
2021 SCSG
GI SYMPOSIUM

Contemporary Issues in Colorectal Cancer: COVID-19 & Early-Onset CRC

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- National Institutes of Health/National Cancer Institute

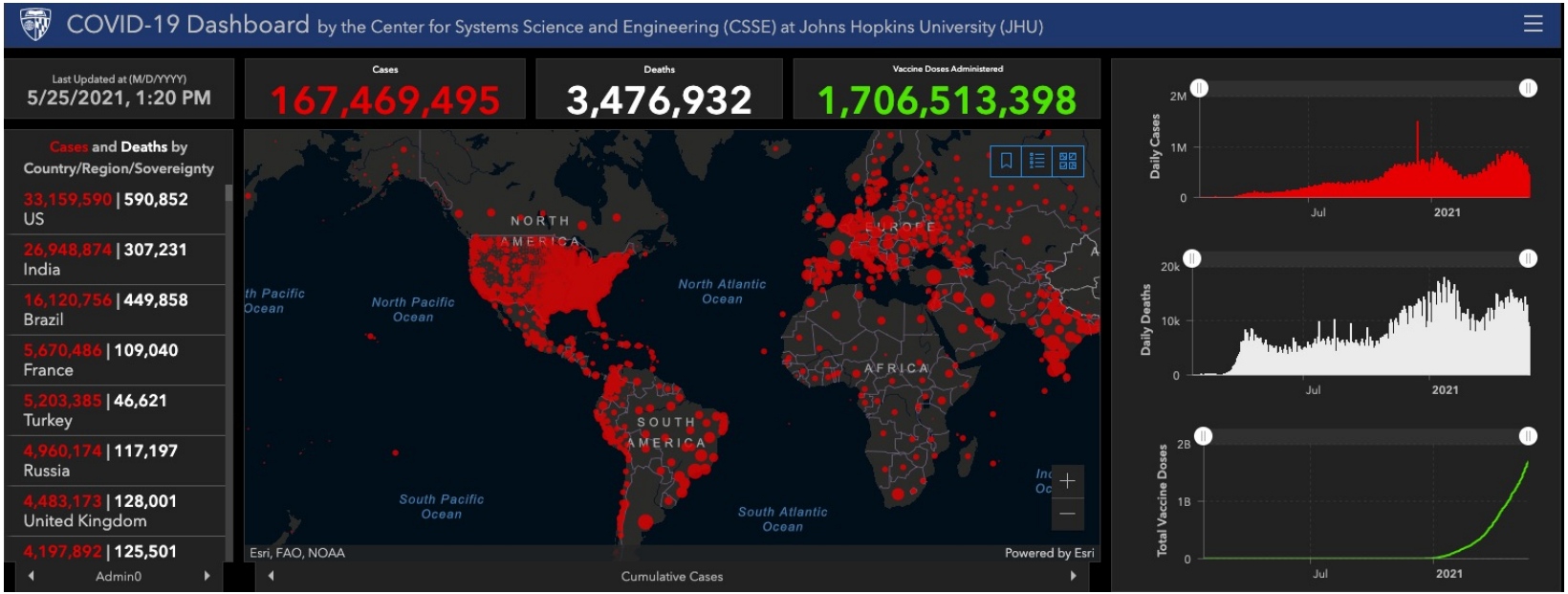
Consultant

- Colorectal Cancer Alliance

Objectives

- Review the current state of COVID-19 and potential implications for colorectal cancer (CRC) outcomes
- Evaluate real-world data on the effect of COVID-19, CRC, and lessons learned
- Discuss the epidemiology for early-onset CRC (EOCRC) and recent updates to CRC screening guidelines
- Share a framework for future research in EOCRC

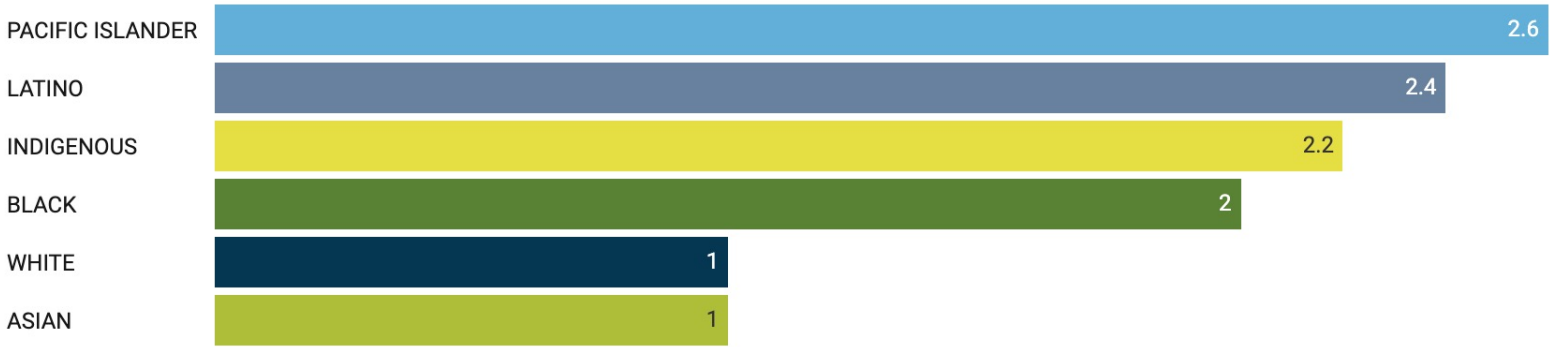
Over 160 million cases of COVID-19 worldwide



Mortality is high for racial & ethnic minorities

Adjusted for age, other racial groups are this many times more likely to have died of COVID-19 than White Americans

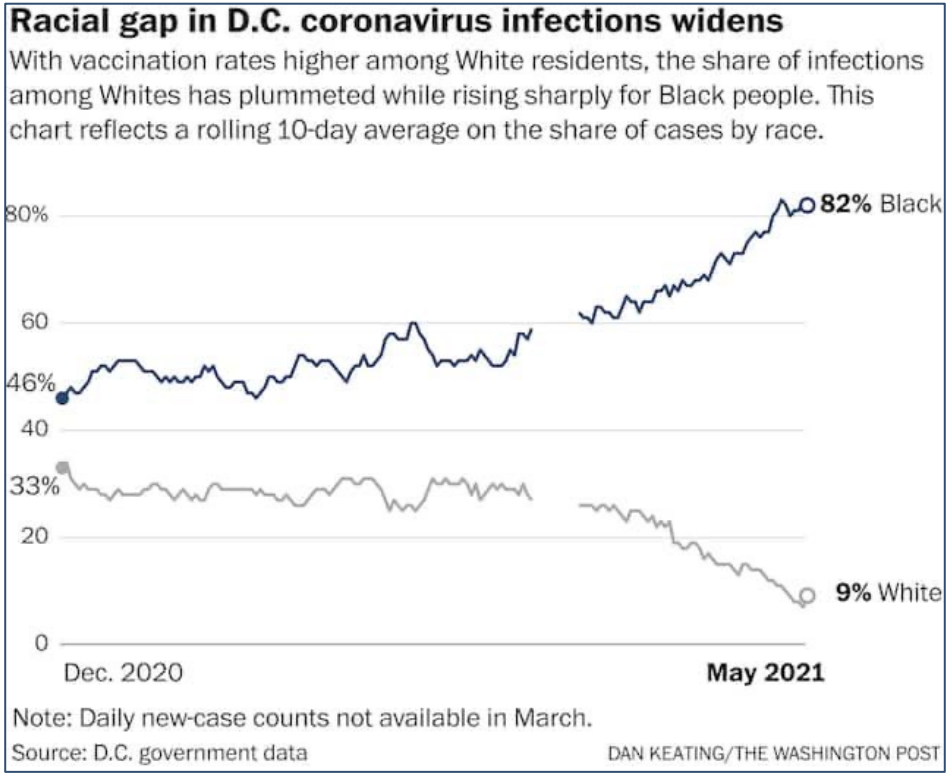
Reflects cumulative mortality rates calculated through March 2, 2021.



Indirect age-adjustment has been used.

Source: APM Research Lab • Get the data • Created with Datawrapper

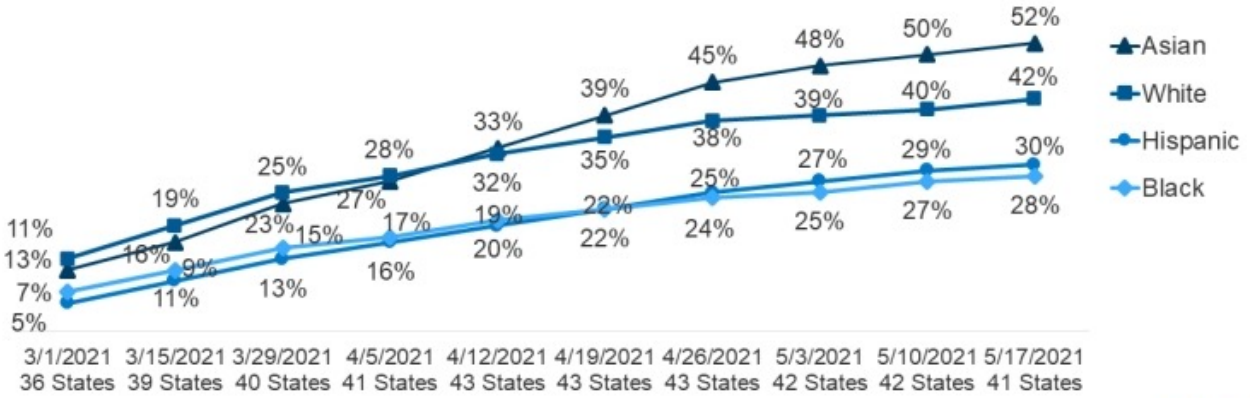
Racial disparities persist in COVID-19 infections



Vaccine distribution has not been equitable

Figure 4

Percent of Total Population that Has Received at Least One COVID-19 Vaccine Dose by Race/Ethnicity, March 1 to May 17, 2021



SOURCE: Vaccination data based on KFF analysis of publicly available data on state websites; total population data used to calculate rates based on KFF analysis of 2019 American Community Survey data.

KFF

COVID-19, GI symptoms and diseases

Gastroenterology 2020;158:2294–2297

BRIEF COMMUNICATIONS

Effect of Gastrointestinal Symptoms in Patients With COVID-19

Zili Zhou,[1,*] Ning Zhao,[1,*] Yan Shu,[2,*] Shengbo Han,[1] Bin Chen,[3] and Xiaogang Shu[1]

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EDITORIAL

COVID-19 and cancer

Norman E. Sharpless is director of the U.S. National Cancer Institute, Bethesda, MD, USA. norman.sharpless@nih.gov

With the spread of coronavirus disease 2019 (COVID-19), countries and states have instituted lockdowns. These decisions have been difficult and are sometimes described as benefiting the public health at the expense of the economy. Fear of contracting the coronavirus in health care settings has dissuaded people from screening, diagnosis, and treatment for non–COVID-19 diseases. The consequences for cancer outcomes, for example, could be substantial. What can be done to minimize this effect?

Cancer is a complex set of diseases whose prognoses are influenced by the timing of diagnosis and intervention. In general, the earlier one receives cancer treatment, the better the results. There already has been a steep drop in cancer diagnoses in the United States since the start of the pandemic, but there is no reason to believe the actual incidence of cancer has dropped. Cancers being missed now will still come to light eventually, but at a later stage ("upstaging") and with worse prognoses. At many hospitals, so-called "elective" cancer treatments and surgeries have been deprioritized to preserve clinical capacity for COVID-19 patients. For example, some patients are receiving less intense chemotherapy and/or radiotherapy, and in other cases, patients' operations to remove a newly detected tumor are being delayed. There can be no doubt that the COVID-19 pandemic is causing delayed diagnosis and suboptimal care for people with cancer.

What will be the likely impact of the pandemic on cancer mortality in the United States? Modeling the effect of COVID-19 on cancer screening and treatment for breast and colorectal cancer (which together account for about one-sixth of all cancer deaths) over the next decade suggests almost 10,000 excess deaths from breast and colorectal cancer deaths; that is, a ~1% increase in deaths from these tumor types during a period when we would expect to see almost 1,000,000 deaths from these two diseases types.* The number of excess deaths per year would peak in the next year or two. This analysis is conservative, as it does not consider other cancer types, it does not account for the additional nonlethal morbidity from upstaging, and it assumes a moderate disruption in care that completely resolves after 6 months. It also does not account for regional variations in the response to the pandemic, and these effects may be less severe in parts of the country with shorter or less severe lockdowns.

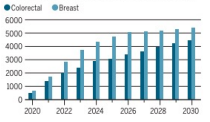
Beyond clinical care, the COVID-19 pandemic has caused an unprecedented disruption throughout the cancer research community, shuttering many labs and slowing down cancer clinical trial operations. Many scientists and clinicians are pivoting their cancer research activities to study the impact of SARS-CoV-2 on cancer. The scientific community must ensure that this pause is only temporary, because trials are the only way to make progress in developing new therapies for cancer. Given the long timeline between basic cancer research and changes to cancer care, the effects of pausing research today may lead to slowdowns in cancer progress for many years to come.

Collective action by the clinical and research communities and by governmental agencies can mitigate this potentially substantial impact. The U.S. National Cancer Institute (NCI), for example, has started to address this challenge (see www.cancer.gov). The NCI has worked with the U.S. Food and Drug Administration to increase flexibility and support for clinical trials during the pandemic. For example, allowances have been made to accept "remote" informed consent, and other protocol deviations. In addition, the NCI has announced several new clinical trials and funding opportunities aimed at addressing the relationship between COVID-19 and cancer. Of particular note is the NCI COVID-19 in Cancer Patients Study, a prospective longitudinal study that will collect blood samples, imaging, and other data to understand how COVID-19 affects cancer patients.

Clearly, postponing procedures and deferring care as a result of the pandemic was prudent at one time, but the spread, duration, and future peaks of COVID-19 remain unclear. However, ignoring life-threatening non–COVID-19 conditions such as cancer for too long may turn one public health crisis into many others. Let's avoid that outcome.

–Norman E. Sharpless

Modeled cumulative excess deaths from colorectal and breast cancers, 2020 to 2030*



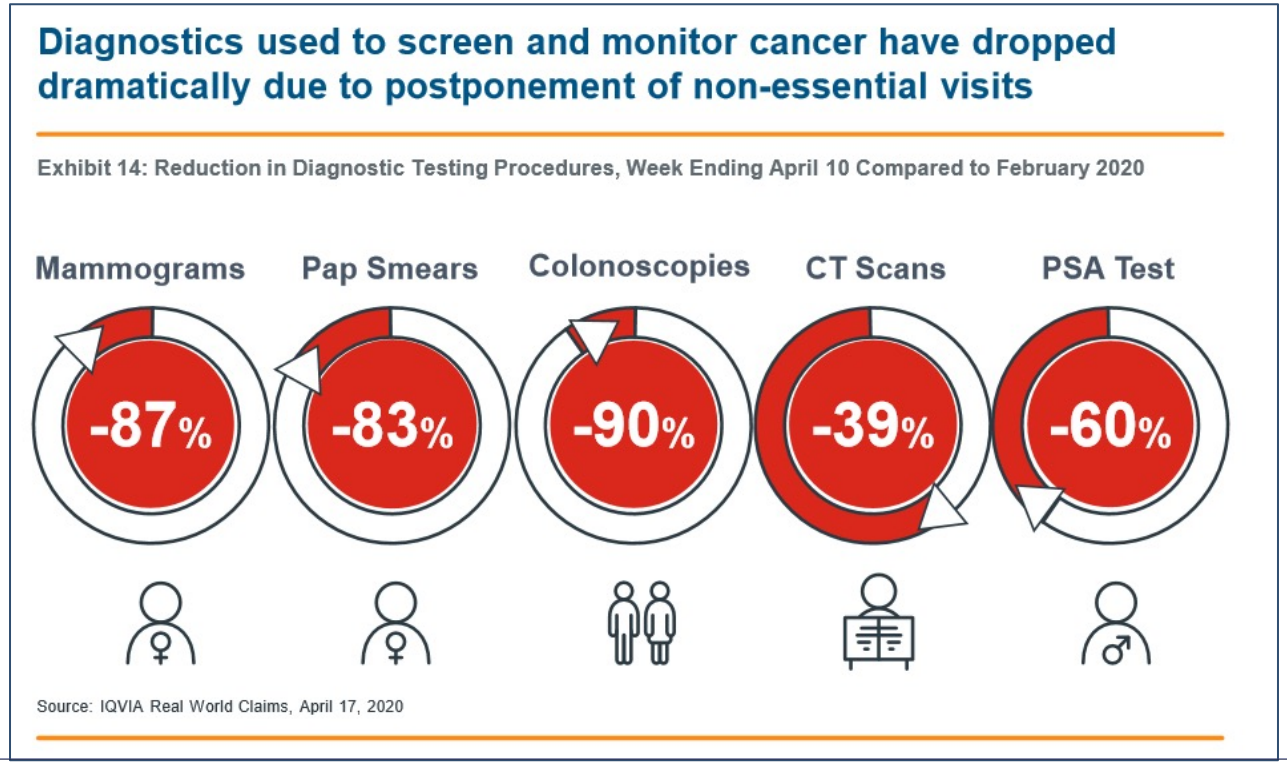
*See supplementary materials (science.sciencemag.org/content/368/6497/1290/suppl/DC1).

10.1126/science.abd3377

Published by AAAS

Estimated impact of COVID-19 on Colorectal Cancer

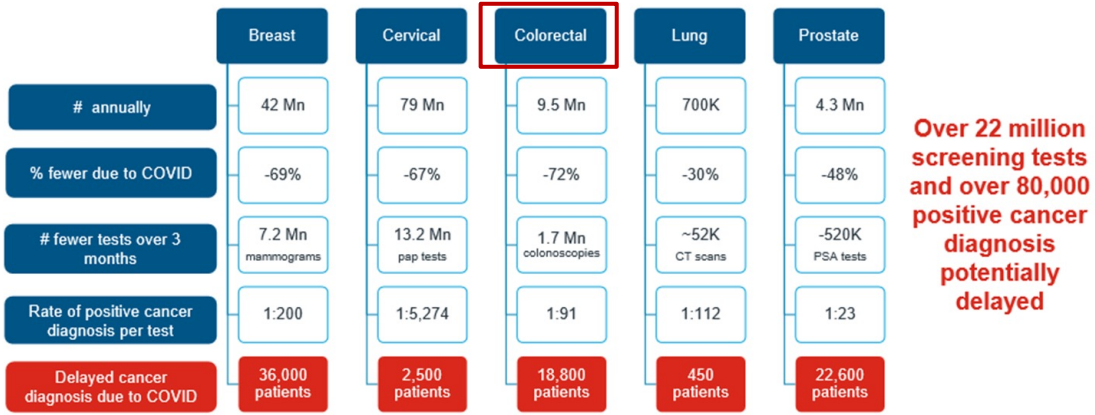
COVID-19 decreased cancer screenings



Potential for delayed or missed diagnoses

Over 22 million screening tests for five common tumors may be disrupted, risking delayed or missed diagnoses for 80,000 patients

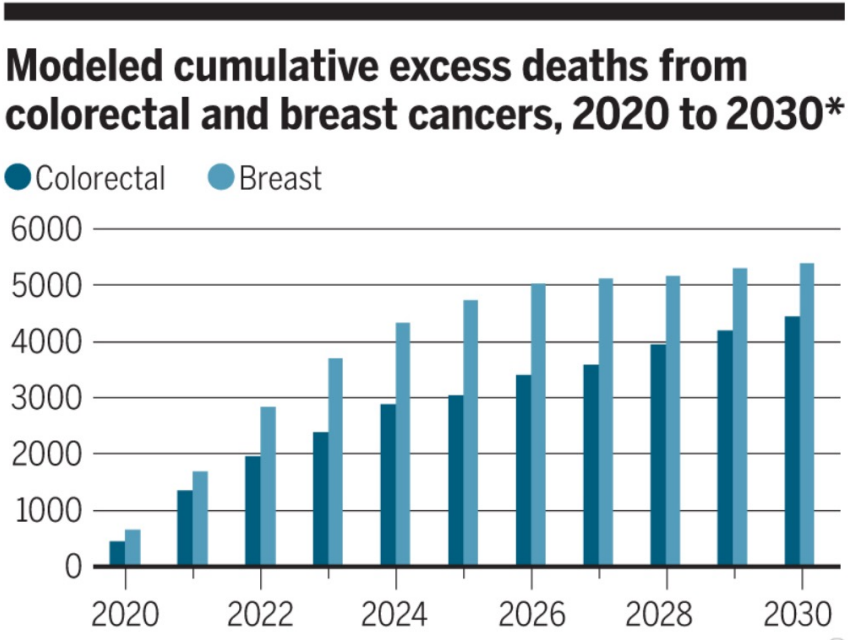
Exhibit 15: Modeled Impact of Reduced Screening Tests Three Months Ending June 5, 2020



Over 22 million screening tests and over 80,000 positive cancer diagnosis potentially delayed

Source: IQVIA Institute, Apr 2020

Modeling the effect of COVID-19 on cancer mortality



Real-World Impact on Colorectal Cancer

FIT and colonoscopy volumes decreased by 85-90%

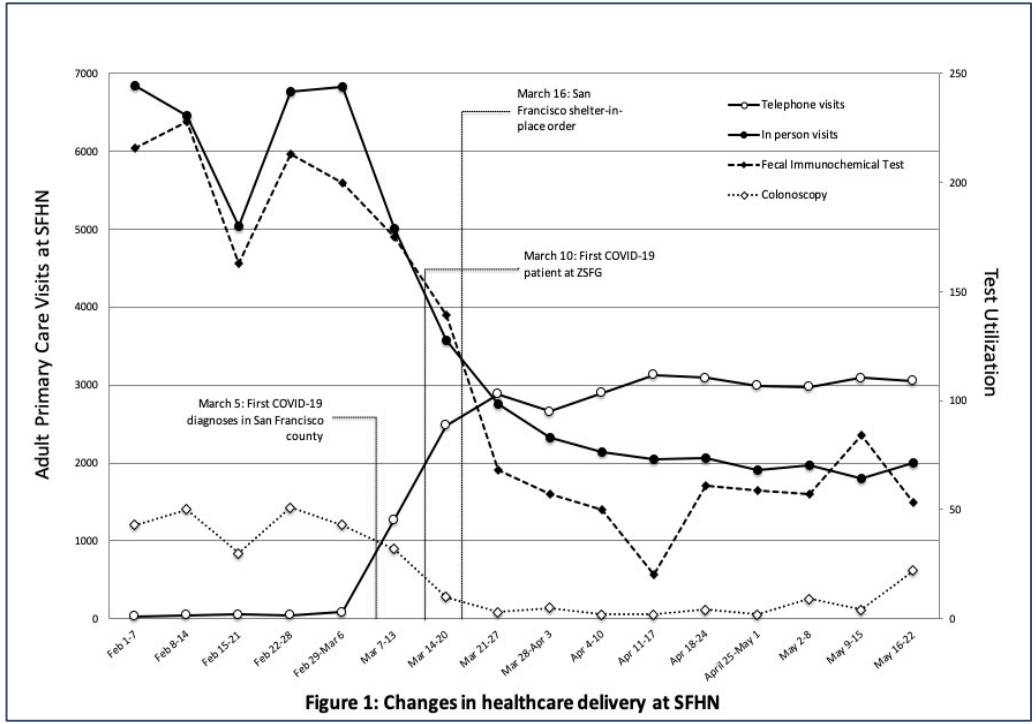
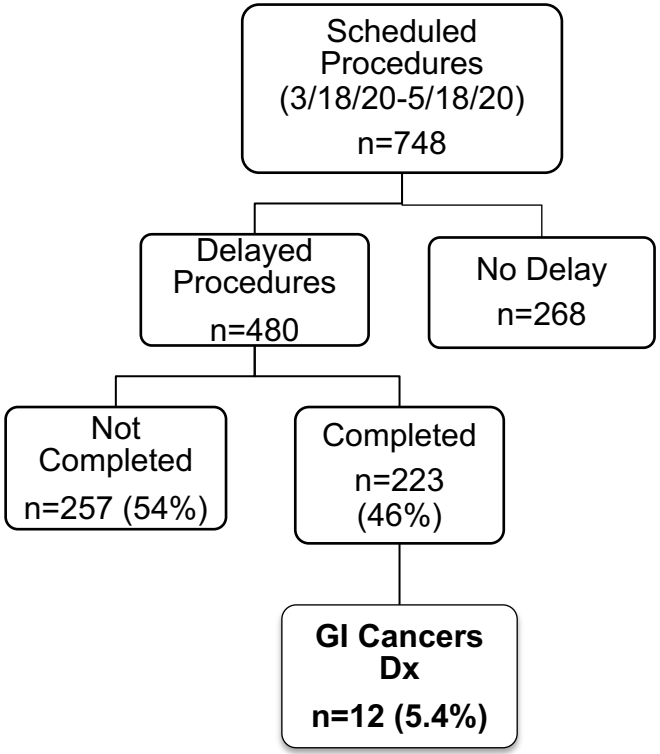


Figure 1: Changes in healthcare delivery at SFHN

In a tertiary health system, 46% of delayed endoscopies have been completed



Analysis of health system data from a large tertiary academic health system found:

- By 12/31/20, 46% of patients with delayed/cancelled endoscopic procedures had returned
- No sociodemographic differences by endoscopic completion status
- Of those who have returned, 5.4% were diagnosed with colorectal, pancreatic, or stomach cancers

Colonoscopy for CRC screening was the most delayed procedure

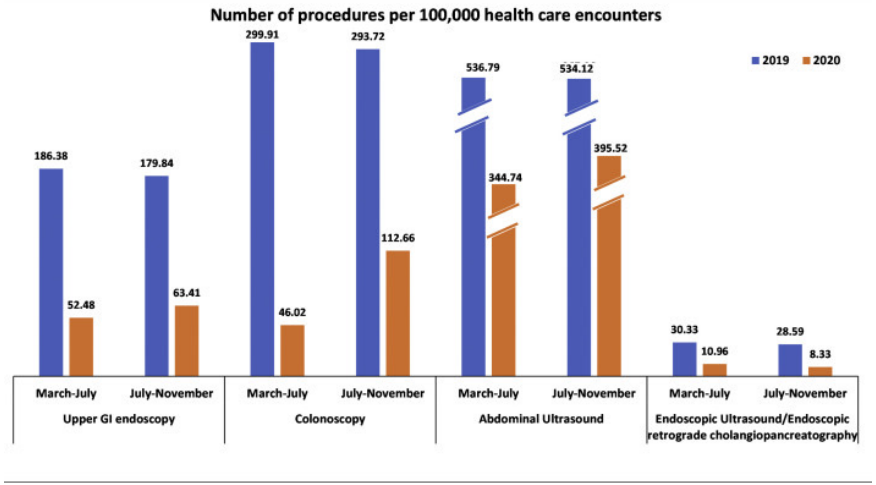
Procedures delayed due to COVID-19 and frequency

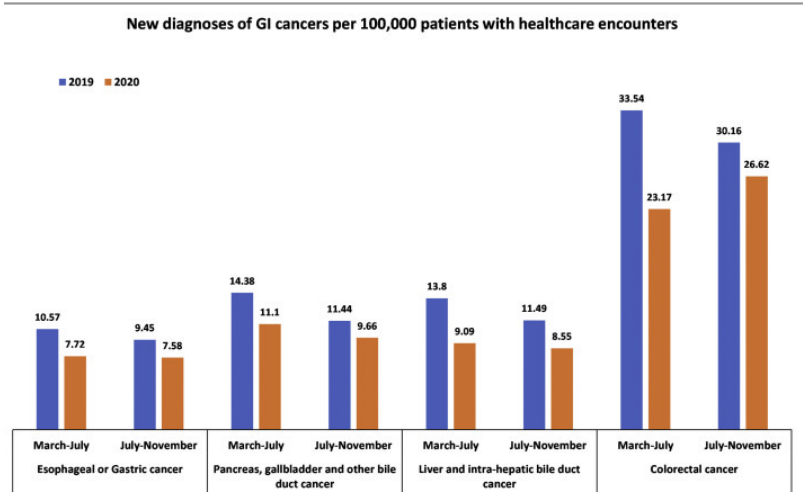
Procedure Delayed	No. (%)
Colonoscopy	234 (49%)
EGD	96 (20%)
EGD + Colonoscopy	106 (22%)
Other (Flex, EUS, ERCP)	44 (9%)
Total	**480**

Median time to procedure completion after initial delay

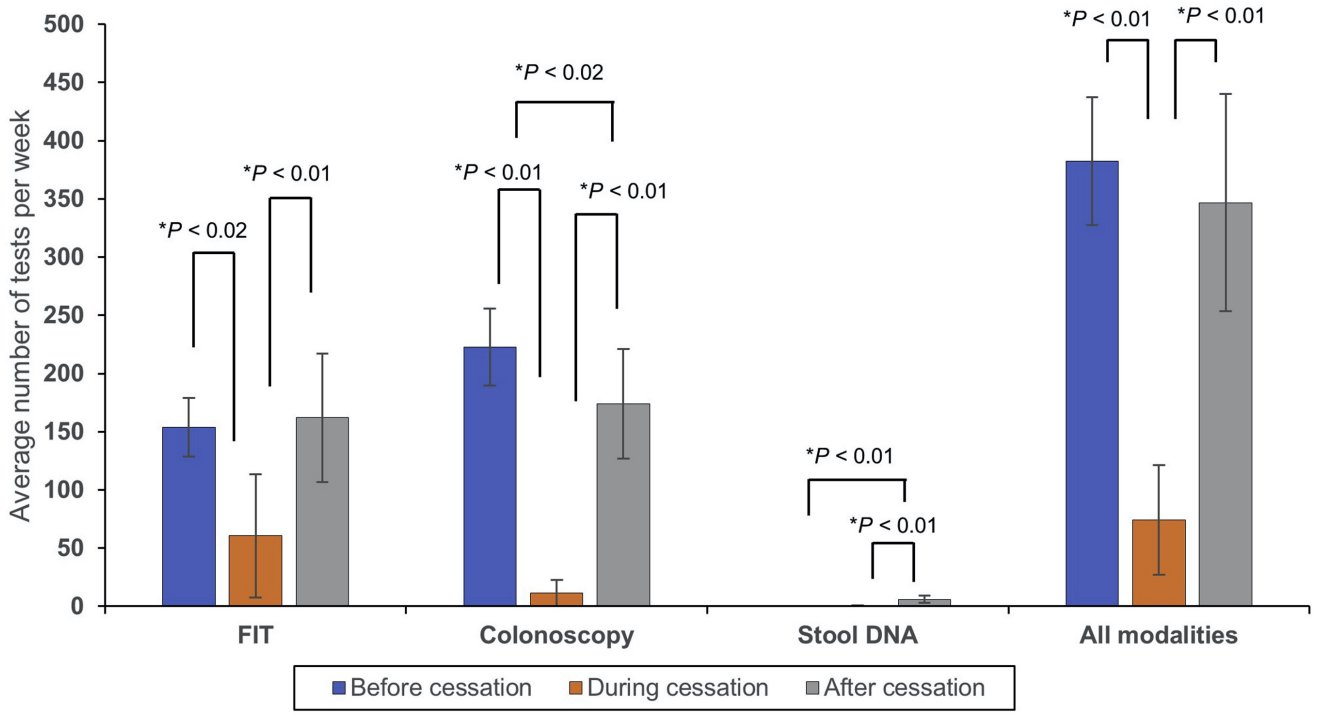
Procedure	No.	Median Days (IQR)	P-value
Colonoscopy	116	91 (67-119)	Ref.
EGD	43	83 (57-112)	0.12
EGD + Colonoscopy	42	91 (66-122)	0.93
Other (Flex, EUS, ERCP)	22	96 (48-114)	0.64
Total	**223**	**88 (63-119)**	

Healthcare organization data confirms decline in CRC diagnoses between 2019 and 2020





Potential COVID-19 related preference for stool-based screening tests



Lessons Learned

COVID-19 will likely exacerbate CRC disparities

- COVID-19 will likely increase persistent CRC disparities
  - ► Decreased screening participation
    - ► Federally qualified health centers and community health centers
  - ► Delayed follow-up of abnormal stool results
  - ► Limited community-based research and partnerships
  - ► Limited community engagement and advocacy

Proposed solutions to mitigate disparities

TABLE 1. Summary of areas related to CRC prevention in the medically underserved that have been impacted by COVID-19 and potential solutions

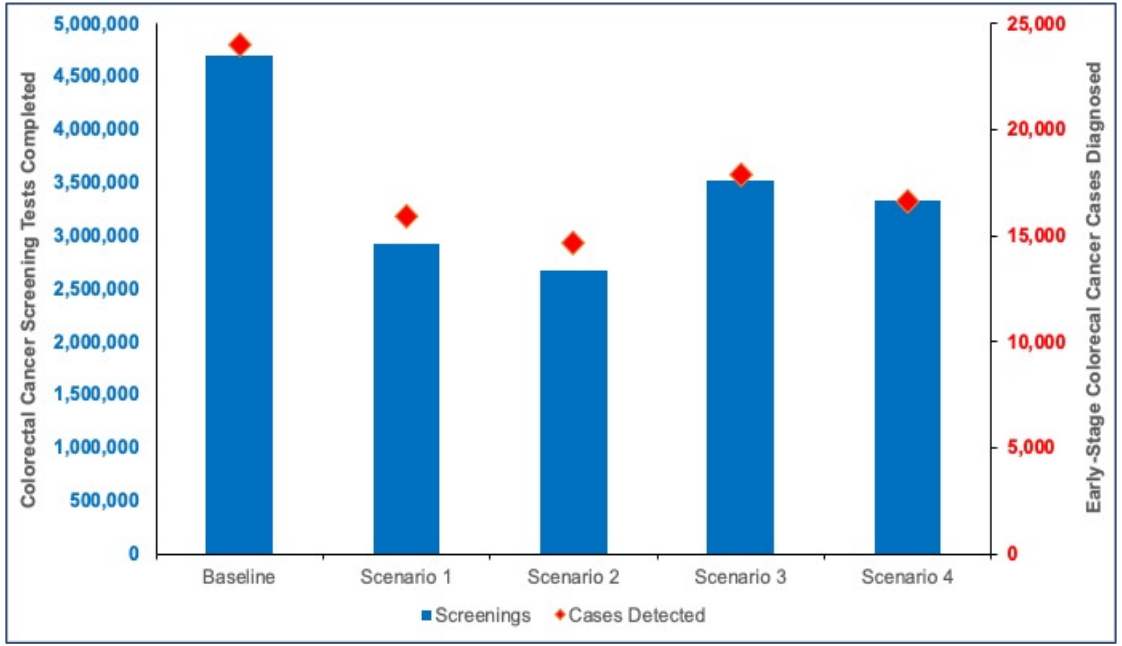
Impacted area	Potential solutions
CRC screening	
CRC screening participation	• Encourage use of noninvasive screening modalities. • Increase use of mailed FIT outreach programs. • Establish safe protocols to pick up and return FIT kits.
Follow-up after abnormal FIT/fecal occult blood test screening	• Identify gastroenterologist partners to improve coordination of care. • Prioritize patients with the earliest abnormal FIT results, highest quantitative FIT values, and/or the development of interval symptoms associated with CRC.
CRC-related research activities	
Community-based research	• Leverage the most accessible technology to sustain communication. • Engage consistently with community partners. • Obtain a waiver of signature for minimal risk studies. • Provide incentives where appropriate.
External factors	• Alert funding programs early of changes in projected research. • Develop contingency budgets for funded projects.
Engagement, advocacy, and policy	
Community outreach and engagement	• Use existing platforms to provide COVID-19 information and offer aid programs. • Extend CRC awareness events to year-round. • Seek timely and innovative opportunities to serve medically underserved populations.
Advocacy and policy	• Shift advocacy events and policy campaigns to virtual platforms whenever possible. • Use social media platforms, calls, and letters to connect with policymakers.

CRC, Colorectal cancer; *COVID-19*, coronavirus disease 2019; *FIT*, fecal immunochemical test.

Increased use of FIT could increase CRC screening

	2020				2021				2022			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Baseline	Normal											
Scenario 1	Normal	No screening	Colonoscopy screening (50%)			Colonoscopy screening (75%)						
Scenario 2	Normal	No screening	Colonoscopy screening (50%)						Colonoscopy screening (75%)			
Scenario 3	Normal	No screening	Colonoscopy screening (50%) + increased FIT			Colonoscopy screening (75%) + increased FIT						
Scenario 4	Normal	No screening	Colonoscopy screening (50%) + increased FIT						Colonoscopy screening (75%) + increased FIT			

Increased use of FIT could increase CRC screening



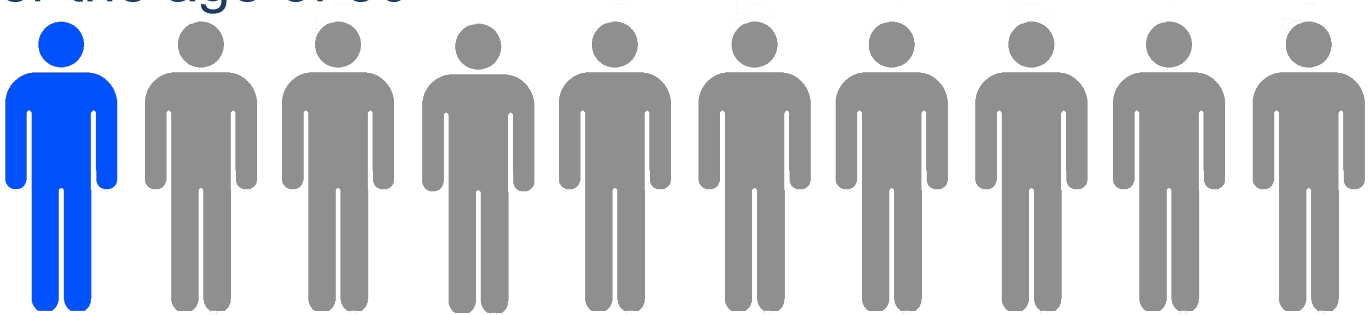
Key Messages

- COVID-19's impact is global with inequitable outcomes, including vaccinations
- COVID-19 has challenged GI patient care from management of infection related symptoms to endoscopic practice
- Declines in endoscopy were projected to adversely impact colorectal cancer
  - Real-world data suggests these projections were accurate, but time will tell more
- COVID-19 will likely exacerbate existing GI disease disparities
- Proactive measures, including increased use of evidence-based interventions and tailored efforts to minimize losses to follow-up are needed to offset these harms

Early-Onset Colorectal Cancer

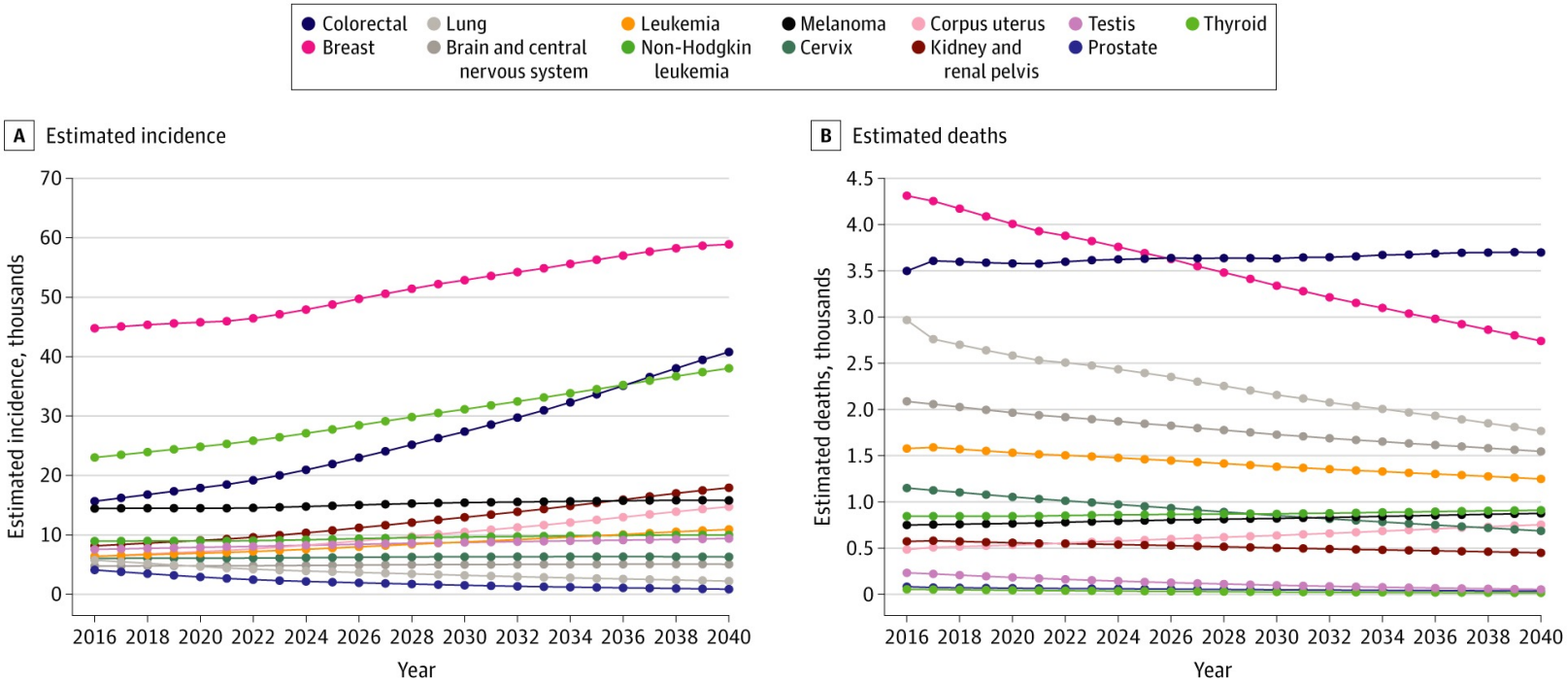
The changing landscape of colorectal cancer

- One in 10 people diagnosed with colorectal cancer today is under the age of 50



- In a 2018 survey of 1200 patients, 72% reported no family history of colorectal cancer and were diagnosed with stage III or IV disease

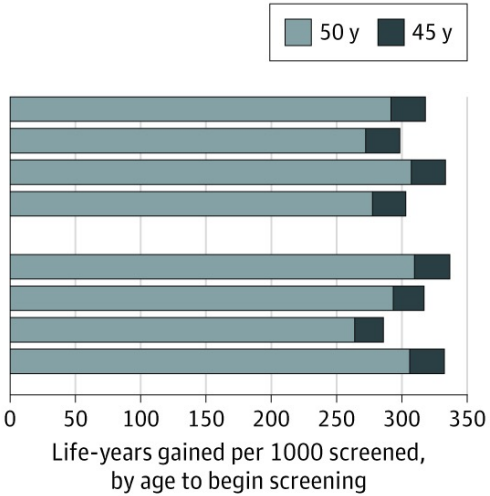
By 2040, CRC will be leading cause of cancer deaths in adults aged 20-49 years



Simulation models suggest benefit of increasing CRC screening at 45

A Benefit: Estimated life-years gained per 1000 individuals screened[a]

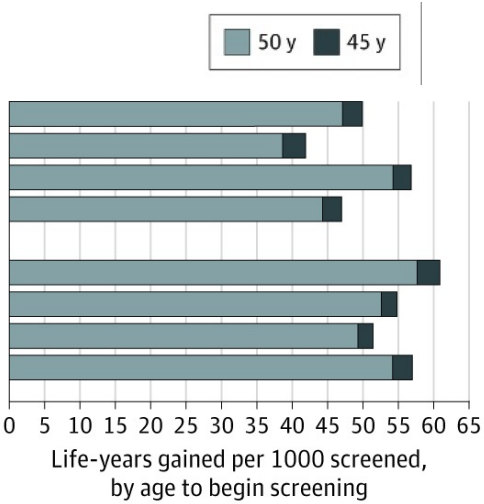
Screening modality and frequency	Mean life-years gained if start screening[b]		Additional life years gained if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	292	318	26
HSgFOBT every year[c,d]	272	298	26
sDNA-FIT every year	307	333	26
sDNA-FIT every 3 y[d]	278	303	25
Direct visualization tests			
COL every 10 y	310	337	27
CT colonography every 5 y	293	317	24
Flexible SIG every 5 y	264	286	22
Flexible SIG every 10 y plus FIT every year	306	332	26



Simulation models suggest benefit of increasing CRC screening at 45

B Benefit: Estimated No. of CRC cases averted per 1000 individuals screened[a]

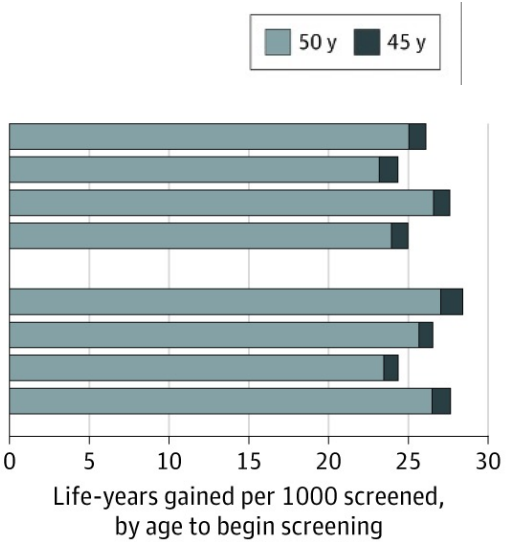
Screening modality and frequency	Mean CRC cases averted if start screening[b]		Additional CRC cases averted if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	47	50	3
HSgFOBT every year[c,d]	39	42	3
sDNA-FIT every year	54	57	3
sDNA-FIT every 3 y[d]	44	47	3
Direct visualization tests			
COL every 10 y	58	61	3
CT colonography every 5 y	53	55	2
Flexible SIG every 5 y	49	51	2
Flexible SIG every 10 y plus FIT every year	54	57	3



Simulation models suggest benefit of increasing CRC screening at 45

C Benefit: Estimated No. of CRC deaths averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC deaths averted if start screening[b]		Additional CRC deaths averted if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	25	26	1
HSgFOBT every year[c,d]	23	24	1
sDNA-FIT every year	27	28	1
sDNA-FIT every 3 y[d]	24	25	1
Direct visualization tests			
COL every 10 y	27	28	1
CT colonography every 5 y	26	26	0.9
Flexible SIG every 5 y	23	24	0.9
Flexible SIG every 10 y plus FIT every year	26	28	1

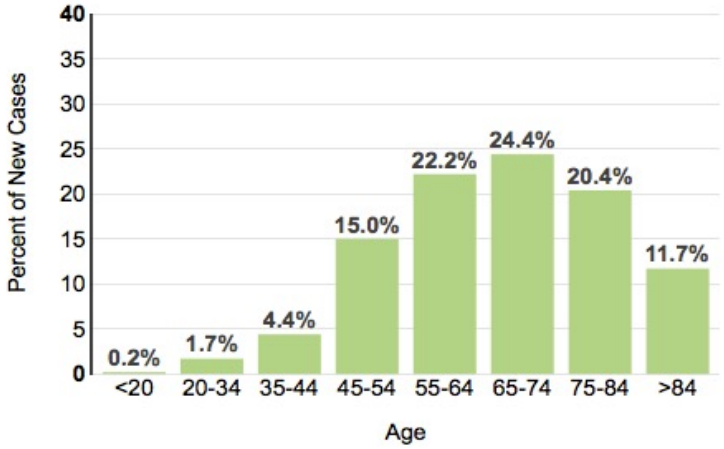


USPSTF Guidelines recommend CRC screening starting at age 45

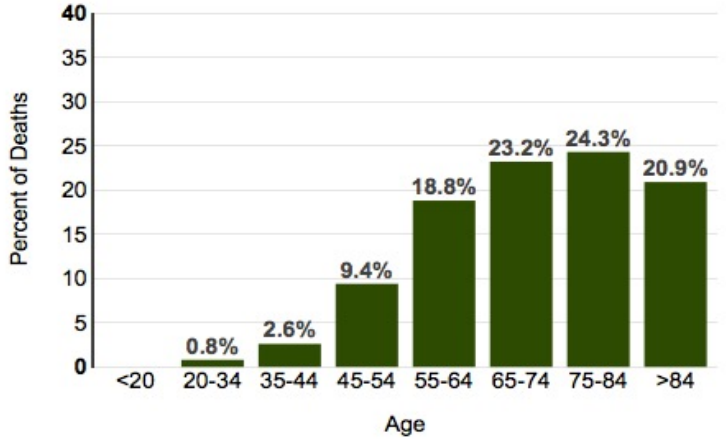
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years.	A
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years.	B
Adults aged 76 to 85 years	The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences.	C

Incidence of Early Onset Colorectal Cancer

Colorectal cancer occurs most frequently between 65-74 years



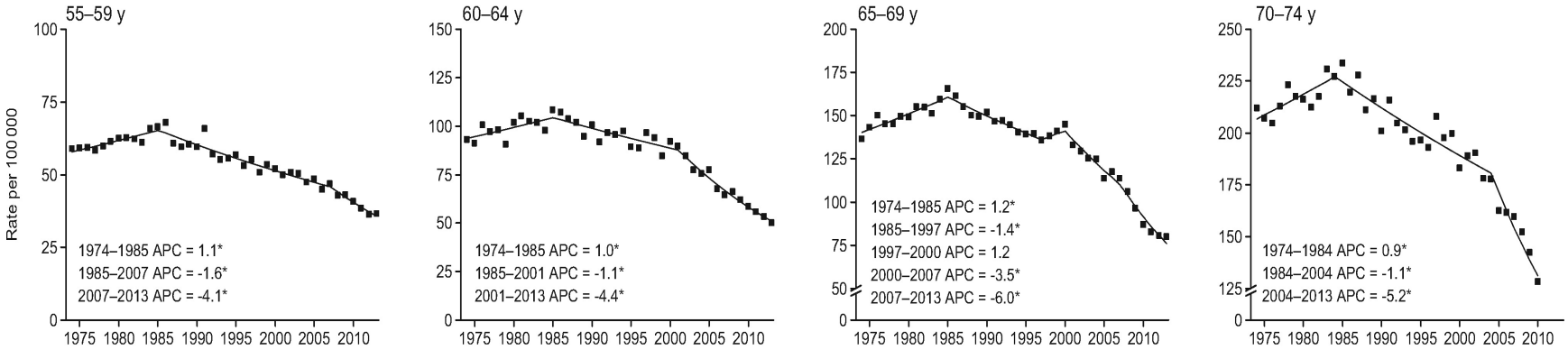
Average age at diagnosis: **67**



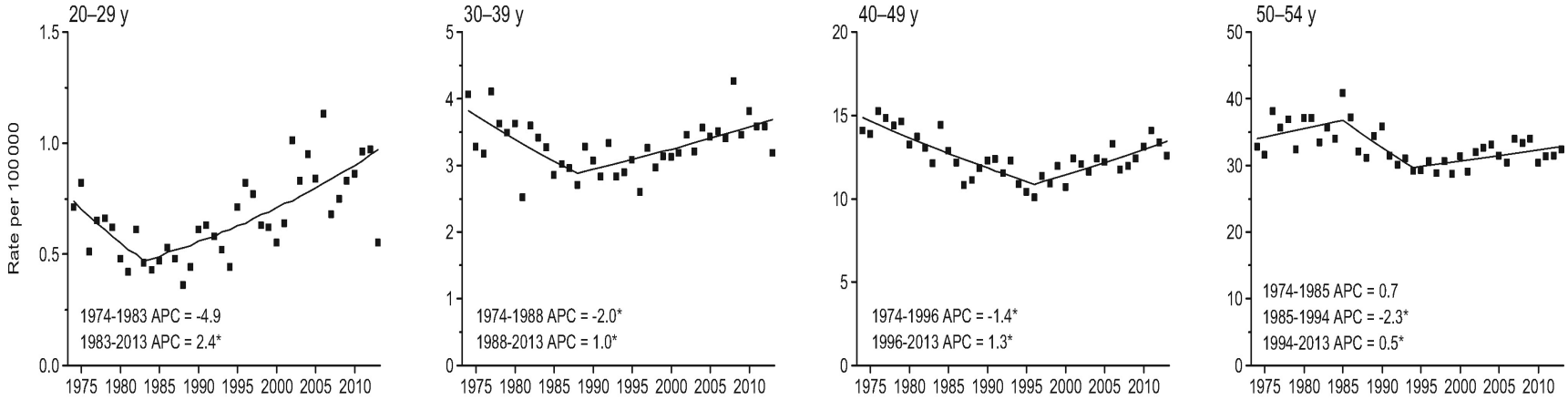
Average age at death: **72**

SEER 21 2013-2017 Cancer Stat Facts" Colorectal Cancer

Colorectal cancer screening has reduced overall incidence



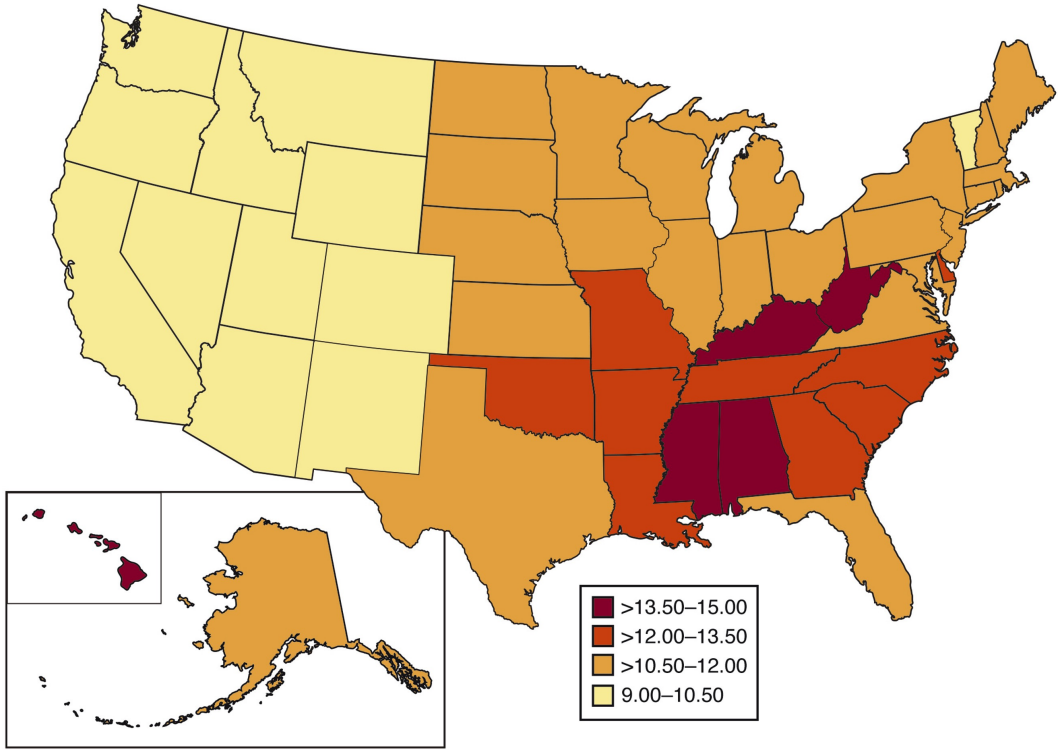
Colorectal cancer incidence trends vary by age group



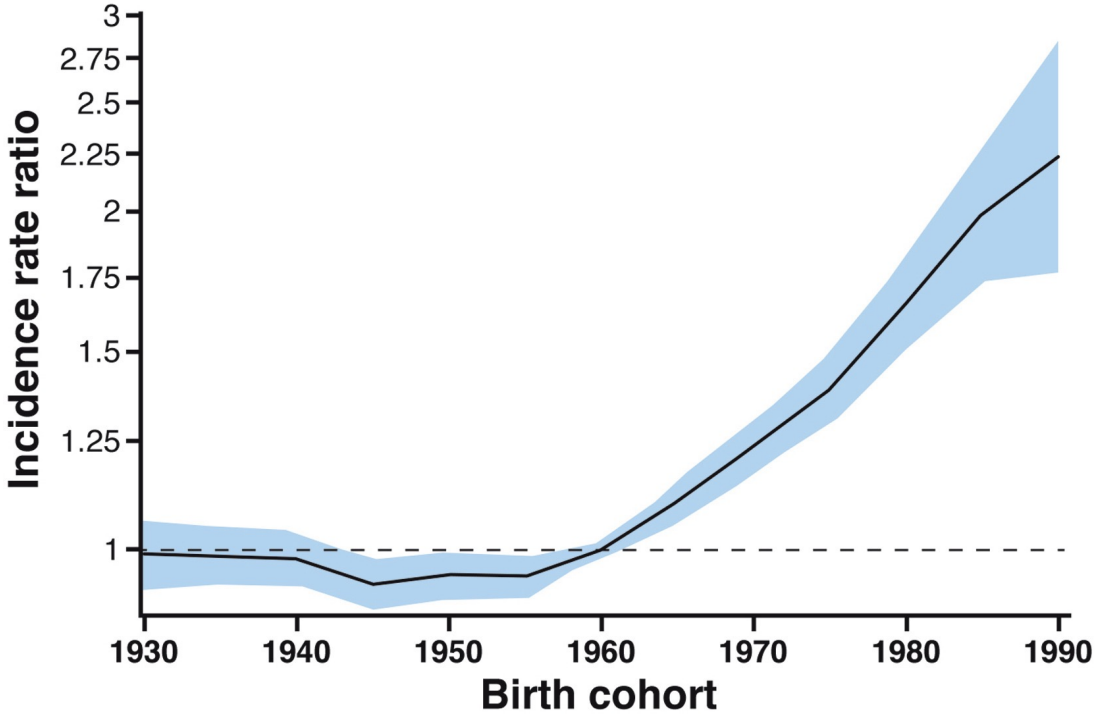
Absolute incidence of colorectal cancer under 50 is low

Age group, y	Incidence rate, 1984-1988	Incidence rate, 2009-2013	Relative change, %	Absolute difference
20-29	0.8	1.8	+125.0	+1.0 per 100 000
30-39	4.5	7.1	+57.8	+2.6 per 100 000
40-49	19.4	23.6	+21.6	+4.2 per 100 000
50-59	73.5	61.2	-16.7	-12.3 per 100 000
60-69	188.9	104.1	-44.9	-84.8 per 100 000
70-79	356.3	190.2	-46.6	-166.1 per 100 000

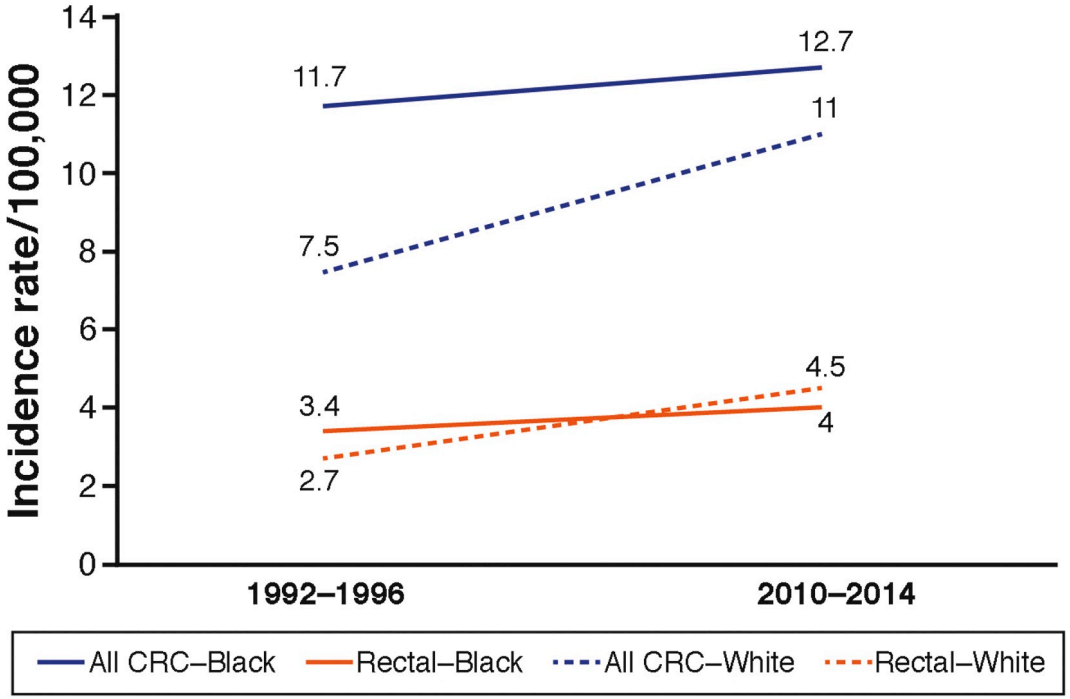
CRC incidence in those under 50 varies by geography



CRC in those under 50 has increased across birth cohorts



Black-White disparities in young onset CRC by site

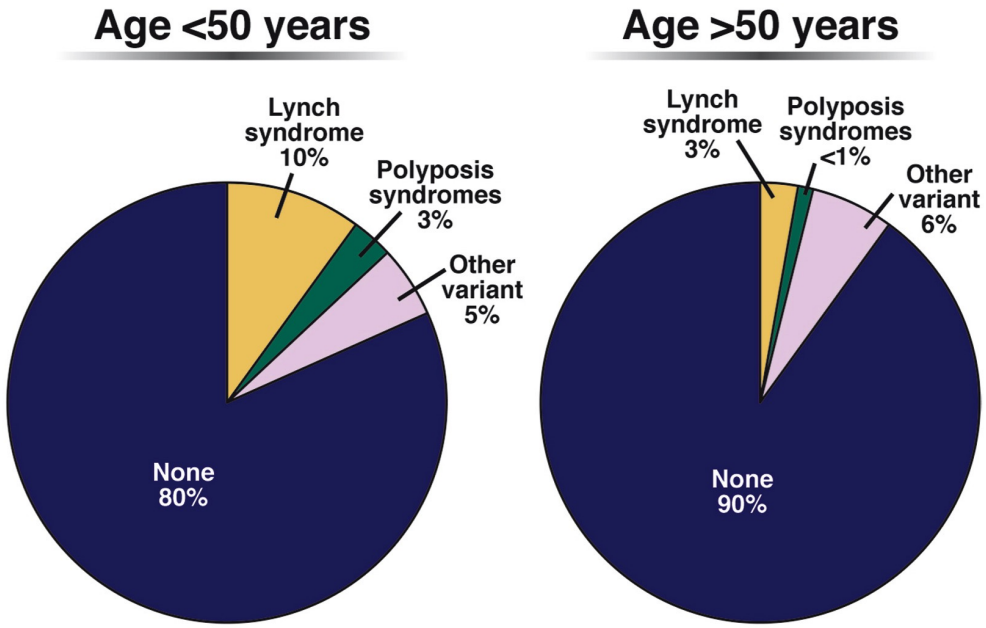


Epidemiology take home points

- Despite relatively lower risk, CRC in those under age 50 has increased by ~2.2% per year since early 1990's
- People born in and after the 1960s are at higher risk of CRC compared to older generations
- In young-onset CRC (20-49), Black-White incidence disparities decreased between 1992-1996 and 2010-2014, but the mortality gap between Whites and Blacks, persists

Pathogenesis and Risk Factors

80% of CRC cases under age 50 have no germline mutation



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		

High proportion of CRC under 50 have late-stage disease

	Early-onset n (%)	Late-onset N (%)	Adjusted OR (CI)
Stage			
1	267 (19)	3,194 (30)	Ref
2	289 (21)	2,731 (26)	1.48 (1.23-1.77)
3	486 (34)	2,761 (26)	2.23 (1.89-2.62)
4	369 (26)	1,819 (17)	2.85 (2.39-3.40)
Anatomical site			
Cecum	125 (9)	1,918 (18)	Ref
Right	209 (15)	2,916 (27)	1.07 (0.84-1.35)
Left	535 (37)	2,973 (28)	2.24 (1.82-2.76)
Rectum	531 (37)	2,683 (25)	2.36 (1.92-2.91)

*Adjusted for smoking, health plan, race/ethnicity, sex, BMI and Charlson comorbidity score

Potential risk factors associated with CRC under 50

Risk Factor	Potential Mechanisms
Harmful	
Obesity	Metabolic syndrome; Insulin resistance; Chronic inflammation
Smoking	Direct ingestion or indirect exposure to known carcinogens
Alcohol	Adverse effects on folate metabolism; toxic effects of acetaldehyde
Red or processed meats	Hydrocarbons- known carcinogenic chemicals
Antibiotics	Altering microbiota patterns
Protective	
Aspirin/NSAIDs	Inhibits cyclooxygenase and phospholipid activity, enzymes involved in tumor growth
Physical Activity	Less weight gain; lower insulin resistance; stimulate digestion and reduce transit time

Pathogenesis and risk factors take home points

- The majority (80%) of CRC cases diagnosed under the age of 50 have no germline mutations on multigene panel testing
- Up to 26% of CRC patients younger than age 50 years are diagnosed with metastatic disease, compared with 17% of patients age 50 years or older
- Because of birth cohort effects, we may need to study risk factors across a lifetime rather than risk factors in the few years before diagnosis

Future research directions

- Due to observed birth cohort effects, research will need to study risk factors across a lifetime
  - Age of smoking initiation and duration of tobacco exposure
  - Birth weight and childhood obesity
  - Antibiotic use in infancy or childhood
  - Age and duration of occupational and environmental exposures (such as mineral dust and plastics)

Thank you!

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