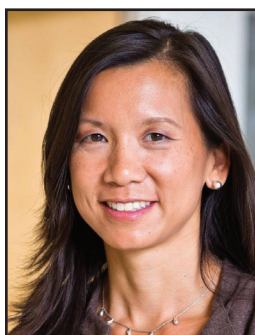


Douglas G. Adler MD, FACP, AGAF, FASGE, Series Editor

Updates to Colorectal Cancer Screening Recommendations and Future Implications



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Colorectal cancer (CRC) remains the second leading cause of cancer death in the United States, although there have been significant improvements in CRC incidence and mortality over time. Despite robust efforts in CRC screening, roughly one-third of eligible adults are not up to date with CRC screening. Trends in CRC incidence and mortality show an alarming increase in individuals below the age of 50, prompting the U.S. Preventive Services Task Force to update their 2016 recommendations on CRC screening. This update now recommends initiation of CRC screening at age 45 years instead of age 50 years for all average-risk adults. This review addresses the rationale for this update, highlights the recommended modalities for screening, discusses the role of programmatic screening, and posits the implications of this update to the gastroenterology community.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death in the U.S. It is estimated that almost 147,950 individuals were diagnosed with CRC in the U.S. in 2020, with an estimated 53,200 CRC deaths.¹ CRC screening has been shown to reduce the incidence and mortality of CRC by an estimated 30 – 60%. Accordingly, a great deal of attention has been placed on

recommendations for screening and methods to increase adherence.^{2,3} The U.S. Preventive Services Task Force (USPSTF), along with several professional societies, publish recommendations for colorectal cancer screening, which were most recently updated in May 2021. The most remarkable update from the USPSTF 2016 recommendations is the endorsement of initiating colorectal cancer screening for average risk individuals beginning at age 45 years.⁴ This recommendation is in response to the body of evidence that rates of colorectal cancer are increasing among individuals younger than 50 years. While other societies had also previously recommended initiation of CRC screening at age 45, the USPSTF recommendations specifically inform insurance coverage and waiver of cost sharing for preventive services. This

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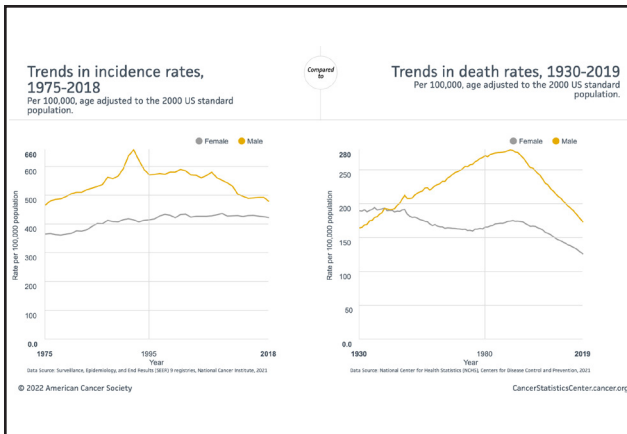


Figure 1. Trends in Colorectal Cancer Incidence (1975-2018) and Death Rates (1930-2019). Source: Surveillance, Epidemiology, and End Results (SEER) 9 registries, National Cancer Institute, 2021; Death Rates – National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2021. Adapted from American Cancer Society Cancer Statistics Center.

recommendation may improve CRC outcomes in younger adults, but may also impact access to care or further widen racial or ethnic disparities in screening and outcomes.

Incidence and Risk Factors

CRC affects approximately 4.4% of men and 4.1% of women in their lifetime.¹ Age is in most cases the most important risk factor for CRC. The incidence rate roughly doubles for each five-year age group up until the age of 50 years, at which point it increases by about 30% for each subsequent 5-year period.⁵ The median age for diagnosis of CRC has been steadily declining, currently at 66 years, down from 72 years in the early 2000s, and nearly one-third of rectal cancers are diagnosed in those younger than 55 years. This downward shift in age is likely multifactorial, with CRC incidence decreasing in older age groups due to increased uptake of screening, and increasing incidence in younger adults.^{5,6} Overall, rates of CRC incidence have been slowly increasing in females while rates are declining in males. However, death rates from CRC have been substantially declining, with a large decline from 2000 to the present, correlating with increased uptake of colonoscopy (Figure 1).

Importantly, there are significant racial disparities in CRC incidence and mortality,

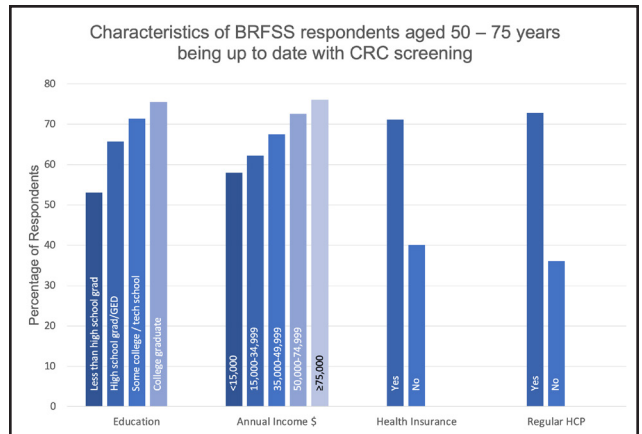


Figure 2. Characteristics of Behavioral Risk Factor Surveillance System (BRFSS) respondents aged 50-75 years being up to date with CRC screening. Adapted from Joseph DA, King JB, Dowling NF, et al. *Vital Signs: Colorectal Cancer Screening Test Use – United States, 2018. MMWR Morb Mortal Wkly Rep 2020;69:253-259.*

with highest rates among Non-Hispanic Blacks, followed by American Indians and Alaska Natives. In these ethnic groups, CRC incidence rates and death rates are 20% and 40 % respectively higher than those in Non-Hispanic Whites.⁷ These disparities are multifactorial, but in large part reflect socioeconomic status in the form of prevalence of risk factors and access to health care.⁸⁻¹⁰ Figure 2.

Modifiable risk factors for CRC include lifestyle and behavioral factors such as heavy alcohol intake, smoking, obesity, and a diet rich in red and processed meat. Nonmodifiable factors that increase risk include hereditary factors, a personal or family history of adenomas or CRC, and a personal history of inflammatory bowel disease.

Rates of CRC Incidence and Mortality Over Time

CRC incidence rates have been declining gradually since the mid-1980s, with an acceleration in the decline starting in the early 2000s, due to a positive change in modifiable risk factors and the widespread adoption of colonoscopy for screening. However, since the mid-1990s, incidence of CRC in younger adults (those aged less than 50 years) has been increasing, accounting for 11% of colon cancers and 15% of rectal cancers in 2020 compared to 5%

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and 9%, respectively, in 2010.^{1,11} These alarming trends provide the foundation for the change in recommendations for CRC screening.

New Screening Recommendations

The USPSTF relies on a panel of experts to provide evidence-based recommendations on a variety of clinical preventive services including preventive care, counseling, and screening. In May 2021, the USPSTF updated their 2016 guidelines for CRC screening, in part due to the growing body of data demonstrating increasing rates of CRC in younger adults. The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years, with a grade A strength of recommendation, indicating substantial net benefit. The USPSTF recommends screening for CRC in adults aged 45 to 49 years, with a grade B recommendation, indicating moderate net benefit. Additionally, the USPSTF recommends that clinicians offer CRC screening in adults aged 76 to 85 years, after consideration of the patient's overall health, screening history, and preferences, with a grade C recommendation, indicating a small net benefit.⁴

The key update to the 2021 recommendation was to begin average risk CRC screening at age 45 years rather than at age 50 years. This recommendation was not based on clinical trials that would be expensive and taken years to perform, but rather microsimulation modeling studies that estimated the benefits of CRC screening beginning at age 45. These simulation studies used known cancer incidence and mortality data to provide updated model-based estimates of the benefits, burden, and harms of CRC screening strategies and to identify those that may provide an efficient balance of life-years gained (LYG) versus colonoscopy burden.¹² Six widely accepted methods for CRC screening were used in the model: fecal immunochemistry testing (FIT), multitarget stool DNA testing, flexible sigmoidoscopy with or without FIT, CT colonography, or colonoscopy.

Two important assumptions were made in these models:

1. all persons with an abnormal result on a non-colonoscopy screening test would subsequently undergo colonoscopy and
2. full adherence with all procedures.

The modeling analysis demonstrated 49 strategies that were considered efficient options, and 41 of those strategies indicated screening starting at age 45 years. Lowering the age to commence screening at age 45 versus 50 was estimated to result in 5 additional LYG (22 vs. 27 LYG), 623 additional colonoscopies (161 vs. 784), and a minimal increase in complications.¹² Keeping in mind that these models assumed 100% adherence, in real life the authors estimated that the true LYG would be diminished by between 4% and 25%. The long-term outcomes from the models may also help inform patients and clinicians to determine the best strategy for that particular patient, balancing LYG for risks and hassle of undergoing colonoscopy compared to more modest LYG with stool-based tests and colonoscopy minimization.

Recommended Colorectal Cancer Screening Strategies

Although CRC screening by colonoscopy is by far the most common method for CRC screening in the U.S., randomized controlled trials have only shown a mortality benefit with the use of fecal occult blood testing (FOBT) followed by colonoscopy if FOBT is abnormal and flexible sigmoidoscopy with subsequent colonoscopy if polyps are detected.¹³ The effectiveness of colonoscopy in reducing mortality from both right and left-sided colon cancers has been demonstrated in observational studies.^{14,15} The USPSTF recommends seven different methods for CRC screening: 1) High-sensitivity gFOBT every year; 2) FIT every year; 3) stool DNA test with FIT (sDNA-FIT) every 1 to 3 years; 4) colonoscopy every 10 years; 5) CT colonography every 5 years; 6) flexible sigmoidoscopy every 5 years; and 7) flexible sigmoidoscopy every 10 years with FIT every year. The stool-based tests are considered two-step tests because any abnormal result requires a follow-up colonoscopy. Of the stool-based tests, annual FIT or annual sDNA-FIT provides a greater LYG than either annual high-sensitivity gFOBT or sDNA-FIT every 3 years. Further, modeling studies demonstrate that annual screening with sDNA-FIT would result in more colonoscopies than annual screening with FIT.^{4,16} Overall, colonoscopy every 10 years yielded the greatest LYG and CRC cases averted compared to the other methods, whether screening begins at age 50 years or at age 45 years,

but this benefit was followed closely by sDNA-FIT annually and flexible sigmoidoscopy every 10 years plus annual FIT.¹²

Given the challenges with CRC screening adherence, the main benefit of endorsing a variety of screening methods is that it allows ordering clinicians and patients to engage in shared decision making about patient-centered approaches to CRC screening while also acknowledging local variation in availability of endoscopy services. While CRC screening among individuals aged 50 years and older increased from 38% in 2000 to 66.8% in 2018, screening rates are still well below the U.S. Department of Health and Human Services Healthy People goal of 74.4%, and far short of prior goals set by the American Cancer Society of 80% by 2020.¹⁰ Each of the included screening tests comes with advantages and disadvantages. Some of the main issues regarding colonoscopy include access to facilities and physicians that perform colonoscopy in an appropriate time frame, the need for fasting and bowel preparation, potentially time off work plus a responsible person to provide transportation, need for sedation or anesthesia, risks associated with an invasive procedure, and up until recently, added costs associated with polypectomy. The main advantage of colonoscopy is the ability to remove any polyps at the time of the procedure, and determination of an appropriate surveillance interval based on the number, size, and pathology of those polyps. Conversely, stool-based or two-step tests may often be performed in the privacy of one's home, require no bowel prep, are non-invasive, but typically require annual adherence. Further, those with an abnormal stool-based test then require a colonoscopy to complete the screening occurrence. Currently, that follow-up colonoscopy may be associated with significant out-of-pocket expenses.

Population-Based Approaches to CRC Screening

In order to achieve the CRC mortality benefit suggested by the USPSTF modelling studies, population-based approaches to CRC screening that are not dependent on an individual's insurance status or access to primary care are needed. CRC screening in the U.S. is largely an opportunistic process, with patients typically offered CRC

screening in the context of a primary care office visit. Given that 25% of U.S. adults did not have an identified source of primary care in 2015, our current approach to CRC screening is unlikely to get us to desired screening targets.¹⁷ Studies have shown that patients who are older, more educated, earn more money, see a health care provider regularly, and have health insurance are more likely to be up to date with CRC screening.¹⁰ Additionally, certain racial and ethnic groups are disproportionately affected by this approach.¹⁰ The inclusion of stool-based tests in the paradigm for CRC screening allows for the implementation of population-based screening programs that provide the ability to systematically offer screening to all eligible members of population with standardized counseling, access, support, and monitoring. Levin and colleagues implemented an organized CRC screening program for Kaiser Permanente Northern California health plan beneficiaries using FIT and colonoscopy for eligible individuals aged 50 – 75 years and followed them for 15 years. Up-to-date status of screening more-than doubled from 38.9% in 2000 to 82.7% in 2015, and was associated with a 25.5% reduction in annual CRC incidence and a 52.4% reduction in cancer mortality.¹⁸ Other countries that have initiated programmatic screening have also shown reductions in CRC incidence and mortality.^{19,20}

Anticipated Impact of 2021 USPSTF Recommendations on Screening and Access to Colonoscopy and Unintended Consequences

Although the USPSTF recommends several accepted approaches to CRC screening, colonoscopy is by far the most commonly employed method. Expanding CRC screening to begin at age 45 could lead to significantly increased demand for colonoscopies, with an additional 20 million Americans now eligible for CRC screening. Continued dependence on colonoscopy as the primary tool for screening will further strain our currently limited endoscopy resources, especially in rural and other areas where endoscopy services are scarce. Further work is needed to better understand whether screening with colonoscopy should be reserved for older patients who will have higher likelihood of polyps and

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CRC, and if other screening modalities, such as stool-based screening, should be encouraged in younger individuals. An unfortunate unintended consequence of the USPSTF update would be if colonoscopy resources are diverted to younger patients, resulting in decreased screening and CRC detection in older, higher risk individuals where CRC screening has been shown to have the greatest impact on LYG, CRC incidence, and CRC mortality. Endoscopists should plan how to be best positioned for these changes. This could mean increasing endoscopy capacity and access, and/or be prepared for more therapeutic procedures that will be required following positive stool- or imaging-based screening tests. As larger polyps are found on colonoscopies that follow stool-based tests, the skills and therapeutic capabilities of endoscopists and their facilities will also need to expand. Our professional societies can play an important role in providing this education for endoscopists in practice, while our trainees in gastroenterology will benefit from this exposure during their standard fellowship.

The Patient Protection and Affordable Care Act (ACA) required most health plans to cover evidence-based preventive services that have been recommended by the USPSTF, including CRC screening. This important legislation has made CRC screening more affordable to many more people; however, health plans stop short by only covering the first screening test itself. If a positive stool-based test leads to a recommendation for

a colonoscopy, that colonoscopy is considered diagnostic and subject to out-of-pocket costs that typically range from \$99-\$231.²¹ Patients who may have otherwise opted for a stool-based screening strategy may choose screening colonoscopy instead to avoid unpredictable cost sharing that may be associated with follow-up diagnostic testing. Even worse, we expect individuals in resource poor locations will forgo CRC screening altogether, further worsening health disparities. Unless follow-up colonoscopies are considered to be part of the screening process that is covered without cost sharing, cost will continue to be a barrier to patient acceptance of non-colonoscopy screening methods.

In addition, we support population-based approaches to CRC screening that do not rely on an individual's insurance status, access to primary care, or geographic region. While programs instituted within individual primary care practices, health systems, and health plans will certainly help, population-based approaches that engage individuals both in and out of the traditional health care system are needed. Without population-based approaches, recommendations to begin CRC screening at age 45 will threaten to worsen health care disparities as those well-positioned to access screening colonoscopies at age 45 will limit availability of screening in patients historically disadvantaged, including older patients.

In summary, we agree that the evidence supports the USPSTF recommendations to commence CRC screening at age 45. However, due to already limited endoscopy resources, the updated recommendations may not result in the intended benefit of decreasing CRC mortality if not associated with other interventions. In geographic areas that cannot support the anticipated demand for colonoscopies, we support studying whether starting with non-colonoscopy-based screening strategies in younger individuals may be preferred. We also advocate for policy changes to recommend follow-up colonoscopies following positive screening tests be covered as part of CRC screening. Finally, institution of population-based CRC screening approaches are needed to ensure that we do not further widen access between individuals already engaged in healthcare and those that are not, which would lead to unintended consequences of worsening health disparities in CRC mortality. ■



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Answers to this month's crossword puzzle:

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