Fecal occult blood testing for colorectal cancer: a perspective

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Colorectal cancer is an important health problem in western countries. Early detection of colorectal cancer reduces mortality. The best evidence for the effectiveness of screening for colorectal cancer is with annual or biennial fecal occult blood testing. While the benefit of fecal occult blood testing is small in absolute terms, the incremental cost-effectiveness of this screening strategy appears acceptable. Combining fecal occult blood testing with periodic flexible sigmoidoscopy or replacing it altogether with infrequent colonoscopy are theoretically attractive screening strategies, but the incremental costs and effectiveness of these more intensive screening strategies have not been well defined. Whether and how to implement population-based screening for colorectal cancer depends largely on available resources.

Key words: colorectal cancer, colorectal neoplasia, fecal occult blood testing, guaiac, mass screening

Introduction

Colorectal cancer (CRC) is a major health problem in developed countries. In the USA, 135 000 cases of CRC are diagnosed annually, with 55 000 deaths [1]. About 15% of all cancer deaths in the USA are a result of CRC. Men and women are affected alike. Most CRCs are believed to arise from adenomatous polyps, though most polyps do not evolve into cancer. The polyp–cancer sequence may take years to evolve, and polyps, as well as early CRCs, are generally asymptomatic [2].

Common risk factors for CRC include: age, with a steep increase in incidence after age 50; a CRC or adenoma in a first-degree relative (particularly at a younger age); and a prior personal history of endometrial, ovarian or breast cancer. However, most CRCs are diagnosed in people at average risk [3].

Screening efforts may be directed at early detection of established CRCs for curative treatment, detection and removal of adenomatous polyps before they evolve into cancers, or both. Current screening tests for CRC include the guaiac-based fecal occult blood test, which is designed to detect minute traces of blood in the stool that might originate from an asymptomatic CRC or polyp; or tests designed to visualize the large intestine to detect these lesions, such as sigmoidoscopy, colonoscopy or barium enema. Newer tests for CRC screening include immunochemical tests [4] and tests for cancer-related DNA sequences in stool [5]; as well as high-resolution computed tomography (CT) scans, or ‘virtual colonoscopy’ [6].

Fecal occult blood testing (FOBT) most commonly involves people collecting samples of stool, usually two samples on three consecutive days, and applying the samples to guaiac-impregnated paper slides. Dietary restrictions are often recommended to reduce the probability of a false-positive result. In the presence of heme or hemoglobin, the hydrogen peroxide in the developing solution changes the guaiac compound from colorless to blue, indicating a positive test. The recommended procedures for FOBT have been reviewed in detail [7, 8].

Does the currently available evidence suggest that FOBT has a proven screening effect?

Evidence for the effectiveness of fecal occult blood screening at reducing CRC mortality comes principally from three well-designed randomized trials from the USA, Denmark and the UK.

In the US trial, 46 551 subjects aged between 50 and 80 years were randomized to annual or biennial FOBT or a control group. Hemoccult slides were used, and for most of the study period, the slides were rehydrated before development. Participants were recruited between 1975 and 1977, and were screened through 1992 (with a hiatus of 4–5 years in the middle of the study). Positive tests were usually investigated with colonoscopy. Compliance with testing and follow-up was relatively high, with ~75% of offered screenings completed, and ~80% of subjects with positive tests completing colonoscopy. After 13 years of follow-up, annual screening was reported to have reduced the cumulative incidence of CRC mortality from 0.00883 to 0.00588, a relative reduction of 33% [95% confidence interval (CI) 13% to 50%]. The corresponding ‘number needed to screen’ to prevent one CRC death is 339 over...
13 years [9]. In a subsequent publication, biennial screening was reported to be associated with a smaller, but significant reduction in CRC mortality (21%) [10]. Another publication from the trial documented that the incidence of CRC was significantly lower in the screened groups, suggesting that part of the benefit came from removal of polyps otherwise destined to become cancers [11]. Because of the low specificity of the rehydrated guaiac cards, a relatively high proportion of subjects (about one-third) in the annual screening group underwent colonoscopy over the course of the trial. Some observers have suggested that the impact of FOBT on mortality may have been actually partially mediated through chance selection for colonoscopy [12].

In the Danish trial, residents of a community aged between 45 and 75 years were randomized to a screening group (n = 30,967) or a control group (n = 30,966). Members of the screening group were invited to a first screening with non-rehydrated Hemoccult II test kits, and the 67% of the group who participated were invited to be rescreened after 2 years. This process continued for 10 years, from 1985 to 1995. Just under half the screening group participated in all five rounds of testing. Eighty-five percent of subjects with a positive FOBT underwent colonoscopy. Rates of test positivity with the non-rehydrated cards were lower than in the US trial, and the proportion of subjects who underwent colonoscopy during the 10-year trial was much lower (~4%). The mortality rate (from CRC and complications from treatment) was reduced from 0.0089 to 0.0073 per 10 person-years, a relative reduction of 18% (95% CI 1% to 32%). The number needed to screen was 625 over 10 years. In this trial, neither CRC incidence nor overall mortality was significantly reduced in the screening group [13].

In the trial from the UK, residents of the Nottingham area were randomized (by household) to a screening group (n = 76,466) and a control group (n = 76,384). Most subjects were recruited between 1985 and 1991, and the trial continued until 1995. Screening group participants were offered biennial testing with non-rehydrated Hemoccult cards. Sixty percent of subjects were screened at least once, and 38% completed all offered screening rounds (between three and six per participant). A positive FOBT was generally repeated with dietary restriction and colonoscopy was recommended only for persistently positive tests; over the course of the trial, 4% of participants who completed at least one screening test underwent colonoscopy. Follow-up varied for participants in the trial given the long accrual period. The estimated mortality rates for CRC were reduced from 0.0070 to 0.0060 per 10 person-years, a relative reduction of 15% (95% CI 2% to 26%). The corresponding number needed to screen was 1000 over 10 years. Like the Danish trial, there was no significant reduction in CRC incidence or overall mortality with screening [14].

Towler et al. [15] have performed a meta-analysis of randomized trials of fecal occult blood screening, which included mortality data from a fourth trial from Sweden, published previously without mortality data [16]. The Swedish trial found a non-significant 12% reduction in CRC mortality over ~8 years, albeit with just two rounds of screening at the beginning of the trial. The estimate of the reduction in CRC mortality across the four trials was 16% (95% CI 7% to 23%); for persons screened the reduction was estimated at 23% (95% CI 11% to 43%).

Other CRC screening options

Newer guaiac-based tests, such as the Hemoccult II Sensa test, have been reported to have a somewhat higher sensitivity than the Hemoccult II tests used in the trials. In one study, the combined sensitivity for cancer and polyps larger than 10 mm (in patients already scheduled to undergo colonoscopy) increased from ~38% with Hemoccult II to 47% with Hemoccult II Sensa [17]. Specificity appeared to be similar, but the specificity estimates in this study were not precise, and even small decrements in specificity can dramatically increase the ‘false alarm’ rate in a screening situation, and greatly increase the number of required colonoscopies.

Sigmoidoscopy also appears to reduce CRC mortality, although this inference is based primarily on one strong case–control study. Selby et al. [18] reported a negative association between prior rigid sigmoidoscopy and fatal cancer of the rectum and distal sigmoid colon (within reach of the 20 cm rigid scope) among members of the Kaiser Permanante Health Plan in Northern California. The estimated protective effect was 59% (95% CI 31% to 75%), and appeared as strong when the prior exposure was 9–10 years earlier. There was no protective effect for cancers proximal to the reach of the scope, suggesting the observed negative association between distal CRC mortality and prior sigmoidoscopy was a true protective effect, and not simply reflective of bias. However, only 15% of the fatal CRCs observed in this population were in fact within reach of the rigid scope.

It is not unreasonable to hypothesize that longer instruments, such as the 60 cm flexible sigmoidoscope or the colonoscope, would have a similar protective effect over a greater length of colon. In fact, another case–control study among American veterans has suggested prior endoscopies of any kind were associated with a reduction in CRC mortality of 59%. The effect lasted at least 5 years, and, as would be expected, was strongest for colonoscopy [19]. Moreover, removing polyps from the colon with periodic colonoscopy appears to dramatically reduce the expected incidence of CRC, by at least 75% [20], but these reductions were not calculated using randomized controls. Lieberman et al. [21] have recently reported that among male US veterans aged between 50 and 75 years (somewhat enriched with subjects with a positive family history of CRC), one-time screening colonoscopy uncovered cancer in ~1%, and advanced polyps (with dysplasia, villous histology or size >10 mm) in ~9% of patients screened. In this study, between 68% and 80% of these advanced neoplastic lesions would have been found by
flexible sigmoidoscopy (depending on depth of insertion), provided colonoscopy was performed in response to any distal adenomatous polyp. In this study, the risk of complications requiring hospitalization from screening colonoscopy was 0.3%. The most common complication was bleeding; a perforation or death was not reported in over 3121 examinations.

Ironically, some of the most attractive strategies for CRC screening, including those strategies widely recommended by national guidelines in the USA [3, 22], have not been tested in randomized trials. These strategies include the combination of annual FOBT with flexible sigmoidoscopy every 5 years, or infrequent total colon examinations with air contrast barium enema or colonoscopy. In theory, if the false-negative rates are independent, the combination of even one-time screening with Hemoccult II Sensa and flexible sigmoidoscopy should be at least ~85% relative to colonoscopy [17, 21], with even higher sensitivity for serial screening. Moreover, flexible sigmoidoscopy, in contrast to colonoscopy, can be performed by trained non-physicians [23], which can prove a huge advantage in the initiation of mass screening programs in some countries.

Is CRC screening cost-effective?

Two recent analyses have examined the cost-effectiveness of different strategies of CRC screening, reaching different results. Both analyses considered only direct medical care costs (payer perspective). Frazier et al. [24] examined the cost-effectiveness of 22 strategies of screening people aged 50 to 85 years, assuming 60% compliance in the base case; costs and life expectancy were discounted at 3%. The incremental cost-effectiveness ratios in 1998 US dollars for annual non-rehydrated FOBT, annual non-rehydrated FOBT plus flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years compared with no screening were $12,667, $16,786 and $20,418 per year of life saved, respectively. The incremental cost-effectiveness ratio for adding periodic sigmoidoscopy to annual non-rehydrated FOBT in this analysis was $27,273 per year of life saved. However, infrequent colonoscopy was actually less effective than the combined strategy with similar costs. On closer inspection, this result reflects a very optimistic calculation for CRC mortality reduction from annual unrehydrated FOBT of 55%. As a result, combined FOBT plus periodic sigmoidoscopy reduced CRC mortality by an estimated 75%, compared with 64% for colonoscopy every 10 years [24].

Sonnenberg et al. [25] also modeled different strategies of screening people for CRC starting at age 50, using the same discount rate of 3% for costs and future life years. However, the combined strategy of FOBT plus sigmoidoscopy was not examined. Based on the model’s assumptions, annual FOBT was calculated to reduce mortality by 18% (which seems more in line with the published trials), at an incremental cost-effectiveness ratio in 1998 US dollars compared with no screening of $9705 per year of life saved. Colonoscopy every 10 years reduced CRC mortality by an estimated 75%, with an incremental cost-effectiveness ratio of $10,983 per year of life saved compared with no screening, and $11,382 per year of life saved compared with annual FOBT.

Both studies, with dramatically different assumptions about the effectiveness of annual FOBT, suggest that the incremental cost-effectiveness of annual FOBT compared with no screening is comparable with other commonly used screening tests.

Should FOBT be recommended to the general population as a CRC screening test?

The weight of evidence strongly suggests early detection of CRC reduces mortality from this disease. The quality of the evidence for the effect of screening on mortality is actually strongest for periodic FOBT, although the absolute benefits of FOBT are small. Despite strong evidence of its effectiveness, FOBT, and CRC screening in general, is not popular. Among Americans aged over 50 years surveyed in 1999, ~40% reported ever having an FOBT, and 21% reported having one in the past year. For sigmoidoscopy, 44% reported having had one, and 34% had had one in the past 5 years [26].

Whether and how population-based screening for CRC should be implemented is largely a question of available resources. Incremental cost-effectiveness ratios for screening with FOBT compared with no screening appear favorable from the perspective of western industrialized nations. Moreover, although neither the incremental costs nor incremental effectiveness of adding periodic flexible sigmoidoscopy to FOBT or simply performing infrequent colonoscopy have been precisely defined, the higher sensitivity of these strategies compared with FOBT alone are attractive. Moreover, the costs of these endoscopic screening strategies will vary between countries depending on labor costs and whether non-physicians can perform some of the examinations. Clearly, any screening strategy, including FOBT alone, should not be implemented until the capacity for follow-up testing and treatment is assured.

In the USA, there are endless debates about the optimal strategy for CRC screening, and particularly about who pays the costs, especially for screening colonoscopy [27–29]. These debates continue in the face of evidence that most Americans have not been screened for CRC by any modality. Historically, recommendations about disease screening have generally been paternalistic, with physicians or public health officials deciding which tests people ‘need’. Going forward, informed patients need to be part of the decision-making process. Woolf [30] has recently suggested, ‘...defining the best [colorectal cancer screening] test as the one the patient wants may save the most lives’ [30]. The author agrees.
References