Review article

Once-only sigmoidoscopy

J. Cuzick

Imperial Cancer Research Fund, London, UK

Abstract

The rationale for infrequent screening for colorectal cancers by sigmoidoscopy of the general population around age 60 is reviewed. A progress report for a trial to evaluate this approach is also presented.

Introduction

Worldwide colorectal cancer is the fourth most common cancer with an estimated 750,000 cases and almost 400,000 deaths every year. Rates are much higher in western, northern, and central Europe and in North America than for most of the rest of the world. Rates have been stable in the UK for many decades, but appear to be decreasing in the USA, especially for white women under the age of 65 years [1]. In contrast, incidence and mortality is increasing in Central Europe both for men and women. Mortality rates in Austria, Hungary and the former Czechoslovakia are among the highest in Europe [2].

Little is known about the specific causative agent(s) for colorectal cancer, but diet appears to be a key factor. Studies have shown broad categories of fat, such as animal fat, or red meat to be risk factors, and fiber, fruit and vegetables to be protective [3]; but the specific food constituents involved are less clear. Protective effects have been observed for non-steroidal anti-inflammatory drugs, especially aspirin [4, 5], exercise [3, 6, 7] and possibly coffee consumption [8]. To date, most prospective trials of colorectal screening have concentrated on evaluating the faecal occult blood test (FOBT). This test is not specific for colorectal neoplasia and recent studies suggest it is not very sensitive [9, 10]. However, a 15%–25% mortality reduction has been documented in a number of studies where FOBT is offered every 1–2 years (Table 1). The largest of these is a British study reported by Hardcastle, et al. [11], in which 152,850 individuals aged 45–74 were randomised to control or biennial Hemoccult tests. Compliance was around 60% and after 7 to 8 years of follow-up there was a statistically significant mortality reduction of 15%. A very similar Danish trial involving 61,933 individuals has produced similar results [12]. After 10 years of follow-up the mortality reduction was 18% in that study. Unlike cervical screening which aims to detect pre-cancerous lesions, FOBT aims to detect cancer at an early stage, and because of the short lead time, would need to be offered every 1 to 2 years.

In contrast, screening by sigmoidoscopy aims to detect and remove precursor lesions, i.e., colorectal adenomas, and for the section of the bowel examined, this may provide more complete protection for a longer duration. The rationale for this approach relies heavily on the fundamental importance of the adenoma-carcinoma sequence in bowel cancer.

Adenoma-carcinoma sequence

Morson [13] first described the adenoma-carcinoma sequence illustrated in Figure 1. In its simplest form, it states that cancers arise from pre-existing adenomas which initially are small and have a tubular architecture, but slowly grow and become more villous. In some cases, a focus of carcinoma eventually develops which subsequently invades the basal membrane. This process is thought to take from 10–35 years. In fact the details of adenoma evolution are still not clear. For example, it is not known if villousness is a property of an adenoma denovo or whether it is acquired during growth. It is also not known whether all adenomas remain small for an extended period before eventually becoming larger, or if some are always destined to remain small and others are programmed to become large quickly. Stryker et al. [14], have estimated the malignant conversion rate of large adenomas. They found that in 226 patients with adenomas greater than or equal to 1 cm in diameter, the progression rate to cancer at 5, 10 and 20 years was 2.5%, 8% and 24%, respectively, based on an actuarial analysis. Fearon and Vogelstein [15] have shown that genetic mutations accrue in adenomas as they become more severe. A mutation in the APC gene appears to be the
Table 1. Effect on mortality of occult blood testing clinical trials.

<table>
<thead>
<tr>
<th>Study (First author)</th>
<th>Date</th>
<th>Median FU (yr)</th>
<th>Frequency (mo)</th>
<th>Screened CRC deaths/pop</th>
<th>Controls CRC deaths/pop</th>
<th>OR (95% CI)</th>
<th>Compliance (%)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandel [28]</td>
<td>1993</td>
<td>13</td>
<td>12</td>
<td>82 / 15520</td>
<td>121 / 15394</td>
<td>0.67 (0.50-0.82)</td>
<td>75</td>
<td>50-80</td>
</tr>
<tr>
<td>Hardecastle [11]</td>
<td>1996</td>
<td>7.8</td>
<td>24</td>
<td>117 / 15587</td>
<td>121 / 15394</td>
<td>0.94 (0.68-1.31)</td>
<td>78.4</td>
<td>50-80</td>
</tr>
<tr>
<td>Kronberg [12]</td>
<td>1996</td>
<td>10</td>
<td>24</td>
<td>360 / 76466</td>
<td>420 / 76384</td>
<td>0.85 (0.74-0.98)</td>
<td>59.6</td>
<td>45-74</td>
</tr>
<tr>
<td>Winawer* [29]</td>
<td>1993</td>
<td>7</td>
<td>12</td>
<td>36 / 12974</td>
<td>28 / 8782</td>
<td>0.75 (0.45-1.21)</td>
<td>76 initially</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancers; OR, odds ratio; FOBT, faecal occult blood test.

*Rigid sigmoidoscopy with or without FOBT.

earliest step, as it is found in a high proportion of adenomas independent of size or histology. Additional changes, including \( \text{ras} \) mutations, then occur that do not appear to follow a particular order, and are not all necessary for malignancy. Mutations in the ‘Deleted in Colorectal Carcinoma’ (DCC) tumor suppressor gene and in p53 appear to occur quite late and may be related to the transition to invasiveness or metastatic spread.

Temporal sequence

Central to the rationale for once-only sigmoidoscopy is that distal adenomas appear many years before a cancer will develop and that there is a window of opportunity in which most of the distal adenomas, which are likely to lead to cancer, have appeared but in which few of the cancers have yet developed. The available data suggest that such an interval does exist and that it is centered at around age 60 years [14]. If regression of adenomas is relatively rare, this can be interpreted to mean that most distal adenomas have appeared by age 60 years. Conversely, most cancers occur after age 60 years, with only 16% appearing before that age in the UK. Screening at a younger age, say 55 years, would hopefully prevent some of these cancers at younger ages (only 9% of colorectal cancer occurs before age 55 years), but may also miss some adenomas destined to develop into cancer before.
old age. Screening at age 65 years is more likely to pick up a higher proportion of adenomas, but 27% of cancer will occur before that age. Further work is needed to discover the best age within that interval for screening, or indeed if two screenings, one at age 55 years and another at age 65 years, is cost-effective.

**Effectiveness of repeated sigmoidoscopy**

A number of studies have examined colorectal cancer rates in patients offered repeated sigmoidoscopy or colonoscopy (Table 2). In an early study, Gilbertson and Nelms [16] reported an 85% reduction in rectal cancer in 21,000 subjects who had annual rigid sigmoidoscopy, but others have suggested that the reduction may not have been so large [17]. Friedman et al. [18], reported a 60% reduction in distal colorectal cancer in 10,000 patients randomised to have a sigmoidoscopy every 3 years, but subsequent analysis showed that use of this procedure was similar in both arms of the study [19]. However, a case-control study on the same population confirmed a benefit associated with sigmoidoscopy [20]. This has also been confirmed in another small, case-control study [21]. More recently Muller and Sonnenberg [22] have found a 59% reduction of colorectal cancer mortality following any endoscopic colorectal procedure (Figure 2). A bigger effect would be expected if only cancers that were within reach of the instrument used had been considered. Two prospective studies have also shown a marked reduction of the anticipated cancer rates in patients who have had adenomas completely removed [23, 24].

**Table 2. Efficacy of sigmoidoscopy.**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Cases/no. of subjects</th>
<th>Reduction in colorectal cancer incidence in region examined (95% CI)</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson [16]</td>
<td>1978</td>
<td>13 / 21150</td>
<td>60-85%</td>
<td>Prospective uncontrolled</td>
</tr>
<tr>
<td>Friedman [18]</td>
<td>1986</td>
<td>110 / 10713</td>
<td>60%</td>
<td>Prospective randomised</td>
</tr>
<tr>
<td>Selby [20]</td>
<td>1992</td>
<td>261 / 1129</td>
<td>70% (52-81)</td>
<td>Case-control</td>
</tr>
<tr>
<td>Atkin [23]</td>
<td>1992</td>
<td>3%/ 1618</td>
<td>85%</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Winawer [24]</td>
<td>1993</td>
<td>5 / 1418</td>
<td>90% (76-97)</td>
<td>Prospective cohort (colonoscopy)</td>
</tr>
<tr>
<td>Muller [22]</td>
<td>1995</td>
<td>4358 / 16531</td>
<td>59%* (50-67)</td>
<td>Case-control</td>
</tr>
</tbody>
</table>

* Any colorectal procedure

**Excluding cancers arising in incompletely excised adenomas
Duration of protection

Two studies have looked directly at the length of protection afforded by an endoscopic procedure [20, 24]. In both studies no diminution of protection was found for up to 10 years after the procedure. Longer follow-up was not attempted. Selby [20] reported a 70% reduction of fatal cancers within reach of the rigid sigmoidoscope, virtually unchanged over 10 years after the procedure, and in a much larger study of American veterans, Muller and Sonnenberg [22] found a 60% reduction in all colorectal cancer, and again this remained unchanged for at least 10 years (Figure 2).

High risk versus low risk adenomas

Several studies have shown that all adenomas do not have the same malignant potential. The most important factor appears to be size. This is closely related to architecture, so that the degree of villousness is also a key risk factor. Severely dysplastic adenomas also indicate high risk, regardless of size, and the appearance of multiple distal adenomas, especially if they are large, also indicates increased risk. In a large prospective study, Atkin et al. [23] followed a cohort of 1618 individuals who had adenomas detected by sigmoidoscopy at a time when few received any follow-up. Patients with a large (≥21 cm), villous or tubular-villous adenoma were classified as high risk and their risk of subsequent colon cancer was 3.6 times that for an age and sex matched general population. The remaining group, with only small tubular adenomas, had a lower risk than the general population. Similar results have been reported by Winawer et al. [24].

Zarchy and Ershoff [25] have directly evaluated the ability of high risk distal adenomas to predict high risk proximal lesions. They found a 24% prevalence of new proximal adenomas in patients with distal lesions, and that high risk adenomas found proximally were well predicted by distal lesions. In particular, high risk proximal lesions were found in 11.8% of individuals with high risk distal lesions, but less than 1% of those with low risk lesions.

Once-only sigmoidoscopy

The evidence presented above makes a strong case for the belief that a once-in-a-lifetime sigmoidoscopy at around age 60 years is a cost-effective way of preventing colorectal cancer and may reduce the risk by more than 50% in those who undergo it. A more detailed rationale is presented in Atkin et al. [26], however, the evidence is all indirect and especially the size of the benefit needs to be validated by a randomised trial. It is still unclear what proportion of cancers arise in pre-existing adenomas, and even less is known about the length of the pre-invasive stage. Such a trial would also provide information on the best age for the test, the duration of protection, and (less directly) the value of a second test 10 years later. Compliance is a key issue both in a trial, where it has a crucial impact on the power to detect important benefits, and also in a national programme, where it is likely to be the major factor determining total mortality reduction. Several factors influence compliance, including public perception of benefit, fear of pain and discomfort, social taboos, as well as more practical issues such as ease in obtaining convenient appointments, well presented information packs, and the type of bowel preparation employed (e.g., oral vs enema).

These issues are currently being addressed in a large multicentre trial which aims to randomise 200,000 individuals aged 55–64 years from 10 centres throughout the UK. This trial has several novel features, including a two-stage randomisation procedure in which randomisation is preceded by an initial questionnaire, asking if potential participants would be prepared to undergo the test if it was offered. Only those who say ‘yes’ are then randomised for screening in a ratio of one treated to two controls. Screening will be undertaken with the 65 cm flexible sigmoidoscope with the goal of visualising the bowel up to the descending-Sigmoid colon junction. Only individuals with ‘high risk’ adenomas found at sigmoidoscopy (see Table 3) will be offered colonoscopy and surveillance. Individuals with ‘low risk’ (small, tubular) adenomas will undergo polypectomy at the time of screening and will receive no further screening tests. Ten to 15 years of follow-up will be needed to obtain clear results on reductions of incidence and mortality from colorectal cancer, although other preliminary indicators of efficacy will be available sooner.

Results on the uptake and yield of neoplasia in the pilot and start up centres have recently been reported [27]. In these 2 centres approximately 60% of those approached indicated an interest in screening and 75% of them actually attended. Adenomas were detected in 10% of those screened and 6% had high-risk adenomas and received a colonoscopy. Nine cancers were found in the 1285 individuals screened, leading to a prevalence of 7.0 cancers per thousand screened, which is more than seven times the expected annual incidence rate. Five of the nine cancers were Dukes stage A.

As of March 1998, more than 130,000 individuals have been randomised and more than 20,000 have been screened in the main trial. It is anticipated that the goal of 40,000 screened individuals will be reached by the end of 1998. Thus far the detection rates have been very similar to our pilot study, i.e., about 25% with some type of polyp, 10% with adenomas and 5% with ‘high risk’ adenomas in need of follow-up. A high latent cancer rate has also been found, mostly of asymptomatic Dukes stage A cancers.

Table 3. Screening policy.

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>• Flexible sigmoidoscopy at age 55–64 years with removal and histology of all polyps</td>
</tr>
<tr>
<td>• Colonoscopy and surveillance of ‘high risk’ population defined by any of the following:</td>
</tr>
<tr>
<td>- size ≥ 1 cm</td>
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<tr>
<td>- three or more adenomas</td>
</tr>
<tr>
<td>- villous or tubulovillous histology</td>
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<tr>
<td>- severe dysplasia</td>
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<tr>
<td>- five or more colonic hyperplastic polyps</td>
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</tbody>
</table>
References


Correspondence to:
Dr. Jack Cuzick
Department of Mathematics, Statistics and Epidemiology
Imperial Cancer Research Fund
61 Lincoln’s Inn Fields
London WC2A 3PX, UK
e-mail: j.cuzick@icrf.icnet.uk