition may be more vulnerable to developing cancer when these inherited risks are combined with changes in environmental and lifestyle factors that have emerged in recent decades.

Lifestyle/ Diet

Many epidemiological studies are attempting to identify which changing factors over the past decades could be contributing to this uptick. Studies have pointed to a lower incidence of EOCRC in those who eat fresh foods compared to heavily processed ones, with the "Western diet" (low fiber, high fat) cited as a strong risk factor. Decreased physical activity has also been linked to rising obesity rates, another key risk factor.

Inflammation/ Microbiome

With nearly 1 in 5 cancer cases originating in tissues or organs affected by infectious agents, chronic inflammation, or autoimmunity, the rising rates of obesity and inflammatory bowel syndrome among younger people are a key area of concern for EOCRC risk. These conditions also disrupt the gut microbiome, often further triggering inflammation. While the gut microbiome is now of heightened interest for its role in a multitude of diseases, with studies suggesting certain differences in the microbiome of those with EO-CRC with late-stage CRC, its exact impact on the incidence and progression of the disease remains uncertain.

Screening and the dilemma of late diagnoses in EOCRC

- Regular screening is crucial for preventing CRC, but younger adults are less likely to be screened, leading to later-stage diagnoses and more aggressive cancers
- In 2021, the US lowered the recommended screening age from 50 to 45 to address the rise in EOCRC, with screening available even earlier in those with familial cases
- Although there's limited justification for lowering the screening age further on a population level, many younger adults, especially those without a family history, face misdiagnoses or delayed diagnoses due to overlooked symptoms
- Establishing additional symptom-based thresholds to trigger screening in adults under 45 is key to tackle the >50% of early-onset cases that occur in this age group

Colonoscopies: The gold standard

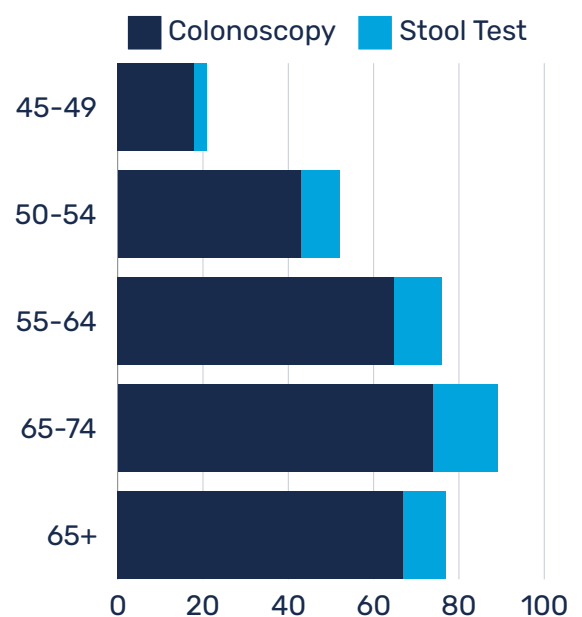


- Colonoscopies are considered the gold standard for CRC screening, offering high sensitivity and the ability to detect and remove polyps in one go, before they become cancerous
- However, colonoscopy adherence remains low in part due to its invasiveness, bowel prep, and inpatient requirement

Non-invasive screening tests

- Non-invasive stool-based tests can increase accessibility and help bridge the gap in screening adherence, followed by a colonoscopy when results are abnormal
- Guaiac-based fecal occult blood test (gFOBT) and faecal immunochemical tests (FIT) are cost-effective, at-home options that don't require bowel prep and work by detecting hemoglobin in stool
- Exact Sciences' Cologuard, a multi-target stool DNA test, was FDA-approved in 2014 with 92% sensitivity and 87% specificity and currently holds ~10% of the CRC screening market in the US. An updated version with 94% sensitivity and 91% specificity is expected by 2025

CRC screening (%) in adults 45+ in the US, 2021



Graphs illustrates results of National Health Interview Survey in 2021 of % of eligible population who received colonoscopy within last 10 years or FOBT/FIT/sDNA test in last 3 years, (ACS 2023)

Blood-based screening tests are welcomed as a promising new option but not yet an alternative

- Blood tests are considered an even more convenient CRC screening option than stool-based tests, easily fitting into regular bloodwork routines, and are followed up by a colonoscopy if results are abnormal
- In July 2024, Guardant Health’s SHIELD test became the first blood test to receive FDA approval as a primary CRC screening option
 - The Centers for Medicare and Medicaid Services will cover a blood test every 3 years if it meets criteria of 74% sensitivity, 90% specificity, and FDA approval
- However, some experts remain skeptical. A recent AGA commentary suggested that while these tests are better than no screening, the lower efficacy would worsen outcomes compared to established screening methods, making them more suitable as a second-line option for those who decline other tests

Blood-based tests advancing to or with FDA approval

Test Name	Company/ Developer	Marker(s) Detected	Sensitivity/ Specificity	Status	Comments
Shield	Guardant Health	ctDNA	83%/90%	Approved	Approved as a primary screening option; covered by Medicare. Ongoing work on improving sensitivity
Blood-based CRC test	Freenome	Multiomics and ML-derived blood biomarker test	79%/92%	In development	Topline data presented in April 2024 showed underwhelming sensitivity; working on improving sensitivity and AA detection
Blood-based CRC test	Exact Sciences	TBD	TBD	In development	Topline results expected in Q4 2024; Alleged to have “an unrivaled cost profile”
Epi proColon	Epigenomics AG	Methylated Septin9	72%/81%	FDA-approved for specific use cases	Not covered by Medicare; concerns over accuracy

Changing practices for a changing population

Early detection of EOCRC is often belied by factors like symptom downplaying, lack of patient and clinician awareness, and a “wait-and-see” approach in young adults, all contributing to delayed diagnoses and poorer outcomes. Identifying high-risk individuals and removing barriers to care is key to tailoring approaches and ensuring timely intervention.

Ignored Symptoms

2/3

of surveyed EOCRC patients experienced symptoms for 3+ months before they're diagnosed⁹

Insurance Barriers

59%

of surveyed EOCRC patients faced difficulties with insurance coverage¹⁰

- **Revising Screening Guidelines and Policies:** Just as the US Multi-Society Task Force on Colorectal Cancer now recommends screening for those with a first-degree family history of CRC starting 10 years before the youngest relative's diagnosis or at age 40, similar tailored approaches should be considered for other high-risk individuals and establishing thresholds to trigger screening in those with select symptoms, such as rectal bleeding. Furthermore, beyond guidelines, policies requiring health insurance plans to cover the costs of screening and other care also need to be stronger.
- **Clinician Practices:** Clinicians need to maintain full access to a patient's symptom history, medical background, family history, and other risk factors to effectively and accurately diagnose and identify CRC
- **Education and Awareness:** Raise awareness among healthcare providers and the public about the rising risk of CRC in younger adults, stressing the urgency of recognizing early symptoms, prioritizing timely screening, and adopting lifestyle changes where possible to lower risk

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