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Why is early detection of colon cancer still not possible in 2023?

Early detection of colon cancer

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Abstract

Colorectal cancer (CRC) screening is a fundamental tool in the prevention and early detection of one of the most prevalent and lethal cancers. Over the years, in fact, screening, particularly in those settings where it is well organized, has succeeded in reducing the incidence of colon and rectal cancer and improving the prognosis related to them. Despite considerable advancements in screening technologies and strategies, the effectiveness of CRC screening programs remains less than optimal. This paper examines the multifaceted reasons behind the persistent lack of effectiveness in CRC screening initiatives. Through a critical analysis of current methodologies, technological limitations, patient-related factors, and systemic challenges, we elucidate the complex interplay that hampers the successful reduction of CRC morbidity and mortality rates. While acknowledging the advancements that have improved aspects of screening, we emphasize the necessity of addressing the identified barriers comprehensively. This study aims to raise awareness of how important colorectal cancer screening is in reducing costs for this disease. Screening and early diagnosis are not only important in improving the prognosis of patients with colorectal cancer, but can lead to an important reduction in the cost of treating a disease, that is often diagnosed at too advanced stage. Spending more sooner can mean saving money later.

Key Words: colorectal cancer; colorectal cancer screening; colorectal screening test

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Core Tip: Colorectal cancer (CRC) screening is a fundamental tool in the prevention and early detection of one of the most prevalent and lethal cancers. Despite considerable advancements in screening technologies and strategies, the effectiveness of CRC screening programs remains less than optimal. This paper examines the multifaceted reasons behind the persistent lack of effectiveness in CRC screening

initiatives. Through a critical analysis of current methodologies, technological limitations, patient-related factors, and systemic challenges, we elucidate the complex interplay that hampers the successful reduction of CRC morbidity and mortality rates. While acknowledging the advancements that have improved aspects of screening, we emphasize the necessity of addressing the identified barriers comprehensively. This study also aims to raise awareness of how important colorectal cancer screening is in reducing costs for this disease. Screening and early detection are not only relevant for an improved prognosis of patients with colorectal cancer, but result in an important reduction in the cost of treating a disease that is too far advanced. Spending more sooner can mean saving money later.

INTRODUCTION

INTRODUCTION

From what is reported in the latest reports of the National Cancer Institute, it is understood how the number of "cancer survivors" is soaring and projections are beginning to alarm. This phenomenon is due, in part, to the natural increase in population numbers, amplified by the lengthening of the average life span, and in part, to improved treatments that allow increasing survival for cancer patients.

<<As of January 2022, it is estimated that there are 18.1 million cancer survivors in the United States. This represents approximately 5.4% of the population. The number of cancer survivors is projected to increase by 24.4%, to 22.5 million, by 2032 and to 26.0 million by 2040. Over the next decade, the number of people who have lived 5 or more years after their cancer diagnosis is projected to increase approximately 30%, to 16.3 million. 67% of survivors are currently age 65 or older. It is estimated that by 2040, 74% of cancer survivors in the US will be age 65 or older.>>

In the light of these data, it can be understood that if up to now, our first goal has been to treat patients with cancer and then to seek ever more effective and often more expensive treatments to achieve a patient's cure or otherwise increase survival, an

additional cause for concern now arises. If cancer survivors are increasing day by day, how are we going to take care of this growing volume of patients in need of treatment in the future? What strategies should we adopt to deal with this problem? Obviously, the first measure is undoubtedly to implement information campaigns on anti-cancer lifestyles, and to put in place screening programs for early detection of the disease. It is intuitive that cancer costs less when diagnosed at an early stage, limiting expenses to surgery, length of stay, and follow-up. If it is diagnosed at a more advanced stage, unfortunately costs will increase in an attempt to keep the disease under control for as long as possible.

The cancers we will have to address first will obviously be the most frequent ones, and among them colorectal cancer. Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide [1] and accounts for 10% of the total cancer burden [2]. Globally, nearly 2 million new cases of colorectal cancer (including anus) and more than 900,000 deaths occur each year [3]. Incidence rates are approximately 4-fold higher in transitioned countries compared with transitioning countries, but there is less variation in the mortality rates because of higher fatality in transitioning countries [3]. The highest incidence rates of colorectal cancer are observed in European regions, Australia/New Zealand, and North America [3,4]. Lifetime risk of CRC is similar between women and men, 4.1% and 4.4%, respectively [5]. The dominant risk factor for CRC is age. Age-specific incidence and mortality increase dramatically over a lifetime, from 6 and 1 per 100,000 people aged 30-34 years to 228 and 105 per 100,000 people aged 80-84 years, respectively [5,6]. In 2021, Fang *et al* [7] performed an analysis of the clinical characteristics of CRC in the Chinese population (cohort of 13,328 patients) and found that 58.1% of CRC cases are observed in individuals over 60 years old. According to an even more recent study of the Chinese population, age > 65 years is a significant risk factor for developing CRC with an odds ratio of 1.4 [8]. The five-year survival rate for stage I colon cancer is 91%, but drops to 72% for locally advanced disease and 14% for stage IV [4].

Sixty-five to seventy percent of colorectal cancers are sporadic forms, while the remaining 30 to 35 percent of cases are genetic or familial forms, which should be recognized as early as possible and included in a close follow-up program. As known, polyps are considered as precancerous lesions. About two-thirds of CRC cases develop through the adenoma–carcinoma sequence, while the remaining one-third of CRC cases originate from the serrated pathway [9]. The neoplastic degeneration of a colorectal polyp to colorectal cancer, as we know, occurs over a very long period, and we would therefore have a lot of time to recognize this polyp early and remove it before it becomes cancer. Resection of the polyp in CRC screening reduces the incidence and mortality of cancer [9,10]. In any case, we could still remove the cancer at a very early stage of the disease. So we are facing a disease that could be prevented by a simple endoscopy, and instead brings an exaggerated number of new cases and deaths every year. ---Unfortunately, even in the most advanced countries, and even in those where screening programs are active, even today diagnosis is often late, when the cancer is already in an advanced stage. As reported in the latest guidelines of the American Society of Colorectal surgery [11], the diagnosis of colo-rectal cancer is made in 70 % of cases when the patient is already symptomatic, often with symptoms such as hemorrhage or occlusion that require emergency surgery.

Colorectal cancer incidence and mortality have declined over time (Figure 1) due to improvements in exposure to risk factors, treatment of diagnosed CRC, and, in particular, widespread uptake of screening [5]. The observed trend correlates with an increase in the proportion of eligible individuals upgrading with screening [12]. From 2000 to 2018, CRC incidence and mortality decreased from 56 and 20 to 37 and 13 per 100,000, respectively [13] while the proportion of individuals aged 50 to 75 years who are up-to-date with screening increased from 34.6% [14] to 67.0% [15]. The benefit of colorectal screening in preventing specific deaths is between 25% and 50% [4,16].

The use of screening and the resulting early detection of more cases, in addition to having benefits in terms of survival and quality of life, could also have economic benefits [17]. In fact, despite of a higher initial cost, because the exams are performed on

a large number of individuals considered healthy, early detection of colorectal cancers results in a global cost reduction. The positive cost impact in the lower cancer stages (stages I-II) can be explained by less invasive surgery, shorter hospital stays, fewer emergency admissions and outpatient visits within 12 mo of diagnosis, less use of chemotherapy and biologic drugs. The potential costs savings associated with an early diagnosis are greater in patients age 18-64 [18].

Gheysariyeha *et al* [19] conducted a systematic review with cost-effectiveness results showing annual fecal immunochemical test (FIT), colonoscopy every 10 years, sigmoidoscopy every 5 years, biennial high-sensitivity guaiac-based fecal occult blood test (HSgFOBT) and Stool DNA Test every 3 years were cost-saving strategies than no-screening. In most of the studies, FIT in comparison with other strategies was cost-saving (less costly and more effective).

SCREENING TESTS

Colorectal cancer is an ideal target for screening because it arises from precursors that take a long time (up to 10 years) to evolve into a malignancy, offering a window of opportunity for polypectomy and cancer prevention [20]. Current CRC screening methods are divided into invasive and non-invasive tests [21]. Noninvasive tests include stool-based tests, blood tests and radiological examinations. Stool-based tests available are HSgFOBT, FIT and fecal DNA test (Multitarget stool DNA, MT-sDNA, Cologuard®). Blood-based tests include Epi proColon, which detects circulating methylated SEPT9, and tests that detect microRNA and plasma protein biomarkers. Radiological examinations include computed tomographic colonoscopy (CTC) and capsule endoscopy (double-contrast barium enema is practically no longer applied in clinical practice) [21]. Invasive tests include flexible sigmoidoscopy and colonoscopy, which offer direct visualization and detection of a colon polyp or neoplasm with the advantage of obtaining a pathological specimen [21]. These are complemented by novel emerging screening modalities such as stool-based microbiome testing, urine-based screening tests using liquid chromatography-mass spectrometry or nuclear magnetic

resonance spectroscopy, and magnetic resonance colonography. However, the novel tests are not optimal in terms of accuracy and depend on colonoscopy in case of abnormal results [22-24]. Currently, there are no data on whether the new screening strategies have an impact on CRC incidence and mortality, and they cannot, therefore, be recommended for CRC screening [22-24].

High-sensitivity guaiac-based fecal occult blood test

HSgFOBT detects colorectal polyps and cancers through an oxidation reaction of guaiaconic acid by hydrogen peroxide when the heme group is present in the stool sample. Sensitivity and specificity for CRC are 0.50-0.75 and 0.96-0.98 [23], while for advanced adenomas are 0.06-0.17 and 0.96-0.99, respectively [23]. A 2019 meta-analysis showed that HSgFOBT screening led to a reduction in CRC-related mortality but did not reduce the incidence of CRC [25]. HSgFOBT has been largely replaced by FIT because it requires more samples, avoidance of red meat and drugs that can cause false positives, and because a positive test could be due to bleeding from anywhere in the gastrointestinal tract [5].

Fecal immunochemical test

FIT is a screening test that detects the presence of the intact globin portion of human hemoglobin in stool using antibodies [26]. Considering the cut-off of 20 μgHb/g stool, the sensitivity and specificity for CRC are 0.74 and 0.94, respectively [23,24], while sensitivity and specificity for advanced adenoma are 0.23 and 0.96 [21]. A 2015 study demonstrated a reduction in CRC mortality with biennial FIT, but no change in CRC incidence [23].

Unlike HSgFOBT, FIT requires only a stool sample, is not influenced by the individual's diet or medications, and does not present abnormal results in the presence of upper gastrointestinal bleeding because hemoglobin is partially digested before reaching the colon [26]. FIT is the most common noninvasive colorectal cancer screening modality among average-risk individuals. In a 2020 analysis, CRC detection rates were similar

when four rounds of FIT in alternate years were compared with a single flexible sigmoidoscopy and a single colonoscopy [27]. An Italian intention-to-screen study evaluated the effectiveness of a two-year screening program with FIT and found a stable 28% decrease in annual CRC incidence after eight years [28].

Multi-target stool DNA testing

The multi-target stool DNA testing (mt-sDNA screening test, also called Cologuard) is an FDA-approved non-invasive CRC screening tool in 2014. Cologuard uses a biomarker panel which analyzes a person's stool sample for DNA markers, as well as blood in the stool. The sensitivity and specificity for CRC are 0.93 and 0.85, respectively [23]. For advanced adenoma, the sensitivity is 0.43 and the specificity is 0.89 [23,24]. With perfect adherence, mt-sDNA reduces the incidence of colorectal cancer by 66% [29]. Challenges of screening with mt-sDNA include cost and a high false-positive rate compared with FIT [29,30,31]. Overall, mt-sDNA is better than FIT in differentiating advanced precancerous lesions from nonneoplastic or negative findings [32]. However, its specificity is lower, which may result in more colonoscopies. [31,22].

Computed tomographic colonoscopy

First described in the literature in 1994, computed tomographic colonoscopy (CTC; also called CT colonoscopy, virtual colography, and virtual colonoscopy) uses traditional computed tomography with image reconstruction techniques (3D rendering) to visualize the inner wall of the colon without the use of an endoscopic probe [33]. Sensitivity for adenomas 10 mm or greater is 0.89, and specificity is 0.94 [23,24]. For adenomas 6 mm or larger, sensitivity is 0.86, and specificity is 0.88 [23,24]. The advantages of CTC are less invasiveness, no need for procedural sedation, and low complication rate. Disadvantages are the need to prepare the bowel, exposure to radiation, the need to undergo colonoscopy in case of positive results, and extracolonic findings involving further examination and potential overtreatment. The use of CTC is limited due to the lack of trained radiologists and imaging centers offering the test [24].

Colon capsule

Colon capsule (CCE) is a non-invasive colon imaging technique involving the ingestion of a wireless pill-sized camera that takes images as it travels through the gastrointestinal tract. The first generation of CCE (PillCam-Colon) showed a sensitivity of 69% and specificity of 86% for detecting a polyp ≥6 mm in size [34]. The second generation of CCE (PillCam-Colon 2), which offers an adaptive frame rate and wider viewing angle, showed better accuracy in detecting polyps ≥6 mm in size, with a sensitivity of 84% and specificity of 88% [35]. It does not require air inflation, sedation, or the use of radiation and thus allows minimally invasive and painless colon evaluation. However, the rate of complete CCE examinations is only 67% [36] and 32% of CCEs result in referral to colonoscopy (polyps ≥ 10 mm) [37]. Interpretation of CCE also requires a physician skilled in reading capsule endoscopy and often takes longer than performing a colonoscopy [36]. The European Society for Gastrointestinal Endoscopy (ESGE) has proposed colon capsule as a screening tool in patients at average risk, in patients with incomplete colonoscopy, in patients who refuse conventional colonoscopy, and in patients with contraindications to conventional colonoscopy [38,39].

Blood-based tests

The detection of circulating and cell-free tumor DNA in blood has opened up potential for blood-based tests for CRC and advanced malignancies, such as the search for SEPT9DNA, C9orf50, KCNQ6, CLIP4, miRNA, Interleukin-6, lectin serine protease 1 mannan binding, integrin alpha 11 [40-42]. Currently only Epi proColon has been approved by the FDA as a blood-based screening test. Epi proColon detects circulating methylated SEPT9DNA and has a sensitivity and specificity of 0.68 and 0.79 for CRC and 0.22 and 0.79 for advanced adenomas, respectively [43]. In general, a blood-based test attracts because of its minimal invasiveness and the possibility of being combined with other routine tests. Adler *et al* [44] reported that 97% of people who refuse screening with colonoscopy accept a noninvasive test and 83% choose a blood test. It can be

offered to medium-risk individuals who have refused other screening tests, with annual testing and a recommendation to have a colonoscopy if the result is abnormal. The United States Preventive Services Task Force (USPSTF) has not approved serum methylated septin-9 for medium-risk screening because of low accuracy [5,21,24]. As of 2021, a blood test must have a specificity of 90% and a sensitivity of 74% for CRC compared to an accepted standard (such as colonoscopy) to meet approval thresholds [33]. Unless high sensitivity is achieved, blood-based CRC screening can cause false positive results, unnecessary colonoscopies, and consequently adverse events. It will be essential to determine and improve test accuracy, cost, and the appropriate clinical work-up after abnormal results [45].

Colonoscopy

Colonoscopy is the most common screening modality in the United States and allows visual examination of the entire colon and rectum for polyps and colorectal cancers. Sensitivity is 0.89-0.95 and specificity 0.89 for adenomas 10 mm or larger [23]. For CRC, the sensitivity is 0.18-1.0 [23,24].

Cancer mortality is 29-68% lower among people who undergo screening colonoscopy than those who do not [16,46-48].

The effectiveness of screening colonoscopy for colorectal cancer prevention was further quantified by a recent large randomized trial [49]. The 10-year risk of colorectal cancer was 0.98% among participants invited to undergo screening colonoscopy, compared with 1.20% among those assigned to receive usual care. Screening colonoscopy was performed in only 42% of participants invited for screening. In analyses adjusted to estimate the effect of screening if all participants randomly assigned to screening actually underwent screening, the risk of colorectal cancer decreased from 1.22% to 0.84% (31% reduction) and the risk of death from colorectal cancer decreased from 0.30% to 0.15% (50% reduction) [49].

The disadvantages of colonoscopy are its invasiveness, risk of complications, need for bowel preparation, resource burden, and associated costs. Because of the financial and

psychosocial barriers to adherence, colonoscopy is best reserved as the second stage of a two-stage screening cascade [50].

Flexible sigmoidoscopy

Flexible sigmoidoscopy is another option for direct visualization of the distal colon. Studies in the United Kingdom, Italy, and United States have reported a reduction in CRC incidence of 23% and 18-23% and CRC mortality of 22-31% [51-53]. However, due to the inability to evaluate the entire colon, the overall reduction in CRC incidence and CRC-related mortality is greater for colonoscopy than for flexible sigmoidoscopy [54]. The resources required for flexible sigmoidoscopy are similar to a colonoscopy, but colonoscopy is needed to follow up on a positive FIT and for those with polyps on flexible sigmoidoscopy. Consequently, rates of screening flexible sigmoidoscopy have declined in the USA [22].

WHY NOT ENOUGH?

Although screening has had a positive effect on incidence and mortality, as previously reported, a significant percentage of colorectal cancer patients arrive at the hospital late, with urgent symptoms and advanced neoplasia [55]. About one-third of patients with colorectal cancer present as a surgical emergency [55].

Large bowel obstruction accounts for nearly 80% (15-30% of CRCs) of CRC-related emergencies, while perforation accounts for the remaining 20% (1-10% of CRCs) [56-59]. The most common site of CRC obstruction is the sigmoid colon, with 75% of tumors located distal to the splenic flexure [60]. Perforation occurs at the tumor site in almost 70% of cases and proximal to the tumor site in about 30% of cases [56,61]. Emergency surgery for colorectal cancer is associated with a worse prognosis than elective surgery, with lower overall and recurrence-free survival rates [59,62,63].

Such a high rate of urgent presentations of colorectal cancer should give pause to the still unsatisfactory results of screening. The ineffectiveness of early detection is due to the suboptimal accuracy of screening tools (particularly for polyps/adenomas), the

poor adherence, the absence of screening programs in some areas of the world, the Covid 19 pandemic, and the early onset of CRC.

SCREENING ADHERENCE AND SCREENING PROGRAM

Despite the various modalities offered for CRC screening, it is still underutilized. In the United States, screening rates remain around 60% [21,64]. Adherence to CRC screening is particularly poor among underserved populations, including low-income and African American and Hispanic populations. Over the past four decades, CRC incidence rates have decreased by 33.9% in U.S. whites but only 6.6% in African Americans [2]. In 2015, 62.4% of men and women reported using a screening test for CRC [65]. Reported screening was lower among those aged 50-64 years (57.9%) than those aged 65-75 years (71.8%) [65]. The lowest use of screening for colorectal cancer was reported by people without a usual source of health care (26.3%) and uninsured people (25.1%) [65]. Adherence rates are no better in Asia-Pacific countries, ranging from 21% in South Korea to 62.9% in Thailand [66,67]. Participation rates ranging from 26% to 73% have been reported in Europe [68]. The EU guidelines have proposed acceptable and desirable CRC screening adherence rates ab ove 45% and 65%, respectively, and colonoscopy adherence among those with a positive primary screening test result above 90% [69,70]. The National Roundtable on CRC proposed an 80% adherence goal for primary screening, and the US MSTF on CRC set an 80% goal for colonoscopy adherence in patients with a positive FIT result [69,71,72].

Several factors play a role in influencing patient participation and sustained adherence. Barriers to screening include high costs, lack of adequate education about colorectal cancer, poor consideration of the benefits of screening, a sense of fatalism, or simply fear of screening tests [68,73].

The screening modality has an impact on the adherence rate. In general, the rule applies that more invasive tests have lower adherence rates [74]. In the COLONPREV randomized trial [75], patients underwent either colonoscopy or FIT, and the authors

found participation rates of 25.0% and 34.2%, respectively. Similarly, in a meta-analysis comparing colonoscopy with CT colonoscopy, the participation rates were 20.0% and 29.0% [68,76].

To achieve the highest level of adherence, it might be better to offer participants a choice, because the "best" strategy is the one they will consistently adhere to [76].

Each step in effective CRC screening is associated with specific barriers. Each of these steps can occur in the opportunistic health care setting, such as independent private practices or individual hospitals, however, there are data demonstrating that implementation of programmatic or organized screening can result in improved adherence with CRC screening and benefits for outcomes [77]. An organized screening program is defined by the following characteristics: (1) an explicit policy with specified screening methods and intervals; (2) a defined target population; (3) a management team responsible for implementation; (4) a health care team for decision-making and assistance; (5) a quality assurance structure; and (6) a method for identifying cancer occurrence in the population [77,78]. Organized screening programs use a variety of evidence-based approaches to improve CRC screening uptake by members of the target population. These include sending patients invitations from their primary care provider, sending reminder letters, phone calls, and sending fecal occult blood test/FIT kits to patients' homes and population-based public awareness campaigns [79-83]

Combinations of interventions have been associated with greater increases than single components [31].

In a randomized trial, Libby *et al* [84] compared the rate of HSgFOBT adherence in 3 groups: invitation letter alone, invitation letter plus a pre-warning letter, and the latter two plus a CRC and screening information booklet. HSgFOBT uptake was highest in the group that received all three mailings. At the provider level, a recommendation to be screened from a primary care provider/general practitioner (GP) is clearly effective in raising participation [31]. Providing GPs with a list of their patients who were noncompliant with CRC screening resulted in a small increase in FIT screening at 1 year [85]. Boguradzka *et al* [86] found a higher participation rate for patients who received GP

counseling on CRC screening than for those who received an information pamphlet (47% *vs* 13.7%).

Organized screening can reduce structural and economic barriers by expanding schedules, combining screening with other visits, such as the flu vaccination clinic and making screening more convenient by offering passes or expanding insurance coverage [77]. Muliira *et al* [87] found improved participation rates from 11 to 91% with a patient navigator. Navigators were more effective in patients from minority groups. Selby *et al* [88] reported an adherence rate to diagnostic colonoscopy by FIT-positive subjects of more than 83% due to a combination of strategies, including insurance coverage that defines this procedure as preventive and telephone contact to schedule colonoscopy directly [87]. Eliminating economic barriers resulted in substantial increase (ranging from 7% to 50%, depending on background rates of use) in population coverage, in particular among the low-income, least-educated subjects [68,89,90]

Organized screening programs can continuously monitor screening performance and clinical outcomes [91] and design interventions to address gaps. There are numerous examples of quality assurance programs related to the performance of colonoscopy, based on training and accreditation of endoscopy services [92-96]. Kaminski *et al* [94] for example tested a program to train endoscopy managers at low-performing facilities. They demonstrated improvements in the adenoma detection rate (ADR) of the trained operator and the facility as a whole. In addition, they have shown that improved ADRs are associated with decreased risk of interval cancer and cancer death [95,96].

Screening programs have reduced incidence, mortality, and surgery for CRC at the population level, but screening rates remain low in several countries [68,97,98]. Most screening in the United States occurs in the opportunistic setting. Organized CRC screening is more common in Europe than in the United States [97]. Opportunistic screening currently occurs in Latvia [99], Greece [99], and Bosnia-Herzegovina [100], while information on screening is lacking in Belarus, Slovakia, Liechtenstein, and Romania [98]. Similarly, most countries in Africa, Central America, South America, and the Middle East do not have organized screening programs [67], mainly due to the limited number

of resources and the type of health system organization. Currently, organized screening is recommended in regions with the highest incidence of CRC (> 30 per 100000) [67,101]. Programs target individuals at average risk, aged 50 to 75 years, and preferably apply the FIT test. Several East Asian countries have organized screening programs in place, including Japan, Korea, China, Hong Kong, Taiwan, and Bangkok [98,102].

In Asia the management of CRC screening is even more complex, as additional challenges are added, such as the lack of awareness of the usefulness of screening by some governments, government reluctance to spend on building relevant infrastructure, inadequate manpower (too few surgeons and endoscopists relative to the population), and the [103-105] issue of ethnicity. In the case of multiethnic countries such as Malaysia, the risk of CRC is very different among Chinese, Malaysians, and Indians [106,107], with the incidence per 100,000 population higher among Chinese and lower among Indians [106]. Therefore, it is difficult to reach consensus on the implementation of a national screening program in these regions [103].

COLORECTAL CANCER SCREENING AND COVID-19

In the United States, CRC screening is primarily based on colonoscopy, while in Europe most countries screen through FIT [108]. In Europe, a positive FIT must be followed by a colonoscopy within one month [108]. Zorzi *et al* [109] reported that delay of 9 months after a positive FIT is associated with worse outcomes in terms of CRC risk and CRC progression. The same conclusion was reached by Lee *et al* [110] using data from the Taiwan Nationwide Screening Program and considering a 6-month delay for colonoscopy after a positive FIT [110]. The COVID-19 pandemic, begun in March 2020, has overwhelmed the global healthcare system capacity and impacted the management of patients with cancer and other chronic diseases [111-113]. In response to the pandemic, preventing hospital acquired COVID-19 infections and the spread of the virus, there were global policy decisions like lockdown and stay at home. There was also redistribution of both human and material resources in the hospital setting [114,115]. This

resulted in drastic reduction of all non-essential services. Non-emergency visits, screenings, and elective surgeries were cancelled [116].

CRC management was severely affected by the pandemic. CRC screening activity decreased by up to 85-95%. Care delivery was disrupted, and after resumption of activities, patients often refused colonoscopy for fear of being exposed to SARS-CoV-2, while planning processes were hampered by the need for viral testing prior to the procedure [117]. Delays in screening and surveillance result in progression of precursor lesions and detection of tumors at a more advanced stage. [108].

Meijer *et al* [118] reported a reduction in patients with stage I and II CRC from 29.5% and 26.6% to 20.0% and 25.5%, respectively, after the onset of pandemic COVID-19. They also noted an increase in patients with stage III and IV from 22.2% and 19.0% to 26.8% and 26.2%, respectively [118]. These changes were attributed to delays in CRC screening and diagnosis caused by the COVID-19 pandemic [112].

As a result, the mode of presentation of malignancy was also affected by the pandemic and the reduction in screening practices. Shinkwin *et al* [119] reported an increase in emergency presentations from 28.6% to 36.0%. Estimates suggest that there would be approximately 10,000 excess deaths from breast cancer and CRC in the United States alone due to pandemic-related treatment interruptions [120] while 18,800 people in the United States may experience delays in colorectal cancer diagnosis [121]. Similarly, population data in the United Kingdom suggest an increase in preventable cancer deaths due to COVID-19, with up to 16.6% of deaths due to CRC in the 5 years after diagnosis [122].

EARLY COLORECTAL CANCER

While overall CRC incidence rates have remained stable or declined in many high-income countries, incidence of early-onset CRC (generally defined as colorectal cancer that is diagnosed in individuals younger than 50 years) has recently been increasing worldwide, especially in United States, Europe, Canada, Australia, New Zealand as well as in some countries in Asia [123]. Although there is still little certainty, early-onset

colorectal cancer appears to be associated with westernization of lifestyle [124]. Among EO-CRC, about 30% of patients have mutations that cause inherited cancer predisposition syndromes, and 20% have familial CRC.

The average annual percent changes in early-onset CRC incidence were 4.0% in New Zealand, 2.8% in Canada and Australia, and 2.2% in the U.S. during 2008-2012 [125]. In the U.S., the age-adjusted early-onset CRC incidence per 100,000 persons was 5.9 cases in 2000 and 8.4 cases in 2017. Increases in early-onset CRC have also been documented in most European countries. Early-onset CRC incidence (per 100,000 persons) increased from 0.8 to 2.3 cases in individuals aged 20-29 years during1990-2016, from 2.8 to 6.4 cases in those aged 30-39 during 2006-2016, and from 15.5 to 19.2 cases in those aged 40-49 during 2005-2016 [126,127]. The average annual percent changes in early-onset CRC incidence were 7.9% in individuals aged 20-29, 4.9% in those aged 30-39, and 1.6% in those aged 40-49 during 2004-2016 [127]. Taken together, early-onset CRC now represents a significant cancer burden among younger adults.

The increase of early-onset CRC incidence in the U.S. was initially largely driven by rectal cancer [126]. Since 2012 early-onset CRC incidence has increased similarly for colon and rectum with the annual percent change of approximately 1.8% [128]. The rise in early-onset CRC incidence appeared more prominent for colon cancer than for rectal cancer in Europe [127]. Within the next decade, the incidence rates of colon and rectal cancer are estimated to increase by 90% and 124%, respectively, among adults aged 20-34 years and 27% and 46% for those aged 35-49 years [129].

Patients with early-onset CRC is more likely to have synchronous and metachronous lesions and generally show a more advanced stage of disease because lack of screening, poor consideration of symptoms, and reluctance to seek medical attention delay diagnosis [130,131]. Early-onset CRCs more frequently exhibit unfavorable histopathologic features, such as poor differentiation, perineural invasion, venous invasion, and mucinous and/or signet cell morphology [132,133].

Current population-based screening strategies need to be adapted to epidemiology, so the Multi-Society Task Force on Colorectal Cancer has recommended starting screening

at age 45 years [134].

Early-onset CRC presents a challenge because most young adults diagnosed with CRC have no obvious risk factors and are classified as medium risk by current algorithms. Furthermore, because age and family history of cancer remain the cornerstones of CRC screening and risk stratification algorithms, empirical data supporting the effectiveness of screening young adults are lacking [135]. In fact, most of the landmark studies on screening involve patients over 50 years of age.

However, half of all patients with early-onset CRC are younger than 45 years old, so lowering the screening age will provide little or no benefit to these patients [136].

Ladabaum [137] reported a very interesting analysis on early colorectal cancer, participation rates and costs. By advancing the age of CRC screening participation in the United States by 5 years, it is estimated that 29,400 cases and 11,100 deaths from CRC could be averted in the next 5 years, at an incremental cost of about $10 billion and requiring nearly 11 million additional colonoscopies [137].

In comparison, achieving the goal of 80% screening participation at age 50 and above has been estimated to avert 2.5 times as many CRC cases and 3 times as many CRC deaths, at an incremental cost of about one-third and requiring 13% more colonoscopies. The author then poses a crucial question: can the new recommendation be introduced without compromising efforts to achieve high screening participation rates in older or higher-risk people and higher FIT follow-up rates [137]?

CONCLUSION

In conclusion, despite significant advancements in medical technology, increased public awareness, and robust efforts to implement colorectal cancer screening programs, it is evident that the effectiveness of such initiatives still falls short of their intended goals. This scientific paper has delved into the intricate web of challenges and limitations that contribute to the persistent ineffectiveness of current CRC screening methodologies. The multifaceted nature of colorectal cancer, its biological heterogeneity, and the dynamic progression of the disease pose substantial hurdles to early detection and

prevention. The limitations in sensitivity and specificity of screening tests, coupled with factors such as patient compliance, societal disparities, and healthcare accessibility issues, create a complex landscape that undermines the potential benefits of CRC screening. Missed lesions, overdiagnosis, interval cancers, and the failure to effectively address serrated lesions are all facets of the overarching problem of inadequate sensitivity and specificity of current screening methods. The invasive nature of certain procedures, the associated risks, and the psychological and emotional factors that deter patient participation, the delay in screening processes brought about by COVID-19 and the growing importance of early diagnosis of CRC further compound the challenge. However, amidst these challenges, there remains room for optimism. Scientific research continues to advance our understanding of the intricate mechanisms underlying colorectal cancer, leading to the development of novel screening approaches and more personalized interventions. The integration of artificial intelligence, machine learning, and risk stratification models holds promise in refining screening algorithms and identifying high-risk populations that demand tailored approaches. Moreover, collaborations between medical professionals, researchers, policymakers, and the public are fundamental to surmounting the existing barriers. Public health campaigns, culturally sensitive education, and improved patient-physician communication have the potential to bolster compliance and participation rates. In the quest to enhance the effectiveness of CRC screening, it is crucial to acknowledge that there is no one-size-fits-all solution. A multifaceted strategy encompassing technological innovation, targeted interventions, policy changes, and patient empowerment is imperative. Only through persistent dedication to research, education, and patient-centered care can the medical community hope to meaningfully impact the trajectory of colorectal cancer and ultimately save lives.

We have always to remember that screening and early diagnosis mean not only reducing mortality and improving patient prognosis, but also reducing health care costs. The positive cost impact in the lower cancer stages (stages I-II) can be explained by less invasive surgery, shorter hospital stays, fewer emergency admissions and

outpatient visits, less use of chemotherapy and biologic drugs. On the other hand, in patients with advanced colorectal cancer disease, we have to consider the costs of surgical reinterventions for recurrence or distant metastases, the high-cost drugs such as monoclonal antibodies and immunotherapy, the costs of radiotherapy, radiofrequency, TACE, and all those techniques used to chase a disease that has gotten out of control. But we have also to take in account the costs of absences from work for the patient and family members, costs of caregivers, colostomy supplies, home care and hospice admissions. Etc. The counts become difficult and especially what is difficult to count is the human material. What is certain is that spending more before, results in a significant cost reduction afterwards.

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