State of the art paper

Colorectal cancer screening challenges in Saudi Arabia. A comprehensive review article

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Submitted: 6 July 2022
Accepted: 4 September 2022

Arch Med Sci Civil Dis 2022; 7: e24–e32
DOI: https://doi.org/10.5114/amscd.2022.119965

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Abstract

Colorectal cancer (CRC) is the leading cause of cancer-related deaths in Saudi Arabia and usually presents late in patients, who become symptomatic in advanced stages; thus, most cases of CRC in Saudi Arabia have poor outcomes. Saudi Arabia currently follows published guidelines and recommends screening for CRC because early diagnosis is critical; the Saudi Arabian healthcare system runs a program "Colorecal Cancer Early Detection" that has been rolled out in a gradual fashion. A screening program would aim to find individuals with asymptomatic CRC, educate patients, and streamline the process of screening for medium- and high-risk people. Currently, the Saudi Arabian population present minimal knowledge regarding CRC, the benefits of screening, and the importance of regular screening. The Saudi population is heavily dependent on physician recommendations for CRC screening, but physicians working in primary healthcare rarely recommend screening for CRC even in patients who have risk factors. The screening program for CRC in Saudi Arabia is cost effective. Public education is necessary along with expanded colonoscopy resources to continue enhance citizen participation and overcome the barriers of CRC screening such as physician recommendation and female gender low participation.

Key words: colorectal cancer screening, guidelines, early-onset colorectal cancer, late-onset colorectal cancer, patient participation.

Introduction

Colorectal carcinoma (CRC) is the most frequent cancer that occurs in people in the Kingdom of Saudi Arabia (KSA) [1, 2]. While breast cancer is the most common cancer occurring in women, when considering both sexes, the most frequent cancer is CRC with incidence rate of 7,6% for colon cancer and 6.6% for rectum in 2020 [1]. Cancer of the rectum and colon cause cancer deaths at rates of 6.7% and 8.3%, respectively, of all cancers, and they account for a total of 15% of all cancer deaths, amounting to almost 2000 deaths in the KSA in a retrospective study before 2017 based on national registry [1]. Recently, the incidence of CRC in 2020 was 14.4% in both sexes (colon: 7.6% and rectum: 6.4%) with mortality in colon 8.3% and rectum: 6.7% and gender distribution

in males 19.3% and in females 9.2% [1]. With the increase in risk factors over time, the incidence of early-onset CRC has increased [2]. In the KSA, the risk of adenoma detection rate also increases with age [3, 4], as shown recently in a study by Karsenti *et al.* in France including data from patients aged below 50 years [5]. In this study the adenoma detection rate (ADR) and advanced neoplasia detection rate (ANDR) were significant higher in the group aged 45–49 years compared to the group aged 40–44 years and significantly lower compared to group aged 50–54 years. In the KSA there limited data available on the adenoma detection rate or even advanced neoplasia during colonoscopy under 50 years of age, as in many other countries. Few data are currently available for the age group below 50 years old. However, Alyabsi *et al.* showed that incidence rates of both early- and late-onset CRC are increasing in Saudi Arabia [1] in contrast to the drop of incidence of late-onset CRC in other countries [2]. According to a retrospective controlled study in 2014, the prevalence of CRC was calculated as 0.72%, with colonoscopy and biopsy being used as the main diagnostic methods [3]. The age-standardized colorectal cancer incidence rates (95% CI) during the years 2012–2016 by gender in Saudi Arabia were 3.57 (3.43, 3.71) in the group of age < 50 years and 16.97 (16.41, 17.54) in the age group > 50 years. The geographic spread is shown in Table I. The highest rates among early-onset CRC (EOCRC) (< 50) age groups were in those in the age group 40–49 years and were even higher than those 50–54 and 55–59 years of age, with a female predominance. Regarding EOCRC, similar results have been shown in studies from Europe [6], the USA [7], and the UAE [8].

Multiple known risk factors for the development of CRC, common for early- or late-onset CRC, are known and can be categorized broadly as genetic, inflammatory bowel disease (IBD), excess body weight, cigarette smoking, lack of physical activity, red and processed meat consumption, high fructose corn syrup consumption, antibiotics, and changes in the microbiome [9]. However, no known studies regarding specific risk factors for Saudi Arabians have been published. Population-specific studies would make assessing the possible risk factors easier and help identify candidates who would benefit from screening.

The genetics of CRC warrants in-depth discussion because certain heritable conditions, such as familiar adenomatous polyposis (FAP) or Lynch syndrome, are potential causes for early-onset

Table I. Saudi Arabia 2016: Geographic dispersion of age-standardized frequency rates per 105 individuals [1]

Area	Age-standardized frequency rate (per 10^5 individuals)
Riyadh	16.45
Eastern	15.45
Al-Qasim	10.65
'Asir	10.55
Makkha	9.85
Al Madhina	9.45
Al Jawf	9.05
Ha'ill	7.75
Northern Frontier	7.5
Tabuk	6
Al Baha	5.1
Jizan	3.5
Najran	3.4

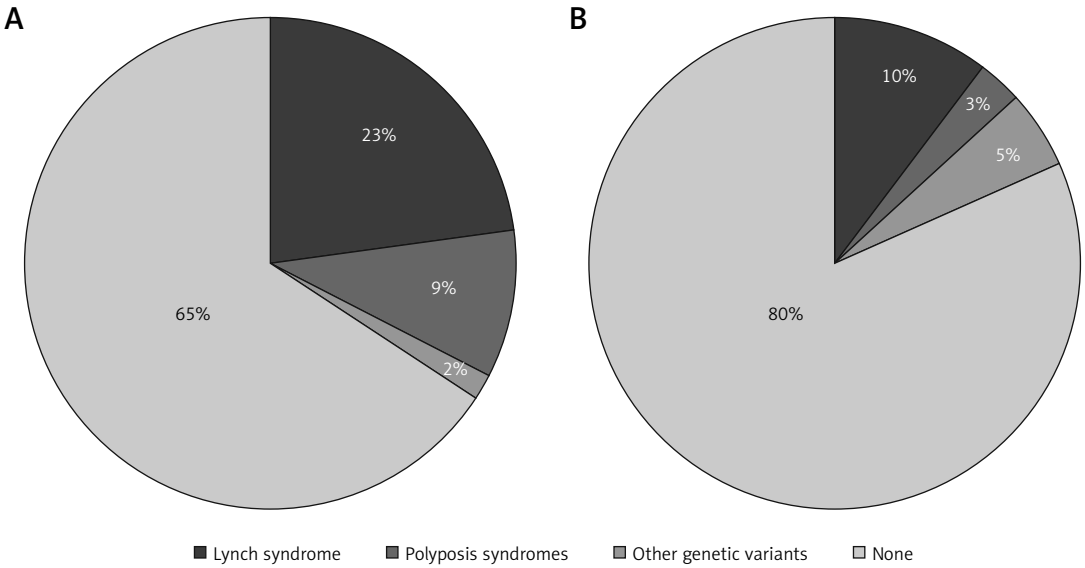

Figure 1. Large share of germline variants in age < 35 (**A**) and < 50 years (**B**) [12]

Table II. Genes with pathogenic variants found during colorectal cancer (CRC) diagnosis [12]

Lynch syndrome	Polyposis syndrome
MLH1	APC
MSH2	MUTYH
MSH6	SMAD4
PMS2	BMPR1A
	PTEN
	POLE

CRC; almost half of the cases have molecular features and are inherited (18%)/familial (28%) [10]. A thesis study done at King Fahad Specialist Hospital, Dammam, King Khaled University Hospital and King Fahad University Hospital, in which genetic testing was carried out, concluded that the prevalence of Lynch syndrome is significantly higher than in equivalent West Australian patients [11]. Early-onset CRC below the age of 35 years constitutes a significantly high proportion of patients who show Lynch syndrome and other polyposis syndromes, such as adenomatous polyposis coli, mutY DNA glycosylase, depleted in pancreatic cancer 4 (APC, MUTYH, and SMAD4, respectively) mutations [12]. Therefore, a clear benefit of genetic-based screening can be found, and the requirement of recommending multigene panel testing will have obvious benefits especially in initiating EO-CRC (< 50 years old) screening and to identify previvors (Figure 1, Table II).

A review and meta-analysis study published in 2021 describes the risk factors of early-onset CRC cancer, as shown in Table III [13].

With the increase in the incidence of cases of CRC, the need for a screening program is paramount. However, certain challenges are found within the Saudi population in addition to its healthcare system that challenge the capability of the health sector to undertake successful screening programs.

The purpose of a screening program is to reveal the asymptomatic population with a certain disease through the use of an effective investigation, which allows physicians to detect and treat the disease before it advances, thus improving the prognosis of such patients and decreasing the mortality of such conditions. Removal of neoplastic polyps such as adenomas, i.e. the precancerous polyps in the colon during colonoscopy, is the cornerstone of CRC screening. The adenoma detection rate is the proportion of screening colonoscopies where at least one adenoma is found; it is a measure of colonoscopy performance quality. Technology has been used in colorectal cancer screening to improve adenoma detection such as mechanical technology (Endocuff) and optical,

Table III. Risk factors for early-onset CRC [13]

Risk factor	Relative risk
First-degree relative	4.21
Hyperlipidaemia	1.62
Obesity	1.54
Alcohol consumption (high versus non-drinker)	1.71
Other risk factors	
1. Hypertension	
2. Metabolic syndrome	
3. Ulcerative colitis	
4. Chronic kidney disease	
5. Dietary factors	
6. Sedentary behaviour	
7. Occupational exposure to organic dusts	

such as as magnification, endocytoscopy, and virtual chromoendoscopy, and recently artificial intelligence [14, 15].

Saudi Arabia is a nation that is significantly affected by CRC and will benefit from screening for CRC. The challenges of screening for CRC are discussed subsequently in this review.

Colon cancer early detection program

Currently, there is a nationwide screening program present in Saudi Arabia for CRC [16, 17]. CRC screening in Saudi Arabia is cost effective as noted in a recent cost-effective analysis [18]. However, many barriers to screening have been reported [19] such as a lack of physician recommendation was the most commonly reported general barrier and female gender low participation. Investigation of CRC awareness among healthy individuals in SA, Zubaidi et al. (2015), strongly recommended implementing a countrywide policy including an education/screening program to improve CRC awareness [20]. Reasons included misconceptions regarding universally accepted screening protocols, atypical symptoms, and general awareness on CRC. However, this approach has been challenged by a national survey that found that it is more complex than just knowledge and that there may be other barriers that need to be addressed [21]. According to a publication by the Saudi Arabian Ministry of Health (MOH), and only 9% of cases of colorectal cancer are detected in their early stages [22]. However, the need for screening has been shown in many studies within the KSA [23]. One of the reasons for the immediate need for a screening system for CRC within the KSA is the increase in the incidence of early-onset CRC, particularly in women, and the poor prognosis associated with it being found at late stages [24].

Studies have also found that not only is early-onset CRC on the rise but there is also an increase in the incidence of late-onset CRC [1]. CRC is the most common cancer as of 2020 within the KSA; thus, this cancer warrants a screening program that is available throughout the country. Research across the decades has shown that screening for colorectal cancer by any method reduces the overall mortality caused by CRC [25–27].

The Saudi MOH has launched a project entitled "Colon Cancer Early Detection", which aims to reduce CRC-related mortality and improve the survival and prognosis through early detection of colon cancer in patients. It aims to do this by catering to patients registered at healthcare centres and classifying them according to their risk: either moderate or high. The project states 2 main investigations; namely, the detection of faecal occult blood and total colonoscopy [17]. Even though projects such as this exist in Saudi Arabia, a prospective study published in 2017 reported that the country does not have a countrywide policy for colorectal cancer screening. The study also recognizes that an effective screening program would need a multidisciplinary approach involving educational programs, significant financial backing, and logistical resources to conduct it successfully [28].

The lack of a comprehensive screening program coupled with increasing incidence rates of CRC in Saudi Arabia is the reason why a comprehensive screening program should be established. Furthermore, in light of current evidence that clearly shows that early screening leads to a reduction in mortality, the Saudi population vulnerable to CRC would benefit from early detection, treatment, and analysis of trends in the Saudi Arabian population, which would help specialists design tailored, individualized guidelines.

Screening programs in other nations

CRC is a major cause of cancer death in many developed nations. In the United States (US) it is the second leading cause of cancer-related deaths. Hence, for early detection and treatment of CRC, the Centers for Disease Control and Prevention (CDC) of the US has launched the Colorectal Cancer Control Program, which aims to increase screening rates among people who are at moderate to high risk of CRC. It went through an initial pilot phase from 2005 to 2009, and then, with funding approved by the US Congress, has been launched throughout the country. The program uses evidence-based methods of reminding healthcare providers and patients of when screening becomes appropriate and by making it available to them, simplifying paperwork and documentation, and even offering transport and escorts to patients undergoing colonoscopies [29]. While the Saudi Arabian MOH website offers locations for anyone searching to obtain screening, it is unlikely that most citizens pursue screening without a physician's recommendation, which is presently a challenge to the Saudi Arabian healthcare sector and will be discussed below.

Patient-related factors for screening compliance

The Saudi Arabian population's knowledge about cancer factors into their willingness to participate in screening programs. Many Saudi Arabians assume that screening for cancer involves running lab tests on blood samples, with about 20% of individuals in a study assuming that the diagnosis of cancer can be made solely by a physician. The same study also mentions that out of the research participants, only 55% were willing to participate in early cancer screening [30]. Further studies assessing the knowledge of teachers in Saudi Arabia regarding colorectal cancer found that 39% of male teachers and 42% of female teachers were unaware of the screening methods involved in colorectal cancer [31]. A study assessing the knowledge of CRC screening in 402 participants concluded that patients of higher age and higher educational status were more knowledgeable about CRC and its screening methods and believed that screening before the disease reaches an advanced stage is beneficial [32].

In a local study, Saudis showed a preference for certain screening modalities over others. In these studied a descending order of preference was found: (1) computed tomography colonography, (2) stool-based tests and colonoscopy, and then (3) flexible sigmoidoscopy [23].

A poor participation rate in CRC screening compared to screening for other types of cancer, such as breast cancer, for which patients undergo mammography, was found. The key to the effectiveness of any screening program is a high participation rate. Poor participation rates even with established screening systems fail to improve the mortality and prognosis of patients who present with later stages of CRC. A review study identified several barriers to CRC screening adherence; namely, being female, younger individuals, low level of education, lower-income, and ethnic minorities [33].

Most studies conclude that there is a lack of knowledge among the Saudi population about the leading cause of cancer-related deaths, which is CRC. This lack of knowledge affects the compliance of patients who wish to screen themselves and leaves them heavily dependent the recommendation of a physician.

Physician-related factors for screening recommendations

While physicians understand that screening for CRC is important in early treatment and reducing mortality, more than half of physicians in this study did not practice CRC screening in Saudi Arabian clinics [34]. However, it is important to note that this study assessed the views of only 130 family clinic doctors, of whom 39 were board-certified family physicians. The study also assessed the knowledge possessed by these doctors and concluded that doctors that knew more about CRC and its screening modalities were more likely to recommend CRC screening than those who did not have comparable knowledge. In addition to challenges specific to CRC, the physician shortage that affects every nation around the globe also affects Saudi Arabia. Currently, according to the most recent literature, there are 3 doctors for every 10,000 people in Saudi Arabia [35]. The same review also recognizes that the primary care sector of Saudi Arabia needs expansion and development for which most screenings and referrals for screening ideally take place. Another study concluded that a greater number of specialist doctors in primary health clinics results in a higher rate of diagnosis of colorectal cancer [36]. The overburdened primary healthcare system is one of the challenges that implementation of CRC screening faces because an efficient and active primary care system is essential for successful establishment of screening tests [37]. Studies show that physician recommendations to obtain screening is the major facilitator for patients to undergo screening for CRC, while at the same time, not receiving a recommendation to undergo screening is its biggest obstacle [17, 28–38].

A lack of understanding regarding CRC and screening methods among medical students studying in Saudi Arabia was found, in which more than half of the research participants did not have a good understanding [39]. This issue could be easily amended by means of a screening program that includes medical education for patients, doctors, and students in Saudi Arabia.

KSA healthcare system

Saudi Arabia funds free healthcare services for all citizens at every level, which makes healthcare accessible to all Saudi citizens [40]. Hence, implementation of a screening program for CRC may be done as a part of the duties of the MOH. Maintaining databases and research projects concerning the findings discovered during the screening program may be the responsibility of these offices.

Existing screening methods in Saudi Arabia

The Saudi Arabian Ministry of health recommends 2 main screening tests on its information page regarding colorectal cancer: faecal occult blood testing and colonoscopy. It recommends faecal occult blood as the screening test to be used between the ages of 45 and 75 years and colonoscopy to be used for screening if the patient is at high risk or has a positive faecal occult blood test result [40]. The website also offers information on clinics that allow for screening and their locations on the same webpage.

Screening guidelines for CRC were published in Saudi Arabia in 2015, in which the general asymptomatic population was targeted. Screening should begin at age 45 years and continue up to age 70 years, and the main modalities described are colonoscopy every 10 years, sigmoidoscopy every 5 years, and a faecal immunochemical test-FIT annually [24].

Screening tests in brief: positives and negatives

The use of colonoscopy as a diagnostic tool is considered the gold standard because it also enables retrieval of tissue biopsy for histological confirmation and molecular profiling in addition to visualizing most, if not all, lesions [41]. However, the effectiveness of a colonoscopy depends heavily on factors related to the patient complying with the screening technique and bowel preparation, and with the specialist who performs the colonoscopy. Studies have shown that gastroenterologists are the most effective at preventing CRC by performing colonoscopies [42]. Furthermore, endoscopists performing the procedure should have fulfilled minimum training benchmarks as found in the US when screening patients ≥ 50 years of age [42]. Overall, a review study discussing the use of colonoscopy in the detection of CRC described 94.7% sensitivity across 49 studies encompassing 11,151 patients [43].

Other endoscopic methods, such as flexible sigmoidoscopy and colon capsule endoscopy, can also be used.

Various methods for endoscopic visualization include chemical methods, such as FIT for blood, the Guaiac faecal occult blood test (gFOBT), and multi-target stool DNA testing. Radiological screening for colorectal cancer consists of CT-colonography [44].

Considering the number of tests that are available globally, the Saudi population would benefit from a variety of options based on their needs. These options would make screening more accessible, less daunting, and more likely to be followed by the patient.

Two types of faecal occult blood test are in use: the faecal immunochemical test for blood (FIT) and the Guaiac faecal occult blood test. A large study in Taiwan in which CRC screening was performed

in the population demonstrated that a statistically significant reduction in mortality of patients who underwent one to three rounds of FIT screening biannually was found compared to those who did not undergo screening [26, 45]. Studies concerning the gFOBT describe mixed results, with one study showing that gFOBT can lead to a reduction in CRC-related mortality even after 30 years, but not all-cause mortality [46]. Another study with 68,000 participants in Göteborg concluded that gFOBT can lead to a significant reduction in mortality [47]. The issue is, however, that because of the nature of the test, gFOBT requires 3 samples from 3 consecutive bowel movements, and many causes of false positives exist in addition to requiring some dietary modifications while the sample for the test is being obtained [43]. FIT requires no such dietary modifications and requires one sample only [44]. There are no major risks to the patient when performing these tests because both are non-invasive [44].

Radiological methods, such as CT-colonography, are also effective screening modalities, and their only major disadvantage is the patient's exposure to radiation. In meta-analysis studies it was estimated that CT had a sensitivity of 83% to 88% for detecting large polyps in asymptomatic patients [48]. The United States Prevention Service Taskforce (USPSTF) guidelines also describe studies that report good sensitivity in the detection of polyps > 10 mm by CT-colonography [26].

Multigene target stool DNA tests are done in conjunction with FIT as a screening method for CRC. These tests involve the collection of a large stool sample with the intention of detecting DNA mutations in the lining of colon cells that are indicative of CRC. DNA testing requires no dietary or laxative preparations, and the sample can be collected at home. No randomized trials on the effectiveness of this test on screening are being done; however, when performed alongside FIT, its sensitivity was found to improve [44].

Established screening guidelines for CRC globally

Looking at established guidelines worldwide, theUSPSTF categorizes screening into three grades based on the net benefit to patients as described below:

(1) Grade A screening recommends screening of average-risk men and women between ages 50 and 75,
(2) Grade B screening recommends screening average-risk men and women starting at age 45, and
(3) Grade C screening involves and an individualized decision based on other comorbidities present to screen patients between the ages of 76 and 85 years. The screening modalities in use as per the USPSTF recommendations include high-sensitivity gFOBT yearly, stool FIT yearly, stool DNA-FIT every 1 to 3 years, CT colonography and flexible sigmoidoscopy every 5 years, and flexible sigmoidoscopy every 10 years, an annual FIT, and colonoscopy every decade [49].

The American College of Gastroenterology (ACG) screening guidelines describe similar guidelines in which screening should begin at age 45 to 49 years, with individualized screening after 75 years, as shown in Table IV. The main recommended screening modalities are FIT and colonoscopy [50].

Figure 2 shows a flowchart representing the recommendations according to the ACG guide-

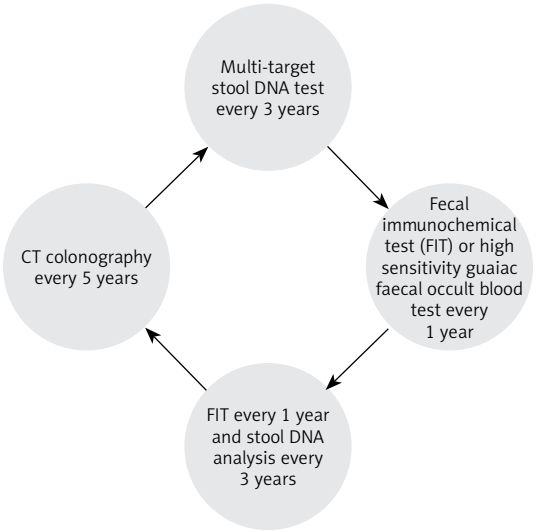

Figure 2. Recommended screening strategies for CRC screening: non-invasive tests, available options [49]

Table IV. American College of Gastroenterology Clinical Guidelines: Colorectal cancer screening 2021 [50]

1	Recommends colorectal cancer screening in average-risk individuals, aged between 50 and 75 years to decrease the incidence of advanced stages of CRC and to reduce the mortality from CRC
2	Suggests colorectal cancer screening in average-risk individuals aged between 40 and 49 years to reduce the incidence of advanced stages of CRC and to reduce the mortality from CRC
3	Decide to screen after 75 years of age on an individualized basis after considering life expectancy and disadvantages and possible risks of invasive screening methods
4	Colonoscopy and faecal immunochemical testing as the major screening methods for colorectal cancer screening

lines and a depiction of the different screening modalities if a patient is unable or unwilling to undergo a colonoscopy.

The 2018 American Cancer Society (ACS) screening guidelines for CRC recommend initiating screening at age 45 years and individualizing screening after 75 years old based on the patient's remaining lifespan and choice. The recommends modalities similar to the current USPTF guidelines.

All abovementioned CRC screening guidelines based on ACS (2018), USPSTF (2021), and the ACG (2021) point towards initiating screening at the age of 45 years in a patient of average risk.

More research must be done on the incidence of early-onset CRC in patients who are < 45 years of age, to see if screening among Saudis should begin earlier. As a safeguard, discussions should be undertaken to consider the beginning of screening at age 35 years for patients who present a risk of genetically based familial cancer syndromes, such as individuals with Lynch syndrome and APC mutations. Separate guidelines should be established that recommend multigene panel testing for individuals with this genetic risk.

A novel approach to CRC cancer screening by artificial intelligence

Artificial intelligence (AI) is used alongside many screening modalities for CRC screening, and its role in improving the sensitivity of existing screening systems is being researched throughout the world. A study assessing the impact of artificial intelligence in CRC screening in Sub-Saharan Africa mentions that CRC screening is well suited to be coupled together with AI technology, because if CRC is detected early, it can be completely cured, and because it can be effectively coupled to assess the risk of having asymptomatic CRC by assessing the results of various blood based and faecal occult blood-based investigations. It can also be altered and changed according to specific local needs. In the case of Sub-Saharan Africa, CRC screening is immensely difficult to perform on a large scale, due to a lack of endoscopists, pathologists, and the necessary chemical reagents needed to investigate biopsies [51].

Artificial intelligence, as well as having many uses in disadvantaged locations such as Sub-Saharan Africa, has also been incorporated into improving the accuracy of multiple modalities of CRC screening.

Colonoscopy assisted by AI has, in one study, shown improved effectiveness in detecting small hyperplastic polyps compared to without AI. This means that it can help establish patients at risk in preliminary screening colonoscopies and assist in the setting up of personalized screening regimens depending on the findings of hyperplastic polyps. CT colonography, capsule endoscopy, and faecal occult blood testing have all benefited in terms of improving accuracy. Studies using computer-aided systems have shown that AI can detect even flat lesions of CRC in AI-assisted CT colonography [52].

Conclusions

The establishment of a CRC screening program is a necessity in Saudi Arabia. While guidelines for screening exist, a requirement for an update and tailorized guidelines based on an unusually high prevalence of early-onset CRC is necessary. With its high incidence and prevalence and its poor prognosis due to late presentation, individuals with CRC would benefit greatly from the early detection provided by screening, improving mortality rates. The screening program should be multifaceted and involve both patient and physician education, and training of physicians in identifying risk factors and directing patients to undergo CRC screening. The provision of a broad range of screening modalities for patients will improve adherence and compliance to screening programs and increase participation in such programs in the Saudi population.

Conflict of interest

The authors declare no conflict of interest.

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