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EDITORIAL

Barriers in early detection of colorectal cancer and exploring potential solutions

Maryam Aleissa, Ernesto Raul Drelichman, Vijay K Mittal, Jasneet Singh Bhullar

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Abstract

This editorial discusses the literature review article by Tonini and Zanni, the paper was published in January 2024, and the authors provided very interesting conclusions regarding existing barriers to the early diagnosis of colon cancer. Many cancers do not have identifiable precursors, or there are currently no screening tests to find them. Therefore, these cancers do not have preventive screening options. Early detection is crucial for reducing mortality rates by identifying cancer at an earlier stage through screening, as opposed to no screening. Colorectal cancer develops from precancerous lesions, which can be detected early and potentially prevented and cured. Early detection leads to improved survival rates, decreased complications, and reduced healthcare expenses. This editorial provides a brief description of the biology of colon cancer, emphasizing the contrast in outcomes between early detection and late detection. We also describe screening programs around the globe and examine the barriers in each program. Finally, we explore potential future solutions to enhance inclusion in screening programs and improve patient compliance.

Key Words: Colon cancer; Rectal cancer; Early detection

Core Tip: The incidence of colon cancer is on the rise, affecting increasingly younger populations. Contributing factors include dietary changes, sedentary lifestyles, genetic predispositions, and environmental influences. To combat this trend, promoting awareness and encouraging preventive measures is crucial. Early detection of colon cancer is critical for improving survival rates and treatment outcomes. However, several barriers impede effective screening. This editorial article provides a detailed analysis of the obstacles outlined in Tonini and Zanni's publication and investigates potential strategies to enhance screening delivery to diverse populations.

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INTRODUCTION

In 2024, the American Cancer Society projects that there will be approximately 152810 newly diagnosed cases of colorectal cancer (CRC). Of the total number, 106590 (70%) cases will be diagnosed as colon cancer, while 46220 (30%) cases will be identified as rectal cancer. CRC is the second most common cause of cancer-related deaths in the United States. It is estimated that there will be 53010 deaths from CRC in 2024, which is a slight increase compared to the estimated 52550 deaths in 2023. The prevalence of CRC has been steadily increasing at an annual rate of 1% to 2% in individuals under the age of 55, a concerning pattern observed since the mid-1990s. Since the mid-2000s, the mortality rate among young individuals has been steadily increasing by approximately 1% per year. It is currently ranked as the primary cause of cancer-related mortality among males below the age of 50 and as the second most common cause among females in the same age bracket[1].

Currently, there is clear evidence that the mortality rate for patients diagnosed with colon cancer decreases significantly when the cancer is detected at an early stage, as opposed to an advanced stage[2]. The article by Tonini and Zanni [3] focuses on the screening methods currently available in practice. The study examines the barriers, such as technological and patient-related factors, that hinder the early detection process. The authors emphasize the importance of implementing strategies to improve the effectiveness of screening, as this can reduce both the incidence rate and the costs associated with advanced CRC treatment. Their analysis concludes that the ineffectiveness of early detection can be ascribed to the low precision of screening tools, the lack of compliance, the absence of screening programs in specific global regions, and the influence of the coronavirus disease 2019 (COVID-19) pandemic. However, the paper might focus narrowly on certain screening technologies without sufficiently exploring newer, promising methods like liquid biopsies or advanced artificial intelligence (AI) algorithms in patient selection. Their discussion may lack integration of multidisciplinary approaches, such as the role of genetic counseling and personalized medicine in early detection strategies. Moreover, the analysis might be predominantly focused on healthcare systems in high-income countries, without adequately addressing challenges and potential solutions applicable to low- and middle-income countries where CRC incidence is rising.

This review focuses on CRC biology, as comprehending the pathway is essential for early screening programs in various patient groups. Additionally, it is crucial for implementing novel approaches in the future. We also highlight the different methods used for CRC screening in various countries worldwide and the difficulties encountered in each system. In addition, we emphasize the barriers and inequalities in CRC screening among different demographic groups.

BIOLOGY OF COLON CANCER

CRC is a heterogeneous disease. Adenomas, which are precursors to cancer, exhibit different molecular signatures, distinct pathological characteristics, and different natural progressions. CRC can develop through different molecular pathways. The most common pathway, known as chromosomal instability (CIN), is responsible for up to 85% of cases. Another major pathway is the CpG island methylator phenotype (CIMP), which includes sporadic microsatellite instability-high (MSI-H) cancers. Lastly, there is the pure microsatellite instability (MSI) pathway, caused by a genetic mutation in a DNA mismatch repair (*MMR*) gene[4].

For cancer to develop, a series of genetic alterations must occur, regardless of the specific pathway involved. Genetic perturbations lead to the formation of successive clones, with a 'successful cancer' requiring around ten clonal events, each marked by a relative growth advantage[5]. For precancerous cells to progress, they must create an environment that allows for genetic and possibly epigenetic changes, such as genomic and epigenomic instability[6]. Understanding the molecular and genetic alterations in colon cancer allows for the identification of distinct biomarkers that can be detected in blood, stool, or tissue samples. This enables the use of non-invasive screening tests.

The CIN pathway

The majority of CRCs originate from CIN. The first abnormality in this pathway is the dysplastic aberrant crypt focus, a

microscopic mucosal lesion that appears before a polyp forms. At this stage, mutations in the adenomatous polyposis coli gene can lead to the activation of the Wnt signaling pathway. Activating mutations of the proto-oncogene KRAS, mutations in TP53, and loss of heterozygosity at chromosome 18q are necessary for the progression to larger adenomas and early carcinomas. In a small percentage of CRCs, the mutational activation of PIK3CA occurs later in the adenoma-carcinoma sequence[7]. CIN can be seen in benign adenomas and tends to increase as the tumor advances[8]. Colorectal carcinogenesis has been extensively studied through the CIN pathway and its adenoma-carcinoma sequence. This has allowed for the molecular classification of CRC and serves as a benchmark for comparing other molecular profiles. However, research has shown that there are alternative pathways through which CRC can develop.

The MSI pathway

Another form of CRC is characterized by the molecular fingerprint of the deficient *MMR* system, which is present in approximately 15% of cases[9]. MSI develops because of different genetic factors, such as mutations in *MMR* genes or epigenetic changes in the *MLH1* gene. These changes can occur in hereditary conditions such as Lynch syndrome as well as sporadic tumors. In sporadic tumors, there is often methylation of CpG islands in gene promoter regions and frequent hotspot mutations in the BRAF oncogene[6]. Tumors with MSI have unique characteristics and consistently show a more favorable prognosis compared with tumors that are microsatellite-stable[10].

The CIMP pathway

The CIMP pathway is the second most common pathway to sporadic CRCs, accounting for approximately 15% of those cases[11]. The CIMP pathway provides the epigenetic instability necessary for sporadic cancers to methylate the promoter regions of, and thus epigenetically inactivate the expression of, key tumor suppressor genes such as *MLH1*[11]. CIMP-positive CRCs are characterized by a well-defined cluster of clinicopathological features, including proximal location and a gender and age risk bias for development in older women[12]. Classically, CIMP-positive CRCs that are MSI-H share characteristics, specifically a relatively good prognosis, but in the absence of MSI-H, the CIMP-positive phenotype is characterized by more advanced pathology, poorer clinical outcomes, and an absence of tumor-infiltrating lymphocytes [12]. CIMP-positive CRCs differ from the other pathways with respect to their precursor lesions. In contrast to CRCs developing *via* the CIN pathway, and also in hereditary non-polyposis CRC, which originate from adenomatous polyps [4], sessile serrated adenomas are the chief pathological precursor in the CIMP pathway[8].

IMPORTANCE OF EARLY SCREENING IN MORTALITY REDUCTION

Throughout the years, there has been a notable improvement in the 5-year survival rate for CRC. It was reported as 50% in the mid-1970s, compared with 65% from 2012 to 2018 in the United States. This improvement is due to advancements in clinical practice, imaging technology, infection control, surgical techniques, and cancer treatments. These advancements have led to enhanced detection, staging, and treatment of CRC over the long term. The stage at diagnosis remains the crucial factor in determining survival rates. The 5-year relative survival rate reaches up to 91% for stage I disease, while it drops as low as 14% for stage IV disease with distant metastasis[13]. Recent research showed that surveillance-compliant patients with polyps (but no cancer) at screening have a long-term CRC risk following polypectomy similar to that of patients without polyps[2,14]. However, 20%-30% of screen-detected CRCs present with lymph nodes or distant metastasis, detrimentally affecting prognosis[1,13], highlighting the significance of early screening and, above all, the necessity of consistent surveillance. In 2021, the United States Preventive Services Task Force revised their guidelines, lowering the recommended age for CRC screening from 50 to 45 for average-risk individuals [15]. Starting screening at an earlier age suggests a focus on preventing cancer since there will likely be fewer cases of CRC in younger individuals, especially those under 50 years old.

SCREENING PROGRAMS AROUND THE WORLD AND BARRIERS

There are currently two prominent screening models worldwide for CRC: Systematic screening and opportunistic screening. Systematic screening encompasses the entire population in a specific area and necessitates the involvement of specialized institutions and professionals, along with substantial resources. This type of screening is conducted on a population-wide scale. Opportunistic screening focuses on individuals who are seeking medical treatment and aims to screen for specific diseases during their treatment or examination. Many European countries have implemented systematic screening programs that involve fecal occult blood tests (FOBTs) and subsequent colonoscopy. Studies have shown that these programs decrease the mortality of colon cancer; however, the participation rate for these protocols remains low. In addition, these tests often yield a high number of false positive results[16,17]. On the other hand, opportunistic screening eliminates the need for additional examinations, despite a slightly higher cost. A major limitation of opportunistic screening is that it only targets individuals who actively seek medical attention or undergo health examinations, leaving out potential patients who do not seek medical treatment. It is important to note that the screening process may not be able to reach certain high-risk populations, which can reduce its overall effectiveness. A recent review article found that organized screening programs have higher rates of participation and lower rates of non-compliance with follow-up testing after a positive screen compared with opportunistic screening[18]. To successfully implement a systematic screening program, it is essential to identify suitable screening methods that are accessible to the entire

population, cost-effective, and culturally accepted by the target population. Monitoring strategies should be implemented for patients who have tested positive and those who are at higher risk. To date, there is no universally agreed-upon screening consensus on which method to choose or which program is the most effective. In Europe, a fecal immunochemical test (FIT) is a systematic stool sample screening test. Studies have shown that the rate of CRC detection was similar when four rounds of FIT were used in alternating years compared with a single flexible sigmoidoscopy and single colonoscopy. Despite its generally high sensitivity for detecting CRC, FIT may fail to detect approximately one-third of stage I cases. According to the manufacturer's recommended threshold, FIT showed a sensitivity of 52% for detecting T1 cancers, 79% for T2 tumors, 93% for T3 tumors, and 84% for T4 tumors[19]. Research has shown that the effectiveness of FIT in detecting tumors in the proximal colon is lower than in the distal colon[20]. Understanding the limitations of the FIT test is essential when advising patients and ensuring the success of screening programs.

The colonoscopy is the most common method used in areas where opportunistic screening is implemented; however, the compliance rate is lower compared to other test methods. This is due to multiple barriers, including financial, cultural, and resource-related factors. Moreover, over the past decade, there has been growing evidence of significant variability in the proficiency of endoscopists to identify and remove polyps effectively. Patients who undergo colonoscopy performed by an endoscopist with a high adenoma detection rate have a significantly reduced risk of developing CRC compared to those examined by an endoscopist with a low detection rate[21,22]. Consequently, in order to establish colonoscopy as a screening program, it is necessary to implement rigorous quality assurance programs that encompass training, supervision, and auditing.

Surveillance protocols following polyp removal differ across regions; the United States implements more frequent and shorter intervals for surveillance, while Europe opts for less surveillance among a smaller population[23]. It is important to note that existing surveillance recommendations are derived from low-quality evidence relying on surrogate endpoints like recurrent adenomas and expert opinion.

There is potential for practitioners to enhance the visibility of opportunistic screening programs. This can be achieved through increased awareness regarding the importance of screening among both patients and physicians. In one study, 81% of patients who tested positive for FOBT were willing to undergo a subsequent colonoscopy after consulting with physicians and receiving their advice[24]. Currently, the majority of CRC screening efforts are conducted by community physicians and other primary healthcare personnel, who often have limited expertise and training in the field. Research indicates that community health providers in the United States frequently rely on patients' preferences when selecting CRC screening programs, rather than adhering to established national screening guidelines[25]. Thus, dissemination of knowledge among healthcare professionals regarding the significance of screening, coupled with the establishment of dedicated organizations tasked with providing guidance and oversight for CRC screening, could potentially facilitate the implementation and enforcement of screening protocols by clinicians.

BARRIERS AND DISPARITIES OF SCREENING PROGRAM AROUND THE WORLD

The barriers to implementing screening programs are not limited to developing countries, in the United States, multiple disparities and barriers hinder the availability of fair screening and treatment for various groups, including Black Americans, American Indians/Alaska Natives, and underserved Americans. The disease disproportionately impacts these groups. African Americans have a 15% higher likelihood of developing CRC and a 35% higher likelihood of mortality. A lower proportion of Hispanic Americans undergo CRC screening, with just over 50% of eligible individuals being screened. Widespread social disapproval, discomfort with screening techniques, lack of trust in healthcare institutions, and prejudice/discrimination in the healthcare system contribute to these disparities. Individuals from lower socioeconomic backgrounds, regardless of their racial background, face significantly increased risks of receiving inadequate treatment and experiencing delays in care. Financial barriers are significant factors that hinder patients from undergoing screening. Individuals with Medicare and private insurance exhibit a higher likelihood of undergoing screening (76.3%) compared to those with Medicare alone (68.8%) or Medicare and Medicaid (65.2%)[20]. In the United States, Section 4104 of the Patient Protection and Affordable Care Act waived previous cost-sharing requirements for many Medicare-covered preventive services. A study conducted between 2015 and 2023 showed a 20% short-term and 25% long-term increase in the probability of undergoing a mammogram in the four years following the implementation of the 1997 deductible waiver. The potential efficacy of eliminating cost-sharing as a strategy for enhancing the utilization of preventive services is worth considering. Medicare beneficiaries faced unexpected financial charges for a significant period when their screening colonoscopy involved polyp removal categorized as therapeutic. Recent research revealed that 48.2% of patients with commercial insurance and 77.9% of patients with Medicare coverage shared the cost of CRC screening[26]. Cost-sharing contributes to disparities in CRC outcomes based on race, ethnicity, and socioeconomic status. In 2020, the United States Congress took action to address a financial loophole by gradually eliminating coinsurance from 2022 to 2030, potentially enhancing patient access to colonoscopy procedures. The primary obstacle identified in developing countries is the scarcity of resources to implement comprehensive programs, including limited access to colonoscopy procedures and a shortage of trained healthcare professionals[27]. In developing countries where CRC screening methods are established, challenges such as insufficient knowledge about CRC, limitations within the healthcare system, cultural factors, and sociodemographic disparities persist. To address these issues, we recommend adopting more personalized approaches. This includes studying existing barriers in specific populations, providing FITs, offering additional training for healthcare practitioners, and expanding educational campaigns targeting patients, physicians, and community leaders. This comprehensive strategy aims to improve screening uptake and effectiveness by addressing both systemic and individual-level barriers.

THE PREVENTIVE MEASUREMENT CULTURE AND ITS ROLE IN SCREENING ADHERENCE

Despite the proven effectiveness of CRC screening, the level of compliance continues to be relatively low, with rates varying from 19% in Croatia and the Czech Republic to 69% in the Basque region of Spain[28]. Approximately 35% of the eligible population in the United States is not currently undergoing screening[29]. In the early 1950s, the Health Belief Model (HBM) was formulated to comprehend the reasons behind individuals' reluctance to participate in disease prevention strategies or undergo screening tests for early disease detection. It consists of perceived benefits, perceived susceptibility, cues to action, self-efficacy, perceived severity, and perceived barriers. HBMs have been extensively employed in the field of breast cancer screening research. Numerous studies have demonstrated a significant correlation between adherence to mammography in female populations and various factors, including a heightened perception of susceptibility to breast cancer, a greater perception of the benefits of screening, reduced barriers to undergoing screening, and the presence of cues to action such as recommendations from healthcare professionals[30]. A systematic review article on CRC screening, involving a sample of 21010 participants from 18 different countries, proposed that the HBM can provide valuable insights into the factors that promote or hinder CRC screening. The review revealed that cues to action consistently correlated with screening adherence. Notably, the most prevalent cue identified across studies was the presence of a physician's recommendation to screen, as well as advice from family or friends. Perceived obstacles were primarily due to limited healthcare accessibility and concerns regarding the financial implications of screening. Psychosocial factors also exerted a substantial influence, such as feelings of embarrassment associated with undergoing screening and fear of outcomes[31]. Other well-studied factors contributing to poor patient compliance include lack of knowledge, fatalism, and low literacy[31].

EMERGING SCREENING TOOLS AND FUTURE TESTS MIGHT BE THE SOLUTION TO CURRENT BARRIERS

A recently developed multi-target DNA test has been introduced to the market, demonstrating enhanced sensitivity compared to the FIT test for diagnosing both adenoma and CRC. The United States Food and Drug Administration has approved this test only for average-risk patients who are asymptomatic and aged 45 years and older. Patients with ongoing melena or hematochezia, a personal history of colorectal adenoma or inflammatory bowel disease, a family history of colorectal adenoma in a first-degree relative diagnosed at any age, or heritable cancer syndromes should not be offered this test[32]. We agree with the authors that the COVID-19 pandemic has presented various obstacles for prompt CRC screening. These challenges can be effectively addressed by carefully deliberating and engaging in informed conversations with patients regarding all accessible, guideline-endorsed alternatives. Additionally, fostering effective communication between primary and specialty care providers is crucial to ensure proper follow-up for positive screening test outcomes. The home-based test is supported by compelling scientific data and increasing practical experience[33]. Other stool-based studies and liquid biopsies analyzing circulating blood DNA have yet to achieve the necessary sensitivity and specificity standards for effective population-wide screening. Despite this, it is recommended to continue developing these biomarkers as part of a comprehensive panel that includes serum protein biomarkers. Current research efforts are focused on identifying screening markers through the analysis of microRNA in feces and blood, as well as the gut microbiome[34]. The primary objective is to determine the most effective combination of molecular biomarkers to optimize screening sensitivity and specificity. The development of non-invasive and cost-effective methods for CRC screening will be crucial in enhancing early detection and improving patient outcomes.

We also agree with the authors regarding the role of AI in enhancing early detection. Using AI in healthcare practice should promote more preventive measures by tracking and identifying patients at high risk and setting reminders for both clinical providers and patients. Currently, AI is used in colonoscopy to enhance the identification and characterization of polyps, thereby improving patient outcomes[35]. AI models can also serve as a valuable tool for training junior endoscopists, acting as a 'second observer' during colonoscopy procedures. AI-based applications on mobile devices, such as the CRC Awareness Application (ColorAppTM), have the potential to enhance community education and engagement in CRC screening programs[36]. Additionally, the use of AI for reviewing images from second-generation colon capsule endoscopy shows promise.

CONCLUSION

CRC screening remains an unmet need due to various barriers, including insufficient education among healthcare providers, patient-related factors, systemic issues, and limitations in current diagnostic methods. Addressing these challenges is crucial for improving CRC screening rates and outcomes, similar to the success achieved with cervical and breast cancer screenings. Implementing strategies that enhance provider education, increase patient awareness, and improve healthcare systems, particularly within the framework of the Health Promotion Model, could significantly advance CRC early detection efforts. Understanding the biology of CRC is crucial for developing screening methods that surpass the limitations of current tools. Although liquid biopsy has yet to achieve significant sensitivity and specificity, ongoing research in this area is highly encouraged to enhance its effectiveness.

FOOTNOTES

Author contributions: Aleissa M wrote the paper; Drelichman ER contributed in writing the paper; Mittal VK contributed in writing the paper; Bhullar JS design research, wrote the paper. Aleissa M is the primary corresponding author, has undertaken the majority of the research work, including designing the paper, reviewing resources, and manuscript preparation. Aleissa M is responsible for handling all communications with the journal, managing the submission process, and addressing any editorial and reviewer comments. Bhullar JS is the senior corresponding author. He will be available to answer any questions from readers, leveraging their extensive expertise to provide comprehensive responses and further insights. We believe that this dual corresponding author arrangement will enhance the clarity and efficiency of our interactions with both the journal and the broader research community.

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