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REVIEW

Colorectal cancer screening from 45 years of age: Thesis, antithesis and synthesis

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Abstract

Colorectal cancer incidence and mortality in patients younger than 50 years are increasing, but screening before the age of 50 is not offered in Europe. Advanced-stage diagnosis and mortality from colorectal cancer before 50 years of age are increasing. This is not a detection-bias effect; it is a real issue affecting the entire population. Three independent computational models indicate that screening from 45 years of age would yield a better balance of benefits and risks than the current start at 50 years of age. Experimental data support these predictions in a sex- and race-independent manner. Earlier screening is seemingly affordable, with minimal impediments to providing younger adults with colonoscopy. Indeed, the American Cancer Society has already started to recommend screening from 45 years of age in the United States. Implementing early screening is a societal and public health problem. The three independent computational models that suggested earlier screening were criticized for assuming perfect compliance. Guidelines and recommendations should be derived from well-collected and reproducible data, and not from mathematical predictions. In the era of personalized medicine, screening decisions might not be based solely on age, and sophisticated prediction software may better guide screening. Moreover, early

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screening might divert resources away from older individuals with greater biological risks. Finally, it is still unknown whether early colorectal cancer is part of a continuum of disease or a biologically distinct disease and, as such, it might not benefit from screening at all. The increase in early-onset colorectal cancer incidence and mortality demonstrates an obligation to take actions. Earlier screening would save lives, and starting at the age of 45 years may be a robust screening option.

Key words: Colonoscopy; Guidelines; Pros and cons; Early onset; Early-onset colorectal cancer

Core tip: Colorectal cancer is a significant public health threat to individuals younger than 50 years of age, but they currently do not receive any screening. We discuss the advantages and disadvantages of screening from 45 years of age.

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INTRODUCTION

Over 1.8 million new colorectal cancer (CRC) cases and 881000 deaths were estimated to occur in 2018, accounting for approximately 1 in 10 cancer cases and deaths. Overall, CRC ranks third in terms of incidence but second in terms of mortality[1]. Assessing incidence and mortality, three distinct global temporal trends were described in the most recent decade: (1) Increasing incidence and mortality (Baltic countries, Russia, China and Brazil); (2) Increasing incidence but decreasing mortality (Canada, the United Kingdom, Denmark and Singapore); and (3) Decreasing incidence and decreasing mortality (the United States, Japan and France)[2]. In the United States and Europe combined, in 2018, CRC was responsible for over 200000 deaths, making it the second most lethal cancer in men and women[3-5].

Lifestyle determines approximately 57.2% and 50.2% of incident CRCs in men and women, irrespective of age[6]. Studies have inconsistently determined how much single foods or nutrients increase the risk for CRC, but the revised World Cancer Research Fund/American Institute for Cancer Research convincingly lists processed and red meat[7], alcoholic beverages[8], and obesity[9] among the CRC risk factors, and physical activity among the protective factors[10]. Thus, there is a great opportunity to reduce risk across the population *via* lifestyle modifications. However, age is one of the most important risk factors for CRC[11,12], and evidence supports that it might be considered the most powerful predictor of CRC[13].

CRC diagnosed before the age of 50 is denoted early-onset CRC (eoCRC), and it used to be considered uncommon. Currently, eoCRC accounts for 11% of all male CRCs and 10% of all female CRCs[14], and recent reports even suggest that 7% of all CRCs occur before 40 years of age[15-17]. These reports come from many high-income countries (Canada, Germany, Australia and Norway[18-22]). Indeed, eoCRC incidence has increased by 51% since the mid-1990s[14,16,23-25] and even more for rectal neoplasms. In 2015, one rectal cancer in every six was diagnosed before the age of 50, and predictions from the MD Anderson Center indicate that by 2030, one in four will affect individuals who will not have received screening[24]. The incidence of rectal cancers for young adults doubled from 1991 to 2014 [data from Surveillance, Epidemiology and End Results program (SEER)], and it is estimated to rise by up to 270% by 2030[3]. An adult born in the 1990s has twice the risk of colon cancer and four times the risk of rectal cancer than an adult born in the 1950s[14]. In contrast, incidence rates among individuals older than 50 years have dropped from a peak of 225.6 (per 100000) in 1985 to 119.3 in 2013[3].

Mortality from eoCRC has likewise increased by 11% in the period 2005-2015 (SEER data)[26]. This has made CRC a serious threat to this young population, and it is the

most commonly diagnosed and the most common cause of cancer death among men younger than 50 in the United States[27-29]. A lack of screening in this age group implies that screening might significantly improve the burden of disease.

Because of the slow progression from adenoma to adenocarcinoma, a substantial proportion of CRC cases and deaths might be preventable. Increased understanding of the oncogenesis and development of screening technologies has supported the implementation of CRC screening in clinical practice and public health programs[30]. Colonoscopy remains an effective screening modality to provide long-term protection against CRC occurrence and death[31-33]. Screening programs reduce CRC risk by detecting and removing adenomas[31,32,34], and increase survival and cure rates by earlier diagnosis[35,36]. Most individuals are counseled to start screening at 50, unless family history supports an earlier start. This strategy produced a temporal decline in CRC incidence and mortality among individuals older than 55 for several decades. The large declines in incidence and mortality since 2000 are largely attributable to increased screening and improved treatment for mortality reduction[14,15,37-39]. However, adherence to CRC screening is often suboptimal, especially among ethnic minorities[40,41].

THESIS: WHY SCREEN BEFORE THE AGE OF 50?

Burden of disease

Advanced-stage diagnosis and mortality from eoCRC are increasing, and it has been urged that it is time to take action[42]. CRC is becoming a health threat for young adults, especially because it is often diagnosed in advanced stages. In fact, incidence has increased mostly for metastatic disease[43,44].

Some have argued that the increasing incidence results from increased use of endoscopy. There is little evidence supporting this claim because negligible screening had been observed in younger cohorts[28]. This makes a detection bias unlikely, especially considering that it should yield a greater increase in early-stage, rather than late-stage, diagnosis or at least a similar increase. Instead, advanced-stage eoCRC cases are increasing faster, a phenomenon that a detection bias cannot account for[23,45]. Mortality is also increasing, contrary to what a supposed increased screening would produce, and the median overall survival of eoCRC is indeed lower than that of the older counterpart[46]. These results imply that implementing screening at younger ages might actually have an impact on the CRC burden. Similarly, Chen *et al* demonstrated that advanced-stage eoCRC is not associated with a longer duration of symptoms or time to diagnosis[47]; therefore, timely screening might be a useful intervention.

The incidence of CRC in the 40-49 age group is lower than that in the 50-55 age group (31.4 *vs* 58.4:100000)[3,14], but this is heavily influenced by a lead-time bias and older age. Indeed, data from the National Health Interview Survey revealed that 45% of 50-54-year-old adults have undergone screening colonoscopy, compared to only 17.8% of those aged 40-49 years[48]. Thus, the intrinsic risk in the 45-49 age group is likely closer to that in the 50-55 age group than apparent, and this might support extending the age for screening.

Selected groups of people are known to be at increased risk for CRC, including inflammatory bowel disease patients (relative risk 2.6-2.8)[49-51] and hereditary cancer gene carriers. However, the proportion of eoCRC attributable to these diseases is relatively small, and most eoCRCs are sporadic; thus, interventions are needed for the general population. Only one in six individuals with eoCRC has an inherited predisposition to cancer, while the other five have the same risk factors as the general population[52]. Lynch syndrome accounts for most hereditary cancer syndromes[52]. Genetic counseling must always be offered for those who develop eoCRC[53], but from a prevention perspective, actions should consider the general population[52,54], because 75%-80% of all eoCRC belong to the average-risk population, and they would benefit from screening.

Expected benefits

Years of potential life lost (YPLL) is an estimate of the average years a person would have lived if he or she had not died prematurely. Measuring the impact of disease in terms of YPLL, this young population is severely compromised. This has been shown very recently by Chen *et al*[55]. They analyzed the YPLL of a hypothetical unscreened 50-year-old German population, and inferentially extended the analysis to a younger 45-year-old cohort. Their data support earlier screening: preventing a younger person from CRC occurrence and death spares more future productive years, and this is more heavily weighted in the analysis, as opposed to simply counting deaths. They ran different simulations, separately for men and women, as once-, twice- or thrice-in-a-

lifetime endoscopy procedures at different ages. In the scenario of repeated colonoscopies, the proportion of prevented YPLL declined with delayed screening, while extending the age of screening below 50 proved useful in maximizing YPLL prevention. Men were estimated to obtain maximal YPLL benefit from the age of 45 years, and women from the age of 47 years. This analysis considered colonoscopies until the age of 65 years, not 75 years, which might provide further benefits.

The expected benefits and harms of screening from 45 years of age have also been estimated by three separately developed simulation software programs. The Cancer Intervention and Surveillance Modeling Network (CISNET) employed three simulations to predict the optimal ages of start, ages of stop, intervals, and methods of screening. These models (SimCRC, CRC-SPIN, and MISCAN-Colon) are sophisticated softwares that simulate the individual lives of a large cohort of people. Each simulated person may develop adenomas that progress to stage I through IV CRC. At each step, adenomas and CRCs may become symptomatic or remain silent in the absence of screening. Screening can detect and remove adenomas and diagnose CRC earlier. The outcomes of these studies were expected benefits (life-years gained, LYG, an estimate of the number of years of life gained compared to no screening) and expected risks (burden of colonoscopies) for each combination of age of start, age of stop, and interval. The optimal strategy was determined from the ratio of incremental benefit-to-burden (Table 1).

Only two of these models initially supported starting colonoscopies at the age of 45 years (SimCRC and CRC-SPIN), because MISCAN-Colon was based on data from 1975-1979[56]. At the end of the 1970s, little to no screening was employed, and MISCAN had assumed that CRC incidence had remained stable. Noticing the bias, the American Cancer Society (ACS) requested the analysis to be rerun with the updated incidence data by Siegel *et al*[15]. After including a 1.591-fold increased risk, finally all models unanimously supported starting colonoscopy at the age of 45 years.

MISCAN alone evaluated 145 screening strategies (132 unique) and developed an efficiency frontier based on the largest increase in LYG per additional colonoscopy[56]. Emphasis was placed on reducing the number of colonoscopies per LYG. The efficiency ratio (ER) measured the incremental number of colonoscopies over the incremental number of LYG. By measuring each strategy against the next less effective strategy, the model predicted that screening every 10 years from the age of 45 to 75 years would increase the ER by 9 points. These recommendations are expected to provide 25 additional LYG (+ 6.2%) and 810 additional colonoscopies (+ 17%) per 1000 45-year-old individuals. Other viable options included annual fecal immunochemical testing (FIT), sigmoidoscopy every 5 years or computed colonoscopy every 5 years, from ages 45-75 years. They all held an ER lower than the benchmark strategy and LYG within 90% of the benchmark option. The MISCAN model also attempted the analysis from age 40 years with current incidence. The incremental burden of colonoscopies, in this case, was not matched with a sufficient increase in LYG and the number of averted deaths. In fact, CRC incidence in the 40-44 age group is half that of the 45-49 age group (17.6 *vs* 31.4 per 100000, respectively)[3,14]. A fascinating aspect of this analysis is that cancer biology and behavior can be modulated. For example, assuming a faster adenoma-to-carcinoma progression, instead of a simple increase in adenoma incidence, screening should start at the age of 40 years[56]. In eoCRC patients, compelling pathology reports point to more aggressive behavior with biologically more ominous characteristics[45,57], including a faster adenoma-carcinoma sequence[58,59]. Authors of the simulation did not explain how much faster the progression was assumed, and this renders comparisons with collected data difficult.

Overall, the most important message of these studies is that screening should be recommended before the age of 50 years, or even as early as at 40 years, in the majority of simulated scenarios. Therefore, screening at 45 years appears to be not only a robust screening option, but also a potentially conservative one. The present approach has estimated today's incidence rate ratio as 1.5, but as soon as it crosses 1.7, screening at 40 years will become the most efficient strategy. Especially considering the increasing incidence with each subsequent birth cohort, this approach may soon become inefficient. Starting at the age of 45 years is a reasonable option today, and as the gradual increase in CRC continues, an even earlier screening should be considered.

Additional expected benefits to the 50-55 age group: It is worth considering the additional benefits that early screening would yield for adults beyond 45-49 years of age. Lowering the starting age is likely to favorably impact the incidence and incidence-based mortality of the 50-54 age group, whose incidence and mortality are increasing.

Disease-predisposing factors have been changing. This is proven by the increase in incidence among white adults aged 50-54 years since 2005, after decades of decline in

Table 1 Model-estimated benefits and burden of colorectal cancer screening starting at age 45 *vs* 50 per 1000 screened over a lifetime[27]

Screening test	Age of start and stop	Life years gained	Number of colonoscopies	Recommendable?
Colonoscopy every 10 yr	45-75	429	5646	Yes
	50-75	404	4836	No
CTC every 5 yr	45-75	390	2666	Yes
	50-75	368	2430	No
Flexible sigmoidoscopy every 5 yr	45-75	403	3761	Yes
	50-75	380	3426	No
FIT every year	45-75	403	2698	Yes
	50-75	377	2402	No
HSgFOBT every year	45-75	403	3364	No
	50-75	377	2956	No
mt-sDNA every 3 yr	45-75	376	2640	No
	50-75	350	2331	No

The model predicted better suitability for fecal immunochemical testing over high sensitivity guaiac fecal occult blood testing (HSgFOBT) because the latter has higher false positive rates (nonsteroidal anti-inflammatory drugs causing upper gastrointestinal bleeding, red meat, dietary peroxidases contained in fruits and vegetables). Thus, it increases the number of unnecessary colonoscopies. However, HSgFOBT is less expensive, making it an attractive option in low-resource settings. Colonoscopy every 10 years from the age of 45 to 75 years provides the greatest reduction of mortality and incidence, as well as more life-years gained and deaths averted, with twice as many colonoscopies as stool-based tests. CTC: Computed tomography colonoscopy; FIT: Fecal immunochemical testing; HSgFOBT: High sensitivity guaiac fecal occult blood testing; mt-sDNA: Multitarget stool DNA.

an age group where screening is already recommended[15]. This is primarily the result of a strong birth cohort effect since the 1950s. This generation, along with the later ones, will carry an escalated risk as they age[15].

It is compelling to consider that adenomas develop over approximately 10 years; therefore, the same adenomas detected at 50-55 years might be detectable at 45-49 years. This might imply a similar adenoma detection rate. From a different perspective, polypectomy could benefit the same individual approximately 10 years later[60-62], so a polypectomy at 45 years would reduce the years of life lost for a 55-year-old individual. In fact, trials indicate that a negative sigmoidoscopy or colonoscopy provides long-term protection from CRC for 17 and 20 years, respectively (the longest duration of completed follow-up)[60,62].

Expected benefits are matched by collected data: Model data are supported by real data from the SEER: of all YPLL from CRC in 2010-2014, 10% came from the 45-49 age group and another 13% from the 50-54 age group. Young individuals combined (45-54 age group) account for almost a quarter of the overall CRC burden. Thus, YPLL and mortality from CRC could be drastically reduced by using 10-year (or less) intervals of colonoscopy from the age of 45 years in men and 47 years in women[55].

Moreover, it has been estimated that the risk of developing CRC in the 45-49-year-old cohort is analogous to the risk in the 50-55-year-old cohort: although the incidence rate is higher for the 50-55 age group, the increase in the rate of screening is over twice that of the 45-49 age group[63]. In fact, the annual percentage change in the incidence rate for adults aged 40-49 years is twice that of the 50-54 age group in recent years[14].

Finally, today's incidence of eoCRC is similar to the CRC incidence of people aged 50 in 1992 and 1993, which was the prescreening era (28 and 32 per 100000, respectively)[3]. Assuming the same principles as those that guided screening decisions at the end of the 20th century, screening in the 21st century should start from the age of 45 years.

These data pertain to invasive diseases, but some limited studies have considered the prevalence of adenomas across age groups. Comparing individuals younger than 50 years of age to the 50-59 age group, the prevalence of large adenomas (9 mm or more) was similar, and this finding was replicable in both white and black individuals[64].

Sustainability

Repeated testing and frequent surveillance after positive findings generate great demands for colonoscopy and might be a challenge. In the United States, there is evidence that endoscopic services can provide for an additional 10 and a half million colonoscopies[65], so this should not be a problem. Moreover, younger adults have a lower rate of complications, so morbidity should be a smaller issue than expected in older populations[66]. However, compliance with screening colonoscopy in younger

individuals needs to be further evaluated, and, at present, it is unpredictable how compliant younger individuals will be.

However, in Europe, a shortage of gastroenterologists has been denounced. For example, in Italy, the Società Italiana di Gastroenterologia ed Endoscopia (SIGE) has recently been in the news, urging the training of more specialists[67].

Society guidelines

Some scientific societies have started to explore and recommend screening from 45 years of age. In May 2018, the American Cancer Society (ACS) initiated a qualified recommendation for average-risk adults to begin screening at 45 years[68]. This comes from the new evidence from predictive models. The results of this approach are much awaited in terms of the number needed to diagnose a case and number needed to save a life. Previous recommendations by the ACS were based on joint analysis of risks by ACS, United States Preventive Service Task Force (USPSTF) and American College of Radiology (ACR) in 2008. Since 2008, evidence has accumulated on the changing risks of CRC[69]. Moreover, 2008 recommendations prioritized mortality reduction over incidence reduction, unlike the 2018 edition. However, the work by Siegel *et al*[14] and prior reports showing the persistence of an increasing eoCRC incidence[16,23,24,45] prompted the ACS to extend the recommendation and evaluate earlier screening.

The American College of Gastroenterology (ACG) and the American Society of Gastrointestinal Endoscopy (ASGE) have started to support colonoscopies from 45 years of age for nonwhite individuals[70]. The American College of Physicians and the Institute for Clinical Systems Improvement have already recommended screening in selected younger patients as well[71,72].

European guidelines similarly recommend screening from the age of 50 years[73], and, with some variation across European countries, most screenings begin between 50 and 60 years of age[74,75]. Following ACS recommendations, some countries have adjusted their screening start age. For example, Germany has decreased the start age from 55 to 50 years, and England lowered the start age from 60 to 50 years.

In 2016, the USPSTF determined that "for all modalities, strategies with screening beginning at age 45 years provided additional LYG at a lower number of additional colonoscopies than strategies with screening beginning at later ages"[56]. Ultimately, the USPSTF did not recommend starting at 45 because they judged the benefit to be modest and because one model (MISCAN) did not agree in the first edition. Correction of the assumptions beneath the MISCAN models then resulted in its agreement with the other two models. This might prompt the USPSTF to change their recommendations accordingly in the near future.

Expected benefits of earlier screening are race- and sex-independent: In spite of the higher relative risk for eoCRC in nonwhites (OR = 1.37)[76], the overall incidence between whites and nonwhites is superimposable, and this further supports the use of screening colonoscopy in the 45-49 age group. While the incidence rates in whites younger than 50 years of age have risen, the incidence rates for nonwhites younger than 50 years of age have remained substantially stable, making the two groups comparable since 2013[14]. However, nonwhite individuals with eoCRC are reported to have a worse stage-matched survival than nonhispanic white individuals[77]. The reason for this difference is still being investigated.

Across all races combined, CRC incidence is not significantly different in males and females until age 35, and then the incidence in males increases, and the disparity widens progressively[3].

Others have suggested that CRC age-specific incidence and mortality are lower for females[55]. In fact, the lifetime risk is comparable across sexes only because women have a longer life expectancy[3] and tend to develop CRC later in life. The cumulative 10-year incidence and mortality are comparable to those of men only 4 to 8 years later[78].

Therefore, the ACS recently requested Meester and colleagues to investigate sex- and race-specific characteristics to optimize test burden and test results. Adjusting for race and sex, the predictive models (MISCAN and SimCRC) still recommended screening from 45 years[79] every 10 years, except for white men who might benefit from screening every 5 years instead.

ANTITHESIS: WHY NOT SCREEN BEFORE THE AGE OF 50?

Burden of disease

Many European countries have reported an increasing incidence in eoCRC, but one recent report has combined epidemiologic data from most European countries and has seemingly denied such trends[5]. Across all ages, age-standardized CRC mortality

has been declining since 2012[5]. In Europe, CRC mortality below the age of 50 is not increasing, but the rates have leveled off since 2012 for both sexes[5]. This raises a fundamental question: could this earlier approach be generalized? Furthermore, if countries are experiencing different epidemiological traits, it is imperative to understand why. Exploring differences across countries is a logical task, although monumental.

Furthermore, although the relative risk for eoCRC is increasing in the United States, the absolute incidence of eoCRC is still moderate, reaching 31.4:10000 in the 45-49 age group, compared to 58.4:100000 in the 50-55 age group[3,14,15,68].

Additionally, the effectiveness of screening among the 45-year-olds is debatable because expert opinion in the past century resulted in screening starting at 50 years[80,81]. As a consequence, most of the randomized controlled trials demonstrated survival benefits from 50 years of age. However, three European studies from the 1980s and 1990s enrolled individuals 45-75 years old and demonstrated an overall mortality reduction using guaiac fecal occult blood testing[82-84]. Unfortunately, they were largely underpowered for age subgroup analysis, and age-specific outcomes were not reported[69]. Much of the available evidence for eoCRC screening therefore comes from sophisticated modeling. As soon as evidence from the implementation of the new guidelines becomes available, the outcomes will accrue.

However, colonoscopies are expected to obtain survival benefits at all ages[85-87]. The rationale is that colonoscopies directly alter the adenoma-carcinoma sequence by removing adenomas, which reduces cancer incidence, and by detecting cancers earlier, which increases curability and survival. This last observation is crucial because the increasing incidence of eoCRC pertains to stage III and stage IV diseases, which account for the greatest mortality burden [23,43-45].

Expected benefits

Some have also criticized how the MISCAN-Colon model was reanalyzed. The model assumes an unrealistic 100% adherence rate to screening, follow up and surveillance. Realistic data demonstrate a compliance of 40-60% to screening[88-90] and of approximately 80% for diagnostic follow up and surveillance[90-92] in European countries and the United States. It is worth noting that all available guidelines similarly assume perfect adherence. If one uses lower adherence, the model ultimately recommends excessive screening to compensate for those who do not partake in screening. The ACS acknowledges the importance of patient preference to improve adherence and recommends either a stool-based test or a morphological assessment at age 45, according to the patient's preference[68]. Fecal immunochemical testing remains a valuable alternative to colonoscopy, but it confers a smaller predicted LYG advantage[27]. Chen and colleagues investigated what would happen when using real-world compliance in a hypothetical cohort of 45-year-old individuals undergoing screening programs. They conducted a sensitivity analysis using 25%, 50%, and 75% rates, and they could still indicate robust sensitivity, even with lower compliance. The absolute mortality reduction and YPLL prevention became progressively smaller with lower compliance, as expected[55].

Perhaps even more importantly, these models predict one's risk of CRC solely based on age. From a population perspective, age is a strong determinant of risk, but on an individual's basis further information must be collected. There are several more risk factors for CRC, including male sex, family history, obesity, smoking, alcohol consumption, diet, and medication use. In the age of "personalized/precision medicine", using solely age as a decision strategy is short-sighted, and it is worth exploring further strategies. For example, software could help predict one's risk for CRC, and decisions might be based on them. Some have attempted to develop predictors of one's risk for advanced adenomas and advanced neoplasia before colonoscopy, with unexceptional results and a moderate discriminative capacity[93-95]. Another scoring system implemented Fecal Immunochemical Testing results (FIT)[96], and others merged risk factors with laboratory results[97-99]. Three studies enrolled subjects younger than 50 years of age[99-100]. The most commonly included risk factors include sex, age, family history, body mass index (BMI), smoking, alcohol, aspirin, physical activity, red meat and vegetable consumption, cardiovascular diseases and hypertension. A recent systematic meta-analysis[13] evaluated the discriminatory power of these studies and found that only 7 had a moderate discriminatory capacity (AUC > 70%)[95,97-99,101-103]. One was developed and validated on two large cohorts (24726 and 24724 individuals)[97]. These models might be used to tailor screening modalities, for example preferring colonoscopies over FIT when the risk is high. Risk-adapted strategies might decrease the number of colonoscopies while keeping the LYGs within range. This might enhance efficiency, compliance, and cost-effectiveness.

Despite appealing and logical, this approach must not be taken too enthusiastically. A recent study demonstrated that a model based exclusively on age had C-statistics of

0.663 and 0.685 for men and women, respectively. Adding another 14 variables generated C-statistics of 0.694 and 0.687 only, and this statistic never crossed the 0.7 threshold. Age still remains the greatest determinant of CRC risk[104]. This proves that additional information conveys little value in predicting one's risk of CRC. Screening could be reduced to 45 years of age, regardless of one never having lit a cigarette. Most importantly, additional risk factors and predictive models can only anticipate screening from 45 years of age, not postpone it. All risk factors only make the recommendation for earlier screening stronger because they increase risks. The absence of risk factors, by definition, is not a protective factor and should not be used to postpone screening.

The starting age, however, is not an absolute value and should be made to fit an individual's personal and family history. Other organizations have updated their guidelines for individuals with inflammatory bowel diseases, hereditary CRC syndromes, a history of abdominopelvic radiation, a history of adenomatous polyps, and/or CRC[105-108], but these topics are beyond the scope of this dissertation. It is nonetheless crucial to recommend appropriate family history collection in all individuals as a fundamental moment of cancer risk assessment[109]. Accurate pedigrees can finely predict one's risk: For example, having one single first degree relative with CRC confers a relative risk of 2.11, reaching 3.9 if that relative was diagnosed before 45 years of age[110]. The ACG recommends all individuals with a family history of one first-degree relative with CRC or advanced adenoma to start screening from the age of 40 years, or 10 years younger than the youngest diagnosed relative[72]. However, few individuals with eoCRC report CRC in first (11.9%) and second degree (32.1%) relatives[111]. Indeed, eoCRC is mostly a sporadic disease[52,54], and this encourages a population-wide intervention. All eoCRC should prompt genetic counseling and then either tumor testing for Lynch syndrome or comprehensive genetic panel testing. The two approaches are not comparable, but it is feasible to test all tumors with "universal tumor testing"[112], and then direct individuals with negative results to germline assessment[46].

Sustainability

Implementing early CRC screening is a societal and political decision, and it must consider public health issues, including societal costs and the relative monetary costs compared to other health care expenditures.

Infrastructural problems include implementation and resource diversion. First, changing recommendations might create confusion and uncertainty among clinicians and patients as to the best course of action, leading to conflicting recommendations. Second, this might unduly strain health care infrastructures and divert resources from other as important tasks. A screening program is only as effective as the number of people participating, and in most countries, the ideal 80% coverage rate is still lagging behind[88], especially in some racial minorities[113]. There is concern that implementing screening before the age of 50 years will shift the focus from a population at high risk to a population at relatively lower risk. It might be more cost-effective to implement more comprehensive screening programs, and focus should be directed to increasing screening rates in those at higher biological risk. However, these two facets are not mutually exclusive. Expanding screening and increasing compliance rates should be two parallel tasks to pursue independently. It is very likely that there are resources and ability within current health care infrastructures to allow for both.

Even if the benefits of earlier screening will be fully attained, they will impose a heavy economic burden on society. No study has yet explored the economic costs and savings of this recommendation. CRC diagnosis and treatment have different costs across countries. It is estimated that CRC diagnosis and treatment can exceed $ 100000 in the United States[114], or €23500-36600 in stages I-IV in the Netherlands[115]. In Europe, the economic burden of CRC encompasses over €13 billion[116], after considering the direct and indirect costs; Luengo-Ferndandez and colleagues employed the human capital approach to estimate these costs, by including the costs of temporary disability, reduced hours, and permanent departure from the workforce, alongside premature mortality costs. It is anticipated that this approach imputes a greater cost per capita for the earlier diagnoses. However, a false-positive from stool-based analysis and colonoscopy surveillance for non-advanced adenomas will produce a substantial increase in health-care expenditures. This has raised the concern of whether earlier screening is an economically viable option.

Society guidelines

Two other authoritative organizations on CRC screening in the United States (United States Preventive Service Task Force and United States Multi-Society Task Force of Colorectal Cancer) still recommend screening from 50 years of age. This conclusion comes from a different perspective than the ACS. The ACS valued the YPLL more

than the absolute number of diagnoses, while they emphasized the absolute number of individuals with eoCRC. Furthermore, the latter two warn that further analysis must be conducted on benefits, costs and harms, and on understanding why incidence is increasing.

Moreover, a significant concern is how guidelines should be written. It stands to reason that they should be modeled after collecting solid experimental data from well-designed and replicated clinical trials. Recommendations should avoid simulations as the level of evidence cannot be as valid. Nonetheless, it should be noted that long-term outcomes are lacking in terms of evidence for the different screening options; therefore, modeling studies are necessary to compare the potential effectiveness of different screening strategies. In fact, even past editions of the USPSTF were based on them[117,118].

After the ACS decision, other guidelines are presumed to follow the lead and add to the earlier recommendation. In Europe, the ACS stance has already caused a trend toward lowering the age of screening, but no country has recommended starting at the age of 45 yet. However, it cannot be assumed that other societies will simply match the ACS position. The ACS recommendation is mainly rooted in computational evidence, which might be accurate but could not reflect reality. Data on screening outcomes are scarce in this age group, and results from this recommendation are much awaited.

Is eoCRC a different disease?

Finally, the last argument against eoCRC screening comes from molecular biology studies. It is still unknown whether eoCRC is caused by the same risk factors as CRC in older age groups[68], and many observations suggest that eoCRC is possibly a biologically distinct cancer than the older counterpart. This raises a fundamental question of whether eoCRC is part of a continuum of disease with later-diagnosed CRC or a biologically distinct disease. As such, it might not benefit from screening. If the adenoma-carcinoma sequence unravels faster than the older counterpart, screening is predicted to yield positive outcomes. However, models have not predicted the benefit that would result from other behaviors, such as faster CRC stage-progression, earlier metastatic spread, and/or chemoresistance. In fact, eoCRC has distinctive clinical features, including more advanced stage at diagnosis[43,44], worse overall survival but better response rates to either chemotherapy or surgery. All these questions need answers.

SYNTHESIS

Many Western and Asian countries reported an increasing incidence and mortality in eoCRC at an alarming rate in the last three decades[14,16,18,20,21,25], mainly for rectal cancers. This has sparked the debate on whether young adults could be better managed, and scientific societies engaged in argument in favor of or against lowering the age for screening colonoscopy[119]. The central reasons in favor of and against earlier screening are broadly summarized in Table 2.

In the context of insufficient scientific evidence from population studies, we cannot recommend lowering the age of screening in all cohorts. More epidemiological studies are urgently needed to accurately describe the impact and burden of eoCRC across countries. We consider adequate lowering of the age of first screening colonoscopy where the incidence of eoCRC has been reported to be increasing. This intervention might represent a momentary decision, while clinical and research studies deepen our understanding of eoCRC physiopathology and oncogenesis. Among many questions, it is essential to clarify whether eoCRC differs from late-onset CRC.

Social awareness actions are indispensable to increasing adherence to the screening and availability of gastroenterology units to face this new epidemic. Therefore, action must be carried out not only from the laboratory bench to the bedside but also from the social to the political environment.

Finally, we advocate scientific societies to comprehensively analyze the rate of eoCRC incidence and mortality in their country and incorporate epidemiological and computational data to reliably predict benefits. Provided there are expected benefits, clinical trials should be started for public health officials to optimize screening strategies.

The ACS has been a pioneer in favor of lowering the age of screening[27], and it eventually recommended all adults to start screening at the age of 45[68]. After the ACS intervention, perhaps sufficient data will accumulate to gauge others' position statements and guidelines, but decisions may be delayed for years. In Europe, the incidence of eoCRC has remained stable overall since 2012, although some European

Table 2 Reasons in favor of and against colorectal cancer screening from 45 years of age

Reasons favoring earlier screening	Reasons against earlier screening
Burden of disease	
The incidence of eoCRC is increasing, and metastatic diseases are increasing faster. 11% and 10% of all males' and females' CRC cases occur before the age of 50; of all years of potential life lost from CRC, 10% were from the 45-49 age group	The absolute risk of eoCRC is still considerably smaller than the older counterpart; incidence reaches 34 *vs* 60:100000, respectively
Expected benefits	
In the absence of data from randomized controlled studies, three computational models predicted a benefit from lowering the age of screening	Computational models have several limits. They assume an unrealistic 100% adherence rate; they failed to consider CRC as a multifactorial disease where other risk factors influence one's risk (*i.e.*, sex, diabetes, diet, lifestyle and others)
Sustainability	
Earlier screening is economically feasible in the United States, and it might be similarly feasible in most European countries; some European countries have also reported a shortage of gastroenterologists	Earlier screening will create care costs that may not balance the reduced incidence and mortality; implementing earlier screening might produce resource diversion. Enhancing compliance rates to colorectal screening is an equally important task that might be overlooked if excessive emphasis is placed on earlier screening
Society guidelines	
The ACS recommends screening from 45 years of age. ACG and ASGE support screening from 45 years of age for African Americans, whose incidence of eoCRC is superimposable on Caucasians	USPSTF, USMSTF and ECCSGWG support screening from 50 years of age

eoCRC: Early-onset colorectal cancer; CRC: Colorectal cancer; ACS:American Cancer Society; ACG: American College of Gastroenterology; ASGE: American Society of Gastrointestinal Endoscopy; USPSTF: United States Preventive Service Task Force; USMSTF: United States Multi-Society Task Force on colorectal cancer; ECCSGWG: European Colorectal Cancer Screening Guidelines Working Group.

countries reported an increase. Probing into differences across populations might not produce immediate results, while the increasing incidence and mortality demand action now. Moreover, the incidence is expected to grow in most countries[24]; under such circumstances, lowering the age of starting colonoscopy might be considered a straightforward solution to a mounting problem.

The biology of eoCRC is also insufficiently understood, but compelling evidence suggests faster development and more aggressive behavior[57-59]. One computational model has explored the hypothesis of a faster adenoma-carcinoma transition, and it concluded that the benefits persisted. However, this is speculative and must be judged cautiously. After all, further knowledge must be gathered on the oncogenesis. No single risk factor has yet satisfactorily explained why eoCRC is increasingly common[69]. Prediction models all lacked sufficient predictive power in estimating an individual's risk for CRC by incorporating age and risk factors (smoking, diet, exercise, and diabetes among others)[93-102]. The starting age is not an absolute value and should be made to fit an individual's personal and family history. Furthermore, risk factors could anticipate one's first colonoscopy but probably not postpone it. Among the many risk factors, the importance of accurately recorded family history can never be overstated as a crucial part of risk assessment.

Moreover, we urge researchers not to consider crude mortality data that fail to consider the impact of the disease. The most recent approaches have emphasized the larger benefit from reducing years of potential life lost[55,56]. Saving a premature death is more heavily weighted because it spares more productive years, making the tradeoff against the increasing colonoscopy burden favorable[68].

Epidemiological data support earlier screening even without sophisticated predictive tools and cost-benefit analysis. Today's incidence of CRC in 45-year-old individuals is similar to that of 50-year-old individuals in the 1990s[80,81]. It is also noteworthy that the current incidence in the 45-49 and 50-55 age groups might be comparable after accounting for the lead-time bias and the difference in screening rate[48,63]. This indicates that the underlying risk for CRC is similar across the two groups.

Lowering the age of the first colonoscopy is a drastic and needed approach, but other measures must accompany this decision. Screening programs work best when compliance rates reach 80%. This must increase across ages[91,92], but there is some concern that earlier screening could divert resources and attention. The two goals (increased adherence and earlier screening) should be separately pursued with equal effort. However, resource allocation might, after all, give privilege to one over the other. Patients' advocacy groups can weigh-in by demanding the expansion of coverage and actively promoting social campaigns in favor of both. Campaigns

should involve patients and their doctors, and gather political interest and support. Younger populations should also be advised on healthier living and eliminating cancer-predisposing behavior. Incorrect alimentary habits and excessive sedentarity contributed to the epidemic increase in diabetes and obesity in Europe[120]. Specifically, obesity has been recently associated with a higher risk for eoCRC in young women[121].

CONCLUSION

Finally, previous recommendations were adequate for the 20th century, but as population characteristics change, clinical recommendations must be adapted for optimal management. In light of the increase of eoCRC incidence and mortality, it is imperative that actions are taken; an earlier screening from age 45 might represent a robust screening option for all countries experiencing an increased incidence of eoCRC.

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