Early-onset colorectal cancer 1

The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection

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This is the first in a Series of two papers about early-onset colorectal cancer (paper 2 appears in *The Lancet Oncology*)

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The incidence of early-onset colorectal cnacer—ie, colorectal cancer diagnosed in patients under the age of 50 years—has been increasing around the world. This Series paper provides a comprehensive review on the topic of early-onset colorectal cancer, including examining the epidemiology of early-onset colorectal cancer around the world, clinical and pathological features, genetic and epigenetic landscapes, and emerging data on the clinical risk factors associated with this malignancy. Evidence-based approaches to prevention and early detection are also presented.

Introduction

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer related mortality. The incidence of colorectal cancer in high-income countries has remained stable or decreased over the last several decades,[1] in large part due to increasing uptake of colorectal cancer screening and colonoscopic polypectomy in older adults,[2] as well as changing risk factors (eg, decreased smoking, increased aspirin use).[3] By contrast, the incidence of colorectal cancer diagnosed in younger individuals, or early-onset colorectal cancer, has been increasing worldwide.[4,5] Early-onset colorectal cancer generally refers to individuals diagnosed with colorectal cancer under the age of 50 years. Although a specific age threshold does not correspond to biologically or pathophysiologically different disease entities, 50 years is an intuitive cut off based on historical recommendations to initiate average-risk screening at this age in many high-income countries.[6–10] In this Series paper, early-onset colorectal cancer will refer to colorectal cancer diagnosed in those younger than 50 years and late-onset colorectal cancer will refer to colorectal cancer diagnosed in those aged 50 years or older, unless otherwise specified. It is important to note that the early-onset colorectal cancer group includes a heterogeneous population of patients, often combining patients at increased risk of colorectal cancer (inflammatory bowel disease, family history of colorectal neoplasia, hereditary cancer syndromes) with patients with no clear predisposition. Given that it is unlikely that hereditary syndrome incidence is increasing, this Series paper focuses on sporadic early-onset colorectal cancer, unless specified. More detailed reviews of the contribution of hereditary colorectal cancer syndromes to early-onset colorectal cancer can be found elsewhere.[11–15] We will review the epidemiology, clinicopathological features, genetic and epigenetic landscape, underlying causes, and evidence-based management approaches to prevention and early detection of early-onset colorectal cancer.

Epidemiology

Over the last several decades, the incidence of early-onset colorectal cancer has increased worldwide (figure 1).[4,16–18] Based on national and regional cancer registries from 20 European countries, colorectal cancer incidence per 100 000 increased from 0·8 in 1990 to 2·3 in 2016 for those aged 20–29 years (an annual percentage change of 7·9% from 2004 to 2016); from 2·8 in 2006 to 6·4 in 2016 for those aged 30–39 years (an annual percentage change of 4·9% from 2005 to 2016); and from 15·5 in 2005 to 19·2 in 2016 for those aged 40–49 years (an annual percentage change of 1·6% from 2004 to 2016).[5] Between 2008 and 2012, the annual percentage change in early-onset colorectal cancer was 4·0% in New Zealand, 2·8% in Canada, 2·8% in Australia, and 2·2% in the USA.[4] Although a more recent trend, Sung and colleagues report a similar increase in early-onset colorectal cancer incidence in Taiwan, Japan, Hong Kong, and South Korea.[19] By contrast, Vuik and colleagues reported that the incidence of early-onset colorectal cancer in Italy decreased in those aged 20–39 years by 1·8% per year from 1998 onwards[5] and Zorzi and colleagues presented data from the Italian Association of Tumour Registries showing early-onset colorectal cancer incidence decreasing in all age groups, with annual percentage change ranging from –2·6% to –1·3% per 100 000.[20,21]

In the USA, when stratified by tumour histology and age from the Surveillance, Epidemiology, and End Results (SEER) 18 registry spanning 2000–16, the annual percentage change for overall colorectal adenocarcinomas was 5·6% (95% CI 0·5–11·1) in those aged 20–29 years, 1·6% (1·2–2·0) in those aged 30–39 years, and 0·9% (0·7–1·2) in those aged 40–49 years.[22] This type of analysis allowed adenocarcinomas to be analysed independently of carcinoids (neuroendocrine tumours, which are classified as colorectal cancers in SEER registries), which are increasing steeply in early-onset subgroups and can bias the reporting of overall colorectal cancer incidence. In this analysis of US data, Montminy and colleagues also stratified results by anatomic site (rectal *vs* colon) and

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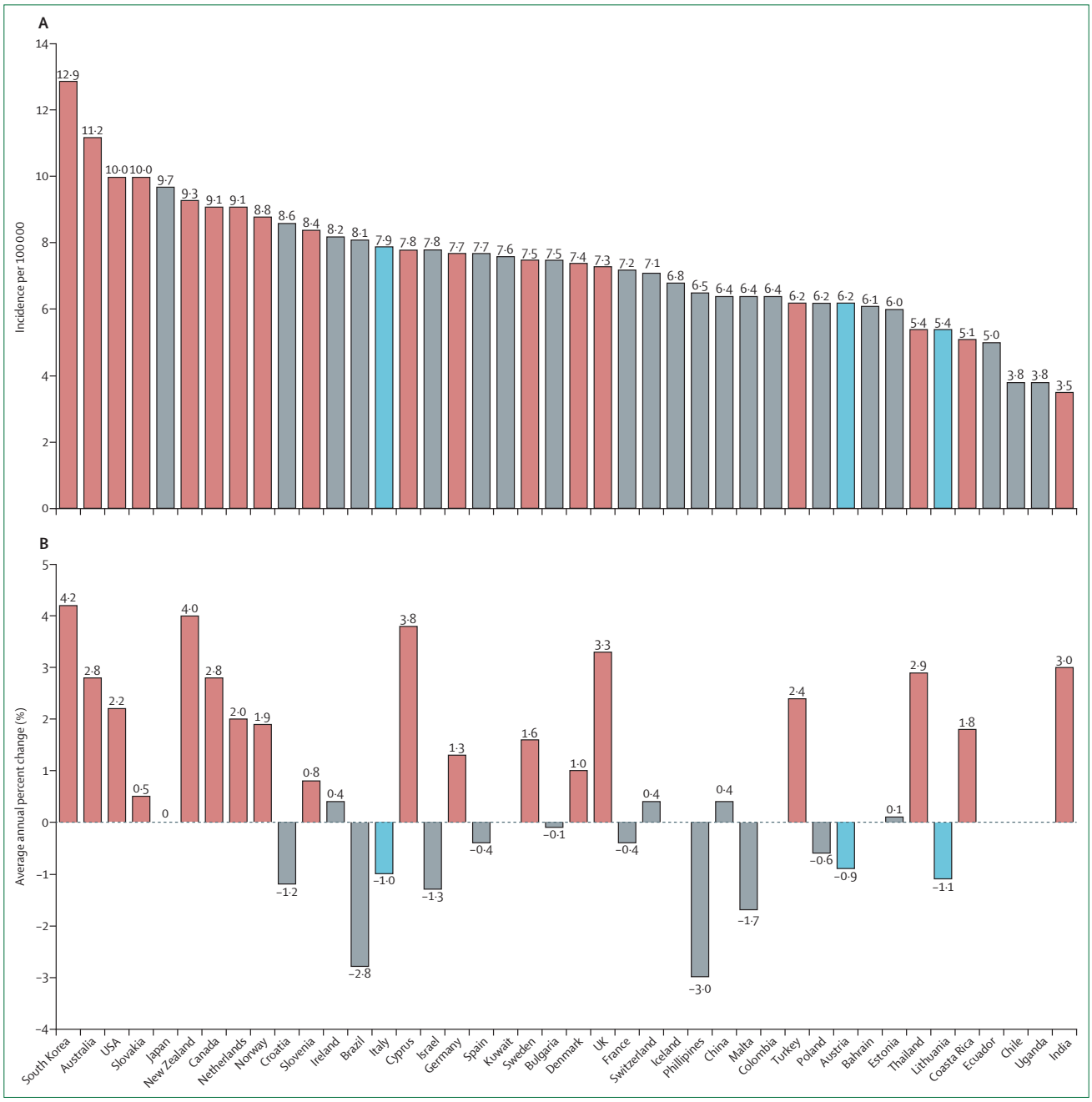


Figure 1: **Worldwide incidence and average annual percentage change in early-onset colorectal cancer**
(A) Incidence per 100 000 in adults aged 20–49 years from 2008-2012. Bars show trend in incidence rates based on 10-year average annual per cent change (red: statistically significant increase; blue: statistically significant decrease; grey: stable or insufficient number of cases for trend). (B) Average annual percent change in colorectal cancer in adults aged 20–49 years. Additional details on data from each country can be found in Siegel and collagues.[4]

reported an annual percentage change for rectal adenocarcinoma of 1·6% (95% CI 0·1–3·1) in those aged 20–29 years, 2·2% (1·7–2·7) in those aged 30–39 years, and 1·2% (0·7–1·7) in those aged 40–49 years.[22] By contrast, the rise in early-onset colorectal cancer in Europe appears to be more prominent for colon cancers than rectal cancers.[5]

There are conflicting observations internationally regarding early-onset colorectal cancer mortality rates.

	Early-onset colorectal cancer (age <50 years)	Late-onset colorectal cancer (age ≥50 years)
Presenting with symptoms, %	85·0–95·6[33-36]	33·9–79·0[34,37]
Incidental or screen detected, %	1·6–5·2[34,38]	3·4–14·6[34,38]
Duration of symptoms, days	243[38]	154[38]
Time to diagnosis, days	152–217[38,39]	29·5–87[38,39]
Family history of colorectal cancer, %	13·8–33·5[37,38,40,41]	8·3–19·3[37,38,40]
Location, %		
Right colon	16·2–39·9[32-34,37,38,40,42-50]	28·5–53·5[37,40,44-46,50,51]
Left colon	24·0–53·0[32,33,38,42-48]	28·9–48·5[34,38,40,44-46]
Rectal	23·5–49·1[32-34,37,38,42-44,46-48]	20·0–35·2[34,37,38,44-46]
Histology, %		
Mucinous	8·1–15·0[34,42,43,45,47,48,50,51]	4·7–16·0[34,45,50,51]
Signet ring	1·0–13·0[34,42,43,45,47,50,52]	0·9–4·0[34,45,50,53,54]
Poor or no differentiation	7·2–27·9[34,42,43,48,50,51]	3·2–18·9[34,50,51,53]
Stage, %		
Early	11·0–47·0[32-34,40,42,43,46,47-50]	37·5–69·7[33,34,38,40,46,50]
Late	58·4–89·0[32-34,37,38,40,42,43,47-50]	30·3–62·5[33,34,37,38,40,46,50]

Table 1: **Clinical and pathologic features of colorectal cancer diagnosed in patients younger than 50 years and in those 50 years and older**

Based on data from the National Center for Health Statistics,[23] in those age 20–49 years in the USA, the overall mortality rate from malignant neoplasms of the colon has increased from 2·6 per 100 000 in 1999 to 2·8 per 100 000 in 2019.[23] When stratified by anatomic site (colon *vs* rectum), mortality over this period for malignant neoplasms of the colon remained stable from 2·1 per 100 000 in 1999 to 2·0 per 100 000 in 2019.[23] By contrast, mortality from malignant neoplasms of the rectosigmoid and rectum increased from 0·5 per 100 000 in 1999 to 0·8 per 100 000 in 2019.[23] In the 20 European countries summarised by Vuik and colleagues, there was no change in mortality rates for those aged 20–29 years. For those aged 30–39 years, mortality rates decreased by 1·1% per year from 1990 to 2016 and for those aged 40–49 years by 2·4% per year from 1990 to 2009.[5]

Siegel and colleagues[24] used age-period-cohort modelling to determine the influence of a birth cohort effect on early-onset colorectal cancer incidence by analysing SEER incidence data from 1974 to 2013. The incidence curve for those aged 50–54 years in the USA is similar to the older age groups in the 1970s and 1980s, but then reflects the younger age group after the mid-1990s. This observation suggests a birth cohort effect, where younger cohorts carry elevated risk with them as they age, in contrast to a period effect due to changes in clinical practice. The inflection point for this effect is for individuals born after 1960. This observed birthcohort effect suggests shared risk factors across a generation might be contributing to early-onset colorectal cancer risk.

Although Black and Alaskan Native individuals have historically had higher absolute incidence of early-onset colorectal cancer compared with non-Hispanic White populations in the USA, the pace and direction of incidence changes are unique based on racial and ethnic subgroups. In an analysis of SEER data, Murphy and colleagues[25] reported that from 1992–96 to 2010–14, colorectal cancer incidence per 100 000 increased from 7·5 to 11·0 White individuals and from 11·7 to 12·7 in Black individuals. The increase in rectal cancer was larger in White (from 2·7 per 100 000 to 4·5 per 100 000) compared with Black (from 3·4 per 100 000 to 4·0 per 100 000) individuals.[25] This study was limited because the SEER data had limited representation of all racial and ethnic subgroups, with SEER databases including only 9–28% of the total US population.[26] Chang and colleagues analysed data from the US Cancer Statistics Database from 2001 to 2016, which combines SEER and National Program of Cancer Registries data to include nearly all of the US population.[26] In the 191 659 early-onset colorectal cancer cases they observed, White individuals were the only group with a consistent increase in incidence across all age groups under 50 years. Hispanic individuals had an increase in incidence for those aged 20–44 years, but no change in those aged 45–49 years.[26] By contrast with previous studies of SEER data with limited racial and ethnic representation,[25,27,28] Black individuals and Asian Pacific Islanders had no change in early-onset colorectal cancer incidence from 2001 to 2016. Chang and colleagues reinforce that Black individuals continue to have the highest absolute incidence compared with other racial or ethnic groups; however, the gap in incidence between Black and White individuals appears to be closing with an incidence rate ratio of 1·31 in 2001 and 1·05 in 2016 (p for trend <0·0001).[26] This emerging data suggests that the rising incidence of early-onset colorectal cancer in the USA is almost entirely driven by White populations.

There is also wide variation in incidence within racial groups based on geography. For example, for those aged 40–44 years, Black individuals in rural Georgia have colorectal cancer incidence that is 136·2% higher than Black individuals residing in California.[29]

The recent increase in mortality rates from early-onset colorectal cancer in the USA is limited to White individuals, among whom there has been a 1·4% increase per year from 2004 to 2014 (from 3·6 per 100 000 to 4·1 per 100 000). Among Black individuals, mortality rates declined by 0·4–1·1% annually.[30] However, Black individuals still have a higher overall risk of cancer-related death (hazard ratio [HR] 1·36, 95% CI 1·27–1·45 for colon cancer; HR: 1·52, 1·38–1·68 for rectal cancer) from 2000 to 2009, when compared with White individuals.[31] 5-year relative survival was 54·9% in Black individuals compared with 68·1% in White individuals.[31]

Clinical and pathological features

Studies describing the clinical and pathological features of early-onset colorectal cancer have not systematically excluded patients with germline pathogenic variants and have largely been retrospective, single-centre series, with

	Cohort characteristics	Genes tested	Pathogenic or likely pathogenic variants	Colorectal germline variants (n)	Non-colorectal germline variants (n)	Variants of uncertain significance
Mork et al[56]	193 patients aged ≤35 years; mean age at diagnosis 29 years	Phenotype driven; all patients had been referred for genetic counselling	44/193 (23%)	*APC* (13), biallelic *MUTYH* (2), CMMRD (2), monoallelic *MUTYH* (1), *MLH1* (6), *MSH2* (5), *MSH6* (2), *PMS2* (1), *EPCAM* (1)	*TP53* (1)	6/193 (3·1%)
Yurgelun et al[57]	336 patients aged <50 years selected from 1058 consecutive patients with colorectal cancer of all ages with mean age at diagnosis 56 years	25-gene panel	52/336 (14%)	*MLH1* (13), *MSH2* (4), *MSH6* (3), *PMS2* (2), *APC* (3), *APC* I1307K (4), biallelic *MUTYH* (3), monoallelic *MUTYH* (6)	*BRCA1* (2), *BRCA2* (4), *BRIP1* (1), *ATM* (6), *CHEK2* (1)	479/1260 (38·0%)*
Pearlman et al[58]	450 patients aged <50 years; mean age at diagnosis 43 years	25-gene panel	75/450 (16%)	*MLH1* (13), *MSH2* (17), *MSH6* (2), *PMS2* (6), *APC* (6), *APC* I1307K (4), biallelic *MUTYH* (4), monoallelic *MUTYH* (8), *SMAD4* (1)	*BRCA1* (2), *BRCA2* (4), *ATM* (4), *CHEK2* (1), *PALB2* (2), *CDKN2A* (1)	145/450 (32·2%)†
Stoffel et al[59]	430 patients aged <50 retrospectively selected from genetic counseling service; mean age at diagnosis 40 years	124-gene or 67-gene panel	79/315 (25%)	*MSH2* (25), *MLH1* (24), *MSH6* (5), *PMS2* (2), *APC* (10), *MUTYH* (8), *SMAD4* (2)	*BRCA1* (1), *TP53* (1), *CHEK2* (1)	21/315 (6·7%)
Uson et al[60]	124 patients aged <50 years; mean age at diagnosis 43 years	83-gene or 84-gene panel	33/124 (22%)	*MSH2* (4), monoallelic *MUTYH* (2), *PMS2* (1), *CHEK2* (2), *APC* (1), *MSH6* (2), *MLH1* (3), biallelic *MUTYH* (1)	*CDC73* (1), *BRCA2* (2), *BRIP1* (1), *HOXB13* (1), *RAD50* (1), *PALB2* (1), *FH* (1), *WRN* (1), *SDHA* (2), *EGFR* (1), *BLM* (2)	53/124 (42·7%)
Toh et al[61]	88 patients aged <50 years; mean age at diagnosis 41 years	64-gene panel, excluding MMR genes	12/88 (14%)	*APC* (4), monoallelic *MUTYH* (2),	*ATM* (1), *BRCA2* (1), *NTHL1* (1), *PALB2* (1), *WRN* (2)	88/236‡

Data are n, or n/N (%). MSI-H=microsatellite unstable. MMR=mismatch repair. CMMRD=constitutional mismatch repair deficiency. *Includes total cohort of patients (data on only < 50 cohort not available). †Patients had more than one variant. Study did not report the number of patients with at least one variant. ‡Excluded patients with MMR-deficient tumours.

Table 2: **Pathological germline variants in early-onset colorectal cancer**

the largest sample size studies including just over 1000 patients with early-onset colorectal cancer.[32] Despite these limitations, it appears that early-onset colorectal cancer presents differently to late-onset colorectal cancer (table 1). Most patients with early-onset colorectal cancer present with symptoms[32] and are more likely to present with haematochezia (28·8% *vs* 23·2%, p<0·01) and abdominal pain (41·2% *vs* 27·2%, p<0·01), when compared with patients with late-onset colorectal cancer, who are more likely to be diagnosed incidentally (14·6% *vs* 5·2%, p<0·01).[38] Patients with early-onset colorectal cancer experience symptoms for a longer duration of time (243 *vs* 154 days)[38] and have a longer delay from symptom onset to diagnosis (152–217 *vs* 29·5–87 days), compared with those with a late-onset disease (table 1).[38,39]

Early-onset colorectal cancers are more likely to occur in the left colon and have more aggressive histopathology. Patients with late-onset colorectal cancer are more likely to have right sided cancers (31·1% *vs* 20·0%, p<0·001) and those with early-onset disease are more likely to have rectal cancer (31·2% *vs* 22·4%, p<0·001; table 1).[55] Mucinous histology is observed in 10·0–14·5%[42,43,51,52] and signet ring histology in 2·0–13·0%[42,43,52] of early-onset colorectal cancers, with up to 27·9% of cancers being poorly differentiated or undifferentiated.[38] Data from the National Cancer Database showed that early-onset disease was more likely to have a mucinous or signet-ring histology (12·6% *vs* 10·8%, p<0·01) and poor or no differentiation (20·4% *vs* 18%, p<0·01), compared with late-onset colorectal cancers.[53]

Early-onset colorectal cancer is diagnosed at a more advanced stage at time of detection than late-onset disease (table 1). Abdelsattar and colleagues reported a relative risk (RR) of 1·37 (96% CI 1·33–1·41) for regional and 1·58 (95% CI 1·53–1·63) for distant metastasis in younger patients compared with older patients.[55] Chen and colleagues found that the difference in stage at presentation between early-onset colorectal cancer and late-onset disease could not be explained simply by a longer time between the onset of symptoms and diagnosis because younger patients with stage III or IV disease had shorter symptom and workup periods compared with those with stage I or II disease.[38] Thus, advanced stage at diagnosis is not likely explained by longer dwell time or time to diagnosis.

Despite more advanced stage and histology at time of diagnosis, patients with early-onset disease have more favourable survival rates. In one large report of SEER data, the stage-adjusted, 5-year cancer-specific survival was better in patients with early-onset colorectal cancer compared with those with late-onset disease (95·1% *vs* 91·9% for local cancer, p<0·001; 76% *vs* 70·3%, p<0·001 for regional; and 21·3% *vs* 14·1%, p<0·001 for distant).[55]

Genetic and epigenetic landscapes

Prevalence and spectrum of germline genetic pathogenic variants

A wide spectrum of pathogenic germline variants can be associated with early-onset colorectal cancer. With the emergence of multi-gene panel sequencing, we now recognise that in addition to germline variants associated with typical hereditary colorectal cancer syndromes, such as Lynch syndrome and polyposis syndromes, there are multiple non-colorectal pathogenic variants and moderate penetrance pathogenic variants that are observed in patients with early-onset disease. Table 2 summarises a series of studies that report the prevalence and spectrum of germline variants observed in patients with early-onset colorectal cancer. Although there are no truly population-based studies that describe the prevalence of germline variants in early-onset colorectal cancer, several studies[57–59] suggest that 14–25% of patients with early-onset disease have a pathogenic germline variant associated with cancer risk. Although recognition of germline pathogenic variants is increasing because of increased access to multi-gene panel testing, there are no data to suggest that the incidence of these inherited variants is increasing in the general population; thus, although hereditary syndromes are associated with a substantial proportion of early-onset colorectal cancers, they are unlikely contributors to the observed increasing incidence.

Patients with early-onset colorectal cancer have a wide spectrum of pathogenic germline variants, often without manifesting the expected phenotype or expected family history. Stoffel and colleagues[59] reported that 79 (25%) of 315 patients with early-onset colorectal cancer who had been selected for germline testing at a single institution had a pathogenic germline variant. 20 patients had variants associated with polyposis, such as *APC* and *SMAD4*, and one each had *BRCA1*, *TP53*, and *CHEK2* variants. Yurgelun and colleagues[57] reported results of 25-gene panel germline testing in 336 patients with early-onset colorectal cancer from a single institution (part of a cohort of 1058 patients with unselected colorectal cancer) and found that 47 (14%) of them had a pathogenic variant, including 22 Lynch syndrome variants, three *APC* variants, three biallelic *MUTYH* variants, six *BRCA1/2* variants, and one *BRIP1* variant. Pearlman and colleagues[58] did similar multi-gene panel testing in 450 patients with early-onset colorectal cancer from a consortium of 51 Ohio hospitals and reported that 72 (16%) of them had a pathogenic germline variant; 38 (8%) had a Lynch syndrome gene variant and 11 patients had polyposis gene variants (six with familial adenomatous polyposis, four with biallelic *MUTYH*, and one with *SMAD4*). Phenotypically unexpected results included six *BRCA1/2*, four *ATM*, two *PALB2*, and one each of *CHEK2* and *CDKN2A* variants. Using a common commercial multi-cancer panel including more than 80 genes, Uson and colleagues identified pathogenic variants in 22% of unselected individuals diagnosed with colorectal cancer under the age of 50 years between 2018 and 2020.[60]

There are several important lessons learned from these studies. In addition to traditionally non-colorectal cancer risk genes, some of the pathogenic variants identified in these patients with early-onset disease were moderate risk genes, such as *MUTYH* heterozygotes and the I1307K allele of *APC*. Yurgelun and colleagues reported that 16 (15%) of 106 variants for their entire (all ages) cohort were in moderate penetrance genes.[57] 15 (21%) of the 72 variants found in the Pearlman and colleagues' study were in moderate penetrance genes.[58] Whether these germline variants drove the early-onset colorectal cancer or were coincidental findings is unclear. These studies also showed high rates of variants of uncertain significance, or variants where there is limited or conflicting information regarding pathogenicity. Yurgelun and colleagues[57] reported that 38% of their entire cohort had at least one variant of uncertain significance and Pearlman and colleagues[58] found such variants in 32% of their patients. Finally, a substantial proportion of patients with pathogenic variants did not meet the expected family history criteria for the associated syndrome. Mork and colleagues[56] reported that 19% of the patients diagnosed with a hereditary syndrome did not have a family history consistent with the identified syndrome. Similarly, 19% of patients with a pathogenic variant in the Yurgelun cohort[57] and 26% of those in the Pearlman cohort[58] had no family history of cancer at all.

Polygenic risk

In addition to single-gene Mendelian syndromes, polygenic risk is also associated with early-onset colorectal cancer. Archambault and colleagues[44] compared a polygenic risk score that included 95 common colorectal cancer risk variants in 12 197 patients with early-onset disease versus 95 865 with late-onset disease and found that there was a stronger association between the score and early-onset disease than with than the late-onset disease (p=0·01).[44] The highest quartile score was associated with a greater risk of colorectal cancer in those under the age of 50 years than in those aged 50 years and older (odds ratio [OR] 3·73, 95% CI 3·28–4·24 *vs* 2·92, 2·80–3·04). Interestingly, the strongest association was in patients with early-onset colorectal cancer who did not have a family history of colorectal cancer (OR 4·26, 95% CI 3·61–5·01).[44]

Familial risk

In the absence of a clear germline predisposition, there are still a large proportion of patients with early-onset colorectal cancer who have a family history of colorectal neoplasia. Up to 33·5% of patients diagnosed with early-onset disease have some family history of colorectal cancer (table 1).[37,38,40,41] Chen and colleagues[62] reported that patients with early-onset disease are more likely to have a

family history of colorectal cancer than those with late-onset disease (24·9% *vs* 16·8%). When definitively excluding patients with germline hereditary syndromes, 14·0[58]–16·3%[59] of patients with early-onset colorectal cancer have a first-degree relative with colorectal cancer. It is unclear how many of these patients have a first-degree relative with an advanced adenoma given poor patient knowledge of personal or family history of advanced adenomas, thus the proportion of patients with early-onset colorectal cancer with familial risk might be under estimated.[63]

Molecular pathology

Early-onset colorectal cancers have heterogenous somatic and molecular profiles. Stoffel and colleagues reported that 43 (9·5%) of their overall cohort of 450 patients diagnosed with colorectal cancer under age 50 years had microsatellite instability-high (MSI-H) tumours (21·5% of those with a germline pathogenic variant were MSI-H and 9·3% of those that had no germline variant were MSI-H).[59] After excluding patients with hereditary syndromes, Liang and colleagues[51] reported that 37 (29·4%) of their cohort of 126 patients with colorectal cancer aged 13–39 years had microsatellite unstable tumours. By contrast, approximately 15% of all colorectal cancers are microsatellite unstable.[58] Microsatellite and chromosomally stable tumours are near-diploid tumours and observed in higher frequency in early-onset colorectal cancer compared with late-onset colorectal cancer. Boardman and colleagues[64] compared 84 microsatellite-stable early-onset colorectal cancers with 90 microsatellite-stable late-onset colorectal cancers (>65 years). The microsatellite-stable tumours in the early-onset colorectal cancer group were more frequently diploid than those in the late-onset group (46% *vs* 26%, p<0·01), at later stage (42% *vs* 18%, p=0·02) and more frequently located in the rectum (50% *vs* 23%, p=0·04).[64] It is unclear what pathological process drives microsatellite and chromosomal stability and whether this stability is reflective of the distal colorectal location of these tumours or whether it is a characteristic unique to early-onset colorectal cancers.

Lieu and colleagues[65] did targeted next-generation genomic sequencing in 18 218 colorectal cancer cases and compared genomic alterations found in the very early-onset group (1420 cases aged <40 years), an intermediate-aged group (3248 cases aged 40–49 years) and an older-onset group (13 550 cases aged ≥50 years).[65] Generally, the genomic alterations were similar between the younger and older cohorts, except that *TP53* and *CTNNB1* alterations were more common in the youngest cohort, whereas *APC, KRAS, BRAF,* and *FAM123B* variants were more frequent in the older cohort.

The consensus molecular subtypes (CMS) of colorectal cancer described by Guinney and colleagues[66] differ based on age at diagnosis. Willauer and colleagues[45] described the subtypes of 626 early-onset colorectal cancers and found that patients diagnosed under age 40 years (n=223) had the highest proportion of CMS1, characterised by hypermutated tumours with microsatellite instability and strong immune activation. CMS2, characterised by marked WNT and MYC signalling, was similar in all age groups. CMS3, characterised by metabolic dysregulation, and CMS4, characterised by prominent transforming growth factor-β activation, stromal invasion, and angiogenesis, were uncommon in patients under age 40 years.[45] CMS1 was present in the highest proportions for patients aged 30–39 years (11 [46%] of 24) and patients aged 70 years or older (61 [23%] of 260).[45] CMS2 was relatively stable across all age groups. In patients aged 30–39 years, CMS3 (one [4%] of 24) and CMS4 (three [12%] of 24) were uncommon.[45]

Early-onset colorectal cancers appear to have unique epigenetic signatures. Long-interspersed nucleotide element 1 sequences comprise approximately 18% of the human genome[67,68] and are retrotransposons and mobile elements that, if expressed (typically by global hypomethylation), facilitate genome rearrangement.[69] Goel and colleagues reported significantly lower levels of long-interspersed nucleotide element 1 methylation in early-onset colorectal cancer compared with sporadic microsatellite-stable late-onset colorectal cancers, sporadic MSI-H colorectal cancers, Lynch syndrome colorectal cancers, and normal colonic mucosa.[70,71] Early-onset colorectal cancers have a lower prevalence of the CpG island methylator phenotype.[70,72]

Gut microbiota

There is evidence that characteristics of the gut microbiome are associated with colorectal cancer risk;[73–75] however, data specific to early-onset colorectal cancer is scarce. Investigators from the Nurses Health Study examined 1069 colorectal cancer cases and found that compared with cancers with no *Fusobacterium nucleatum* species, those with high *F nucleatum* had a mortality hazard ratio of 1·58 (95% CI 1·04–2·39).[76] *Escherichia coli* carrying the polyketide synthase island encodes enzymes that synthesise colibactin, a compound believed to alkylate DNA on adenine residues and induce double-strand breaks.[77] Pleguezuelos-Manzano and colleagues exposed human intestinal organoids to *E coli* with the polyketide synthase island and showed that a subset of human cancer genomes, predominantly colorectal cancers, had the same mutational signature as was observed in the organoids.[78] Dejea and colleagues showed that polymicrobial bacterial biofilms were found in 89% of right-sided neoplastic lesions (13 of 15 colorectal cancers, four of four adenomas), but only 12% of left-sided neoplastic lesions (two of 15 colorectal cancers, none of two adenomas). Of note, this group also found that normal mucosa distant to the tumour tissue exhibited similar biofilm communities as tumour tissue.[79] These studies describe associations, thus specific aetiologic mechanisms still need to be elucidated.

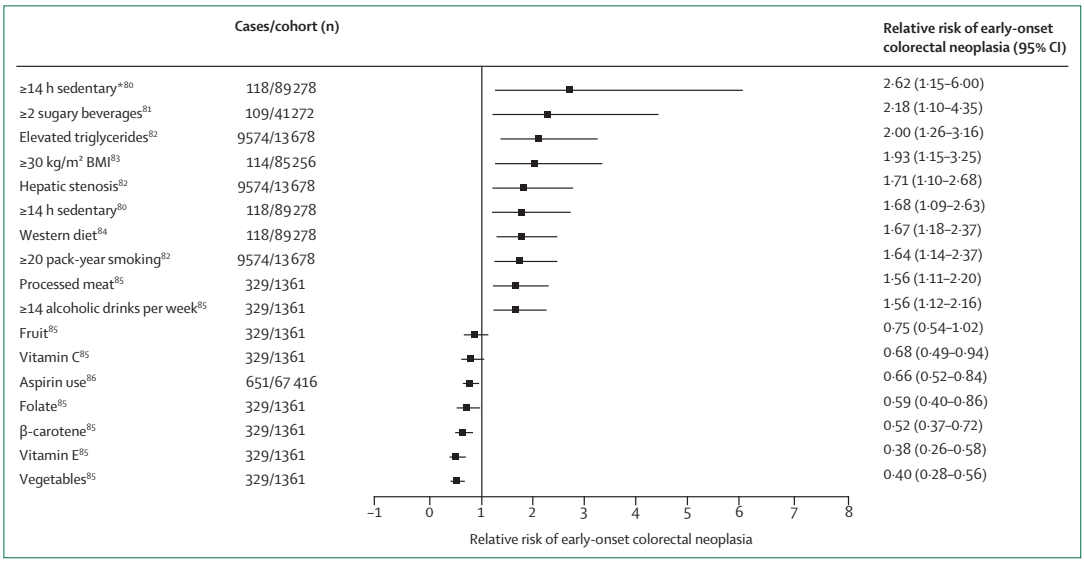


Figure 2: **Diet and lifestyle factors associated with early-onset colorectal cancer or neoplasia**
BMI=body-mass index. Western diet=diet high in ultra-processed foods. *Rectal cancer.

Nonetheless, microbiome characteristics might have diagnostic and prognostic importance.

Risk factors

There are a growing body of data on early-onset colorectal cancer risk factors (figure 2). Liu and colleagues[83] reported data from the Nurses' Health Study II, of 89 278 women aged 25–42 years, and showed a 1·93 (95% CI 1·15–3·25) adjusted RR for early-onset colorectal cancer in those with a body mass index of 30 kg/m² or higher. From the same cohort, Zheng and colleagues reported that those who had the most components of a western diet (ie, a diet high in ultra-processed food; fifth quintile) had an OR of 1·67 (95% CI 1·18–2·37) for development of early-onset advanced adenomas compared with those with the lowest western diet (first quintile).[84] The same group also reported that those who consumed two or more servings of sugar-sweetened beverages a day had a higher risk (RR 2·18, 95% CI 1·10–4·35) of early-onset colorectal cancer.[81] Nguyen and colleagues recently reported that women who were sedentary for more than 14 h per week had higher risk (RR 1·68, 95% CI 1·09–2·63) for early-onset colorectal cancer. The risk was more pronounced for rectal cancers (RR 2·62, 95% CI 1·15–6·00).[80] When comparing 329 cases of colorectal cancer diagnosed under age 45 years with controls (individuals admitted to the hospital for a variety of acute non-neoplastic medical conditions without any dietary modifications), Rosato and colleagues[85] found that 14 or more alcoholic drinks per week (OR 1·56, 95% CI 1·12–2·16) and the highest tertile of processed meat consumption (OR 1·56, 95% CI 1·11–2·20) were associated with risk of early-onset colorectal cancer. Consumption of vegetables (OR 0·40, 95% CI 0·28–0·56), fruit (0·75, 0·54–1·02), β-carotene (0·52, 0·37–0·72), vitamin C (0·68, 0·49–0·94), vitamin E (0·38, 0·26–0·58) and folate (0·59, 0·40–0·86) were all associated with reduced risk.[85] Jung and colleagues[82] reported that 20 or greater pack-year smoking history (OR 4·41, 95% CI 1·80–10·80 in those aged 30–39 years; 1·64, 1·14–2·37 in those aged 40–49 years), hepatic steatosis (1·71, 1·10–2·68 in those aged 30–39 years) and elevated triglyceride levels (2·00, 1·26–3·16 in those aged 30–39 years) were risk factors for advanced colonic neoplasia (where the reference group was average risk women aged >50 years). Low and colleagues[86] compared 651 early-onset colorectal cancer cases in US veterans aged 18–49 years to age-matched controls. As expected, they identified increasing age (OR 1·05, 95% CI 1·03–1·07) and male sex (2·21, 1·68–2·91) as risk factors for early-onset colorectal cancer whereas aspirin use was reported as protective (0·66, 0·52–0·84). Interestingly, overweight and obesity were associated with a lower odds of colorectal cancer in this cohort (0·69, 0·55–0·87), perhaps reflecting weight loss before being diagnosed. Similarly, Gausman and colleagues[46] compared 269 patients with early-onset colorectal cancer with matched controls and reported no association between obesity and early-onset colorectal cancer. These data are limited by cross-sectional design and do not address the important question of when in a patient's lifetime exposure to a risk factor influences developing cancer later in life.[87]

Cause of rising incidence

Although the exact cause of the rising incidence of early-onset colorectal cancer in high-income countries

is unknown, the epidemiological, clinical, and biological observations described here provide clues to factors that might be driving this phenomenon. The birth cohort effect, in combination with the decades-long latency in transformation of normal mucosa to malignancy, highlights the likelihood of early life physiologic or metabolic changes predisposing to cellular vulnerability over the lifecourse, by way of epigenetic changes in colorectal epithelial cells, changes in the gut microbiota, or alterations in host immunity. These changes might be modulated by exposures as early as the prenatal or perinatal period, such as increasing use of reproductive technologies,[88] caesarean sections,[89] and bottle feeding,[90] to those extending into the adolescent periods of life, such as increasing use of antibiotics in childhood,[91] antibiotics in the food chain,[92] western diet,[93] obesity,[94] and physical inactivity.[95] Countries where western lifestyles have only recently been adopted are likely to see similar rises in early-onset colorectal cancer. Rates are already increasing in Taiwan, Japan, Hong Kong, and South Korea, probably because of westernisation.[19]

Regional variations in early-onset colorectal cancer, such as the higher rates observed in the southern and Appalachian USA[29] and decreasing incidence observed in Italy,[20,21] might be potentially reflective of differences in diet and lifestyle causing differential burden of medical co-morbidities (such as diabetes and obesity), and the possibility of water supply or ambient exposures.[96–98]

Although Jung and colleagues reported smoking as a risk factor for early-onset colorectal neoplasia,[82] it is unclear whether this factor is causative for early-onset colorectal cancer, given the long induction period for colorectal carcinogenesis, the overall decreasing smoking rates among young individuals in countries where early-onset colorectal cancer incidence is rising,[99,100] and conflicting findings about smoking as a risk factor for early-onset colorectal cancer in other studies.[86,101]

Ongoing research is needed to understand the complex interplay of how these exposures modulate colorectal cancer risk over the lifecourse. Ideally, prospective cohort studies, with detailed collection of diet, lifestyle, and exposures along with longitudinal biospecimen collection can provide the opportunity to analyse biomarkers to help shed light on pathogenesis.

Early detection and prevention of early-onset colorectal cancer

As research is completed over the next several decades to understand the pathogenesis of early-onset colorectal cancer, there are immediate steps that can be taken to start curbing the burden of this disease.

Prompt symptom evaluation

As mentioned previously, there are considerable delays from symptom onset to diagnosis of early-onset colorectal cancer. The cause of the delay is likely multi-factorial, including delays in seeking care, barriers to accessing care, and medical provider dismissal or delayed evaluation of symptoms. Although bleeding is the most common presenting symptom of early-onset colorectal cancer, it is one of the most common presenting complaints to primary care providers and gastroenterologists, and most often caused by benign pathology such as haemorrhoids or fissures.[102] However, the presence of haemorrhoids does not exclude more proximal pathology and bleeding haemorrhoids can obscure subtle symptoms suggestive of a more proximal source.[103] Comparing a cohort of US veterans aged 18–49 years who had iron deficiency anaemia (n=191 200) and those who had haematochezia (n=130 748) with matched controls, Demb and colleagues[104] found that iron deficiency anaemia is associated with a HR of 10·81 (95% CI 8·15–14·33) for early-onset colorectal cancer and haematochezia is associated with a HR of 10·66 (95% CI 8·76–12·97) for early-onset colorectal cancer. The US Multi-society Task Force on Colorectal Cancer recommends that all patients under age 50 years with unexplained bleeding symptoms or iron deficiency anaemia undergo colonoscopy.[7]

Burnett-Harman and colleagues[105] present a framework for symptom evaluation and suggest that the following steps should be completed within 60 days of initial presentation to health-care providers: (1) systematic recognition of symptoms; (2) guideline-based triage for lower endoscopy, when appropriate; (3) timely and systematic follow-up to confirm alternate diagnoses and symptom resolution; and (4) placement of referrals for colonoscopy for unexplained or unresolved symptoms. Successful implementation of this type of framework would require alignment of multiple stakeholders, including multi-specialty medical providers (gastro-enterology, surgical endoscopy, primary care, emergency or urgent care, and gynaecology), ancillary staff, electronic health record analysts, and health-care system administrators to ensure processes and resources are in place to navigate patients presenting to different practice environments through this standardised, closed-loop, and timely process.

Approach to screening: improving screening in high-risk groups, precision, and population screening

As discussed, approximately 16% of all patients with early-onset colorectal cancer have an associated hereditary syndrome.[58] An additional 25% have a family history of colorectal cancer that would have qualified them for earlier screening[41] based on current screening guidelines in the USA and UK.[7,106,107] Unfortunately, there is gross under recognition of hereditary syndromes[108] and poor collection and documentation of family history,[109] resulting in low uptake of colorectal cancer screening in those aged 40–49 years who have a family history of the disease.[110] In a statewide (Louisiana) population-based study of 274 patients with early-onset colorectal cancer, only 23% of

patients were screened for Lynch syndrome through testing tumours for microsatellite instability.[111] Although first-degree relatives of those with advanced adenomas have a similarly increased risk of colorectal cancer as those with a first-degree relative with colorectal cancer,[112–115] there is poor knowledge and communication of familial risk associated with advanced adenomas.[63] Improving identification and management of those at increased risk for colorectal cancer based on family history and genetics are important efforts to reduce the burden of early-onset colorectal cancer and are reviewed in detail elsewhere.[116,117] In addition, ensuring that there is direct closed-loop communication between different specialties (including gastroenterology, pathology, oncology, genetics, and surgery) can help ensure that genetic testing is done, abnormal results are acted upon, and patients newly diagnosed with hereditary cancer syndrome are cared for by a multi-disciplinary team. If such communication does not take place, there is a risk of diffusion of responsibility whereby one specialty incorrectly assumes that another will take ownership of the genetic testing process for a given patient.[118]

The challenge with risk-based screening is that the specific risk factors for early-onset colorectal cancer are not fully elucidated, thus it is not surprising that available risk models have relatively weak discriminatory power.[119] Furthermore, many of the existing models have not been specifically applied to early-onset colorectal cancer populations and have not included racially diverse populations. Emerging models which include incorporation of clinical risk factors as well as polygenic risk scores[44] might provide more precise risk assessment;[120] however, they are not currently widely used in clinical practice.

An alternate approach to decreasing the burden of early-onset colorectal cancer is to decrease the age at which all average-risk individuals begin screening. Abualkhair and colleagues[29] reported a sharp increase in colorectal cancer incidence in individuals aged 50 years compared with those aged 49 years in the USA, probably due to screen-detected asymptomatic cancers that were likely present in individuals aged 45–49 years. These data suggest that expanding screening to those under age 50 years can detect these cancers at earlier stages, and might even prevent some colorectal cancers via colonoscopic polypectomy. Of note, screening rates among those aged 50–54 years in the USA are suboptimal (under 50%).[121] Similarly low screening rates might occur when patients aged 45–49 years enter the screening pool and thus it is crucial that we find ways to optimise these rates to maximise cancer prevention.

Data on the yield of colorectal cancer screening in average risk individuals under age 50 years are scarce. Kolb and colleagues[122] did a systematic review and meta-analysis of screening colonoscopy in 51 811 average-risk individuals under age 50 years from 17 international studies published from 2002 to 2020. Among average-risk individuals aged 45–49 years, 3·6% had advanced colorectal neoplasia (carcinoma or advanced polyp)—a similar prevalence to that for individuals aged 50–59 years (4·2%, p=0·69). Based on these findings, the authors concluded that 28 average-risk individuals aged 45–49 years would need to get a colonoscopy to diagnose one advanced colorectal lesion and expanding screening to this age group could reduce colorectal cancer risk. Butterly and colleagues[123] reported colorectal neoplasia rates in an average-risk equivalent population (individuals undergoing diagnostic colonoscopy for symptoms such as constipation) and reported very similar findings—3·7% prevalence of advanced colorectal neoplasia in those aged 45–49 years versus 3·6% in those aged 50–54 years and 5·1% in 55–59-year age group.[123]

There are currently scarce data on the yield of two-step screening approaches for those younger than 50 years. Levin and colleagues reported that of the 10 232 Black individuals aged 45–50 years who were offered faecal immunochemical test (FIT), 3390 (33·1%) completed testing.[124] Of these individuals, 136 (4·0%) had an abnormal (ie, positive) FIT and 116 (85·3%) of the individuals with an abnormal FIT completed a colonoscopy. Of those undergoing colonoscopy, 67 (57·8%) had any adenoma, 39 (33·6%) had an advanced adenoma, and three (2·6%) were diagnosed with colorectal cancer.[124] Test characteristics (sensitivity and specificity) of FIT in this population cannot be determined from this study since not all average-risk individuals underwent colonoscopy.

In a cross-sectional study of 816 average-risk individuals aged 45–49 years who underwent FIT–faecal DNA testing and colonoscopy, no participants were diagnosed with colorectal cancer and 49 (6%) had an advanced neoplasm.[125] Of the 53 (7%) of 816 who had a positive FIT–faecal DNA test, 16 (30%) had an advanced neoplasm. Of all 49 participants who had an advanced precancerous lesion on colonoscopy, 16 had an abnormal FIT–faecal DNA; thus FIT–faecal DNA has a sensitivity of 33% for detection of advanced neoplasm. This study was limited by small sample size and no colorectal cancers were detected. There are currently no available data on the yield of other two-step screening tests, such as computed tomography (CT) colonography, flexible sigmoidoscopy, or capsule colonoscopy, in people under age 50 years.

There are no controlled studies assessing the impact of screening on colorectal cancer incidence, colorectal cancer-related mortality, or the risks and costs of colorectal cancer screening versus no screening in individuals under age 50 years. The Cancer Intervention and Surveillance Modeling Network (CISNET) uses three independently developed microsimulation models that incorporate available data to predict life-years gained, colorectal cancer incidence and mortality, number of screening tests required, and complications of screening for a variety of different screening strategies.[126–128] Results from these models have informed US Preventative Services Task Force guidelines on colorectal cancer screening

since 2008.[8,129] Incorporating the changing epidemiology of early-onset colorectal cancer, an update of the modelling report by CISNET in 2021[130] compared outcomes for different screening tests (colonoscopy, FIT, FIT–faecal DNA test, flexible sigmoidoscopy, and CT colonography) at different intervals and at different starting and stopping ages. Of the 57 screening strategies that were considered efficient, the majority (47 of 57) began average-risk screening at age 45 years.[130] All three models showed a favourable balance of life-years gained compared with complications when starting screening at age 45 versus age 50 years. It is important to note that these models assume 100% adherence.

Ladabaum and colleagues showed that starting colorectal cancer screening at age 45 years in the USA would cost $33 900 per quality-adjusted life-year (QALY) for colonoscopy every 10 years or $7700/QALY for annual FIT screening.[131] This study also explored hybrid screening options and found that one-time flexible sigmoidoscopy at age 45 years, then colonoscopy at age 50–75 years (every 10 years) would cost $55 900/QALY and annual FIT from 45–49 years followed by colonoscopy at age 50–75 years (every 10 years) would cost $2500/QALY. This study did not compare other screening modalities such as CT colonography or FIT–faecal DNA test. Azad and colleagues[132] reported cost-effectiveness over a 10-year time horizon of single episode screening at age 40 versus age 50 years and found that all modalities were cost-effective against a $50 000/QALY willingness to pay threshold, but that FIT–faecal DNA test had the highest cost per QALY.

Based on these available data, multiple professional societies in the USA have recently recommended decreasing the starting age from 50 years to 45 years for the general population.[106,126,133–135] As these recommendations are operationalised in the USA, attention to ensuring equitable access to screening for all eligible populations and improving low adherence rates among younger individuals will be critical.

Expanding average-risk screening to younger age groups, particularly in resource restricted environments, remains controversial given the low absolute incidence. Given that up to 34% of patients with early-onset disease have a family history of colorectal cancer and over 95% present with symptoms (table 1), it is essential to continue collecting and acting on family history of colorectal cancer and promptly evaluating symptoms.

Conclusion

In conclusion, early-onset colorectal cancer incidence is rising worldwide without an obvious cause. This incidence gives rise to a greater proportion of distal colorectal cancers, is over-represented with familial cancer syndromes, has a small number of genetic, epigenetic, and clinical features, and no feasible targeted screening or treatment interventions are currently available. As ongoing research elucidates pathogenesis and evaluates whether our approach to screening average-risk individuals should be modified, the principal clinical interventions at present are aimed at countering the rising incidence through early genomic testing in all individuals with early-onset colorectal cancer, identification of those with hereditary syndromes, improved collection of family history and appropriate screening in those with a family history of colorectal cancer, and thorough evaluation of those with red-flag symptoms.

Search strategy and selection criteria

On March 5, 2021, we did a comprehensive literature search in Ovid Medline, Embase, and Web of Science limited to human participants, with no limitations on language, country of publication, or publication date. This search resulted in 10 123 unique citations. We also searched the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews and Effects. We searched manually review papers, meta-analyses, and editorials for additional pertinent references. We identified relevant publications by searching a combination of keywords and database-specific indexing terms for the colorectal cancer.

Contributors

SGP supervised the project. SGP, JJK, and TY did the figures. All authors did the literature search, drafted and critically reviewed the manuscript for important intellectual content and final read and approved it for publication.

Declaration of interests

SGP reports research support from Olympus America and Freenome, and honoraria from Erbe USA. JJK is an Advisor for Exact Sciences and reports Equity position and Chief Medical Officer position at Gastro Girl and GI OnDEMAND. CRB reports honoraria from Ambry Genetics. All other authors declared no competing interests.

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