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# The Current Guidelines and Recommended Protocols for Screening Colorectal Cancer

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**ABSTRACT**

Colorectal cancer (CRC) is a major cancer with significant morbidity and mortality among men and women, particularly in the Western countries. With more countries adopting a western lifestyle, the burden of CRC continues to grow across the globe. Coinciding with the alarming rise in the incidence of CRC, there is a pressing need for a reciprocal concerted effort to underpin the significance of CRC screening strategies and to modernize the cutting-edge CRC screening modalities. Depending on the cancer subsite distribution, available resources and expertise, and geographic representation of cancer, a myriad of CRC screening techniques are employed worldwide. Colonoscopy is the gold standard test that carries great promise owing to its diagnostic and therapeutic potentials, however, its current use is limited to surveillance colonoscopy for high risk patients or when highly suspicious lesions are detected by flexible sigmoidoscopy. Fecal occult blood testing (FOBT) is effective and reliable but a low compliance rate jeopardizes its cumulative usefulness as this test needs to be done annually by adults people aged 50 years and above. Computed tomographic (CT) colonography is recommended after positive FOBT in cases when colonoscopy is not feasible or incomplete. The value of flexible sigmoidoscopy in CRC screening is fading out except for the low socio-economic regions primarily due to its limited visualization of the colon and the need for colonoscopy in case of detecting polyp in distal colon by flexible sigmoidoscopy. Fecal DNA testing is another promising screening technique that can potentially detect advanced precancerous and cancerous growths in the lower gastrointestinal tract. The World Health Organization (WHO) has recommended that all adults above 50 years of age are potentially at risk of developing CRC, and should have FOBT annually and colonoscopy every 5 years. However, the preferences for choosing cancer screening strategies are primarily driven by individual risk, available resources and personal choice.

**Keywords:** Colorectal cancer; cancer screening; colonoscopy; CT colonography; Fecal occult blood test

## INTRODUCTION

### The burden and epidemiology of colorectal cancer

Although the incidence and mortality rates of CRC vary widely up to 10-fold worldwide, generally, there is a wide geographical variation and world has witnessed a staggering upsurge of the incidence of CRC with an estimated increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030[1]. In the USA, CRC is the 3rd deadliest of all cancers and, in 2016, there will be an expected estimated number of 134,490 new CRC cases (70,820 in males and 63,670 in females) along with 49,190 CRC deaths[2]. CRC ranks 3rd, only behind prostate and lung cancer, for new cases in men (8% of all newly diagnosed cancers), and behind breast and lung cancer in all newly diagnosed cases in women (8% of all new cancers)[3-4]. In Asia, Japan has reported an

estimated cumulative lifetime risk of CRC of 8.6% in men and 6.8% in women in 2008; whereas in 2011, due to 124 921 new CRC cases, this data has risen to 14.5% of all cancers in men and14.9% in women[5].

In addition to a an ever increasing burden of CRC, research has provided sufficient evidence of a rightward or proximal shift of CRC in the subsite distribution in the Western[6] as well as in the Asian populations[7-8]. In addition to the well-known established risk factors for CRC such as Western lifestyle and the usage of processed food[9], more recent evidence has shown the associations of vitamin D deficiency[10], type 2 diabetes mellitus[11], genetic predisposition[12], and the biochemical derangements resulting from hyperlipidemia with CRC[13]. Such emerging etiopathological confounders for CRC pose a challenge to the healthcare authorities for adopting and embedding world-class diagnostic and screening tools to combat the rising incidence and mortality rates from CRC. Also, the wide age range for CRC screening (50–75 years) warrants a long-term continuing screening program that needs resources, expertize, task force and quality assurance. This narrative review aims to explore different CRC screening modalities that are in practice worldwide, with the primary purpose of highlighting merits and demerits of each screening tool.

**Research design**

In October 2016, the databases of Medline, CINAHL, Scopus, Cochrane library, and ISI web of knowledge were searched using the MeSH terms colorectal cancer AND cancer screening tests OR colonoscopy OR CT colonography OR fecal occult blood test. The full text English language original, review, meta-analysis and systematic review, recommendations, protocols and policies about CRC screening were included in this search. The editorial articles, personal opinions, conference proceedings, and letters to editors were excluded from this search.

**Modern cutting-edge diagnostic tools for colorectal cancer**

In addition to the symptoms and patients factors[14], colonoscopy and CT colonography[15], positron emission tomography using fluorodeoxyglucose (FDG-PET)[16], barium enema, microRNA21[17], narrow band imaging and confocal laser endoscopy[18] have been shown to carry convincing promise in diagnosing and staging CRC. Furthermore, endocystoscopy[19] and endoscopic ultrasound[20] have been claimed to be useful and effective in the cytological diagnosis of CRC. However, there is no consensus about the standard protocol for diagnosing CRC as the institutional practice is mainly driven by available resources and expertise.

**Screening modalities for colorectal cancer and their implications**

This research work exhibits recommendations for CRC screening in asymptomatic adults aged 50 years and older who are not known to be at risk for CRC. Literature has shown a wide range of CRC screening tests that have been described and practiced worldwide. This literature review lays down the most popular CRC screening modalities that are classified as invasive and non-invasive screening tests (Table 1).

**Invasive screening test for colorectal cancer**
**Colonoscopy**

Pathologically, CRC arises in pre-existing benign polyps following genetic transformations in normal colonocytes[21]. With the passage of time, further accumulation of genetic abnormalities helps some polyps to enlarge that eventually become severely dysplastic and later transform into invasive malignancy. Pino and Chung have argued that approximately 80% of CRC that arise from adenomatous polyps develop due to a genetic alterations in a primarily benign lesion[22]. This highlights the significance of removal of colorectal polyps during colonoscopy that is considered to be a single and foremost tool in effectively reducing CRC mortality as well as in screening CRC in asymptomatic population[23]. Colonoscopy is the ultimate and the most popular step in all CRC screening protocols, regardless of the choice of screening tests used. Several case–control and cohort studies have convincingly proved significant reductions in CRC incidence affected by initial screening colonoscopy by up to 70% [24-25] and up to 68% drop in CRC mortality rates after over 15 years of follow up[26]. Australian clinical practice guidelines for surveillance colonoscopy in adenoma follow up

and following curative resection for CRC has recommended a 5-year follow up of patients with low risk tubular adenomas (<10 mm), a 3-year follow up for tubulovillous or villous adenoma ( e”10 mm), and 1-year or sooner for patients with multiple polyps or post-surgical status[27]. Thus, the role of colonoscopy is essentially limited to surveillance colonoscopy for high risk groups and for those patients who had incomplete flexible sigmoidoscopy or where flexible sigmoidoscopy detected larger and/or multiple adenomas.

Colonoscopy is not without hazards as complete protection against CRC after colonoscopy cannot be guaranteed; about 6% of CRC occur within 5 years of a colonoscopy[28]. The development of such early lesions, missed or interval cancers, after clearing colonoscopy poses a serious challenge to the protective nature of polypectomy by colonoscopy on the long-term population-based incidence of CRC. Nevertheless, world-class innovations and technologic improvements in endoscopic technology in enhancing imaging and ancillary techniques have enriched the capacity of colonoscopy in detecting subtle precancerous transformation[29]. “These technologies include high deûnition imaging, dye spray chromocolonoscopy, cap-ûtted colonoscopy (application of a transparent plastic cap to the instrument tip), and repeated or retroûexed inspection in the proximal colon”[30]. However, colonoscopy is operator dependent and the quality of colonoscopy should be professionally reviewed and quality assurance programme should be upheld to audit all dimensions of CRC screening[31]. In a broader perspective, CRC screening colonoscopy is not adopted as a primary population-based screening modality because of lack of expertize in relation to large population sizes, burden on healthcare resources and budget, and potential complications e.g. perforation and drug-induced anaphylaxis[5].

**Non-invasive screening tests for colorectal cancer**

**Fecal occult blood testing**

The US Preventive Services Task Force recommends screening for CRC with annual FOBT or sigmoidoscopy every 5 years with FOBT every 3 years or colonoscopy every 10 years[32]. In case of strong family history for CRC or previous cancer, a more rigorous CRC screening is warranted. FOBT for CRC screening is an acceptable, effective, lower-cost screening modality particularly suitable for low socio-economic regions[33]. A wealth of literature has argued that there is low patient compliance for FOBT and has reported that less than 25% of eligible patients complete a second round of FOBT test within 2 years[34-35].

Two types of FOBT are used; a guaiac-based (gFOBT) that detects peroxidase like activity of haem and an immunohistochemical subtype (iFOBT) that utilizes antibodies to human globin with an automated and quantitative analysis carrying significant sensitivity and speciûcity[36-37]. On the other hand, gFOBT is cheap but its interpretation is not automated. Furthermore, the usual dietary restriction of meat and discontinuity of aspirin to minimise upper gastrointestinal bleeding have been suggested to decrease false positive results. Research has provided a “Level 1 evidence that a protocol of annual or biennial gFOBT for at least two or three rounds decreases CRC mortality by 16% (95% CI 10–22) by intention-to-treat analysis and by 25% (CI 16–22) by per-protocol analysis”[38]. In contrast, there is no need of dietary restrictions and sample collection by the participant is easier; thus showing a 13–15% higher participation rate using iFOBT than that for gFOBT[39]. Published work has shown that iFOBT detects cancer or advanced adenomas at least three times more frequently than gFOBT[40].

**Computed tomographic colonography**

The mere detection of fecal occult blood loss does not reflect a serious outcome unless cancer is diagnosed and treated, or large bleeding adenomas are excised. For the majority, colonoscopy both identifies as well as enables endoluminal excision of small adenomas and cancers. However, in some cases, colonoscopy may be refused, incomplete, or infeasible, and in these given cases, an alternative screening modality is required. In such cases, CT colonography or virtual colonoscopy is an attractive alternative [41]. CT colonography is a new emerging radiological tool for imaging the large bowel that is less invasive than colonoscopy, with reported better compliance by the patients[42]. “For CT colonography, multi-detector row scanners (minimum four rows) are

**Table 1. The colorectal screening tools with the reported merits and demerits**

| Colorectal cancer screening test | Advantages | Disadvantages |
|---|---|---|
| Colonoscopy | Offers direct visualization of entire colon<br>Immediate therapeutic solution<br>Standalone test for evaluation and therapy<br>High definition colonoscopy precisely localizes and identifies suspicious lesions<br>- - | Interval cancers can be missed<br>Sessile adenoma that are flat, pale with indistinct margins can be missed Operator dependent, and results vary with expertize<br>Cumbersome and low compliance by patients |
| Flexible sigmoidoscopy | Easy and quick to perform<br>Well accepted by patients<br>adenomas, precancerous or cancerous growths in left-sided colon<br>Carries the promise to reduce CRC mortality | Limited visualization of colon<br>Need to do colonoscopy in case of finding<br>Increasing age (more than 75 years, female gender, and hysterectomy |
| | are predictors of incomplete examination with poor diagnostic yield | |
| Fecal occult blood testing | Cheap and effective<br>Reduces CRC mortality<br>iFOBT does not require dietary restriction of meat or cessation of aspirin<br>- - | Limited sensitivity of gFOBT<br>gFOBT fails to detect adenomas<br>gFOBT requires dietary restriction of meat and cessation of aspirin |
| CT colonography | Non-invasive and convenient<br>Highly sensitive<br>Can also detect extra-colonic lesions<br>Sensitive for lesions e≥ mm<br>- - | Radiation hazard<br>Biopsy may be required for detected lesions<br>additional tests may be required for final diagnosis |

used with a maximum detector collimation of 2·5 mm and a pitch that allows abdominal coverage (40 cm) within one breath-hold (20 s) in supine and prone positions"[43].

Since the screenees with positive gFOBT and/or iFOBT values have such a remarkably high prevalence of abnormality, subsequent high profile tests are required to confirm to exclude cancer. CT colonography is approximately 89 % sensitive for adenomas e" 6 mm, while its specificity is lower and variable, reported to be about 75 % [44)]A large number of patients undergoing colonoscopy need sedation that is not necessary for CT colonography. CT colonography also identifies extra-colonic lesions, which might explain non-cancerous manifestations but may necessitate further investigations that ultimately with no clinical beneût. In case of detection of a suspicious lesion by CT colonography, a colonoscopic biopsy may be needed[45].

**Flexible sigmoidoscopy**

The rationale of using flexible sigmoidoscopy for CRC screening is based on the hypothesis that the majority of people who would develop a distal colon cancer will have developed an adenoma by the age of 60 years[46]. Hence, ûexible sigmoidoscopy screen performed on population between 55 and 64 years is a cost-eûective and attractive CRC screening strategy that can remove adenomas with a great potential to reduce cancer-related mortlity. Atkin et al. conducted a randomized controlled trail to investigate the effectiveness of flexible sigmoidoscopy for CRC screening and have deduced that this procedure was safe and convenient when oûered only once between ages 55 and 64 years[47]. The researchers also inferred a significant long lasting beneût in terms of reduced CRC mortality. A wealth of studies have elucidated a high diagnostic yield by flexible sigmoidoscopy when performed by a trained specialist colorectal expert, nevertheless, the need for colonoscopy in patients with pathologies detected by flexible sigmoidoscopy is a major limitation of this investigation [48-49]. The high-risk criteria for referral to colonoscopy includes; 1 cm or larger adenomas, three or more adenomas, tubulovillous or villous variants of adenomas, severe dysplasia or clear malignancy, or 20 or more hyperplastic polyps above the distal rectum[50].

Rutter et al. conducted a randomized controlled trial using 3 validated CRC microsimulation models against outcomes from the United Kingdom Flexible Sigmoidoscopy Screening Trial that assessed the effectiveness of one-time flexible sigmoidoscopy screening for reducing mortality from CRC[51]. These models tend to incorporate several hypothesis about the time from the development of adenoma to the preclinical and advanced CRC. "All 3 models objectively identified the relative reduction in CRC mortality with 10 years screening (predicted hazard ratios, with 95% percentile intervals: 0.56 [0.44, 0.71], 0.63 [0.51, 0.75], 0.68 [0.53, 0.83]; estimated with 95% confidence interval: 0.56 [0.45, 0.69])" [51]. In addition to detecting distal adenomas, all 3 models also predicted a high number of proximal adenomas that necessitated referral to gastroenterologists for colonoscopy. Hence, colonoscopy following flexible sigmoidoscopy proves more expensive as well as more cumbersome to the patients undergoing a series of endoscopies, thus reaffirming the value of colonoscopy as a stand-alone screening and therapeutic tool for precancerous and early cancerous lesions.

**Fecal DNA testing**

The fecal DNA testing is based on the premise that mutations in genes controlling the WNT and MAPK pathways, such as *Kras* and *APC*, complemented by gene methylation, can be detected in the neoplastic cells of adenomas, polyps and cancers that are sloughed directly into the bowel lumen [25]. A recent evidence-based observational study objectively compared the performance of a multi target DNA stool testing for a range of DNA abnormalities associated with CRC or precancerous adenomas with standard colonoscopy, and reported a 92% sensitivity and 90% specificity for identifying precancerous lesions by the stool DNA test[52]. Recently, due to its high cost, the faecal DNA testing has been performed in extremely selected cohorts of patients who had colonoscopy suggesting malignancy, large polyp or no abnormality[53]. The sensitivity of fecal DNA testing for CRC has been estimated to be > 85%

and > 50% for large adenomas[25]. However, such data needs to be examined with average-risk, asymptomatic people over 50 years of age.

**Summary of the current recommended protocols for screening colorectal cancer worldwide**

There is no unified CRC screening protocol worldwide and each region has its own screening strategy mainly driven by CRC burden, resources, personal preferences, and expertize and subsite distribution of CRC. According to recommendations by WHO and American Association of Cancer Prevention, all adults above 50 years of age are potentially at risk of developing CRC, and should have FOBT annually and colonoscopy test every 5 years [54]. The 2001 Canadian Task Force on Preventive Health Care recommendations suggested an annual or biennial FOBT (grade A recommendation) and flexible sigmoidoscopy every five years (grade B recommendation) in asymptomatic people older than 50 years. This dossier, however, failed to elaborate whether the mentioned screening tools be used alone or in combination (grade C) or whether to include or exclude colonoscopy as an initial screening modality[55]. Owing to the major technological and innovative developments, the recently updated guideline strongly recommends to screen adults aged 60 to 74 years for CRC with FOBT (gFOBT or iFOBT) every two years or flexible sigmoidoscopy every 10 years. (Strong recommendation; moderate-quality evidence) and to screen adults aged 50 to 59 years for CRC with FOBT (gFOBT or iFOBT) every two years or flexible sigmoidoscopy every 10 years. (Weak recommendation; moderate-quality evidence)[56-57].

Screening for CRC with FOBT or flexible sigmoidoscopy reduces cancer-related mortality and the non-invasive nature of these tests render them convenient to patients and cost effective. Research work has failed to predict a significant difference while comparing the sensitivity of gFOBT and fecal immunochemical testing as neither test appears to have measureable hazard (58). The recommendations by the US Preventive Services Task Force, published in 2008, have advised CRC screening of adults aged 50 to 75 years with FOBT, flexible sigmoidoscopy or colonoscopy (32). From the Asian perspective, the recommended Korean guidelines for CRC screening and surveillance suggests either iFOBT or colonoscopy, or by CT colonography or double-contrast barium enema starting at the age of 50 years (59). If the iFOBT is positive, or a e" 6-mm polyp is found by double-contrast barium enema or CT colonography, further colonoscopic evaluation is recommended. In patients aged more than 50 years with average-risk, if colonoscopy by a qualified practitioner is negative, then the next colonoscopy should be performed after 5 years. In China, adults aged 50–75 years are the target population for CRC screening and a two-stage CRC screening program is recommended: The iFOBT and a quantitative high-risk factor questionnaire as the primary screening test, and a complete colonoscopy during the follow-up stage is practiced (60). Another school of thought has argued that the results of a combination of flexible sigmoidoscopy (every 5 years) with sensitive FOBT (performed periodically) are similar to that of colonoscopy (performed every10 years) (61).

## CONCLUSION

This research work sheds light on the state-of-the-art CRC screening techniques by providing a robust comparison of the beneûts and harms of screening strategies that are employed in terms of the starting age, stopping age, and testing intervals. Although there is no consensus about a standard CRC screening protocol but colonoscopy, flexible sigmoidoscopy, gFOBT/iFOBT and CT colonography are invariably used with differing frequency and combinations worldwide. A great majority of CRC arise from slowly growing colonic polyps and this lesson is the landmark rationale for all CRC screening programs that should target at their early diagnosis and thus aiming to reducing deaths due to CRC by identifying and removing polyps and/or early-stage colorectal cancers.

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