

# National Guidelines for Colorectal Cancer Screening in Saudi Arabia with strength of recommendations and quality of evidence

*Tripartite Task Force from Saudi Society of Colon & Rectal Surgery, Saudi Gastroenterology Association and Saudi Oncology Society*

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**BACKGROUND:** Colorectal cancer is the most common cancer among Saudi men and the third commonest among Saudi women. Given the predominance of colorectal cancer compared with other cancers in Saudi Arabia, context-specific guidelines are needed for screening.

**METHODS:** The Saudi Centre for Evidence-Based Healthcare assembled a panel of experts from the Saudi Society of Colon and Rectal Surgery, Saudi Gastroenterology Association, the Saudi Oncology Society, the Saudi Chapter of Enterostomal Therapy, the Family Medicine and Department of Public Health at the Saudi Arabian Ministry of Health and a patient advocate. The panel collaborated with a methodological team from McMaster University, Canada to develop national guidelines for colorectal cancer screening. After identifying key questions, the panel conducted a systematic review of all reports on the utility of screening, the cost of screening for colorectal cancer in Saudi Arabia and on the values and preferences of Saudi patients. Meta-analyses, when appropriate, were performed to generate pooled estimates of effect. Using the GRADE approach, the panel used the evidence-to-decision (EtD) framework to assess all domains important in determining the strength and direction of the recommendations (benefits and harms, values and preferences, resource implications, equity, acceptability, and feasibility). Judgments related to the EtD domains were resolved through consensus or voting, if consensus was not reached. The final recommendations were developed during a two-day meeting held in Riyadh, Saudi Arabia in March 2015. Conflicts of interests among the panel members were handled according to the World Health Organization rules.

**LIMITATIONS:** There is lack of national data on the incidence of adenomatous polyps or the age groups in which the incidence surges. There were no national clinical trials assessing the effectiveness of the different modalities of screening for colorectal cancer and their impact on mortality.

**CONCLUSION:** The panel recommends screening for colorectal cancer in Saudi Arabia in asymptomatic Saudi patients at average risk of colorectal cancer. An infrastructure should be built to achieve that goal.

Colorectal cancer (CRC) is the most common cancer among Saudi men and the third commonest among Saudi women according to the Saudi Cancer Registry 2010.<sup>1</sup> The age-standardized rate is 9.6/100 000.<sup>1</sup> The median age at presentation is 55 years for Saudi women and 60 years for Saudi men.<sup>1</sup> In 2008, The US Preventive Services Task Force published the screening guidelines for CRC in the US.<sup>2,3</sup> Given the predominance of CRC compared with other cancers in Saudi Arabia, context-specific guidelines are needed for CRC screening.

The aim of these evidence-based national guidelines is to prevent CRC and improve the overall survival rate of persons diagnosed with CRC through earlier detection. In 2007, The Saudi Cancer Registry reported a 5-year overall survival of 44.6% among persons diagnosed with CRC for the period of 1994-2004.<sup>4</sup> Finally, screening for CRC uses different modalities and it is important to identify the appropriateness and cost-effectiveness of those modalities among Saudi patients.

## METHODS

The Saudi Centre for Evidenced-Based Healthcare

(EBHC) assembled a team of experts in collaboration with the Saudi Society of Colon & Rectal Surgery, the Saudi Gastroenterology Association, the Saudi Oncology Society and the Saudi Chapter of Enterostomal Therapy. A consultant epidemiologist was added from the Department of Public Health at the Saudi Ministry of Health. Family medicine was represented by two members; one from the Ministry of Health and another from the private sector. Additionally, a patient representative who had a past history of CRC was added to the panel to represent the views of Saudi patients. Potential conflicts of interest among all the panel members and the team from McMaster University were managed according to the rules of the World Health Organization (WHO).<sup>4</sup>

A team of methodologists from the McMaster GRADE Centre (MacGRADE Centre) in the Department of Clinical Epidemiology & Biostatistics at McMaster University in Hamilton, Ontario, Canada were employed to help with the process of developing the guidelines. The team has vast experience in developing clinical and public health guidelines for different topic areas using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.<sup>5-8</sup>

The panel identified the target population for the guidelines as persons in the general Saudi population who were asymptomatic and with an average-risk for the development of CRC. The target population excluded persons with a prior family history of CRC or co-morbid conditions, as they would require different screening guidelines. The panel developed key questions to be answered by these guidelines. Those questions addressed the following domains:

1. The need for screening in Saudi Arabia for CRC.
2. The age at which screening should be initiated and abandoned.
3. The modality of screening to be used in Saudi Arabia.
4. A comparison among those modalities to allow the clinician to choose the most appropriate modality.

Seven key questions were identified after detailed discussion and prioritization. Outcomes were generated and prioritized (a priori based on panel input). A webinar was held on several occasions to review the methodology used in the development of the guidelines. The team from McMaster University conducted systematic reviews addressing each of the seven research questions. Previously published systematic reviews on screening for colorectal cancer were retrieved and updated if possible with careful attention to Saudi-specific data. The panel members provided all relevant information regarding

**Table 1.** Databases researched and references retrieved and included in the guidelines development.

Topic of search	Harms and benefits	Patient's values and preferences	Cost-effectiveness
Total retrieved	146	676	419
PubMed	87	-	-
Ovid	-	676	419
Medline	-	-	-
Embase	59	-	-
PsychINFO	-	-	-
Cochrane	5	-	-
Excluded duplicates	5	106	217
Excluded not matching search objective through title and abstract review	136	524	195
Included for full text review	5	46	7
No. excluded after full text review	1 <sup>a</sup>	40 <sup>b</sup>	5 <sup>c</sup>
<b>Total included as references</b>	<b>4</b>	<b>6</b>	<b>2</b>

Reasons for exclusion:

<sup>a</sup>Symptomatic patients, abstract only;

<sup>b</sup>Did not address values or preferences of screening, not available, patients previously diagnosed with CRC, did not address cost-effectiveness;

<sup>c</sup>No screening costs included, full article not available.

colorectal cancer specific to the Kingdom. The systematic review also included searches for data about benefits and harms, patient values and preferences, cost of screening, equity, applicability, and feasibility specific to Saudi Arabia (Table 1).

For each question, an evidence profile was developed to assess the certainty in the evidence across patient-important outcomes. Overall certainties of estimates were evaluated using the GRADE approach.<sup>5-7</sup> This included assessing the following criteria across outcomes: risk of bias, imprecision, inconsistency, indirectness, publication bias, presence of dose-effect relationship, magnitude of effect, and the effect of plausible residual confounders.<sup>9</sup> Those profiles were shared among the panel members.

According to the GRADE approach,<sup>5</sup> overall quality of evidence is defined as:

1. High: There is confidence that the true effect of screening lies close to that estimated by research. More research will not change this confidence.
2. Moderate: There is moderate confidence in the estimated effect of screening according to the current research, but there is a possibility that more research will change the estimated effect of screening.
3. Low: The confidence in the estimated effect of screening is limited. Further research is very likely to change the estimated effect of screening.
4. Very low: The confidence in the estimated effect of screening is very little. In fact, the estimated effect is uncertain.

The panel along with the members from the MacGRADE Centre from McMaster University met in Riyadh, Saudi Arabia on March 15th and 16th, 2015 to review the evidence and formulate the final recommendations. The panel developed recommendations based evidence profiles for each recommendation. The GRADE evidence-to-decision (EtD) framework was used to help organize discussion for each recommendation. According to the GRADE EtD framework, each recommendation was evaluated according to benefits and harms, patient values and preferences, cost of screening, equity, applicability, and feasibility specific to Saudi Arabia. Within these domains, specific items for discussion included the desirable and undesirable consequences of CRC, CRC-related mortality, CRC-related incidence, number and proficiency of endoscopists in the country, monitoring of the process of screening, and future research possibilities.

Recommendations including their strength (strong vs. weak) and direction (for vs. against) were generated after consideration of these factors and consensus

among panel members. The recommendations were either strong or weak according to the GRADE approach.<sup>5</sup> We used the terminology “we recommend” for strong recommendations or “we suggest” for conditional recommendations. A strong recommendation is offered when the desirable effects of the intervention clearly outweigh the undesirable effects of not intervening. A weak (conditional) recommendation is offered when the desirable effects and the undesirable effects are closely balanced or when there is less certainty in the desirable effects compared with the undesirable effects.

#### *Use of the guidelines*

The guidelines target asymptomatic Saudi persons at average risk of developing CRC. In Saudi Arabia, the average risk of developing colorectal cancer is 9.6/100 000.<sup>1</sup> The recommendations should never be extrapolated to other clinical scenarios. The recommendations are not dictums and they are not to be applied in isolation of the clinical situation.

## DISCUSSION AND RECOMMENDATIONS

**Question 1:** Should CRC screening be used in asymptomatic average-risk persons compared with no screening?

Pooled results from eight randomized controlled trials<sup>2,10,11</sup> with a total population of 743 587 subjects who underwent colorectal cancer screening found high quality evidence for reducing colorectal cancer mortality (relative risk (RR) 0.8; 95% confidence interval (CI): 0.75-0.85). The evidence was moderate quality for reducing the incidence of colorectal cancer (RR 0.88; 95% CI: 0.80-0.96). A meta-analysis of six observational studies found low quality evidence with 34 serious complications per 100 000 procedures (95% CI: 0.06-1.9) with flexible sigmoidoscopy (FS) compared with no screening.<sup>2</sup> Serious complications included: perforation, bleeding or death. A local study found 71% of Saudis questioned are willing to undergo CRC screening. Saudis preferred the following modalities in descending order: CT colonography (CTC), stool based-test, colonoscopy and FS.<sup>12</sup> There were no cost-analysis studies from Saudi Arabia. Indirect evidence on the incidence of adenomatous polyps<sup>13,14</sup> and median age at presentation, which is 55 years for women and 60 years for men,<sup>1</sup> suggests screening should start at the age of 45 years.

**Recommendation 1:** The panel recommends offering colorectal cancer screening to asymptomatic, average-risk persons rather than no screening (strong recommendation; low quality evidence).

The recommendation was based on overall low quality evidence; however, it was agreed that future research is unlikely to change this recommendation.

**Question 2:** Should CRC screening be used in average-risk persons aged 70 years or older compared with no screening?

There are no clinical trials addressing this question specifically other than the previous trials presented in recommendation 1.<sup>10-12</sup> This age group may experience a higher risk of serious complications coupled with increased cost due to co-interventions related to their co-morbidities. Consequently, the undesirable effects outweigh the desirable effects. One should also consider that if cancer is discovered, surgery or chemotherapy might not be offered or feasible due to frailty. In healthy individuals with no co-morbidities and a predicted survival beyond 10 years at the time of screening, there may be a benefit in screening.

**Recommendation 2:** The panel suggests not offering CRC screening for asymptomatic persons at average risk aged 70 years or older (conditional recommendation; low quality evidence).

**Remarks:**

\*Consider that some persons aged 70 years or older might still benefit from screening (if healthy, lack comorbidities, and life expectancy is judged to be greater than 10 years at time of screening).

**Question 3:** Should colonoscopy be used for CRC screening in asymptomatic average-risk persons compared with no screening?

A meta-analysis of three observational studies<sup>11</sup> found low quality evidence for screening using colonoscopy compared with no screening for CRC-related mortality (RR 0.32; 95% CI: 0.32-0.43). A meta-analysis of five observational studies found very low quality evidence for screening using colonoscopy over no screening for CRC-related incidence (RR 0.31; 95% CI: 0.12-0.77).<sup>11</sup> A meta-analysis of 12 non-randomized studies with 57 742 participants found low-quality evidence for increased complications and death from colonoscopy (2.8 events per 1000 [1.5-5.2 events per 1000]).<sup>2</sup> A local study found 71% of Saudis questioned are willing to undergo CRC screening. Saudis preferred the following modalities in descending order: CTC, stool based-test, colonoscopy and FS.<sup>12</sup> There is a shortage of endoscopists in Saudi Arabia. Consideration to privilege other clinicians was discussed. Studies from the region suggests indirectly that colonoscopy is cost-effective.<sup>15,16</sup> Colonoscopy is considered the golden standard against

which all other modalities of screening are tested. It must be repeated every 10 years.<sup>2</sup>

**Recommendation 3:** The panel recommends screening colonoscopy rather than no screening for asymptomatic, average-risk persons (strong recommendation; low quality evidence).

**Remarks:**

\* Colonoscopy is considered the “gold standard” and there is high confidence in the estimate of its effect, even though that is based on low quality evidence.

\*As with the other recommendations a small amount of uncertainty is recognized given the indirect evidence on resources, values and preferences, health inequalities, and feasibility.

**Question 4:** Should FS be used for CRC screening in asymptomatic average-risk persons compared with no screening?

A meta-analysis of four trials with 413 945 participants found high-quality evidence that FS reduces CRC-related mortality (RR 0.72; 95% CI: 0.65-0.80) and low quality evidence that FS reduces CRC-related incidence (RR 0.82; 95% CI: 0.75-0.89).<sup>11</sup> A meta-analysis of six observational studies found moderate-quality evidence for 34 serious complications per 100 000 procedures (95% CI 0.06-1.9) in association with FS compared with no screening.<sup>2</sup> Serious complications included: perforation, bleeding or death. FS was least appreciated by Saudis as a screening modality.<sup>12</sup> FS fails to rule out right-sided polyps or tumors. These can be detected if FS is combined with guaiac fecal occult blood testing (gFOBT).<sup>2</sup> Fecal immunochemical testing (FIT) is superior to guaiac fecal occult blood testing (gFOBT).<sup>2</sup> FS is more feasible than colonoscopy since it does not require sedation or oral preparation. Studies from the region suggests indirectly that FS is cost-effective.<sup>15,16</sup> The desired effect of FS clearly outweighs the undesired effects. FS must be repeated every 3 years if performed alone or every 5 years if combined with FIT.<sup>2</sup>

**Recommendation 4:** The panel recommends offering FS for CRC screening rather than no screening for asymptomatic persons at average risk (strong recommendation; moderate quality evidence)

**Remarks:**

\* This recommendation refers to FS screening every 5 years when combined with annual FIT or every 3 years without annual FIT.

**Question 5:** Should CTC be used for CRC screening in asymptomatic, average-risk persons compared with colonoscopy?

There are no clinical trials comparing colonoscopy directly to CTC. A meta-analysis of four non-randomized studies with 4018 participants found low-quality evidence for a sensitivity of 0.83 (95% CI: 0.74-0.89) and a specificity of 0.91 (95% CI: 0.84-0.96) for CTC compared with colonoscopy for polyps or adenomas  $\geq 10$  mm.<sup>17</sup> A meta-analysis of 12 non-randomized studies with a total of 57742 participants found low quality evidence of increased complications for colonoscopy<sup>2</sup> while CTC had a low complication rate. CTC is associated with additional harm related to radiation exposure; however, the new CT scans use lower radiation doses.<sup>18</sup> Saudis preferred CTC over colonoscopy.<sup>12</sup> CTC is more cost effective in Britain,<sup>19</sup> but requires bowel preparation-like colonoscopy and confirmatory screening when in doubt using colonoscopy.

**Recommendation 5:** The panel suggests using colonoscopy rather than CT colonography for the diagnosis of asymptomatic, average-risk persons (conditional recommendation; low quality evidence).

**Remarks:**

- \* The decision to use colonoscopy instead of CT colonography should be driven by feasibility and availability of the tests.
- \* For persons preferring non-invasive screening, one may choose to undergo CT colonography.

**Question 6:** Should FS be utilized in screening for CRC in average-risk persons compared with gFOBT?

There are no clinical trials comparing FS directly to gFOBT. A meta-analysis of 4 trials with a total of 329642 participants found moderate quality evidence

for gFOBT; it was not significantly associated with a reduction in CRC incidence (RR 0.93; 95% CI: 0.84-1.04), but it reduced all-cause mortality (odds ratio (OR) 0.84; 95% CI: 0.78-0.90).<sup>10</sup> There are no serious direct complications resulting from the use of gFOBT, while there are in association with FS. FIT is superior to gFOBT with regard to sensitivity and specificity.<sup>2</sup> Saudis preferred a stool-based test over FS.<sup>12</sup> Both FS and gFOBT are cost-effective based on regional studies.<sup>15,16</sup> The two modalities FS and gFOBT complement each other rather than compete with each other. FS cannot rule out polyps or tumors in the right colon while gFOBT can help close that gap.<sup>2</sup>

**Recommendation 6:** The panel suggests offering FS rather than gFOBT for CRC screening among asymptomatic, average-risk persons (conditional recommendation; very low quality evidence)

**Remarks:**

- \* gFOBT is a less sensitive method, but depending on the availability of other screening modalities, setting, and resources it can still be used.
- \* FS is often performed in combination with FOBT or FIT to ensure the entire colon is screened.

**Question 7:** Should FS be utilized for CRC screening in average-risk persons compared with colonoscopy?

There are no clinical trials that compared FS to colonoscopy directly. A meta-analysis of four trials with 413945 participants found high-quality evidence that FS reduces CRC-related mortality (RR 0.72; 95% CI: 0.65-0.80). Moreover, FS reduces CRC-related incidence (RR 0.82; 95% CI: 0.75-0.89).<sup>11</sup> A meta-analysis of three observational studies found low-quality evidence for screening using colonoscopy over no screening with regard to CRC-related mortality (RR 0.32;

Guideline	Strength of Recommendation	Quality of Evidence
Persons above the age of 45 years should undergo screening.	Strong	Low
No screening to be offered to persons aged 70 years or older.	Conditional	Low
Screening colonoscopy is recommended over no screening	Strong	Low
Flexible sigmoidoscopy is recommended over no screening	Strong	Moderate
Screening colonoscopy is recommended over colonography	Conditional	Low
Flexible sigmoidoscopy is recommended over guaiac fecal occult blood test	Conditional	Very low
Screening colonoscopy is recommended over flexible sigmoidoscopy	Conditional	Low

95% CI: 0.23 to 0.43).<sup>11</sup> A meta-analysis of five observational studies found very low-quality evidence for screening utilizing colonoscopy with regard to CRC-related incidence (RR 0.31; 95% CI: 0.12 to 0.77).<sup>11</sup> A meta-analysis of six observational studies found low quality evidence with 34 serious complications per 100 000 procedures (95% CI: 0.06-1.9) with FS compared with no screening; while there were 2.8 serious complication events per 1000 (range: 1.5-5.2)<sup>2</sup> for colonoscopy. Serious complications included: perforation, bleeding or death. Saudis preferred colonoscopy over FS.<sup>12</sup> Since it does not require sedation or oral bowel preparation, FS is more feasible and less costly in comparison to colonoscopy. Patients may appreciate the lower frequency of colonoscopy screening every 10 years over that of FS every 5 years and the certainty offered with colonoscopy with regard to right-sided polyps or tumors.

**Recommendation 7:** The panel suggests offering colonoscopy rather than FS for CRC screening among asymptomatic, average-risk persons (conditional recommendation; low quality evidence)

**Remarks:**

\* Benefit of FS may be more if combined with FOBT or FIT.

**IMPLEMENTATION AND CHALLENGES**

The panel identified the need to increase awareness and knowledge of CRC screening among the population. Moreover, the panel recognized that any implementation process must be monitored using key performance indicators that gauge every step including patient acceptability, population uptake of screening, quality of screening, quality of the supportive services like pathology, cost of screening and waiting time to undergo screening. All participants' data must be included in an electronic health record that is analysable for epidemiological and quality assurance reporting. Subject identification must be linked to the national

identification system and must be conducted through a central call center to secure confidential communication. The panel recognized the urgent need to develop a local certification process for endoscopy and to train into endoscopy to meet the high demand of the population. Finally, the Joint Advisory Group on GI Endoscopy has released guidelines for the screening colonoscopists, which should be reviewed and adopted locally.<sup>20</sup>

**LIMITATIONS**

The panel noticed that the literature from Saudi Arabia lacked national data on the incidence of adenomatous polyps and the age groups most affected by the surge in its incidence. Moreover, it noted that there were no national clinical trials assessing the effectiveness of the different modalities of CRC screening and their impact on mortality to weigh the benefit-to-risk ratio.

**CONCLUSION**

Screening for CRC among asymptomatic persons at average-risk in Saudi Arabia is recommended. It should probably be initiated at the age of 45 years; however, further research on the threshold age for screening is needed. Screening is not recommended for persons above the age of 70 years in most cases. Colonoscopy alone every 10 years is the recommended modality; however, if unavailable, FS every 5 years coupled with annual gFOBT or FIT should be considered. FIT is preferred over gFOBT. The least recommended modality is CTC. All CRC screening modalities should be performed at high load centres where skilled and experienced clinical staff is available.

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