Early- Age Onset Colorectal Cancer Updates: Understanding the Latest Science and Practice to Inform Care Across the Continuum

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Concurrent Session
November 21, 2024
11:00 AM - 12:15 PM

Speakers

Moderator: **Xavier Llor**, MD, PhD, Yale School of Medicine

- **Caitlin Murphy**, PhD, UTHealth Houston
- **Tala Mahmoud**, MD, University of Virginia @TalaMahmoudMD
- **Yi-Qian Nancy You**, MD, MHSc, FACS, MD Anderson Cancer Center

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Epidemiology of Early-onset Colorectal Cancer:

Progress and Next Steps

Caitlin C. Murphy, PhD, MPH
UTHealth Houston School of Public Health

National Colorectal Cancer Roundtable
Thursday, November 21, 2024
Fort Worth, TX

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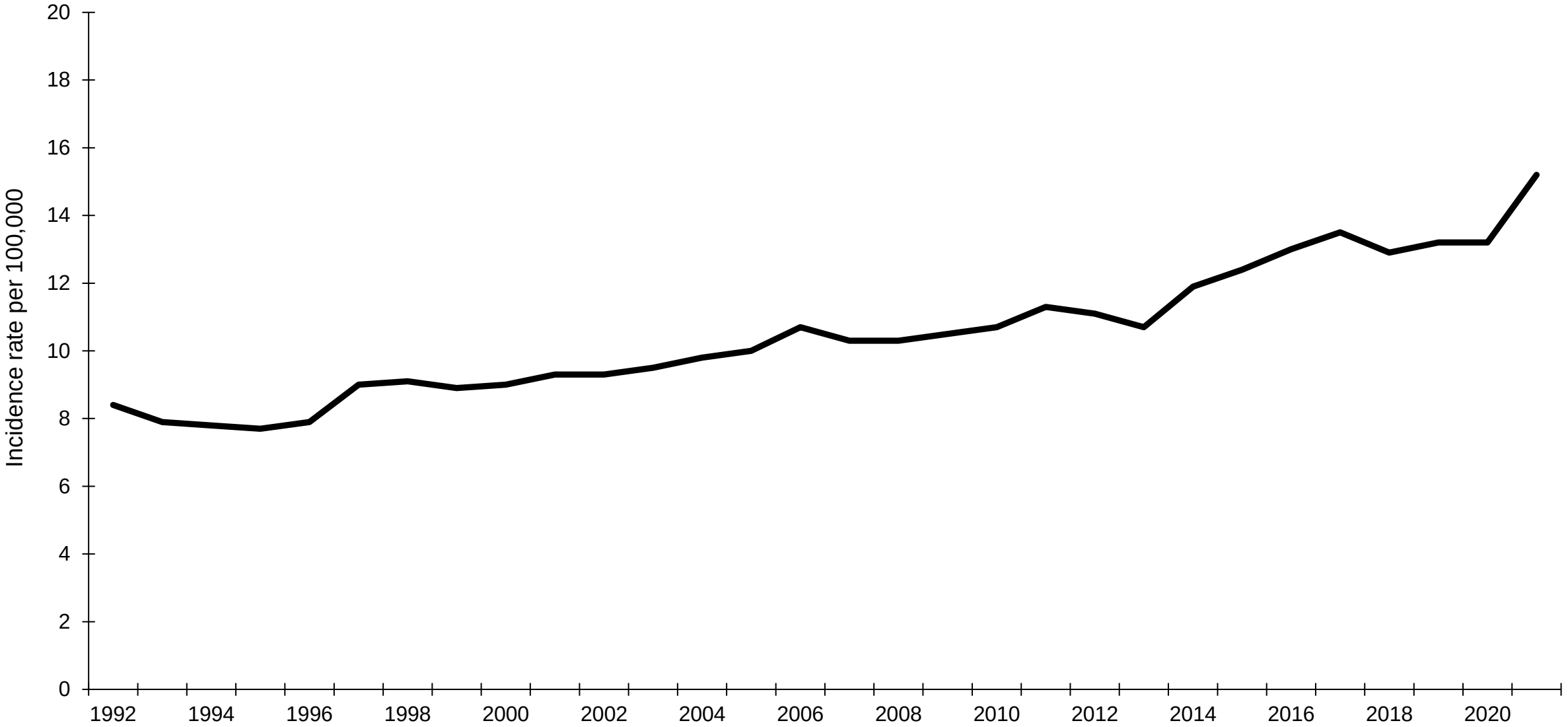
Consulting fees: Freenome, Universal Diagnostics

Increasing rates of early-onset colorectal cancer since early 1990s



SEER 12 Incidence, 1992-2021, Age 20-49

In 2017, the NCCRT prioritized unanswered research questions:

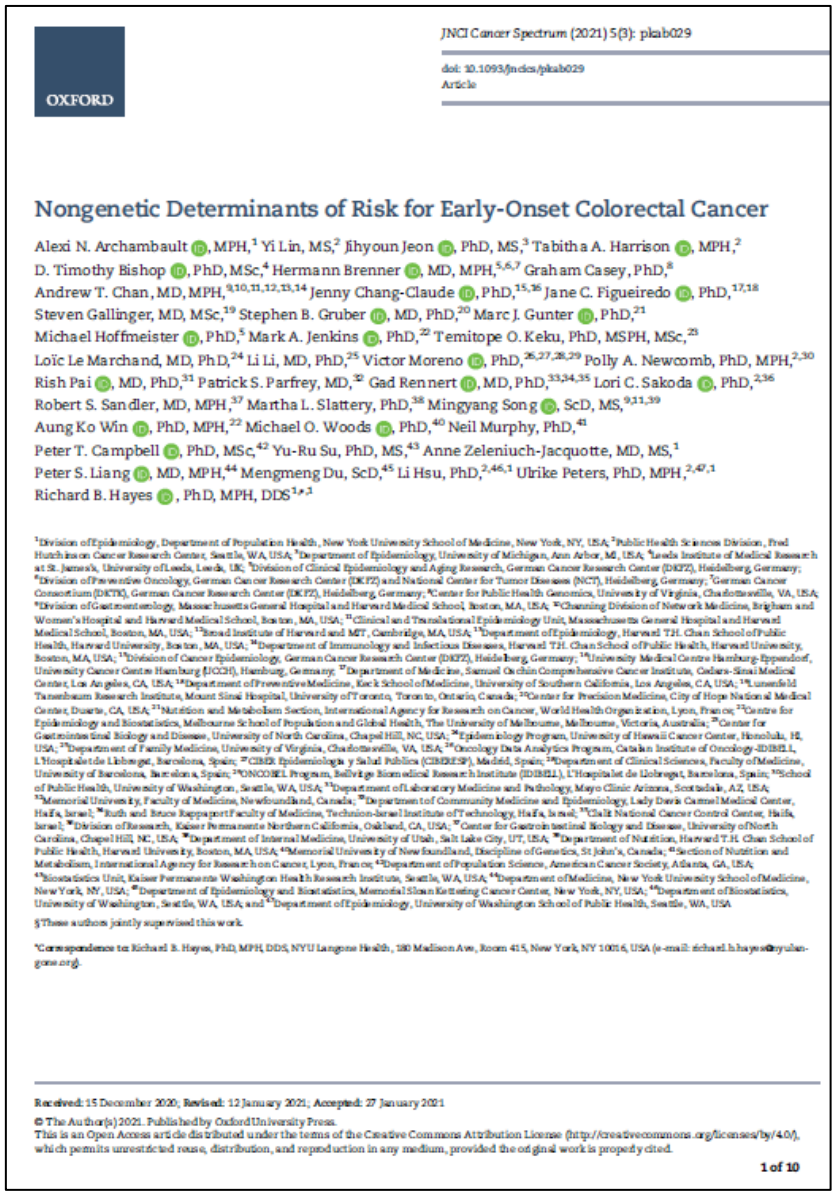
1. What is the role of known risk factors?
2. Do risk factors differ by site, i.e., colon vs. rectum?
3. What is the role of novel/proposed risk factors?
4. Are there vulnerable times of exposure related to risk for early-onset colorectal cancer?
5. Is early-onset colorectal cancer molecularly different than colorectal cancer in older adults?
6. What are best practices for implementing current recommendations for identifying and managing early-onset colorectal cancer?

Lowery JT, et al. Colorect Cancer 2020; 9(3).

1. What is the role of known risk factors?

Well-established risk factors, such as obesity, increase risk of early-onset colorectal cancer.

1. What is the role of known risk factors?



JNCI Cancer Spectrum (2021) 5(3): pkab029

doi: 10.1093/jncics/pkab029
Article

Nongenetic Determinants of Risk for Early-Onset Colorectal Cancer

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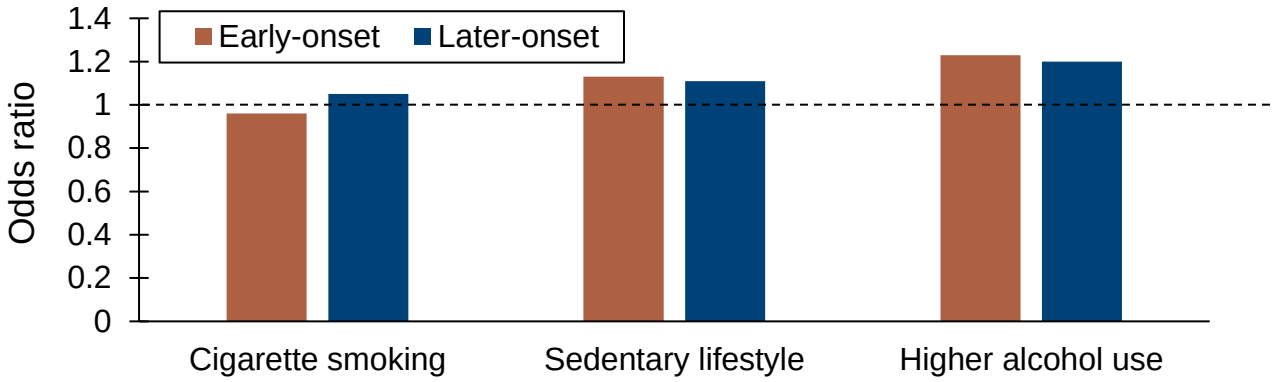
Near identical associations between dietary risk factors and early- vs. later-onset colorectal cancer

	Early-onset	Later-onset
	OR (95% CI)	OR (95% CI)
Lower folate	1.08 (0.98, 1.18)	1.04 (1.01, 1.07)
Lower fruit	1.01 (0.96, 1.07)	1.06 (1.04, 1.08)
Lower vegetable	1.00 (0.94, 1.06)	1.01 (0.99, 1.04)
Higher red meat	1.10 (1.04, 1.16)	1.07 (1.05, 1.10)
Higher processed meat	1.03 (0.95, 1.12)	1.06 (1.03, 1.14)
Lower fiber	1.11 (1.00, 1.23)	1.10 (1.06, 1.14)
Lower calcium	1.09 (0.99, 1.34)	1.13 (1.10, 1.16)

...and lifestyle-related risk factors



1. What is the role of known risk factors?

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GI CANCER

Association Between Metabolic Syndrome and the Risk of Colorectal Cancer Diagnosed Before Age 50 Years According to Tumor Location

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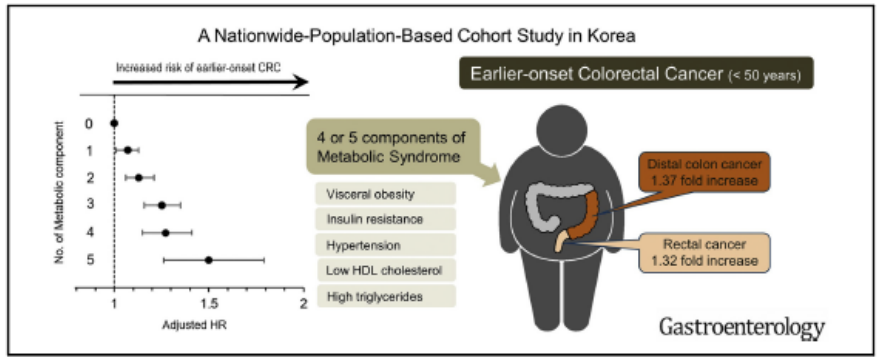


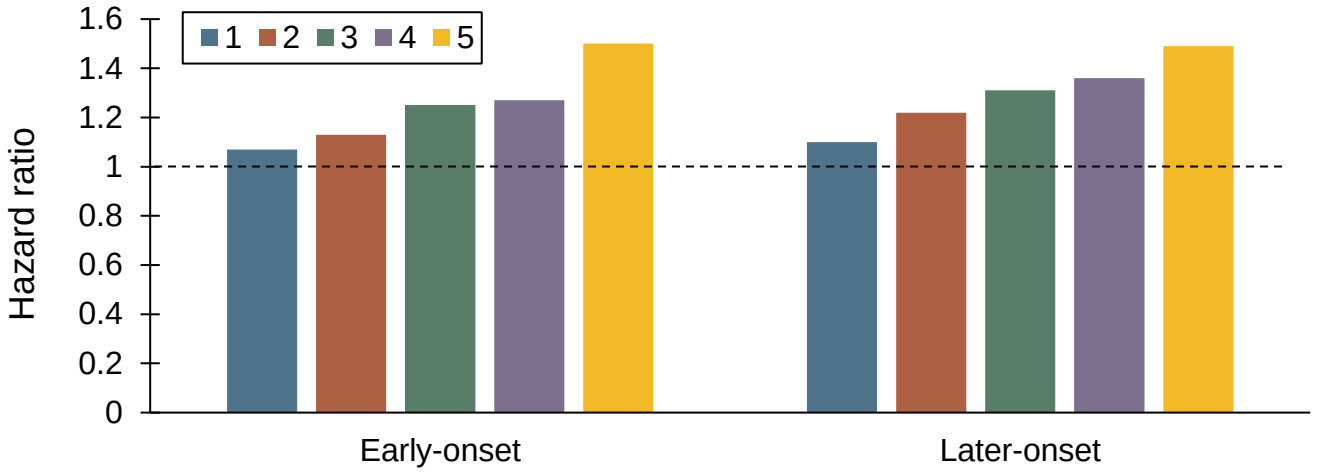
See editorial on page 574.

BACKGROUND & AIMS: The increasing prevalence of obesity at younger ages is concurrent with an increased earlier-onset colorectal cancer (CRC) (before age 50 years) incidence, particularly left-sided colon cancer. We investigated whether obesity and metabolic syndrome (MetS) are associated with increased earlier-onset CRC risk according to tumor location. **METHODS:** Our nationwide population-based cohort study enrolled 9,774,081 individuals who underwent health checkups under the Korean National Health Insurance Service from 2009 to 2010, with follow-up until 2019. We collected data on age, sex, lifestyle factors, body mass index (BMI), waist circumference (WC), blood pressure, and laboratory findings. A multivariate Cox proportional hazards regression analysis was performed. **RESULTS:** A total of 8320 earlier-onset and 57,257 later-onset CRC cases developed during follow-up. MetS was associated with increased earlier-onset CRC (adjusted hazard ratio, 1.20; 95% CI, 1.14–1.27), similar to later-onset CRC (adjusted hazard ratio, 1.19; 95% CI, 1.17–1.21). The adjusted hazard ratios for earlier-onset CRC with 1, 2, 3, 4, and 5 MetS components were 1.07 (95% CI, 1.01–1.13), 1.13 (95% CI, 1.06–1.21), 1.25 (95% CI, 1.16–1.35), 1.27 (95% CI, 1.15–1.41), and 1.50 (95% CI, 1.26–1.79), respectively (P for trend < .0001). We found that higher body mass index and larger waist circumference were significantly associated with increased earlier-onset CRC (P for trend < .0001). These dose–response associations were significant in distal colon and rectal cancers, although not in proximal colon cancers. **CONCLUSIONS:** MetS and obesity are positively associated with CRC before age 50 years with a similar magnitude of association as people diagnosed after age 50 years. Thus, people younger than 50 years with MetS require effective preventive interventions to help reduce CRC risk.

Similar association between metabolic syndrome and early- vs. later-onset colorectal cancer

	Early-onset	Later-onset
HR (95% CI)	1.20 (1.14, 1.27)	1.19 (1.17, 1.21)
P-value	<0.001	<0.001

Risk of early- vs. later-onset colorectal cancer similarly increases by number of components of metabolic syndrome



2. Do risk factors differ by site, i.e., colon vs. rectum?

Yes and no.

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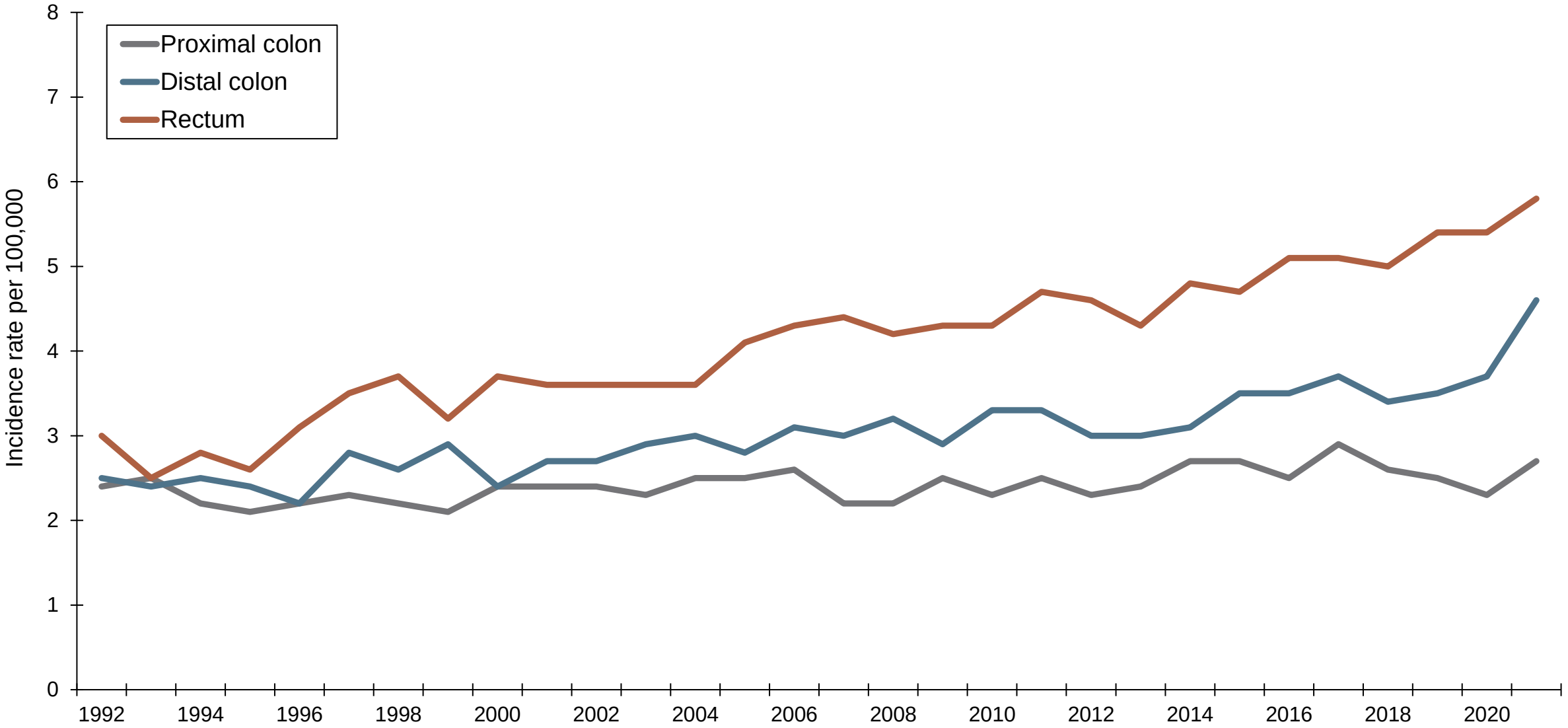

SEER 12 Incidence, 1992-2021, Age 20-49

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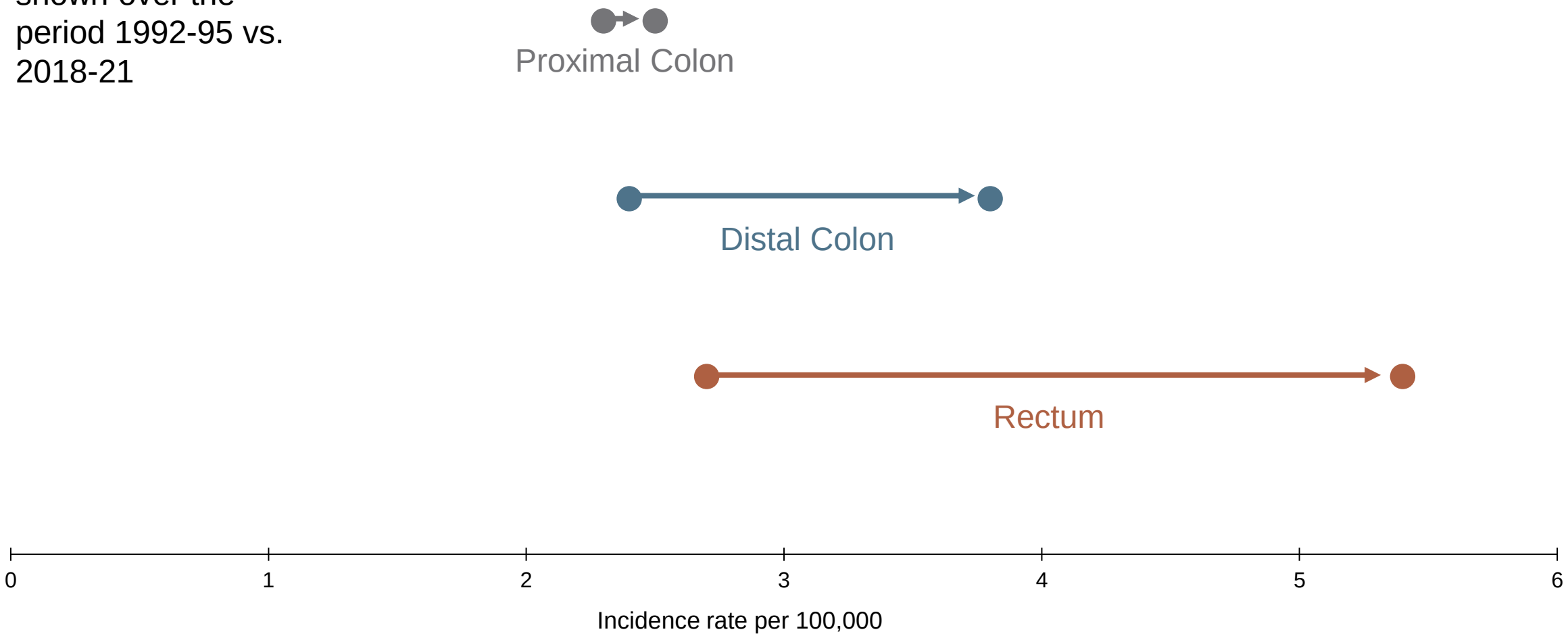
Incidence rates shown over the period 1992-95 vs. 2018-21



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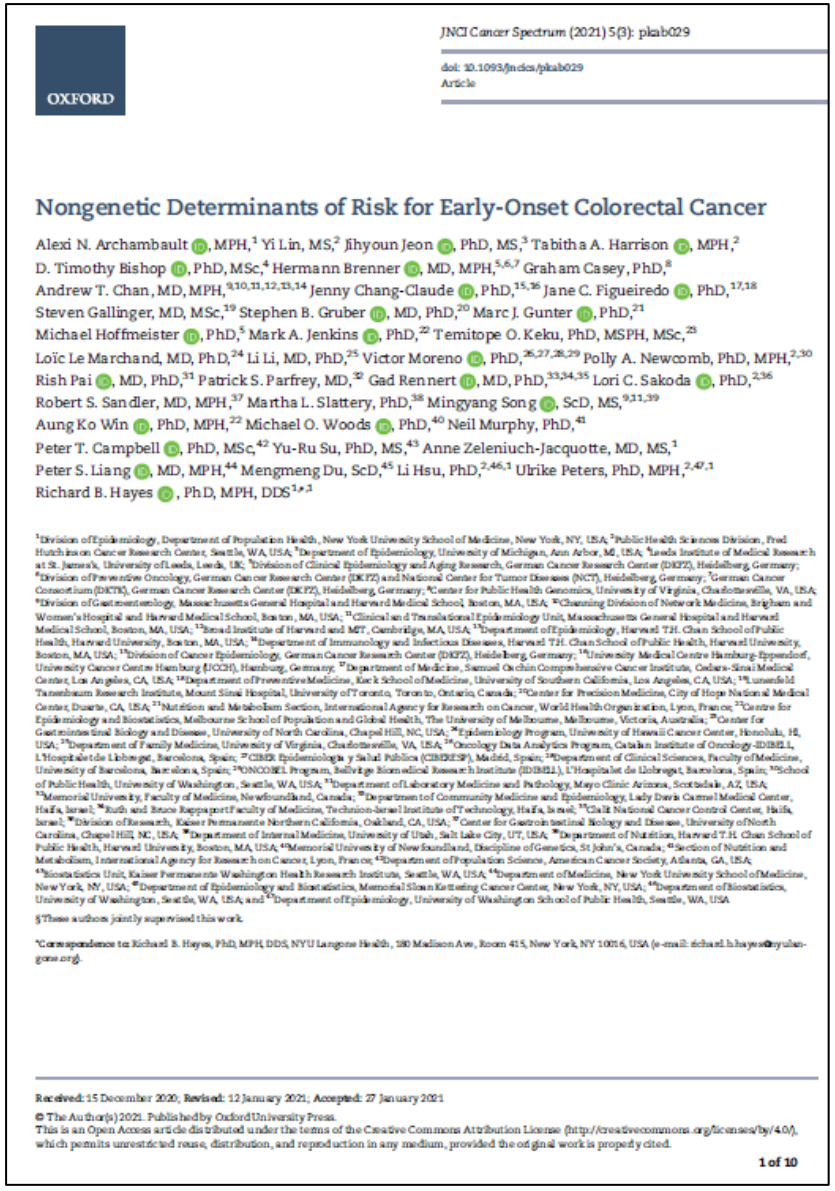

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Article

OXFORD

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Similar risk of early-onset colon and rectal cancer associated with known risk factors

	Colon	Rectum
	OR (95% CI)	OR (95% CI)
Cigarette smoking	0.99 (0.94, 1.04)	0.99 (0.94, 1.05)
Sedentary lifestyle	1.15 (0.88, 1.51)	1.09 (0.78, 1.53)
Higher alcohol use	1.29 (1.06, 1.47)	1.34 (1.08, 1.67)
Lower fruit	1.05 (0.99, 1.10)	1.10 (1.03, 1.17)
Lower vegetable	1.03 (0.97, 1.10)	1.08 (1.01, 1.16)
Higher red meat	1.12 (1.06, 1.18)	1.12 (1.05, 1.19)
Higher processed meat	1.06 (0.97, 1.16)	1.09 (0.98, 1.21)

…but some suggestion of differences

Lower folate	1.14 (1.04, 1.24)	1.24 (1.11, 1.37)
Lower fiber	1.14 (1.02, 1.27)	1.30 (1.14, 1.48)
Lower calcium	1.15 (1.05, 1.26)	1.24 (1.11, 1.39)
No NSAID use	1.33 (1.12, 1.60)	1.66 (1.31, 2.09)

3. What is the role of proposed/novel risk factors?

The environment is a top suspect.

3. What is the role of proposed/novel risk factors?

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Article

Disinfection by-products in drinking water and risk of colorectal cancer: a population-based cohort study

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Abstract

Background: Colorectal cancer is the third most common malignancy worldwide and is strongly linked to lifestyle and environmental risk factors. Although several drinking-water disinfection by-products are confirmed rodent carcinogens, the evidence in humans for carcinogenicity associated with these by-products, including colorectal cancer, is still inconclusive.

Methods: We assessed the association of long-term exposure to trihalomethanes (THMs), the most prevalent disinfection by-products in chlorinated drinking water, with incidence of colorectal cancer in 58 672 men and women in 2 population-based cohorts. Exposure was assessed by combining long-term information of residential history with drinking water–monitoring data. Participants were categorized according to no exposure, low exposure (<15 μg/L), and high exposure (≥15 μg/L). Incident cases of colorectal cancer were ascertained by use of the Swedish National Cancer Register.

Results: During an average follow-up of 16.8 years (988 144 person-years), 1913 cases of colorectal cancer were ascertained (1176 cases in men and 746 in women, respectively). High THM concentrations in drinking water (≥15 μg/L) were associated with increased risk of colorectal cancer in men (hazard ratio = 1.26, 95% confidence interval = 1.05-1.51) compared with no exposure. When subsites were assessed, the association was statistically significant for proximal colon cancer (hazard ratio = 1.59, 95% confidence interval = 1.11 to 2.27) but not for distal colon cancer or rectal cancer. In women, we observed overall no association of THMs with colorectal cancer.

Conclusion: These results add further evidence that disinfection by-products in drinking water may be a possible risk factor for proximal colon cancer in men. This observation was made at THM concentrations lower than those in most previous studies.

Colorectal cancer is ranked as the third most common malignancy globally and is the second most common cause of cancer death. The incidence is about 4 times higher in transitioned countries than in transitioning countries, likely due to differences in lifestyle and exposure to environmental risk factors (1). Colorectal cancer is a heterogenous disease, with molecular cancer subtypes that are unevenly distributed along the colorectum (2). Proximal (right sided) and distal (left sided) colon cancers have distinct embryological origins, display different pathological and clinical features, and have been proposed to have different sensitivity toward environmental risk factors (3,4). In addition, although the incidence of overall colorectal cancer is higher in men, there is a female dominance in proximal colon cancer (5).

Disinfection by-products are reactive and potentially carcinogenic chemical substances that are formed when chlorine reacts with natural organic matter in drinking water. Trihalomethanes (THMs) are the class of by-products that are found at the highest concentrations in chlorinated drinking water, and several of these substances are genotoxic in vitro and rodent carcinogens (6). In carcinogenesis studies of rats, 2 of the most common THMs induced aberrant crypts and large-intestine carcinomas, which are anatomically and functionally analogous to colorectal cancer tumors in humans (7,8). In 2010, a meta-analysis summarized the epidemiological evidence for the association of disinfection by-products and colorectal cancer, and estimated that by-product exposure was associated with 27% and 30% increased odds of colon and rectal cancer, respectively (9). Nevertheless, the number of studies included was small, and each had important methodological limitations. In addition, although colorectal cancer is a highly heterogenous disease, to our knowledge no previous studies have investigated whether the association of colorectal cancer with THMs differs by subsites within the colon or rectum, and only a few studies have addressed potential differences associated with patient sex.

The aim of this study was to assess the association of exposure to disinfection by-products in drinking water, proxied by THMs concentrations, with incidence of colorectal cancer overall

Drinking water treatment plants mapped to residential address → 988,144 person-years of follow-up → Colorectal cancer ascertained from national cancer registry

Compared with no exposure, low and high exposure to disinfection by-products was associated with colorectal cancer in men but not women

	Men	Women
	HR (95% CI)	HR (95% CI)
No exposure	1.00	1.00
Low exposure (< 15 μg/L)	1.23 (1.03, 1.47)	0.93 (0.74, 1.17)
High exposure (≥ 15 ug/L)	1.26 (1.05, 1.51)	0.97 (0.77, 1.23)

3. What is the role of proposed/novel risk factors?

Research | Article

Organochlorine Exposure and Colorectal Cancer Risk

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Organochlorine compounds have been linked to increased risk of several cancers. Despite reductions in their use and fugitive release, they remain one of the most important groups of persistent pollutants to which humans are exposed, primarily through dietary intake. We designed a case–control study to assess the risk of colorectal cancer with exposure to these chemicals, and their potential interactions with genetic alterations in the tumors. A subsample of cases (n = 132) and hospital controls (n = 76) was selected from a larger case–control study in Barcelona, Catalonia, Spain. We measured concentrations in serum of several organochlorines by gas chromatography. We assessed point mutations in K-*ras* and *p53* genes in tissue samples by polymerase chain reaction/single-strand conformation polymorphism and assessed expression of p53 protein by immunohistochemical methods. An elevated risk of colorectal cancer was associated with higher serum concentrations of mono-*ortho* polychlorinated biphenyl (PCB) congeners 28 and 118. The odds ratio for these mono-*ortho* PCBs for middle and higher tertile were, respectively, 1.82 [95% confidence interval (CI), 0.90–3.70] and 2.94 (95% CI, 1.39–6.20). α-Hexachlorocyclohexane, hexachlorobenzene, and *p,p′*-DDE (4,4′-dichlorodiphenyltrichloroethene) showed nonsignificant increases in risk. Risk associated with mono-*ortho* PCBs was slightly higher for tumors with mutations in the *p53* gene but was not modified by mutations in K-*ras*. Mono-*ortho* PCBs were further associated with transversion-type mutations in both genes. These results generate the hypothesis that exposure to mono-*ortho* PCBs contributes to human colorectal cancer development. The trend and magnitude of the association, as well as the observation of a molecular fingerprint in tumors, raise the possibility that this finding may be causal.
Key words: case–control study, colorectal cancer, K-*ras* mutations, organochlorines, *p53* mutations, PCBs. *Environ Health Perspect* 112:1460–1466 (2004). doi:10.1289/ehp.7143 available via *http://dx.doi.org/* [Online 15 July 2004]

Colorectal cancer is the third most common human cancer and the second most important cause of cancer-related death in Western countries, affecting men and women about equally. The etiology of sporadic colorectal cancer is relatively poorly understood, although diet is thought to play an important role in modifying risk. Vegetables, fruit, and dietary fiber are protective, whereas red and processed meats, fat, total energy intake, and obesity all increase risk (Potter 1996).

Diet is also an important source of exposure to many synthetic organic chemicals used in industry, agriculture, or accidentally released to the environment. Among them, the industrial organochlorine compounds (OCs) hexachlorobenzene (HCB) and poly- [Agency for Toxic Substances and Disease Registry (ATSDR) 2000, 2002].

Despite reductions in their use and fugitive release, OCs remain one of the most important groups of persistent pollutants to which humans are exposed, primarily via dietary intake. More lipophilic OCs, and those that are not easily metabolized, accumulate in adipose tissue, and the half-lives of these compounds in the body can be on the order of years or decades, whereas those compounds that are more water soluble or more easily metabolized have half-lives on the order of hours or days. Eventually, OCs recirculate in blood and are excreted in feces (Moser and McLachlan 2001). Serum concentrations are strongly correlated with fecal concentrations, However, the physicochemical characteristics of the compound (specifically, its solubility in water) will be more important in determining the relative importance of these exchange processes in the colon than in the small intestine, given the predominantly aqueous nature of the colonic milieu (Moser and McLachlan 2001; Schlummer et al. 1998). Therefore, colon epithelium is likely to be a major target for putative carcinogenic effects of OCs via luminal and blood-borne exposure.

OCs have been shown to mimic hormones, and this has been postulated as a mechanism for carcinogenesis in hormone-dependent cancers (Davis et al. 1993). Although colorectal cancer cannot be considered a hormone-dependent cancer, there is evidence that hormones play a role, at least in women: hormone replacement therapy and, possibly, high parity and oral contraceptive use are all protective factors (Potter 1999). Studies of cancers of the pancreas and breast have shown that OCs may interact with genetic alterations in tumors such as K-*ras* mutations or p53 overexpression (Hoyer et al. 2002; Porta et al. 1999; Slebos et al. 2000). Research on these interactions is relevant because they are frequent in colorectal cancer, and one potential mechanism of OC toxicity may be the induction of mutations in these genes.

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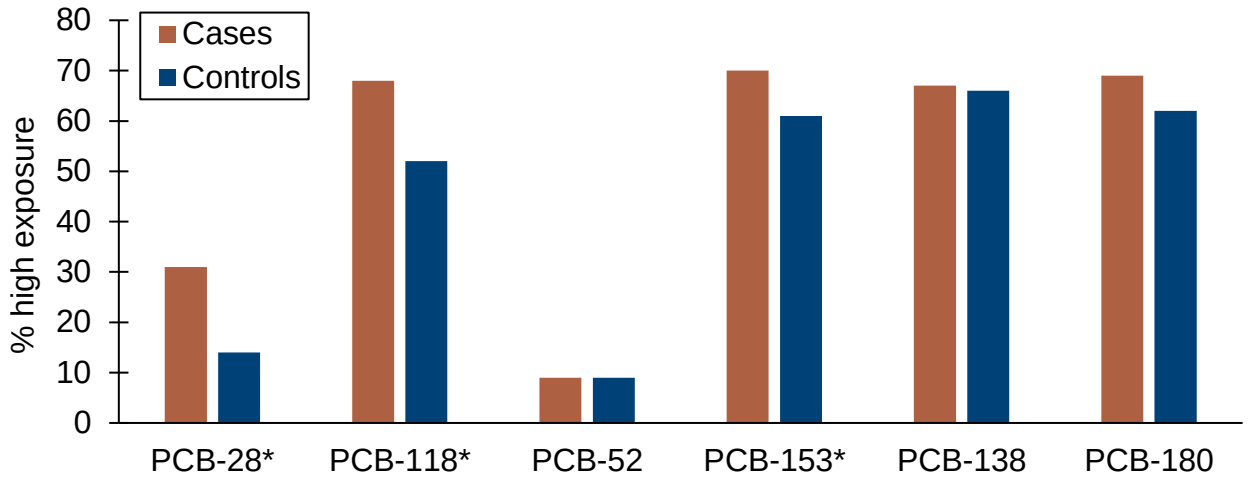
Serum concentrations of several polychlorinated biphenyl congeners (PCBs) higher in cases vs. controls



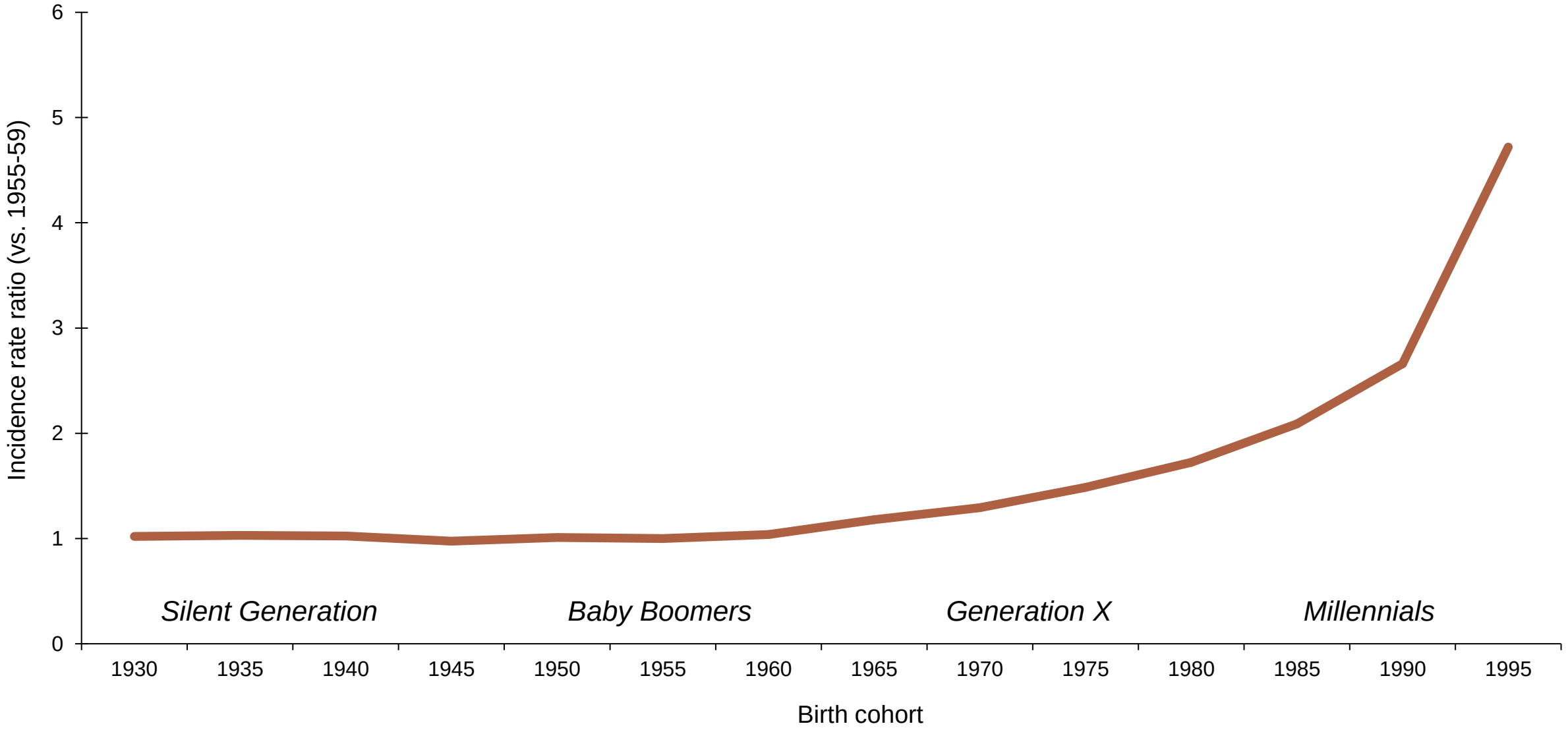
High exposure to PCB-28 and PCB-118 was also linked to KRAS and TP53 mutations

	KRAS		TP53	
	Wild-type	Mutated	Wild-type	Mutated
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
PCB-28	2.78 (1.24, 6.25)	2.83 (1.13, 7.06)	2.16 (0.79, 5.91)	2.06 (0.85, 5.01)
PCB-118	2.27 (1.04, 4.96)	1.64 (0.67, 4.01)	1.40 (0.52, 3.75)	2.79 (1.22, 6.37)

4. Are there vulnerable times of exposure related to risk?

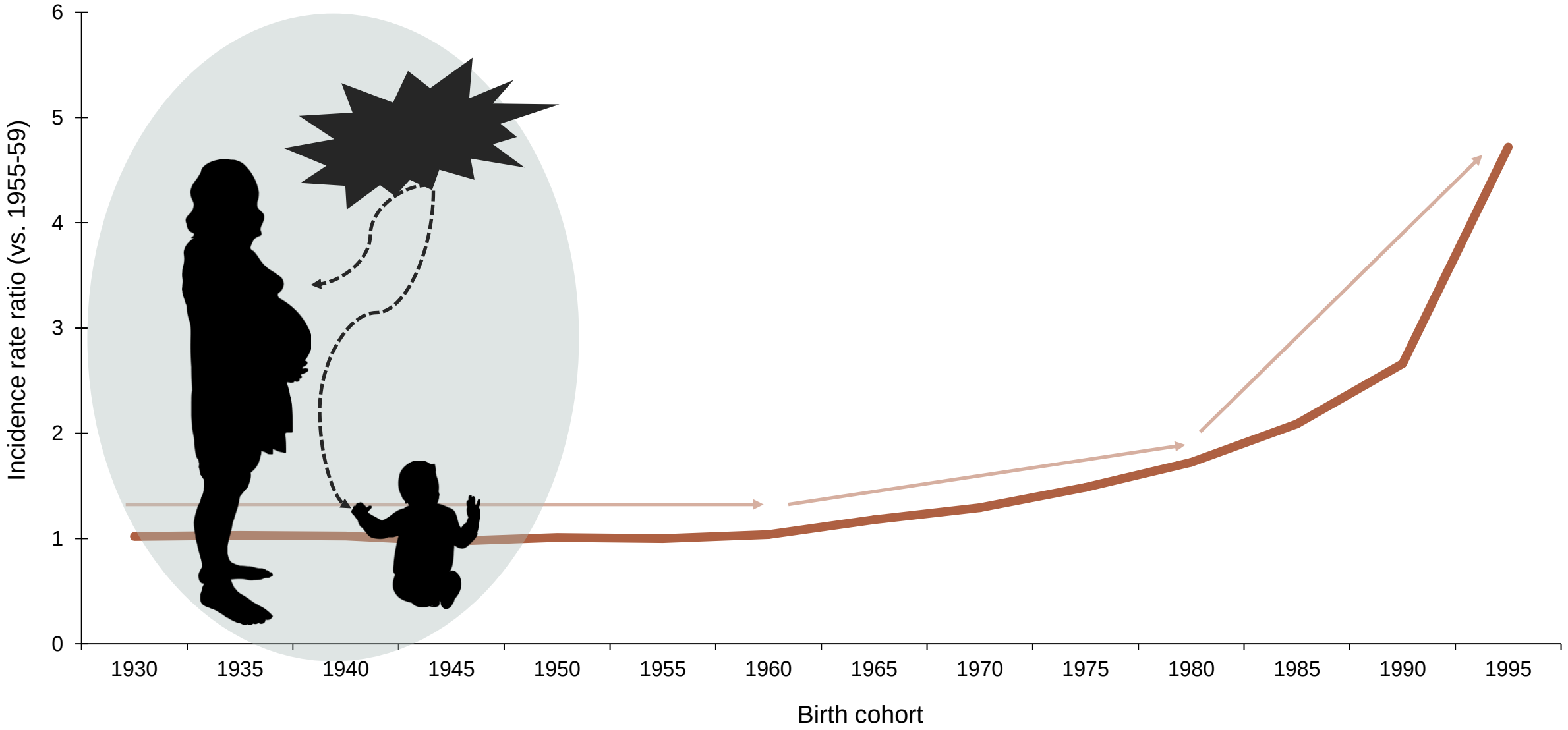
Yes. Exposures in early life, beginning *in utero*, may set the stage for colorectal cancer diagnosed in adulthood.

4. Are there vulnerable times of exposure related to risk?



SEER 9 Incidence, 1975-2021, Age 20-49; estimated with the NCI's APC Web Tool (https://analysistools.cancer.gov/apc/)

4. Are there vulnerable times of exposure related to risk?



SEER 9 Incidence, 1975-2021, Age 20-49; estimated with the NCI's APC Web Tool (https://analysistools.cancer.gov/apc/)

4. Are there vulnerable times of exposure related to risk?

OXFORD

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Article

In utero exposure to antiemetic and risk of adult-onset colorectal cancer

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Abstract

Background: Incidence rates of colorectal cancer (CRC) are increasing among adults born in and after the 1960s, implicating pregnancy-related exposures introduced at that time as risk factors. Dicyclomine, an antispasmodic used to treat irritable bowel syndrome, was initially included in Bendectin (comprising doxylamine, pyridoxine, and dicyclomine), an antiemetic prescribed during pregnancy in the 1960s.

Methods: We estimated the association between in utero exposure to Bendectin and risk of CRC in offspring of the Child Health and Development Studies, a multigenerational cohort that enrolled pregnant women in Oakland, CA, between 1959 and 1966 (n = 14 507 mothers and 18 751 liveborn offspring). We reviewed prescribed medications from mothers' medical records to identify those who received Bendectin during pregnancy. Diagnoses of CRC in adult (aged ≥18 years) offspring were ascertained by linkage with the California Cancer Registry. Cox proportional hazards models were used to estimate adjusted hazard ratios, with follow-up accrued from birth through cancer diagnosis, death, or last contact.

Results: Approximately 5% of offspring (n = 1014) were exposed in utero to Bendectin. Risk of CRC was higher in offspring exposed in utero (adjusted hazard ratio = 3.38, 95% confidence interval [CI] = 1.69 to 6.77) compared with unexposed offspring. Incidence rates of CRC were 30.8 (95% CI = 15.9 to 53.7) and 10.1 (95% CI = 7.9 to 12.8) per 100 000 in offspring exposed to Bendectin and unexposed, respectively.

Conclusions: Higher risk of CRC in offspring exposed in utero may be driven by dicyclomine contained in the 3-part formulation of Bendectin used during the 1960s. Experimental studies are needed to clarify these findings and identify mechanisms of risk.

Incidence rates of colorectal cancer (CRC) are increasing among younger (aged 18-49 years) adults in the United States (1), and more recent evidence suggests rates are also increasing in midlife (aged 50-59 years) (2). Rates of CRC have increased successively by birth cohort (1,3), starting with persons born in the 1960s, therefore renewing interest in identifying risk factors (4-6). Birth cohort effects implicate exposures in early life as risk factors: pregnancy-related exposures introduced in the 1960s may contribute to higher rates of CRC among offspring exposed in utero (7). A well-established experimental literature also supports the importance of gestation for several adult cancers (8-12).

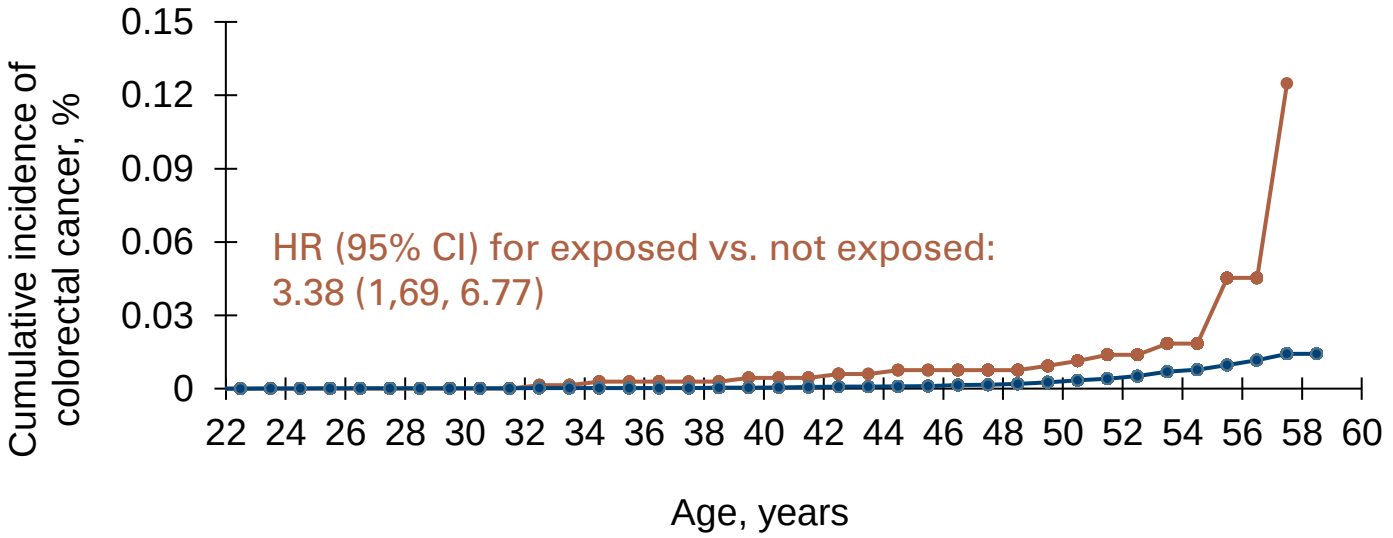
In the 1960s, Bendectin (doxylamine/pyridoxine/dicyclomine) was frequently prescribed to pregnant women to manage nausea and vomiting (13). Bendectin was initially approved in 1956 (14) and quickly became the most common treatment for nausea or vomiting in pregnancy in the United States as its use grew in the 1960s and 1970s (15). After reports of birth defects (16) and concerns in the wake of the thalidomide tragedy (17), in 1976, the manufacturer removed dicyclomine from the 3-part formulation (18). An 8-way randomized trial comparing the relative efficacy of doxylamine, pyridoxine, and dicyclomine suggested no clinical benefit of dicyclomine for nausea or vomiting in pregnancy (19). Production of the 2-part formulation (doxylamine/pyridoxine) was subsequently discontinued in 1983 in the face of ongoing lawsuits (20). Notably, dicyclomine, an antispasmodic (21), continues to be used in clinical practice to treat irritable bowel syndrome and is designated as Pregnancy Category B by the US Food and Drug Administration.

Exposure to Bendectin in utero, and specifically to dicyclomine contained in the 3-part formulation, may directly target the developing gastrointestinal tract of the fetus. This is consistent with some epidemiologic studies demonstrating excess risk of gastrointestinal anomalies (eg, pyloric stenosis, esophageal atresia) in infants of mothers prescribed Bendectin during pregnancy (22-24). Here, we examined the association of in utero exposure to Bendectin and CRC in adult offspring of the Child Health and Development Studies (CHDS), a population-based cohort of more than 18 000 mother-child dyads receiving care in the Kaiser

The Child Health and Development Studies is a multi-generational cohort of pregnant mothers and their now-adult offspring followed prospectively for more than 60 years

14,507 mothers receive prenatal care in 1959-1967 → Colorectal cancer diagnosed in **83** adult offspring through 2021

In utero exposure to Bendectin (doxylamine/pyridoxine/dicyclomine) increased risk of colorectal cancer in adult offspring



5. Is early-onset colorectal cancer molecularly different than colorectal cancer in older adults?

Not really.

5. Is early-onset colorectal cancer molecularly different?

OXFORD

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Article

A Comprehensive Comparison of Early-Onset and Average-Onset Colorectal Cancers

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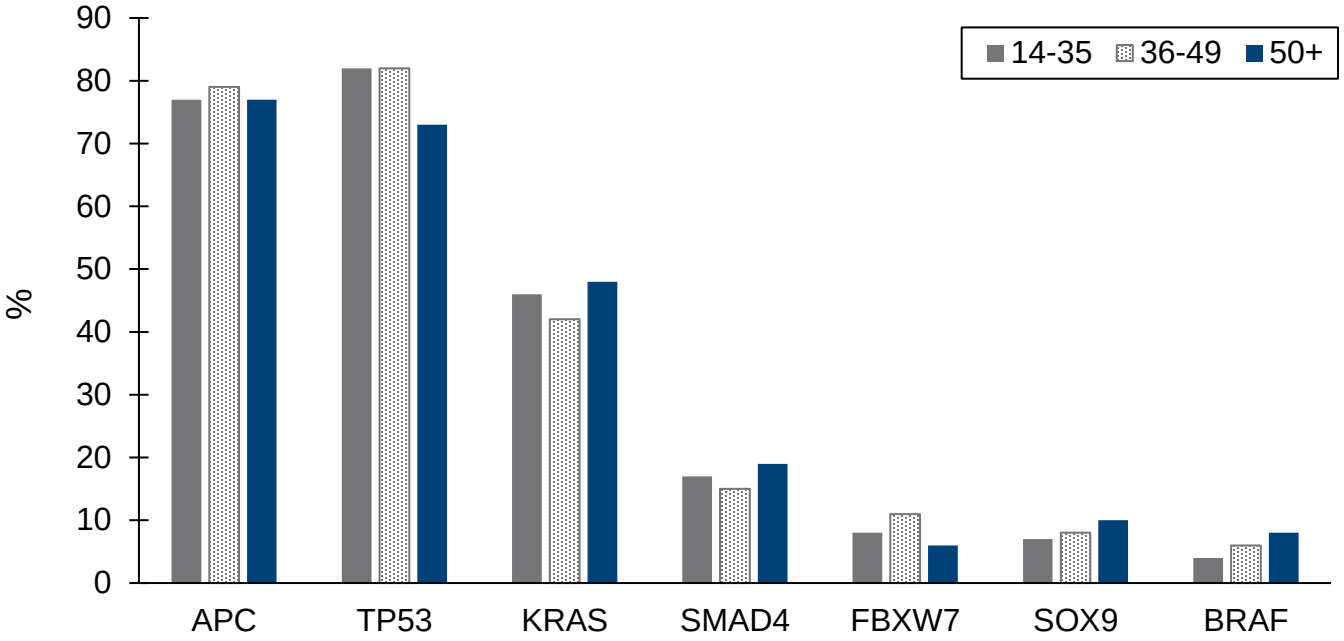
Abstract

Background: The causative factors for the recent increase in early-onset colorectal cancer (EO-CRC) incidence are unknown. We sought to determine if early-onset disease is clinically or genomically distinct from average-onset colorectal cancer (AO-CRC). **Methods:** Clinical, histopathologic, and genomic characteristics of EO-CRC patients (2014-2019), divided into age 35 years and younger and 36-49 years at diagnosis, were compared with AO-CRC (50 years and older). Patients with mismatch repair deficient tumors, CRC-related hereditary syndromes, and inflammatory bowel disease were excluded from all but the germline analysis. All statistical tests were 2-sided. **Results:** In total, 759 patients with EO-CRC (35 years, n = 151; 36-49 years, n = 608) and AO-CRC (n = 687) were included. Left-sided tumors (35 years and younger = 80.8%; 36-49 years = 83.7%; AO = 63.9%; P < .001 for both comparisons), rectal bleeding (35 years and younger = 41.1%; 36-49 years = 41.0%; AO = 25.9%; P = .001 and P < .001, respectively), and abdominal pain (35 years and younger = 37.1%; 36-49 years = 34.0%; AO = 26.8%; P = .01 and P = .005, respectively) were more common in EO-CRC. Among microsatellite stable tumors, we found no differences in histopathologic tumor characteristics. Initially, differences in TP53 and Receptor Tyrosine Kinase signaling pathway (RTK-RAS)alterations were noted by age. However, on multivariate analysis including somatic gene analysis and tumor sidedness, no statistically significant differences at the gene or pathway level were demonstrated. Among advanced microsatellite stable CRCs, chemotherapy response and survival were equivalent by age cohorts. Pathogenic germline variants were identified in 23.3% of patients 35 years and younger vs 14.1% of AO-CRC (P = .01). **Conclusions:** EO-CRCs are more commonly left-sided and present with rectal bleeding and abdominal pain but are otherwise clinically and genomically indistinguishable from AO-CRCs. Aggressive treatment regimens based solely on the age at CRC diagnosis are not warranted.

No difference in frequency of oncogenic alterations between early- and later-onset colorectal cancer



Similarly, no difference in tumor mutational burden, fraction of genome altered, whole-genome duplication, or loss of heterozygosity between early- and later-onset colorectal cancer

5. Is early-onset colorectal cancer molecularly different?

Precision Medicine and Imaging

Clinical Cancer Research

Comprehensive Genomic Landscapes in Early and Later Onset Colorectal Cancer

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Abstract

Purpose: The incidence rates of colorectal cancers are increasing in young adults. The objective of this study was to investigate genomic differences between tumor samples collected from younger and older patients with colorectal cancer.

Experimental Design: DNA was extracted from 18,218 clinical specimens, followed by hybridization capture of 3,769 exons from 403 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer. Genomic alterations (GA) were determined, and association with patient age and microsatellite stable/microsatellite instability high (MSS/MSI-H) status established.

Results: Overall genomic alteration rates in the younger (<40) and older (≥50) cohorts were similar in the majority of the genes analyzed. Gene alteration rates in the microsatellite stable (MSS) younger and older cohorts were largely similar, with several notable differences. In particular, *TP53* (FDR < 0.01) and *CTNNB1* (FDR = 0.01) alterations were more common in younger patients with colorectal cancer, and *APC* (FDR < 0.01), *KRAS* (FDR < 0.01), *BRAF* (FDR < 0.01), and *FAM123B* (FDR < 0.01) were more commonly altered in older patients with colorectal cancer. In the MSI-H cohort, the majority of genes showed similar rate of alterations in all age groups, but with significant differences seen in *APC* (FDR < 0.01), *BRAF* (FDR < 0.01), and KRAS (FDR < 0.01).

Conclusions: Tumors from younger and older patients with colorectal cancer demonstrated similar overall rates of genomic alteration. However, differences were noted in several genes relevant to biology and response to therapy. Further study will need to be conducted to determine whether the differences in gene alteration rates can be leveraged to provide personalized therapies for young patients with early-onset sporadic colorectal cancer.

Introduction

Colorectal cancer is the third most common cancer in men and the second most common in women worldwide (10.0% and 9.2% of total, respectively), and global incidence is estimated at 1.4 million cases annually, with 694,000 deaths (1). In 2019, there will be an estimated 145,600 new diagnoses of colorectal cancer and an estimated 51,020 deaths from this disease in the United States (2). Death rates from colorectal cancer have been declining in the United States since 1992, with an annual decline of 2.6% for males and 3% for females (3).

In contrast to the downturns among screeningaged individuals, colorectal cancer incidence rates in adults aged <50 years rose by 1.6% from 2000 to 2013, for an overall increase of 22% (from 5.9 to 7.2 per 100,000; ref. 4). This increase has been driven by increasing incidence of distal colon cancer and rectal cancer, which has been increasing 3.2% annually from 1974 to 2013 in adults age 20–29 years (5, 6). Patients younger than 50 years of age are not routinely screened for colorectal cancer and are at risk for delayed diagnosis and more advanced stage of disease at the time of diagnosis. A retrospective review found a significantly higher proportion of stage III–IV tumors in young adults (69.3%) compared with older adults (46.4%; refs. 7, 8). There is also evidence that patients diagnosed with colorectal cancer before the age of 50 have had worsened progression-free survival and overall survival compared with older patients (9, 10).

Patients with early-onset colorectal cancer present with unique challenges, as younger patients may have young children, early career goals, financial toxicity, and concerns such as fertility preservation that are not as prevalent in older patients (11). Clinically, patients with early-onset colorectal cancer may present differently than older-onset colorectal cancer with prolonged hematochezia, multiple office visits, and delayed time from onset of symptoms to diagnosis (12). These issues emphasize the importance of specifically investigating underlying biological differences in younger versus older patients with colorectal cancer (9).

Although etiologies for the increase seen in young adults are yet to be fully elucidated, environmental factors may contribute including changes in lifestyle and dietary patterns. There is

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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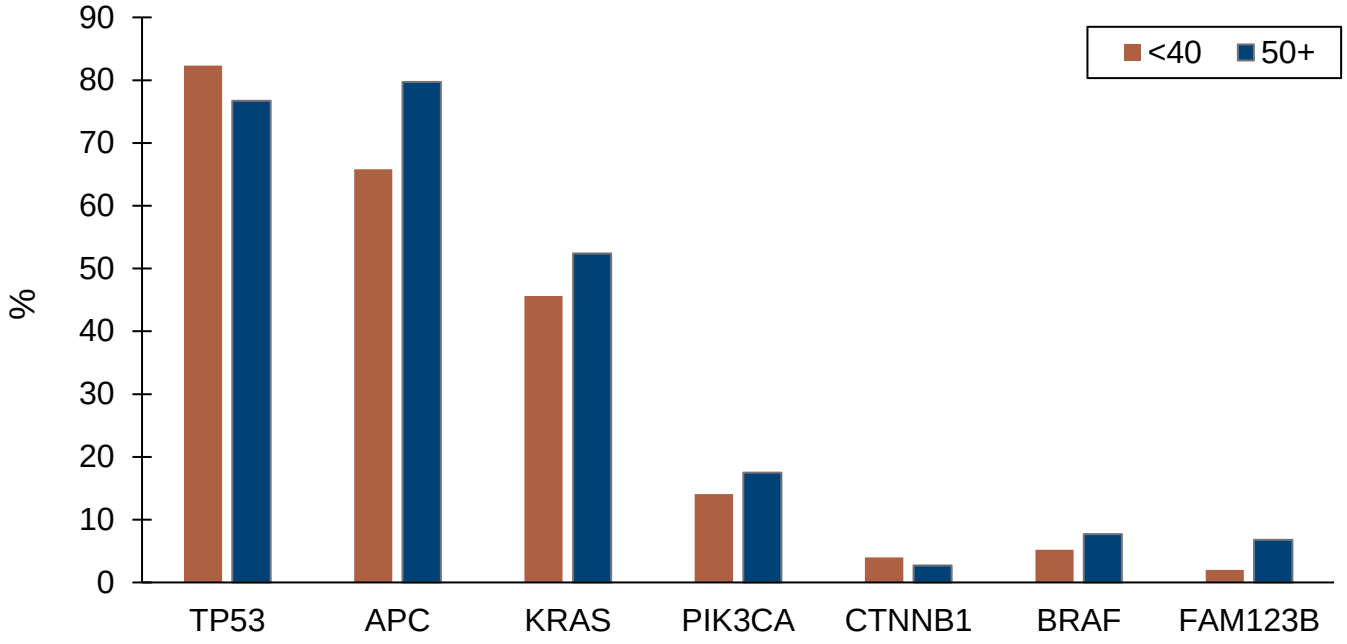
doi: 10.1158/1078-0432.CCR-19-0899

Some differences in frequency of oncogenic alterations for age <40 years vs. age 50+ years



When age was modeled as a continuous variable:

- Mutations in ASXL1, BRAF, CEBPA, CDKN2A, DNMT3A FAM123B, RNF43, SF3B1, SOX9, and TET2 increased with increasing age
- Mutations in CTNNB1, GEN1, MYC, POLE, and TP53 decreased with increasing age

6. What are best practices for implementing current recommendations for identifying and managing early-onset colorectal cancer?

Act upon family history.

Minimize time from symptoms to diagnosis.

6. What are best practices? Act upon family history.

Original Article

Potential Impact of Family History–Based Screening Guidelines on the Detection of Early-Onset Colorectal Cancer

Samir Gupta, MD, MDCS, AGAF [1,2,3]; Balambal Bharti, MBBS, MPH, PhD[2,3]; Dennis J. Ahnen, MD[4,5]; Daniel D. Buchanan, PhD[6,7,8]; Iona C. Cheng, PhD, MPH[9]; Michelle Cotterchio, PhD[10]; Jane C. Figueiredo, PhD [11]; Steven J. Gallinger, MD, MSc[12]; Robert W. Haile, DrPH, MPH[11]; Mark A. Jenkins, PhD[7,13]; Noralane M. Lindor, MD[14]; Finlay A. Macrae, MD, AGAF[15]; Loïc Le Marchand, MD, PhD[16]; Polly A. Newcomb, PhD, MPH[17]; Stephen N. Thibodeau, PhD[18]; Aung Ko Win, MBBS, MPH, PhD[7,13]; and Maria Elena Martinez, PhD [3,19]

BACKGROUND: Initiating screening at an earlier age based on cancer family history is one of the primary recommended strategies for the prevention and detection of early-onset colorectal cancer (EOCRC), but data supporting the effectiveness of this approach are limited. The authors assessed the performance of family history–based guidelines for identifying individuals with EOCRC. **METHODS:** The authors conducted a population-based, case-control study of individuals aged 40 to 49 years with (2473 individuals) and without (772 individuals) incident CRC in the Colon Cancer Family Registry from 1998 through 2007. They estimated the sensitivity and specificity of family history–based criteria jointly recommended by the American Cancer Society, the US Multi-Society Task Force on CRC, and the American College of Radiology in 2008 for early screening, and the age at which each participant could have been recommended screening initiation if these criteria had been applied. **RESULTS:** Family history–based early screening criteria were met by approximately 25% of cases (614 of 2473 cases) and 10% of controls (74 of 772 controls), with a sensitivity of 25% and a specificity of 90% for identifying EOCRC cases aged 40 to 49 years. Among 614 individuals meeting early screening criteria, 98.4% could have been recommended screening initiation at an age younger than the observed age of diagnosis. **CONCLUSIONS:** Of CRC cases aged 40 to 49 years, 1 in 4 met family history–based early screening criteria, and nearly all cases who met these criteria could have had CRC diagnosed earlier (or possibly even prevented) if earlier screening had been implemented as per family history–based guidelines. Additional strategies are needed to improve the detection and prevention of EOCRC for individuals not meeting family history criteria for early screening. *Cancer* 2020;126:3013-3020. © *2020 American Cancer Society.*

KEYWORDS: case-control study, family history, guidelines, sensitivity, specificity, young-onset colorectal cancer.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States, and the third leading cause of cancer death worldwide.[1] Currently in the United States, 10% to 11% of CRC cases occur among individuals aged <50 years,[1,2] resulting in CRC being the third leading cause of cancer death among adults aged <50 years.[3] Furthermore, the incidence of CRC among those aged <50 years is rising, with an increase of 1.6% per year noted from 2009 to 2013.[4] Among cases of early-onset CRC (EOCRC) (defined in this study as those occurring at age <50 years), approximately 72% occur between age 40 and 50 years.[4]

A primary strategy for identifying individuals at risk of EOCRC is based on family history. For example, in 2008, the American Cancer Society (ACS), the US Multi-Society Task Force on Colorectal Cancer (USMSTF; representing the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American

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We thank Allyson Templeton, Colon Cancer Family Registry Consortium Program Manager, for administrative support and facilitating data access and use.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32851, **Received:** October 19, 2019; **Revised:** February 4, 2020; **Accepted:** February 6, 2020, **Published online** April 20, 2020 in Wiley Online Library (wileyonlinelibrary.com)

Diagnosed with CRC at age 40-49 years (n=2,473)

↓

Met criteria for early screening: 25% (n=614/2,473)

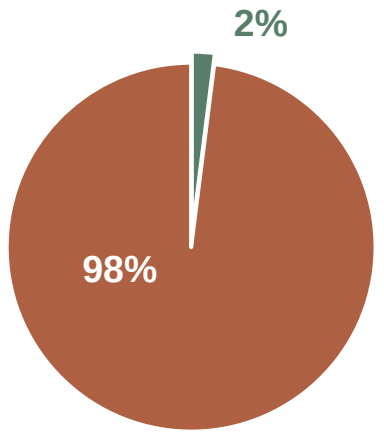
→ Guidelines recommend screening initiation age <u>same or older</u> than actual diagnosis age: 2% (n=10/614)

↓

Guidelines recommend screening initiation age <u>younger</u> than actual diagnosis age: 98% (n=604/614)

About 1 in 4 patients with early-onset colorectal cancer met criteria for earlier screening based upon family history

Almost all of these cancers could have been diagnosed earlier or prevented if screening had been implemented per family history guidelines



6. What are best practices? Minimize time from symptoms to diagnosis.

JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Red Flag Signs and Symptoms for Patients With Early-Onset Colorectal Cancer
A Systematic Review and Meta-Analysis

Joshua Demb, PhD, MPH; Jennifer M. Kolb, MD, MS; Jonathan Dounel, MD; Cassandra D. L. Fritz, MD, MPHS; Shailesh M. Advani, MD, PhD; Yin Cao, ScD, MPH; Penny Coppernoll-Blach, MLS; Andrea J. Dwyer, BS; Jose Perea, MD, PhD; Karen M. Heskett, MSI; Andreana N. Holowatyj, PhD, MS; Christopher H. Lieu, MD; Siddharth Singh, MD, MS; Manon C. W. Spaander, MD, PhD; Fanny E. R. Vuik, MD, PhD; Samir Gupta, MD

Abstract

IMPORTANCE Early-onset colorectal cancer (EOCRC), defined as a diagnosis at younger than age 50 years, is increasing, and so-called red flag signs and symptoms among these individuals are often missed, leading to diagnostic delays. Improved recognition of presenting signs and symptoms associated with EOCRC could facilitate more timely diagnosis and impact clinical outcomes.

OBJECTIVE To report the frequency of presenting red flag signs and symptoms among individuals with EOCRC, to examine their association with EOCRC risk, and to measure variation in time to diagnosis from sign or symptom presentation.

DATA SOURCES PubMed/MEDLINE, Embase, CINAHL, and Web of Science were searched from database inception through May 2023.

STUDY SELECTION Studies that reported on sign and symptom presentation or time from sign and symptom presentation to diagnosis for patients younger than age 50 years diagnosed with nonhereditary CRC were included.

DATA EXTRACTION AND SYNTHESIS Data extraction and quality assessment were performed independently in duplicate for all included studies using Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines. Joanna Briggs Institute Critical Appraisal tools were used to measure risk of bias. Data on frequency of signs and symptoms were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES Outcomes of interest were pooled proportions of signs and symptoms in patients with EOCRC, estimates for association of signs and symptoms with EOCRC risk, and time from sign or symptom presentation to EOCRC diagnosis.

RESULTS Of the 12 859 unique articles initially retrieved, 81 studies with 24 908 126 patients younger than 50 years were included. The most common presenting signs and symptoms, reported by 78 included studies, were hematochezia (pooled prevalence, 45% [95% CI, 40%-50%]), abdominal pain (pooled prevalence, 40% [95% CI, 35%-45%]), and altered bowel habits (pooled prevalence, 27% [95% CI, 22%-33%]). Hematochezia (estimate range, 5.2-54.0), abdominal pain (estimate range, 1.3-6.0), and anemia (estimate range, 2.1-10.8) were associated with higher EOCRC likelihood. Time from signs and symptoms presentation to EOCRC diagnosis was a mean (range) of 6.4 (1.8-13.7) months (23 studies) and a median (range) of 4 (2.0-8.7) months (16 studies).

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis of patients with EOCRC, nearly half of individuals presented with hematochezia and abdominal pain and one-quarter

Key Points

Question In patients with early-onset colorectal cancer (EOCRC), what are the most common presenting signs and symptoms, what is their association with EOCRC risk, and what is the time from presentation to diagnosis?

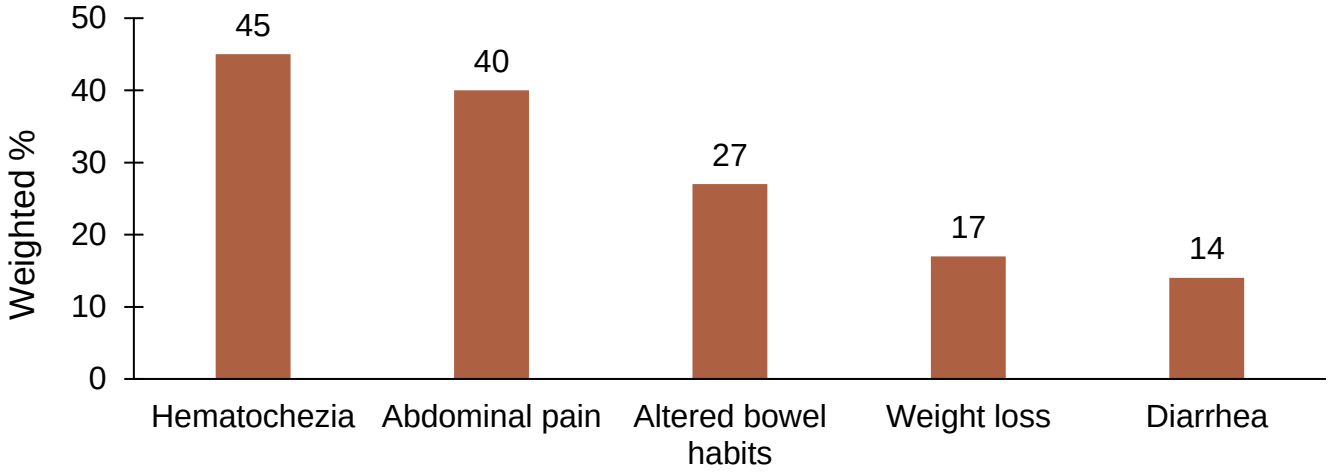
Findings In this systematic review and meta-analysis including 81 studies and more than 24.9 million patients, nearly half of individuals with EOCRC presented with hematochezia and abdominal pain and one-quarter presented with altered bowel habits. Delays in diagnosis of 4 to 6 months from time of initial presentation were common.

Meaning These findings underscore the need to identify signs and symptoms concerning for EOCRC and complete timely diagnostic workup for individuals without an alternative diagnosis or sign or symptom resolution.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Patients frequently present with “red flag” symptoms such as hematochezia, abdominal pain, and altered bowel habits

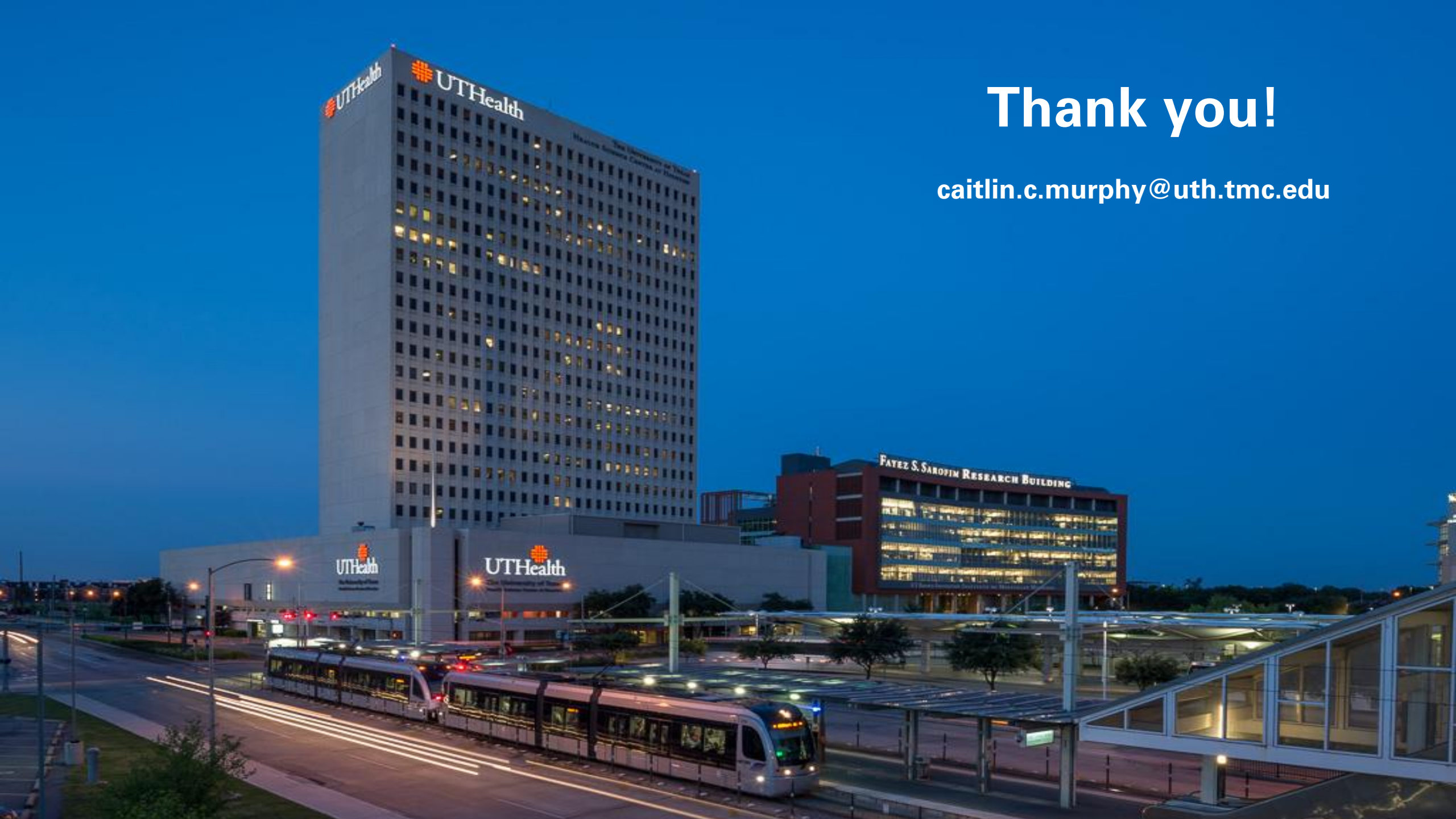


These same symptoms increase risk of early-onset colorectal cancer in the general population, for example, hematochezia:

Study	Population	HR/OR (95% CI)
Demb et al, 2021	U.S. Veterans	10.66 (8.76, 12.97)
Fritz et al, 2023	IBM MarketScan	5.13 (4.36, 6.04)
Glover et al, 2019	Explorys	13.66 (11.61, 16.08)
Stapley et al., 2017	UK Clinical Practice Research Datalink	54.00 (26.25, 111.07)
Syed et al., 2019	Explorys	9.83 (9.12, 10.60)

In 2024, the NCCRT pushed the research agenda forward:

1. Move beyond known risk factors and comparisons by age +/- 50 years.
2. Re-focus efforts to identify risk factors for rectal cancer.
3. Conduct innovative studies of environmental exposures.
4. Identify opportunities to measure exposures across the life course.
5. Implement evidence-based interventions for family history.
6. Test non-invasive strategies for triaging patients with symptoms.



Thank you!

caitlin.c.murphy@uth.tmc.edu

University of Virginia's Battle Against Early Onset Colorectal Cancer

March Colorectal Awareness Month 2024

TALA MAHMOUD, MD, LINDSEY BIERLE, DO,
NEERAL SHAH, MD, CYNTHIA YOSHIDA, MD

•NOVEMBER 21-22, 2024

UVA

Agenda

- BACKGROUND
- INITIATIVE OVERVIEW
- CAMPAIGN EXECUTION
- RESULTS & IMPACT
- KEY TAKEAWAYS
- FUTURE DIRECTIONS

Background

NCCRT Leadtime Messaging Guidebook:

- By 2030, 1 in 10 Americans aged 20-49 will be diagnosed with colorectal cancer
- Colorectal cancer is now a leading killer in young adults
- The rates of colorectal cancer in adults aged 20-39 has been increasing every year since 1980s

Personal connection with the cause and initiative.

Initiative Overview

Rationale

Our campaign aimed to raise awareness on early onset CRC among young adults, including young healthcare professionals, educating them about symptoms and the importance of early action.

We focused on individuals ages 18-35, a demographic often overlooked in traditional CRC awareness efforts.

The NCCRT Lead Time Messaging guidebook showed that younger adults desire information on CRC screening from healthcare providers.

Collaborative Approach

This initiative brought together diverse members of the UVA community:

- Undergraduates
- Medical students
- Internal medicine residents
- Gastroenterology fellows
- Faculty members

Lead Time Messaging Guidebook

A Tool to Encourage On-Time Colorectal Cancer Screening

American Cancer Society

NATIONAL COLORECTAL CANCER ROUNDTABLE

80% IN EVERY COMMUNITY

Message

Did you know colorectal cancer is expected to be the leading cause of cancer-related death among 20–49-year-olds by 2030? It's never too early to talk to your doctor about when it's appropriate to start screening.

Why It Works

This message is compelling because people can identify with it since they fall within the age range/young adult demographic referenced in the message.

We asked, "What comes to mind when hearing this message?"

- "It illustrates that you're never too young." (35–39-year-old)
- "I am between the ages of 20–49, so this directly applies to me." (30–34-year-old)
- "Because that's my age range, and the numbers kind of surprised me." (40–44-year-old)

Message

Colorectal cancer is on the rise among young adults and among those who are too young to begin screening, two thirds experience symptoms for many months before they're finally diagnosed. Be sure to alert your doctor if you're experiencing blood in your stool, persistent abdominal pain, changes in bowel habits, or unexplained weight loss. If these symptoms persist, the possibility of colorectal cancer must be considered.

Why It Works

This message is compelling because participants can identify with it since they fall within the age range/young adult demographic referenced in the message.

We asked, "What comes to mind when hearing this message?"

- "It informs you that young adults like me can get it. It's best we get tested soon." (20–24-year-old)
- "It stands out because silent killers are the scariest to me, and I am a young adult, so it speaks directly to my demographic." (30–34-year-old)
- "Cancer is on the rise with younger generations and can be cured if detected early." (35–39-year-old)
- "It mentioned how even young people are susceptible to getting the disease, so it resonated with me since I am still in my 20s." (20–24-year-old)

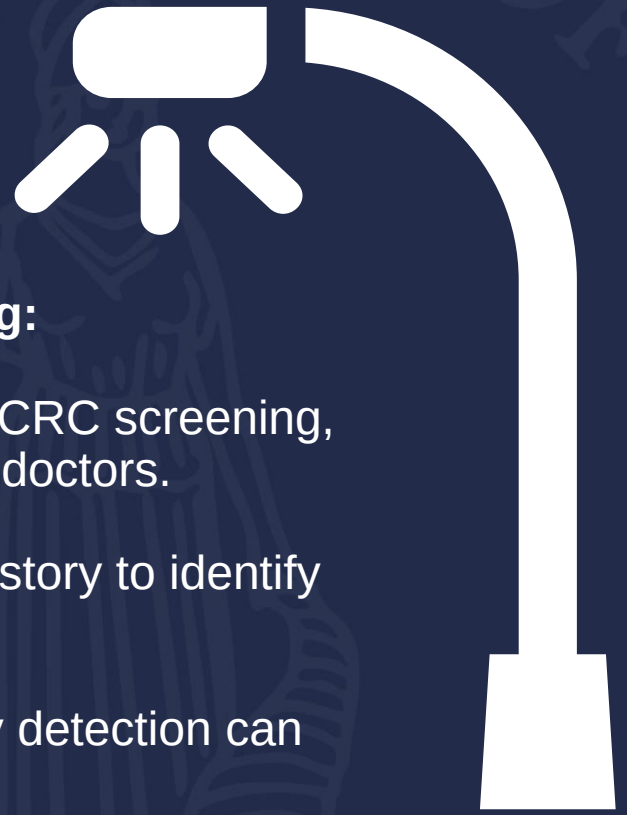
Ages 20–29

This age group...	Helpful tailored messages should focus on...
• Believes it's important to be screened on time • Finds it important to establish trust with their medical providers • Uses YouTube as a top platform for social media • Is more likely to be on TikTok than other age groups	• Symptoms related to CRC and how to have a conversation with clinicians about symptoms they may be experiencing. • The importance of knowing your family history • Encouraging conversations with family about medical history related to CRC

Ages 30–39

This age group...	Helpful tailored messages should focus on...
• May be less likely to bring up screening and will wait on their doctor to bring it up • Uses Instagram as a top platform for social media	• The recommended screening age for CRC for those of average risk • Recommendations for those at a higher risk of getting CRC • The importance of getting screened even without experiencing symptoms

Spotlight

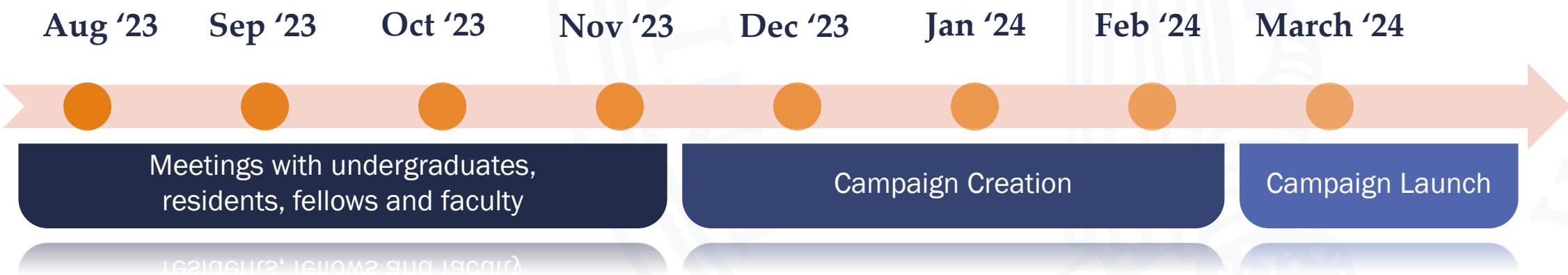


Focus on Healthcare Providers Training:

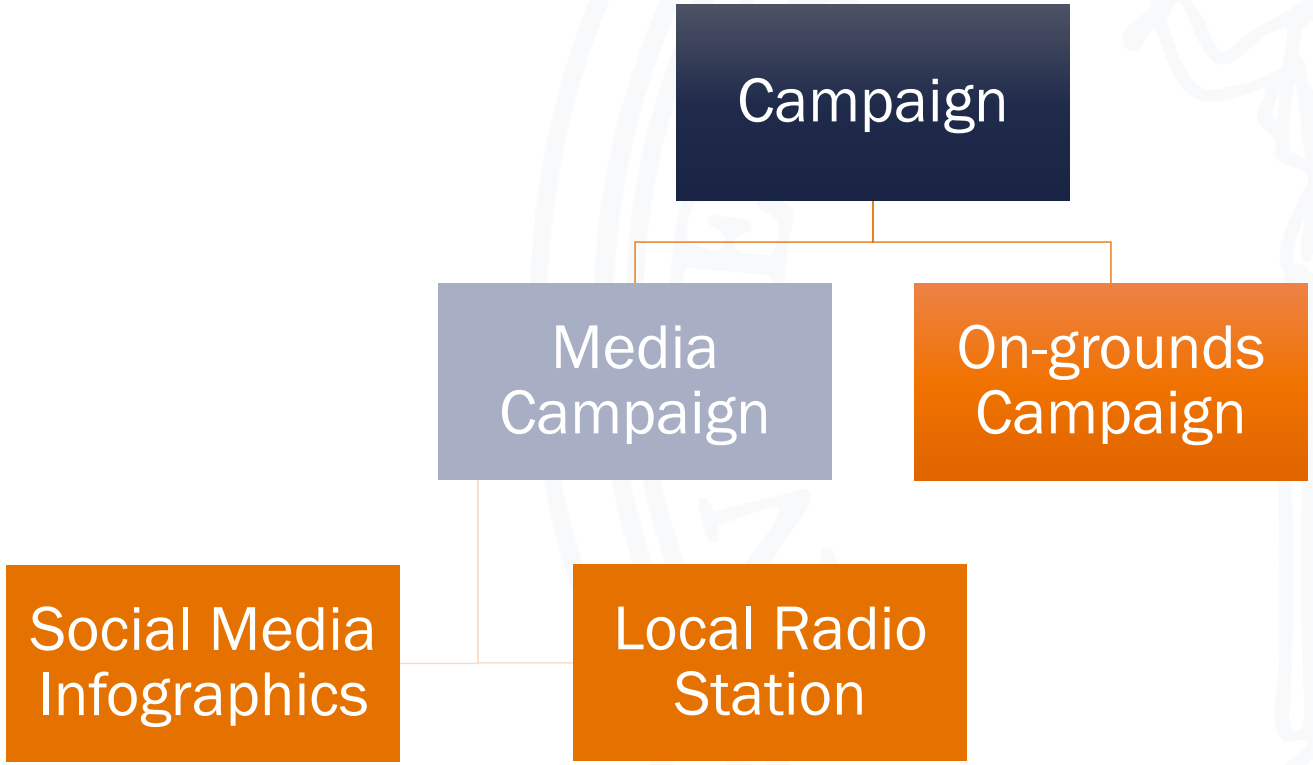
- Young people are less likely to discuss CRC screening, symptoms, and family history with their doctors.
- Clinicians should routinely use family history to identify individuals at increased risk for CRC.
- Promoting primary prevention and early detection can help reduce CRC mortality.
- Clinicians should consider CRC as a potential diagnosis when evaluating patients with relevant signs and symptoms, regardless of the patient's age.

Campaign Execution

Timeline


Aug '23
Sep '23
Oct '23
Nov '23
Dec '23
Jan '24
Feb '24
March '24
Meetings with undergraduates, residents, fellows and faculty
Campaign Creation
Campaign Launch

Layout


Campaign
Media Campaign
On-grounds Campaign
Social Media Infographics
Local Radio Station

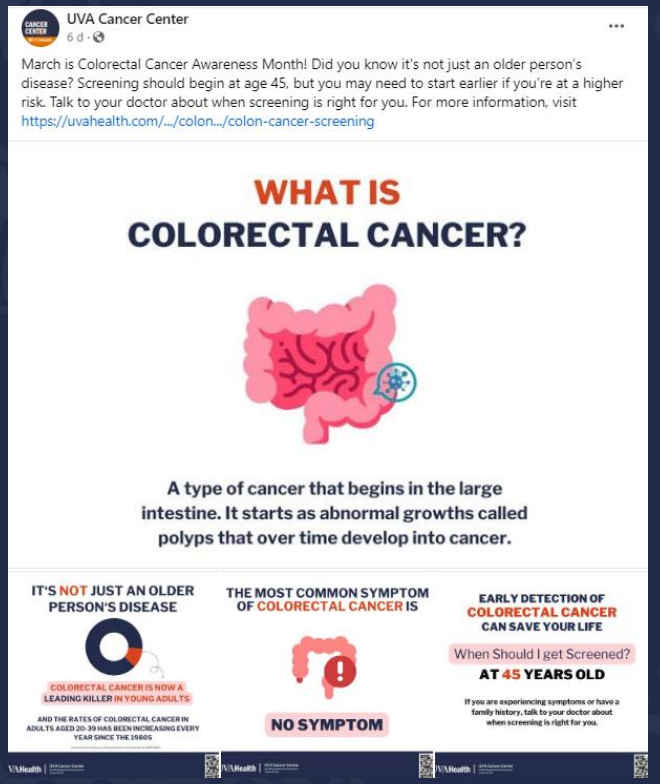
Social Media Campaign

Instagram

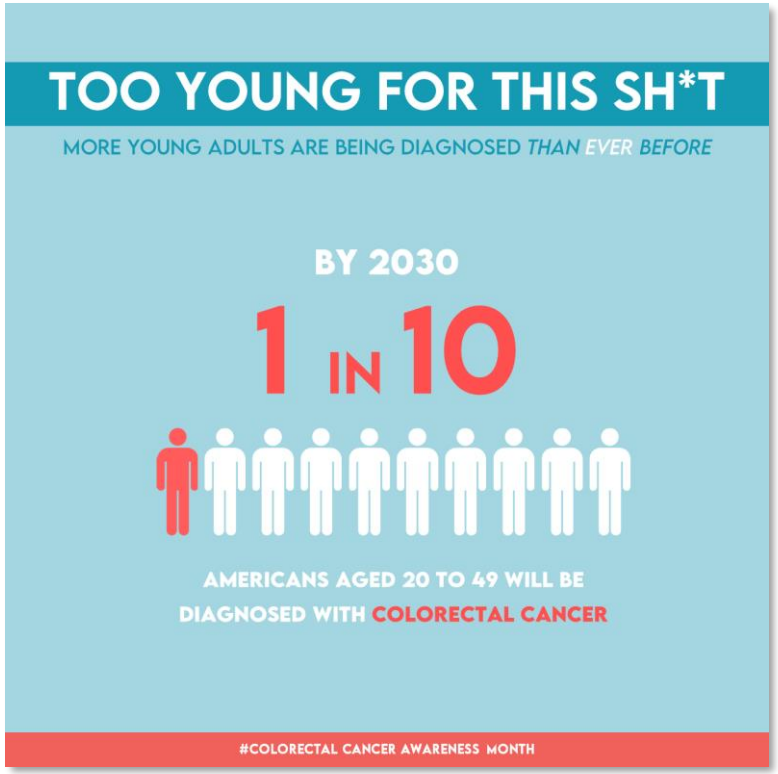
- @uvagastro
- @uvaimr
- @hittingcancerbelowthebelt

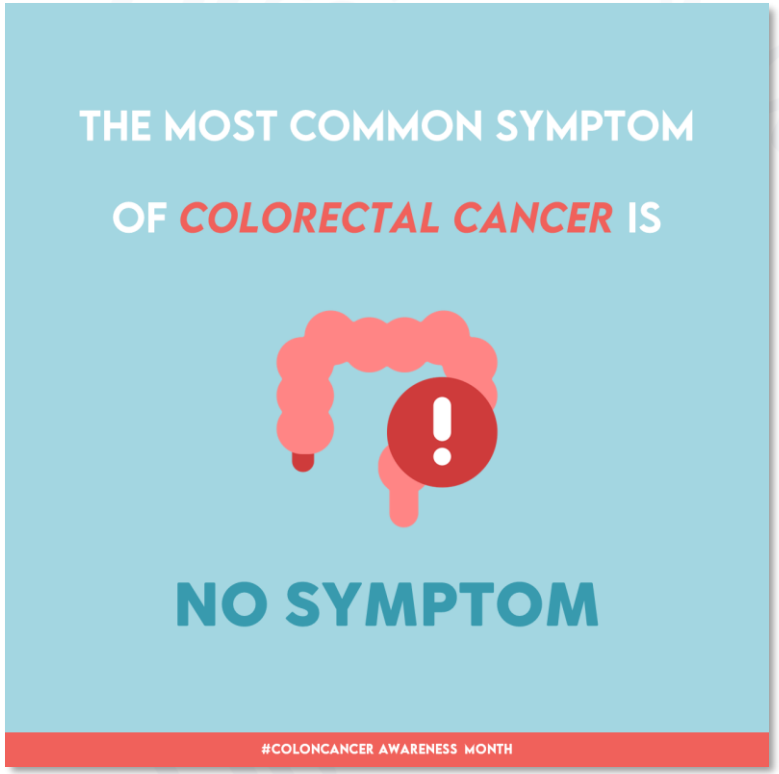
Facebook

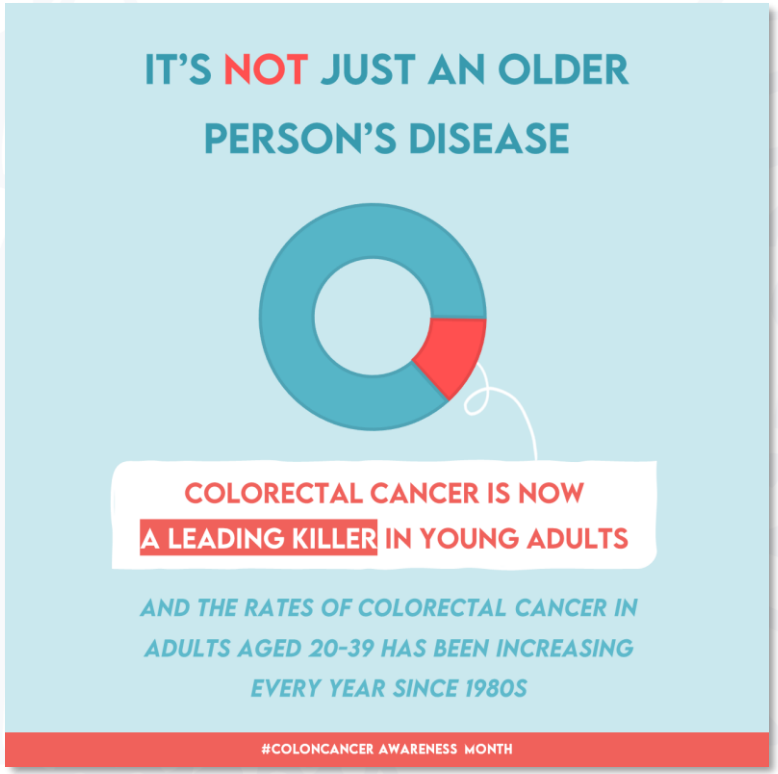
- UVA Cancer Center



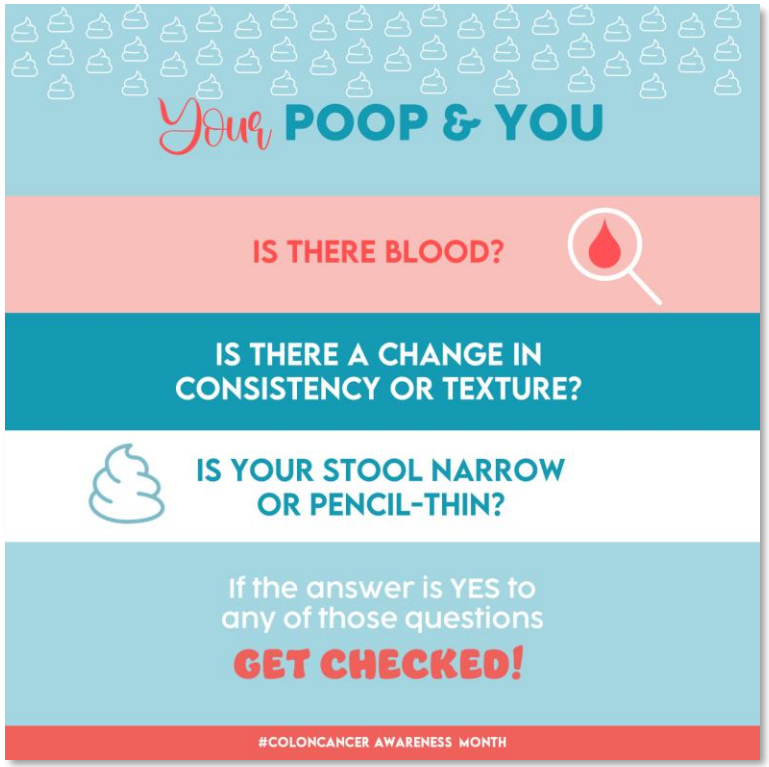
Infographics

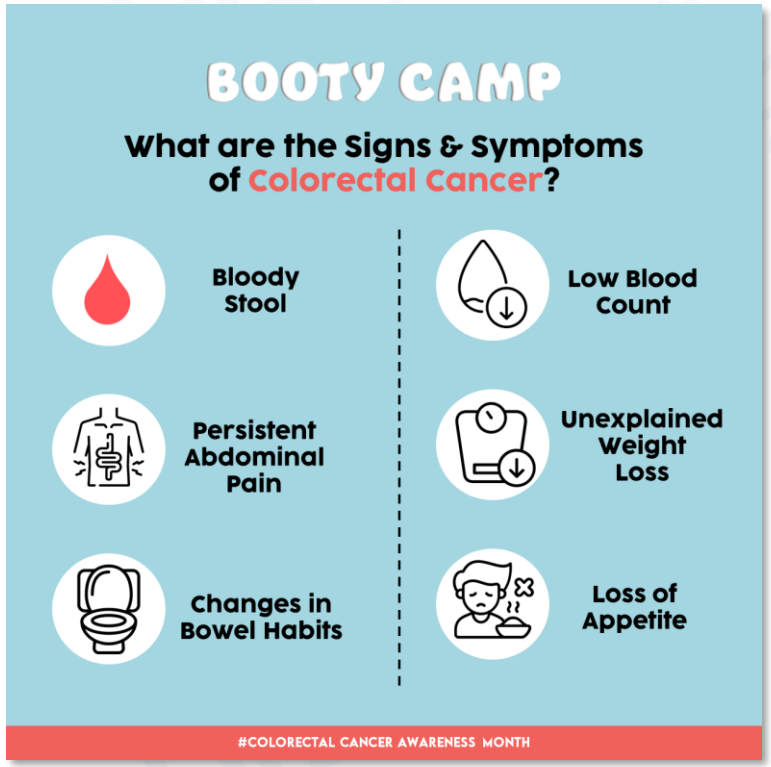




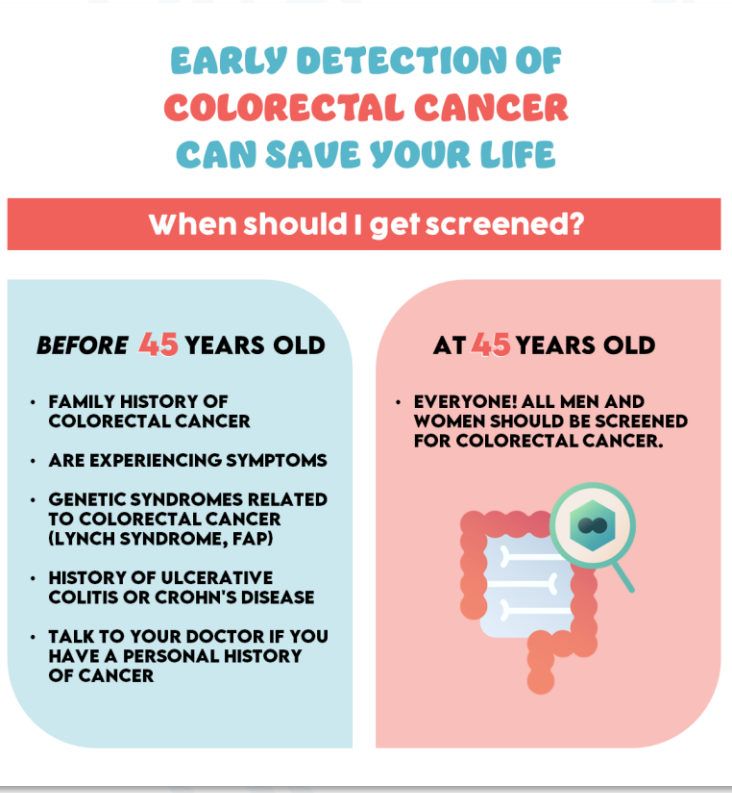


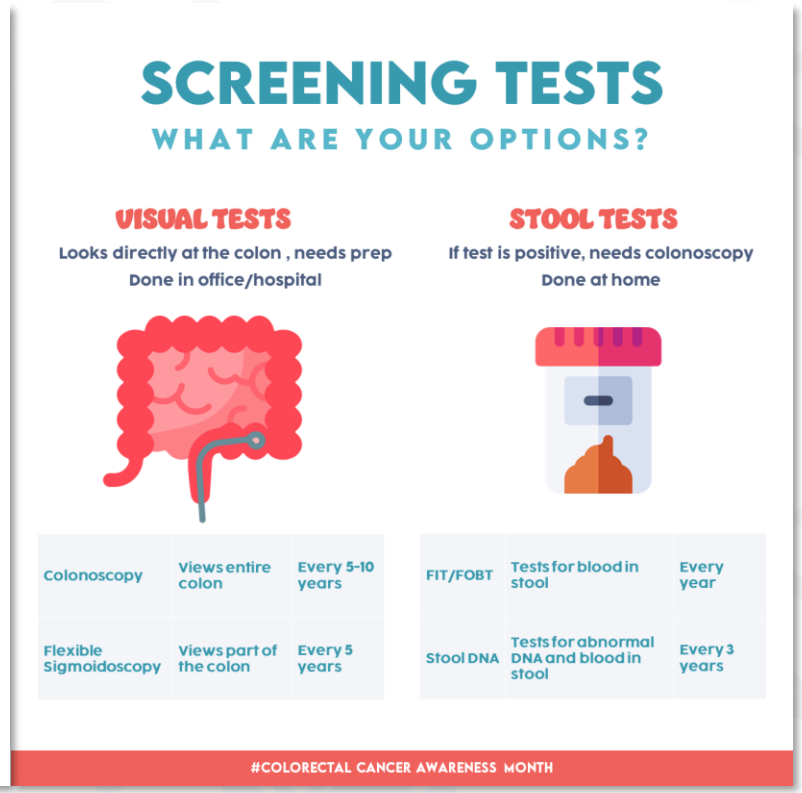
Infographics





Infographics





Radio Segment

SEARCH

CVILLE RIGHT NOW

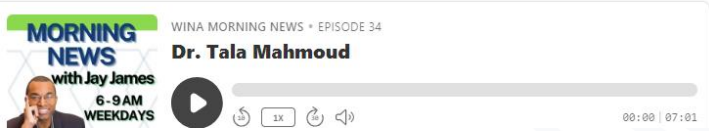
HOME NEWS LIFESTYLE EVENTS SPORTS WINA RADIO PODCASTS ABOUT

Dr. Tala Mahmoud

By Jay James March 12, 2024 7:09 am

Source: clipart.com

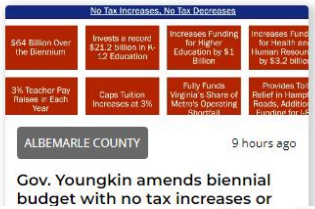
Dr. Tala Mahmoud joined the show to discuss a critically important health care issue for young people.



ALBEMARLE COUNTY 4 hours ago

Outside counsel to temporarily serve as acting city attorney

CHARLOTTESVILLE, VA (CVILLE RIGHT NOW) – The City of Charlottesville has retained the services [...]



ALBEMARLE COUNTY 9 hours ago

Gov. Youngkin amends biennial budget with no tax increases or

On-grounds Campaign

Colorectal Cancer (CRC) Awareness Week

Highlighting Early Onset CRC

Week of Events

March 13th

Guest Lecturer

Dr. Priyanka Kanth, MD MS
MedStar Georgetown
7:30-8:30 am
UVA SOM MR5 Room 2005

March 14th

Inflatable Colon Day

Join Hitting Cancer Below the Belt for colon cancer awareness, experience the 10ft inflatable colon
10 am -2 pm, UVA Medical Center Cafeteria

March 15th

Wear Blue Day

Join us for Wear Blue Day, the official color for colon cancer awareness!

Did you Know?

- 1 in 5 colorectal cancer (CRC) patients are between the ages of 20 and 54.
- Early onset CRC has doubled since 1990!
- By 2030, CRC is predicted to be the leading cause of cancer death in men and women, 20 to 49 years of age.

Instagram Handles

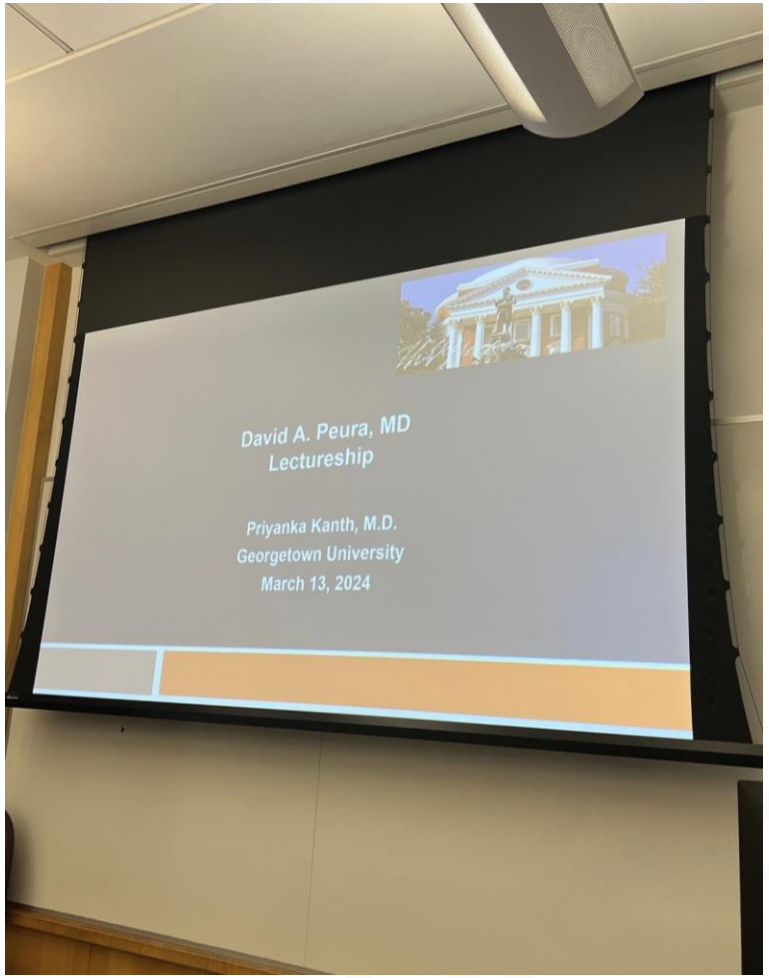
- UVA Medical School: @Uvaschoolofmedicine
- UVA IM Residency: @Uvaimrr
- UVA GI Fellowship:@Uvagastro

A special thanks to "Hitting Cancer Below the Belt" for their partnership this year!

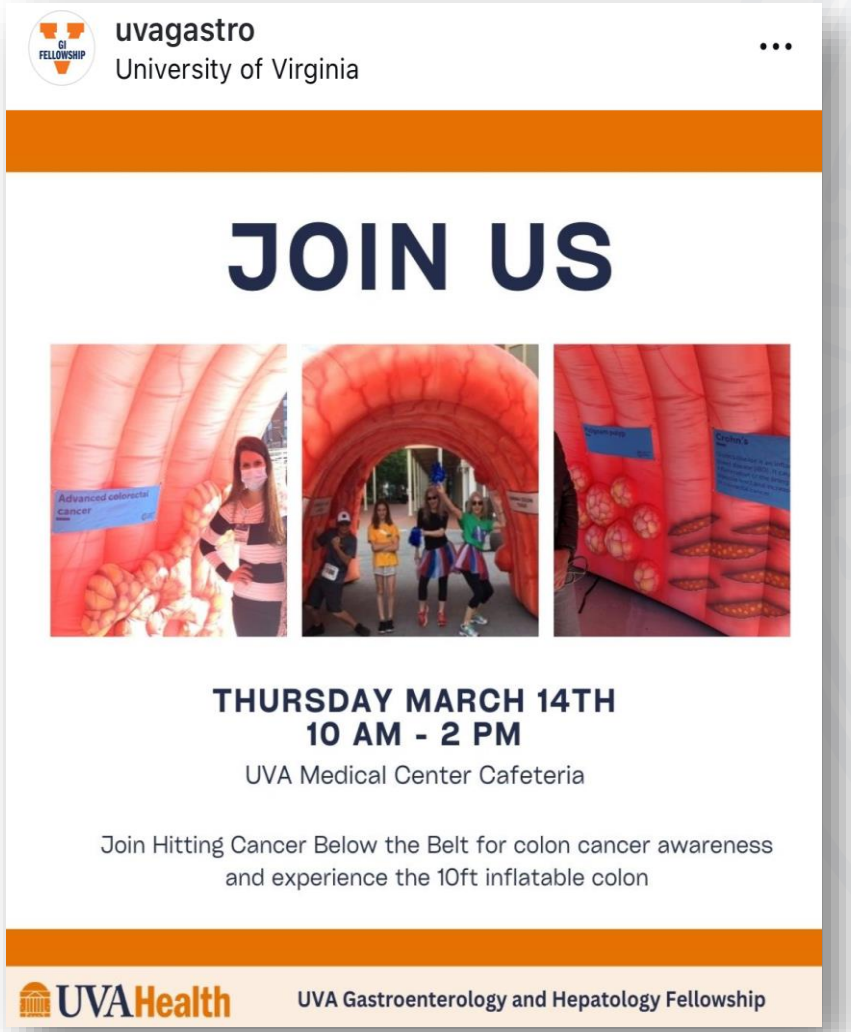
UVA Health | UVA Gastroenterology & Hepatology

For more info, email Lindsey
bicrlc@virginia.edu

Guest Lecturer



Inflatable Colon Day



Wear Blue Day

Medical School Newsletter

March is Colon Cancer Awareness Month

Hitting Cancer Below the Belt

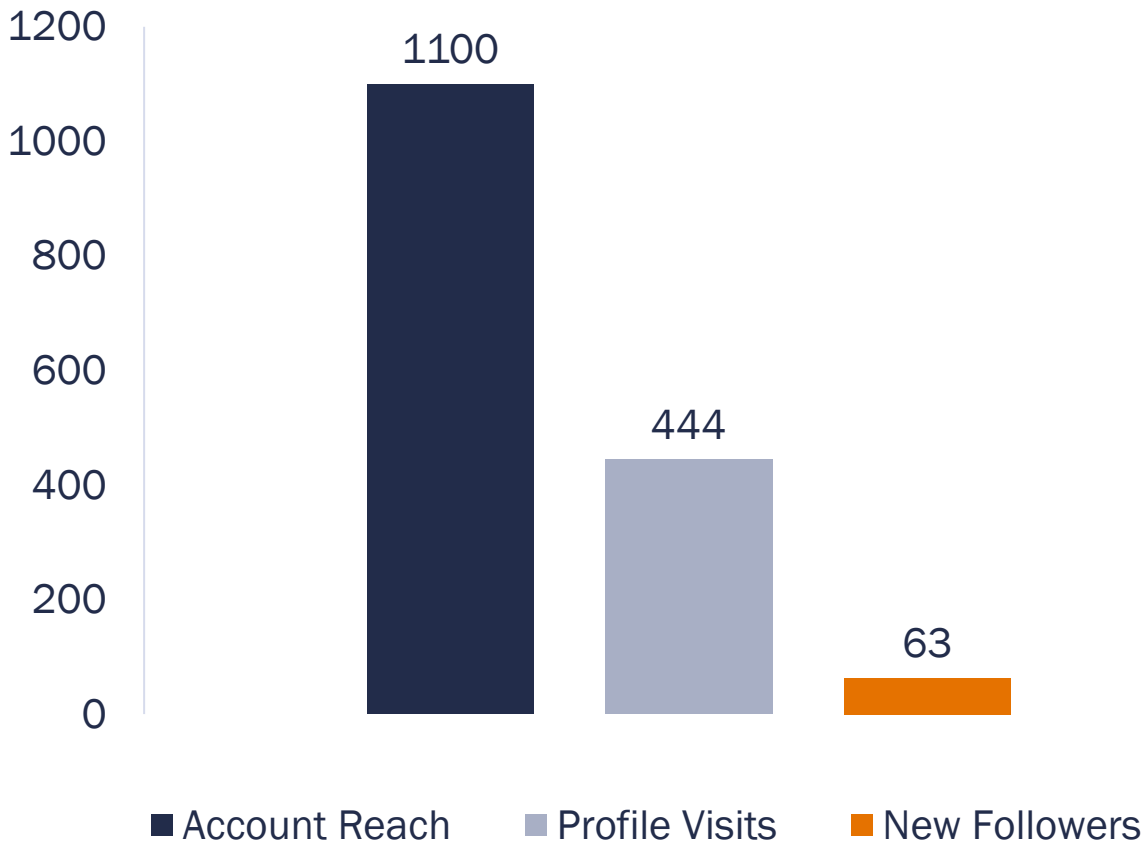
- Thursday March 14th from 10am - 2pm at the UVA hospital cafeteria
- There will be a 10ft inflatable colon as a conversation starter to discuss signs/symptoms of early-onset CRC.
- The UVA cancer center will also be on-site with navigators available to assist you in signing up for age-related cancer screenings for which you may be eligible.

Wear Blue Day

- March 15th all-day
- We hope to have the larger UVA community wear blue this day as it is the official color for colon cancer awareness.

Results & Impact

Campaign Reach



Instagram Data

10,000-20,000
Daily listeners

NEWSRADIO WINA 1070AM 98.9FM

Radio Listenership

Key Takeaways

Lessons Learned

- Importance of tailored messaging for young adults
- Power of collaborative, multi-level university engagement
- Importance of making young healthcare trainees aware of early onset CRC and its symptoms
- Effectively engaged the local and UVA Health community
- These efforts signify significant progress towards building a professional network dedicated to addressing early-onset CRC

Future Directions

Moving Forward

Where do we go from here?

- Sustainability at our institution
- Potential for replication at other institutions
- Continued focus on EOCRC awareness
- Expanding the initiative to include underrepresented communities

Thank You!

QUESTIONS?

Making Cancer History®

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Early-age Onset Colorectal Cancer

Standards of Care, Treatments and Survivorship

Y. Nancy You, MD MHSc

Professor, Department of Colon and Rectal Surgery

Clinical Medical Director, Colorectal Service Line

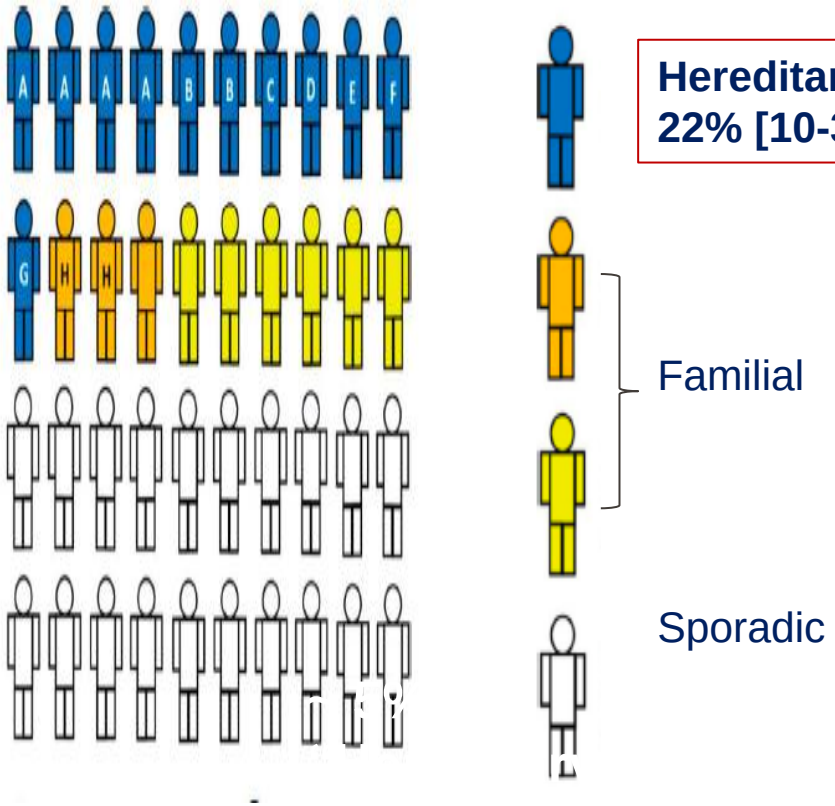
University of Texas MD Anderson Cancer Center

Updates on Treatment and Survivorship

1. **Personalized Medicine, Expanding role of molecular diagnostics**
   - Germline testing
   - Genomic profiling
   - Circulating tumor elements
2. **Metastatic Disease**
3. **Local Therapy**
   - Local excision
   - Organ preservation
4. **Survivorship: Treating the Whole person**

Personalized medicine - Expanding role of molecular diagnostics

Categorizing Germline Risk



Hereditary
22% [10-33%]

Familial

Sporadic

Mauri et all, *Molecular Oncology* 2019

Polyposis Syndromes

Adenoma predominant

- Classic FAP (*APC*, *dominant*)
- Attenuated FAP
- *MYH*-polyposis *(recessive)*

Hamartoma predominant

Hyperplastic/Serrated adenoma

Non-polyposis Syndromes

Mismatch repair deficient (dMMR)

- Lynch Syndrome (*MLH1, MSH2, EPCAM, MSH6, PMS2*)

Mismatch repair proficient (pMMR)

- Familial Colorectal Cancer Type X
- Other

Personalized Medicine: Expanding role of molecular diagnostics

Targetting DNA Mismatch repair : Metastatic, adjuvant, neoadjuvant, pre-emptive settings

PHASE III ATOMIC TRIAL

N = 700

Eligibility Criteria

- Stage III colon adenocarcinoma with any tumor (Tx-T4, N1-2M0; including N1C) originating or entirely located in colon
- Completely resected tumor
- dMMR
- No residual involved lymph node or metastatic disease at time of registration
- No prior chemotherapy, immunotherapy, biologic, targeted therapy, or radiation therapy; 1 previous cycle of mFOLFOX6 permitted.
- ECOG performance status ≤2
- No known active autoimmune disease or hepatitis B or C

Experimental arm: mFOLFOX6 with atezolizumab (12 cycles) followed by atezolizumab (6 months)

Control arm: mFOLFOX6 (12 cycles)

Endpoints:

Primary DFS

Secondary OS, AEs

AE indicates adverse event; DFS, disease-free survival; dMMR, DNA mismatch repair; mFOLFOX6, modified leucovorin calcium, fluorouracil, and oxaliplatin; OS, overall survival.

Neoadjuvant Pembrolizumab for Patients with Mismatch Repair Deficient Localized and Locally Advanced Solid Cancers
ESMO 2021

N ENGL J MED 386;25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

Nivolumab plus relatlimab in patients with previously treated microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study

EA2201: An ECOG-ACRIN phase II study of neoadjuvant nivolumab plus ipilimumab and short course radiation in MSI-H/dMMR rectal tumors.
ASCO *2022*

Personalized Medicine : Expanding role of molecular diagnostics

Who Really Needs Adjuvant Therapy

Overtreatment of Young Adults With Colon Cancer
More Intense Treatments With Unmatched Survival Gains

Table 2. Likelihood of Receiving Postoperative Systemic Chemotherapy and Multiagent Regimens for Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers[a]

Patients Who Received Chemotherapy	Any Chemotherapy, No. (%)	Odds Ratio for Receiving Chemotherapy (95% CI)	Multiagent Regimens, No. (%)	Odds Ratio for Receiving Multiagent Regimen (95% CI)
Stage I				
Ages 65-75 y (n = 8991)	162 (1.8)	1 [Reference]	52 (43.0)	1 [Reference]
Ages 18-49 y (n = 1926)	109 (5.7)	2.88 (2.21-3.77)	43 (48.3)	1.38 (0.71-2.68)
Stage II Overall				
Ages 65-75 y (n = 11 011)	2748 (25.0)	1 [Reference]	773 (41.7)	1 [Reference]
Ages 18-49 y (n = 3083)	1732 (56.2)	3.93 (3.58-4.31)	670 (54.9)	1.71 (1.48-1.97)
Stage II Low Risk				
Ages 65-75 y (n = 4822)	923 (19.1)	1 [Reference]	313 (39.6)	1 [Reference]
Ages 18-49 y (n = 1636)	826 (50.5)	4.22 (3.70-4.81)	388 (52.5)	1.67 (1.34-2.09)

Kneuertz et al. *JAMA Surg 2015*
Dasari et al, *Nat Rev Clin Onc* 2020

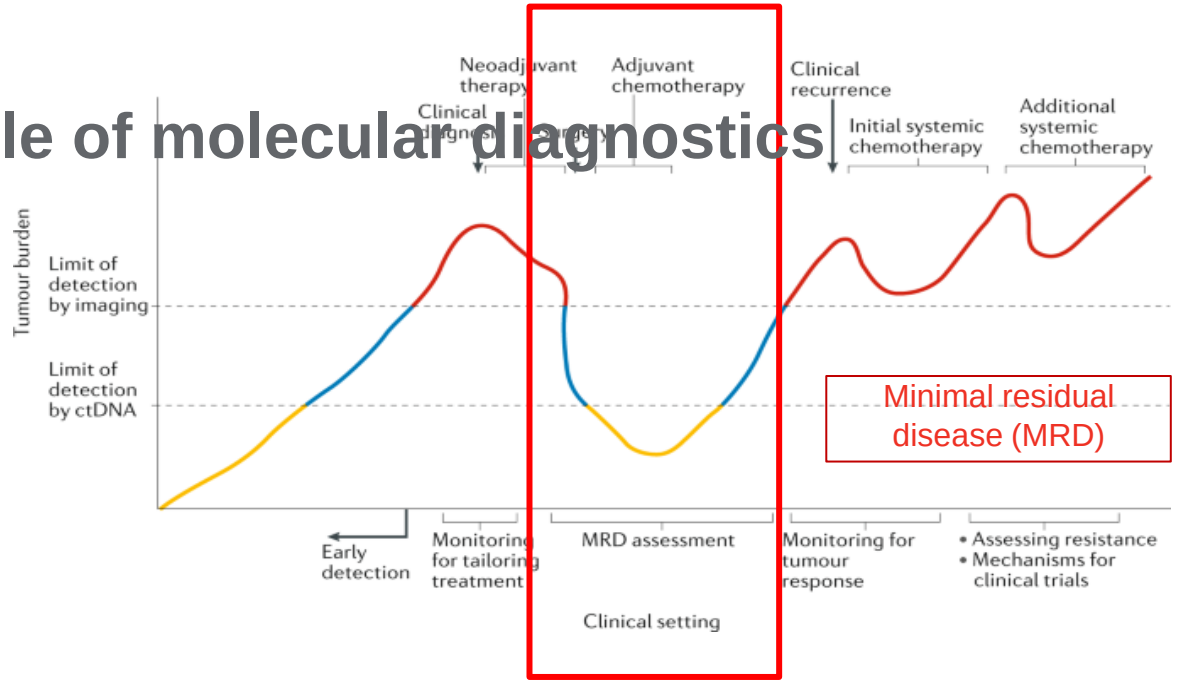


Table 1 Summary of reports that investigated ctDNA to detect MRD of various cancer types

Cancer type	Cancer, stage(s)	N[a]	Methodology	Brief summary [hazard ratio (HR), ctDNA positive compared with negative][b]	References
CRC	Stage I–III	130	Signatera™	Recurrence in 87.5% of patients with ctDNA (+) after treatment, post-operative, post-ACT, and post-definitive therapy HR for RFS = 7.2, 17.5, and 43.5	[8]
	Stage II	230	Safe-SeqS	Recurrence in 79% of patients with ctDNA (+) without CTx versus 9.8% of patients with ctDNA (−) without CTx (HR for RFS = 18), post-CTx HR for RFS = 11	[31]
	Stage III	96	Safe-SeqS	Post-operative HR for RFS = 3.8, Estimated 3-year recurrence-free interval (RFI): ctDNA (+) versus (−) = 77% versus 30%, post-CTx HR for RFI = 6.8	[32]
	Stage I–IV	103	Guardant Reveal™	Sensitivity and specificity of landmark recurrence: 55.6% and 100%, landmark HR for RFS = 11.28	[33]
	Stage I–III	150	ddPCR	Post-operative HR for DFS = 17.56, serial HR for DFS = 11.33, post-ACT HR = 10.02, median lead time = 11.5 (m)	[34]
	Stage II–III	240	Geneseeq Prime™ 425 genes	Post-operative HR for RFS = 10.98, post-ACT HR for RFS = 12.76, post-definitive therapy HR = 32.02, mean lead time = 5.01 (m)	[35]
	Stage II	302	Safe-SeqS	Relative risk of receiving ACT in ctDNA-guided group: HR = 1.82, 2-year RFS = 93.5% in the ctDNA-guided group versus 92.4% in the standard care group	[36]
	Stage II–IV	1039	Signatera™	Post-operative HR = 10.0, ctDNA (+) was the most significant prognostic factor in multivariate analysis (HR 10.82), postoperative HR for benefit from ACT = 6.59	[14]

Updates on Treatment and Survivorship

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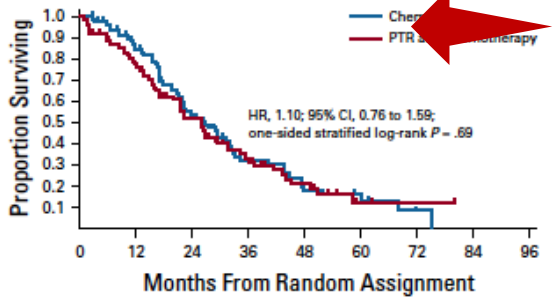
Managing Metastatic CRC: Sequencing Therapies

Upfront Primary Tumor resection: No survival benefit; High morbidity; Risk never receiving systemic therapy

Primary Tumor Resection Plus Chemotherapy Versus Chemotherapy Alone for Colorectal Cancer Patients With Asymptomatic, Synchronous Unresectable Metastases (JCOG1007; iPACS): A Randomized Clinical Trial

Yukihide Kanemitsu, MD[1]; Kohei Shitara, MD[2]; Junki Mizusawa, ME[1]; Tetsuya Hamaguchi, MD, PhD[3]; Dai Shida, MD, PhD[1]; Koji Komori, MD, PhD[4]; Satoshi Ikeda, MD, PhD[5]; Hitoshi Ojima, MD, PhD[6]; Hideyuki Ike, MD, PhD[7]; Akio Shiomi, MD[8]; Jun Watanabe, MD, PhD[9]; Yasumasa Takii, MD[10]; Takashi Yamaguchi, MD[11]; Kenji Katsumata, MD, PhD[12]; Masaaki Ito, MD, PhD[2]; Junji Okuda, MD, PhD[13]; Ryoji Hyakudomi, MD[14]; Yasuhiro Shimada, MD[15]; Hiroshi Katayama, MD[1]; Haruhiko Fukuda, MD[1]; and JCOG Colorectal Cancer Study Group

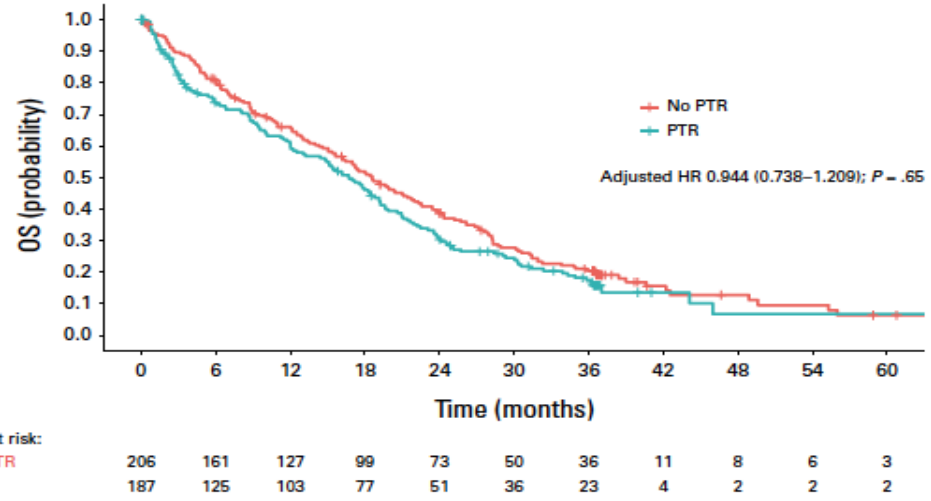


Postoperative mortality	3 (4%)
Early postoperative morbidity	
Grade 2/3/4	29 (38%)

J Clin Oncol 39:1098-1107.

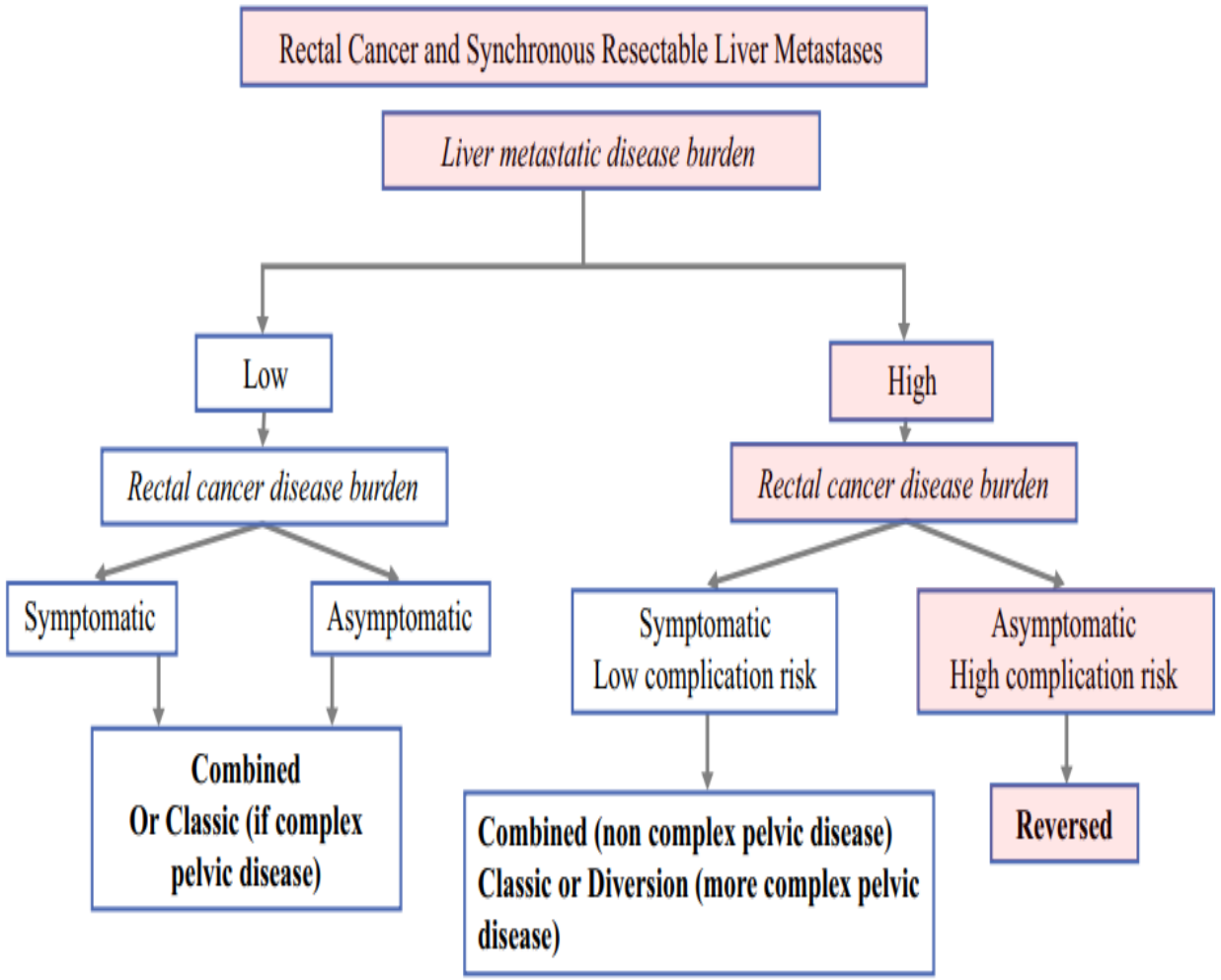
Primary Tumor Resection Before Systemic Therapy in Patients With Colon Cancer and Unresectable Metastases: Combined Results of the SYNCHRONOUS and CCRe-IV Trials

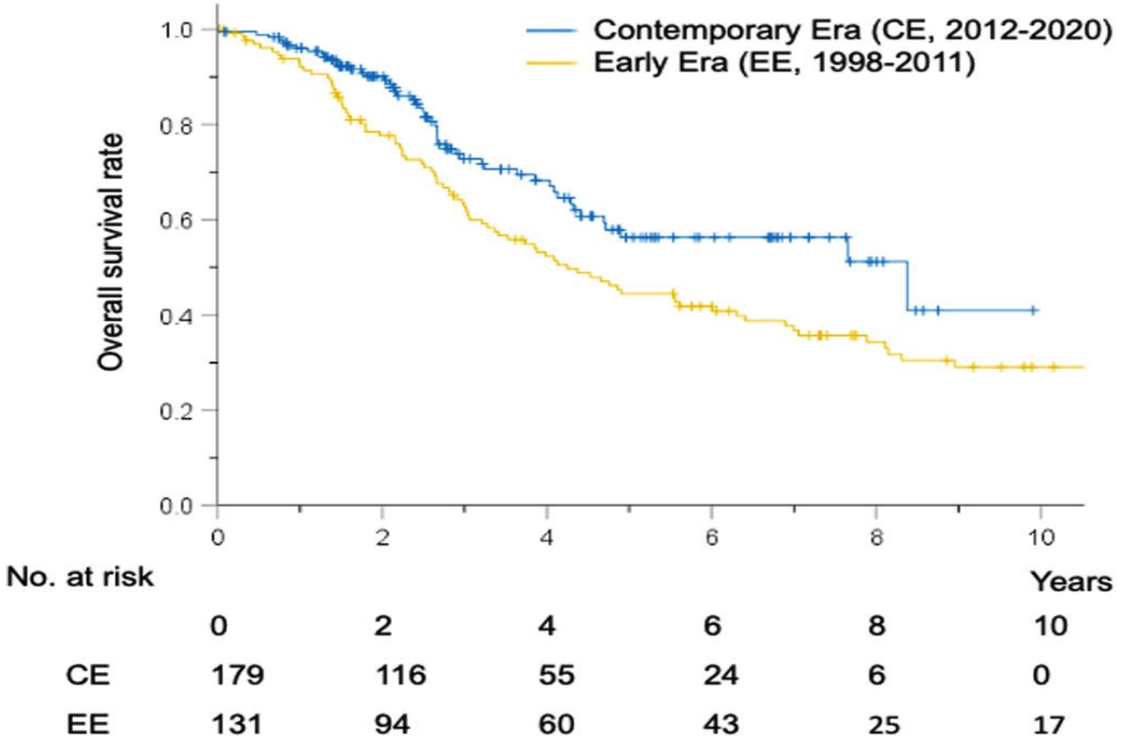
Nuh N. Rahbari, MD[1]; Sebastiano Biondo, MD[2]; Ricardo Frago, MD[2]; Manuel Feißt, PhD[3]; Esther Kreisler, MD[2]; Inga Rossion, MD[4]; Monica Serrano, MD[2]; Dirk Jäger, MD[5]; Monika Lehmann, PhD[6]; Florian Sommer, MD[7]; Axel Dignass, MD[8]; Claus Bolling, MD[8]; Ilka Vogel, MD[9]; Ulrich Bork, MD[10]; Markus W. Büchler, MD[11]; Gunnar Folprecht, MD[12]; Meinhard Kieser, PhD[3]; Florian Lordick, MD[13]; and Jürgen Weitz, MD, MSc[10,14]; on behalf of the SYNCHRONOUS and CCRe-IV Trial Groups



J Clin Oncol 42:1531-1541

Individualized Treatment Sequencing Selection Contributes to Optimized Survival in Patients with Rectal Cancer and Synchronous Liver Metastases





Median OS survival: 5.6 years (2.7–12.6)

5-year OS: 56.3% (CE)

Conrad C, Vauthey JN, You YN *Ann Surg Oncol* 2017; Maki H, Vauthey JN, You YN *Eur J Surg Onc* 2024

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Surgery For Optimal Local Control

Proximal & Distal margins
Radial margins
Vascular dissection, high ligation, nodal harvest

Long-term morbidity of limited vs. extended colon resection

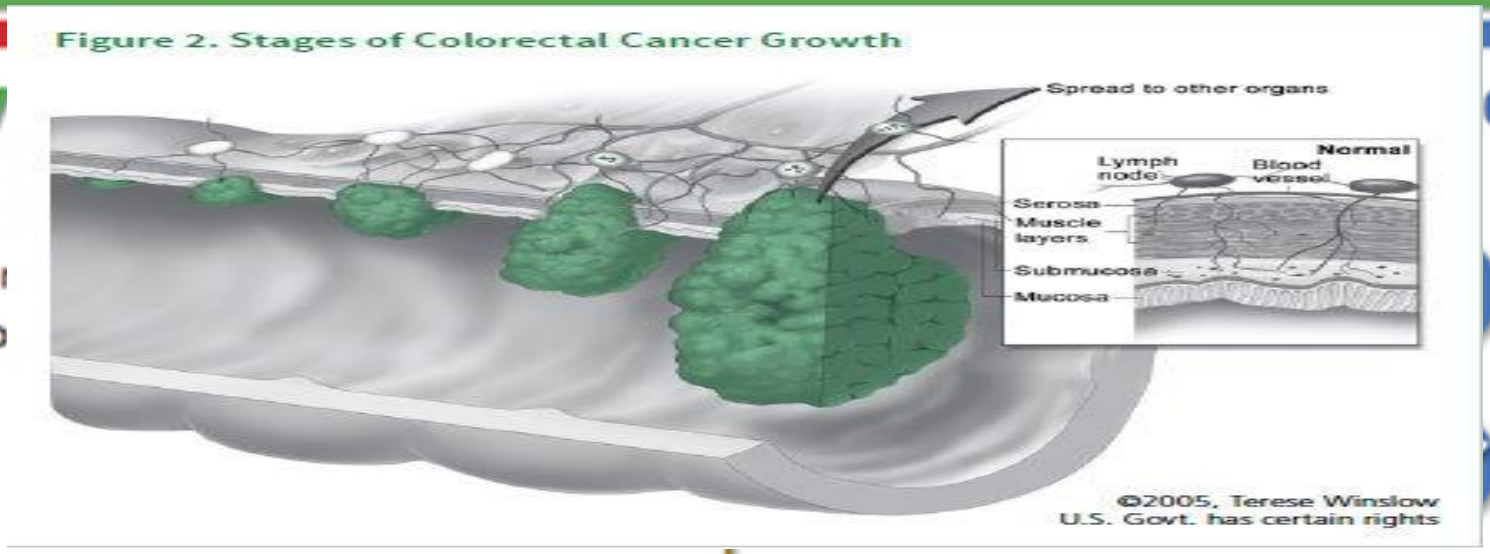
	SEG (n=145)	TC-IRA (n=56)	P value SEG vs. TC-IRA
Bowel frequency			
Day	2 (1–3)	4 (3–8)	<0.001
Night	0 (0–0)	1 (1–2)	<0.001
Dietary restriction	34 (23.5)	30 (55.6)	<0.001
Restriction of preoperative			
Social activity	13 (9)	17 (31.5)	<0.001
Housework	10 (6.9)	11 (20.4)	0.0092
Recreation	11 (7.6)	17 (31.5)	<0.001
Family relationships	6 (4.14)	7 (13)	0.042
Travel	20 (13.8)	23 (42.6)	<0.001
Urgency			
>once/week	4 (2.8)	1 (1.8)	1
Incontinence			
Day, > once/week	24 (16.6)	17 (31.5)	0.029
Night, > once/week	2 (1.4)	0 (0)	1
Perianal irritation, >once/week	10 (6.9)	10 (18.5)	0.03
Mucus leak			
Daytime	14 (9.7)	5 (9.3)	1
Nighttime	5 (3.5)	5 (9.3)	0.14
Pad use			
Always daytime	4 (2.8)	1 (1.9)	1
Always nighttime	0	1 (1.85)	0.27
Overall satisfaction and emotional well-being			
Satisfied/very satisfied	134 (92.4)	47 (87.04)	0.27
Emotionally well/excellent	138 (95.2)	47 (87)	0.061

	SEG (n=145)	TC-IRA (n=56)	P value SEG vs. TC-IRA
Overall	98.5 (93.4, 100)	91.2 (84.6, 96.3)	<0.001
Dysphoria	100 (96.9, 100)	96.9 (90.6, 100)	<0.001
Interfere with activity	100 (89.3, 100)	85.7 (71.4, 92.9)	<0.001
Body image	100 (93.8, 100)	100 (87.5, 100)	0.15
Health worry	100 (91.7, 100)	91.7 (83.3, 100)	0.028
Food avoidance	100 (91.7, 100)	83 (66.7, 91.7)	<0.001
Social reaction	100 (93.8, 100)	100 (87.5, 100)	0.036
Sexual activity	100 (100, 100)	100 (100, 100)	0.16
Relationships	100 (100, 100)	100 (91.7, 100)	0.33

You et al DCR2008

Functional Sequelae of Pelvic Surgery

Low Anterior Resection Syndrome



Sy

ces

Variable, unpr
bowel functio

Altered stool consistency

Increased stool frequency

Repeated painful stools

Incontinence

Soiling

Impact on:

Mental and emotional wellbeing

Social and daily activities

Dissatisfaction with bowels

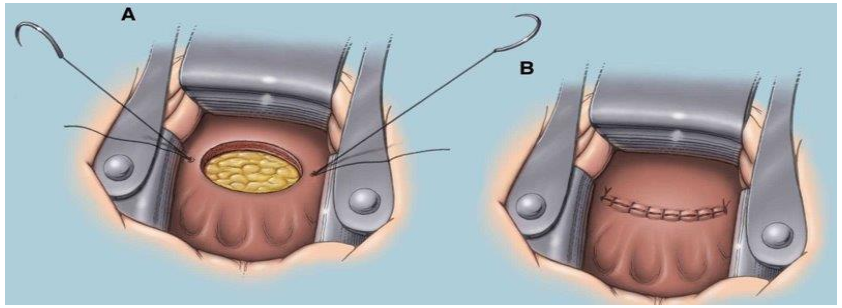
Relationships and intimacy

Strategies and compromises

Roles, commitments and responsibilities

Local excision of Rectal Cancer: Can we “convert” some tumors to be “safe”?

Trade off = radiation, chemotherapy, outcomes



- ACOSOG Z6041

- 1- and 2- year locoregional relapse-free survival = 98% (95% CI, 86 to 100) and 90% (95% CI, 58 to 98)
- Preserved quality of life and rectal function scores

Organ Preservation Non-operative Management Watch & Wait

Initial Staging

- Digital rectal exam
- Complete, high-quality colonoscopy
- CT chest/ abdomen/pelvis
- High quality rectal MRI

Key Features on Rectal MRI

- T category
- Tumor distance from anal verge
- Circumferential resection margin (CRM)
- Extramural vascular invasion (EMVI)
- Locoregional nodal disease

Risk Stratification

Low Risk

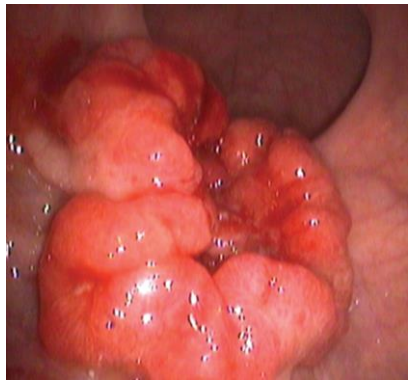
- T2, T3a-b
- Node negative
- CRM clear
- No EMVI

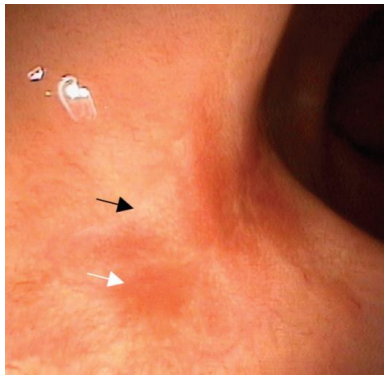
Intermediate Risk

- T3c-d ***and/or*** node positive
- CRM clear
- No EMVI

High Risk

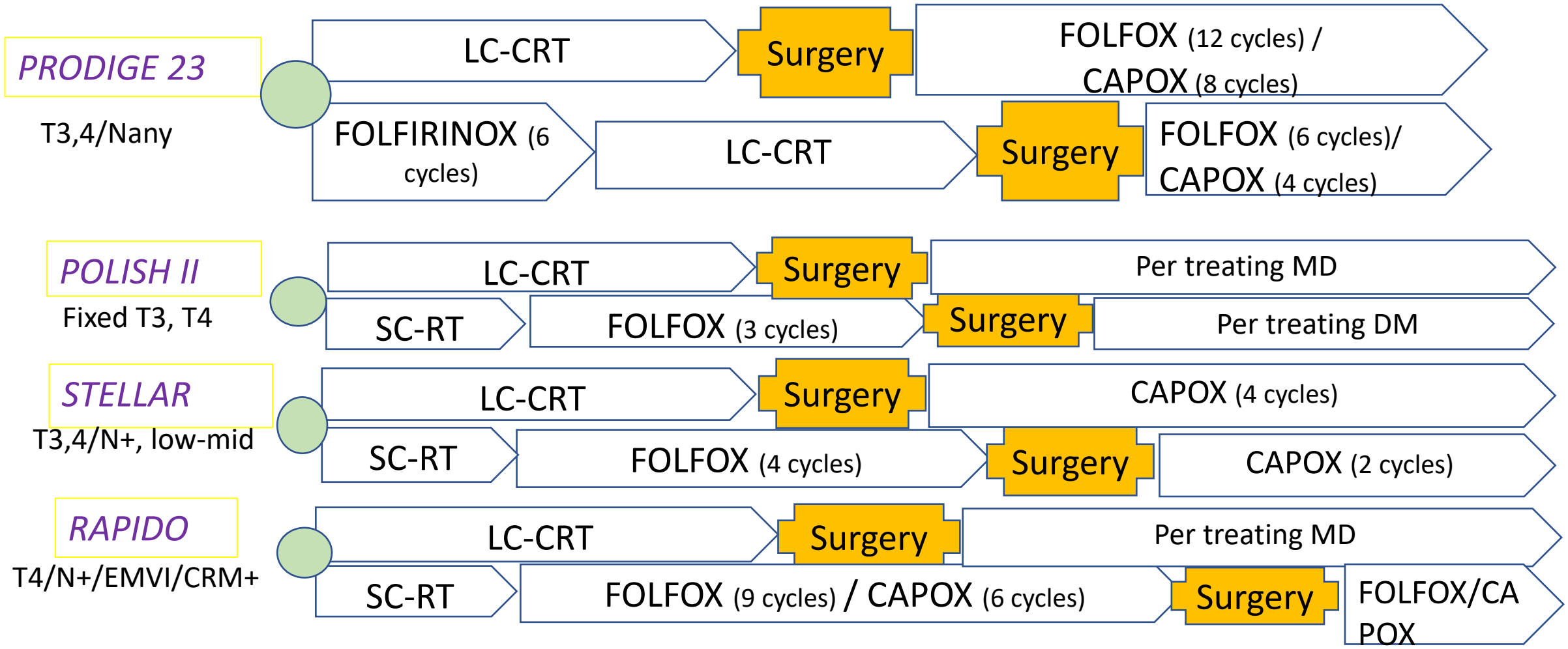
- T3c-d ***and/or*** node positive
- CRM threatened or positive ***and/ or*** EMVI positive





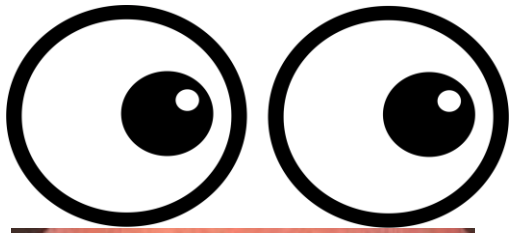
Neoadjuvant Treatment Strategies in Colon and Rectal Cancer

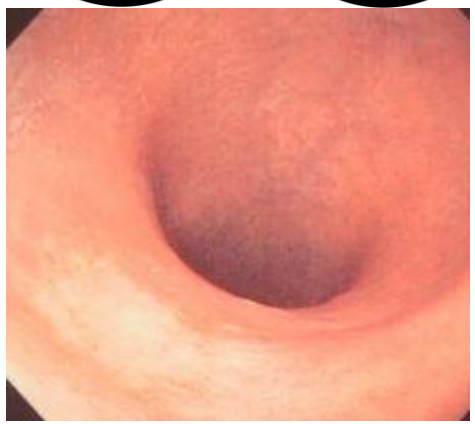
- **Toward "Total Neoadjuvant Therapy"**

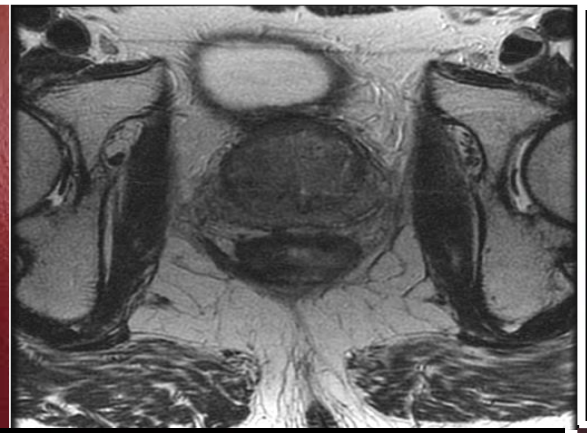


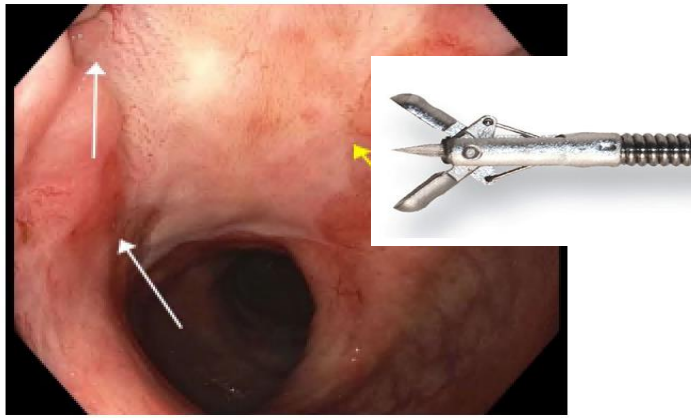
Neoadjuvant Treatment Strategies in Colon and Rectal Cancer:

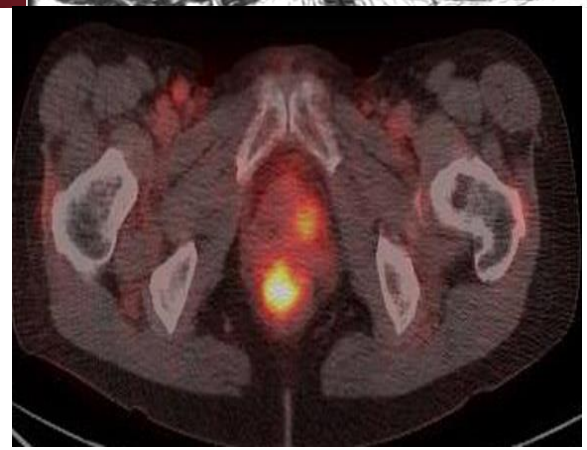
Assess response to neoadjuvant therapy











- No residual mass, ulceration, or stenosis
- Whitening of the mucosa
- Telangectasia

Habr-Gama A, et al. Dis Colon Rectum 2010; 53:1692-8.

Updates on Treatment and Survivorship

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Survivorship of Watch & Wait patients

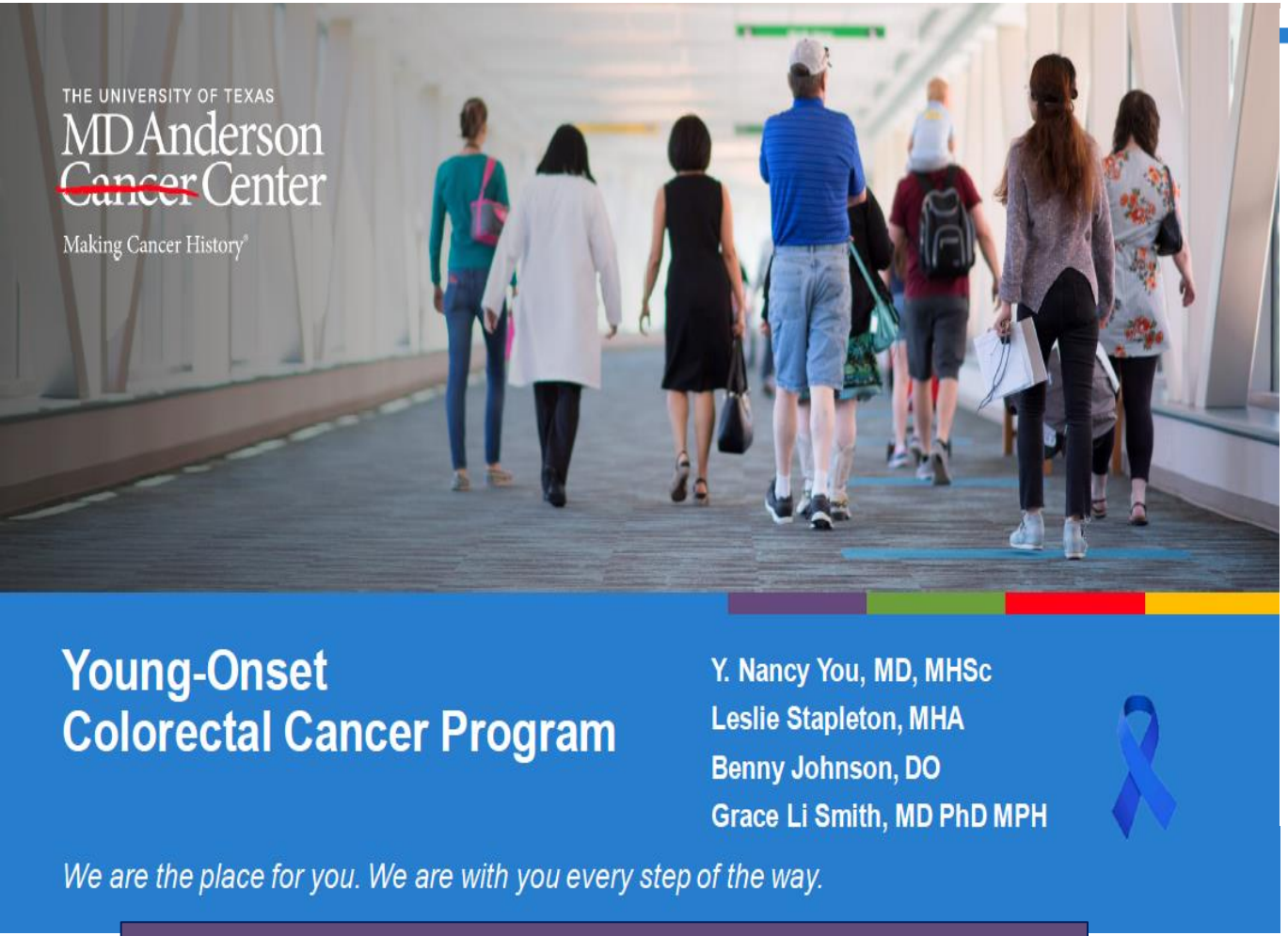
Tasks of Cancer Survivorship Care (NCCN)

1. Surveillance for CRC recurrence
2. Management of treatment-related consequence
3. Prevention of second cancer / general health
4. Coordination of care within healthcare system

Generic	Cancer-specific
Negative feeling	Appearance concerns
Positive feeling	Financial problems
Physical pain	Distress over recurrence
Fatigue	Family-related distress
Social avoidance	Benefits of cancer
Cognitive problems	
Sexual problems	

Table 2: 12 domains examined by QLACS

Standardized care pathway for multi-dimensional needs



In partnership with AYA Oncology Program

Mission

To offer the best integrated care for young-onset colorectal cancer patients across the cancer spectrum, including diagnosis, treatment, survivorship and prevention

Vision

To be a worldwide leader dedicated to ending the burden of young-onset colorectal cancer

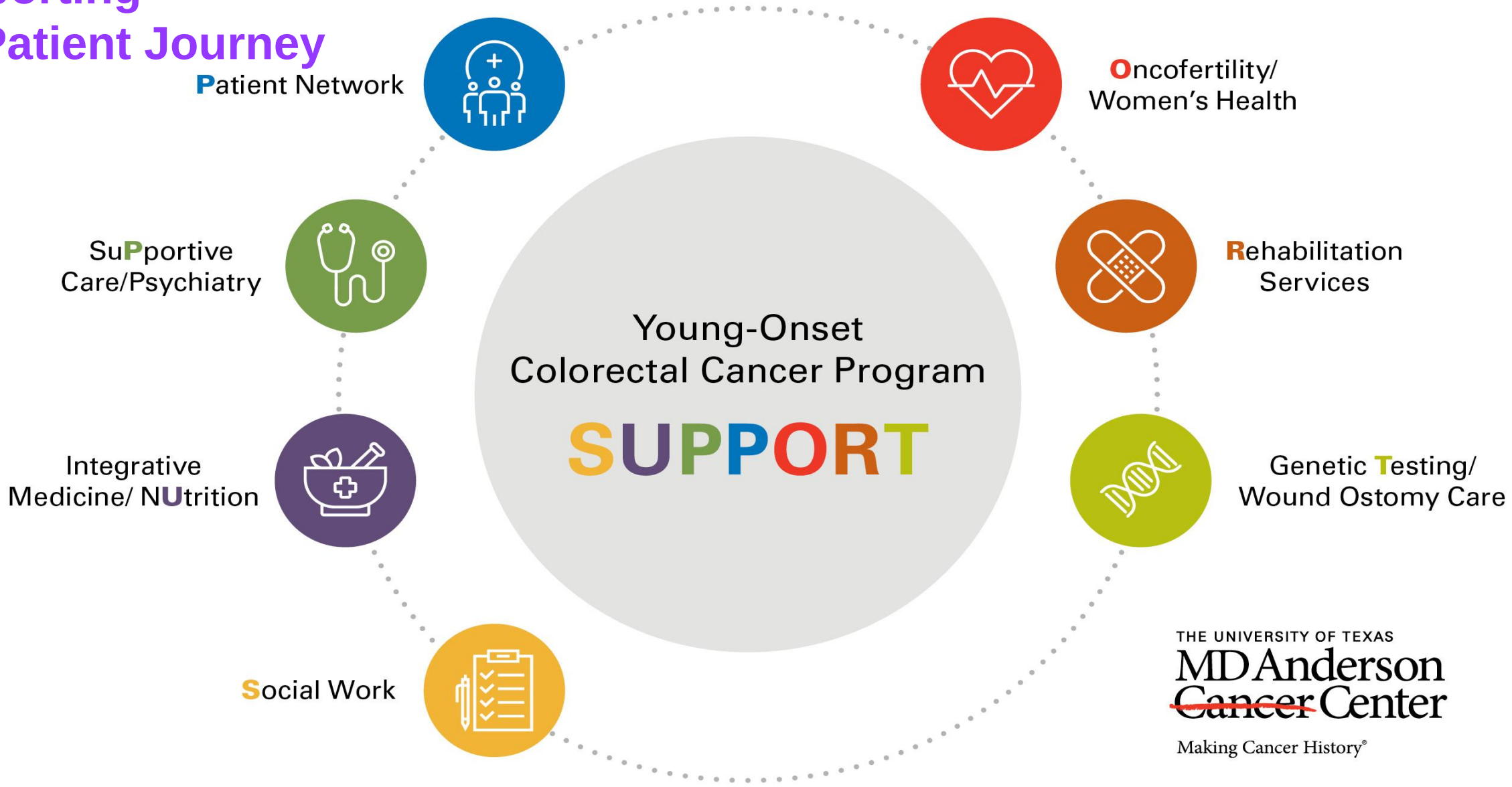
Values

PATIENT CENTRICITY
We focus on coordinated and whole-person care to provide a personalized, holistic and caring experience.

INNOVATION
We strive for modern, innovative approaches and utilize technology to advance the mission.

EXCELLENCE
We deliver state-of-the-art, expert clinical care integrated with research.

Supporting the Patient Journey



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Updates on Treatment and Survivorship

1. Expanding role of molecular diagnostics

- Germline, genomic, liquid biopsy
- More precision and personalization

2. Metastatic Disease

- Continued progress

3. Local Therapy

- Tradeoffs

4. Survivorship

- Treating the Whole person

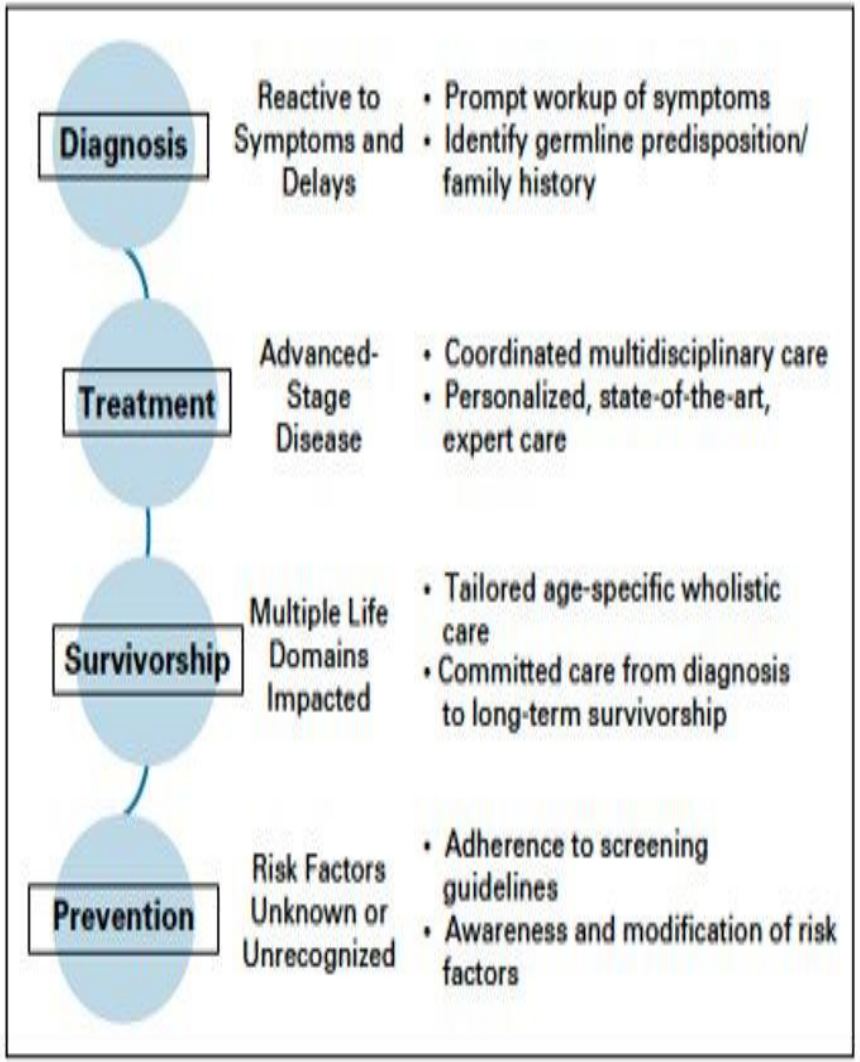

FIG 1. Challenges and associated opportunities for improvement throughout the spectrum of care for young adult patients with colorectal cancer.

You et al. *JOP 2020*

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Questions

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Thank You