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EARLY-ONSET COLORECTAL CANCER

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- **Prof. Hans Prenen** has no relevant financial relationships to disclose
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EDUCATIONAL OBJECTIVE AND CLINICAL TAKEAWAY

EDUCATIONAL OBJECTIVE

- Help healthcare professionals understand special considerations for the management of colorectal cancer (CRC) in younger patients

CLINICAL TAKEAWAY

- The incidence of early-onset colorectal cancer (EOCRC) is rising globally for reasons including an increasingly westernised diet, obesity, and alterations in the gut microbiota
- EOCRCs are more commonly left-sided and present with rectal bleeding and abdominal pain
- Aggressive treatment regimens based solely on patient age at CRC diagnosis are not warranted

DEFINITION AND EPIDEMIOLOGY

DEFINITION OF EOCRC AND EPIDEMIOLOGY

- **EOCRC** is generally accepted to be **any CRC diagnosis at age <50 years**, as this is the age at which most national screening programmes commence
- The median age of CRC diagnosis dropped from 72 years in the early 2000s to 66 years today
- **Incidence of EOCRC has risen sharply** since 1988 from 7.9 to 12.9 cases in 2015 per 100,000 people in the United States
  - In contrast to LOCRC (better screening?)
- Approximately 12% of all new diagnoses will be in individuals age <50 years, the equivalent of 49 new cases per day
  - By 2030, 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in individuals age <50 years
- **Key question is whether EOCRC and LOCRC** are the same disease, and if EOCRC is caused by a unique underlying mechanism that is impacted by different risk factors
- Most EOCRC studies are retrospective and include small number of patients

CRC, colorectal cancer; EOCRC, early- onset colorectal cancer; LOCRC, late-onset colorectal cancer

Akimoto N, et al. Nat Rev Clin Oncol. 2021;18:230-43; American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Available from: www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf. Accessed November 2022; Bailey CE, et al. JAMA Surg. 2015;150:17-22; REACCT Collaborative. JAMA Surg. 2021;156:865-74; Siegel RL, et al. Gut 2019;68:2179-85; Siegel RL, et al. CA Cancer J Clin. 2020;70:145-64; Sinicope FA, et al. N Engl J Med. 2022;386:1547-58; Surveillance, Epidemiology, and End Results (SEER) Program. Available from: https://seer.cancer.gov/data/. Accessed November 2022; Vuik FE, et al. Gut. 2019;68:1820-6

INCIDENCES OF EOCRC ARE INCREASING WORLDWIDE

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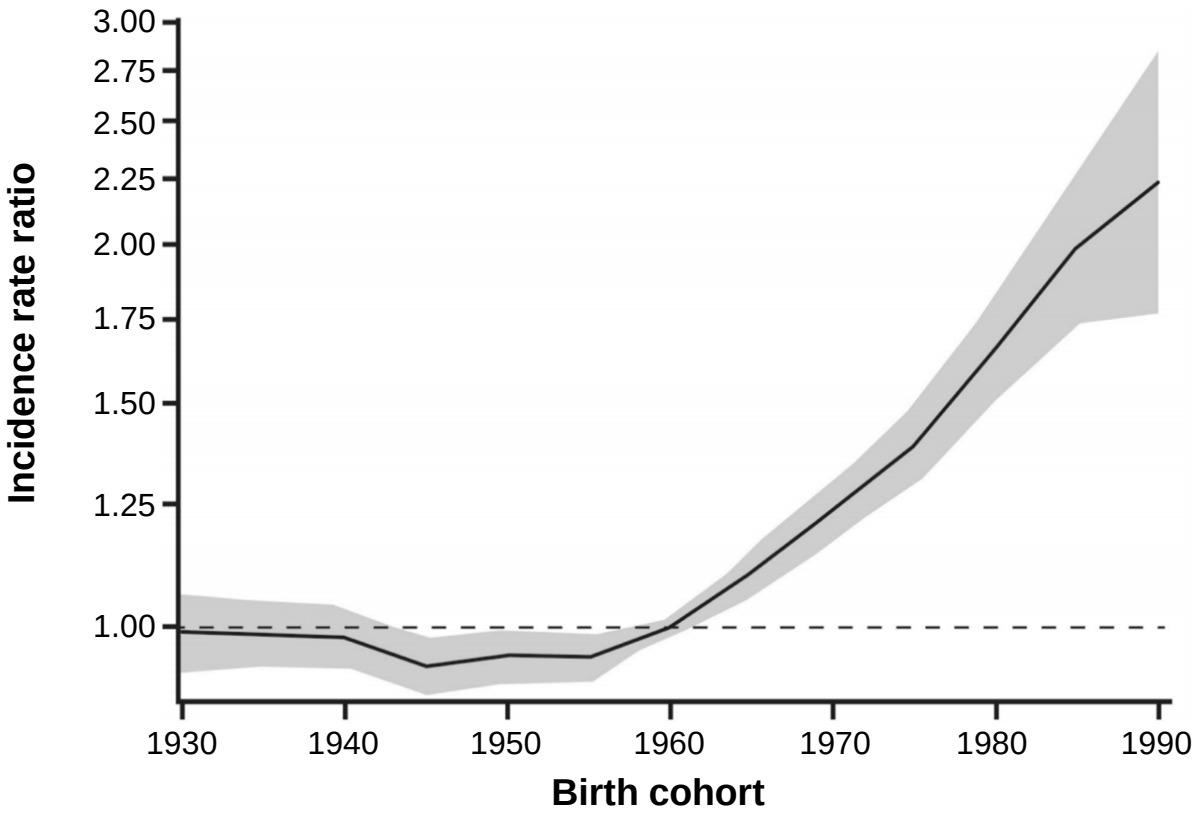
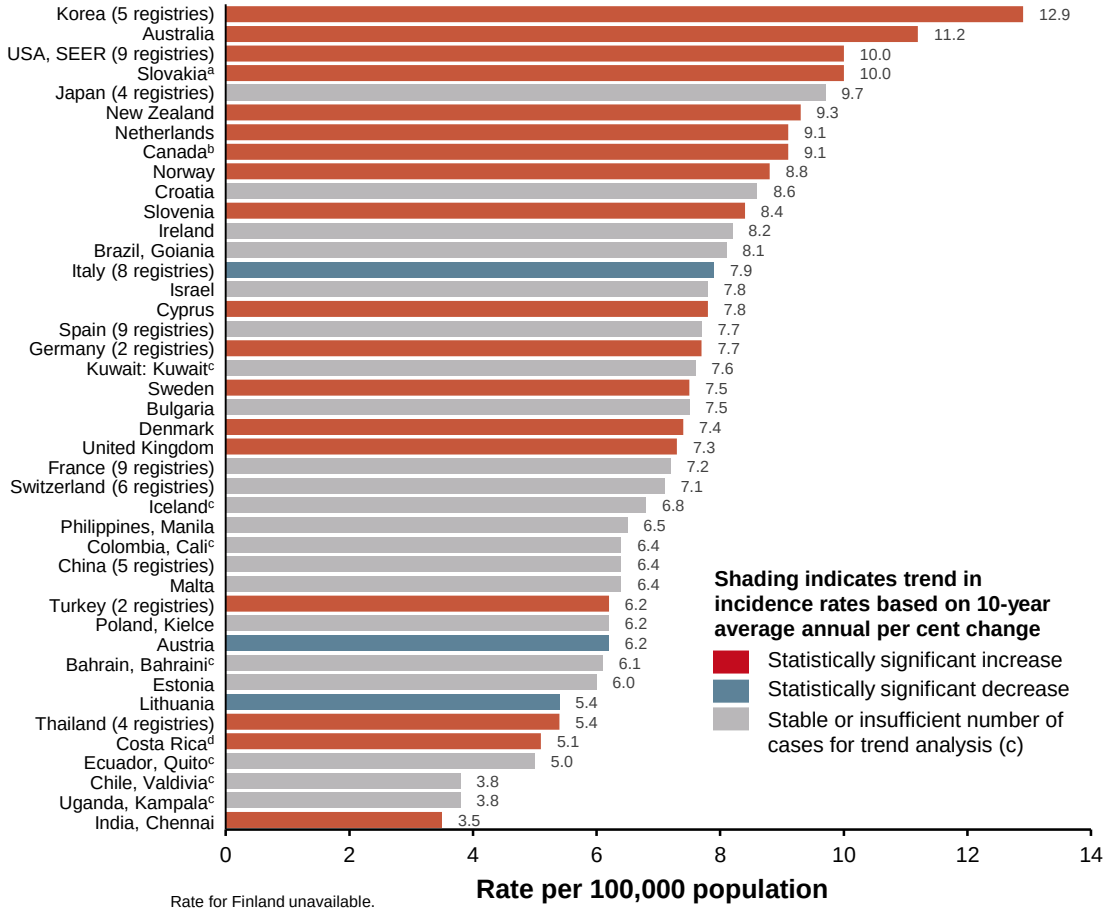
Incidence rate ratio by birth cohort in the United States[1]



Age-standardised incidence rate during 2008-2012 for CRC among adults age 20-49 years[2]



Rate for Finland unavailable.
[a] Rate based on data during 2008-2010; [b] Excludes Nunavut, Quebec, and Yukon; [c] Excluded from trend analysis due to insufficient number of annual cases; [d] Rate based on data during 2008-2011.

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer

Adapted from: 1. Stoffel EM, Murphy CC. Gastroenterology. 2020;158:341-53; 2. Siegel RL, et al. Gut. 2019;68:2179-85

EOCRC PATIENTS HAVE A HIGHER 5-YEAR SURVIVAL THAN PATIENTS WITH LOCRC FOR ALL STAGES OF DIAGNOSIS…

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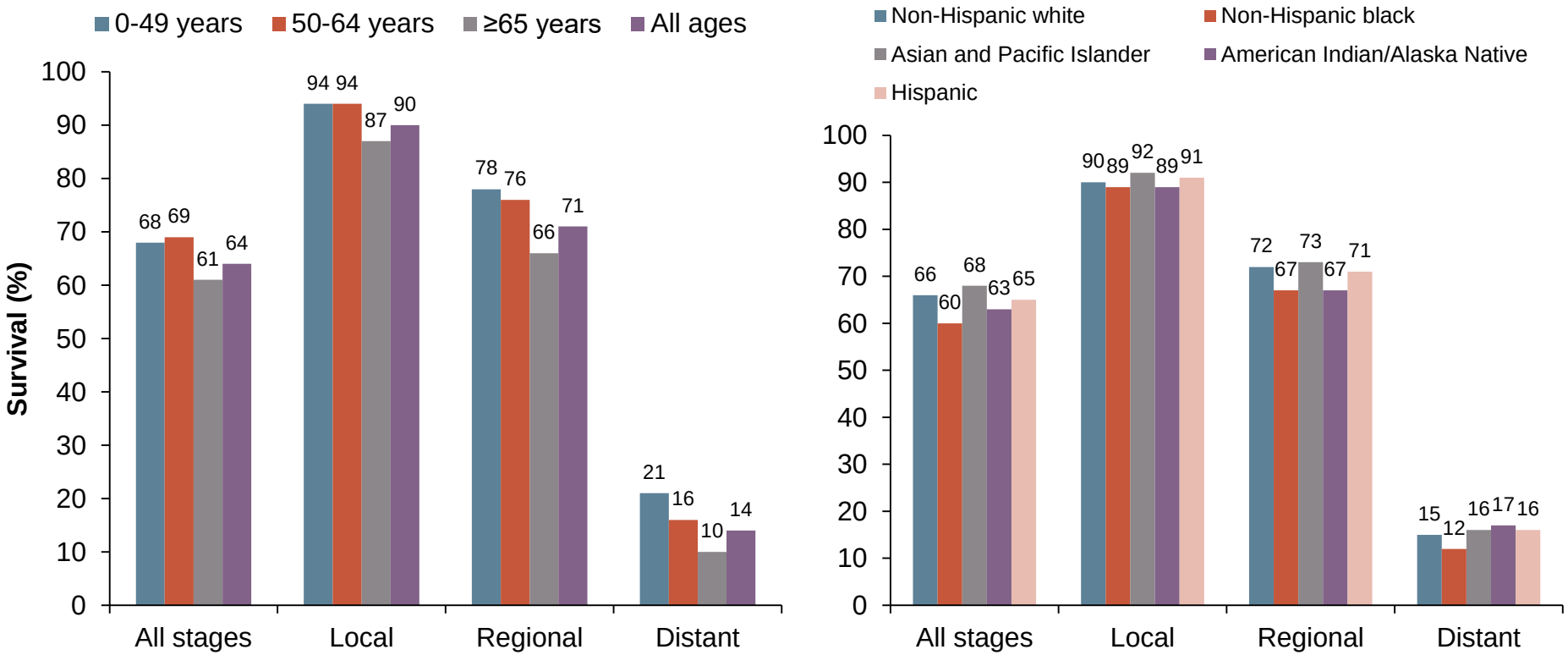
CRC: 5-year survival by age and race/ethnicity, 2009-2015



… yet overall survival among patients age <50 years (68%) is similar to that in patients age 50-64 years (69%) because of a later stage at diagnosis

Cause-specific survival rates are the probability of not dying from colorectal cancer within 5 years of diagnosis.

Rates are based on cases diagnosed from 2009 to 2017, all followed through 2016. Rates for American Indians/Alaska Natives are based on small case numbers, particularly for distant-stage disease.

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer

American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Available from: www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf. Accessed November 2022; Surveillance, Epidemiology, and End Results (SEER) Program. Available from: https://seer.cancer.gov/data/. Accessed November 2022

Adapted from: American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022.

RISK FACTORS

POTENTIAL CAUSES/RISK FACTORS

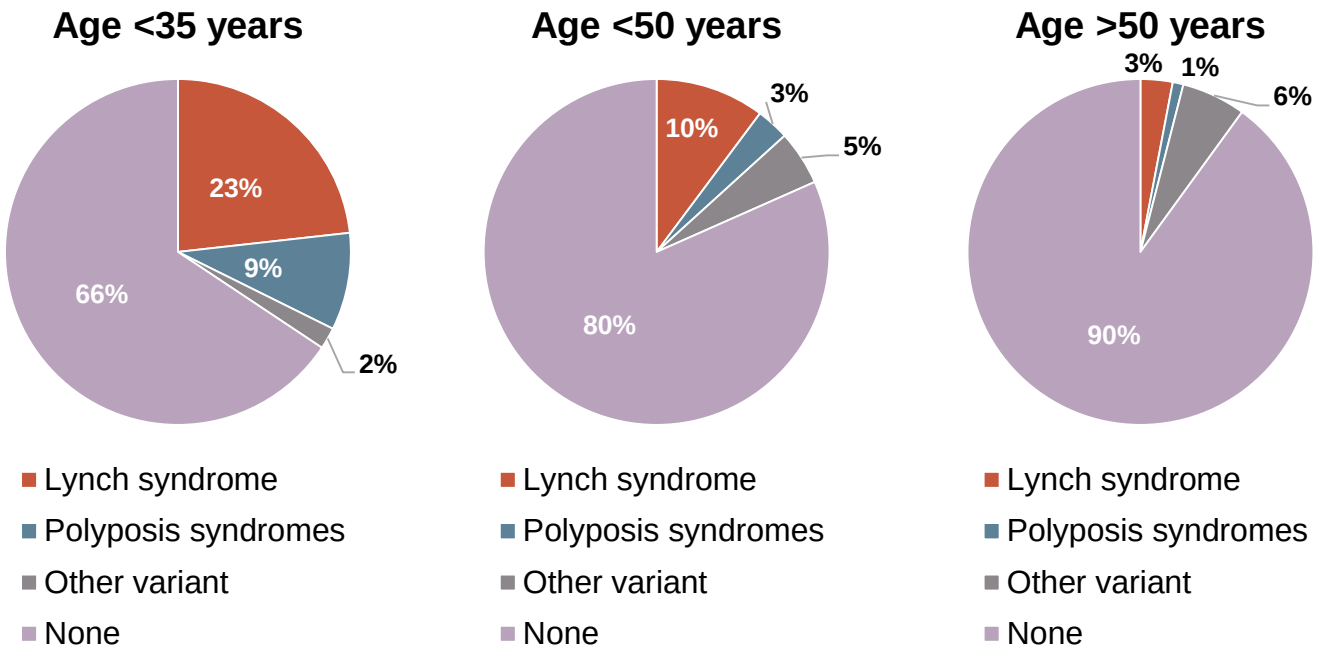
- **Most cases are sporadic**
  - Hereditary syndromes are more frequent in EOCRC vs LOCRC (16-25% vs 10-15%)
    - Lynch syndrome being the most frequent
  - Pathogenic germline variants are present in 1 in 6 patients with EOCRC
  - Incidences of familial syndromes are stable and are not likely contributing to the overall rise in EOCRC cases
- **Factors affecting the gut microbiome**:
  - Changing dietary habits/westernised diet
    - More red and processed meat
    - More refined grains
    - More processed sugar
  - Obesity (especially abdominal fat)
  - Smoking
  - Sedentary behaviour
  - Prolonged use of antibiotics

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer

Hur J, et al. Gut. 2021;70:2330-6; Møller P, et al. Gut. 2018;67:1306-316; Nguyen LH, et al. JNCI Cancer Spectr. 2018;2:pky073; REACCT Collaborative. JAMA Surg. 2021;156:865-74; Schumacher AJ, et al. Cancer Epidemiol Biomarkers Prev. 2021;30:1792-8; Sinicope FA, et al. N Engl J Med. 2022;386:1547-58; Tabung FK, et al. JAMA Oncol. 2018;4:366-73; Wan QY, et al. Gut. 2020;69:2059-2060; Yurgelun MB, et al. J Clin Oncol. 2017;35:1086-95; Zheng X, et al. J Natl Cancer Inst. 2021; 113:543-52

MOST CRC CASES (~80%) ARE SPORADIC, REGARDLESS OF AGE

Prevalence of pathogenic variants by age at CRC diagnosis



Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
MLH1	*APC*	*BRCA1*	*CHEK2*
MSH2	*MUTYH*	*BRCA2*	*ATM*
MSH6	*SMAD4*	*TP53*	*NBN*
PMS2	*BMPR1A*	*PALB2*	*BARD1*
	PTEN	*CDKN2A*	*BRIP1*
	POLE		

CRC, colorectal cancer

Adapted from: Stoffel EM, Murphy CC. Gastroenterology. 2020;158:341-53

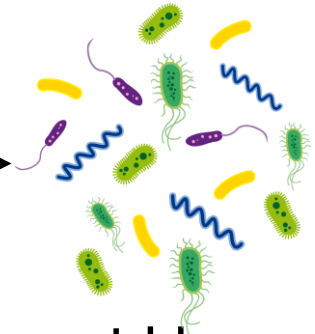
FACTORS IMPACTING THE GUT MICROBIOTA AND THE DEVELOPMENT OF EOCRC?

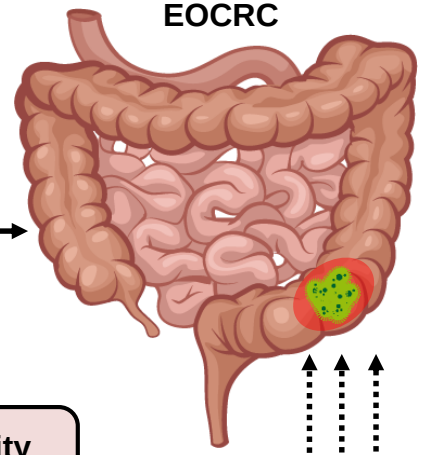
Early-life exposures

- Mode of nutritional provision
  - Breastfeeding
  - Diet formula
  - Pre-probiotic supplement
- Mode of delivery
  - Caesarean
  - Vaginal
- Environment
  - Psychological and/or physical stress
- Family environment and pets
- Genetics
- Antibiotics
  - 2.7 courses by age 2 years
  - 10.9 courses by age 10 years
- Maternal infection, disease and/or medication
- Maternal nutrition
- Maternal stress

Exposomal elements

- Global westernisation of diet
- Unhealthy cooking practices
- Red and processed meats
- Synthetic dyes
- Monosodium glutamate (MSG)
- Titanium dioxide
- High-fructose corn syrup





Immunity and/or inflammation

Obesity

Diabetes

Infancy → **Childhood** → **Adulthood**

EOCRC, early-onset colorectal cancer

Adapted from: Hofseth LJ, et al. Nat Rev Gastroenterol Hepatol. 2020;17:352-64

GUT MICROBIOME

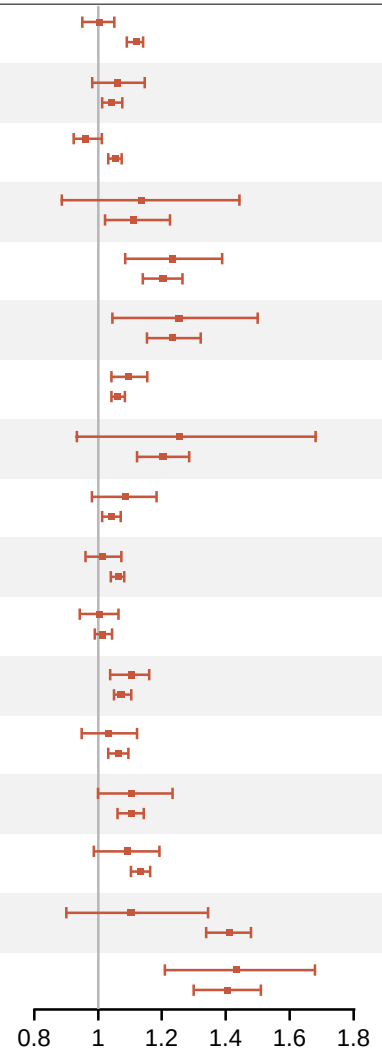
- **Gut microbes** interact with the host immune system and **influence the antitumour immune response**
- Patients with CRC have **reduced bacterial diversity** compared to healthy persons
- Firmicutes, Bacteroidetes, enterotoxigenic *Bacteroides fragilis*, oral anaerobe *Fusobacterium nucleatum* are enriched in CRC
- **There are age-related differences in gut microbial composition**
  - *Flavonifractor plautii* is an important bacterial species in EOCRC
  - Genus Streptococcus contains the key phylotype in the LOCRC

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer

Flemer B, et al. Gut. 2017;66:633-43; Garrett WS. Science. 2019;364:1133-5; Ghosh TS, et al. ELife. 2020;9:e50240; Yang Y, et al. Nat Commun. 2021;12:6757

RISK ESTIMATES FOR EOCRC VS LOCRC

Risk Factor		ORR (95% CI)
BMI	Early-onset CRC	1.00 (0.95, 1.05)
	Late-onset CRC	1.12 (1.09, 1.14)
Height	Early-onset CRC	1.06 (0.98, 1.14)
	Late-onset CRC	1.04 (1.01, 1.07)
Pack-years of smoking	Early-onset CRC	0.96 (0.92, 1.01)
	Late-onset CRC	1.05 (1.03, 1.07)
Sedentary lifestyle	Early-onset CRC	1.13 (0.88, 1.44)
	Late-onset CRC	1.11 (1.02, 1.22)
Alcohol use (0 g/day)	Early-onset CRC	1.23 (1.08, 1.39)
	Late-onset CRC	1.20 (1.14, 1.26)
Alcohol use (>28 g/day)	Early-onset CRC	1.25 (1.04, 1.50)
	Late-onset CRC	1.23 (1.15, 1.32)
Lower educational attainment	Early-onset CRC	1.10 (1.04, 1.16)
	Late-onset CRC	1.06 (1.04, 1.08)
Diabetes diagnosis	Early-onset CRC	1.25 (0.93, 1.68)
	Late-onset CRC	1.20 (1.12, 1.28)
Lower total folate intake	Early-onset CRC	1.08 (0.98, 1.18)
	Late-onset CRC	1.04 (1.01, 1.07)
Lower fruit intake	Early-onset CRC	1.01 (0.96, 1.07)
	Late-onset CRC	1.06 (1.04, 1.08)
Lower vegetable intake	Early-onset CRC	1.00 (0.94, 1.06)
	Late-onset CRC	1.01 (0.99, 1.04)
Greater red meat intake	Early-onset CRC	1.10 (1.04, 1.16)
	Late-onset CRC	1.07 (1.05, 1.10)
Greater processed meat intake	Early-onset CRC	1.03 (0.95, 1.12)
	Late-onset CRC	1.06 (1.03, 1.09)
Lower total fiber intake	Early-onset CRC	1.11 (1.00, 1.23)
	Late-onset CRC	1.10 (1.06, 1.14)
Lower total calcium intake	Early-onset CRC	1.09 (0.99, 1.19)
	Late-onset CRC	1.13 (1.10, 1.16)
No aspirin use	Early-onset CRC	1.10 (0.90, 1.34)
	Late-onset CRC	1.41 (1.34, 1.48)
No NSAID use	Early-onset CRC	1.43 (1.21, 1.68)
	Late-onset CRC	1.40 (1.30, 1.51)



BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio

Adapted from: Archambault AN, et al. JNCI Cancer Spectr. 2021;5:pkab029

DISEASE CHARACTERISTICS AND DIAGNOSIS

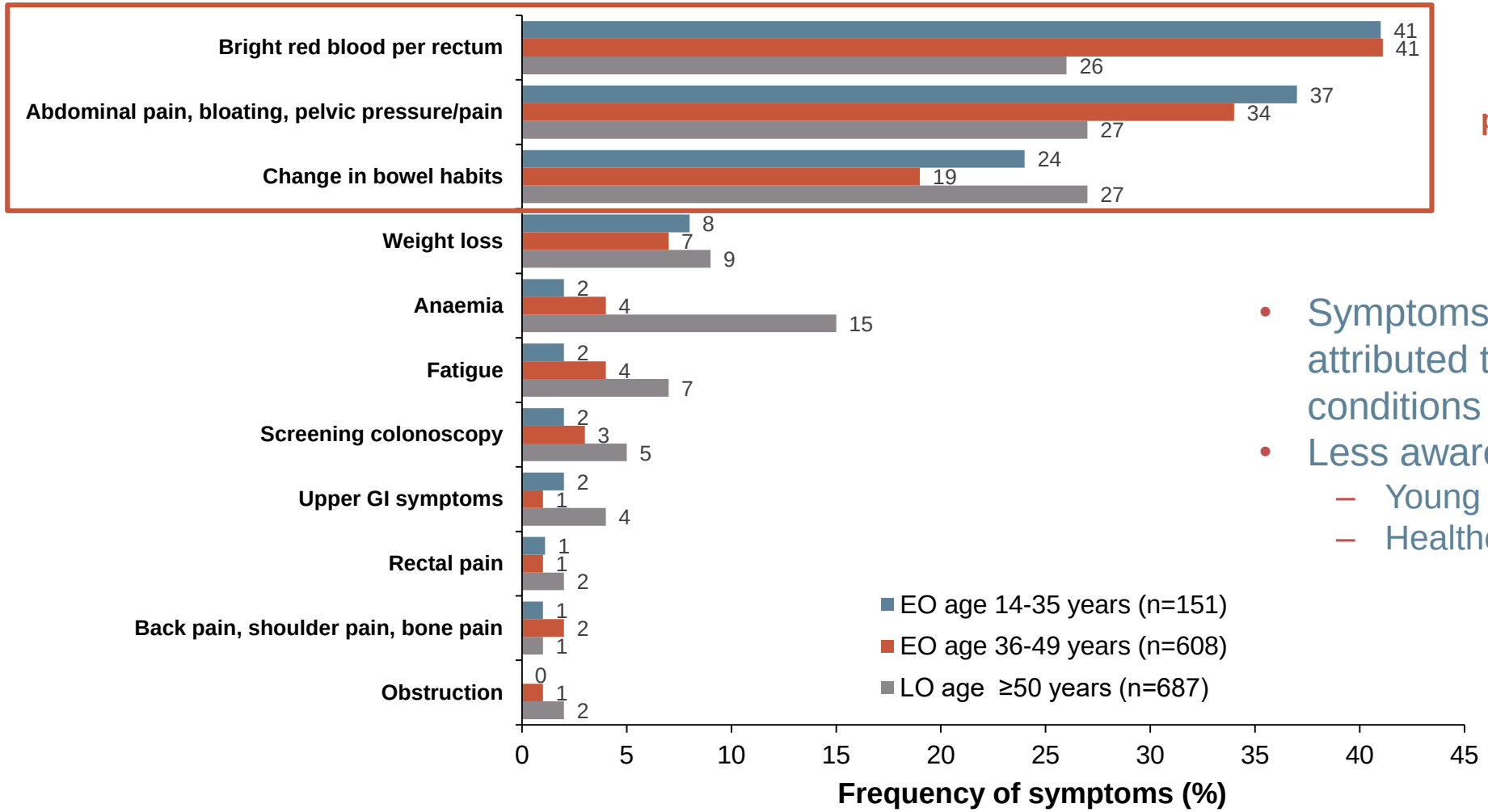
EOCRC: DISEASE CHARACTERISTICS

- **More than 70%** of EOCRCs are in the **left colon** at presentation
- Higher rates of **poorly differentiated tumours** and more **frequent signet ring cells**
- Approximately 1 in 5 individuals diagnosed with CRC at age <50 years carries a germline mutation associated with cancer
- Higher frequencies of microsatellite instability high (MSI-H; Lynch syndrome)
- Higher risk of **metachronous disease**
- **EOCRC** more likely to be **diagnosed at advanced stages** (stage III-IV) compared to LOCRC
  - Significantly longer time to diagnosis and longer duration of symptoms compared to older patients

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer

Akimoto N, et al. Nat Rev Clin Oncol. 2021;18:230-43; Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92; Chang DT, et al. Mod Pathol. 2012;25:1128-39; Dozois EJ, et al. Medicine (Baltimore). 2008;87:259-63;
Meyer JE, et al. Cancer. 2010;116:4354-9; Mork ME, et al. J Clin Oncol. 2015; 33:3544-9; Pearlman R, et al. JAMA Oncol. 2017;3:464-71; Saraste D, et al. Br J Surg. 2020;107:301-9; Stoffel EM, et al. Gastroenterology. 2018;154:897-905.e1

CLINICAL PRESENTATION OF EOCRC VS LOCRC



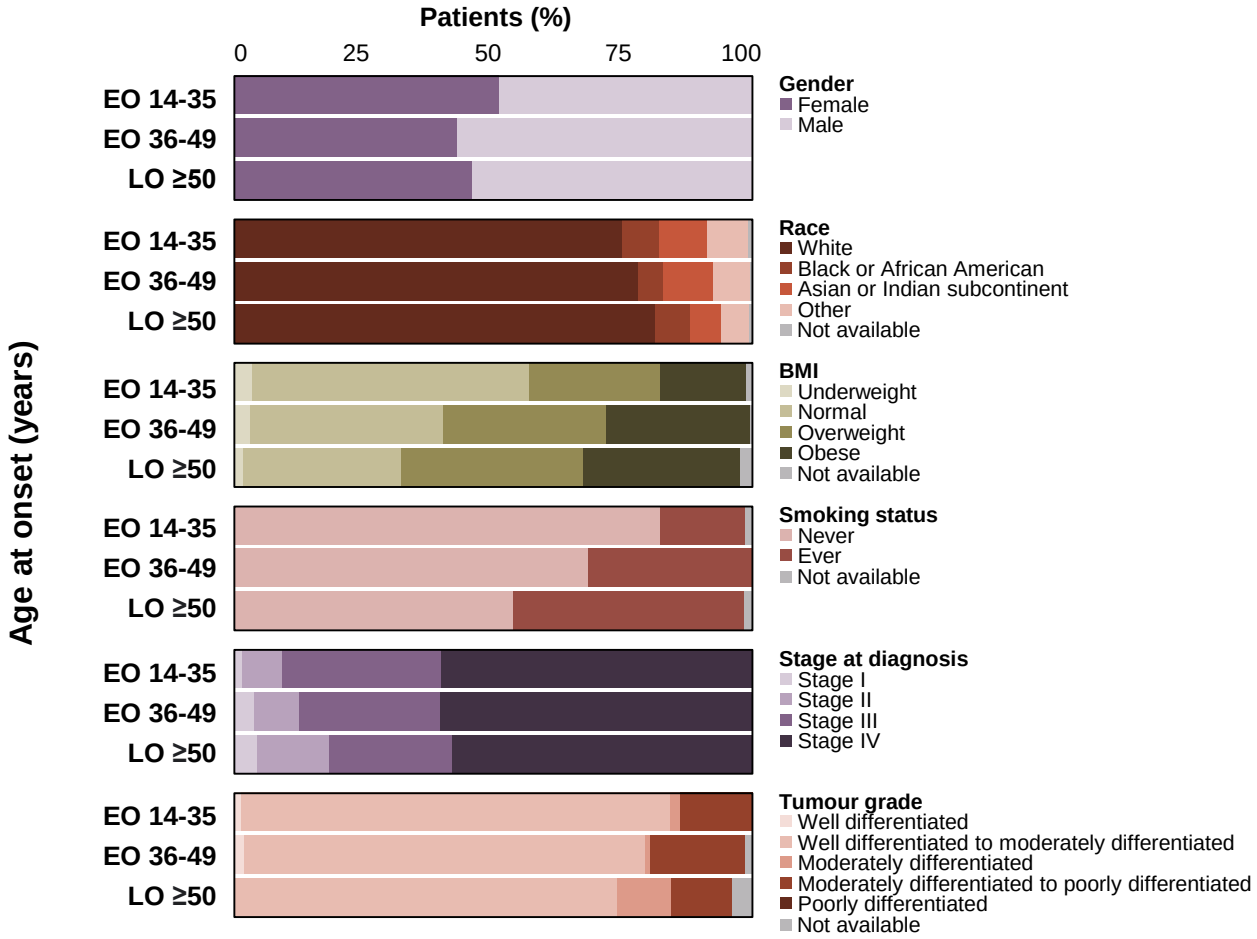
Most common symptoms at presentation for EOCRC

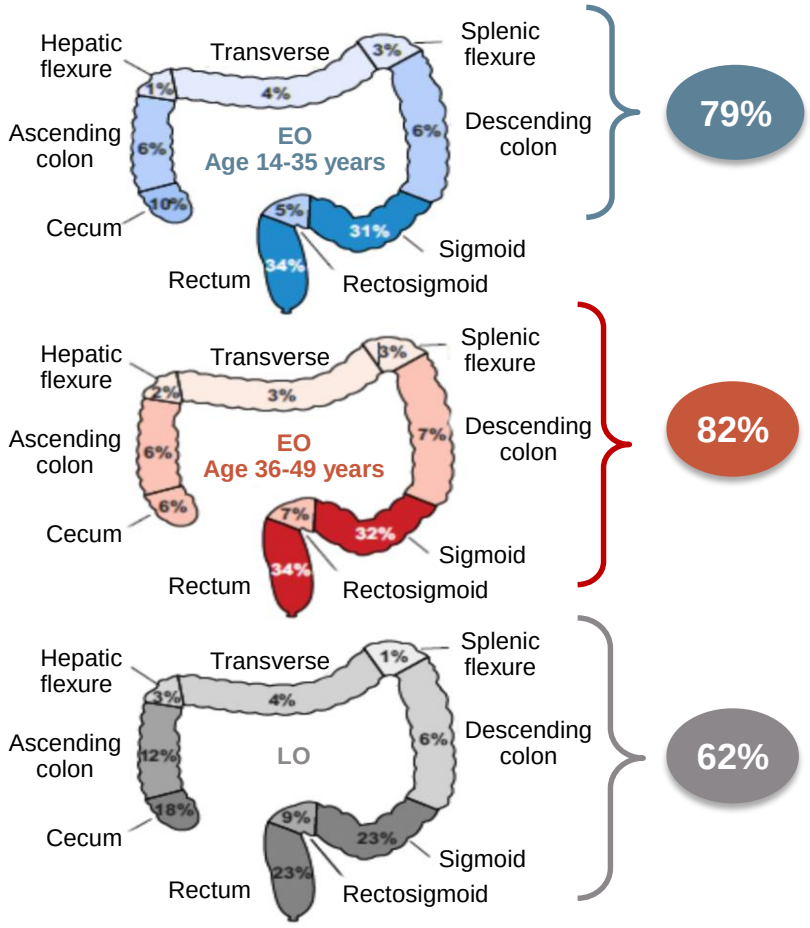
- Symptoms are frequently attributed to common, benign conditions
- Less awareness of CRC:
  - Young patients
  - Healthcare providers

CRC, colorectal cancer; EO, early onset; EOCRC, early-onset colorectal cancer; GI, gastrointestinal; LO, late onset

Adapted from: Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92

CLINICAL CHARACTERISTICS ARE SIMILAR REGARDLESS OF AGE AT ONSET





No significant clinical or histological differences
EO less likely to be diagnosed early

Higher incidence of left-sided tumours in EOCRC

CRC, colorectal cancer; EO, early onset; EOCRC, early-onset colorectal cancer; LO, late onset

Adapted from: Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92

PATHOLOGICAL AND MOLECULAR FEATURES OF EOCRC

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Pathological features and molecular profile of EOCRC

Pathological features	Molecular profile
Poor differentiation	Microsatellite stability
Mucinous tumours	More likely to exhibit LINE-1 hypomethylation and TP53 sequence variations
Signet-ring morphology	Less frequently harbour *KRAS, BRAF* V600E, and *APC* sequence variations
Perineural/venous invasion	Promoter methylation of CpG islands

EOCRC, early-onset colorectal cancer; LINE-1, long interspersed nuclear elements; TP53, tumour protein 53

Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92; Lieu CH, et al. Clin Cancer Res 2019;25:5852-8; REACCT Collaborative. JAMA Surg. 2021;156:865-74

Adapted from: REACCT Collaborative. JAMA Surg. 2021;156:865-74

TREATMENT AND QOL CONSIDERATIONS

QOL, quality of life

TREATMENT CHARACTERISTICS OF EOCRC

- Younger patients with EOCRC are:
  - More likely to receive **more adjuvant treatments**
  - More likely to receive **more intense regimens**
  - More likely to complete the planned treatment (and with a high dose intensity)
- **No apparent OS difference** between EOCRC and LOCRC in either initial or advanced settings
  - After adjusting for staging differences
- Attention should be given to long-term cancer survivorship in patients with EOCRC as they face distinct survivorship challenges from older CRC patients

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer; OS, overall survival

Fontana E, et al. J Clin Oncol. 2021;39:4009-19; Jin Z, et al. J Natl Cancer Inst. 2021;113:1693-704; Knuertz PJ, et al. JAMA Surg. 2015; 150:402-9; Lipsyc-Sharf M, et al. J Natl Cancer Inst. 2022;114:427-35

IDEA DATABASE ANALYSES EOCRC VS LOCRC: CANCER SPECIFIC SURVIVAL

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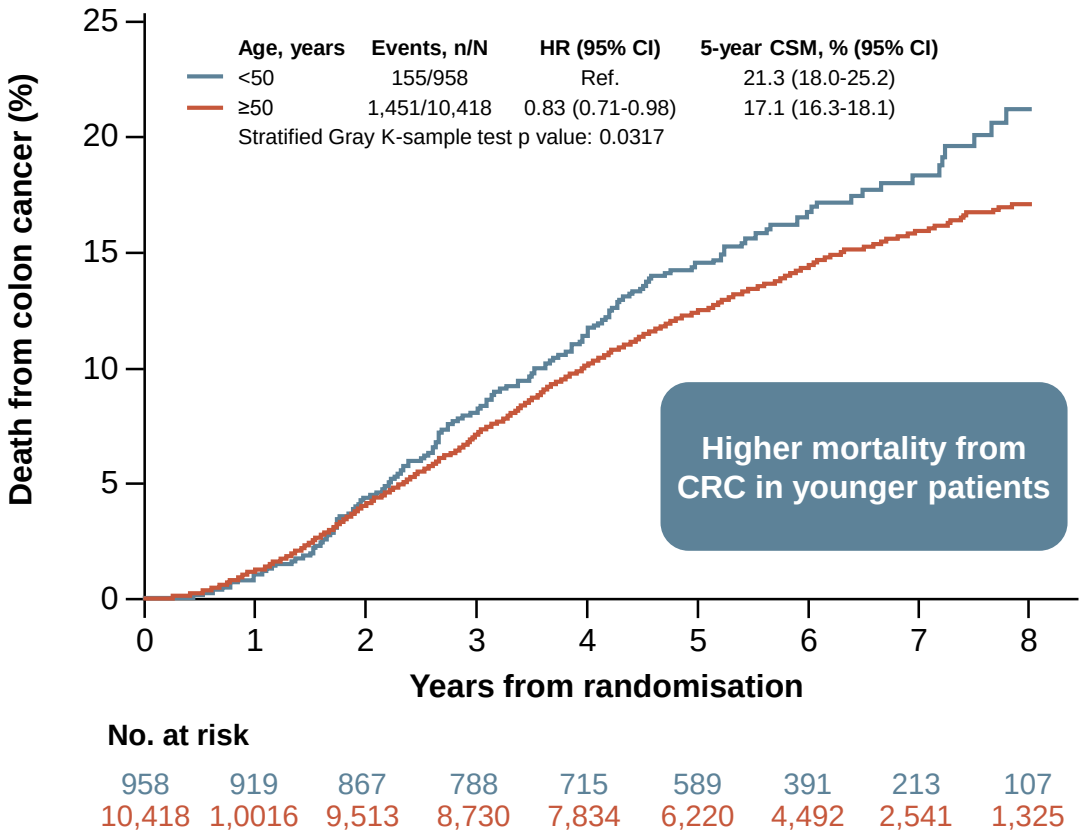
Cancer-specific survival: stage III patients



		EOCRC	LOCRC	Adjusted HR (95% CI)	p value
3-year RFS rate,%	High-risk stage II	87.6 (84.1-91.3)	88.0 (86.8-89.2)	0.98 (0.72-1.34)	0.91
	Low-risk stage III (T1-3 N1)	81.6 (78.0-85.3)	84.0 (83.0-84.9)	0.99 (0.80-1.22)	0.90
	High-risk stage III (T4 and/or N2)	**54.5 (49.7-59.9)**	**64.5 (63.1-65.9)**	**0.74 (0.64-0.87)**	**0.0003**
				10% difference in RFS	
5-year CSM rate, %	High-risk stage II	4.8 (2.9-7.8)	7.6 (6.6-8.7)	1.38 (0.84-2.27)	0.21
	Low-risk stage III (T1-3 N1)	7.1 (5.1-9.8)	6.9 (6.3-7.5)	0.96 (0.70-1.30)	0.78
	High-risk stage III (T4 and/or N2)	**23.9 (20.0-28.6)**	**20.7 (19.5-21.9)**	**0.81 (0.67-0.99)**	**0.040**
				3% difference in CSM	

CI, confidence interval; CRC, colorectal cancer; CSM, cancer-specific mortality; EOCRC, early-onset colorectal cancer; HR, hazard ratio; LOCRC, late-onset colorectal cancer; RFS, recurrence-free survival

Adapted from: Fontana E, et al. J Clin Oncol. 2021;39:4009-19 (ASCO 2021, oral presentation)

TREAT BY STAGE NOT BY AGE

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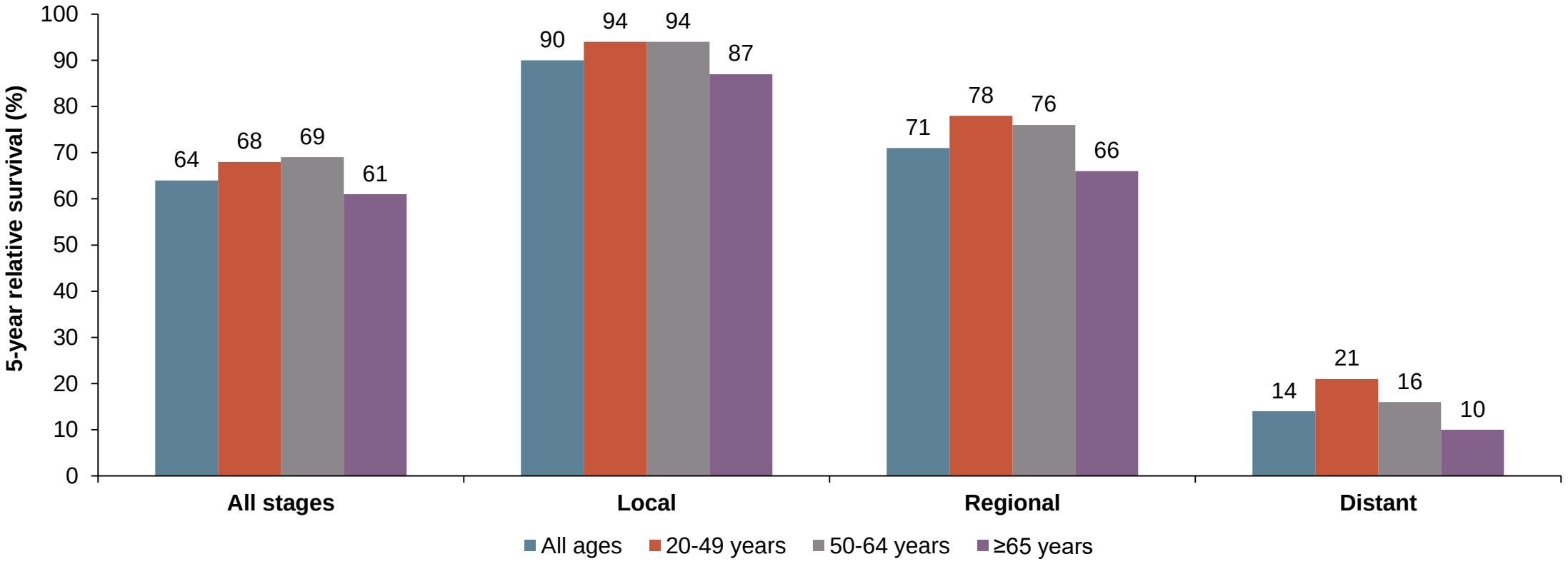
Relative survival by age at diagnosis[1]



Aggressive treatment regimens based solely on the age at diagnosis are not warranted[2]

1. Siegel RL, et al. CA Cancer J Clin. 2020;70:145-64; 2. Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92

Adapted from: Siegel RL, et al. CA Cancer J Clin. 2020;70:145-64

OUTCOMES ARE SIMILAR REGARDLESS OF AGE OF ONSET

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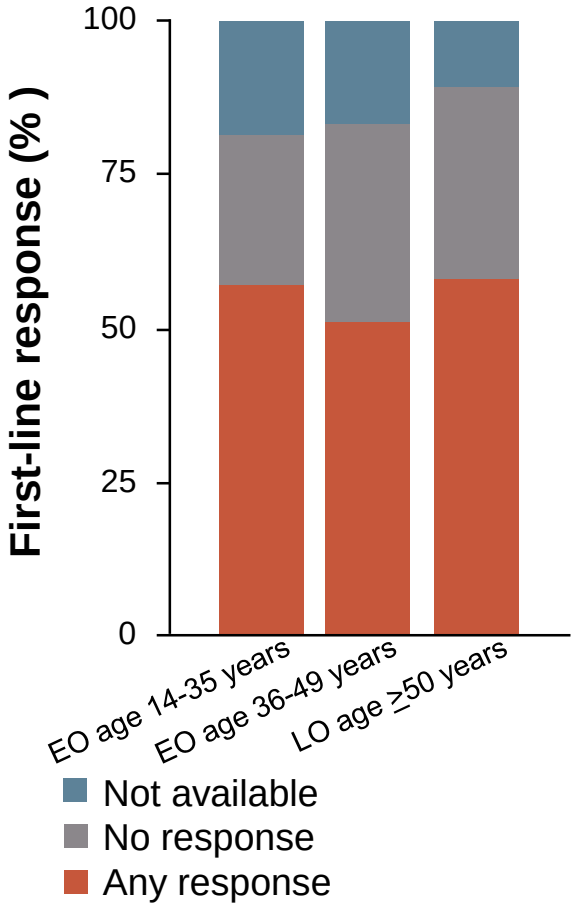
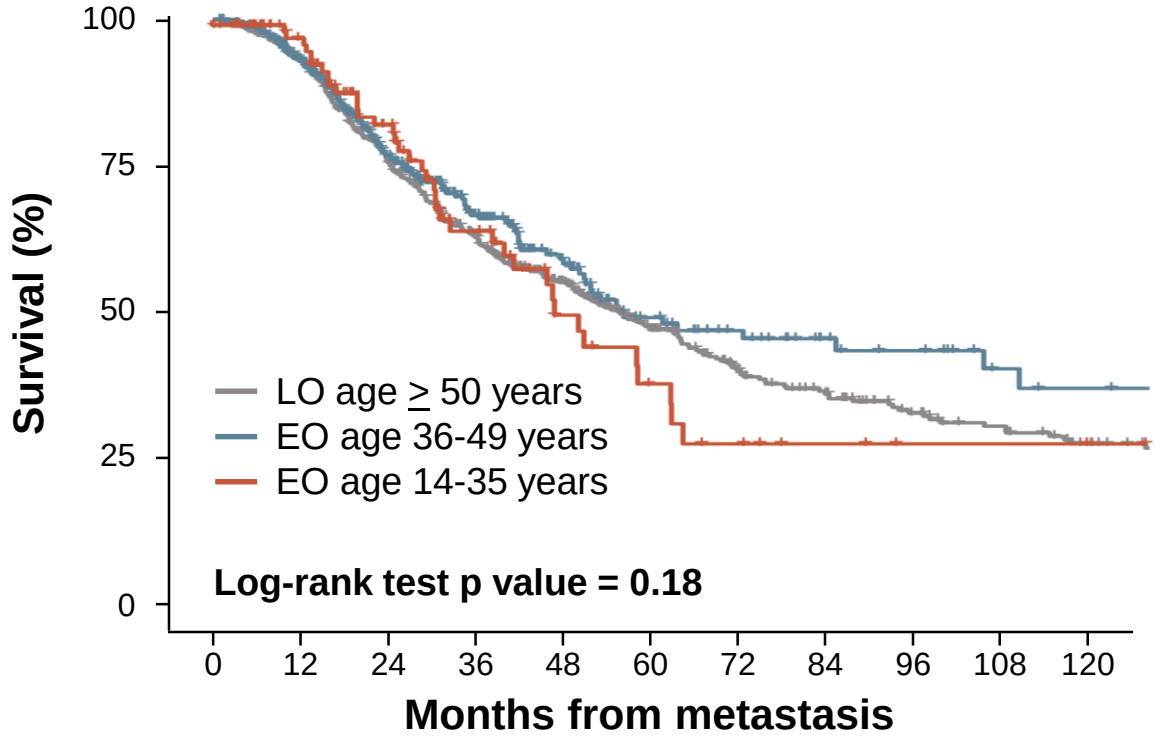
Best response to first-line chemotherapy at time of metastasis





No. of cases at risk

574	529	417	320	230	149	103	85	63	53	42
455	349	210	120	73	46	34	24	19	12	10
110	85	56	33	18	11	7	4	2	2	1

EO, early onset; LO, late onset

Adapted from: Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92

EOCRC VS LOCRC: NO DIFFERENCE IN SURVIVAL DESPITE FAVOURABLE BASELINE CHARACTERISTICS AND HIGHER TREATMENT INTENSITY

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HRs for OS and PFS by age (N=2,326)

Outcome and analysis	Age <50 years	Age ≥50 years	p value
OS			
Events/patients, n/n	416/514	1,557/1,812	–
Median OS, months (95% CI)	27.07 (25.04-30.06)	26.12 (24.94-27.30)	0.12[a]
Unadjusted HR (95% CI)	0.92 (0.82-1.02)	Ref.	0.12[b]
Multivariable adjusted HR (95% CI)[c]	0.98 (0.88-1.10)	Ref.	0.78[b]
PFS			
Events/patients, n/n	473/514	1,700/1,812	–
Median PFS, months (95% CI)	10.87 (9.99-11.50)	10.55 (10.12 to 10.94)	0.67[a]
Unadjusted HR (95% CI)	0.98 (0.88-1.08)	Ref.	0.67[b]
Multivariable adjusted HR (95% CI)[c]	1.02 (0.92-1.13)	Ref.	0.67[b]
ORR, n (%)	297 (57.8)	1,009 (55.7)	0.40[d]

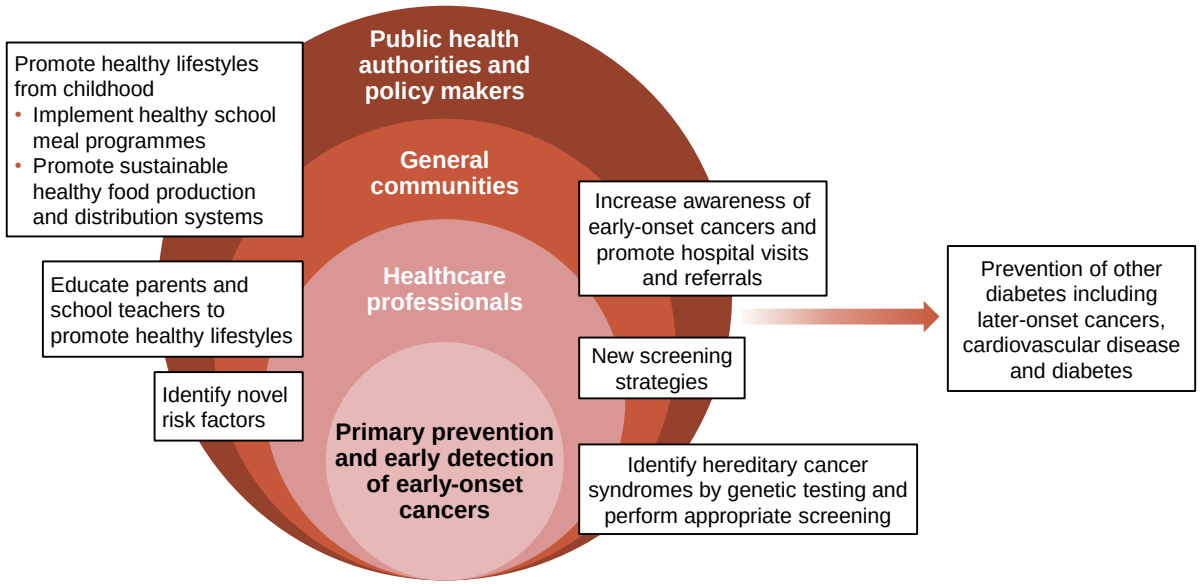
[a] p values and associated median OS and PFS were calculated using the Kaplan-Meier method. All tests were 2-sided
[b] p values for hazard ratios were calculated in corresponding Cox model. All tests were 2-sided
[c] Adjusted with Cox proportional hazards analysis for patient sex (male vs female), race (white vs black vs other), Easter Cooperative Oncology Group performance status (0 vs 1 to 2), primary tumour location (right and transverse colon vs left colon vs unknown), primary tumour unresected (no vs yes), prior radiation (no vs yes), prior adjuvant chemotherapy (no vs yes), *KRAS* mutation status (wild-type vs mutant vs unknown), diabetes (no vs yes, as reported in a diet and lifestyle questionnaire), BMI at study entry (<21 vs 21 to <25 vs 25 to <30 vs 30 to <35 vs ≥35 kg/m^2, 3 patients with missing BMI were recoded into the majority category in 25 to <30 kg/m^2, protocol chemotherapy received (FOLFIRI vs mFOLFOX6), and arm of trial (bevacizumab vs cetuximab vs dual-antibody therapy)
[d] p value for the ORR is based on 2-sided χ^2 test

BMI, body mass index; CI, confidence interval; EOCRC, early-onset colorectal cancer; FOLFIRI, leucovorin, fluorouracil, and irinotecan; HR, hazard ratio; LOCRC, late-onset colorectal cancer; mFOLFOX6, leucovorin, fluorouracil and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ref., referent

Adapted from: Lipsyc-Sharf M, et al. J Natl Cancer Inst. 2022;114:427-35

SCREENING AND PREVENTION

Implications and benefits of prevention efforts for early-onset cancers



CRC screening

- The increasing incidence of CRC in younger populations recently led to the United States lowering the age of CRC screening from age 50 years to age 45 years
- It was projected that this could prevent 29,400 CRC cases and 11,100 deaths over the next five years but at a cost of $10.4 billion
- Cost-effective screening solutions are required

CRC, colorectal cancer

Ugai T, et al. Nat Rev Clin Oncol. 2022;19:656-73; Ladabaum U, et al. Gastroenterology 2019; 157: 137-148

Adapted from: Ugai T, et al. Nat Rev Clin Oncol. 2022;19:656-73

THE PSYCHOSOCIAL IMPACT OF EOCRC

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Challenges for people with EOCRC

Emotional Distress

- Worsening anxiety
- Embarrassment with bowel movements
- Low mood
- Financial burden
- Premature confrontation with mortality

Physical Burden

- CRC has a unique and damaging stigma
  - Bowel movements
  - Digestive/GI symptoms
  - Ostomy bags
  - Sleeping disorders
  - Impact on body image and intimacy
  - Reproductive health and family planning

Social impact

- Time away from family due to treatment
- Physical symptoms affect interpersonal relationships
- Difficulties coping with children
- The need for family members to provide care to patient
- Inability to perform social roles

Work impact

- Impact on ability to perform role
- Most are juggling various roles
  - Marriage/partnerships
  - Caring responsibilities
  - Career
  - Education

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; GI, gastrointestinal

Khoo A, et al. Cancer Medicine 2022; 11: 1688-1700; Eng C, et al. Lancet Oncol 2022; 23: e116–28

SUMMARY

SUMMARY

- The **incidence of EOCRC is rising globally**, but the reason for this is unclear
- **Potential risk factors** include a **westernised diet, obesity, antibiotics** and alterations in the **gut microbiome**
- Patient with EOCRC tend to **present with advanced disease stage** and unfavourable histopathological features
- Lower awareness of CRC, lack of screening, an underappreciation of symptoms, and reluctance to seek medical care may contribute to delayed diagnosis and advanced stage at diagnosis
- **EOCRCs are more commonly left-sided** and present with rectal bleeding and abdominal pain, but are otherwise **clinically and genomically indistinguishable from LOCRCs**
- Although genetic predisposition plays a role in EOCRC, **most cases are sporadic**
- Survival data are limited and conflicting; despite accessing more neoadjuvant and adjuvant therapy, **patients with EOCRC appear to have oncological outcomes equivalent to those of older counterparts**
- Aggressive treatment regimens based solely on the age at CRC diagnosis are **not warranted**
- More clinical trials in this population are required

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer

Akimoto N, et al. Nat Rev Clin Oncol. 2021;18:230-43; Cercek A, et al. J Natl Cancer Inst. 2021;113:1683-92; REACCT Collaborative. JAMA Surg. 2021;156:865-74

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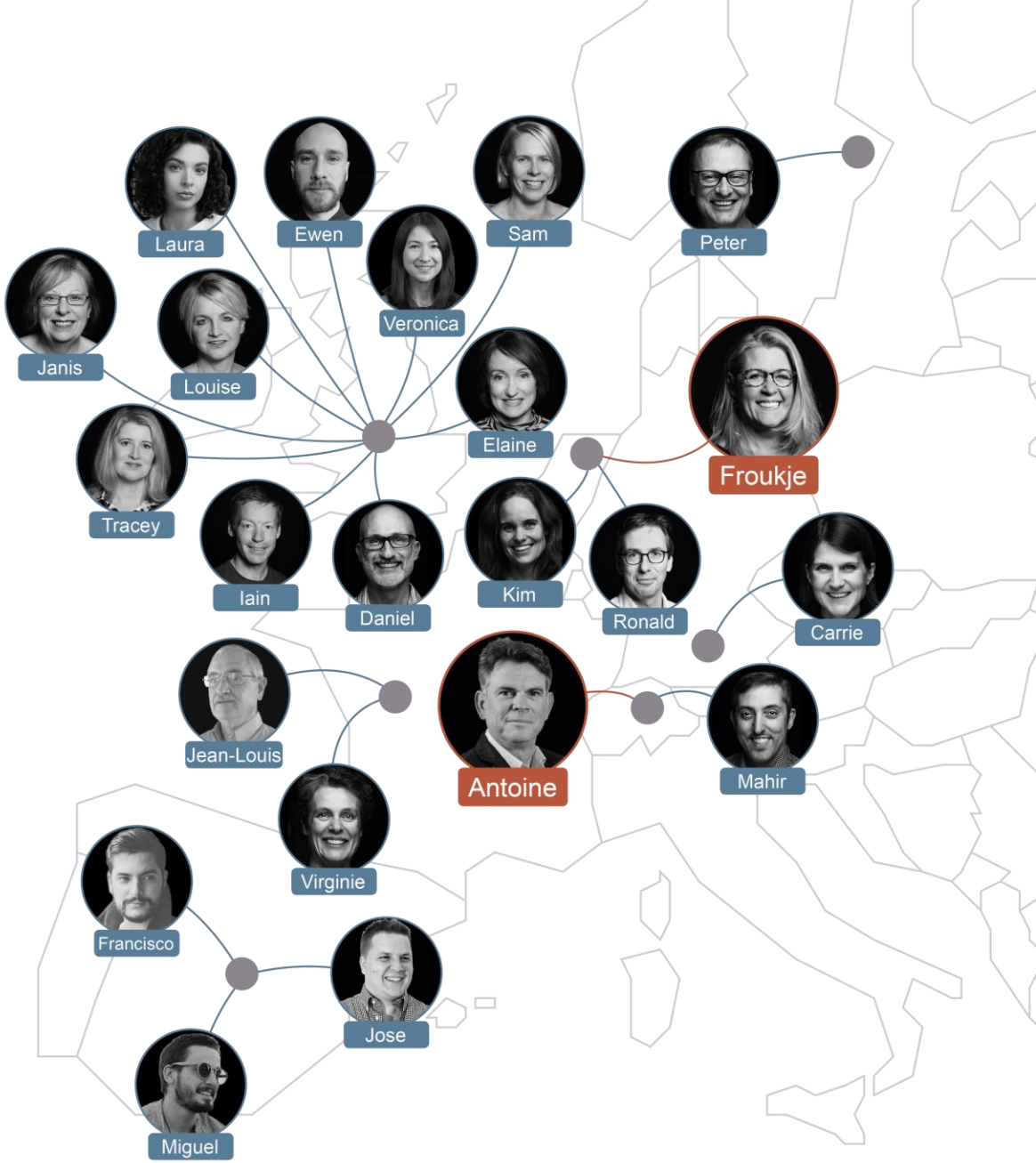

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