Impact of screening colonoscopy on outcomes in colorectal cancer

Takahisa Matsuda1,2,*, Akiko Ono3, Yasuo Kakugawa2, Minori Matsumoto2, and Yutaka Saito2

1Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, 2Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan, and 3Department of Gastroenterology, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

*For reprints and all correspondence: Takahisa Matsuda, Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Endoscopy Division, National Cancer Center Hospital, Tokyo, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tamatsud@ncc.go.jp

Received 8 March 2015; Accepted 5 July 2015

Abstract

Colorectal cancer is one of the most common cancers in both men and women worldwide and a good candidate for screening programs. There are two modalities of colorectal cancer screening: (i) population-based screening and (ii) opportunistic screening. The first one is based on organized, well-coordinated, monitored and established programs with a systematic invitation covering the entire target population. In contrast, opportunistic screening tests are offered to people who are being examined for other reasons. Recently, a variety of colorectal cancer screening tests have become available; each country should make a choice, based on national demographics and resources, on the screening method to be used. Fecal occult blood test, especially the fecal immunochemical test, would be the best modality for decreasing colorectal cancer mortality through population-based screening. In contrast, if the aim includes the early detection of colorectal cancer and adenomas, endoscopic methods are more appropriate.

Key words: colorectal cancer, population-based screening, opportunistic screening, total colonoscopy

Introduction

Colorectal cancer (CRC) is one of the most common cancers both in men and women worldwide, accounting for ~1.3 million new diagnoses and nearly 700,000 deaths each year (1). Approximately 50% CRC patients are >70 years of age and in this age group CRC is the second most common cause of cancer death (2). CRC has several characteristics that make it a good candidate for a screening program. There is general agreement derived from epidemiologic data that screening in an asymptomatic population is recommended to begin at the age of 50 years. Several methods are available for CRC screening, ranging from non-invasive stool or blood tests to various imaging modalities [e.g. flexible sigmoidoscopy, colonoscopy, capsule endoscopy and computed tomography (CT)-colonography]. At present, the most acceptable strategies for screening in the average risk population (individuals between 50 and 74 years of age and without a family history of CRC) are fecal occult blood test (FOBT) every year or biannually, flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years. In particular, it has been a long-standing belief that flexible sigmoidoscopy and colonoscopy can affect the incidence and mortality of the disease in two ways: by detecting cancers at an early, curable stage and by detecting and removing precancerous lesions. In this review, we mainly focus on the current status and future perspective of CRC screening using colonoscopy, including flexible sigmoidoscopy.

Current status of CRC screening

There are two modalities of CRC screening: population-based screening and opportunistic screening. The first one is based on organized, well-coordinated, monitored and established programs with a systematic
invitation covering the entire target population. Such programs are evaluated through a quality improvement framework. Alternatively, in opportunistic screening, tests are offered to patients who are being examined for other reasons, often as part of a routine medical evaluation. Patients are generally referred by their primary healthcare physicians to this type of screening.

The modalities of CRC screening differ in Europe and the USA. In Europe, most of the countries use FOBT as a screening method. In 2003, the European Commission recommended CRC screening with FOBT (3). Furthermore, in 2010 the European Guidelines for CRC screening were published so that screening programs could follow recommended practices as decided by input from many experts. In the USA, on the contrary, the Preventive Services Task Force endorses several tests for CRC screening: annual high sensitivity FOBT, flexible sigmoidoscopy every 5 years, with a high sensitivity FOBT every 3 years, or screening colonoscopy every 10 years (4).

However, screening rates for CRC, although rising in the USA over the past few years, are generally below national targets. In 2012 in the USA, 65.1% of adults between ages 50–75 years were up to date with CRC screening while 27.7% had never been screened (5). Colonoscopy was the most commonly used screening test (nearly 62%).

FOB testing

It has been demonstrated that screening reduces CRC incidence and mortality. Several prospective randomized trials using FOBT with the guaiac method have reduced CRC-related mortality by 13–33% (6–10). Table 1 shows the different studies and the respective rates of mortality reduction. Nevertheless, FOBT is not a good test for the detection of polyps that usually do not bleed. The sensitivity of guaiac FOBT for advanced adenomas and cancer is low at 16–31% and 25–38%, respectively (11).

Presently, guaiac-based FOBT has been replaced by fecal immunochromatic test (FIT). FIT, also known as i-FOBT, for hemoglobin is more specific than guaiac tests because it responds only to human globin and does not detect upper gastrointestinal bleeding (because the globin is digested in transit) or foods with peroxidase activity. Although there are no randomized controlled trials (RCTs) on the effect of FIT on CRC mortality, a number of trials have compared the test accuracy of guaiac FOBT versus FIT, the latter demonstrating a higher sensitivity for both CRC (61–91%) and for advanced adenomas (27–67%) compared with results for guaiac FOBT, but with lower specificity (12–15). Compared with guaiac tests, FIT is relatively simple. No dietary restriction is required and therefore such testing is suitable for mass screening programs; one of the factors to be taken into account when choosing a screening strategy is the acceptability of the test. In the study of van Rossum et al. (13), a higher participation rate was observed in the FIT group compared with the guaiac test-screening group. However, the main limitation of any FOBT is the necessity to perform it every 1–2 years due to its low sensitivity for premalignant lesions. The European Guidelines recommend FIT as a screening method for programs adopting a strategy based on FOBT (16).

DNA stool testing

DNA, RNA and protein biomarkers in stool samples have been explored as screening modalities for CRC and premalignant lesions. A large prospective study compared a stool test consisting of a fecal DNA panel of 21 mutations and a guaiac FOBT (17). The fecal DNA panel detected 16 of 31 invasive cancers, whereas guaiac FOBT identified 4 of 31 (51.6 vs. 12.9%, P = 0.003). However, the sensitivity for advanced neoplasia (defined as a tubular adenoma at least 1 cm in diameter, a polyp with a villous histologic appearance, a polyp with high-grade dysplasia or cancer), was low for both tests (18.2 vs. 10.8%). Recently, methylated genes have been shown to be associated with CRC. In a large prospective study, a DNA stool test consisting of KRAS mutation analysis, two methylation markers and Hb measurement was compared with a FIT (18). The sensitivity of the DNA stool test was significantly higher for the detection of CRC (92.3 vs. 73.8%), advanced precancerous lesions (advanced adenomas or sessile serrated polyps measuring ≥1 cm) (42.4 vs. 23.8%) and polyps with high-grade dysplasia (69.2 vs. 46.2%). However, the specificity of DNA stool test was significantly lower than that of FIT (86.6 vs. 94.9%). DNA stool test might be a promising screening modality. To improve uptake of screening, testing intervals, tailoring and cost effectiveness of such test still require further assessment in the community setting.

CT-colonography

CT-colonography has the potential advantage of requiring limited bowel preparation and can detect ≥70% of the advanced neoplasia, however, the results of large prospective studies in average risk screening population have been variable (19–23). In general, a high detection rate (≥90%) for polyps ≥9 mm has been reported, while the detection rate for polyps ≥5 mm was lower (78–91%) (21,22,24). The referral rate for colonoscopy in the studies varied between 7.5 and 17.3% for a cutoff of 10 mm and 17.5 and 29.7% for a cutoff polyp size of >5 mm, therefore, it is still now controversial what the ideal threshold for colonoscopy referral is (25). In a randomized trial comparing CT-colonography and colonoscopy for primary screening, the participation rate of CT-colonography was significantly higher (34 vs. 22%, P < 0.0001), whereas the detection rate of advanced neoplasia was higher with colonoscopy (6.1 vs. 8.7%, P = 0.02) (19). This result suggests diagnostic yield for advanced neoplasia per 100 invitees was similar with both strategies, indicating both techniques can be used as population-based screening modalities. However, there are several points to be addressed when considering the feasibility of a screening program using CT-colonography, such as radiation exposure and the incidence of unknown clinical significance of extracolonial findings which may require further examination or treatment.

*Table 1. Screening with FOBT (guaiac) randomized controlled trials*

<table>
<thead>
<tr>
<th>Study country</th>
<th>Population</th>
<th>Age group (years)</th>
<th>Positivity</th>
<th>Test interval</th>
<th>Relative mortality reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (6,7)</td>
<td>46,551</td>
<td>50–80</td>
<td>Rehydrated: 9.8%</td>
<td>Annual</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 2.4%</td>
<td>Biennial</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 2.4%</td>
<td>Biennial</td>
<td>13%</td>
</tr>
<tr>
<td>UK (8)</td>
<td>132,303</td>
<td>45–74</td>
<td>Unrehydrated: 0.8–3.8%</td>
<td>Biennial</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 1.9%</td>
<td>Biennial</td>
<td>16%</td>
</tr>
<tr>
<td>Denmark (9)</td>
<td>61,933</td>
<td>45–75</td>
<td>Rehydrated: 5.8%</td>
<td>Biennial</td>
<td>16%</td>
</tr>
<tr>
<td>Sweden (10)</td>
<td>68,308</td>
<td>60–64</td>
<td>Rehydrated: 9.8%</td>
<td>Annual</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 2.4%</td>
<td>Biennial</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 2.4%</td>
<td>Biennial</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 0.8–3.8%</td>
<td>Biennial</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unrehydrated: 1.9%</td>
<td>Biennial</td>
<td>16%</td>
</tr>
</tbody>
</table>
Endoscopic methods
In many countries, particularly in the USA, the dominant screening method is endoscopy (sigmoidoscopy and colonoscopy). A high participation rate in a screening program enables the process to become cost effective. Although many factors may influence screening program participation, the screening method chosen may play an important role. A meta-analysis that evaluated such factors found higher participation rates for less invasive methods: 47% for FOBT, 42% for FIT, 35% for sigmoidoscopy, 41% for sigmoidoscopy combined with FIT/FOBT, 28% for colonoscopy and 22% for CT colonography (26).

Flexible sigmoidoscopy
The use of flexible sigmoidoscopy as a screening test was evaluated in four large scale RCTs (see Table 2). A high participation rate was observed in the NORCCAP and PLCO trials (67 and 86%) while in the other two the rates were much lower.

Three of the four randomized trials have shown a reduction in CRC incidence (18–23%) and mortality (22–31%) with this screening modality, depending on whether the analysis is intention-to-treat or as screened (27–30). Most of the studies found that sigmoidoscopy had a protective effect for left-sided CRC only. However, in some studies, a slight protective effect for right-sided colon cancer was observed, but this trend was not statistically significant (28,31).

Although the participation rate for screening sigmoidoscopy is variable, sigmoidoscopy participation was shown to be non-significantly lower than that for fecal testing according to a meta-analysis published recently; however, when compared with that of fecal testing, the detection rate of advanced neoplasia is higher with sigmoidoscopy (32). In the Italian SCORE trial the participation rates were similar for sigmoidoscopy and FOBT, but the detection rate for advanced neoplasia was three times higher following screening by sigmoidoscopy compared with that by FOBT (33).

A combination of FOBT and sigmoidoscopy might increase the detection of lesions in the left colon while also increasing the detection of lesions in the right colon assuming that all patients with an adenoma in the distal colon undergo complete colonoscopy. A previous study estimated that combined screening with one-time guaiac FOBT and sigmoidoscopy would detect 75.8% (95% CI, 71.0–80.6%) of advanced neoplasms. Among all patients with proximal advanced neoplasia, combined testing would identify 76 out of 150 patients (50.7%). Therefore, this screening method failed to identify about one quarter of subjects with advanced neoplasia and half of subjects with advanced proximal neoplasia, suggesting the combined strategy could be more effective when repeated in appropriate intervals (34). In another trial where the aim was to evaluate the sensitivity of one-time screening using a flexible sigmoidoscopy and FIT to detect advanced colorectal neoplasia, FIT alone resulted in a sensitivity of 58.3% and specificity of 94.5% for a proximal cancer diagnosis. FIT plus the finding of advanced neoplasia in the rectosigmoid colon yielded a sensitivity of 62.5% and a specificity of 93%. Thus, in this trial, the addition of sigmoidoscopy to FIT did not substantially improve the detection of right-sided colon cancers, compared with FIT alone (35).

Capsule endoscopy
Colon capsule endoscopy is a minimally invasive technique specifically designed to explore the colon without sedation and air insufflation. In the largest prospective study examining colon capsule endoscopy, the sensitivity and specificity for detecting polyps that were ≥6 mm were 64 and 84%, respectively, and for detecting advanced adenoma, the sensitivity and specificity were 73 and 79%, respectively (36). Unfortunately, the diagnostic accuracy of polyp is low when compared with conventional colonoscopy. Nevertheless, with the recent introduction of the second generation colon capsule endoscopy the diagnostic accuracy for polyp detection has significantly improved (sensitivity and specificity for polyps >5 mm: 84 and 64%, sensitivity and specificity for polyps >9 mm: 88 and 95%, respectively) (37). Limitations include the inability to take biopsies, the procedural costs and the necessity of an excellent bowel preparation for a high polyp detection rate. Further prospective and comparative studies are required.

Colonoscopy
Colonoscopy is considered the gold standard to detect and remove colorectal neoplasms. The efficacy of colonoscopy with polypectomy to reduce CRC incidence and mortality has been long demonstrated. Such evidence comes from the US National Polyp Study published in 1993, where in a cohort of patients undergoing colonoscopy with polypectomy of adenomas, CRC incidence was reduced up to 90% (38). Zauber et al. (39) from the National Polyp Study Workgroup has recently published the mortality reduction associated with CRC of this same cohort as 53%. However, to date, there are no RCTs evaluating the effect of screening colonoscopy on incidence or mortality showing indirect benefit. Most indirect evidence comes from screening colonoscopy in case control studies where the prevalence of advanced neoplasia was observed in an asymptomatic population. In a study of US veterans, among patients with no adenomas distal to the splenic flexure, 2.7% had advanced proximal neoplasia, while patients with large adenomas (≥10 mm) or small adenomas (<10 mm) in the distal colon were more likely to have advanced proximal neoplasia than were patients with no distal adenomas (OR, 3.4; 95% CI, 1.8–6.5 and OR, 2.6; 95% CI, 1.7–4.1, respectively) (40). Furthermore, in another study of asymptomatic individuals more than 50 years old who underwent colonoscopy, 46% of the patients with advanced proximal

Table 2. Features of flexible sigmoidoscopy randomized controlled trials

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Number (age, years)</th>
<th>Study arms</th>
<th>CRC incidence reduction$^a$</th>
<th>CRC mortality reduction$^a$</th>
<th>Time frame (years)</th>
<th>Proportion requiring colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flex Sig (UK) (27)</td>
<td>170 432 (55–64)</td>
<td>1. FS, 2. no screening</td>
<td>Yes (23%/33%)</td>
<td>Yes (31%/43%)</td>
<td>11</td>
<td>5.2%</td>
</tr>
<tr>
<td>SCORE (Italy) (28)</td>
<td>34 272 (55–64)</td>
<td>1. FS, 2. no screening</td>
<td>Yes (18%/31%)</td>
<td>Yes (22%/38%)</td>
<td>11</td>
<td>5.3%</td>
</tr>
<tr>
<td>PLCO (USA) (29)</td>
<td>154 900 (55–74)</td>
<td>1. FS, 2. no screening</td>
<td>Yes (21%/NR)</td>
<td>Yes (26%/NR)</td>
<td>12</td>
<td>21.9%</td>
</tr>
<tr>
<td>NORCCAP (Norway) (30)</td>
<td>55 736 (55–64)</td>
<td>1. FS, 2. FS and FIT, 3. no screening</td>
<td>No</td>
<td>Yes (27%/59%)</td>
<td>7</td>
<td>20.4%</td>
</tr>
</tbody>
</table>

$^a$Intention-to-treat/per protocol analysis.
neoplasia had no distal polyps. Other case control studies have suggested a CRC reduction in mortality and incidence by colonoscopy (41,42).

Nevertheless, the effectiveness of screening colonoscopy to reduce CRC incidence and mortality still remains unclear. Several RCTs are ongoing that compare screening colonoscopy versus no screening (NordLCC trial) or screening colonoscopy versus FIT (COLONPREV trial) (43,44). Such trials will provide results addressing mortality and incidence in the future.

Colonoscopy is not a perfect modality as a diagnostic tool even when intubation to the cecum is achieved. Adenomas, advanced adenomas and cancers can be missed during screening/surveillance colonoscopy, particularly by endoscopists with a poor technique (45). In a US cohort of patients after adenoma removal, CRC was identified in ~0.5% of patients within a 3-year follow-up period (46). Miss rates for small adenomas ≤5 mm at back-to-back colonoscopies are ~15–30% (47–49); however, the significance of this is as yet unclear. Of more concern is the observation that up to 6% of adenomas >1 cm are missed during colonoscopy (49). Presently, the adenoma detection rate in screening colonoscopy is the most relevant issue as a quality indicator for screening colonoscopy because this is significantly associated with the risk of interval cancer (50). Sanduleanu et al. (51) have proposed two major categories of factors which might be responsible for the development of interval cancers, namely technical, endoscopist-dependent factors and biological characteristics of the cancer that lead to more rapid tumor progression. Although CRC prevention using colonoscopy has proven to be generally safe, its effectiveness, especially in the proximal colon, seems to be limited due to the high incidence of interval cancers. In population-based studies from Canada, colonoscopy screening reduced mortality caused by distal CRC by 47–67%; however, this had no effect on the mortality caused by proximal CRC (52,53).

Although colonoscopy is recommended as a primary screening option for people at average risk of CRC by expert panels in various countries (54,55) there are several issues to be addressed when considering the feasibility of a screening process, such as screening compliance and cost effectiveness. As previously mentioned, the COLONPREV trial of screening colonoscopy versus FIT is still ongoing, but one of the limitations of the trial is the low compliance to the colonoscopy group, where among patients aged 50–69 years, only 24.6% accepted once-only screening colonoscopy, while 34.2% agreed to initial FIT (44). Because the compliance to screening is a modifiable factor, low adherence can be improved over the following rounds of the biennial FIT testing. Furthermore, the number of endoscopists required, and complication risk (e.g. ileus due to bowel preparation, perforation during insertion, etc) have to be considered. The risk of serious complications defined as those requiring hospital admissions and/or medical or surgical treatment has important implications for the overall benefits of CRC screening programs. Many studies have addressed clinically significant adverse events from colonoscopy being the perforation rate of 0.02–0.2%, while bleeding occurred in 0.09–0.14% (20,56–58).

Another important issue is the surveillance interval after polypectomy. When considering colonoscopy as a screening method, it is essential to stratify the risk of CRC. For this purpose, an ideal surveillance interval after polypectomy must be determined based on evidence. The National Polyp Study was a randomized comparison of two different surveillance intervals in 1418 patients with newly diagnosed adenomas removed at baseline colonoscopy (39). In this study, the cumulative incidence of advanced adenomas or cancer was 3.3% at 3 years, irrespective of whether one or two examinations were performed within the 3-year period. The Funen Adenoma Follow-up Study was another randomized comparison of surveillance intervals (60). This study found that the incidence of advanced neoplasia was higher in patients examined at 4 years compared with 2 years (8.6 vs. 5.2%), although the difference was not significant. However, these randomized control trials were conducted prior to the recent epidemiologic studies documenting the importance of flat/depressed (non-polypoid) lesions (61). Moreover, Martinez et al. (62) has shown that 3-year screening colonoscopy may not be adequate to prevent a small minority of patients who are at high risk of both advanced adenomas and cancer. On the other hand, not only in Japan but also in Asian countries, there are no established recommendations for post-polypectomy surveillance based on reliable evidence. The Japan Polyp Study is the largest clinical study conducted in ethnic Japanese communities, documenting for the first time follow-up surveillance strategies for patients who have undergone two complete colonoscopies for control of CRC, with the removal of all detected polyps (63). It will provide pre-existing comorbidity data, including the prevalence of both flat and depressed colorectal lesions, the quality of colonoscopy, and the risk of colon cancer. Furthermore, these follow-up data will help to clarify the long-term impact of colonoscopic removal on mortality due to CRC. The evidence will form a basis for the surveillance and management of CRC in community-dwelling individuals who undergo colonoscopy in Japan.

The risks and benefits of surveillance colonoscopy must be balanced at all ages, particularly in patients who have significant comorbidity. The cutoff age for stopping surveillance is usually 75 years; however, this should also depend on patients’ wishes, comorbidity and the findings at surveillance examinations.

Conclusions

Recently, a variety of CRC screening tests have become available. In this review, the characteristics of each modality are given. Based on national factors and resources, each country should make a choice on the screening method to be used. FOBT, especially FIT, would be the best modality for the purpose of decreasing CRC mortality as population-based screening. In contrast, if the aim includes the early detection of CRC and adenomas, endoscopic methods are more appropriate. Decreases in both CRC incidence and mortality have already occurred and are considered attributable to screening efforts. Quality assurance and control of the screening process is one of the major issues facing both present and developing screening tests.

Funding

This work was supported in part by the National Cancer Center Research and Development Fund (27-A-5).

Conflict of interest statement

None declared.

References


